Medical Education Systems, Inc.

Course 602

CARDIO–PULMONARY PHARMACOLOGY

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Cardio-Pulmonary Pharmacology

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Introduction

This continuing education course is designed to provide you with an overall review of the pharmacology associated with treating cardio-pulmonary disorders. While the focus is more on the pulmonary disorders, the inter-relatedness of the two systems requires some discussion of the medications focused on heart problems. Since the respiratory system cannot be disassociated from cardiac and vascular systems, respiratory care pharmacology necessarily involves a relatively broad scope of drug classes.

RCPs and nurses are involved in administering drugs that are specifically designed to treat the so-called *pathological triad* of pulmonary disease: bronchospasm, airway inflammation, and retained secretions.

The front line arsenal for treating pulmonary diseases consists of bronchodilators, antimuscarinics, corticosteroids, mucokinetics, mucolytics, and decongestants. There are also a variety of other agents available for treating pulmonary ailments, including: oxygen, antibiotics, local anesthetics, respiratory stimulants, and muscle relaxants. Because of the inter-connectedness of the body systems, additional groups of drugs that may be administered to patients with respiratory diseases include: anti-infectives, CNS drugs, antiarrhythmic agents, anticoagulants, antihypertensives, and diuretics.

You will review the broad categories of medications used, subgroups of medications, articles published about those medications, and, finally, some of the equipment used to deliver medications to patients. USE THE FOLLOWING LINK TO ALWAYS HAVE THE MOST CURENT INFORMATION REGARDING PULMONARY MEDICATIONS:

http://www.medilexicon.com/drugsearch.php?a=18

The course includes detailed discussions of aerosol therapy, nebulizers, and humidifiers. Therapeutic procedures and medication functions are also examined in this valuable continuing education unit. The resources drawn upon for the following material can be found in the **References** section at the end of the course.

Learning Objectives

Upon successful completion of this CEU, you will be able to:

1. Identify and discuss the categories of medications used to treat cardio-pulmonary disorders.

2. Identify complications and side effects of some of at least three of the most common respiratory medications.

3. Identify and explain the functions of the various types of equipment utilized for delivery of medications in respiratory care.

4. Discuss the advantages and disadvantages of aerosolized medications, and explain the principles associated with humidification.

5. Discuss at least one of the clinical practice guidelines for choosing and using equipment to deliver medications.

The Respiratory System

INTRODUCTION

Before we begin reviewing the medications used to treat respiratory (and cardio-respiratory) problems, we believe it would be good to first present you with a brief review of the respiratory system:

a. **Respiration.** Respiration is the exchange of gases between the atmosphere and the cells of the body. It is a physiological process. There are two types of respiration-external and internal. External respiration is the exchange of gases between the air in the lungs and blood. Internal respiration is the exchange of gases between the blood and the individual cells of the body.

b. **Breathing**. Breathing is the process that moves air into and out of the lungs. It is a mechanical process. There are two types of breathing in humans--costal (thoracic) and diaphragmatic (abdominal). In costal breathing, the major structure causing the movement of the air is the rib cage. In diaphragmatic breathing, interaction between the diaphragm and the abdominal wall causes the air to move into and out of the lungs.

1-2. COMPONENTS AND SUBDIVISIONS OF THE HUMAN RESPIRATORY SYSTEM

See Figure 1-1 for an illustration of the human respiratory system.

a. **Components**. The components of the human respiratory system consist of air passageways and two lungs. Air moves from the outside of the body into tiny sacs in the lungs called alveoli (pronounced al-VE-oh-lie).

b. **Main Subdivisions**. The main subdivisions of the respiratory system may be identified by their relationship to the voice box or larynx. Thus, the main

subdivisions are as follows:

SUBDIVISION	FUNCTION
(1) SUPRALARYNGEAL STRUCTURES (su-prah-lah-RIN-je-al)	cleanse, warm, moisten, and test inflowing air
(2) LARYNX (voice-box) (LARE-inks)	controls the volume of inflowing air; produces selected pitch (vibration frequency) in the moving column of air
(3) INFRALARYNGEAL STRUCTURES (in-frah-lah-RIN-je-al)	distribute air to the alveoli of the lung where the actual external respiration takes place

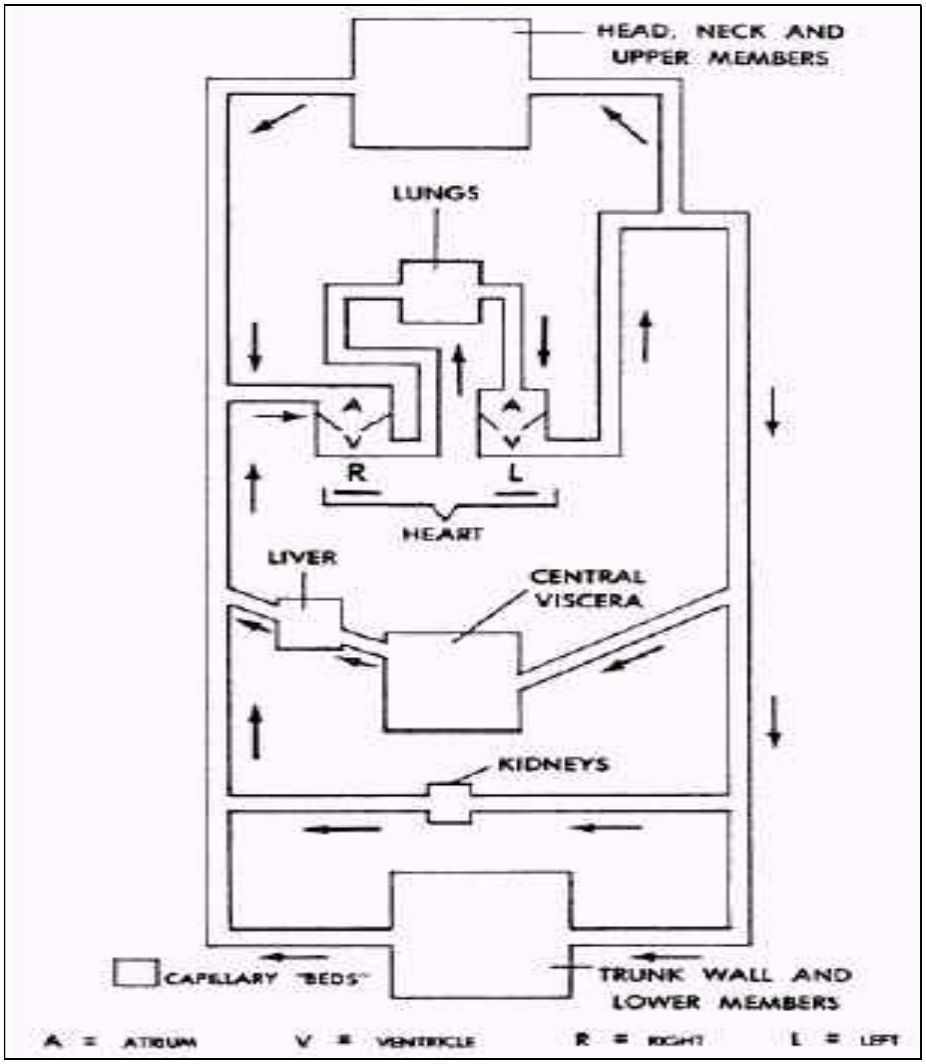


Figure 1-1. The human respiratory system.

1-3. SUPRALARYNGEAL STRUCTURES

a. **External Nose**. The external nose is the portion projecting from the face. Primarily cartilages support it. It has a midline divider called the nasal septum, which extends from the internal nose. Paired openings (nostrils lead to paired spaces (vestibules). Guard hairs in the nostrils filter inflowing air.

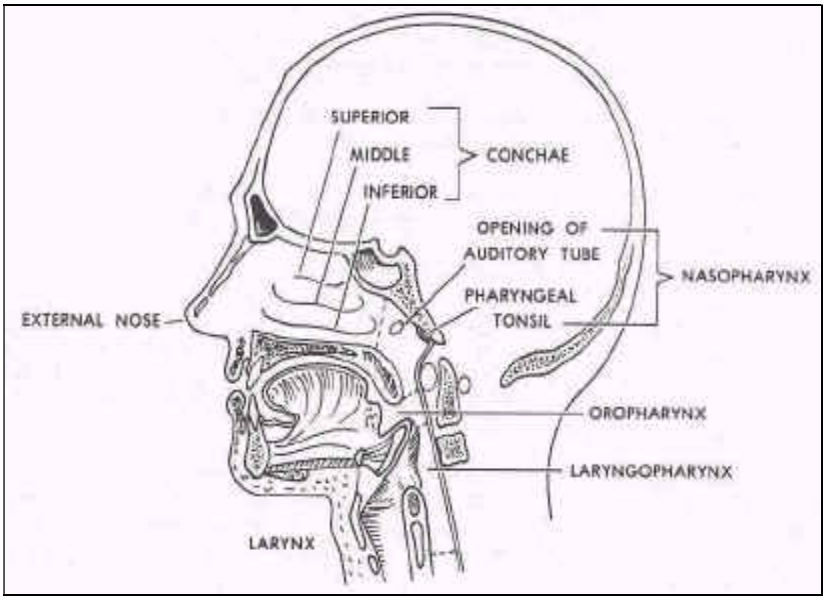


Figure 1-2. Supralaryngeal structures.

b. **Nasal Chambers (Internal Nose)**. Behind each vestibule of the external nose is a nasal chamber. The two nasal chambers together form the internal nose. These chambers too are separated by the nasal septum.

(1) Mucoperiosteum. The walls of the nasal chambers are lined with a thick mucous-type membrane known as the mucoperiosteum. It has a ciliated epithelial surface and a rich blood supply, which provides warmth and moisture. At times, it may become quite swollen.

CILIATED = Provided with cilia (hair like projections that move fluids to the rear)

(2) Conchae. The lateral wall of each chamber has three scroll-like extensions into the nasal chamber, which help to increase the surface area exposed to the inflowing air. These scroll-like extensions are known as conchae.

CONCHA =sea shell CONCHA (singular), CONCHAE (plural)
(pronounced KON -kah)

(3) Olfactory epithelium. The sense of smell is because of special nerve endings located in the upper areas of the nasal chambers. The epithelium containing the sensory endings is known as the olfactory epithelium.

(4) Paranasal sinuses. There are air "cells" or cavities in the skull known as paranasal sinuses. The paranasal sinuses are connected with the nasal chambers and are lined with the same ciliated mucoperiosteum. Thus, these sinuses are extensions of the nasal chambers into the skull bones. For this reason, they are known as paranasal sinuses.

c. **Pharynx.** The pharynx (FAIR-inks) is the common posterior space for the respiratory and digestive systems.

(1) Nasopharynx. That portion of the pharynx specifically related to the respiratory system is the nasopharynx. It is the portion of the pharynx above the soft palate. The two posterior openings (nares) of the nasal chambers lead into the single space of the nasopharynx. The auditory (eustachian) tubes also open into the nasopharynx. The auditory tubes connect the nasopharynx with the middle ears (to equalize the pressure between the outside and inside of the eardrum). Lying in the upper posterior wall of the nasopharynx are the pharyngeal tonsils (adenoids). The soft palate floor of the nasopharynx is a trap door that closes off the upper respiratory passageways during swallowing.

(2) Oropharynx. The portion of the pharynx closely related to the digestive system is the oropharynx. It is the portion of the pharynx below the soft palate and above the upper edge of the epiglottis. (The epiglottis is the flap that prevents food from entering the larynx (discussed below) during swallowing.) (3) Laryngopharynx. That portion of the pharynx that is common to the respiratory a digestive systems is the laryngopharynx. It is the portion of the pharynx below the upper edge of the epiglottis. Thus, the digestive and respiratory systems lead into it from above, and lead off from it below.

1-4. LARYNX

The larynx, also called the Adam's apple or voice box, connects the pharynx with the trachea. The larynx, located in the anterior neck region, has a box-like shape. See Figure 1-3 for an illustration. Since the voice box of the male becomes larger and heavier during puberty, the voice deepens. The adult male's voice box tends to be located lower in the neck; in the female, the larynx remains higher and smaller and the voice is of a higher pitch.

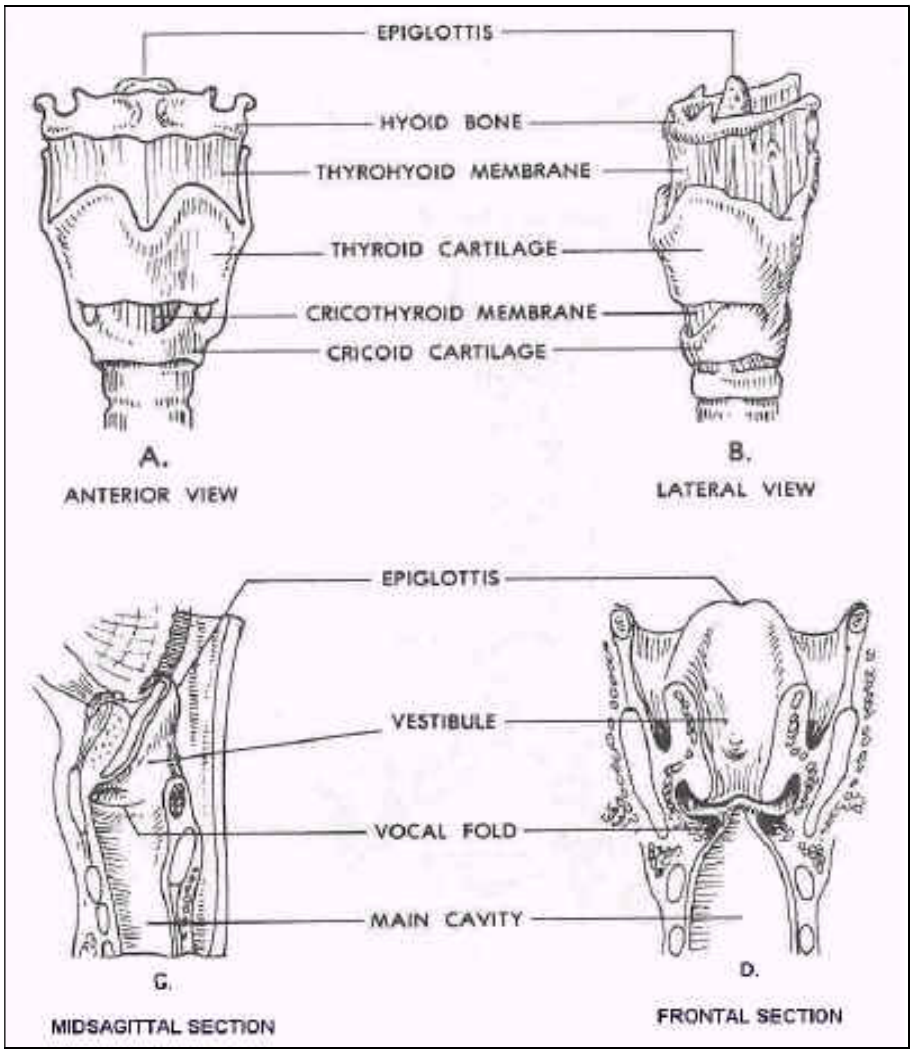


Figure 1-3. The larynx.

a. **Parts and Spaces**. The larynx has a vestibule ("entrance hallway") that can be covered over by the epiglottis. The glottis itself is the hole between the vocal cords. Through the glottis, air passes from the vestibule into the main chamber of the larynx (below the cords) and then into the trachea. The skeleton of the larynx is made up of a series of carti1ages.

b. **Muscles.** The larynx serves two functions and there are two sets of muscles- - one for each function.

(1) One set controls the size of the glottis. Thus, it regulates the volume of air passing through the trachea.

(2) The other set controls the tension of the vocal cords. Thus, it produces vibrations of selected frequencies (variations in pitch) of the moving air to be used in the process of speaking.

1-5. INFRALARYNGEAL STRUCTURES

a. **Trachea and Bronchi.** The respiratory tree (Figure 1-4) is the set of tubular structures that carry the air from the larynx to the alveoli of the lungs. Looking at a person UPSIDE DOWN, the trachea is the trunk of the tree and the bronchi are the branches. These tubular parts are held open (made patent) by rings of cartilage. Their lining is ciliated to remove mucus and other materials that get into the passageway.

b. **Alveoli.** The alveoli (alveolus, singular) are tiny spherical (balloon-like) sacs that are connected to the larger tubes of the lungs by tiny tubes known as alveolar ducts and bronchioles. The alveoli are so small that there are millions in the adult lungs. This very small size produces a maximum surface area through which external respiration takes place. External respiration is the actual exchange of gases between the air in the alveolar spaces and the adjacent blood capillaries through their walls.

c. **Lungs**. A lung is an individual organ composed of tubular structures and alveoli, bound together by fibrous connective tissue (FCT). In the human, there are two lungs, right and left. Each lung is supplied by a primary or mainstem bronchus leading off from the trachea. The right lung is larger in volume than the left lung. The left lung must leave room for the heart. The right lung is divided into 3 pulmonary lobes (upper, middle and lower) and 10 bronchopulmonary segments (2 + 3 + 5). The left lung is divided into 2 pulmonary lobes upper and lower) and 8 bronchopulmonary segments (4 + 4). A pulmonary lobe is a major subdivision of a lung marked by fissures (deep folds. Each lobe is further partitioned into bronchopulmonary segments. Each lobe is supplied by a secondary or lobar bronchus. A tertiary or segmental bronchus, a branch of the lobar bronchus supplies each segment.

d. **Pleural Cavities.** Each serous cavity has inner and outer membranes. In the case of the lungs, the inner membrane, is known as the visceral pleura which very closely covers the surface of the lungs. The outer membrane is known as the parietal pleura, forming the outer wall of the space. The pleural spaces are the potential spaces between the inner and outer membranes. The opening between the pleural layers contains a slick fluid called pleural fluid. The pleural fluid serves as a lubricant and allows the lungs to move freely with a minimum of friction.

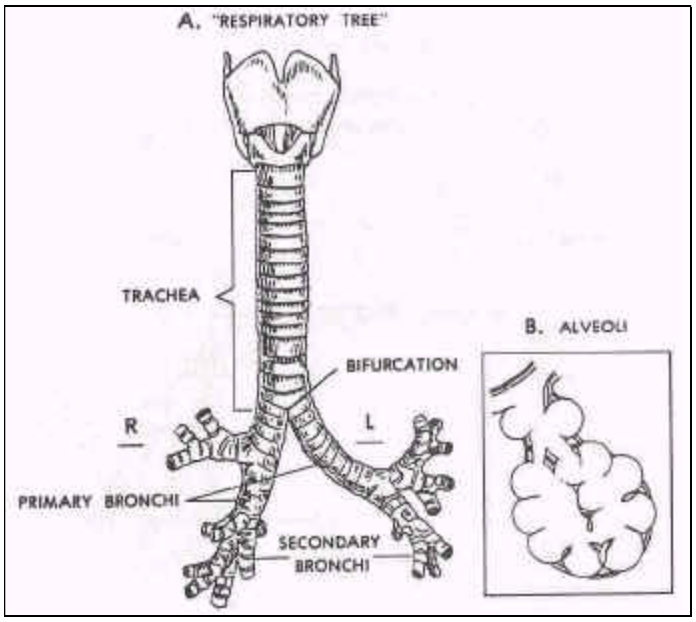


Figure 1-4. Infralaryngeal structures.

Breathing and Breathing Mechanisms in Humans

1-6. INTRODUCTION

a. Boyle's law tells us that as the volume (V) of a gas-filled container increases, the pressure (P) inside decreases; as the volume (V) of a closed container decreases, the pressure (P) inside increases. When two connected spaces of air have different pressures, the air moves from the space with greater pressure to the one with lesser pressure. In regard to breathing, we can consider the air pressure around the human body to be constant. The pressure inside the lungs may be greater or less than the pressure outside the body. Thus, a greater internal pressure causes air to flow out; a greater external pressure causes air to flow in.

b. We can compare the human trunk to a hollow cylinder. This cylinder is divided into upper and lower cavities by the diaphragm. The upper is the thoracic cavity and is essentially gas-filled. The lower is the abdominopelvic cavity and is essentially water-filled.

1-7. COSTAL (THORACIC) BREATHING

a. **Inhalation**. Muscles attached to the thoracic cage raise the rib cage. A typical rib might be compared to a bucket handle, attached at one end to the sternum (breastbone) and at the other end to the vertebral column.

The "bucket handle" is lifted by the overall movement upward and outward of the rib cage. These movements increase the thoracic diameters from right to left (transverse) and from front to back (A-P). Thus, the intrathoracic volume increases. Recalling Boyle's law, the increase in volume leads to a decrease in pressure. The air-pressure outside the body then forces air into the lungs and inflates them.

b. **Exhalation.** The rib cage movements and pressure relationships are reversed for exhalation. Thus, intrathoracic volume decreases. The intrathoracic pressure increases and forces air outside the body.

1-8. DIAPHRAGMATIC (ABDOMINAL) BREATHING

The diaphragm is a thin, but strong, dome-shaped muscular membrane that separates the abdominal and thoracic cavities. The abdominal wall is elastic in nature. The abdominal cavity is filled with soft, watery tissues.

a. **Inhalation**. As the diaphragm contracts, the dome flattens and the diaphragm descends. This increases the depth (vertical diameter) of the thoracic cavity and thus increases its volume. This decreases air pressure within the thoracic cavity. The greater air pressure outside the body then forces air into the lungs.

b. **Exhalation**. As the diaphragm relaxes, the elastic abdominal wall forces the diaphragm back up by pushing the watery tissues of the abdomen against the underside of the relaxed diaphragm. The dome extends upward. The process of inhalation is thus reversed.

Conditions Affecting the Respiratory System

1-9. INTRODUCTION

Many conditions affect the respiratory system. Some of the conditions are life-threatening, while many are chronic conditions which affect thousands of patients. Many of the patients who suffer from these conditions will be standing in front of the outpatient pharmacy in order to receive prescriptions to obtain some relief.

1-10. PNEUMONIA

Pneumonia is caused by an infection of the lung. This infection is caused by either bacteria (like the pneumococcus bacterium) or viruses.

In pneumonia the walls of the alveoli become inflamed and filled with fluid and the air spaces in the alveoli become filled with blood and fluid.

As you might expect, the exchange of gases in the alveoli becomes impaired. Death can result from pneumonia.

1-11. ASTHMA

Asthma, a condition usually caused by allergic reactions to substances in the environment, affects many people. The allergic reactions cause the bronchioles to spasm. Hence, the flow of air into and out of the lungs becomes impaired. For some unknown reason, the flow of air out of the lungs is more impeded than the flow of air into the lungs. Hence, the person with asthma often finds it more difficult to expire (expel the air) than to inspire. Furthermore, such labored breathing, after many years, often results in the asthma-sufferer having a barrel-shaped chest.

1-12. STATUS ASTHMATICUS

Status asthmaticus is a very sudden, continuous, and intense asthmatic attack.

1-13. EMPHYSEMA

Emphysema is a condition in which the patient has large portions of the alveolar walls destroyed. Consequently, the patient finds it necessary to breathe faster and more deeply in order to obtain the oxygen needed to live. Emphysema is often associated with smoking. Emphysema may also be referred to as Chronic Obstructive Pulmonary Disease (COPD).

1-14. PULMONARY EDEMA

Pulmonary edema is a condition in which fluid collects in the interstitial spaces of the lungs and in the alveoli. Obviously, the exchange of gases in the alveoli becomes impaired. Pulmonary edema is usually caused when the left side of the heart fails to pump efficiently; when this happens blood backs up into the pulmonary circulation and causes fluid in the lungs.

General Principles of Pharmacology

Pharmacology involves the study of drugs, and drugs are defined as chemical substances that exert a biologic effect on the recipient. Medical drugs are used for the treatment or prevention of disease, and drugs are considered useful when they can maintain, enhance or alter bodily function when a patient is cannot cope with a particular disease. Pharmacology is concerned with the following:

- the chemical and physical properties of drugs
- the physiologic effects and site of action of drugs

- how drugs exert their effects
- how the body absorbs, distributes, metabolizes, and excretes the drugs
- dosages and routes of administration of drugs
- side effects, toxicity, and contraindications

The safe administration of drugs requires awareness of the following factors:
- mode of action
- side effects
- toxicity
- range of common dosages
- rate and route of excretion
- individual differences in responses
- interaction with other drugs or food
- contraindications

For drugs to exert their expected therapeutic benefits, they need to be made available for absorption in the body's systems. Availability depends to a large extent on the route of administration of the drug. Drugs can be administered gastrointestinally, parenterally, or topically. Topical administration includes application to the skin and directly to the lungs by inhalation.

In order for a drug to be administered via inhalation, it must first either be vaporized or placed in an aerosol suspension. This generally requires the use of special equipment. The following discussion reviews the types of equipment available for administering drugs via inhalation.

Delivery Systems for Respiratory Medications

In addition to activities related to gas exchange, the respiratory system is responsible for a variety of other vital functions. One function of the upper airway to assure that inspired gases are warmed and adequately humidified. Another function involves protecting the lungs by filtering inspired gas. RCPs need to understand basic concepts of humidification and aerosol systems in order to treat patients whose airway mechanisms are compromised.

Aerosol and humidity therapy are provided to maintain normal physiologic conditions and as therapy for pathologic conditions. One of the most important, but least understood, aspects of pulmonary care is the role of humidity therapy. Many care providers and most patients do not appreciate the role of hydration in liquifying secretions and facilitating the natural flow of mucus from the lower airways.

Pulmonary patients need adequate humidification of their inspired gases and controlled fluid balance, otherwise patients can become dehydrated. Dehydration can make secretions more viscous and inhibit the mucociliary escalator activity of the airways, making secretions difficult to dislodge. If this blocks functional gas flow through the distal airways, infections, atelectasis and other respiratory problems can easily occur.

Principles of Humidification

Since humidification and humidity therapy are so important to respiratory well-being, you need to take a moment and review the basic physical principles of humidity. Humidity is essentially the water vapor in a gas. This water vapor can be described in several ways, as:

1. Absolute humidity - The actual content of water vapor in a gas measured in milligrams per liter.

2. Potential humidity - The maximum amount of water vapor a gas can hold at a given temperature.

3. Relative humidity - The amount of water vapor in a gas as compared to the maximum amount possible, expressed as a percentage.

When these three are presented in equation form, their relationship becomes more clear:

$$\text{Relative Humidity} = \frac{\text{Absolute Humidity}}{\text{Potential Water Vapor Content}} \times 100$$

When a gas or air becomes heated, it expands and more spaces are created between the molecules. The resulting warmer gases have greater capacity for "holding" more water vapor than do cooler gases. Therefore, potential humidity increases as the temperature of a gas increases. As a result, warm, humidified gas traveling through tubing tends to "rain-out" water vapor as the gas cools and has a lower water-carrying capacity. The table below illustrates the relationship of temperature and potential humidity:

Temperature		Water Content	Water Vapor Pressure
C°	**F°**	**(mg/L)**	**(mm Hg)**
0	32.0	4.85	4.58
10	50.0	9.40	9.20
20	68.0	17.30	17.51
30	86.0	30.35	31.71
37	98.6	43.90	46.90
40	104.0	55.10	55.13
100	212.0	598.00	760.00

Water Vapor Content of Air

One of the more important gases found in air is water vapor. The amount of water vapor in the air can vary widely day-to-day, while gases like oxygen and nitrogen are present in relatively constant amounts. In general, water in vapor form is governed by gas laws and can be treated as a gas.

All bodies of water or moist organic bodies are capable of giving off water vapor. When water enters the air as a gas, the air's humidity increases. The measure of how much water vapor is contained in the air is identified as the humidity level, and the factors determining the humidity include:

1. The availability of water. Clearly the air over a desert has less chance of picking up water vapor than the air over a lake.

2. Temperature is also a factor since the spacing of warmer air's molecules allows water vapor's molecules to fit more easily. Recalling the principles of Charles' law, the volume of a gas increases as its temperature increases. If the number of molecules of the gases increases as the temperature rises, the humidity will not increase as much.

Summarizing, if there is water available there will be a specific amount of water vapor in the air at each ambient temperature. That amount equals the air's total capacity for water vapor at that temperature. Air that contains its total capacity for water vapor at a specific temperature is said to be 100% saturated.

Amounts of water found in air are generally measured as grams per cubic meter of air (gm/ml) or as milligrams per liter of air (mg/1). These measurements can then be converted to moles of water by dividing by the gram molecular weight of water (which is 18). The total capacity of the air for water vapor is measured in milligrams per liter, with total capacity of the air for water vapor in milligrams per liter is referred to as the air's potential water vapor. Table 1 identifies the various values of the potential water vapor content at several different temperatures.

THE POTENTIAL WATER VAPOR IS THE MAXIMUM THE AIR CAN HOLD AT A CERTAIN TEMPERATURE.

Temperature	**Potential Water Vapor**
5°C	6.8 mg/l
10°C	9.5 mg/l
20°C	17.3 mg/l
25°C	23.0 mg/l
30°C	30.4 mg/l
37°C	43.96 mg/l

Air's capacity for water cannot be met if there is not enough water available, and to discover the actual amount of water vapor present in the air it is necessary to measure the absolute humidity.

Relative humidity is another important measurement, and it represents the actual amount of water vapor in the air (absolute humidity) compared to the total possible water vapor content of the air at the given ambient temperature (potential water vapor). The measurement of relative humidity is expressed as a percentage (of saturation). For example, if the air contained only 17 mg/l of water vapor at 25°C, then it would not be totally saturated (see Table 1).

Calculating the relative humidity involves dividing the absolute humidity (actual water vapor content of the air) by the potential water vapor (maximum possible water vapor content of the air), and multiplying by 100 to convert the decimal percentage:

$$\text{Relative Humidity} = \frac{\text{Absolute Humidity}}{\text{Potential Water Vapor Content}} \times 100$$

For the example above where the air had 17 mg/l of water vapor at 25°C:

Relative Humidity = 17/23 x 100

Therefore: Relative Humidity = 73.9%

Humidity Deficit

Another factor to consider is the humidity deficit. For example, if the atmosphere's relative humidity is less than 100%, the air of the atmosphere has what is referred to as a *humidity deficit*. If outside air at 20°C has 14 mg/l of water vapor, and needs to have 17.3 mg/l to be fully saturated, it is said to have a primary humidity deficit of 3.3 mg/l. To calculate the primary humidity deficit simply subtract the absolute humidity of the air from its potential water vapor at the appropriate temperature and the difference between the two is the primary humidity deficit:

Primary Humidity Deficit =
Potential Water Vapor Content - Actual Water Vapor Content

The *secondary humidity deficit* also needs to be considered. This is the moisture deficit in the inspired air that the nose and upper airway needs to compensate for. When air is breathed into the nasal cavity and heated to body temperature, its potential water vapor rises to 44 mg/l that is the potential water vapor content of air at 37°C.

Therefore, unless the air of the atmosphere is at least 37°C and fully saturated, there exists a moisture deficit. For example, if the atmosphere's air was 98.6°F (37°C) and the relative humidity 100%, people in such conditions would be very hot and sweaty! Luckily, inspired air is generally not that warm or humid, so most inspired air does have a secondary humidity deficit.

The secondary humidity deficit is calculated by subtracting the absolute humidity of the air from the potential water vapor content. The difference from the calculations for primary humidity deficits is that the potential water vapor content is always 44 mg/l, the potential water vapor of air at body temperature:

Secondary Humidity Deficit = 44 mg/l - Absolute Humidity.

Therefore, if inspired air's absolute humidity is 16 mg/l at 25°C before being warmed in the nasal cavity, there is a primary humidity deficit of:

Primary Humidity Deficit = 23 mg/l - 16 mg/l = 7 mg/l

For this same absolute humidity for the atmosphere, the secondary humidity deficit is

Secondary Humidity Deficit = 44 mg/l - 16 mg/l = 28 mg/l

Here are some other calculations for you to consider:

If the absolute humidity of the same inspired air at 25°C were 23 mg/l, there would be no primary humidity deficit because the potential water vapor of air at 25°C is 23 mg/l (see Table above). There would still be a secondary humidity deficit of 21 mg/l because 44 mg/l minus 23 mg/l is 21 mg/l. This illustrates that at 100% relative humidity, it is still possible that the nasal cavity's lining will have to supply moisture to the inspired air.

- You may sometime need to calculate a primary or secondary humidity deficit when you only know the relative humidity. To perform this calculation, you first need to convert the relative humidity into absolute humidity before calculating the humidity deficit. Remember the formula for relative humidity:

$$\text{Relative Humidity} = \frac{\text{Absolute Humidity}}{\text{Potential Water Vapor Content}} \times 100$$

- When the temperature and relative humidity are known, you can look up the potential water vapor for the air temperature by using the Table shown above. Then substitute into the above formula the values for relative humidity and potential water vapor and calculate the absolute humidity. For example, the relative humidity at 10°C is 75% for the air in the atmosphere. Using the Table, you can see that the potential water vapor content at 10°C is 9.5 mg/l, so:

$$\text{Relative Humidity} = \frac{\text{Absolute Humidity}}{\text{Potential Water Vapor Content}} \times 100$$

Absolute Humidity = 7.125 mg/l

This measurement of the absolute humidity can be used to calculate the primary and secondary humidity deficits of the same air. At 10°C, we know that the potential water vapor content is 9.5 mg/l, so the primary humidity deficit is:

Primary Humidity Deficit =

Potential Water Vapor Content - Absolute Humidity

9.5 - 7.125 = 2.375 mg/l

The secondary humidity deficit for the same air would be:

Secondary Humidity Deficit = 44 - Absolute Humidity

44 - 7.125 = 36.875 mg/l

To summarize:

- The primary humidity deficit occurs in the atmosphere and represents the difference between what humidity there is and what there could be.

- The secondary deficit occurs in the body and represents the difference between what humidity there is and what there needs to be at body temperature (37°C).

Water Vapor Correction

Since we've already ascertained that water vapor acts in most ways like any other gas, air creates a partial pressure when its in a mixture of gases.

That partial pressure depends on the amount of water vapor present, which in turn depends on the temperature. However, water vapor differs from the behavior of other gases in the air since changes in the barometric pressure of the atmosphere under normal conditions do not have much impact on the partial pressure of water.

As a result, it is best to calculate the partial pressures of the other gases in the air after the partial pressure of water vapor has been determined—especially when measuring the air within the lungs. Inside the lungs, the partial pressure of water vapor is approximately 47 mm Hg. This value is relatively constant because the air entering the lungs is normally saturated and at 37°C.

By subtracting the partial pressure of the water vapor from the total atmospheric pressure, you will find what is referred to as the dry gas pressure. In the lungs:

Dry Gas Pressure = Atmospheric Pressure - 47 mmHg

At one atmosphere (760 mmHg), the dry gas pressure would be:

Dry Gas Pressure = 760 - 47 = 713 mmHg

Aerosol and Humidity Therapy

As you have seen from the previous discussion, there are a number of reasons why humidity is an important aspect of the pulmonary system, including:

- It is needed to maintain normal bronchial hygiene
- It promotes functions of the normal mucociliary escalator
- It maintains the body's vital homeostasis
- Without humidity the cleansing activities of the cilia could not function properly, and the nearly 100 ml of mucus secreted daily would become quite thick and tenacious.
- Without humidity the actual lung parenchyma would dry up, causing a loss of normal compliance which would restrict lung movement and reduce ventilation.

If normal use of the route of humidification and recapture of water were lost, problems would most certainly present themselves. If the upper airway were bypassed or dry gases were inhaled, a series of adverse reactions could occur, including:

- Impairment of ciliary activity
- Slowing of mucus movement
- Inflammatory changes and possible necrosis of pulmonary epithelium
- Retention of thick secretions and encrustation
- Bacterial infiltration of mucosa (bronchitis)
- Atelectasis
- Pneumonia

As a result of the importance of maintaining humidity, humidity and aerosol therapy are also important, and their general goals are to:

1. Promote bronchial hygiene
2. Loosen dried and/or thick secretions
3. Promote a effective coughs to clear secretions
4. Provide adequate humidity in the presence of an artificial airway
5. Deliver adequate humidity when administering dry gases therapies
6. Delivering prescribed medications

Clinical Evaluation of the Need for Humidity and/or Aerosol Use

There are a variety of factors to be considered when deciding to add humidity to dry gas therapies, including:

- patient's age and ability to move normal secretions
- neuromuscular status
- recent or planned surgeries
- trauma
- disease conditions

The presence of any of these may impair the patient's ability to cough and move secretions. Another problem may occur when patients develop very thick and abundant amounts of secretions that cannot be moved with normal muscle activity—making humidity or aerosol therapy necessary.

Indications for delivery of humidified gases and aerosols

Primary indications for humidifying inspired gases include:

- Administration of medical gases
- Delivery of gas to the bypassed upper airway
- Thick secretions in non-intubated patients

Additional indications for warming inspired gases:

- Hypothermia
- Reactive airway response to cold inspired gas

Primary indications for aerosol administration:

- Delivery of medication to the airway
- Sputum inductions

Sources of Mucus

Mucus generally comes from two sources: secretion from goblet cells and bronchial (mucous) glands. The goblet cells, which are distributed throughout the epithelium of the mucosa, synthesize and secrete mucus into the airway. The mucous glands, which are in the submucosa, are the greater source of mucus. Chronic irritation or disease can cause the number and size of goblet cells and mucous glands to increase, resulting in a larger and more viscous mucous blanket.

Effects of Mucous Layer

Ciliary activity, which moves the mucus, can be adversely affected if the mucous layer is changed. Changes in the ratio of gel to sol layer will affect the flow of mucus. A higher ratio, due either to a decrease in the watery sol layer or an increase in the viscous gel layer, could make the workload of the cilia too difficult to be effective. The cilia are capable of continuing to beat even if the workload increases, but only to a certain level. If the cilia become tangled in the thick mucus or are unable to penetrate the dense layer, the transport of the mucous blanket would stop, causing secretions to become retained in the respiratory tract.

Increases in the amount of watery sol fluid would also decrease the transport of mucus. The cilia must be able to extend through the sol layer to the gel layer to transport the mucus. Transport would be impaired if the thickness of the sol layer were to eliminate ciliary contact with the gel layer.

Other factors that can impede ciliary activity and the flow of mucus include:

- tobacco smoke
- local environmental conditions
- and pathology of the airway can impede clearance due to changes in the epithelium.
-

Humidification Devices

The effectiveness of humidifiers' ability to adequately supply vapor to a gas depends on three factors: temperature, surface area and time.

Temperature increases cause increases in vapor pressure and potential humidity. The greater the surface area of water/gas contact and the longer time this contact takes place, the greater the number of water molecules that can enter the gas mixture. These principles are used by humidifiers to provide increased relative humidity to the gas.

Blow-By Humidifier

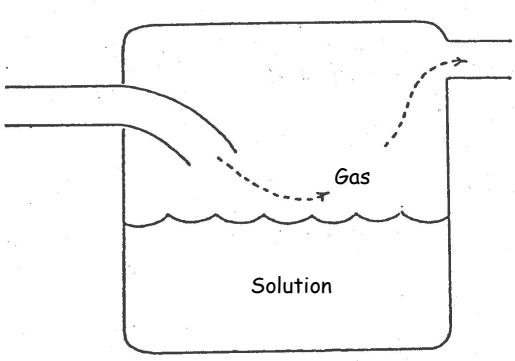


Figure 1. The blow-by humidifier.

The purpose of humidifiers is to deliver a gas with a maximum amount of water vapor content. These humidifiers may be heated or unheated, and the factors affecting the efficiency of humidification devices include:

- temperature
- time of exposure betw Gas gas and water
- and the surface area involved in the gas/water contact

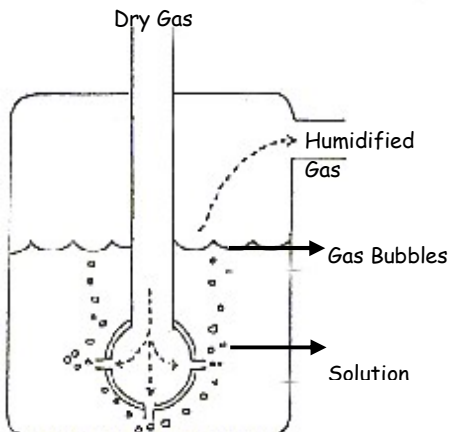
As temperature ris Solution ce exerted by the water molecules increases, enabling their escape into the gas, adding to the humidity. Longer exposure of a gas to the water increases the opportunity for the water molecules to evaporate during the humidifier's operation.

The pass-over type humidifier directs a dry gas source over a water surface area, and flowing it to the patient. Because exposure area and time of contact is limited and it is not heated, this unit is not very efficient. These units are often used in incubators and in certain ventilators, although many times the use of a heated element is added to improve this humidification system.

Bubble Diffusion Humidifier

This type of system uses conduction to introduce the gas into the water below its surface. The gas passes through the liquid in the form of bubbles of various sizes. This is more effective because it increases exposure time and contact area. These units are called diffusers. The bubble or diffuser-type humidifiers are most commonly used.

The ability to hold water vapor falls as the temperature of gas falls, with room temperature's relative humidity falling between 30 and 50%. Since a very low water content actually reaches the patient, this type of humidification is not recommended for patients with an endotracheal tube, tracheostomy or tenacious secretions. Gas flow through these humidifiers affects humidity. The higher the flow rate of a gas, the less the exposure time to the airway. These units function best at a flow rate of 2 liters/minute and should not be run at greater than 6 liters/minute.



Jet Humidifier

This type of humidifier actually forms an aerosol, but employs baffles to break the particles into small droplets, allowing them to evaporate. The gas is humidified further before it leaves the unit. The aerosol is formed by Bernoulli's principle. A low pressure zone at the top of the water inlet tube draws water into the jet stream and the water is then aerosolized by the flow of gas.

Bernoulli's principle is employed as follows: Gas flows into the chamber through a restricted orifice, causing a high velocity flow which passes across a capillary tube that is immersed in water. The pressure drops around the opening of the capillary tube and water is forced up the capillary tube. The jet stream of air blows the liquid off in small particles as it reaches the top of the capillary tube.

The jet humidifier produces a high humidity output by employing Bernoulli's principle to form an aerosol and using baffles to break up the particles.

The underwater jet humidifier utilizes the principles of two other humidifiers: the bubble and the jet humidifiers. In the underwater jet, the restricted orifice and capillary tube are both below the surface of the water. The aerosolized gas then bubbles through the water, increasing surface area and water/gas contact time, increasing efficiency.

Heated Humidifier

These humidifiers are indicated when it is necessary to deliver a humidified gas directly to the tracheobronchial tree (for example if the patient has a tracheostomy tube or an intubation tube), bypassing the natural humidification and heating system (nasal pharyngeal route). The gas must be delivered at 100% relative humidity at body temperature.

These devices (like the Cascade humidifier) incorporate a bubble pass-over type of system. Gas is moved down a tower, passes through a grid that has a thin layer of water covering it and then over the warm water before being expelled out of the unit and more humidification takes place. This humidifier can deliver 100% relative humidity at various temperatures.

These humidifiers can go well above body temperature, creating the potential for tracheal burns or possible aspiration if tubing is not drained frequently. Wide bore tubing should always be used with these humidifiers, and be sure to humidify the gas during delivery.

Aerosols

It is important to remember that an aerosol is not the same as humidity. Humidity is water in a gas in molecular form, while an aerosol is liquid or solid particles suspended in a gas. Examples of aerosol particles can be seen everywhere: as pollen, spores, dust, smoke, smog, fog, mists, and viruses.

Aerosols can be created for therapeutic uses by physically shattering or shearing matter or liquid into small particles and dispersing them into a suspension. This can be accomplished by a variety of ways, including using gas jets, spinning disks, or ultra high frequency sound.

The particle size of an aerosol depends on the device used to generate it and the substance being aerosolized. Particles of this nature, between 0.005 and 50 microns, are considered an aerosol. The smaller the particle, the greater the chance it will be deposited in the tracheobronchial tree.

Particles between 2 and 5 microns are optimal in size for depositing in the bronchi, trachea and pharynx.

Aerosol therapy is designed to increase the water content delivered to the pulmonary tree, and to deliver drugs to this area. Deposition location is of vital concern, and factors that affect aerosol deposition are aerosol particle size and particle number.

Table: Particle size and area of deposition.

Particle Size in Microns	Area of Deposition
1 to 0.25	Minimal settling
1 to 2	Enter alveoli with 95% deposition
2 to 5	Deposit proximal to alveoli
5 to 100	Trapped in nose and mouth

Deposition of particles is also affected by:

- Gravity - Large particles are deposited before smaller particles; and gravity affects large particles more than small particles, causing them to rain-out.

- Viscosity - The viscosity of the carrier gas plays an important role in deposition. For example, if a gas like helium, which has a low viscosity and molecular weight, is used as a carrier gas, gravity will have more of an effect upon the aerosol. Helium is very light and hence can't carry these particles well, leading to rain-out and early deposition.

- Kinetic activity - As aerosolized particles become smaller, they begin to exhibit the properties of a gas, including the phenomenon of "Brownian movement." This random movement of these small (below l mm) particles causes them to collide with each other and the surfaces of the surrounding structures, causing their deposition. As particle size drops below 0.1m, they become more stable with less deposition and are exhaled.

Particle inertia - Affects larger particles which are less likely to follow a course or pattern of flow that is not in a straight line. As the tracheobronchial tree bifurcates, the course of gas flow is constantly changing, causing deposition of these large particles at the bifurcation.

- Composition or nature of the aerosol particles - Some particles absorb water, become large and rain-out, while others evaporate, become smaller and are conducted further into the respiratory tree. Hypertonic solutions absorb water from the respiratory tract, become larger and rain-out sooner. Hypotonic solutions tend to lose water through evaporation and are carried deeper into the respiratory tract for deposition. Isotonic solutions (0.9% NaCl) will remain fairly stable in size until they are deposited.

Heating and humidifying - As aerosols enter a warm humidified gas stream, the particle size of these aerosols win increase due to the cooling of the gas in transit to the patient. This occurs because of the warm humidified gas cooling and depositing liquid (humidity) upon the aerosol particles through condensation.

- entilatory pattern - RCPs easily control this by simple observation and instruction. For maximum deposition, the patient must be instructed to:

1. Take a slow, deep breath.
2. Inhale through an open mouth (not through the nose).
3. At the end of inspiration, use an inspiratory pause, if possible, to provide maximum deposition.
4. Follow with a slow, complete exhalation through the mouth.

In many cases, aerosols are superior in terms of efficacy and safety to the same systemically administered drugs used to treat pulmonary disorders. Aerosols deliver a high concentration of the drugs with a minimum of systemic side effects. As a result, aerosol drug delivery has a high therapeutic index; especially since they can be delivered using small, large volume, and metered dose nebulizers.

Methods of Aerosol Delivery

Aerosols are produced in respiratory therapy by utilizing devices known as nebulizers. There are a variety of nebulizers in use today, but the most common is one in which the Bernoulli principle is used through a Venturi apparatus.

As discussed earlier, the Bernoulli principle states that when gas flows through a tube, it exerts a lateral wall pressure within that tube due to its velocity. As the gas reaches a smaller diameter in the tube, the velocity is increased, which decreases lateral wall pressure. This decrease in diameter within the tube is at a structure called a jet. Just distal to the jet is a capillary tube that is immersed in a body of fluid. The decreased pressure is transmitted to the capillary tube and fluid is drawn up it. When the fluid reaches the jet, it is then atomized.

The absolute humidity that will be delivered from these devices can be increased by the use of a heater. A baffle is distal to this atomization process in the stream of gas/fluid flow. Nebulization takes place here as the liquid is impelled against the baffle. This baffle causes the larger particles to coalesce and collect in the reservoir. The smaller particles will be delivered to the patient in aerosol form. If the baffle is not used, the device is known as an atomizer. When the baffle is

used, it is then called a nebulizer. In addition to the physically placed baffle, any 90° angle to gas flow can be considered a baffle. Large bore corrugated tubing should be used with baffles. This will enable the aerosol particles to be delivered to the patient.

There are several ways to deliver aerosol therapy, and the modalities available today include:
1. Aerosol mask
2. Face tent
3. Mouthpiece
4. Aerosol tent (mist tent)
5. In conjunction with IPPB

Physician orders for aerosol therapy should contain identification of:
1. Type of aerosol
2. Source gas (FIO_2)
3. Fluid composition (NaCl, water, etc.)
4. Delivery modality
5. Duration of therapy
6. Frequency of therapy
7. Temperature of the aerosol

When a prescribed aerosol therapy has been completed, be sure to chart your actions and observations, making sure to include the following information:
- time of administration
- duration of therapy
- type or composition of the aerosol (NaCl)
- pulse
- respiratory rate and pattern
- breath sounds
- characteristics of sputum
- if sputum was or was not produced
- the ease of breathing
- any benefits observed
- and any other relevant observations.

The reasons for administering aerosol therapies include:
1. For bronchial hygiene
a) Hydrate dried secretions
b) Promote cough
c) Restore mucous blanket
2. Humidify inspired gas
3. Deliver prescribed medications
4. Induce sputum lab culture

Aerosol delivery is accomplished in a variety of ways:

- nasal spray pump

- metered-dose inhaler (MDI)
- dry powder inhaler (DPI)
- jet nebulizer
- small volume nebulizer (SVN)
- large volume nebulizer
- small-particle aerosol generator (SPAG)
- mainstream nebulizers
- ultrasonic nebulizer (USN)
- intermittent positive pressure breathing (IPPB) devices

Spray pumps are the most common devices used for nasal aerosol administration of: antiallergics, sympathomimetics, antimuscarinics, and anti-inflammatory drugs. The spray pump generates low internal pressure, and produces large particles that are well-targeted for nasal deposition.

Metered dose inhalers (MDIs) consist of a pressurized cartridge and a mouthpiece assembly. The cartridge, which contains from 150-300 doses of medication, delivers a pre-measured amount of the drug through the mouthpiece when the MDI is inverted and depressed.

One controversial problem with MDIs involves their use of chlorofluorocarbons (CFCs) which have been identified by scientists as culprits in causing the growing hole in the earth's ozone layer, contributing to global warming and increased ultraviolet radiation. While the manufacture and importation of other sources of CFCs, like refrigerants, have been banned in the U.S. since 1996, the FDA exempted CFCs used in "medically essential" products like MDIs. Alternatives (such as hydrofluorocarbons—HFAs) to CFCs for use in MDIs have been discovered, and the FDA has already formulated plans for facilitating a transition from CFCs to alternatives like HFAs.

However, the FDA has stipulated that CFC-medications will not be phased out until:

- acceptable treatment alternatives exist for a particular MDI or other drug product so that the patient can find a product that meets his or her medical,

- the alternatives are marketed for at least one year and are acceptable by patients, and

- the supply of alternative products is sufficient to ensure that there will be no shortages of the drug.

Successful delivery of medications with an MDI depends on the patient's ability to coordinate the actuation of the MDI at the beginning of inspiration. Patients need to be alert, cooperative, and capable of taking a coordinated, deep breath. Patients should be instructed to:

1. Be sure to shake the MDI canister well before using.

2. Hold the MDI a few centimeters from the open mouth.

3. Holding the mouthpiece pointed downwards, actuate the MDI at the beginning of a slow, deep inspiration, with a 4-10 second breath hold. Late actuation, or at the end of the inspiration, or stopping inhaling when the cold blast of propellant hits the back of the throat will cause the medication to have only a negligible effect.

4. Exhale through pursed-lips, breathing at a normal rate for a few moments before repeating the previous steps.

5. Patients should also be instructed to rinse their mouths after taking the medication.

After instructing the patient, the RCP should ask the patient to act out the procedure, observing to see if the patient has really understood the instructions. Proper instruction and observation of the patient are crucial to the success of MDI of therapy.

The particle size of the drug released is controlled by two factors: the vapor pressure of the propellant blend, and the diameter of the actuator's opening. Particle size is reduced as vapor pressure increases, and as diameter size of the nozzle opening decreases. The majority of the active drug delivered by an MDI is contained in the larger particles, many of which are deposited in the pharynx and swallowed.

The advantages of MDI aerosol devices include:

- They are compact and portable.
- Drug delivery is efficient.
- Treatment time is short.

On the other hand, the disadvantages of using MDIs to deliver aerosolize medications include:

- They require complex hand-breathing coordination.
- Drug concentrations are pre-set.
- Canister depletion is difficult to ascertain accurately.
- A small percentage of patients may experience adverse reactions to the propellants.
- There is high oropharyngeal impaction and loss if a spacer or reservoir device is not used.
- Aspiration of foreign objects from the mouthpiece can occur.

Pollutant CFCs, which are still being used in MDIs, are released into the environment until they can be replaced by non-CFC propellant material.

Extension or *reservoir* devices can be used to modify the aerosol discharged from an MDI. The purposes of these *spacers* or extensions include:

- Allow additional time and space for more vaporization of the propellants and evaporation of initially large particles to smaller sizes.
- Slow the high velocity of particles before they reach the oropharynx.

- As holding chambers for the aerosol cloud released, reservoir devices separate the actuation of the canister from the inhalation, simplifying the coordination required for successful use.

Dry powder inhalers (DPIs) consist of a unit dose formulation of a drug in a powder form, dispensed in a small MDI-sized apparatus for administration during inspiration. Because these devices are breath-actuated, using turbulent air flow from the inspiratory effort to power the creation of an aerosol of microfine particles of drug, they don't require the hand-breath coordination needed with MDIs.

Cromolyn sodium and albuterol are the two primary drugs available in powder form. Cromolyn sodium is dispensed in a device called the *Spinhaler*, which pokes holes in capsules containing the powdered drug. The albuterol formulation is dispensed in a device called the *Rotahaler*, which cuts the capsule in half, dropping the powdered drug into a chamber for inhalation. In both cases, a single-dose micronized powder preparation of the drug in a gelatin capsule is inserted into the device prior to inhalation.

Powder flow properties in DPIs depend on particle size distribution, with very small particles not flowing as well as the larger ones. A third drug, budesonide, is available in a pre-loaded, multi-dose (up to 200 doses) DPI unit called a *Turbuhaler*. The advantages of using DPI devices for drug administration include:

- They are small and portable.

- Brief preparation and administration time.

- Breath-actuation eliminates dependence on patient's hand-breath coordination, inspiratory hold, or head-tilt needed with MDI.

- CFC propellants are not used.

- There is not the *cold* effect from the freon used in MDIs, eliminating the likelihood of bronchoconstriction or inhibited inspiration.
- Calculation of remaining doses is easy.

The disadvantages encountered when relying on DPIs for drug administration include:

- Limited number of drugs available for DPI delivery at this time.

- Dose inhaled is not as obvious as it is with MDIs, causing patients to distrust that they've received a treatment.

- Potential adverse reaction to lactose or glucose carrier substance.

- Inspiratory flowrates of 60Lpm or higher are needed with the currently available cromolyn and albuterol formulations.

- Capsules must be loaded into the devices prior to use.

Small volume nebulizers (SVNs) are gas powered (pneumatic) and are a common method of aerosol delivery to inpatients, and there are a variety of different SVNs available. Each has specific characteristics, especially in regard to output. These nebulizers fall into two subcategories: mainstream and sidestream. The mainstream nebulizer is one in which the main flow of gas passes directly through the area of nebulization. The sidestream nebulizer is one in which the nebulized particles are injected into the main flow or stream of gas as with IPPB circuits. The main difference, based upon their construction, is that the larger particles tend to rain-out with a sidestream nebulizer.

The advantage of SVN therapy is that it requires very little patient coordination or breath holding, making it ideal for very young patients. It is also indicated for patients in acute distress, or in the presence of reduced inspiratory flows and volumes. Use of SVNs allows modification of drug concentration, and facilitates the aerosolization of almost any liquid drug.

Another advantage of a SVN is that dose delivery occurs over sixty to ninety breaths, rather than in one or two inhalations. Therefore, a single ineffective breath won't ruin the efficacy of the treatment. Disadvantages of SVNs include:

- The equipment required for use is expensive and cumbersome.

- Treatment times are lengthy compared to other aerosol devices and routes of administration.

- Contamination is possible with inadequate cleaning.

- A wet, cold spray occurs with mask delivery.

- There is a need for an external power source (electricity or compressed gas).

In a 1990 study comparing the effectiveness of MDIs, DPIs, and SVNs, it was found that approximately the same amount of drug is delivered to the lung, regardless of the type of device used, given that all three devices contain the same loading dose. The clinical response measured by the improvement in FEV_1 is also similar among the three devices, although the change with the MDI was statistically significantly greater than with DPI or SVN.

The greater response with the MDI correlates with the greater amount of drug delivered by the MDI in that study. However, the study concluded, “The amount of bronchodilation obtained is a reflection of the dose of drug given, and not the method of delivery.”

Since mainstream nebulizers are normally used for continuous administration of a bland aerosol (H_2O, normal saline) for airway humidification or secretion mobilization, they are not usually considered as medication delivery systems.

Also in use today is a pneumatic nebulizer that operates on the “Babbington Principle”. This is called the hydrosphere or Babbington nebulizer. In this nebulizer, a source of gas enters a hollow sphere which is covered by a thin film of water. The hollow sphere has small ports in it, where the gas escapes to the outside. These ports act as jets. When the gas moves through these ports (jets), a negative pressure is produced and the flow of water is then drawn into the flow of gas producing an aerosol. A baffle is usually used in this system also. The baffle is placed distal to the atomization process in the flow of gas/aerosol. Particle sizes in these units are usually between three and five micron.

Large-Volume Nebulizers - These units also have the capability for entraining room air to deliver a known oxygen concentration. They can deliver varying concentrations of oxygen. When using these units, you should always match or exceed the patient’s peak inspiratory flow rates. This assures delivery of oxygen and nebulized particles. These units produce particle sizes between two and ten microns and may be heated to improve output.

Centrifugal Room Nebulizers - This nebulizer works on the principle of a rotating disk that spins on a hollow tube. This action draws water up the hollow tube that acts as a center shaft. Once the water reaches the rotating disk (which is spinning at a rapid rate), it is thrown outward by centrifugal force through comb-like structures that break up the water and produce an aerosol.

Although these are in fact nebulizers, they are used as room humidifiers. The aerosol particles are expelled into the room. Since they are very small particles, they evaporate to become humidity. Humidification is more effective if the door to the room is left closed.

Small-particle aerosol generator (SPAG) - This is a highly specialized jet-type aerosol generator designed to for administering ribavirin (Virazole), the antiviral recommended for treating high risk infants and children with respiratory syncytial virus infections.

Ultrasonic nebulizers - Ultrasonic nebulizers (USN) have been in use and production since the mid 1960s and have gained high popularity. Ultrasonic nebulizers work on the principle that high frequency sound waves can break up water into aerosol particles. This form of nebulizer is powered by electricity and uses the piezoelectric principle. This principle is described as the ability of a substance to change shape when a charge is applied to it.

An ultrasonic nebulizer contains a transducer that has piezoelectric qualities. When an electrical charge is applied, it emits vibrations that are transmitted through a volume of water above the transducer to the water surface, where it produces an aerosol. The frequency of these sound waves is between 1.35 and 1.65 megacycles, depending on the model and brand of the unit.

Their frequency determines the particle size of the aerosol. The transducers that transmit this frequency are of two types. One type is the flat transducer, which creates straight, unfocused sound waves that can be used with various water levels. The other type is a curved transducer, which needs a constant water level above it because its sound waves are focused at a point slightly above the water surface. if the water level falls below this point, the unit loses its ability to nebulize.

As stated, the frequency of an ultrasonic nebulizer determines the particle size of the aerosol. In ultrasonic nebulizers, the particle size falls in the range of .5 to 3 microns. The amplitude or strength of these sound waves determines the output of the nebulizer, which falls in the range of 0 to 3 ml/minute and 0 to 6 ml/minute. Ultrasonic nebulizers also incorporate a fan unit to move the aerosol to the patient. This fan action also helps cool the unit. The gas flow generated by this fan falls in the range of between 21 and 35 liters/minute. This flow of air also depends on the brand and model of the unit.

The transducer of an ultrasonic nebulizer is often found in the coupling chamber, which is filled with water. This water acts to cool the transducer and allows the transfer of sound waves needed for the nebulizer, which takes place in a nebulizer chamber. The nebulizer chamber is found just above the coupling chamber. A thin plastic diaphragm that also allows sound waves to pass usually separates these two chambers.

Ultrasonic nebulizers are useful in the treatment of thick secretions that are difficult to expectorate, and they can help to stimulate a cough. The therapy can be delivered through a mouthpiece or facemask. Therapy can be given with sterile water, saline or a mixture of the two.

Although IPPB has been used to deliver aerosolized drugs from a SVN, the consensus of clinical findings is that IPPB delivery of aerosolized medication is no more clinically effective than simple, spontaneous, unassisted inhalation from SVNs. If the patient is able to breathe spontaneously without machine support, the use of IPPB for delivery of aerosolized is not supported for general clinical or at-home use, and should be reserved for patients who are not capable of taking deep, coordinated breaths.

Advantages and Disadvantages of Aerosol Therapy

Aerosol generation and delivery to the lung is a complex and dynamic topic, with clinicians and researchers finding out more about its dynamics every day. The aerosol route of drug administration has become a preference for those treating pulmonary disease for a variety of reasons. The advantages of aerosol delivery of drugs include:

- Aerosol doses are smaller than those for systemic treatments.
- Onset of drug action is rapid.
- Drug delivery is directly targeted to the respiratory system.
- Systemic side effects are fewer and less severe than with oral or parenteral therapy

- Inhaled drug therapy is painless and relatively convenient.

As with nearly everything that has advantages, aerosol delivery of drugs also has its disadvantages, including:

- Special equipment is often needed for its administration.
- Patients generally must be capable of taking deep, coordinated breaths.
- There are a number of variables affecting the dose of aerosol drug delivered to the airways.
- Difficulties in dose estimation and dose reproducibility.
- Difficulty in coordinating hand action and breathing with metered dose inhalers.
- Lack of physician, nurse, and therapist knowledge of device use and administration protocols.
- Lack of technical information on aerosol producing devices.
- Systemic absorption also occurs through oropharyngeal deposition.
- The potential for tracheobronchial irritation, bronchospasm, contamination, and infection of the airway.

The common hazards of aerosol therapy are:

Airway obstruction - Dehydrated secretions in the patient's airways may absorb water delivered via aerosol and swell up large enough to obstruct airways. To avoid this, watch the patient very closely and let him progress with therapy at a reasonable rate. You may want to have suction apparatus on hand.

Bronchospasms - It is common for aerosol particles to cause this condition (especially among asthmatics) and it is more prevalent when administering a cold aerosol as compared to a heated one. If a very large amount of coughing occurs, stop therapy and give the patient a rest. If this persists in farther therapy, stop treatment and notify the physician.

Fluid overload - This can occur when administering continuous aerosol therapy. It can happen quite frequently when treating infants or patients in congestive heart failure, renal failure or patients who are very old andimmobile. In the infant, because of the smaller body size and possible underdeveloped fluid control mechanism, a quantity of water that an adult can easily handle will cause fluid overload. In a patient with congestive heart failure, any addition of fluid to the vascular system will put an increased strain on the heart. In a patient with renal failure who is probably already in fluid overload, it is easily seen that you will not want to increase the fluid volume. In older patients, the fluid control mechanisms may be impaired due to age.

Procedures

The following are sample instructions for procedures to be followed related to aerosol applications:

Procedure for Aerosol Medication Delivery

The following procedure is provided for use when delivering medications by means of an aerosol generator:

A. Check Order. Verify the physician's order as follows:
Compare the requisition with the physicians order to ensure that no discrepancies exist

1. Review the order to ensure that the following are prescribed:
- FIO_2
- Medication to be used
- Frequency of therapy
- Duration of therapy
- If any part of the order is unfamiliar, question its accuracy.

B. **Review Chart.** Use the following procedure to review the patient's chart: On the patient's chart, identify all pertinent data in the following areas:
- History and physical
- Admitting diagnosis
- Progress notes
- Blood gas analysis
- Chest x-rays

2. Based on the patient data, identify the following:
- Conditions that indicate the need for aerosol medication delivery
- Potential hazards of aerosol medication delivery for the patient

C. **Maintain Asepsis**. While performing the remainder of this procedure, you are expected to maintain aseptic conditions. This includes following universal precautions and washing your hands:
- Before obtaining equipment
- Following performance of step K. Conclude Procedure
- Anytime during the procedure that contamination is suspected

D. **Obtain Equipment** Collect the following equipment and supplies:
- Flowmeter or air compressor
- Miniature nebulizer
- Supply tubing
- Prescribed medication
- Stethoscope

E. **Assemble Equipment.** Prepare the equipment for use as follows:
1. Connect the supply tubing to the nebulizer.
2. Attach the other end of the supply tubing to the flowmeter.
3. Insert the prescribed medication into the nebulizer.

F. **Test Equipment.** Test the aerosol medication delivery equipment as follows:
1. Connect the flowmeter to the correct gas source.
2. Turn on the flowmeter.
3. If a fine mist is absent, tighten all connections and adjust the jets, if applicable.

4. If a fine mist is still absent:
    a. Label the nebulizer as defective and replace it
    b. Reassemble and retest the new equipment

G. **Confirm Patient.** Ensure that the procedure is performed with the correct patient as follows:

1. Match the information on the order with the following:
- Room number
- Name on the door or bed
- Name on the wristband

2. Greet the patient by name (in a questioning manner if unknown).
3. Resolve any discrepancies in the patient identification information by conferring with the nursing staff.

H**. Inform Patient**: Interact with the patient as follows:

1. Introduce yourself by name and department (if not already acquainted).
2. Tell the patient what procedure is to be performed.
3. Explain the procedure by describing:
- Why it is to be performed
- How it will be performed
- What the patient is expected to do
- What you will be doing
- How frequently it will be performed

I. **Implement Procedure.** Perform the following tasks:

1. Position the patient in an upright position (45 to 90° angle).
2. Administer the aerosol medication as follows:
    a. Turn on the flow meter.
    b. Attach the aerosol medication delivery device to the patient
    c. Ensure that the delivery device fits comfortably.
3. Coach the patient to breathe in the following manner:
- Diaphragmatically
- Through the mouth
- Slowly and deeply
- Pause at end-inspiration, maintaining an I:E ratio of at least 1:2

J. **Monitor Patient.** Determine the patient's response to therapy as follows:

1. Determine the pulse rate. (Count for at least one minute.)
2. Determine the respiratory rate. (Count for at least one minute.)
3. Observe respiration to identify any abnormalities in the breathing pattern.
4. Auscultate the patient's chest
5. Note any abnormalities in the patient's appearance or behavior.

K. **Conclude Procedure.** Complete the following tasks:

1. Place the patient in a comfortable position.

1. Assure that the call bell and bedside table are within the patient's reach.

2. Ask if the patient has any needs.
3. Answer any questions as effectively as possible.
4. Unplug and cover all equipment and move it away from the patient's bed (or remove it from the room).

L. Rec**ord Results.** Document the therapy as follows:
1. Record the following data on the patient's chart:
- Aerosol medication administered
- Pulse rate
- Respiratory rate
- Volume, color, and consistency of sputum
- Abnormal patient characteristics
- Therapy-related patient complaints
2. Sign the patient's chart (first initial and full last name).

M. **Report Observations.** Report the following information:
1. Report any significant adverse changes in the patient's condition to the nurse or physician whenever observed.
2. Following the procedure, inform the appropriate personnel of:
- Patient requests
- Patient complaints
- Unexpressed patient needs
3. Following the procedure, report to the nurse or physician:
- Any non-critical adverse reactions to the therapy
- Other pertinent observations of the patients condition

Procedure for Administering Metered Dose Inhaler

The following procedure is provided for use when delivering medications by means of a metered dose inhaler:

A. **Check Order.** Verify the physician's order as follows:
1. Compare the requisition with the physician's order to ensure that no discrepancies exist.
2. Review the order to ensure that the following are prescribed:
- Medication to be used
- Frequency of therapy
- Duration of therapy
- Any special devices or chambers required

B. **Review Chart.** Use the following procedure to review the patient's chart:

On the patient's chart, identify all pertinent data in the following areas:

- History and physical
- Admitting diagnosis
- Progress notes
- Blood gas analysis
- Chest x-rays

Based on the patient data, identify the following:

- Conditions that indicate the need for metered dose inhaler delivery
- Potential hazards of aerosol medication delivery for the patient

C. **Maintain Asepsis.** While performing the remainder of this procedure, you are expected to maintain aseptic. This includes the use of universal precautions and handwashing. Hands should be washed:

- Before obtaining equipment
- Following performance of Step J. Conclude Procedure
- Anytime during the procedure that contamination is suspected.

D. **Obtain Equipment.** Collect the following equipment and supplies:

- Metered Dose Inhaler (as prescribed)
- Any special devices or chambers (as applicable)
- Stethoscope

E. **Assemble Equipment.** Prepare the equipment for use as follows:

1. Shake the inhaler to mix the medications.
2. Remove the cap and attach the mouthpiece.
3. If a chamber is ordered, attach the device to the mouthpiece.

F. **Confirm Patient.** Ensure that the procedure is performed on the correct patient as follows:

1. Match the information on the order with the following:
   - Room number
   - Name on the door or bed
   - Name on the wristband
2. Greet the patient by name (in a questioning manner if unknown).
3. Resolve any discrepancies in the patient identification information by conferring with the nursing staff.

G. **Inform Patient.** Interact with the patient as follows:

1. Introduce yourself by name and department (if not already acquainted).
2. Tell the patient what procedure is to be performed.
3. Explain the procedure by describing:
   - Why it is to be performed
   - How it will be performed
   - What the patient is expected to do
   - What you will be doing

- How frequently it will be performed

H. **Implement Procedure.** Perform the following tasks:

1. Position the patient in an upright position (45 to 90° angle).
2. Instruct the patient as follows:

a) Grasp the MDI medication chamber between the thumb and first two fingers with the thumb on the bottom of the chamber.
b) Hold the mouthpiece of the medication chamber (or additional chamber device if ordered) in front of the mouth with the lips around the mouthpiece but not closed on.
c) If the patient has difficulty holding the device without closing his lips, instruct him to rest the mouthpiece on the lower lip for balance.
d) Exhale completely. Begin to inhale deeply through the mouth and immediately compress the medication chamber between the thumb and fingers to release the medication.
e) Following complete inhalation, hold his/her breath for 5 to 10 seconds.
f) If an additional chamber was used, inhale from the device again, without compressing the medication chamber, to ensure complete aerosol delivery.
g) Repeat the process until the prescribed duration is accomplished.

I. **Monitor Patient.** Determine the patient's response to the therapy as follows:

1. Determine the pulse rate. (Count for at least one minute).
2. Determine the respiratory rate. (Count for at least one minute).
3. Observe respiration to identify any abnormalities in the breathing pattern.
4. Auscultate the patient's chest
5. Note any abnormalities in the patient's appearance or behavior.

J. **Conclude Procedure.** Complete the following tasks:

Place the patient in a comfortable position.
Assure that the call bell and bedside table are within the patient's reach.
Ask if the patient has any needs.
Answer any questions as effectively as possible.

K. **Record Results.** Record the following data on the laboratory data form and on the patient's chart as required:

- Patient name Room number
- Aerosol medication delivered
- Pulse rate
- Respiratory rate
- Breath sounds
- Volume, color and consistence of sputum
- Any adverse patient reactions
- Therapy-related patient complaints

L. **Report Observations.** Report the following information:

1. Report any significant adverse changes in the patient's condition to the nurse or physician.
2. Following the procedure, inform the appropriate personnel of:

- Patient requests
- Patient complaints
- Unexpressed patient needs

3.Following the procedure, report to the nurse or physician:

- Any non-critical adverse reactions to the therapy
- Other pertinent observations of the patient's condition

Respiratory System Drugs

1-15. INTRODUCTION

Drugs affecting the respiratory system have been in use for years. In the 20th century, for example, various members of the morphine family (that is, heroin) were used in the treatment of coughs. In the 21st Century, people are using both legend and over-the-counter cough preparations. At certain times of the year you will see many prescriptions for cough medicines and expectorants. You have probably seen such increases when winter arrives. This section of the course will discuss some of the respiratory systems medications commonly seen in the pharmacy.

Medications Used in Respiratory Pharmacology

The goal of respiratory pharmacology is to prevent or relieve the pathologic triad discussed earlier: bronchospasm, airway inflammation or mucosal edema, and retained secretions. The medicating agents used to relieve these symptoms can be referred to as the "treatment triad." The pathologic triad and treatments include:

Pathologic Condition	**Treatment**
Bronchoconstriction	Bronchodilator (e.g., albuterol)
Airway edema	Decongestant (e.g., racemic epinephrine)
Retained secretions	Hydration or mucolytics

The actions of the various categories of pharmacologic agents used to relieve the pathologic triad can be briefly summarized as:

- **Bronchodilators** increase airway patency by relaxing the bronchial muscle spasm triggered by disease or irritation.

- **Decongestants** cause contraction of the muscle fibers of the arterioles and small arteries, triggering a reduction of blood flow to the affected area and lowering of hydrostatic pressure that permits fluid to move into the tissues.

- **Mucokinetics** facilitate loosening and mobilization of secretions.

Throughout this part of the course we will present information regarding individual drugs. Some will contain more information than others. Regarding some of the medications, we will include the full text of what can be found in drug reference books such as the Physicians Desk Reference or other texts which go into respiratory medications in great. For the purposes of this CEU, will not do so for every drug mentioned as to do so would turn this into a textbook rather than what it is: a continuing education unit.

General Medication Information

There are a wide variety of patient circumstances that can necessitate the modification of recommended dosage or frequency of medications administered to pulmonary patients. Following administration, most drugs go through several steps in a well-defined sequence before being excreted from the body, including:

1. Absorption from the site of administration
2. Distribution via the circulatory system
3. Metabolism
4. Excretion from the body

Metabolism, also known as *biotransformation*, is the step in which a drug circulating in the bloodstream is transformed from its original active form to a less active form. While other organs participate to a limited degree in the metabolism process, the liver is the principal site of drug metabolism. Drugs absorbed through the mucous membrane of the stomach or intestines, enter the bloodstream via the portal vein. Before this vein empties into the general circulation system, it passes through the liver where the drugs carried by the vein are exposed immediately to metabolism by liver enzymes.

Because the liver plays such a key role in the metabolism of most drugs, a decreased rate of drug metabolism can occur in patients with liver diseases or hepatitis. Drug dosages for these patients need to be adjusted in order to avoid toxicity, and to compensate for the prolonged pharmacologic action of un-metabolized drug in the blood stream.

The kidney is the principal organ involved in the excretion of drugs from the body. Poor renal function can significantly prolong the effects of some drugs, and altered pH levels can inactivate some drugs, such as bronchodilators. Since mechanical ventilation can affect kidney function by decreasing perfusion pressure, drug dosages may need to be modified for patients on ventilation.

Also, since many patients are being treated with more than one drug at a time, drug interaction and synergism needs to be taken into account when setting dosages and administration frequencies. All of these factors contribute to making the task of prescribing proper dosage of medications for respiratory patients a more complex undertaking.

Drug interactions

Types of drug interactions

There may be two outcomes of drug interaction. Antagonism occurs when the action of one drug opposes that of another, while synergism occurs when the effects of coadministration of drugs is additive. When the sum of two drugs is more than a simple additive effect, this is known as "potentiation." Not all drug interactions are harmful. For example, the ISIS-2 study showed that aspirin and streptokinase each improve outcome in myocardial infarction, and that the combination of both these drugs has an additive therapeutic effect.[1]

Drug interactions may be divided into three main types

Pharmaceutical interactions
This is probably the least important of the types of interactions. It is the interaction of drugs on a chemical, not a pharmacological, level. An example is the formation of a complex between thiopentone and suxamethonium, which cannot therefore be mixed in the same syringe. These types of interactions are best avoided by giving drugs as bolus injections where appropriate, avoiding the mixing of drugs before administration except when this is known to be safe and making up infusions immediately before use.

Pharmacodynamic interactions
This is the reduction or enhancement of the effect of one drug by another without altering its concentration at its site of action. These are usually predictable from the knowledge of the pharmacological mechanism of action of the drugs, and usually occur through competition at receptor sites or through an action on similar physiological systems. An example of this type of interaction is that between loop diuretics and digoxin. Loop diuretics lower plasma potassium and this reduces competition between the glycoside and potassium for the sodium potassium pump in the heart muscle. The consequent increased glycoside binding enhances the risk of arrhythmias.

Pharmacokinetic interactions
This is the alteration of drug concentration reaching its target site by a second drug. The four determinants of drug pharmacokinetics may each be affected by this coadministration: absorption, distribution, metabolism, and excretion. These types of interaction are not easily predicted and the severity of interaction, unlike the pharmacodynamic variety, often differs markedly between patients.

- Absorption may be affected from the gut either because two drugs form an insoluble complex (seen sometimes with antacids and prednisolone) or because one drug alters gut motility, as seen with drugs such as loperamide or metoclopramide, and affects the time available for drug absorption to occur. In the skin, reduced absorption (and hence redistribution or metabolism) of lignocaine after subcutaneous injection is usefully achieved by combining this with the vasoconstrictor adrenaline. This prolongs the anesthetic action of lignocaine.

- Distribution is commonly a factor in those drugs that are extensively protein bound in the plasma, where they may be displaced from their binding sites by a second drug. This is rarely important pharmacologically, because although the free drug accounts for its pharmacological action, it is this same fraction which is available for redistribution and metabolism, which usually restores free levels. Thus most serious interactions are seen when displacement from plasma proteins occurs in addition to other effects such as inhibition of drug metabolism. An example of this is sodium valproate, which not only displaces phenytoin from plasma proteins but also reduces the rate at which it is metabolized.

- Metabolism of a drug is most commonly altered by enzyme inducers such as phenytoin combined with another drug--for example, the contraceptive pill. The pill is metabolized more frequently, and the resultant reduced plasma levels may result in pregnancy. Enzyme inhibitors also exist. The most common drugs in this category are those with an action which includes inhibition of isoenzymes of cytochrome --for example, cimetidine and erythromycin.

- Elimination becomes a factor in those drugs sharing common transporter mechanisms in the kidney. An example of this is the lithium accumulation seen in patients treated with concomitant diuretics.

Identifying possible drug interactions

Drug interactions may manifest as a lack of effect of a newly introduced drug treatment, or more seriously as a clinical deterioration. It should always be considered in people who are severely ill, in whom interactions may be difficult to identify, and in the elderly. Both these groups are likely to be taking several medications simultaneously. Patients with renal or hepatic impairment are also more likely to suffer the effects of interactions, as metabolism and excretion will be impaired. Others at risk include those taking drugs long term where the precise plasma level is important--for example, people with epilepsy.

With so many drugs available to prescribers, it is not possible to learn all the different combinations and interactions. An understanding of the above principles should allow a reasoned approach to the problem. In general terms, certain drugs are more likely to be involved in interactions. These include drugs with a small therapeutic index (a small change in drug concentration resulting in a substantial change in therapeutic effect). Drugs that are known to be enzyme inducers or inhibitors or those with a saturable metabolism should also be used with caution.

Finally, there are several drugs that, although used for treating the same disease, are capable of causing serious drug interactions when used together. These include digoxin with thiazide or

loop diuretics, theophylline with ß adrenoceptor agonists (both combinations may cause cardiac arrythmias), phenytoin with sodium valproate (phenytoin toxicity), and verapamil with ß adrenoceptor antagonists (bradycardia).

How to minimize drug interactions

- Avoid polypharmacy (multiple drugs) where possible
- Ask patients about all current medications before prescribing new treatments
- Review medications and clinical progress regularly
- When in doubt consult your local pharmacist for advice

Bronchodilators

Most drug effects are mediated through the agency of a *receptor*, which is special protein molecule on the cell membrane that is specifically designed to interact with natural body chemicals, and it also interacts with drugs.

There are many types of receptors throughout the body. For example, *adrengic receptors* are part of the *sympathetic nervous system* and are activated by the natural neurotransmitters epinephrine, norepinephrine, and dopamine, or by drugs. There are three types of adrenergic receptors (*alpha, beta$_1$, and beta$_2$*). *Cholinergic receptors* are part of the *parasympathetic nervous system*, and are activated by the natural neurotransmitter acetylcholine.

The *G protein*-linked receptors mediate both bronchodilation and bronchoconstriction in the airways, in response to endogenous stimulation by neurotransmitters epinephrine and acetylcholine. These same airway responses can also be elicited by *adrenergic bronchodilator* drugs, or blocked by acetylcholine blocking (*anticholinergic*) agents.

Bronchodilators relax the smooth muscle that surrounds the bronchi, thereby increasing airflow. This dilation of the bronchi is due either to stimulation of beta$_2$ receptors in the smooth muscle of the bronchi, the release of epinephrine which itself stimulates beta$_2$ receptors, or to inhibition of acetylcholine at cholinergic receptor sites in the smooth muscle.

Parasympathetic Drugs

Drugs, which produce bronchodilation via the parasympathetic pathway, do so by blocking the action of acetylcholine at the parasympathetic synapse. Remember that sympathetic stimulation elicits a bronchodilation effect, while the parasympathetic system offers counter balancing by eliciting a bronchoconstricting effect. Therefore, a drug that can block the parasympathetic system's action will increase airway diameter by *allowing* bronchodilation to occur.

Drugs, which block the actions of the parasympathetic system, are called parasympatholytics because of their inhibitory action. Because they are competitively blocking the action of acetylcholine, they are also called anticholinergics. As the nerve impulse arrives at the synapse, the head of the presynaptic neuron releases acetylcholine into the synaptic cleft. The acetylcholine then diffuses to the receptor sits located on the surface of the postsynaptic neuron, where they bind and elicit an impulse in that neuron. All anticholinergics exert their action by competitively binding to those receptor sites on the postsynaptic neuron.

Because the receptors are already bound, acetylcholine cannot bind, and no neuro-impulse is transmitted. The target areas for bronchodilation with anticholinergics seem to emphasize the larger airways, while beta agonists seem to emphasize the lower airways. The effects of co-administered sympathomimetics and parasympatholytics are additive.

In general, parasympatholytic drugs have pulmonary indications consisting of the treatment of cholinergic-mediated bronchospasm. This has been suggested as particularly useful in the treatment of chronic bronchitis, although parasympatholytics may be used with other chronic obstructive diseases. These drugs are typically not used for acute obstructive disease.

Atropine was the first drug to be used as an anticholinergic bronchodilator. It elicits a fairly good bronchodilatory effect; unfortunately, it also has fairly significant side effects. Systemic actions of atropine include decreased gastric motility, dryness of mouth, thirst, dryness of eyes, increased heart rate, palpitations, pupillary dilation, urinary retention, and blurring of vision. These effects are certainly dose related. Other parasympatholytic drugs have much fewer side effects relative to atropine. It should be mentioned that a common misconception regarding atropine and other parasympatholytic drugs is their presumed effect on drying pulmonary secretions. The dryness of mouth that occurs with atropine administration results because the salivary glands are innervated with the parasympathetic pathway. (Remember the SLUD effects of stimulation of the parasympathetic system... Salivation, Lacrimation, Urination, Defecation) The mucous secreting glands and cells of the lower respiratory tract are not affected by administration of parasympatholytics, and therefore administration of this kind of drug does not produce significant dryness of pulmonary secretions.

Contraindications for parasympatholytics are relative, and include hypersensitivity, glaucoma, prostatic hypertrophy, and tachycardia.

Specific parasympatholytic drugs include:

1. Atropine
    1. None
    2. Actions
        1. Onset: approximately 15 minutes
        2. Peak: 1-2 hours
        3. Duration: 3-6 hours (dose-related)
    3. Dosage and Dosage form available in injectable ampules, 1 mg/ml (typically a vial containing 1 ml of that concentration) Nebulize between 1.0-2.5mg (typically 1.0 mg) diluted in 3.0ml saline. May repeat dose every 4-6 hours
2. Glycopyrrolate
    1. Trade Names: Robinul
    2. Actions
        1. Onset: within 30 minutes
        2. Peak: 1-2 hours
        3. Duration: 6-8 hours
    3. Dosage and Dosage form: available in injectable form only, not FDA-approved for use as inhaled drug. Solution is supplied in a concentration of 0.2 mg/ml. Aerosol administration is suggested with a dose of 1 mg given three or four times a day. This drug has the same action as atropine, but fewer adverse side effects.
3. Ipratropium Bromide
    1. Trade Names: Atrovent
    2. Actions
        1. Onset: 15 minutes
        2. Peak: 1-2 hours
        3. Duration: 4-6 hours
    3. Dosage and Dosage form: Available as a solution for inhalation, 0.5 mg in a pre-diluted unit dose. Also available as an MDI, for administration of 2 puffs taken four times a day.
    4. Note: This drug is related to atropine, but is chemically different enough that some very desirable characteristics are produced. First, the drug is not broken down very quickly, and so its effect is relatively long lasting. Second, it has essentially no systemic side effects, so it does not increase heart rate significantly, or cause oral dryness, or any of the other side effects common to atropine. Third, it has really no known toxic levels because the drug is not absorbed well systemically, so the drug is very safe. One last characteristic worth noting about ipratropium bromide is that there seems to be no real added benefit to additional dose once the four times daily dose has been met. Patients with persistent bronchoconstriction will receive no added benefit from further doses past the QID regimen.

Receptor Theory of Drug Action

Drugs are thought to produce their effects either by acting directly at some specific receptor site, or by acting diffusely at many tissues. Those acting diffusely are called *saturation-dependent* or *non-receptor* drugs, and include alcohol, hypnotics, anesthetics, and mucus-diluting agents such as water or saline. However, the majority of drugs act at specific receptor sites.

A *receptor* is a specific protein-related molecule embedded within and protruding out from cell membranes, where reversible bonds can be formed with specific drugs. When a drug binds to the receptor, a chemical change occurs which is transmitted to the inside of the cell. This changes the biochemistry within the cell.

Receptor-drug interactions have been described as a lock and key mechanism. Receptors (the lock) are very specific as to what drugs (the keys) that will bond there. The shape, size, and polarity (electric charge) of the drug molecule have to reasonably match the receptor's specifications, or no reaction and thus no drug effect will occur. *Affinity* is the tendency a drug has to combine with a receptor. If a drug has affinity and produces an effect, it is called an *agonist*. A *partial agonist* is a drug, which has affinity but cannot produce the total effect. In contrast, an *antagonist* is a drug that has affinity for a receptor but produces no effect. An antagonist is capable of blocking any effect that an agonist would produce, if the antagonist gets to the receptor and binds first. This might be like inserting a toothpick into a lock. The lock cannot open, but neither can the key be inserted into the lock when the toothpick is in there. An antagonist can be competitive (it forms a reversible bond with the receptor) or it can be noncompetitive (the bond formed is irreversible).

Specificity of the part of a drug is very important. A receptor will not respond to simply any molecule that happens by; only specific chemicals will react and bond with the receptor. This characteristic allows drugs to be designed to target one specific organ system with one specific receptor site and one specific biophysiologic effect. The challenge is to create medications that are in fact very specific for their intended receptor sites. An example of this is that the first bronchodilators were very non-specific to the receptor sites in he airways; consequently, there were many systemic side effects of the drugs used as they interacted with receptor sites distributed in other organ systems, particularly the cardiovascular system. Today's bronchodilators have been chemically designed to have more specificity, so that the desired pulmonary effect remains, but there are significantly fewer cardiovascular side effects.

Pharmacodynamics of the Nervous System

The nervous and endocrine systems are the body's internal communication pathways. The nervous system is specifically capable of rapid response and specific control, whereas the endocrine system is slower in its response and less precise in its effects. Both systems help regulate the body internally, a process referred to as *homeostasis*. Both systems are similar pharmacologically in that drugs can interact with them both at receptor sites and thereby modify functions at selected tissue locations.

The Nervous System:

1. Can be grouped into two general categories according to location of structures:
    1. Central Nervous System (CNS) consists of the brain and the spinal chord and related structures.
    2. The Peripheral Nervous System consists of all nerve pathways outside the CNS.
2. Can also be grouped into two general categories according to conscious control:
    1. The somatic system
        1. Under conscious control
        2. Typically innervates and controls skeletal muscle
    2. The autonomic nervous system,
        1. Not under conscious control
        2. Typically innervates cardiac and the various pulmonary and GI smooth muscles, sweat glands, and certain endocrine glands
        3. Name comes from the fact that it is the pathway for the automatic control of these organs
        4. Autonomic system maintains homeostasis
        5. Autonomic system itself is divided into two functional subdivisions:
            1. Sympathetic system
                1. Fibers arise in the thoracic and lumbar area of the spinal chord
                2. Once leaving the spinal chord, the fibers travel a rather short uninterrupted distance until they reach a ganglion (simply a neurological relay point). Ganglia are typically near the spinal chord.
                    1. The ratio of sympathetic preganglionic and postganglionic fibers is roughly 1:15, which suggests that a single preganglionic impulse can result in many outgoing impulses. As a result, sympathetic stimulation typically results in a diffuse response throughout the body.
                        1. The post-ganglionic neurotransmitter chemical is mostly norepinephrine, but may also be epinephrine.

2. Parasympathetic
    1. Fibers arise in the cervical and sacral areas of the spinal chord
    2. Once leaving the spinal chord, the fibers travel uninterrupted for relatively long distances. Their ganglia are typically located near the effector organs.
        1. The ratio of parasympathetic preganglionic and postganglionic fibers is roughly 1:2, which results in a very local and specific response.
            1. The post-ganglionic neurotransmitter is acetylcholine.
3. Balance between the sympathetic and parasympathetic and the fact that the pathways typically oppose each other in their effects result in the body's ability to control the various organ and tissue systems. Each exerts a constant and steady antagonistic force on the other, much like pulling on the two ends of a rope. The balance of the two systems is called the *tone*. The effects of stimulation of the parasympathetic and sympathetic systems very from organ to organ. Stimulation of the sympathetic system cause bronchial muscle dilation, increased heart rate and contractility, increased peripheral vasomotor tone. Stimulation of the parasympathetic system produces bronchial constriction and decreased heart rate and contractility, as well as decreased vasomotor tone. In addition, parasympathetic stimulation causes increased activity in the SLUD organs, or Salivation, Lacrimation, Urination, and Defecation.

A Note About Synapses

The synapse is the connection between one neuro fiber and the next, such as occurs at the ganglia. When a nerve impulse arrives on the incoming axon, a chemical transmitter is released into a cleft between the axon of the incoming fiber and the axon of the outgoing fiber or effector organ. Once the synaptic neurotransmitter is released, enzymes in the cleft work quickly to break down the transmitter so that the effect of the impulse transmission will be temporary. Also, some neurotransmitter chemical is reabsorbed back into the incoming axon.

At the synapse, the parasympathetic system's neurotransmitter acetylcholine is released into the synaptic cleft and carries the nerve impulse to the outgoing nerve fiber. Because of this, the parasympathetic system is often referred to as the cholinergic system. Acetylcholine is broken down into he synaptic cleft and deactivated by acetylcholinesterase.

The sympathetic system transmits its nerve impulses across the synaptic cleft using norepinephrine (nor-adrenaline). Because of this, the

sympathetic system is often called the adrenergic system. In the cleft, the norepinephrine may be removed via a combination of several mechanisms.

4. The norepinephrine can be reabsorbed back into the incoming axon
5. It can be deactivated by the enzyme, catechol-o-methyl transferase (COMT)
6. It can be deactivated by monamine oxidase (MAO) enzyme

A Final Note About Receptors

The receptors of the sympathetic system can be divided into four major categories:

- Beta1 receptors are located mainly in the cardiac muscle, and stimulation of them increases cardiac rate and contractility.

- Beta2 receptors are located mainly in the bronchial smooth muscle, and stimulation cause smooth muscle relaxation.

- Alpha1 receptors are located mainly in the peripheral arterioles and stimulation causes contraction of the smooth muscle in those vessels with resultant increase systemic vascular resistance (SVR).

- Alpha2 receptors less important than the other three but are located in the pre-synaptic sympathetic nerves and in the CNS, and stimulation can decrease the norepinephrine released at the synapse, as well as decrease sympathetic nervous outflow from the CNS.

Steroids

This discussion covers the classification of drugs known as glucocorticoids, or steroids.

Glucocorticoids are a subtype of the general classification of corticosteroids. These substances are produced in vivo by the adrenal cortex.

Recall that the hypothalamus is located on the inferior surface of the brain, just posterior to the nasal cavity. As part of the brain, it receives incoming sensory impulses and coordinates these afferent signals with chemical information arriving continually through the blood supply. In addition, the hypothalamus is capable of producing its own chemical messengers and releasing them into the blood stream. Glands such as the hypothalamus lack secretory ducts, and are referred to as endocrine glands.

Hormones, the products of such glands, are regulatory substances released into the blood supply and carried to target areas. Hormones have the ability to alter a preexisting reaction, usually by enhancing it in some way.

Most hormones are composed of proteins, or modified amino acids. But a few possess a complex ring structure and are referred to as steroid hormones. The word "steroid" means sterol-like, and a sterol is a compound with a complex alcohol ring. Cholesterol is one such alcohol-ringed compound. Other compounds sharing this characteristic include testosterone, progesterone, and the adrenal corticosteroids.

Within the hypothalamus, distinct groupings of cells synthesize specific hormones. The anterior portion of the hypothalamus controls the glandular portion of the pituitary gland (the anterior pituitary). When physiological stressors occur, such as infection, trauma, emotional stress, exercise, surgery, or thermal changes, the hypothalamus secretes a hormone called corticotropin releasing factor, or CRF.

This hormone travels the short distance to the anterior pituitary via specialized blood channels, and stimulates the production and release of corticotropin, or adrenocorticotropic hormone (ACTH). ACTH travels via the blood stream to the adrenal glands, and stimulates the adrenal cortex to synthesize and release corticosteroid hormones. These corticosteroids travel throughout the body to accomplish two purposes: restore homeostasis by minimizing the effects of the original stressor, and inhibit the hypothalamus from producing more CRF. If the physiological stress persists, the suppression of the hypothalamus is incomplete, and another round of hormonal release is initiated.

When corticosteroids are administered therapeutically, they mimic the action of native corticosteroids. In addition, they have the ability to influence the production of native corticosteroids via suppression of the hypothalamus with resultant suppression of the adrenal cortex.

The adrenal glands are interesting little fellows. They are small highly vascularized glands located on the anterior aspect of both kidneys. Within a single gland, two distinct endocrine glands are found. They share a blood supply but little else. Their embryonic origins, cell populations, hormone chemical types, physiologic controls, and functions differ significantly. They are as separate as two glands can be, yet they appear grossly as one organ, approximately 5 cm long, 3 cm wide, and only 1 cm thick. The outer portion, or adrenal cortex, is a relatively thin layer over the catecholamine-producing adrenal medulla. The adrenal cortex possesses three distinct cell populations each located in a separate layer of the cortex, and each responsible for the synthesis of a different class of corticosteroid hormone.

The steroid hormones synthesized in the three layers of the adrenal cortex can be described in functional terms. One group regulates plasma electrolytes, another is involved in the maintenance of blood glucose levels, and a third promotes protein synthesis. The relatively complex chemical structure of the steroid base-molecule is common to all three of the adrenocortical hormones.

The differences in them result from the differences in the location and type of substituted chemical groups attached on the steroid base. The slight structural differences in the chemical structure of these complex molecules account for the observed differences in activity of the hormones. However, the differences are better viewed as differences in potency: there is

overlapping of physiological effects among the corticosteroids; the chemical structure of each, however, makes each more potent for a given set of effects versus the others.

The ability of one class of corticosteroid to influence body functions usually regulated by another is the cause of many of the side effects seen with steroid drug therapy. The recognized side effects are simply the exaggeration of body functions normally controlled by the adrenocortical hormones. The overlapping effects of various steroid compounds are due to their close chemical similarity. For example, steroid hormones that have gained notability for their potent anabolic effects on the muscular system also produce unwanted side effects, including salt and water retention. This occurs because the structure of the anabolic steroids is similar to that of the steroids that promote electrolyte and fluid shifts.

The middle layer of the adrenal cortex produces hormones that are especially potent to increase blood glucose levels, and as such, is referred to as glucocorticoids. The two naturally occurring steroids of this class are cortisone and cortisol. These substances increase blood glucose levels by converting fats and proteins to glucose, when the body is deprived of glucose, or perhaps when a severe stress depletes blood glucose. Overall, the mechanism diverts resources from dispensable tissues such as muscle and adipose, and converts these resources for use by indispensable tissues such as brain and heart.

Glucocorticoids are also potent anti-inflammatory and immunosuppressive agents, for several reasons:

1. inflammatory substances such as collagen and mucoproteins that are associated with the inflammatory reaction in tissue are used as non-carbohydrate sources of glucose.
2. glucocorticoids suppress the activities of common connective tissue cells called fibroblasts, which normally respond to tissue trauma by producing collagen.
3. proteins in lymphoid tissue are another non-carbohydrate source of blood glucose, the metabolism of which is mediated by glucocorticoids. As a result, antibody formulation, which normally occurs in lymphoid tissue, is suppressed. Circulating antibody concentrations are decreased. In addition, glucocorticoids suppress plasma immunoglobulins, the material from which antibodies are made. With decreased antibody levels, the severity of inflammatory reactions decreases.
4. glucocorticoids inhibit the synthesis and release of histamine from target cells.
5. glucocorticoids decrease the release of arachidonic acid; consequently, the serum levels of leukotrienes and prostaglandins decrease.
6. glucocorticoids act on smooth muscle cells by increasing the number of beta-2 adrenergic receptors, and increasing the affinity these receptors have for beta agonists. The result of this is improved efficacy of beta agonist therapy.

Because glucocorticoids are systemically active, the side effects they have when administered systemically can be very diverse, and stem from the mimicking of normal activities of the native hormones, as well as repression of the adrenal cortex via the previously mentioned feedback loop. Some specific side effects along these lines include:

- Endocrine gland repression. Administration of exogenous steroids when circulating systemically, inhibit the hypothalamus' output of CRF. The decreased CRF levels fail to stimulate the anterior pituitary to produce ACTH. Decreased levels of ACTH fail to stimulate the adrenal cortex, and blood levels of endogenous steroids decrease. This suppression of the feedback loop by exogenous corticosteroids results in physiologic dependency. The body becomes dependent on exogenous corticosteroids while the levels of native hormones gradually decrease. The hypothalamus, anterior pituitary, and adrenal cortex enter a physiological dormancy as a result of exogenously administered corticosteroids, and will only slowly emerge from their suppressed states when the exogenous corticosteroids are cautiously withdrawn.

- Cushingoid effects. Cushing’s disease is a tumor of the anterior pituitary, which causes hypersecretion of ACTH. The result is an increase in endogenous corticosteroids, and classic body morphology, including central obesity, exophthalmus, dowager's hump (a fatty deposit between the shoulder blades resulting in the appearance of a 'buffalo hump'), edema, hypertension, and masculinization of females. Administration of exogenous glucocorticosteroids over the long run can cause these symptoms to appear as well, a condition referred to as "Cushing's syndrome" or "Cushingism."

- Withdrawal and Addisonian crisis. Addison's disease is a condition of pathological suppression of the adrenal cortex, leading to hyposecretion of the corticosteroids. Symptoms include diuresis, fluid loss, hypotension, hyponatremia, hyperkalemia, hypoglycemia, weakness, and weight loss. Sudden withdrawal of exogenous steroid therapy that has been given for an extended period can result in systemic drops in serum corticosteroid levels, with resultant production of symptoms similar to Addison's disease. The production of these symptoms from the sudden withdrawal of steroid therapy is referred to as 'Addison's Syndrome.'

One further note about the effects of systemic steroids: The secretion and balance of corticosteroids follows a normal ebb and tide over the course of a day. Levels of cortisol typically peak in the morning to help meet the stress of starting the day, and then decrease in the evening to prepare for sleep. The normal fluctuation of cortisol is the basis of the circadian rhythm, or diurnal variation.

If there is no major change to upset this pattern, diurnal variation quietly functions to provide the body with the optimal levels of the hormones required to respond to various physiologic stressors. Interruptions in this normal biological pattern can occur with interruptions in normal day night patterns, or possibly with administration of exogenous corticosteroids. The effect of

exogenous steroid therapy, or shift work, or jet lag, all can affect the body's circadian rhythm of corticosteroid hormones. Administration of systemic steroid therapy often follows an alternate-day regimen, to help minimize the effects of the exogenous steroid on circadian rhythm and hypothalamic CRF production. In addition, systemic steroid therapy that is administered in "boluses" such as with p.o. administration should be done in the morning.

Indications for Glucocorticoids:

In general, indications include an inflammatory process such as atopic processes, asthma, chronic bronchitis, rheumatoid arthritis, bursitis, and soft-tissue or joint injury. In addition, these drugs are useful in conjunction with tissue transplantation because of their reduction of the rejection phenomenon. Finally, these drugs may be used as replacement hormones in patients with adrenal insufficiency.

Contraindications for Glucocorticoids:

These drugs, via their ability to cause fluid retention, can worsen preexisting conditions of heart disease or hypertension. Fluid retention may also elevate intraocular pressure and aggravate glaucoma. Glucocorticoids are relatively contraindicated in conjunction with serious infections, because of their ability to decrease serum antibody concentrations. Because of the ability to elevate serum glucose levels, glucocorticoids can overload the glucose-processing ability in people with diabetic conditions.

Systemic Glucocorticoids:

The major differences in the various glucocorticoids are the duration of action, their potency, and their relative mineral corticoid effects. Potency is expressed as anti-inflammatory action relative to Cortisol (the potency number is h0w many times more potent the drug is versus Cortisol)

Short-Acting Glucocorticoids (8 - 12 hours)

Generic	Trade	Potency	Mineral effects
Hydrocortisone	Cortisol Solu-Cortef S-Cortilean	1	Significant
Cortisone	Cortone	0.8	Significant

Intermediate-Acting Glucocorticoids (12 - 36 hours)

Generic	Trade	Potency	Mineral effects
Methylprednisolone	Medrol Solu-Medrol Depo-Medrol	5	None
Prednisolone	Delta-Cortef	4	Less than cortisone
Prednisone	Colicine Deltasone Win pred	4	Less than cortisone
Triamcinolone	Aristocort Kenacort	5	No appreciable activity

Long-Acting Glucocorticoids (36 - 72 hours)

Generic	Trade	Potency	Mineral effects
Betamethasone	Celestone Betnelan Betnesol	25	Relatively few
Dexamethasone	Decadron Hexadrol Dexasone	25	Relatively few
Fluprednisolone	Alphadrol	12	Relatively few
Paramethasone	Haldrone	10	Relatively few

INHALED GLUCOCORTICOID THERAPY

In striking contrast to the cushingism and adrenal suppression seen with systemic administration, nonsystemic steroid drugs have virtually no systemic side effects unless high doses are given. At their therapeutic doses, nonsystemic steroids produce a local anti-inflammatory effect without significant systemic absorption.

The local effect is similar to the systemic actions; however, the action of the nonsystemic drug is limited to the site of administration. These drugs typically are in various forms of inhalers. Some are dry powder inhalers (DPI) which use no chlorofluorocarbon (CFC) propellants, some are

metered does inhalers (MDI) which do have CFC propellants, and some are sprays that are intended for nasal action alone, to treat seasonal rhinitis or nasal polyps.

These drugs have come to the forefront in the arsenal of medications to combat reactive airway disease. As recently as 12 years ago, these were add-on drugs to include in treatment regimens for relatively severe, difficult-to-manage asthmatics; however, within the last 7 years or so, there has been a greater understanding about the significant role inflammation has in asthma, and these drugs have become the first-line medications in the treatment of moderate to severe asthma. Much research has been done to develop stronger, more potent anti-inflammatory action in new drugs; as a result, there are many new-generation drugs available.

Adverse side effects unique to inhaled steroids include thrush, or oral candida albicans infection. Rinsing the mouth and gargling following administration can avoid this.

It should be reiterated that any inhaled agent has the ability to cause cough and bronchospasm. Nasal preparations may cause sneezing, nasal irritation, or bleeding.

Because of the wide variety of doses seen with inhaled steroids, the specific doses will not be addressed here. Check the package insert or Physicians Desk Reference, but be aware that higher doses than listed are relatively common. Specific drugs include:

Generic Name	Trade Name	MDI	DPI	Nasal
Beclomethasone	Beclovent	X		
	Vanceril	X		
	Beclodisk		X	
	Beconase			X
	Vancenase			X
Triamcinolone	Azmacort	X		
Flunisolide	Bronalide	X		
	AeroBid**	X		
	Nasalide			X
	Rhinolar			X
Fluticasone	Flovent	X**		
Budesonide	Pulmicort	X	X	
	Rhinocort			X

*AeroBid has such a horrible taste that a newer version came out after the original inhaler had been on the market a while. It is AeroBid-M and it has a mint flavor!

**Flovent comes in three different strengths so that a person requiring higher doses does not have to take lots of more puffs. To the best of my knowledge, its the only metered dose inhaler to do that.

Corticosteroids

Steroids comprise five general groups of complex organic compounds which are produced in the adrenal cortex. The group that has clinical relevance to respiratory therapy is the *glucocorticoids*. Cortisol and glucocorticoids regulate the metabolism of carbohydrates, fats, and proteins to generally increase levels of glucose for energy to be used by the body. That is why cortisol and its analogues are called glucocorticoids.

One of the major therapeutic effects seen with analogues of natural adrenal cortical hormone hydrocortisone is an antiinflammatory action. Glucocorticoid analogs are used for their antiinflammatory effects in treating asthma, which is basically a disease in which there is chronic inflammation of the airway wall that causes airflow limitation and hyperresponsiveness to a variety of stimuli.

Steroids can be administered orally, intravenously (IV), or aerosolized for respiratory symptoms. The IV drug of choice is usually hydrocortisone or methylprednisolone. Oral drug of choice is prednisone or prednisolone. Aerosolized corticosteroid preparations that have antiinflammatory effectiveness in the treatment of asthma include: *hydrocortisone, cortisone, prednisone, prednisolone, and methylprednisolone*.

In treating respiratory diseases, steroids are administered orally for more significant exacerbations of bronchospasms, and by IV for serious bronchospasm. However, the potential side effects of systemic administration of corticosteroid treatments are well recognized, and include:

- HPA suppression
- immunosuppression
- increased glucose levels
- fluid retention
- hypertension
- increased white blood cell count
- peptic ulcer
- osteoporosis
- psychiatric reactions
- growth retardation
- myopathy of skeletal muscle
- cataract formation
- dermatologic changes

The quantity, severity, and frequency with which these complicating side effects appear when systemic steroid treatments are used have provided the motivation for transferring patients to aerosolized, inhaled steroids whenever possible. The introduction of synthetic analogues of hydrocortisone, which have a high topical antiinflammatory activity, have paved the way for effectively using aerosolized steroids with little systemic side effects. These drugs include: beclomethasone, triamcinolone, flunisolide, budesonide, and fluticasone.

While the switch to inhaled aerosol steroids has reduced the number of side effects previously seen with systemic steroid therapy, there remain some local and system side effects that need to be considered by caregivers. The following table illustrates the potential hazards and side effects associated with using inhaled aerosol corticosteroids:

Systemic	Local (topical)
Adrenal insufficiency[1]	Oropharyngeal fungal infections
Extrapulmonary allergy[1]	Dysphonia
Acute asthma[1]	Cough, bronchoconstriction
HPA suppression (minimal, dose dependent)	Incorrect use of MDI
Possible growth retardation	
Possible osteoporosis in asthmatic patients	

[1] Following transfer from systemic corticosteroid therapy.

Aerosol corticosteroid therapy is currently considered clinically indicated for:

- control of asthma
- treatment of related steroid-responsive bronchospastic states not controlled by other therapies
- control of seasonal allergic or non-allergic rhinitis

The increased emphasis on viewing asthma as primarily a disease of inflammation leading to bronchial hyperresponsiveness has shifted the indicated use of inhaled aerosol steroids from second or third line to front line, primary therapy. The NIH's 1997 *Guidelines for Diagnosis and Management of Asthma* now identify aerosolized corticosteroids as long-term control therapy rather than as quick-relief for acute, severe asthmatic episodes.

The late-phase response of allergic induced bronchospasm can be mitigated or prevented by early application of inhaled steroids. In general, steroids do not replace bronchodilators, but should be used to supplement them.

Corticosteroid Medications

Dexamethasone (Decadron) is one of the first successfully aerosolized agents (available since 1976) for inhalation, and it has an antiinflammatory potency of 30 times that of hydrocortisone. However, because it does not potentiate the $beta_2$ receptors and the systemic side effects associated with it, the use of aerosolized dexamethasone has declined in favor of newer medications. It is available as a nasal spray (Turbinaire) and MDI (Respihaler). Each activation of the MDI delivers approximately 0.1 mg. Adult dose is 3 puffs TID or QID, up to a maximum of 12 per day. Pediatric dose is 2 puffs TID or QID, up to 8 per day. Each MDI delivers about 170 puffs.

Beclomethasone dipropionate (Vanceril, Beclovent) was the second aerosolized corticosteroid made available in this country, and is indicated for controlling intrinsic, extrinsic, and mixed asthma in patients over six years of age who require steroid therapy. The drug's success as an aerosol in reducing or replacing the use of systemic steroids is due to its high topical to systemic activity ratio (approximately 500 times that of dexamethasone). Beclomethasone has also been reported to minimize symptoms of perennial rhinitis in patients susceptible to antigens such as pollen.

An aerosol dose of 400 mcg of beclomethasone is approximately equivalent to 5-10 mg of oral prednisone. Adult dose is 0.5 to 1 mg QID. For the Vanceril MDI, one to four puffs are given 3-4 times a day. Each puff delivers about 42 mcg. The maximum daily adult dose is 840 mcg, with the pediatric dosage being about half of this. Asthmatic symptoms decrease in about 80% of patients concurrent with an improvement in pulmonary function. This occurs without the systemic side effects of oral steroids, although Candidiasis has been reported in some cases.

Betamethasone is a synthetic corticosteroid indicated for severe inflammation, immunosuppression, or adrenocortical insufficiency. Its duration of action is similar to dexamethasone, and has about 75% of the potency of beclomethasone. Daily dosage is 4 applications of 200 mcg each.

Triamcinolone Acetonide (Azmacort) an aerosol that is also topically active, and was available as Kenalog and Aristocort prior to its release as an aerosol. Available in an MDI preparation with a built-in spacer device, inhalations doses of about 100mcg, four times daily allow most steroid-dependent asthmatics to stop taking oral steroids. Aerosolized triamcinolone can cause hoarseness, voice weakness, and oropharyngeal candidiasis; however, rinsing the mouth and gargling after use generally prevents these side effects.

Flunisolide (AeroBid), another topically active MDI-packaged aerosol, is similar to triamcinolone in potency, but is longer acting. Like beclomethasone, it shows a peak plasma level after inhalation between 2 and 60 minutes, indicating good absorption from the lungs. Because it is more potent than many steroids, its recommended dosage is reduced: two inhalations (250 mcg each) twice daily for adults, with half of this recommended for pediatric patients.

Fluticasone propionate (Flowvent, Flonase) is a further analogue of previous agents with high topical potency, synthesized in order to avoid systemic side effects. It is part of androstane analogues which has a very weak HPA inhibitory activity, but high antiinflammatory effect. Available as a nasal spray and in MDI form in three different strengths, recommended adult dosage is 44-220 mcg BID. Fluticasone propionate is contraindicated in patients with acute status asthmaticus, respiratory tract infections, or tuberculosis.

Budesonide is a topically active inhaled corticosteroid less potent than fluticasone, but greater than beclomethasone. After inhalation with a spacer device, peak plasma concentrations occur between 15-45 minutes with a half-life of 2 hours, and there appears to be minimal metabolism in the lung (about 70% of inhaled dose reaches the circulation). The recommended adult dosage is one puff (200 mcg) BID. Half this dose is used for children using a 50 mcg MDI. Budesonide may be given up to 3 puffs (600 mcg) BID, and is available as a nasal aerosol for treating allergic rhinitis.

Hydrocortisone (variety of trade names including Hydrocortone, Acticort, and Cetacort) is a steroid that can be administered orally, parenterally, and only rarely by aerosol. Its plasma concentrations of 100-150 mcg/ml are generally high enough to diminish the symptoms of status asthmaticus. The adult daily dose can range from 300 to 2000 mg.

Prednisone (Deltasone) is an oral steroid in tablet form that has an anti-inflammatory potency 3-4 times that of hydrocortisone. Its onset of action is somewhat delayed because it becomes active only after its been converted to prednisolone in the liver. As an aerosol, it is completely ineffective. Indications include severe inflammation or immunosuppression, nephrosis, or acute exacerbations of multiple sclerosis. Adult dosage is PO 1.5-2.5 BID-QID, followed by once daily or QOD, with maintenance dosage up to 250 mg daily.

Prednisolone (numerous trade names include Prelone, Predicort, Key-Pred) is an intermediate acting synthetic steroid that is available by injection, orally, and is rarely aerosolized. Anti-inflammatory potency is 3-4 times that of hydrocortisone but it takes longer to reach its peak effect. The half-life is 2 to 4 hours and pharmacological effects last up to 36 hours. Usual adult dose is PO 2.5-15 mg BID-QID; IM 2-30 mg Q 12 hours; IV 1-30 mg daily..

Methylprednisolone (Duralone, Medralone, Depopred, et al) has 4-5 times the anti-inflammatory potency of prednisolone, and is used frequently because it has little effect on electrolyte balance. Available orally, but is usually administered intravenously. Methylprednisolone is indicated for severe shock, status asthmaticus, ARDS, and aspiration pneumonia. Onset of action is rapid, half-life is 78-188 minutes, and pharmacological effects remain for up to 36 hours. Dosage varies depending upon symptoms.

Mediator Modifiers

Asthma is essentially an inflammatory disorder of the airways, in which allergic stimuli often trigger *IgE*-mediated *mast cell* release of *mediators* of inflammation. Airway reactivity can be triggered by such nonspecific stimuli as cold air or dust. Allergic inflammation of the airway is a product of an immune response, and the T-lymphocyte plays a central role in attracting mast cells and eosinophils, which in turn release mediators that attract other cells and damage epithelial cells.

The clinical result of asthma is a chronic persistent inflammation of the airway, coupled with occasional acute episodes of wheezing and airway obstruction caused by bronchoconstriction, mucosal swelling and mucus secretion. There are drugs available to inhibit the *mediators* of inflammation, including: cromolyn sodium, nedocromil sodium, zafirlukast, and zileuton. These agents, sometimes referred to as mediator modifiers, are *prophylactic* and are intended to assist the management of chronic asthma, **not** to relieve acute airway obstruction or provide bronchodilation in an acute asthma attack. Patients who show an improvement in bronchospastic symptoms with steroids may benefit from mediator modifier

Cromolyn sodium (Disodium Cromoglycate) is considered an antiasthmatic, antiallergic, and mast cell stabilizer. Cromolyn is available as a dry powder inhaler, a nebulizer solution, and an MDI. It does not block cholinergic, muscarinic receptors, and has no intrinsic bronchodilating capability. Pretreatment with inhaled cromolyn sodium results in inhibition of mast cell degranulation, thereby blocking release of the chemical mediators of inflammation. While the dosage varies at the discretion of the physician, the usual adult dose of cromolyn is 20 mg TID or QID.

Nedocromil sodium (Tilade) is another prophylactic drug used in the management of mild to moderate asthma. It exerts its antiinflammatory and antiasthmatic effect by inhibiting the activation and activity of multiple inflammatory cells, including mast cells, eosinophils, airway epithelial cells, and sensory neurons. Available as an MDI with 1.75 mg per actuation, the recommended dosage for maintenance therapy in asthma is two inhalations 4 times a day.

Zafirlukast (Accolate) is a relatively new (approved for use in U.S. in 1996) *prophylactic* agent that acts on a portion of the inflammatory process as a leukotriene receptor antagonist, preventing the inflammatory response of airway contractility, vascular permeability, and mucus secretion caused by certain leukotrienes.

While its been in use a relatively short period of time, Zafirlukast gives evidence of being effective in preventing bronchoconstriction and other asthmatic airway responses, against LTD_4-induced constriction, allergen, exercise, and cold air challenge. Side effects have included headache, respiratory infection, nausea, diarrhea, generalized and abdominal pain.

Zileuton (Zyflo) also new (approved in 1997), inhibits the 5-lipoxygenase enzyme, which would otherwise catalyze the formation of leukotrienes from arachidonic acid. It is indicated for the prophylaxis and chronic treatment of asthma in patients over 12 years of age, and has been effective in attenuating the asthma response to allergen challenge, cold air, and aspirin challenges. It is available in a 600 mg tablet form, with dosage being recommended at one tablet 4 times daily.

There are at least four classes of drugs which provide antiinflammatory activity within the arachidonic acid cascade, and which are being investigated for possible use in assisting the treatment of asthma (some only have code names at this time):

1. **Cysteinyl LT antagonists**
   Zafirlukast, ICI-204, 219 (Accolate)
   Pobilukast, SKF 104353-Q
   Pranlukast ONO-1078
   Verlukast MK-679

2. **5-lipoxygenase inhibitors**
   Zileuton, A-64077 (Zyflo)
   Z-02128

3. **FLAP** binding inhibitors
   M-886
   MK-0591
   BAY x1005

4. **LTB_4** antagonists
   ONO-4057
   U-75,302

Inhibitors of 5-lipoxygenase either inhibit the enzyme directly or bind to a membrane protein called FLAP. FLAP then combines with 5-lipoxygenase to inhibit leukotriene synthesis. Zileuton is an agent that directly inhibits 5-lipoxygenase. While there are still questions regarding the usefulness of blocking the synthesis or activity of a single family of mediators such as leukotrienes, there has been a high efficacy in clinical trials of these drugs that supports the thesis that these may prove useful in the future.

Prostaglandins
Prostaglandins are synthesized in all tissues, and the three that are of substantial interest in respiratory therapy are PGE_1, PGE_2, AND PGF_{2A}. The first two because they cause relaxation of bronchial smooth muscle, and the latter because it causes contraction of bronchial muscle. Prostaglandins, unlike adrenergic or anticholinergic drugs, act directly on smooth muscle.

Prostaglandins are used for vasodilation of the pulmonary vascular bed in patent ductus arteriosus (PDA). Increased pulmonary vascular resistance in PDA helps maintain a shunt through the patent ductus, and lowered resistance allows more blood to flow through the pulmonary system and less through the ductus. It is important to release the prostaglandin via a line located distal to the ductus, otherwise the ductus becomes dilated and the problem is worsened.

Anticholinergic bronchodilators
Anticholinergics or parasympatholytic bronchodilators, which are also often referred to as *antimuscarinics* because they act at the muscarinic receptors of the parasympathetic nervous system, achieve bronchodilation through a different pathway in the autonomic nervous system. As a result, anticholinergics can be used either alone or in combination with beta adrenergics.

Because they tend to decrease secretion production, drying of the airways can be a problem if significant doses are administered. Additional side-effects can include: drying of the mouth and skin, blurred vision, and an increase in speech, swallowing, and micturition problems. Among these drugs, the most common include:

Atropine sulfate which has traditionally been the model antimuscarinic bronchodilator agent used in the treatment of airway disease. It has an additive effect to the Beta-adrenergic agonists when given together. However, the development and increased use of adrenergic drugs has tended to gradually displace atropine as a bronchodilator.

Atropine is available as a nebulized solution administered via injection or aerosol (Dey-Dose). Because it is a tertiary ammonium compound, atropine is readily absorbed by aerosol, and side effects are seen in the dosages required for effective bronchodilation. Duration and incidence of side effects are therefore dose dependent. Normal inhaled dose for atropine is around 0.025 mg/kg for adults (2.5 mg per 24 hours maximum), with onset in 15 minutes, peak at .5-1.0 hour, and duration 3-4 hours. Atropine is also available in tablets and elixirs.

Ipratropium Bromide (Atrovent) is approved specifically for the maintenance treatment of airflow obstruction in COPD. It is considered a first-line medication for COPD patients, particularly those with chronic bronchitis. It is currently available in two formulations for bronchodilator use: an MDI with 18 mcg per puff, and a nebulizer solution of 0.02% concentration in a 2.5 ml vial, providing a 500 mcg dose per treatment. Usual adult dose is 2 puffs QID via MDI (12 puffs per 24 hours maximum).

The side-effects of antimuscarinics are minimal or absent in most patients using ipratropium, and systemic absorption via the GI tract and mucosal surface is also minimal. It has an additive effect to the Beta-adrenergic agonists and, provides better bronchodilation for many COPD patients. It should be delivered prior to Beta agonists in order to achieve the best results.

Some other antimuscarinics include:

Glycopyrrolate, a derivative of atropine, which is usually administered parenterally, is used as an alternative to atropine because it has fewer ocular or central nervous system side effects. The injectable solution has been nebulized into a 1 mg dose for bronchodilation.

Oxitropium bromide is a derivative of scopolamine that has been investigated as an aerosolized anticholinergic bronchodilator in patients with obstructive airway disease. An MDI-delivered dose of 200 mcg provides a peak effect on FEV_1 within 1-2 hours, with a duration of 6-8 hours. Normal dosage is 2 puffs BID or TID, and systemic anticholinergic effects are rare. Side effects include local irritation of the throat and nose, dry mouth, nausea, wheeze, cough, and a tightness in the chest in a few patients.

Tiotropium bromide is still an investigational, long-acting antimuscarinic drug that may offer an attractive and safe alternative for maintenance treatment of COPE, and protection for nocturnal asthma.

Vasoactive Drugs

Vasoactives encompass a general group of chemicals that some of which can cause vasodilation to respond to hypertension, and others of which cause vasoconstriction to respond to hypotension. Also worth briefly noting along with this discussion is the importance of diuretics for treating hypertension. While not vasoactive, they still have an important role to play in correcting high blood pressure.

Before discussing vasoconstrictors, it would be appropriate to review shock, or hypotension, and its various forms and causes.

Hypovolemic shock is the result of the loss of intravascular volume. This loss of volume may be real, as with hemorrhage, or it can be an effective volume loss, such as occurs with post-traumatic systemic vasodilation. The result is the same: a decrease in cardiac preload and a consequent drop in both cardiac output and oxygen delivery to the tissues. Problems in contractility generally do not accompany hypovolemic shock, unless there is preexisting cardiac disease or if the blood volume falls to such critically low levels that coronary circulation is impaired.

The body's response to hypovolemic shock is to compensate by 1) shifting fluid from the interstitial space to the intravascular space; 2) reducing urinary output by increasing the reabsorption of sodium in the kidneys, and 3) increasing antidiuretic hormone (ADH) which prevents the loss of solute-free water by the kidneys. In addition, cardiac compensatory mechanisms act to re-establish cardiac output by increasing the heart rate.

The treatment of hypovolemic shock is composed of two concurrent strategies: First, the effective and rapid control of any volume loss, for example by controlling hemorrhage; and second, replenishment and maintenance of the volume lost and the restoration of normal cardiovascular mechanisms through the appropriate selection of replacement fluids and the use of pharmacologic agents that support blood pressure and maintain the delivery of oxygen.

Cardiogenic shock is hypotension that results from an inability of the heart to pump away the blood volume returned to it. The approach to the management of cardiogenic shock depends on whether the patient has pulmonary edema, which is usually assessed by an evaluation of chest x-ray and a measurement of pulmonary capillary wedge pressure (PCWP). Recall that PCWP measures left ventricular end-diastolic pressure (LVEDP) and reflects the preload on the left heart. In cardiogenic shock, if the PCWP is less than 18 mm Hg (normal) cardiogenic pulmonary edema is unlikely. In this case, fluid loading is attempted while the PCWP is monitored to judge the degree of ventricular compliance. If the presence of pulmonary edema is documented by a PCWP of greater than 18 mm Hg, diuretics, vasodilators, and inotropic agents may be used. In addition, antiarrhythmic agents, circulatory assist devices, and cardiac surgery may be indicated.

Septic shock results from an infective agent in the blood, which causes changes in the systemic microvasculature. A high cardiac output, a normal pulmonary vascular resistance, and a systemic vascular resistance that is low characterize septic shock. Microvascular changes shunt blood from arterial to venous systems bypassing tissues; as a result, the oxygen saturation of mixed venous blood is typically high.

As in hypovolemic shock, the restoration of intravascular fluid volume is indicated unless cardiac problems or fluid overload complicate the situation. Indices of particular value are the serum lactate, oxygen uptake (VO2) and oxygen delivery (DO2). If preload correction does not result in an improvement in the delivery of oxygen, inotropic agents and afterload reduction must be considered.

The appropriate identification of the underlying septic conditions is necessary for the control of septic shock, with appropriate selection of antimicrobial therapy. However, the origin of a septic condition may not be identified.

Pharmacologic Agents for Preload Correction. A high preload indicates that the heart is not pumping away the blood volume that is returned to it; in such cases, an inotropic agent should be considered, depending on the mechanism for increasing the preload. Some instances of atrial fibrillation or flutter can increase preload secondary to the loss of the "atrial kick" and an agent such as antiarrhythmics or digitalis preparations should be considered.

A low preload in the face of a low systemic blood pressure suggests shock, and volume replacement therapy should be instituted. This discussion will not address the rationale for the various choices for fluid replacement therapy; however, the following are the major categories of volume replacement therapy:

Type	Product	Special notes
Water	Sterile water, D5W	Distribution includes intracellular spaces, as well as intravascular and interstitial spaces; not typically used for volume expansion due to hypo-osmolarity.
Crystalloid	Normal Saline, Lactated Ringer's	Distribution basically limited to intravascular and interstitial spaces. Normal osmolarity. Crystalloid solutions are most commonly used for volume replacement in all forms of shock

		where the preload is diminished. Careful titration is required for patients who have cardiac or renal failure, and may require placement of a central catheter for pressure monitoring.
Colloid	Albumin, Dextran	Human serum albumin is available in preparations of 5% and 25%. 25% is hyperosmolal, and the infusion of 100 ml of the solution causes approximately 350 ml of interstitial fluid to be drawn to the intravascular space within one hour. Because of its cost and it potential for precipitating pulmonary edema, particularly in the patient with compromised myocardial contractility, albumin is not recommended for routine fluid replacement. It has been recommended for a major blood volume loss; for third space fluid collection; and for rapid shifts of fluid in patients who have low serum albumin in such diseases as cirrhosis and nephrosis. There is no risk of transmitting hepatitis or HIV through albumin infusion, although anaphylaxis has been reported in 2% or fewer of the patients who receive albumin. The dextran molecule is a large polymer of glucose whose molecular weight averages 40,000 to 70,000 amu. Depending on the average weight of the dissolved polymer, solutions are characterized as D-40 or D-70. These molecules are filtered and excreted through the kidney, but while they are in the vascular bed, they exert the same type of oncotic influence as albumin. 500 ml of D-40 can cause an intravascular volume expansion of 1 liter within 2 hours. The half-life or dextran depends on its molecular weight; for particles less than 18,000 amu, the half-life is less than 15 minutes. For particles greater than 55,000 amu, that half-life is measured in days. Dangers associated with the use of dextran include renal failure, allergic reactions, and coagulation problems.
Blood Products	Whole blood, packed RBCs, plasma (FFP), Platelets, Cryoprecipitate, Specific coagulation factors	Volume expanders include the whole blood especially, and packed RBCs as well. Other products address specific coagulation disorders and are not truly volume expanders. The infusion of these products may lead to hemolytic and allergic reactions, and may transmit viral diseases such as hepatitis, cytomegalovirus, or HIV. One specific advantage for infusing whole blood or packed RBCs is that they replenish a hemoglobin deficit incurred by hemorrhage, thereby restoring oxygen delivery capability

AFTERLOAD REDUCTION AGENTS: VASODILATORS

Since the 1970s, vasodilators have been shown to be improving hemodynamics through afterload reduction in patients with heart failure, mitral or aortic valvular disease, or cardiogenic shock. Therapy for cardiogenic shock begins typically with optimization of preload. 50 ml fluid challenges with normal saline are used in succession, while monitoring the PCWP. When PCWP is below 18 mm Hg, additional fluid challenges are given until either the blood pressure stabilizes, or the PCWP rises above 18 mm Hg. When that occurs, and provided the MAP is not less than 50 mm Hg, vasodilator therapy is begun to decrease afterload. Refractory situations may call for inotropic agents, mechanical assist devices, or cardiac surgery.

Vasodilators may be classified according to their predominant site of action:

Arterial Vasodilators

Hydralazine induces a relaxation of arteriolar smooth muscle by a mechanism that is not yet clear. By its effect on arteriolar resistance, hydralazine increases cardiac output and stroke volume through reduction of afterload. The drug may be given orally, but the preferred method is intravenously provided the patient is in an intensive care unit. The side effects are headache, nausea, vomiting, cardiac and GI complaints. Administration of Hydralazine over a period of at least several months may induce a collagen-vascular syndrome suggestive of systemic lupus erythematosus; the syndrome usually subsides after the drug is withdrawn, but may persist for long periods.

Minoxidil is another vasodilator used for decreasing afterload by relaxation of systemic arteriolar smooth muscle. The preparation is only available in p.o. form. A side note is that chronic use of minoxidil was noted to slow or reverse male pattern baldness, and a topical preparation was developed: Rogaine.

Venous Vasodilators

Nitrates have been used extensively for more than a century for the treatment of anginal symptoms. Nitrates activate guanylate cyclase and thereby increase guanosine monophosphate (c-GMP) in vascular smooth muscle. Nitrates are believed to exert their smooth muscle relaxing effect by forming nitrous oxide (NO), which is thought to be related to the body's own vascular relaxing factor, endothelium-derived relaxing factor, or EDRF.

In a healthy patient, one without heart disease, the sublingual application of nitroglycerin decreases cardiac output. The arterial dilation of the face and neck, which may accompany the use of this drug, produces a characteristic flushing and headache.

However, in a patient suffering from angina, the relief of coronary insufficiency by nitroglycerine may result from a reduction in both preload and afterload and a resultant decrease in the myocardial oxygen requirement, and also from coronary dilation in the case of coronary spasm (Prinzmetal Angina). In acute cardiac failure, the reduction of preload and afterload increases cardiac output.

Nitroglycerin is far less effective in patients with chronic cardiac failure. In the critical care setting, nitrates are administered IV in the interests of quick administration and rapid discontinuation. The principle side effects are headache and cardiac insufficiency in the case of rapid withdrawal.

Arterial & Venous Vasodilators

Nitroprusside is an extremely powerful drug that, given intravenously via infusion, treats hypertensive emergencies and is also useful for the treatment of severe refractory heart failure. This drug reduces both preload and afterload, as it dilates both venous and arteriolar vessels. Its

effect begins very rapidly and disappears within minutes after the infusion is stopped. By titrating the intravenous drip, blood pressure may be maintained at normotensive levels. Administration of excessive amounts of the drug may lead to hypotension, and its prolonged use leads to an accumulation of cyanide, the drug's metabolite. Toxicity usually occurs two to three days following initiation of administration, so that substitution to other vasodilator drugs should be accomplished before that time.

Captopril is the first agent in a series of antihypertensive agents that work by inhibiting the renin-angiotensin system. Other agents in this category include enalapril and lisinopril.

Renin is an enzyme that is stored in the juxtaglomerular cells within the kidneys. When renin is released into the circulation, it transforms angiotensinogen to angiotensin I. Then, angiotensin I is transformed into angiotensin II by the action of angiotensin converting enzyme (ACE), which is located in the membranes of the endothelial cells that line the pulmonary vasculature. Angiotensin II is a potent vasopressor that increases afterload; it also stimulates release of aldosterone to promote sodium retention. When electrolytes are retained, so is fluid, and as a result, intravascular volume increases also.

In a patient with severe heart failure, captopril improves cardiac function by both a reduction in afterload and a reduction in preload. As such, these agents are useful for the treatment of heart failure that is refractory to diuretic and other conventional therapies. The drug is increasingly becoming a first-line drug for the treatment of CHF.

Captopril is an oral agent that is generally tolerated well. Side effects include an intractable cough, hypotension, and some blood disorders.

AFTERLOAD AUGMENTATION AGENTS: VASOPRESSORS

The goal of vasopressor and inotropic agents is to both ensure the perfusion of vital organs by enhancing cardiac output and ensuring a more appropriate distribution of blood flow. Like inotropes, the principle agents used as vasopressors are catecholamines, exerting their action via alpha-adrenergic receptors in the arteriolar smooth muscle. All have similar toxicities, namely, induction of tachyarrhythmias, myocardial ischemia and angina, and even possibly myocardial infarction and severe hypertension. All these catecholamines require the correction of any fluid deficits or pH abnormalities (particularly acidic pH) for proper function.

Epinephrine

This drug is an endogenously produced hormone whose primary source is the adrenal gland, and it appears to be a hormone that is important to the homeostasis of the body's hemodynamic equilibrium. It is potent for both alpha and beta receptors, but because of its very potent alpha effects it is a strong vasoconstrictor that causes a rise in both systolic and diastolic systemic pressures. Cardiac output is increased as a result of increases in both stroke volume and heart rate. Its use in shock, particularly that associated with myocardial disease, is somewhat limited because of its potential to cause ventricular arrhythmias. It is also commonly used for the treatment of anaphylaxis and status asthmaticus.

Norepinephrine

Norepinephrine (Levarterenol, Levophed) is also an endogenous catecholamine from the adrenal gland, but the more important role of this chemical is that of neurotransmitter for the sympathetic nervous system. As with epinephrin, Norepinephrine exerts stimulation strongly on alpha and less strongly on beta-receptors; however, its action is, in general, less potent than epinephrine. Intravenous administration of norepinephrine results in an increase in both systolic and diastolic systemic blood pressure, with a resultant increase in mean arterial pressure (MAP). Systemic vascular resistance is increased with the use of this drug, and in particular, the blood flow to the kidneys is reduced. Heart rate tends to stay normal because of vagal reflexes, and cardiac output is increased generally because of an increase in stroke volume alone. This drug has such vasoconstrictive properties that it should be only administered via a central line, lest tissue damage should occur at a peripheral administration site.

Beta Adrenergic Agonists

As discussed earlier adrenergic bronchodilators are the most widely used of all medications in respiratory therapy. The name *adrenergic* comes from their ability to act like adrenaline on the beta sites and cause smooth muscle relaxation.

At the effector site, the bronchial smooth muscle cell, the stimulation of the beta site results in the stimulation of adenyl cyclase, which in turn catalyzes the formation cyclic 3',5' adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). The presence of cAMP causes the smooth muscle to relax, leading to bronchodilation. cAMP is inactivated by the enzyme *phosphodiesterase* into AMP, losing the bronchodilatory effect. Stimulation of the bronchial smooth muscle beta site, whether by sympathetic system or by sympathomimetic drug, increases the level of 3'5' AMP, and results in dilation.

The bronchodilating action of the adrenergic drugs is primarily caused by stimulation of $beta_2$ receptors located on bronchial smooth muscle. In addition, some adrenergic bronchodilators can stimulate alpha and $beta_1$ receptors. The clinical effects of these stimulations include:

- **Alpha-receptor stimulation** causes vasoconstriction and a vasopressor effect; in the upper airway (nasal passages) this can provide decongestion.

- **$Beta_1$ receptor stimulation** causes increased myocardial conductivity, increased heart rate, and increased contractile force.

- **$Beta_2$ receptor stimulation** can cause:
  relaxation of bronchial smooth muscle
  inhibition of inflammatory mediator release
  stimulation of mucociliary clearance

The general indication for the use of adrenergic bronchodilators is relaxation of airway smooth muscle to reverse or improve airflow obstruction. They are used clinically to reverse bronchoconstriction seen with asthma, acute and chronic bronchitis, emphysema, bronchiectasis, cystic fibrosis, and other obstructive airway diseases.

The sympathomimetic bronchodilators are all either catecholamines or derivatives of catecholamines. Catecholamines, or sympathomimetic amines, mimic the actions of epinephrine fairly precisely, causing tachycardia, elevated blood pressure, smooth muscle relaxation of bronchioles and skeletal muscle blood vessels, glycogenolysis, skeletal muscle tremor, and central nervous system stimulation.

Complications

The effects of bronchodilators, including the side effects, occur as a result of the aerosolized medications being absorbed into the circulation. The most common complications experienced in relation using adrenergic bronchodilators include:

Side Effect	Cause
Increased heart rate	$beta_1$ stimulation
Arrhythmias, palpitation	$beta_1$ stimulation
Skeletal muscle tremor	$beta_2$ stimulation
Anxiety, nervousness insomnia, nausea	$beta_2$ stimulation
Decreased PaO_2 (occasional)	$beta_2$ vasodilation producing altered V/Q

While all patients using adrenergic bronchodilators will experience one or more of these side effects, some will be more sensitive to the adverse effects than others. Careful monitoring is essential when treating respiratory patients with adrenergic bronchodilators, and should include:

- assessment of pulse and respiratory rate before, during and after treatment
- auscultation of lungs before and after treatment
- observation for systemic symptoms of side effects such as tremor, sweating, or fatigue

Treatments should be suspended or terminated should serious side effects occur.

1-16. ANTITUSSIVE AGENTS

a. **Background**. Antitussives are agents that relieve or prevent coughing. These agents, in general, act on the central nervous system to depress the cough reflex center in the medulla of the brain. Antitussives are used to reduce respiratory irritation. Such reduction of respiratory irritation results in the patient's being able to rest better at night because he is not kept awake by his coughing.

b. **Antitussive Agents**.

(1) Codeine. Codeine is considered to be the most useful narcotic antitussive agent. Codeine aids in relieving the pain (that is, producing analgesia) associated with a hacking cough. The main side effects associated with codeine include drowsiness, nausea, vomiting, and constipation. When a preparation containing codeine is dispensed to a patient that patient should be told that the product may cause drowsiness, and that he should not drink alcohol while taking the medication. Codeine is a Note R drug alone and cannot be refilled. It is a Note Q item when it is found in combination products (for example: Robitussin A-C Syrup). The usual oral dosage of codeine alone is 15 milligrams (1/4 grain) every 4 to 6 hours as needed for cough. The dosage can be increased but should not exceed 120 milligrams in 24 hours because of its central nervous system (CNS) depressant effects.

(2) Benzonatate (Tessalon®). Benzonatate is a nonnarcotic antitussive that produces its effect through a CNS depressant effect similar to codeine. Furthermore, it produces a local anesthetic effect on the stretch receptors in the lower respiratory tract, which control coughing. Benzonatate is usually given in 100 milligram doses--three to six times daily. This drug has few side effects except that it will numb the mouth, tongue, and pharynx if the capsules are chewed (this is because of its topical anesthetic effect). Benzonatate is available in the form of 100 milligram capsules.

(3) Dextromethorphan, DM (Pertussin CS®). Dextromethorphan is another non-narcotic antitussive. It is found alone or in combination--usually with expectorants. The most common side effect associated with this drug is gastrointestinal (G.I.) upset. Dextromethorphan is a non-legend drug, which may be written as a prescription drug or as a hand-out item depending on the local policy of your hospital. The usual oral dosage of this drug is 10 to 30 milligrams, every four to eight hours. Do not exceed 120mg in 24 hours. There are many products on the market, which contain dextromethorphan in combination. Examples of such products include Robitussin-DM® and Baytussin-DM®.

1-17. EXPECTORANT AGENTS

a. **Background**. Expectorants are agents, which facilitate the removal of secretions of the bronchopulmonary mucous membrane. Most of the expectorants discussed below act reflexively by irritating the gastric mucosa. This, in turn, stimulates secretions in the respiratory tract. Expectorants are used to remove bronchial secretions which are purulent (containing pus), viscid (thick), or excessive. The loosened material is then moved toward the pharynx through ciliary motion and coughing.

b. **Expectorant Agents**.

(1) Guaifenesin (Robitussin®, Baytussin®). Guaifenesin is the most commonly used expectorant today. This nonlegend drug has the side effect of gastrointestinal (G.I.) upset. Guaifenesin may be found alone as a syrup (100 milligrams per 5 milliliters), tablet 600 mg (Humibid® L.A.), or in many combination products such as Robitussin-DM®.

(2) Saturated Solution of Potassium Iodide. Saturated Solution of Potassium Iodide (SSKI) is an expectorant administered as 300 milligrams (10 drops) in a glass of water or fruit juice every three or four times daily. SSKI has a very unpleasant taste. Overdoses of this product may lead to a condition known as iodism that produces an acne-type rash, fever, and rhinitis or runny nose. Patient compliance with this product may be low because of its unpleasant taste. Consequently, when the medication is dispensed you should tell the patient to place the required amount of SSKI in fruit juice in order to mask its taste. This drug is available in a saturated solution of 1 gram per milliliter in 30 milliliter containers.

(3) Elixir of Terpin Hydrate. Elixir of Terpin Hydrate (ETH) is an expectorant, which works directly on the bronchial secretory cells in the lower respiratory tract to facilitate the removal of bronchial secretions. It is usually given in doses, which range from 85 to 170 milligrams (1 or 2 teaspoonsful) 3 or 4 times daily. The side effects of this drug are related to its alcohol content (42 percent or 84 proof). If enough ETH is consumed it will produce significant CNS depression. Even with the high alcohol content, ETH is an Over the Counter (OTC) product. It is available as a syrup (85 milligrams per 5 milliliters) in 120 milliliter containers.

> **NOTE:** Terpin Hydrate is no longer approved for use as an expectorant; it is used mainly as a vehicle for cough mixtures.

1-18. ANTITUSSIVE-EXPECTORANT COMBINATION PRODUCTS

The antitussive-expectorant combinations are used for a hyperactive nonproductive cough. The side effects of these drugs, or course, will be dependent on the antitussive-expectorant combination used. Some typical combination products used by the military are Robitussin-DM®, Robitussin® A-C Syrup, and Novahistine® Expectorant Liquid.

1-19. MUCOLYTICS

a. **Background.** Mucolytics are respiratory drugs that dissolve mucous in the respiratory tract. They are used by inhalation in an attempt to reduce the viscosity (thickness) of respiratory tract fluid. The loosened material can then be moved toward the pharynx more easily by ciliary motion and coughing. Like the expectorants, the mucolytics are used in the treatment of respiratory disorders in which the secretions are purulent (contain pus), viscid, or excessive. Consequently, the mucolytics represent an alternative to the oral use of expectorants.

b. **Mucolytic Agents**.

(1) Acetylcysteine (Mucomyst®). This is a mucolytic given by inhalation or nebulization. Nebulization is treatment by spray. Two to twenty milliliters of a 10 percent drug solution or 1 to 10 milliliters of a 20 percent Mucomyst® solution is nebulized into a face mask or mouth piece every two to six hours daily. Acetylcysteine has an unpleasant (like rotten eggs) smell. Side effects associated with this agent include nausea and vomiting and broncho-spasms with higher concentrations (with the 20 percent solution). This medication is only dispensed for inpatient use--usually to the respiratory therapy clinic or to the nursing station. The sterile solution should be covered, refrigerated, and used within 96 hours after the vial is opened. It is available in 10 percent and 20 percent solutions in containers of 4, 10, or 30 milliliters.

(2) Sodium Chloride Solution U.S.P. (0.9 percent sodium chloride solution). This agent is used alone or in combination with other mucolytic agents. Sodium chloride solution increases the respiratory fluid volume by osmosis, which tends to decrease the viscosity of the respiratory fluid. It is also administered by inhalation in a nebulized form as a dense mist in a tent or delivered through a face mask or mouth piece. The main side effect seen with sodium chloride solution occurs after prolonged inhalation. This will cause localized irritation of the bronchial mucosa. Sodium chloride solution for this purpose is for inpatient use by respiratory therapy personnel or by nursing personnel. Concentrated Sodium Chloride (23.4%) is used by respiratory therapy to induce sputum production (sputum induction procedure).

Mucokinetic Drugs

This class of drugs encompasses those agents that improve the overall effectiveness of the mucociliary system of the pulmonary tree. To get an understanding of this system let's do an anatomy and physiology review.

The mucous blanket of the normal lung consists of a highly viscous mucopolysaccharide 'gel' layer, which floats on top of a low-viscosity serous 'sol' layer. The interesting nature of the gel layer is that, although it is mostly comprised of water, it is relatively impervious to, and insoluble in water. In addition to the mucopolysaccharides, it has proteins, lipids, and carbohydrates. All these components have varying degrees of water-insolubility.

A balance between the goblet cells and the mucous glands in the airways produces the secretions in normal lungs. The goblet cells are primarily responsible for producing the gel layer, whereas the bronchial mucous glands produce most of the watery sol layer. The goblet cells are under local control, increasing their production mainly in response to local irritation from, for example, noxious gasses (such as cigarette smoke) or infective agents.

The mucous glands can respond locally, but they are mainly under central control through vagal nerve stimulation. Therefore, drugs that act locally, through topical cholinergic stimulation, or systemically, though agents that evoke a vagal response can affect the bronchial glands. Oral expectorants such as glyceryl guaiacolate or the iodides (found in common over-the-counter expectorants) act by evoking a vagal response by irritating the lining of the stomach.

Within the sol layer, tiny fibers called cilia beat at a rate of approximately 60 times per second. There are nearly 6000 cilia on each epithelial cell lining the airways, each approximately 4-6 microns long. The cilia beat together in a pattern that looks much the same as when a breeze creates waves in a field of grain. Chemical and physical agents, being increased by adrenergic drugs and methylxanthines, also affect ciliary activity. In contrast, ciliary activity is decreased by dehydration, cigarette smoke, ozone, alcohol, and anticholinergics such as atropine. Ipratropium Bromide (Atrovent) does not appear to affect mucociliary beat frequency (MCBF)

Therefore, normal secretion clearance depends on correct composition of the sol and gel layers, as well as optimum functioning of the ciliary system. Mucokinetic therapy aims to maintain or improve functioning of the mucociliary mechanism, thereby promoting effecting secretion mobilization and clearance.

Mucokinetic drugs fall into one of five categories: diluting or hydrating agents, wetting agents, mucolytics, proteolytics, and ciliary stimulants.

One of the major clearing and defense mechanisms of the airway- conducting zone of the lung is referred to as the *mucociliary system*. Mucokinetics is primarily concerned with the movement of mucus in the respiratory tract, and the overall effectiveness of the mucociliary system.

The effectiveness of the system depends largely on the interactions between the cilia and the mucus *blanket*, whose composition represents a delicate balance between the secretions of the goblet cells and bronchial glands. Failure of this system results in mechanical obstruction of the airway with thickened,

adhesive secretions. A significant slowing of mucus transport is associated with the abnormal mucociliary function seen in bronchitis, asthma, and cystic fibrosis. Mucokinetic therapy is designed to maintain or improve functioning of the mucociliary mechanism, thereby promoting clearance of respiratory tract secretions and reducing the potential for infection.

Mucokinetic/mucolytic agents achieve their effect through a variety of ways, including:

- acting directly upon the chemical constituents of mucus to decrease mucus viscosity or tenacity
- diluting the mucus resulting in disadherence from the airway
- making the ciliary action more effective by replenishing or increasing the watery sol layer of mucus
- directly stimulating the cilia
- stimulating the bronchial glands to produce secretions that are less viscous
- a combination of several of these actions

DILUTING or HYDRATING AGENTS

Of all the agents used to modify the character of pulmonary secretions, none is more important than water. Water can be aerosolized or vaporized, but THERE IS NO SUBSTITUTE FOR ADEQUATE SYSTEMIC HYDRATION. Any patient for whom secretions present potential problems should be assessed for their systemic hydration. Two good rules of thumb for normal adults are approximately 100 cc of water per hour, or approximately 1.4-1.6 cc/kg/hr. Water is one of the few agents we can use that has no side effects unless taken in extremely large quantities. Wherever there are no fluid restrictions, systemic water should be used first, and generously for patients having difficulty mobilizing bronchial secretions.

Water is one of the most important and safest agents used to modify the character of respiratory tract secretions. Consumption of adequate amounts of water is crucial for optimal functioning of the respiratory system, and is even more important for a patient who has difficulty mobilizing bronchial secretions. Water can also be vaporized or aerosolized for delivery to patients whose upper airway has been bypassed by intubation. However, caution should be taken to avoid either over- or under-hydration if normal mucus is to be achieved. This is especially true for patients on fluid restriction or with congestive heart failure.

Aerosolized water is at best only marginally effective for enhancing mucociliary clearance. Remember that pulmonary secretions are largely made of water, but are relatively water-insoluble. Water applied systemically allows secretions to be made more thinly in the first place; however, topical water does little more than coat the secretions. The next time you have a really good, raging chest cold with lots of thick, nasty junk to be coughed out, try a little experiment. Get a clear glass and fill it with water. Get a spoon and then cough up a nice sizable bit of gook from your lungs. Spit the creature into the water and stir. What you should notice is that the little

critter does not dissolve, it merely swims around. That is because the secretions aren't water soluble, and are not thinned to any great degree by adding topical water.

Water may be aerosolized in various forms. Sterile water is sometimes used, but is a bit irritating to the airways because of its hypotonism. Normal saline (0.9% NaCl) is also frequently used, and is less irritating; however, as the aerosol is inhaled the water droplets may evaporate to a certain extent and as this occurs, the actual salinity of the particles will increase, because the water decreases but the salt stays. For this reason, half-normal saline (0.45% NaCl) is sometimes used. Hypertonic saline (1% to 15% NaCl) is used for sputum inductions.

Saline (NaCl) is commonly nebulized for diluting the mucus and enhancing clearance, and small amounts (1-3 cc) of normal saline (0.9% NaCl) are used to dilute other medications for aerosolization. Like water, saline is absorbed into the sol layer to disadhere mucus from the airway. Many clinicians prefer to use half-normal saline (0.45% NaCl) for mucosal hydration, especially with ultrasonic nebulization, because the evaporation of water from droplets of this solution results in a solute concentration like that of normal saline.

Hypertonic saline solutions (1-15% NaCl) are the agents of choice for sputum inductions, because its elevated osmolarity can result in increased movement of fluid into the bronchorrhea. These solutions are obviously contraindicated for sodium-restricted patients.

The increased salinity is thought to possibly promote bronchorrhea through increasing the osmolarity of the mucous blanket. Also, the hypertonism is irritating to the airway, and may promote coughing. Care should be taken in regard to frequent or repeated use of hypertonic saline in sodium-restricted patients. In practice, the use of hypertonic saline is also only marginally effective at best in creating a productive cough with expectoration.

Propylene Glycol, which is both a solvent and hygroscopic agent, is used to stabilize aerosol droplets from bronchodilators and to inhibit the potential for bacterial growth. It is safe in low concentrations, creating a soothing effect on the respiratory mucosa. In concentrations greater than 5%, it is often used to induce sputum.

Oral Expectorants

This class of drugs is mimokinetic through promoting dilution of mucus indirectly. Examples of this class include potassium iodide; commonly referred to as SSKI (saturated solution of potassium iodide), and currently the most frequently used expectorant, guaifenesin (glyceryl guaiacolate). In addition, this class of drugs includes some common home remedies such as spices, garlic, or onion. All these agents work by irritating the lining of the stomach, thereby stimulating the afferent fibers of the vagus nerve. Impulses sent to the CNS elicit an efferent vagal response, stimulating bronchial glands to increase secretion.

WETTING AGENTS

These are chemical substances designed to lower the surface tension of respiratory tract fluids.

Some agents represent true detergents, interacting with the mucus to produce emulsification of the hydrophobic bonds between water and the mucopolysaccharide molecules. In concept, these agents should disperse the mucus into smaller particles, thereby improving water penetration and facilitating transport and removal. This, however, has not been shown. Currently, there are no true detergents on the market; two detergents have been offered on the market in the past, Alevaire and Tergemist. Both these preparations were withdrawn from the market due to unproved efficacy.

Ethyl Alcohol (ETOH) is a wetting agent that has been used to destabilize the alveolar plasma exudates occurring in cardiogenic pulmonary edema. It acts to destabilize the *froth* observed in the alveoli and bronchioles in cardiogenic pulmonary edema. Normally, 5-15 mL of 30-50% ETOH is vaporized by positive pressure. Temporary irritation of the airway mucosa is the only side effect experienced in this treatment.

Ethyl alcohol acts by destabilizing the alveolar plasma exudates in acute cardiogenic pulmonary edema. The characteristic thin, watery exudate that fills the alveoli and bronchioles in cardiogenic pulmonary edema contains a significant amount of surfactant from the pulmonary alveoli. Because of this, it tends to foam, and does not easily mobilize upward through the tracheobronchial tree. The stable bubbles that are formed can obstruct ventilation, decreasing gas exchange.

Introduction of ethyl alcohol probably destabilizes these bubbles by changing the properties of the lecithin component of the surfactant, and increases surface tension, thereby allowing the bubbles to burst. Normally, 5 - 15 cc of 30% - 50% ethyl alcohol is nebulized. The only side effect is airway irritation. We used to have a small bottle of Smirnoff's vodka in the equipment we took on aeromedical transport years ago. The vodka has the appropriate alcohol content and can be used without dilution.

MUCOLYTICS

The high viscosity of sputum in certain respiratory diseases is largely due to the mucoproteins found in pulmonary secretions. One of the early substances studied was L-cysteine, a naturally occurring amino acid. The results of L-cysteine were very favorable in terms of its ability to break the proteinaceous bonds within sputum; however, it had substantial irritating properties. These irritating properties were minimized by chemically altering the acid into an acetyl form. The resultant N-acetylcysteine is the generic name of Mucomyst. Within the protein molecules of sputum, there are two chains of proteins held together with a disulfide bond; that is, both chains have a sulfur atom such that the two sulfur atoms bind together. Mucomyst breaks up the chain by replacing the sulfurs with weaker bonds between sulfhydryl molecules.

Mucomyst is available in a 10% and a 20% solution; the 10% is just as effective as the 20% solution, while the latter exhibits stronger tendencies toward irritation and bronchospasm. Therefore, it is common to nebulize 3-5 cc of the 10% solution, or dilute the 20% solution to

make a 10% solution. It is most common (and very advisable) to co-administer a beta agonist bronchodilator with Mucomyst to minimize bronchospastic side effects, although the Mucomyst package insert specifically states that this is unnecessary.

The only other significant recognized side effect is patient complaint of the unpleasant rotten-egg odor characteristic of the drug. One unpublished study suggested that Mucomyst might cause eye tissue breakdown. In this study, Mucomyst was nebulized, with the mist directed at a cow eye sitting in a Petri dish. After several hours, there was visible tissue breakdown on the eye. For this reason, it is advisable that Mucomyst should not be nebulized into infant oxygen hoods or isolettes.

Mucomyst is fairly well-recognized and commonly used for its potential for thinning sputum; however, some studies suggest that while it has been shown effective with in vitro testing, it has not shown any benefit in patients and is of insignificant clinical value. A second drug has been widely used to thin secretions, but is not commonly used anymore because of the popularity of Mucomyst. I personally feel that nebulization of Sodium Bicarbonate should be considered when choosing a mucolytic agent. The large mucoid molecular chains in sputum tend to break as the pH of their environment rises, and local bronchial alkalinity can reach a pH of 8.3 without untoward irritation or tissue damage. Nebulizing 3-5 cc of pediatric strength (4.2%).

Sodium Bicarbonate has been fairly useful in thinning secretions, and has not shown the airway irritation and bronchospastic characteristics common to Mucomyst. Patients tolerate the nebulization well because of its lack of bad taste, bad odor, or airway irritation. Patients requiring long-term treatment of thick secretions can prepare a solution of sodium bicarbonate at home by mixing a teaspoon of baking soda in a cup of sterile water.

Mucolytics

True mucolytics are drugs intended to control mucus and bronchial secretions. The two primary agent approved for administration as aerosols to treat abnormal pulmonary secretions are *acetylcysteine* and *dornase alfa*. Both act to disrupt the disulfide bond in mucus and break down DNA materials in airway secretions.

Acetylcysteine (Mucomyst) is an aerosolized medication indicated for treatment of the thick, purulent, viscous mucus secretions that can occur in COPD, especially chronic bronchitis, tuberculosis, cystic fibrosis, and acute tracheobronchitis. It is also administered orally as an antidote to reduce hepatic injury with overdoses of acetaminophen, and is designated as an *orphan drug*.

Aerosol doses of Mucomyst are available in either 10 or 20% solutions, and normal dosage with 20% solution is 3-5 ml TID or QID, and 6-10 ml TID or QID with the 10% solution. The most serious potential side effect is bronchospasm, especially with hyperreactive airways seen in asthmatics, so using bronchodilators mixed with acetylcysteine or administer previously by MDI or nebulizer is recommended. Other potential side effects include stomatitis, nausea, and rhinorrhea.

Dornase Alfa (Pulmozyme) is an *orphan drug* that was produced by recombinant DNA techniques, and is indicated for the treatment and management of the viscid respiratory secretions seen in patients with

cystic fibrosis (CF). In CF patients, Pulmozyme helps reduce the frequency of respiratory infections requiring parenteral antibiotics, and generally improves their overall pulmonary function.

Pulmozyme available as a single use ampule, with 2.5 mg drug in 2.5 ml of clear solution. Recommended dosage is 2.5 mg daily, delivered by nebulizers specifically approved for this use. Few side effects have been observed, including voice alteration, pharyngitis, laryngitis, rash, chest pain, and conjunctivitis.

Sodium bicarbonate ($NaHCO_3$) helps break up large mucoid molecular chains because of its alkalinity. Some patients benefit from occasional aerosolized 2% sodium bicarbonate, which is a readily available solution for home use by simply putting a teaspoonful of the soda in a cup of sterile water. However, with the availability of more potent mucolytics like acetylcysteine, it is rarely used.

In addition to these most commonly used mucus-controlling agents, other muco-active agents that have been or are now being explored include:

Beta-adrenergic agonists can aid in mucokinesis, possibly by increasing the beat frequency of cilia. Active transport of the chloride ion into the airway lumen, augmented with a resulting water flux, may produce a less viscous, thinner mucus and enhance ciliary movement.

S-Carboxy methylcysteine (Mycodone), an oral mucokinetic investigated in Britain, decreases sputum viscosity in vitro, but is not considered effective for mucolysis when administered orally. It is chemically related to garlic, a common *home remedy* mucokinetic, and other home remedies for mucokinesis including chicken soup, horseradish, pepper, and mustard.

Glyceryl guaiacolate, which is generally considered an expectorant, also has shown potential for improving mucociliary clearance in chronic bronchitis.

Potassium iodide, which is also generally considered an expectorant, has also shown potential for decreasing mucus elasticity, but has also shown a potential for harmful effects on cilia.

Sodium 2-mercaptoethane sulfonate, a compound containing a sulfhydryl group that is being explored in Britain, acts similar to acetylcysteine in reducing mucous viscosity.

Several **enzymes** have been shown to reduce the viscosity of mucus by breaking down the mucoprotein and deoxyribonucleic acid, which contribute to mucus viscosity. One example is the previously discussed *dornase alfa*. These continue to be explored as mucus controlling agents, but to date have generally proven to be too costly, irritating, and toxic.

Ambroxol is another orally administered drug that has been investigated as a mucokinetic agent. It stimulates ciliary beat frequency, but its ability to increase mucociliary clearance by result from stimulation of pulmonary surfactant or bronchial secretion.

Given the nature of inflammation in disease states of mucus hypersecretion, the use of mucolytic agents alone is not considered an adequate program of mucus control. Other therapeutic options that are considered necessary for controlling mucus hypersecretion include:

- Remove causative factors where possible, including cessation of smoking, and avoidance of pollution and allergens.

- Optimize tracheobronchial clearance by: using a bronchodilator, taking bronchial hygiene measures (like hydration, coughing, deep breathing, postural drainage), using mucolytics and expectorants.

- Reduce inflammation by treating infection with antibiotics, and using corticosteroids.

PROTEOLYTICS

Members of this group achieve mucus thinning by lysing the protein material found in purulent sputum. High levels of protein, particularly cellular DNA, make purulent sputum viscous and difficult to expectorate. Early attempts with proteolytic enzymes included trypsin from Ox Pancrease, and bovine pancreatic dornase (trade name Dornavac). These enzymes used the digestive capabilities found in pancreatic enzymes, but were found to be largely ineffective for secretion thinning, and caustic to the airway. Both these drugs are no longer marketed.

However, recent developments in recombinant human deoxyribonuclease (rh DNAse) have shown that this enzyme can be significantly successful for cystic fibrosis patients. This enzyme is now cloned in vitro, and thereby produced in quantities sufficient for distribution on the market.

In studies, the cloned rh DNAse greatly reduced the viscosity of the purulent sputum in C.F. patients, quickly turning the viscous gel sputum into a free-flowing liquid. Further studies in C.F. patients demonstrated objective improvements in lung function and dyspnea. The standard dose is 1 unit dose ampule nebulized once a day. The drug must be administered via a separate nebulizer (rather than simply reusing a nebulizer the patient uses for a bronchodilator) because of the possibility of a precipitate forming. At this time, C.F. is the only indication for the use of this drug, but it seems that it may prove effective for thinning mucus with thick, purulent secretions.

CILIARY STIMULANTS

Recall at the beginning of this discussion that it was alluded to that adrenergic drugs may stimulate a faster MCBF. This has been shown to be true in some studies, while other studies suggest that the patient most likely to demonstrate an increase in MCBF is the patient for whom the bronchodilator is indicated anyway: one with an obstructive process. Until there is more clear data regarding the effect of a beta agonist on secretion clearance, its use should be considered possibly helpful as an adjunct to enhancing secretion mobilization and elimination. As such, it may be given a trial to determine if secretion clearance is enhanced.

The goal of all mucokinetic drugs is to enhance secretion mobilization, and all should be re-evaluated after therapy has been administered for about 24-48 hours to determine if the goals of therapy (i.e., increased secretion mobilization and elimination) have been achieved. With all these drugs, but particularly with the use of a beta agonist for secretion mobilization, there is

some question regarding the potential effectiveness of the drug, and a careful assessment of outcome should be done after a day to determine if there is merit to continuing the therapy.

1-20. BRONCHODILATOR AGENTS

a. **Background**. The bronchodilators are agents that cause expansion of the air passages of the lungs. This allows the patient to breathe more easily and are of value in overcoming acute bronchospasms. They are employed as adjuncts in prophylactic and symptomatic treatment of the individual complications of obstructive pulmonary diseases such as asthma, bronchitis, and emphysema. Most of these agents have been discussed in other lessons of the pharmacology series.

b. **Bronchodilator Agents (Sympathomimetics).** Sympathomimetic bronchodilators act by relaxing contractions of the smooth muscle of the bronchioles. These agents are often referred to as "Beta agonists".

(1) **Albuterol** (Proventil®, Ventolin®). Albuterol is a short acting beta-agonist or bronchodilator. It is used in the relief and prevention of bronchospasm and in the prevention of exercise-induced bronchospasm. Albuterol is available as an inhalation aerosol, inhalation solution, inhalation capsules, regular and sustained release tablets, and syrup. Other than the sustained release products, it is prescribed every 4 to 6 hours. Albuterol is often used as "rescue therapy" due to its quick onset of action.

(2) **Salmeterol** (Serevent®). Salmeterol is indicated for the same conditions as albuterol, however its distinct advantage is that it is administered twice daily. It is available as an inhalation aerosol. Salmeterol CANNOT be used for "rescue therapy"; a short acting beta agonist such as albuterol must be used.

(3) **Epinephrine** (Adrenalin®). Epinephrine is used as a bronchodilator because of its beta effects on the bronchi and a pharmacologic antagonist of histamine. Epinephrine is employed for the treatment of acute attacks of bronchospasms associated with emphysema, bronchitis, or anaphylaxis. The inhalation route is not the preferred route of administration, however, it may be used. Epinephrine is usually administered subcutaneously when used and is fairly effective at reducing bronchospasms.

(4) **Metaproterenol** (Alupent®, Metaprel®). This is an adrenergic agent that has primary beta2 activity. That is, its main effect is to relax the bronchioles. It has the same indications as epinephrine. It may be used for the prevention of bronchospasms associated with chronic obstructive pulmonary diseases. Inhalation of metaproterenol may be used in the treatment of mild bronchospasm

attacks. Metaproterenol is somewhat more effective than inhaled isoproterenol. Metaproterenol's duration of action is substantially longer than that of isoproterenol.

(5) **Ephedrine** Ephedrine has actions of those similar to those of epinephrine. Ephedrine is not frequently used because of the availability of other more suitable agents. Ephedrine is administered orally. It is used to treat mild bronchospasm attacks and prophylactically to prevent bronchospasm attacks. Ephedrine is not as suitable as epineprhine for the treatment of severe attacks of bronchial asthma because its bronchodilator action is weaker.

(6) **Isoproterenol** (Isuprel®). Isoproterenol is an adrenergic agent used to treat asthma, bronchitis, and emphysema. Like metaproterenol, isoproterenol is administered by inhalation for the treatment of mild bronchospasms. Isoproterenol may be administered intravenously with great caution to treat status asthmaticus.

(7) Other sympathomimetic bronchodilators include terbutaline (Brethine®), pirbuterol (Maxair®), and bitolterol mesylate (Tornalate®).

c. **Bronchodilator Agents (Xanthine derivatives).** The methylxanthines (theophylline and derivatives) directly relax the smooth muscle of the bronchi and pulmonary blood vessels. They may also reduce the fatigability and thereby improve contractility in patients with chronic obstructive airway disease. Xanthine derivatives are often used in the treatment of apnea and bradycardia of prematurity in infants.

(1) Aminophylline. Aminophylline is a xanthine derivative containing 80% theophylline. It is prescribed as a bronchodilator to treat asthma. It will also relieve bronchospasms associated with emphysema and bronchitis. Aminophylline may be administered orally or rectally to prevent severe attacks of bronchial asthma but is generally administered intravenously (I.V.) to relieve acute bronchospasms or status asthmaticus resistant to adrenergic drugs.

(2) Theophylline (Theolair®, Slo-Phyllin®, Theodur®). Theophylline is often prescribed as the xanthine of choice for oral administration (tablets, capsules, elixir, syrup, or solution). One must take care when dispensing theophylline products. Each different brand varies in the actual amount of theophylline contained in the product and in the duration of action. Theophylline is a drug with a very narrow therapeutic index (the treatment dose is very close to the toxic dose). For this reason, patients should have their theophylline blood levels monitored on a routine basis.

Beta Adrenergic Bronchodilators

These drugs, as the name implies, all act via adrenaline receptors of the sympathetic nervous system. Remember that these receptors in the lungs are the Beta2 sympathetic receptors, and because of this, this class of drugs is also commonly known as the Beta Adrenergics or the Sympathomimetics (stimulating the action of the sympathetic system).

There are three divisions of the adrenergic group, as characterized by their specific chemical characteristics. In general, these names are not that significant for the bedside practitioner; however, it may be noted that there are some differences in certain clinical aspects of the divisions of these drugs:

1. Catecholamines: a group of compounds having a sympathomimetic action, the aromatic portion of whose molecule is catechol and the diathetic portion. Examples of catecholamines are dopamine, epinephrine, isoproterenol, norepinephrine, and isoetharine

2. Resorcinols: modification of the catechol nucleus produces a resorcinol, which is not metabolized by the enzyme COMT, giving them a longer duration of action, while the size of the amine side chain confers $beta_2$ specificity for metaproterenol and terbutaline.

3. Saligenins: a different modification of the catechol nucleus results in the saligenin *albuterol*. *Pirbuterol* is structural similar to albuterol, is less potent on a weight basis, but is similar in both efficacy and toxicity to metaproterenol.

This series of drugs--the adrenergics--are recognized to cause bronchodilation through active stimulation of the sympathetic innervation of bronchial smooth muscle. In addition, there is some evidence that these drugs also inhibit the release of histamine from mast cells. Finally, there seems to be some evidence that these drugs enhance the mucociliary clearance through increasing mucociliary beat frequency (MCBF) and thereby may produce some enhancement to secretion mobilization. Causing an increase in MCBF is controversial, however.

Indications, then, would include:

1. Acute or chronic pulmonary obstructive disease
    1. As evidenced by diagnosis
        1. Asthma
        2. Chronic Bronchitis
        3. Emphysema
        4. Bronchiectasis
        5. Cystic Fibrosis
    2. as evidenced by symptoms
        1. severe, harsh cough that is associated with allergic triggers

        2. wheezing on auscultation of breath sounds
    3. as evidenced by pulmonary function testing
        1. obstructive pattern to flow-volume loop with response to bronchodilator demonstrated
2. inhalational injury
    1. mechanical (as in a foreign body aspiration)
    2. chemical (as in aspiration of stomach acid)
    3. thermal (an inhalational burn)
3. retained secretions
    1. as evidenced by breath sound or chest x-ray abnormality
        1. because of the relative controversy regarding this indication, treatment with a beta agonist may be initiated to treat retained secretions, but sputum production should be closely monitored and assessed for efficacy. If there is no significant increase in secretion mobilization after 1-2 days of therapy, the drug can be reasonably discontinued.
4. prevention of exercise-induced bronchospasms.

    1. beta agonists have been shown most effective to prevent bronchospasm associated with physical activity. The drug should be taken typically 10-20 minutes prior to exercise.

Contraindications are relative, because the potential of an undesired effect must be weighed against the benefit of administration. Contraindications include:

1. Hypersensitivity to the drug
    1. This is often a result, not of hypersensitivity to the drug itself, but to preservatives commonly added to the medication. Some manufacturers do not use preservatives, and others use different compounds for preservatives. A patient who demonstrates a reaction to one form of a beta agonist may not demonstrate the same reaction to another, or to a different manufacturer of the same medication. Check the package insert or Physician's Desk Reference (PDR) for information regarding the specific additives used for a given medication.
2. Cardiac Arrhythmias associated with tachycardia
    1. Most beta agonists have some undesired cardiac effect, generally an increased heart rate, in addition to the desired pulmonary effects. Certain patients will suffer ill effects should their heart rate be driven upward as a result of administration of beta agonists. The cardiac effect is certainly dose-related, with the cardiac effects increasing the more drug is given.
    2. Strategies to decrease these unwanted effects with patients for whom tachycardia presents severe problems include:
        1. decreasing the dose of the drug
        2. decreasing the frequency
        3. changing to a different, more specific beta agonist
        4. discontinuing use of the beta agonist while the patient demonstrates cardiac side effects, and relying on other non-adrenergic bronchodilators.

Precautions for adrenergics include:

1. Excessive use of inhalants can lead to the development of paradoxical bronchospasm and an increase in work of breathing. Tolerance and tachyphylaxis can also occur.
2. Concomitant use with adrenergic beta-blockers antagonizes the effects of bronchodilators. Such concomitant use may lead to systemic vasoconstriction and reflex bradycardia.
3. Use cautiously in patients with known cardiovascular disease, including coronary insufficiency, cardiac arrhythmias, history of stroke and hypertension (because of possible toxic symptoms)
4. Any inhalant has the potential for causing bronchoconstriction
5. These drugs may cross the placental barrier: use cautiously in pregnancy
6. If bronchial irritation, nervousness, or restlessness occur, reduce dosage
7. Use cautiously in children under 1 year old, as the safety and efficacy of these drugs has not yet been established in this population
8. co-administered sympathomimetics have additive effects
9. if a sympathomimetic crisis should occur, the effects can be counteracted by injection of a beta adrenergic blocker
10. catecholamines are much less effective or ineffective when taken orally, as the gut has increased levels of Monoamine Oxidase (MAO) which inactivates adrenergics
11. catecholamines must also be stored out of direct light--many are supplied in brown bottles. Exposure to light metabolizes the adrenergics into inert adrenochromes. If there is a pink or reddish tinge to the medication, it has been inactivated and should be discarded.

Adverse Reactions:

1. CNS effects: anxiety, fear/apprehension, tremors, irritability, lightheadedness, headache, flushing, pallor, sweating, insomnia
2. Cardiovascular effects: hypertension, arrhythmias, palpitations, and reflex tachycardia from peripheral vasoconstriction. Overdose may also cause angina and hypotension.
3. Pulmonary effects: coughing, bronchospasm, pulmonary edema (IV use)
4. GI effects: nausea, vomiting, heartburn

The first sympathomimetic used was epinephrine itself, in the 1950s. Epinephrine, a catecholamine, is an excellent drug in that it has a very fast onset of action and is a very powerful bronchodilator; however, it is not such a desirable drug because of its lack of beta2-specificity. Epinephrine has just as strong effects on the heart and peripheral vasculature, and has the potential for causing some very significant side effects. Since then, pharmaceutical companies have engineered drugs with more and more beta2-specificity. Each generation of these drugs has demonstrated more beta2-specificity, and as this has happened, the frequency and severity of adverse side effects have significantly decreased.

Also, the onset and duration of action has lengthened with each successive drug generation. Epinephrine, for instance, had an onset of action at about 3 minutes, a peak effect at about 5 minutes, and duration of less than 2 hours. Salmeterol, a saligenin, is the most recent adrenergic drug on the market. It has an onset of action at about 30 minutes, and duration of action of 12 hours. In general, the catecholamines were the earlier forms of adrenergics, and also had the shorter onset and duration of action relative to the saliginens or resorcinols.

The following is an itemization of the most common beta-adrenergic drugs, listed in a historical sense as they have entered the market. Compare the various onset and durations of action, and identify which are catecholamines. Also, "strength" values compare the potency of each drug relative to Metaproterenol. The higher the number, the more potent.

1. Epinephrine
    1. Trade Names:
        1. MDIs are over the counter drugs including AsthmaHaler, Bronitin Mist, Bronkaid Mist, Primatene Mist
        2. Nebulizer solution exists from many companies, and is simply a 1:100 concentration of injectable epinephrine
    2. Structure: catecholamine
    3. Actions
        1. Onset: 3-5 minutes
        2. Peak: 5 to 20 minutes
        3. Duration: less than 60 minutes
        4. strength: not rated
    4. Dosage and Dosage form
        1. nebulizer 0.25 - 0.50 cc of a 1:1000 solution diluted in 3.0 cc normal saline
        2. over-the-counter inhalers are available in 0.16, 0.2, and 0.27 mg/inhalation. 1-2 puffs of the inhaler are taken each dose. It should be noted that these OTC inhalers have extremely small levels of the drug in them, because of the potential for adverse side effects, and are much less effective when compared to prescription Metered Dose Inhalers (MDIs)
        3. doses may be repeated up to 6 times daily
2. Isoproterenol
    1. Trade Names: Isuprel, Vapo-Iso, Medihaler-Iso (MDI)
    2. Structure: Catecholamine
    3. Actions
        1. Onset: within 2 minutes
        2. Peak: 3-5 minutes
        3. Duration: 1.5 to 2 hours
        4. strength: 10
    4. Dosage and Dosage form: 0.25 to 0.5 cc of 1:200 solutions diluted with 2.5 to 3.0 cc NS. Inhalers 1 to 2 inhalations per dose, dosages may be repeated every 3-4 hours.
3. Isoetharine Hydrochloride
    1. Trade Names: Bronkosol, Bronkometer (MDI)

2. Structure: Catecholamine
3. Actions
    1. Onset: 5 minutes
    2. Peak: 15 - 60 minutes
    3. Duration: 1.5 to 3 hours
    4. strength: 1.7
4. Dosage and Dosage form: 0.25 to 0.5 cc of a 1:100 solution, MDI 1-2 inhalations per dose. Dosages may be repeated every 3 to 4 hours.

4. Metaproterenol Sulfate
    1. Trade Names: Alupent, Metaprel
    2. Structure: Resorcinol
    3. Actions
        1. Onset: 1-5 minutes
        2. Peak: 5-30 minutes
        3. Duration: 3-4 hours
        4. strength: 1
    4. Dosage and Dosage form: 0.2-0.3 cc of a 5% solution nebulized; MDI 2-3 inhalations per dose. Doses may be repeated every 3-4 hours.
5. Terbutaline Sulfate
    1. Trade Names: Brethaire, Brethine, Bricanyl
    2. Structure: Resorcinol
    3. Actions
        1. Onset: 5-15 minutes
        2. Peak: 30-60 minutes
        3. Duration: 2-6 hours
        4. strength: 2.5
    4. Dosage and Dosage form: 1-2 mg of a 0.1% solution diluted with NS. This solution is the injectable form, and although frequently given via nebulizer, the FDA does not approve it for inhalational administration. MDI 2 inhalations per dose. Dose may be repeated every 4 to 6 hours.
6. Albuterol Sulfate
    1. Trade Names: Proventil, Ventolin, (Salbutamol in Europe)
    2. Structure: Saligenin
    3. Actions
        1. Onset: 2-10 minutes
        2. Peak: 30-60 minutes
        3. Duration: up to 6 hours
        4. strength: 5
    4. Dosage and Dosage form2.5 mg diluted in 3 cc NS. MDI 2 inhalations. Dosages may be repeated every 4-6 hours.
    5. note: this drug is the most commonly prescribed beta agonist over the last several years. It is also is available as a pill and an elixir for PO administration.
7. Pirbuterol Acetate
    1. Trade Names: Maxair
    2. Structure: Saligenin
    3. Actions

1. Onset: within 5 minutes
2. Peak: 30 - 60 minutes
3. Duration: up to 5 hours
4. strength: 3

4. Dosage and Dosage form: MDI only1-2 inhalations given every 4-6 hours
5. note: this MDI is unique in that it is breath-activated, so that coordination is easier, and individuals who are physically unable to squeeze to activate the cannister on other inhalers can use this inhaler successfully.

8. Bitolterol Mesylate
    1. Trade Names: Tornalate
    2. Structure: Saligenin
    3. Actions
        1. Onset: 3-4 minutes
        2. Peak: 60-90 minutes
        3. Duration: 5-8 hours
        4. Dosage and Dosage form: MDI only, 2 inhalations every 4-6 hours
        5. strength: 5
    4. Note: This inhaler is unique in that other inhalers utilize powdered drug that is loaded into a chamber and sprayed with gas pressure. This inhaler uses a liquid medication that is spritzed out using gas pressure.
9. Salmeterol
    1. Trade Names: Serevent
    2. Structure: Saligenin
    3. Actions
        1. Onset: 30-40 minutes
        2. Peak: 60 minutes
        3. Duration: 12 hours
        4. strength: not rated
    4. Dosage and Dosage form: MDI only, 2 puffs per dose repeated every 12 hours.
    5. **Note**: This MDI is a beta agonist that has such a long onset of action and duration of action that it is the first agonist used specifically as a preventative medication. In fact, when the drug first came out, people were not properly educated regarding the appropriate use of this drug, and it was often prescribed as a replacement for albuterol. When these patients went home, and experienced an exacerbation, they often times took their Serevent inhaler, with no immediate effect (remember the onset of action is 30-40 minutes). Being used to MDIs that produced a noticeable effect within only several minutes, these patients would take more puffs of their Serevent. A significant number of patients reported adverse side effects resulting from this improper use of their Serevent inhaler, and a significant number of deaths were attributed to it as well. Patients with Serevent inhalers MUST be educated regarding the proper use, and have a short-acting beta agonist prescribed at the same time. Instruction should include:
        1. use only as directed, and only at directed frequency
        2. if the patient suffers an exacerbation, DO NOT increase the frequency of the Serevent inhaler

3. Use the short acting (such as Albuterol) inhaler as "rescue" drug for acute exacerbations.

Alpha Adrenergic Bronchodilators

These drugs have been chemically engineered to emphasize the alpha1 effects of the sympathetic system. This effect causes vasoconstriction, and is useful in the treatment of airway obstruction that is caused by local edema and erythema. These drugs are NOT good bronchodilators because they do not have significant effects on bronchial smooth muscle.

What kinds of problems would these drugs be appropriate for? See if you can come up with two or three problems that would indicate the administration of these drugs via inhalational route.

The major drug used for alpha stimulation is Racemic Epinephrine. Epi is a chemical that actually has several different forms, or isomers of its chemical structure. Racemic Epinephrine is a drug that contains only two of those forms, and this is very Alpha specific.

- Racemic Epinephrine
    1. Trade Names: MicroNefrin, Vaponefrin
    2. Structure: Stereoisomer of epinephrine
    3. Actions
        1. Onset: 1-5 minutes
        2. Peak: 5-15 minutes
        3. Duration: 1-3 hours
    4. Dosage and Dosage form: Solution only, 0.25 to 0.5 ml of a 1.25% solution diluted with 3.0 cc NS. May be given as frequently as every 1-2 hours.
    5. **Note**: remember that this drug is really only useful for decreasing airway edema

Miscellaneous Respiratory Agents

(1) Cromolyn (Intal®). Cromolyn is a unique product that works by inhibiting the release of histamine and other spasm-causing compounds from mast cells located in the lungs and prevents bronchoconstriction. It is used mainly for the treatment or prevention of mild bronchospasms associated with asthma. It is available as an inhalation aerosol and nebulization solution.

(2) Leukotriene modifiers. The production of leukotrienes (immunologic proteins) and the binding of leukotriene receptors appears to be responsible for airway edema, smooth muscle constriction and altered inflammatory processes contributing to the signs and symptoms of asthma. For this reason, several new agents have been developed.

(a) Zafirlukast (Accolate®), montelukast (Singulair®). Both of these agents are leukotriene receptor antagonists which cause inhibition of bronchoconstriction. Zafirlukast is available as a tablet prescribed twice daily. Montelukast is prescribed as a once daily tablet.

(b) Ziluton (Zyflo®), Ziluton works a little differently in that it inhibits the formation of leukotrienes to prevent bronchoconstriction. Ziluton is administered four times daily.

Cough and Cold Medications

The number of medications available for dealing with the common cold and the coughs that accompany it is mind-boggling. Between the host of over-the-counter medications and those requiring a prescription, there is enough information to warrant a separate CEU. In this unit we will only discuss the most significant cough suppressants and expectorants. The medications that work centrally are designed to increase the cough threshold in the medullary cough center. Peripherally active medications inhibit the cough at the mucosa, usually by coating supraglottic receptors with a thick syrup. Expectorants are agents that facilitate removal of mucus from the lower respiratory tract, and their mechanisms include

- vagal gastric reflex stimulation
- absorption into respiratory glands to directly increase mucus production
- topical stimulation with inhaled volatile agents

Super Saturated Potassium Iodide (SSKI) is available under a variety of trade names, and has been used for quite a long time as an expectorant in asthma and chronic bronchitis. In sufficient orally administrated concentrations, it has a direct mucolytic effect and an indirect effect on mucus viscosity by stimulating submucosal glands to produce more serous secretions. Iodide also stimulates the gastropulmonary reflex, can stimulate ciliary activity, and has a cucolytic effect. In some individuals, iodides are associated with hypersensitivity reactions.

Five to ten drops (3-600 mg) in a glass of water given 34 times a day may be given, with the pediatric dosage being about half that amount. Patients can develop acne or rashes and long-term use may disrupt thyroid function. SSKI is contraindicated for patients with thyroid disease.

Guaifenesin (Glycerol Guaiacolate), available in a variety of trade name products, is thought to reduce the adhesiveness and surface tension of mucus secretions when taken orally. Dosage for children 6-12 years old is 2-400 mg every 4 hours with a maximum of 2,400 mg in 24 hours. Dosage for children 2-6 years old, half of this may be given, and for even younger children, half again (50-100 mg every 4 hours).

Iodinated Glycerol (Organidin) is available as a tablet, solution, or elixir. The adult dose of the 5% solution is 20 drops in a liquid QID. The 30 mg tablet dose is 2 tablets QID. The 1.2% elixir dose is 1 teaspoon QID. Pediatric dose is one half the adult dose.

Chicken soup, flavored with garlic and curry has been suggested as a tasty and effective stimulant via the gastric reflex. Garlic's major constituent is alliin, which has a structure similar to mucolytic drug S-carboxy methylcysteine. Other spices that could have similar potential include Tabasco sauce, horseradish, and mustard.

Codeine sulfate is a popular ingredient in variety of brand name cough suppressants. Compared to morphine, it is less addictive, has much less respiratory depressant activity, and is much less likely to cause bronchospasm or constipation. In doses below 15 mg, codeine does not produce analgesia in adults, with doses in the 10-20 range there is an antitussive action, and doses above 30 mg, codeine produces analgesia. Dosage is 10-20 mg every 4-6 hours, not to exceed 120 mg in 24 hours. For children 6-12 years old, dosage is 2.5-5 mg every 4-6 hours.

Benzonatate (Tessalon) is a nonnarcotic that has a local anesthetic effect with topical application. It acts on the sensory vagal receptors in the upper airway, and is though to inhibit the transmission of the afferent (cough and gag) impulse to the motor nerves through the medulla.

Dextromethorphan hydrobromide is a popular nonnarcotic antitussive that is available in a variety of brand name products, and is popular because it has no analgesic, respiratory depression, or addictive properties. Cough suppression is comparable to codeine. Dosage is 10-30 mg Q 4-8 hours up to a maximum of 120 mg in 24 hours. For children 6-12 years old, dosage is 5-10 mg Q 4 hours. For children 2-5 years old, dosage is 2.5-7.5 mg Q 4-8 hours.

Diphenhydramine hydrochloride, available in a host of brand name products (including Benadryl, Sominex, and Maximum Strength Nytol), is an antihistamine with antitussive properties, and is available in tablets, capsules elixirs, injections, lotions, and syrups. It can cause sedation and has anticholinergic effects. Adult dosage PO is 25-50 mg Q 4 hours, not to exceed 400 mg/day, and pediatric dosage is one-half that.

Hydrocodone (Hycodan Syrup) produces an antitussive effect with a dose of approximately 5 mg. However, it is an addictive derivative of opium, more potent than codeine, and can cause respiratory depression.

While there is still no *cure* for the common cold, that hasn't stopped pharmaceutical companies from producing a bewildering number of compounds that purport to treat and even cure colds. The ingredients in these *cold remedies* include: adrenergics, antihistamines, expectorants, and antitussives. Since most of these remedies are available over-the-counter, there is a very real potential for overdosing. Patients need to be cautioned that just because no prescription is needed, that doesn't mean the compounds are not both powerful and potentially hazardous to their health.

Anti-infective Agents

Respiratory infections caused by bacterial, fungal, protozoal, and viral organisms occur in patients with pneumonia, acute and chronic bronchitis, bronchiectasis, sinusitis, and cystic fibrosis. Antibiotics represent one of the most commonly used anti-infective agents in the respiratory therapist's arsenal.

The term *antibiotic* means a substance that is produced by microorganisms (bacteria, fungi, molds) that is capable of inhibiting or killing bacteria and other microorganisms. The mechanisms by which antibiotics inhibit or kill microorganisms include:

- **Inhibition of cell wall synthesis**. Bacterial cells have rigid protective walls, without which they explode. Antibiotics that inhibit bacterial cell wall synthesis include: penicillins, bacitracin, cephalosporins, vancomycin, and cycloserine.

- **Alteration of cell membrane permeability**. Disruption of the cell's membrane function upsets the necessary flow and storage of cell material required for growth. Membranes of certain bacteria and fungi are especially susceptible to antibiotics such as polymyxins.

- **Inhibition of protein synthesis**. Antibiotics that interfere with the ribosome's ability to synthesize needed proteins include: chloramphenicol, tetracyclines, erythromycin, lincomycin, streptomycin, kanamycin, and gentamicin.

- **Inhibition of nucleic acid synthesis**. Antibiotics that attach to the DNA strands and block further DNA replication or formation of messenger RNA include: fluoroquinolones (like ciprofloxacin), trimethoprim, sulfonamides, and rifampicin.

Antibiotics are usually administered systemically, but several (carbenicillin, gentamicin, streptomycin) have been aerosolized for localized infections (lung abscess and bronchiectasis). Tobramycin has been used for chronic infections in cystic fibrosis. Parenteral medications are often ineffective in lung infections because the presence of edema, fibrosis, or thick exudates limit diffusion of the drug into the lung.

Aerosolized antibiotics also may be useful when infections appear resistant to systemic therapy. However, aerosolized antibiotics should be considered a supplement to systemic therapy, not a replacement. They are probably most useful for stubborn gram-negative infections.

Results on aerosolized antibiotics have been mixed, and there are several disadvantages to aerosolized antibiotics, including:

- Bronchospasm is very common.

- DNA inactivates some antibiotics and enzymes found in mucus.

- Doses for aerosolized administration have not been clearly established.

- Resistant microorganisms are created, as mentioned above.

- Expensive equipment may be needed and considerable staff time required for administration.

Despite these above, aerosolized antibiotics may be considered for children with cystic fibrosis, fungal infections (pulmonary coccidioidomycosis, endobronchial histoplasmosis), and when systemic therapy appears ineffective or toxicity has been reached.

Antibiotic Medications

Penicillins, one of the oldest classes (dating back to the early 1940s), are considered the most important of the beta-lactam antibiotics. These bactericidal antibiotics are used for pneumococcal pneumonias, non-hospital-acquired aspiration pneumonia, and lung abscesses. The penicillin group is divided into three subgroups: the natural penicillins like penicillin G, penicillinase-resistant agents like methicillin, and the broad-spectrum penicillins like ampicillin.

Penicillin G is the agent of choice for streptococcus pneumonia, streptococcus pyogenes, and non-penicillinase-producing staphylococcus aureus. Intramuscular or intravenous delivery is the preferred route of administration for acute and serious pulmonary infections.

Bacterial resistance to penicillin is caused by the production of the enzyme penicillinase, so a subgroup of the penicillins was created that are resistant to penicillinase, including: methicillin, nafcillin, oxacillin, and cloxacillin, which are effective against penicillinase-producing *S-aureus*.

Semisynthetic *broad-spectrum* penicillin derivatives used to treat gram-negative microorganisms include: ampicillin, amoxicillin, carbenicillin, piperacillin, and ticarcillin.

Ampicillin, available in several trade names (including Omnipen, Principen, Ampicillin) is indicated treating systemic infections, acute and chronic urinary tract infections, and meningitis. It is used for pneumococcal pneumonia, bronchitis, bacterial exacerbations of COPD, streptococcus pneumoniae, and haemophilus influenzae.

Amoxicillin, an extended-spectrum penicillin, is indicated for lower respiratory infections. It is used for the same and is closely related to ampicillin. Both may be given orally but amoxicillin achieves an effective plasma concentration lasting twice as long as ampicillin. Recommended dosage for adults and children weighing more than 20 kg is PO 250-500 mg Q 8 hours.

Carbenicillin is effective against pseudomonas and other gram-negative bacteria, but not as effective as ampicillin against gram-positive organisms. It is generally used with another antibiotic to prevent development of resistant strains, and dosage may be administered in aerosol form in a 1-3 gram dose. Side effects frequently seen with the penicillins consist mainly of hypersensitivity reactions, and rashes, fever, and anaphylactic shock can occur. Cerebral irritation and gastrointestinal upset can be seen with higher doses.

Cephalosporins are a group of antibiotics originally derived from a fungus in the late 1940s. Like penicillin, they act by inhibition of bacterial cell synthesis, but they are resistant to penicillinase. Cephalosporins are active against both gram-negative and gram-positive bacteria, and are effective against staphylococcal, streptococcal, and klebsiella pneumonias, along with proteus mirabilis and Escherichia coli. Their primary use in pulmonary disease is concurrent with gentamicin for undiagnosed sepsis and for cephalosporin-sensitive gram-negative organisms.

Carbapenems are members of the beta-lactam group of antibiotics that act by inhibition of bacterial cell wall syntheses, and have a wide spectrum of activity against both gram-positive and gram-negative organisms.

Monobactam (Azactam) is a synthetic bactericidal that is effective against a wide range of gram-negative aerobic organisms.

Aminoglycosides, a group of agents derived from different species of *Streptomyces*, act by preventing and distorting bacterial protein synthesis. Gentamicin, amikacin kanamycin, tobramycin, and streptomycin are used for treating gram-negative bacillary pneumonias. Aminoglycosides are inhaled to control *Pseudomonas* infection in cystic fibrosis. Their most significant side effect is damage to renal tubules.

Tetracyclines are derived from *Streptomyces* species, and can be bacteriostatic or bactericidal, depending on dosage. They interfere with protein synthesis, and are effective against streptococcus pneumoniae, haemophilus influenzae, and mycoplasma pneumoniae. Tetracyclines are used as a prophylactic and for acute exacerbations of chronic bronchitis. Milk and milk products interfere with their absorption from the gastrointestinal tract. Side effects from using tetracyclines include gastrointestinal irritation, vomiting and diarrhea, bone marrow depression and skin rashes. Since they are temporarily incorporated in the liver and kidneys, they should be used with caution, if at all, for patients with liver or renal disease.

Fluoroquinolones are synthetic quinolone derivatives with broad-spectrum activity against bacterial activity. Examples include ciprofloxacin, norfloxacin, ofloxacin, enoxacin, and lomefloxacin. When orally administered, these drugs provide high lung bioavailability.

Sulfonamides are not classed as antibiotics, but were the first effective group of chemotherapeutic agents used to treat systemic bacterial infections. With the availability of many natural and semisynthetic antibacterial agents, their use has declined. They are still used to treat intestinal and urinary tract infections, but are generally longer used for treating gonococcal, staphylococcal, or streptococcal infections.

Trimethoprim-Sulfamethoxazole (TMP-SMX) is not an antibiotic, but a chemical agent produced in the laboratory. It is an antibacterial agent commonly used to treat respiratory infections, and is the drug of choice for treatment of *P. carinii* in AIDS patients. Side effects include rash, fever and leukopenia.

Polymyxins, B and E, are polypeptide antibiotics. **Polymyxin B** is effective against gram-negative organisms, particularly pseudomonas. It disturbs osmotic properties of the cell membrane in its action. It can be aerosolized for both pseudomonas and gram-negative bacteria colonizing the airway. Polymyxin B is usually given intramuscularly. Renal damage is the major problem with its use. When aerosolized, severe bronchospasm may result. It also can cause a neuromuscular blockade leading to respiratory paralysis. Polymyxin E is known as colistin and is similar to polymyxin B.

Erythromycins are macrolide antibiotics that are used for respiratory, genital, gastrointestinal tract, and skin/soft tissue infections. These agents bind to a site on the 50S ribosomal subunit of organisms, thereby acting to inhibit protein synthesis. They are drugs of choice in treating against gram-positive organisms including pneumococcus, mycoplasma pneumoniae, chlamydia psittaci, beta hemolytic streptococcus and some haemophilus influenzae. Erythromycin also has been used for Legionnaires disease, and for patients who are allergic to penicillin.

Erythromycin, one of the safest antibiotics, is available by oral, IM, or IV administration. Possible side effects include nausea, vomiting, diarrhea, phlebitis and pain on injection. Erythromycin is primarily used for community-acquired pneumonia. **Clarithromycin and azithromycin** have been effective in treating disseminated *Mycobacterium avium-intracellulare* in AIDS patients. **Clindamycin** is effective against some staphylococcus aureus, diplococcus, bacteroides and other gram-positive organisms. Specific

pulmonary indications for its use are aspiration pneumonias, empyema. and lung abscess. Side effects include diarrhea and skin rashes.

Antifungal Drugs

The body contains a variety of potentially pathogenic fungi that can cause local inflammation or disease if:

- a person becomes immunocompromised
- the balance of resident bacterial flora is suppressed by broad-spectrum antibiotics
- or if an inhaled corticosteroid is used without a reservoir device.

Drugs that are antifungal include amphotericin B, nystatin, and some newer azole antifungal agents.

Amphotericin B, which is administered by IV, has been the drug of choice for serious fungal infections since the 1950s, but its toxic effects such as nephrotoxicity, fever, and hypotension have limited its use. Nystatin is applied topically, and is effective against yeast-like infections.

Antituberculosis Drugs

First line agents to treat against tuberculosis include isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. These primarily inhibit the growth of the mycobacterium tuberculosis, but can be bactericidal with proper dosage. Usually two or more of the above agents are given simultaneously for 6-9 months. Isoniazid is the most effective, and is believed to act as an antimetabolite in the bacilli. This inhibits most enzyme systems in the organism. Side-effects are directly related to dosage, duration of treatment, and increasing patient age. Complications include: mouth dryness, visual problems, headache, insomnia, constipation, anemia, orthostatic hypotension, skin rashes, seizures, peripheral neuritis and hepatitis. Vitamin B_6 (pyridoxine) can decrease the neurotoxic effects.

Resistant strains develop rapidly when any of the above are given by themselves, so multidrug combinations are used to fight TB. Second-line antituberculosis drugs consist of: capreomycin, kanamycin, ethionamide, paraaminosalicylic acid, and cycloserine.

Pentamidine

Pentamidine Isethionate is an antiprotozoal drug which is active against Pneumocystis carinii pneumonia (PCP). It can be given either parenterally or via aerosol, and aerosolized pentamidine reaches significantly higher concentrations in the lung than when given by IV. Inhaled pentamidine (NebuPent) is specifically approved for the prevention of PCP in HIV-infected patients who:

- have a history of one or more episodes of PCP
- have a peripheral $CD4^+$ lymphocyte count of 200/mm_3, or less

The aerosol form has also been used in the treatment of acute episodes of PCP. Dosage approved for prophylaxis of PCP in AIDS subjects is 300 mg, given by inhalation once every 4 weeks. If there is a response to pentamidine, respiratory function may improve within 24-48 hours. Improvement generally

takes between 2-8 days for most patients. Improvement in the chest X-ray may take a week or longer, particularly with an AIDS patient.

While pentamidine administered by aerosol has fewer side effects than it does when given parenterally, it still has the potential for side effects, including: cough and bronchial irritation, shortness of breath, bronchospasm and wheezing, conjunctivitis, rash, renal insufficiency. Using a beta-adrenergic bronchodilator before inhaling aerosolized pentamidine can reduce or prevent local airway reaction.

The greatest danger of inhaling aerosol pentamidine exists when the patient coughs or removes the mouthpiece from their mouth while nebulization continues. Proper instruction of the patient on controlling aerosol particles by coughing into a tissue minimizes the former.

Ribavirin

The antiviral drug **Ribavirin** (Virazole) is active against respiratory syncytial virus (RSV), influenza virus, and herpes simplex virus. It has been approved as an inhaled aerosol for treating some infants and children who have, or are at increased risk for, severe lower respiratory tract infections caused by RSV. The American Academy of Pediatrics' recommendations for using Ribavirin include:

- For use to treat patients hospitalized with RSV lower respiratory tract disease, at high risk for severe/complicated RSV infection caused by the following:
- complicated congenital heart disease
- bronchopulmonary dysplasia, cystic fibrosis, or other chronic lung conditions
- premature infants
- those with immunodeficiency
- recent transplant recipients
- those receiving chemotherapy for malignancy
- infants who are severely ill (PaO_2 <65 torr, SaO_2 <90%, increasing $PaCO_2$)
- patients on mechanical ventilation for RSV infection
- hospitalized infants at increased risk of progressing from mild to complicated course because of young age or underlying condition

Ribavirin is supplied as a powder of 6 grams per 100 ml vial. Sterile H_20 is injected into the vial to achieve a concentration of 20 mg/ml (final total volume for administration is 300 ml). The mixture is good for 24 hours and then must be discarded. It is administered through a small particle aerosol generator (SPAG). The aerosol is delivered into an 0_2 hood, tent, or ventilator circuit.

Treatment with Ribavirin is usually for 12-18 hours per day for 3-7 days, and the package insert instructions should be consulted for more complete information. Side effects commonly seen include pulmonary function deterioration, and skin irritation from excess drug precipitation.

Exogenous Surfactants

Surfactant is a surface-active agent that lowers surface tension. One of the most common examples is detergent. The term *exogenous* describing this class of drugs refers to the fact that surfactant preparations are obtained from outside the patient's own body (i.e., from other humans, from animals, or synthesized in the lab).

Lung immaturity, which causes a lack of pulmonary surfactant is the primary problem in RDS. It results in high surface tension in the liquid-lined, gas filled alveoli. The clinical use of exogenous surfactants has traditionally been to replace the missing pulmonary surfactant of the premature, or immature, lung in respiratory distress syndrome (RDS) of newborns. These agents are also being investigated in treating adult respiratory distress syndrome (ARDS).

The clinical indications for exogenous surfactants are for the following applications:

- prevention of RDS in low birth weight infants
- prevention of RDS in other infants with evidence of immature lungs
- retroactive, or rescue treatment of infants with RDS

Exogenous surfactants act to replace and replenish a deficient endogenous surfactant pool in neonatal respiratory distress syndrome. Exosurf, colfosceril palmitate, is a protein-free, synthetic surfactant preparation. An indication for its use is the presence or risk of RDS. Dosage is 5 ml/kg of the reconstituted suspension, given as two divided doses of 2.5 ml/kg by direct tracheal administration. Details of preparing the suspension should be reviewed in the manufacturer's literature.

Beractant (Survanta) is a modified natural surfactant that has similar indications as Exosurf, and the recommended dose is 100 mg/kg of birth weight. The primary complications in exogenous surfactant therapy are caused by the dosing procedure, and include: airway occlusion, high PaO_2 levels, over-ventilation, apnea, and pulmonary hemorrhage.

Drugs for ARDS

At the present time, medications do not play a major role in treating ARDS. However, there are two basic strategies for the using drugs to treat ARDS: improve/correct lung function and prevent/correct lung and systemic inflammation. Drugs for the former consist of almitrine, nitric oxide, surfactant replacement, and prostaglandin E_1. For the latter, drugs consist of antioxidants, anti cytokines, antiendotoxins, corticosteroids, and monoclonal antibodies.

Almitrine improves PaO_2 and decreases $PaCO_2$ in COPD patients through decreasing V/Q mismatch. In ARDS, almitrine has been effective in redistributing blood flow from areas of shunt to normal areas. It gives a similar increase in PaO_2 to 10 cm H_2O PEEP without the side effects of positive Pressure.

Nitric Oxide (NO) is a potent pulmonary vasodilator when inhaled. It has relatively no effect on the systemic circulation because it is inactivated by hemoglobin.

Inhaled NO selectively improves perfusion of ventilated areas, and improves oxygenation in ARDS. Nitric oxide significantly decreases pulmonary artery pressure, decreases shunting and improves PaO_2.

However, NO is a toxic component of air pollution, and exposure to it can result in pulmonary edema and unacceptable levels of methemoglobin. Not all patients respond to NO and it is impossible to predict which patients will respond. Effective doses of inhaled NO are less than 20 parts per million (ppm), and at doses less than 20 ppm, NO is considered relatively free of toxicity.

Prostaglandin E_1 decreases systemic and pulmonary vascular resistance, decreases blood pressure, increases stroke volume, increases cardiac output, and increases heart rate. It may be useful to decrease pulmonary hypertension and improve cardiac function, but doesn't appear to enhance survival in ARDS.

Antioxidants also may be of use in ARDS. N-acetylcysteine has improved lung function, 0_2 delivery, and cardiac output in one study. A larger study showed no improvement in oxygenation, but an improvement in compliance. There was no difference in survival with the use of N-acetylcysteine.

Cytokines, such as interleukins, play a major role in causing the systemic effects associated with the sepsis syndrome. Clinical trials of **anti cytokines** have been conducted. Studies of interleukin-1 receptor antagonist showed a minor but statistically insignificant improvement in mortality.

Antiendotoxins may prove useful, particularly in gram-negative sepsis. Endotoxins produced by gram-negative bacteria cause severe disturbances. Several antibodies against endotoxins have been studied. HA-lA showed an improvement in mortality in patients with gram-negative bacteremia.

Corticosteroids were tried in ARDS treatments in the past, but were relatively unsuccessful. Current emphasis is on the damaging potential of WBCs, however, if WBCs are interfered with by steroids, patients run the risk of increased infection. Steroids may be useful in minimizing fibrosis formation in the latter stages of ARDS. They are recommended if the patient is hypotensive from adrenal insufficiency. They also may be useful in aspiration, fat embolism, and chemical injuries to the airway.

Monoclonal antibodies are being studied to inhibit WBC-adhesion molecules, particularly those of the neutrophil. Neutrophil adhesion to tissue is a critical step in ARDS lung injury.

Use of ibuprofen has showed a decrease in the incidence and development of ARDS, increased rate of reversal, and improved survival. Some soluble protective agents against lung damage are tocopherol, ascorbate, and beta-carotene. These help protect membranes and other cellular elements from oxidant injury, however their value in ARDS remains unconfirmed.

Smoking Cessation Therapy

Approximately 10% cigarette smokers per year try to quit. By the end of one year only about 20% of those "would-be-quitters" have been successful. The problem is that cigarettes create both a psychological and physiological dependence, and both need to be treated with behavioral and pharmacological therapies for maximum success. For the latter, there are nicotine and non-nicotine replacements. They are most effective when combined with appropriate behavior modification therapy.

Nicotine replacements come in the form of gum, patches, pills, nasal spray, and inhalers. Nicotine polacrilex gum has been used the longest. Nicotine patches are available in 16 and 24-hour forms. The 16-hour patch was created to prevent excess nicotine release during sleep. The patches are available in 21

mg, 14 mg, and 7 mg doses for weaning. Nicotine nasal spray and inhalers are uncommon at this time (1997). The pills are fairly new, and there is little data on success rates.

Non-nicotine replacements consist of CLONIDINE and BUSPIRONE. The primary use for clonidine is for hypertension, but it also relieves withdrawal symptoms from nicotine and the opiates. It is available as tablets or patches in doses of 0.1 to 0.3 mg/day. Buspirone is an antianxiety drug from the benzodiazepine family. Early trials of buspirone for nicotine withdrawal are encouraging.

Miscellaneous

Doxapram is a respiratory stimulant used for post-operative depression and alveolar hypoventilation syndromes. It stimulates peripheral chemoreceptors and brainstem respiratory centers. Dosage is 1-3 mg/mm by IV, up to a maximum of 600 mg. Doxapram can cause arrhythmias and hypertension by stimulating the release of epinephrine from the adrenals. It also can result in excessive CNS stimulation.

Progesterone is also a respiratory stimulant. It is used for Pickwickian syndrome. Progesterone is administered sublingually for outpatients. Inpatients are given a bolus of 100 mg/day IM. Progesterone takes 2-3 weeks for maximum effects to develop.

Naloxone is used to reverse ventilatory depression as a result of opiate administration (morphine, methadone, heroin). It is also effective in diazepam, propoxyphene, and ethanol overdoses. A bolus of 0.4-2.0 mg is given, but some patients may only require 0.1 mg/kg. Naloxone is short-acting so continuous infusion may be necessary.

Muscle relaxants and sedatives are used to improve the balance between gas exchange and the rate of metabolism. Muscle relaxants (paralyzers) must be used in combination with adequate sedation. If not, patients become extremely frightened and possibly psychotic. Indications for their use are: shivering after bypass surgery, difficult intubations, and temporary control of the ventilator patient.

Pancuronium (Pavulon) is probably the most common paralyzer used. Intermittent bolus administration is recommended. If tachycardia develops from its use, Vecuronium should be substituted. Vecuronium can be given as a continuous infusion. Atracuronium can also be used, but is shorter-acting and can cause histamine release.

Agitation causes catecholamine release, can produce auto-PEEP in ventilator patients, and causes an imbalance between 0_2 delivery and 0_2 consumption. Sedatives prevent these adverse conditions from occurring. Haloperidol (Haldol) is the preferred sedative because of its lack of ventilatory depression or hypotension. It can cause cardiovascular depression if hypovolemia is present or if given with propranolol. A 3-5 mg bolus is given IV and if there is no response in 15-20 minutes the dose is doubled. Another option if there is no response is to add a Ben Zodiazepine (Valium, Ativan, Versed). However, these can cause ventilatory depression, and can result in rapid sedation and accumulate in the body.

Morphine Sulfate (MS) is used for vasodilation, CNS sedation, and has a mild inotropic effect in patients with pulmonary edema. If the patient is not hypotensive, 5-10 mg of MS is given slowly via IV over several minutes. MS lowers pulmonary capillary pressure resulting in less leakage. Patient anxiety is also relieved. Ventilatory depression is possible but is rarely a problem.

Problems associated with MS are rapidly reversed with naloxone. One should avoid the use of MS as a sedative for asthmatic patients. MS (and other narcotics) cause histamine release and worsen asthma symptoms. Both oral and aerosolized MS have been used to increase exercise tolerance in the COPD patient. MS may reduce perceptions of dyspnea by acting directly on lung afferent nerves. This increases exercise capacity. An oral dose of 0.8 mg/kg or aerosol dose of 5 ml of a 1 mg/ml MS solution improve exercise endurance in these patients.

Propylene Glycol is a physiologically inert substance found in many aerosol preparations. It is used as a solvent and stabilizing agent. It is hygroscopic and used to minimize shrinkage of aerosol particles as they travel through the respiratory tract.

Pulmonary hypertension is defined as a mean pulmonary artery pressure >25 mm Hg at rest or >30 mm Hg with exercise. Most cases of pulmonary hypertension are secondary, meaning they are a result of another process. For example, hypoxia causes pulmonary vasoconstriction and therefore hypertension. Treatment for these causes of hypertension consist of fixing the primary problem, rather than treating the hypertension. "Primary" pulmonary hypertension is not a result of another problem. It is treated with a vasodilator or anticoagulants.

Primary pulmonary hypertension (PPH) usually develops in the third or fourth decade of life. Without treatment, most patients die within 2-3 years. PPH is a result of pulmonary capillary lumen cellular proliferation, thrombi, or fibrosis. Warfarin and Heparin have been used for anticoagulation and to prevent further thrombi. Vasodilators are effective for some patients, but not all. However, those who respond initially have a favorable response over the long term. Epoprostenol is given to test the patient's response. If favorable, continue its use. The alternative is heart-lung or single lung transplantation.

Summary

Respiratory pharmacology consists of medications used to treat the pathological triad of bronchospasm, airway inflammation, and retained secretions. Drugs used for these are bronchodilators, decongestants, corticosteroids, and mucokinetic/mucolytic agents. There are several routes of administration with the aerosol route being the most often used by the RCP.

Some of the advantages of aerosol therapy include:

- rapid therapeutic effect
- a small total dose may be given
- topical administration minimizes systemic side-effects

The disadvantages of aerosol therapy consist of:

- underdosage or overdosage
- very little medication actually deposited in the lung
- airway irritation
- systemic absorption through oropharyngeal deposition

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Excluding mainstream nebulization of large volumes of H_20, there are 4 methods of aerosol medication delivery. They are:

1. metered-dose inhaler (MDI)
2. dry powder inhaler (DPI)
3. small volume nebulizer (SVN)
4. IPPB

The patient must be able to take a deep coordinated breath for the first three. IPPB is reserved for the patient who cannot spontaneously hyperinflate their lungs. Many conditions require modification of the recommended dose. Conditions such as liver dysfunction, kidney dysfunction, and mechanical ventilation, emaciation, and obesity, very young or very old patients require appropriate adjustment of dosage.

Bronchodilation is most often achieved through SNS stimulation. SNS stimulation results in conversion of ATP to cAMP through activation of the enzyme adenylate cyclase. This leads to airway smooth muscle relaxation. Beta-adrenergic agonists increase the production of cAMP through the above mechanism. The enzyme phosphodiesterase inactivates cAMP thereby removing its bronchodilating influence.

Theophylline may work by inhibiting phosphodiesterase but this is unproved. Another mechanism to achieve bronchodilation is to block PNS stimulation of the airway. PNS stimulation leads to bronchoconstriction. Antimuscarinics are used to block PNS stimulation thereby leading to bronchodilation. Complications of the Beta-adrenergic agonists include tachycardia, skeletal muscle tremor and tachyphylaxis. Tachycardia is a result of excessive $Beta_1$ stimulation. A worsening of V/Q relationships is also possible with these drugs. $Beta_2$ stimulation can result in both bronchodilation and vasodilation. If the circulatory response exceeds the airway response, hypoxia may ensue. Complications of theophylline include tachycardia and tremors. It also can cause nausea and headache. Therapeutic levels should be maintained between 10-20 mcg/ml.

Decongestants and corticosteroids are not "bronchodilators" but their effects can lead to an increase in lumen size. Decongestants, through stimulation of receptors, cause vasoconstriction and decrease fluid in the airway. The resulting decrease in airway wall thickness and fluid in the lumen have the same effect as a bronchodilator.

Corticosteroids can have the same result through their anti-inflammatory properties. They also help prevent episodes of bronchospasm through inhibition of the allergic response to irritants. Chronic or excessive steroid use can result in adrenal insufficiency, cushingoid effects, decreased resistance to infection and osteoporosis. Acute complications include fluid and electrolyte imbalances. If steroids prove successful, cromolyn sodium may be of benefit to the patient. It is a prophylactic drug only, preventing bronchospasm through inhibition of mast cell degranulation.

Mucokinetic/mucolytic drugs aid secretion removal by one or more of several mechanisms. They dilute mucus, replenish the sol layer, stimulate bronchial glands, stimulate cilia, or chemically destroy components found in mucus. The safest and most common mucokinctic is water. Normal saline solutions also are very common, particularly for lavage purposes.

A common mucolytic is N-acetylcysteine. Its action is to rupture disulfide bonds of mucus making it less tenacious and viscous. Bronchospasm is a possible complication of its use. Complications of the mucokinetic/mucolytic agents are overhydration, bronchospasm and tissue irritation.

Antibiotics are rarely aerosolized. Several (carbenicillin, streptomycin, gentamicin) have been aerosolized with mixed results. Antibiotic lavage solutions are administered during a bronchoscopy for severe infections. Cystic fibrosis is a condition that may benefit from this. The penicillins and aminoglycoside are common antibiotics. Complications of various antibiotics include: hypersensitivity reactions, nausea, vomiting, diarrhea, inner ear problems, renal problems, and rarely, a blockade of the phrenic nerve.

Appendix

In this appendix, we will review some of the more common drugs used for treating respiratory diseases and present you with some articles (or excerpts from articles) that have been published regarding these drugs. The list is by no means comprehensive, but is intended to give you some information to review regarding these drugs, what has been written about them, and how they are used in respiratory care. Drugs are listed alphabetically by generic name. Trade names appear in parentheses after the generic names.

- Albuterol (**Proventil**)
- beclomethasone dipropionate(**Vanceril**
- budesonide(**Rhinocort**, **Pulmicort**)
- cromolyn sodium(**Intal**)

DNase(**Pulmozyme**)

- flunisolide(**AeroBid**)
- fluticasone propionate(**Flonase**)
- montelukast(**Singulair**)
- pranlukast(**Ultair**
- salmeterol(**Serevent**)
- terbutaline(**Brethaire, Brethine, Bricanyl**)
- theophylline
- triamcinolone acetonide(**Azmacort**)
- **Viozan**
- zafirlukast(**Accolate**)

albuterol

Tradename Proventil
Manufacturer Schering
Treatment Class Respiratory
Indication Asthma, bronchospasm

Focus On... Asthma
March/April, 1997 issue (No. 237; pp. 12-15) of *Medical Sciences Bulletin*

Drugs Used for Asthma

Generic Name	Trade Name(s)
Bronchodilators: *Beta$_2$-Agonists*	
albuterol	**Proventil, Ventolin**
terbutaline	**Brethaire, Brethine, Bricanyl**
bitolterol	**Tornalate**
pirbuterol	**Maxair**
salmeterol	**Serevent**
fenoterol *	**--**
formoterol *	**--**
Bronchodilators: *Other*	
theophylline	**Various**
Mast Cell Inhibitors	
cromolyn sodium	**Intal**
nedocromil sodium	**Tilade**
Corticosteroids: *Metered-Dose Inhaler*	
flunisolide	**AeroBid**
triamcinolone acetonide	**Azmacort**
beclomethasone dipropionate	**Beclovent, Vanceril, Vanceril DS**
budesonide	**Pulmicort**
fluticasone propionate	**Flonase**
Corticosteroids: *Oral*	
methylprednisolone	**Various**
prednisone	**Various**
prednisolone	**Various**
Leukotriene Inhibitors or Antagonists	
zafirlukast	**Accolate**
zileuton	**Zyflo**
pranlukast *	**Ultair**
montelukast *	**Singulair**
pobilukast *	**--**
tomelukast *	**--**
verlukast *	**--**
Anticholinergics	
ipratropium bromide	**Atrovent**

*Investigational

Bronchodilators: Beta$_2$-Agonists, Theophylline

The introduction three decades ago of bronchodilating **beta$_2$-agonists** -- adrenergic agonists selective for the beta$_2$ receptor -- revolutionized the treatment of asthma. These agents proved to be more potent and longer acting (4-6 hours) than the nonselective adrenergic receptor agonists such as isoproterenol, which stimulate both alpha- and beta-adrenergic receptors. Beta$_2$-agonists give rapid symptomatic relief and also protect against acute bronchoconstriction caused by stimuli such as exercise or the inhalation of frigid air. Frequency of use can also serve as an indicator of asthma control. Recently, an extra long- acting beta$_2$-agonist-salmeterol (duration up to 12 hours)-was introduced in the United States. Salmeterol is so potent that it may mask inflammatory signs; therefore, it should be used with an anti-inflammatory.

Theophylline is a relatively weak bronchodilator with a narrow therapeutic margin (blood level monitoring is recommended to avoid toxicity) and a propensity for drug interactions (competition for hepatic cytochrome P450 drug-metabolizing enzymes alters plasma levels of several important drugs metabolized by that same system). On the plus side, theophylline has some anti-inflammatory activity, can be taken orally, and is available in long-acting formulations; patient compliance is good with once- or twice-daily oral formulations.

About 60% to 70% of asthmatics have mild disease that can be managed with inhaled beta$_2$-agonists alone, when pretreatment is provided before allergen exposure or exercise (cromolyn or nedocromil sodium can be substituted). Asthmatics with more severe disease are generally treated with inhaled beta$_2$-agonists as needed, along with other antiasthma medications, in particular, inhaled corticosteroids (regular use of inhaled corticosteroids, but not beta-agonists, has been shown to reduce the number of exacerbations of asthma, even in patients with mild disease). Theophylline is generally reserved for use in conjunction with other antiasthma agents for patients with moderate to severe disease.

Before 1990, beta$_2$-agonists were often administered on a regular schedule, which was thought to provide better asthma control. However, recent studies have shown that scheduled use is associated with poorer control and possibly with increasing asthma mortality worldwide. This association was first noted in the late 1960s with the use of a potent formulation of the nonselective isoproterenol. A second dramatic increase in asthma mortality was associated with the introduction in the late 1970s of a high-dose formulation of fenoterol. Later, frequent use of fenoterol or albuterol (primarily via nebulizer, and not metered-dose inhaler) was found to increase the risk of death in patients with severe asthma.

It is possible that the overuse of inhaled beta$_2$-agonists is simply a marker for severe uncontrolled asthma, and may not be the cause of death. However, it is also possible that the transient deterioration of airway responsiveness observed when the medication is stopped contributes to the risk. Also, beta-agonists have been associated with a rebound increase in bronchoconstrictor response to allergens, and with a partial loss of protection against exercise-induced bronchoconstriction. Several studies have shown that as-needed administration is at least as effective as regularly scheduled administration; therefore, using beta$_2$-agonists on demand is preferred. One recent trial involved 255 patients with mild asthma who received albuterol inhalation therapy either on a regular schedule (126 patients) or as needed (129 patients).

The follow-up period lasted 18 weeks, and outcomes measured included peak expiratory flow, forced expiratory volume in one second, asthma symptoms, asthma exacerbations, quality of life, need for additional albuterol, and airway responsiveness to methacholine.

The average total use of albuterol in the scheduled group was 9.3 puffs per day, and in the as-needed group, 1.6 puffs per day. Basically, there were no clinically important differences between the two groups, although bronchodilator response to albuterol was increased in the scheduled-treatment group at the end of the trial. The investigators concluded, "In patients with mild asthma, neither deleterious nor beneficial effects derived from the regular use of inhaled albuterol beyond those derived from use of the drug as needed. Inhaled albuterol should be prescribed for patients with mild asthma on an as- needed basis."

Salmeterol vs. Albuterol: Which provides better quality of life?

From issue No. 251 (August, 1998) of *Medical Sciences Bulletin*

Asthma affects 14 to 15 million adults and children in the United States. It is a chronic disease that requires daily supervision by the sufferer. Although it is presently incurable, it is manageable, and a central focus in asthma therapy has been to provide treatment options that provide a better quality of life for patients.

A recently published clinical trial focused on the safety and efficacy of salmeterol as compared with albuterol; it also assessed the impact each therapy had on the patient's quality of life.

Salmeterol and albuterol are analogs. Salmeterol is a long-acting, highly selective, beta2-adrenergic agonist that provides up to 12 hours of bronchodilation, which is approximately two to three times that of albuterol. Previous clinical trials have demonstrated salmeterol's superiority to albuterol in improving pulmonary function and reducing symptoms of asthma. The safety profiles of both drugs are generally similar with both being well tolerated when used as directed.

This randomized, parallel group, multicenter study consisted of 539 nonsmoking subjects, 12 years of age or older, who were diagnosed with asthma. As a requirement, all had been receiving daily bronchodilator treatment for 6 weeks or longer. Eligible subjects had a forced expiratory volume in one-second (FEV1) measurement of 40% to 80% of predicted values, which increased by greater than 15% within 30 minutes of inhalation of 180-mcg albuterol, after bronchodilator therapy had been withheld. Subjects were excluded for several reasons, including chronic obstructive pulmonary disease, current pulmonary infection, history of hospitalization for asthma within the previous 3 months, and the use of more than two albuterol inhalers per month during one of the previous 3 months.

The study involved 40 clinical sites. A two-week assessment period was followed by a 12-week treatment period. During the first period, baseline assessments were obtained for peak expiratory flow (PEF) rate, asthma-related symptoms, nocturnal awakenings, and use of albuterol aerosol. On the first treatment day, patients were assigned randomly either salmeterol 42 mcg twice daily or albuterol 180 mcg four times daily. Patients were given two metered-dose inhalers that had either active drug or placebo. They were told to take two puffs from inhaler "A" in the morning

and at bedtime and two puffs from inhaler "B" in the late morning (11AM and 1PM) and in the early evening (5 and 8 PM). Salmeterol was administered as the first and last dose. All patients used albuterol aerosol when needed to relieve breakthrough symptoms.

Subjects kept rating cards of daytime symptoms such as shortness of breath, chest tightness and wheezing, and nighttime symptoms, including nocturnal awakenings due to asthma. Use of albuterol was also recorded, as were patient-obtained PEF measurements. These were assessed in the morning before the first does of the study drug and in the evening before the last dose of the study drug.

This study showed the enhanced effectiveness of salmeterol over albuterol with regards to quality of life. At the end of the first 4 weeks, a significant improvement in the Asthma Quality of Life Questionnaire ratings was demonstrated among subjects using salmeterol when compared to albuterol. This trend continued throughout the subsequent weeks of the trial. Albuterol did not meet the criteria for a small change from baseline until week 12, and this occurred in the asthma symptom domain only. However, improvements from baseline were noted in both daytime and nighttime symptom ratings for the salmeterol group. Also, this group experienced a greater mean change from baseline in symptom-free days (28.6%) than did the albuterol group (13.4%).

Salmeterol provides the physician with the ability not only to abate asthma symptoms, but also to improve the quality of the lives of patients with asthma.

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What Is the Role of Theophylline in Moderate Asthma?

Paper: A Comparison of Low-Dose Inhaled Budesonide plus Theophylline and High-Dose Inhaled Budesonide for Moderate Asthma

Authors: Evans D, Taylor D, Zetterstrom O, Chung K et al

Ref: N Engl J Med 1997; 337: 1412-8

Summary: Inhaled glucocorticoids are the mainstay of treatment in patients with moderate asthma. The dose used is usually titrated against symptoms. They are a relatively expensive medication particularly valued for their anti-inflammatory effects on the lungs. Theophylline is an oral bronchodilator used in asthma for over 50 years.

Its use is decreasing probably due to a perceived lack of anti-inflammatory effect (although new evidence is challenging this assumption) and fears over toxicity associated with high plasma levels. It is, however, extremely cheap. Recent National Asthma Education and Prevention Program (NAEPP) guidelines advise the addition of theophylline (or long-acting beta-agonist) to medium dose inhaled glucocorticoids before initiating the long-term use of high-dose inhaled glucocorticoids. This randomized, double blind controlled trial from Britain and Sweden investigates the effectiveness of such a strategy.

All patients recruited had typical symptoms of asthma and fulfilled the American Thoracic Society criteria for asthma. Despite treatment with inhaled budesonide 800-1000 mcg daily (or other inhaled glucocorticoid at equivalent dose) patients had continuing asthma symptoms. Forced expiratory volume in one second (FEV1) was greater then 50% predicted and improved by at least 15% following albuterol inhalation. Following a two-week run-in period, patients were randomized to receive theophylline with lower dose inhaled budesonide or high dose budesonide alone. The theophylline group received twice daily oral theophylline 250 mg (or 375 mg if over 80 kg) and 400 mcg inhaled budesonide. The high dose budesonide group received 800 mcg-inhaled budesonide twice daily with a placebo tablet matched to the theophylline.

Study treatment was given for three months. Patients were monitored every three weeks and one week after treatment ended. Lung function tests were performed at each visit and theophylline levels measured. After 12 weeks blood cortisol levels were also performed. Diary cards were completed daily. Peak expiratory flow (PEF), symptoms, and use of rescue albuterol medication were recorded.

Sixty-six patients underwent randomization, 31 in each group completed the study. Mean age was 39 years. Compliance with study treatment was high. Both treatments resulted in improvements in lung function that were sustained throughout the trial. In the high dose budesonide group the FEV1 had increased from 2.50 L to 2.62 L by 9 weeks, in the theophylline group the increase was from 2.48 L to 2.76 L; only the latter increase was statistically significant. PEF measurements increased by the end of the trial significantly in both groups: from 411 to 436 L/min in the high dose budesonide group and from 430 to 464 L/min in the theophylline group. Overall changes in PEF were statistically similar in the two groups, the FEV1 improved more in the theophylline group.

There were significant and similar reductions in albuterol use and home recorded variability in peak flow in both groups. There were small and similar reductions in symptom scores in both groups, it is not clear how clinically important these were. Serum cortisol levels fell significantly from 18.4 mcg/dl to 15.9 mcg/dl in the high dose budesonide group but were unchanged in the theophylline group; the clinical significance of this difference is again uncertain. The median serum theophylline concentration in the theophylline group was 8.7 mcg/ml, which is

lower than the usual therapeutic range of 10-20 mcg/dl. There were no discontinuations due to treatment side effects.

The clinical benefits to patients achieved with either regime in this study were arguably small. The median daytime daily use of albuterol fell from around two puffs to around one puff in both groups. Perhaps the patients' asthma was already too well controlled on study entry to require a significant increase in therapy. The main finding is that there were virtually no significant differences between the two treatment regimens in any of the outcome variables measured. Long-term outcomes were not recorded, over time differing anti-inflammatory effects may produce more of a divergence. These results suggest that the addition of low-dose theophylline to inhaled glucocorticoid is at least as good as increasing the dose of inhaled glucocorticoid. It can be done without significant risk of toxicity occurring and is very much cheaper.

Three Studies Published on Turbuhaler Device

Mar. 31, 1998: A dry-powder inhalation device, the Turbuhaler, performed well in three company-sponsored studies:

- Salbutamol delivered via Turbuhaler was two to three times more potent than when given with a pressurized metered-dose inhaler (pMDI). The relative dose potency as measured by the bronchodilating effects was 3.0 with Turbuhaler; when assessed using the hypokalemic effect of salbutamol, the relative dose potency was 2.0 in this Respiratory Medicine article (1998; 92: 325-30). A small but statistically significant increase in adverse effects also occurred with Turbuhaler, including heart rate, QTc interval, and tremor. Reprints: E. Bondesson, Astra Draco AB, P.O. Box 34, S-22100 Lund, Sweden.
- In an emergency department study, salbutamol at one-half doses administered by Turbuhaler was as effective as full doses given with pMDI plus Volumatic spacer. The study, conducted in Thailand and published in Respiratory Medicine (1998; 92: 167-72), showed no significant differences in efficacy between the two modes of administration. Reprints: E. Stahl, Astra Draco AB, P.O. Box 34, S-22100 Lund, Sweden.
- A study of budesonide in the Journal of Allergy and Clinical Immunology (1998; 101: 312-9) showed no significant suppression of the hypothalamic- pituitary-adrenal axis when the drug was given at clinically recommended doses (800 or 1,600 mcg/day) via Turbuhaler. After six weeks of treatment plasma cortisol levels were reduced by 4% in the placebo group; 13%, 11%, and 27% in the budesonide groups (800, 1,600, and 3,200 mcg/day); and 35% in the prednisone group. Reprints: D. Aaronson, 9301 Golf Rd., Des Plaines, IL 60016

Update on Asthma Pharmacotherapy

Apr. 21, 1999: Pharmacotherapy of asthma is addressed in several reports in the Journal of Allergy and Clinical Immunology (1999; 103; www1.mosby.com).

Therapeutic doses of fluticasone had little effect on the hypothalamic-pituitary-adrenal axis in a 28-day study (pp. 622-8). Mean plasma cortisol response to cosyntropin was similar among fluticasone, triamcinolone, and placebo and significantly less than in patients taking prednisone. Triamcinolone was statistically similar to placebo on most measures but reduced the area under the cortisol concentration time curve.

Reprints: J. T. C. Li, Mayo Clinic Foundation, 200 1st St. SW, Rochester, MN 55905.

Levalbuterol, the R isomer of albuterol, produces fewer side effects while providing similar efficacy to the racemic mixture, concludes a study of 33 pediatric patients (pp. 615-21). FEV1 values with levalbuterol "were comparable with or better than those observed with racemic albuterol," the authors write. "Beta-mediated side effects were lower for an equipotent dose of levalbuterol when compared with racemic albuterol." The product was recently approved for marketing as Xopenex (Sepracor; approved for treatment and prevention of bronchospasm. The nebulizer product contains the therapeutically active R-isomer of albuterol.).

Reprints: S. M. Gawchik, President's House, 1 Med. Ctr. Blvd., Chester, PA 19013.

Use of oral prednisone to treat 66 hospitalized children with asthma could reduce costs while providing similar effectiveness (pp. 586-90). Compared with i.v. methylprednisolone, oral prednisone produced similar mean lengths of hospital stay, similar time to weaning to beta agonists, and significantly less need for supplemental oxygen.

Reprints: J. M. Becker, Allergy, St. Christopher's Hosp. for Children, Front at Erie St., Philadelphia, PA 19134

beclomethasone dipropionate

Tradename Vanceril
Manufacturer Schering
Treatment Class Respiratory
Indication Asthma

NEJM: Raloxifene, Steroids

Two important studies are in the New England Journal of Medicine (1997; 337).

Results are reported from a French clinical trial of just-approved raloxifene for prevention of osteoporosis (pp. 1641-7). Over a two-year period, the selective estrogen-receptor modulator increased bone mineral density, lowered serum total cholesterol and LDL concentrations, and did not stimulate the endometrium in 601 postmenopausal patients, in comparison with placebo. An accompanying editorialist notes, "The decrease in estrogen-related adverse effects with the selective estrogen-receptor modulators in general and raloxifene in particular should improve compliance and decrease the incidence of cardiovascular events and fractures while not increasing breast cancer."

Beclomethasone overall performed better than did salmeterol in treating asthma in 241 children, according to results of a Canadian study (pp. 1659-65). The 12-month, placebo-controlled trial showed that beclomethasone reduced airway hyperresponsiveness and controlled symptoms, but the steroid was associated with decreased height. Salmeterol, while effective as a bronchodilator, did not have as much effect on the airways and symptom control. In an accompanying editorial (pp. 1690-2), British physicians endorse the first-line use of steroids in children with more severe cases, but they maintain that "the jury remains out" for children with milder cases. In those patients, they recommend use of NIH guidelines (cromolyn or nedocromil as initial therapy during a trial of four to six weeks).

High-Dose Beclomethasone Does Not Affect HPA

Feb. 17, 1998: Use of inhaled beclomethasone dipropionate at 840 mcg/day did not suppress the hypothalamic-pituitary-adrenocortical axis in adult patients with moderate asthma, reports Annals of Allergy, Asthma, and Immunology (1998; 80: 39-44). Some 64 patients were challenged with an ACTH stimulation test using cosyntropin 250 mcg after 36 days of high-dose therapy with the inhaled steroid.

Responses in patients receiving beclomethasone -- including those receiving double-strength product -- were not significantly different from those taking placebo. In patients receiving oral prednisone 10 mg/day, HPA activity was significantly suppressed, with lower plasma cortisol levels produced by the cosyntropin test.

Reprints: M. D. Brannan, Schering-Plough Research Inst., 2000 Galloping Hill Rd., Kenilworth, NJ 07033.

Asthma and Side Effects of Inhaled Corticosteroids

Apr. 27, 1998: Asthma and side effects of inhaled corticosteroids are covered in these recent articles:

- Risk of acute adrenal insufficiency is slight in patients on low- or medium-dose inhaled corticosteroids, but patients on long-term, high-dose therapy may need supplemental therapy during stress challenges such as sepsis, report authors in the Journal of Allergy and Clinical Immunology (1998; 101: S447-50). The authors recommend care in adults taking 1,500 mcg/day or children inhaling 400 mcg/day of beclomethasone, budesonide, flunisolide, triamcinolone, or fluticasone. Reprints: R. G. Dluhy, Brigham and Women's Hosp., 221 Longwood Ave., Boston, MA 02115.
- Knemometry detected no "significant suppression of lower leg growth velocity" in 21 asthmatic children ages 6-10 years during six weeks of therapy with inhaled fluticasone 100 mcg twice daily (Chest. 1998; 113: 584-6). Reprints not available.
- In 38 adult Chinese patients with asthma, long-term administration of high- dose inhaled steroids (> 1.5 mg/day) induced bone loss in an 18-month trial reported in the Journal of Allergy and Clinical Immunology (1998; 101: 445-50). The side effect was preventable with calcium supplementation with or without etidronate. Reprints: K. S. L. Lam, U. Dept. of Med., U. Hong Kong, Queen Mary Hosp., Pokfulam, Hong Kong.
- Budesonide, delivered by Turbuhaler in adult patients with asthma, "exhibited a dose response and was effective at low doses," reports the Journal of Allergy and Clinical Immunology (pp. 457-63). FEV1 values were initially 63-66% of predicted normal values. Mean changes in morning peak expiratory flow were 12, 22, 27, and 30 L/min, respectively, for groups taking total daily budesonide doses of 200, 400, 800, and 1,600 mcg; the placebo group’s mean value fell by 27 L/min. Reprints: W. Busse, U. Wisconsin-Madison Med. Sch., Madison, WI 53792.
- A survey of 604 Canadian patients with asthma revealed many misconceptions and fears about inhaled corticosteroid therapy, including concerns about corporeal image, bone density, and reduced medication efficacy over time. The Chest (1998; 113: 587-92) survey concluded that "these observations stress the importance ... of questioning patients about their understanding of the role of asthma medications." Reprints: L-P Boulet, Hospital Laval 2725, Chemin Sainte-Foy, Quebec G1V 4G5, Canada.

Intranasal Steroids May Suppress Adrenal Function

Apr. 29, 1998: Three corticosteroids used intranasally reduced overnight urinary cortisol levels in 16 healthy volunteers, according to new data just published in the Journal of Allergy and Clinical Immunology (1998; 101: 470-4). The reductions "which indicate systemic availability of nasally administered steroids" were significant only for fluticasone 200 mcg/day (43%), while reductions from triamcinolone 220 mcg/day (23%) and beclomethasone 336 mcg/day (21%) did not reach significance.

The researchers also measured the subjects' response to low-dose ACTH, another marker of adrenal suppression. Serum cortisol concentrations before and after ACTH administration did not indicate significant impact on adrenal response. The authors conclude that, based on the results of this four-day study, further investigation into the systemic effects of intranasal corticosteroids is needed, including whether these effects are additive.

Reprints: B. J. Lipworth, Clin. Pharmacology and Therapeutics, Ninewells Hosp. and Med. Sch., U. Dundee, Dundee DD1 9SY, Scotland, U.K

Articles Analyze Asthma

July 24, 1998: From the Archives of Diseases in Children (1998; 79) come two studies assessing steroid therapy in asthma and proper treatment of recurrent cough in children.

Increasing the dosage of inhaled corticosteroids at the beginning of an asthmatic exacerbation is "ineffective and should not be included in asthma self-management plans," concludes the first article (pp. 12-7). The report considers 18 exacerbations that occurred in 28 children aged 6-14 years with mild to moderate asthma over a six-month period. Compared with inhaled placebo, steroid inhalations had no significant effect on peak expiratory flow, diurnal peak flow variability, and symptoms scores over the following two weeks, or parents' opinions of the effectiveness of asthma medications.

Reprints: D. Holdaway, Paediatrics and Child Health, Dunedin Sch. of Med., P.O. Box 913, U. Otago Med. Sch., Dunedin, New Zealand.

Neither salbutamol nor beclomethasone was beneficial in children with recurrent cough but with no other evidence of airway obstruction, concludes a second group of authors (pp. 6-11). The study included 43 children aged 6-17 years who received either salbutamol or placebo for five to seven days and then either beclomethasone or placebo for either four to five weeks or eight to nine weeks. The drugs had no significant effect on cough frequency or scores, regardless of whether airway hyperresponsiveness was present.

Reprints: A. B. Chang, Resp. Med., Mater Children's Hosp., South Brisbane, Queensland 4101, Australia; achang@mater.org.au.

budesonide

Tradename Rhinocort
Manufacturer Astra
Treatment Class Respiratory
Indication seasonal or perennial allergic rhinitis

Nebulized Budesonide for Croup

From the September 1994 issue of *Medical Sciences Bulletin* , published by Pharmaceutical Information Associates.

Croup causes acute upper-airway obstruction in 3 of every 100 children younger than 6 years of age, with hospitalization being required in 1.3 % of cases. **Glucocorticoid therapy** has proven beneficial for croup patients who have been hospitalized, but some clinicians argue against routine use in less severely ill children. In a recent randomized, double-blind, placebo-controlled trial, Canadian researchers randomized 54 emergency-room patients (27 per group) between 3 months and 5 years of age who had mild to moderate croup to receive either 2 mg (4 mL) **budesonide** solution or 4 mL 0.9% saline solution, delivered by updraft nebulizer with a continuous flow of 5 to 6 liters of oxygen per minute. Initially, the children had croup scores of 2 to 7 on a 17-point scale. Patients were evaluated every hour for 4 hours, until croup score diminished to 1, or until the treating physician discharged the patient. A two- point decrease in croup score or the reduction of the croup score to 1 was considered clinically important.

Results

At the final assessment, budesonide patients had significantly lower croup scores than placebo patients. Nineteen of the budesonide patients (70%) demonstrated a response, compared with only 10 of placebo patients (37%). Of those patients who remained in the emergency room for 4Êhours, median croup scores were 2.5 for the budesonide group and 4.0 for the placebo group. Thirteen patients receiving budesonide had been discharged, compared with eight patients receiving placebo. One budesonide and three placebo patients had worsened conditions. Two placebo patients received racemic **epinephrine**. Six budesonide patients (22%) and 8 placebo patients (30%) received **dexamethasone** while in the emergency room. Nine budesonide patients (33%) and 11 placebo patients (41%) received dexamethasone before discharge.

Budesonide patients were discharged significantly earlier than placebo patients. One budesonide patient (4%) was hospitalized for 2 days. Six placebo patients (22%) were hospitalized during the study period for a median stay of 2 days. One additional placebo patient was hospitalized by the end of the first week. There were no adverse effects in the budesonide group, nor did any budesonide patient show clinical deterioration. One placebo patient had a burning sensation on the face.

Significant Reductions in the Cost of Treatment
Since the cost of a single dose of nebulized budesonide is dwarfed by the cost of hospital admission, the researchers concluded that significant reductions in the cost of treating croup can be achieved. With nebulized budesonide there is no risk of gastrointestinal hemorrhage or painful injection (which can occur with dexamethasone); therefore previous admonitions against the routine use of glucocorticoids for the treatment of croup are unwarranted. Budesonide exerts rapid action and prolonged effect and may, therefore, be effective against subglottic inflammatory edema. However, caution must be used when treating patients with preexisting immunodeficiency, possible tuberculosis, or recent exposure to varicella. (Klassen TP et al. *N Engl J Med*. 1994; **331**: 285-289.)

Commenting on the Klassen trial, doctors in Australia note that there may be two types of croup: spasmodic croup, a short episode of cough and stridor without fever; and infectious laryngotracheobronchitis, croup (often with fever) that occurs after 12 to 72 hours of cough and coryza. The underlying pathophysiologic features of these two different forms of croup may influence the response to corticosteroid therapy. Studies must therefore be undertaken to identify the patients most likely to benefit from steroid therapy and to compare the relative effectiveness of different doses and routes of administration. (Landau LI & Geelhoed GC. *N Engl J Med*. 1994; **331**: 322-323.)

Cromolyn sodium

Tradename Intal
Manufacturer Fisons
Treatment Class Respiratory
Indication Cough due to ACE inhibitor therapy

Cromolyn Sodium for ACE Inhibitor Cough

From the February 1994 issue of *Medical Sciences Bulletin* , published by Pharmaceutical Information Associates, Ltd.

- Indication: **Cough due to ACE inhibitor therapy**
  - Drug Tradename: **Intal**
  - Manufacturer: **Fisons**

Angiotensin-converting enzyme (ACE) inhibitors are widely used to treat hypertension and congestive heart failure and have also proved effective for early left ventricular dysfunction and diabetic nephropathy. Although ACE inhibitors are generally well tolerated, a major side effect is a persistent, nonproductive, irritating cough. This appears to be inherent in the mechanism of action of ACE inhibitors (ACE itself is located in the endothelial lining of the vasculature of the lungs). In some patients, the cough is severe enough to lead to drug withdrawal. Various therapies have been tried -- theophylline, nonsteroidal antiinflammatory drugs, and even inhaled local anesthetics -- but response has been inconsistent.

Recently cardiologist M. Hargreaves reported that inhaled cromolyn sodium (**Intal/Fisons**) may be effective for suppressing cough in patients taking ACE inhibitors. Hargreaves described five men aged 65 to 82 who experienced cough 2 to 7 days after drug therapy initiation with captopril or lisinopril. Coughing disappeared after ACE inhibitor withdrawal, then returned immediately upon re challenge. When cromolyn sodium was given by inhalation (20 mg 4 times daily), coughing disappeared in three patients, was much improved in the fourth patient, and was unchanged in the fifth. A literature review turned up seven additional cases of ACE inhibitor-induced cough treated with cromolyn sodium; cough was completely suppressed in four patients, partially suppressed in two patients, and unchanged in one patient. How cromolyn sodium protects against ACE inhibitor cough is not known, said Hargreaves, who nevertheless concludes that the value of cromolyn inhalation therapy should be examined further.

References

1. Hargreaves M. *Brit J Clin Pract*. 1993; **47**: 319-320.

The following is taken from the "Highlights of the 1997 Meeting of the American Academy of Allergy, Asthma & Immunology

New Therapies in Asthma and Allergy

Recently, we have seen the development of many new asthma therapies, each attempting to target a different mechanism through which to combat this chronic inflammatory disease of the airways. The combination of short-term and long-term (acute and chronic) medications is important for the successful management of asthma.

Long-term control medications include corticosteroids, cromolyn sodium and nedocromil, long-acting beta2-agonists, methylxanthines, and leukotriene modifiers. Quick-relief medications include short-acting beta2-agonists, anticholinergics, and systemic corticosteroids. Despite the recognized value of these therapies, new approaches are constantly being identified. For example:

Intravenous Immunoglobulin (IVIG) has numerous immunomodulatory and anti-inflammatory activities. One study used IVIG for the treatment of severe asthma and showed it was significantly effective in allowing for steroid reduction in the subgroup of patients who had higher steroid requirements. This suggests that IVIG should be reserved for the treatment of severely afflicted asthmatic patients.

Hydroxychloroquine (HCQ) was tested for its use in antiallergic, antiasthmatic therapy. HCQ is a generally well-tolerated and safe immunomodulating drug; its proven efficacy in the treatment of rheumatic diseases suggests potential utility in the treatment of non-steroid-dependent asthma. Findings suggest that a late improvement in symptoms occurs in the HCQ group, which is consistent with its known slow onset of action. Additional studies are needed to confirm the antiasthmatic, antiallergic, and possibly disease-modifying effects of HCQ.

Montelukast, a leukotriene receptor antagonist, was shown to decrease peripheral blood eosinophils and improve signs and symptoms of asthma over a 3-month period. Researchers have concluded that montelukast caused a significant improvement in symptoms of chronic asthma, which correlates with changes in peripheral blood eosinophil levels.

Many new products have come to market for the treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and nonallergic rhinitis (PNAR). Allergic rhinitis is an immunologically mediated disease in which histamine plays a central mediator role in producing most of the typical ocular and nasal signs and symptoms such as sneezing, nasal stuffiness, and postnasal drip.

Mometasone furoate (Nasonex TM) is an aqueous nasal spray in which 200 mcg QD is shown to be as effective and as well tolerated as 400 mcg of **beclomethasone dipropionate** in treating symptomatic SAR and PAR. **Fluticasone propionate** is also an aqueous nasal spray and is used in the treatment of PNAR. This condition is etiologically different from allergic rhinitis and is often refractory to treatment with antihistamines, decongestants, and mast cell inhibitors. PNAR is, however, characterized by symptoms that may respond to intranasal corticosteroids such as fluticasone propionate. Antihistamines such as **cetirizine** and **ebastine** (not currently available in the United States) have been used for treating PAR; in a study comparing the two, cetirizine was shown to provide total relief in a greater number of patients and was also more effective than ebastine in relieving nasal obstruction. **Levocabastine** nasal spray is another antihistamine that is used for the treatment of SAR.

These drug studies were collected from the poster sessions at the annual meeting of the AAAAI, February 1997, San Francisco, CA.

DNase (dornase alpha)

Tradename Pulmozyme
Manufacturer Genentech
Treatment Class Respiratory
Indication Congestion due to cystic fibrosis

Pulmozyme DNase Approved for Treatment of Cystic Fibrosis

Reprinted from the February 1994 issue of *Medical Sciences Bulletin*, published by Pharmaceutical Information Associates, Ltd.

- Indication: **Congestion due to cystic fibrosis**
  - Drug Tradename: **Pulmozyme**
  - Manufacturer: **Genentech**

Cystic fibrosis (CF) is the most common fatal genetic disease in the western world. It occurs when the affected individual inherits two abnormal copies of the gene that codes for the chloride channel protein (the "cystic fibrosis transmembrane conductance regulator" or CFTR). Heterozygotes (with one normal and one defective gene) are asymptomatic carriers. Chronic progressive lung disease is the major cause of death and disability in CF patients. Normally, cyclic AMP regulates the chloride channel in airway epithelial cells, allowing the movement of chloride along an electrochemical gradient from the cell cytoplasm to the lumen. In CF patients, however, CFTR does not respond normally to cyclic AMP and the chloride channel remains closed. Not only is chloride secretion defective, but airway epithelial cells also show increased sodium reabsorption. The result is increased salt within the epithelium, which draws in water, thus dehydrating airway secretions and making them thick, tenacious, and difficult to expectorate. These secretions obstruct the airways, contribute to reduced lung volume and expiratory flow rates, and promote growth of pathogenic microorganisms. DNA that spills from white blood cells fighting infection also contributes substantially to sputum viscosity and tenacity.

Managing lung congestion includes chest physiotherapy to help clear secretions and drug therapy to reduce lung infection and inflammation and to improve airflow and sputum clearance. Recently the FDA approved a new drug for managing lung congestion in CF patients: recombinant deoxyribonuclease or DNase (dornase alpha, **Pulmozyme/Genentech**). A genetically engineered copy of a natural human enzyme, Pulmozyme DNase increases the fluidity of airway secretions by snipping DNA strands in sputum. In clinical trials, aerosolized DNase was easily administered, well tolerated, and efficacious; it reduced sputum viscosity, improved forced expiratory flow rates, and improved patient well being. It was particularly effective in patients with purulent sputum. DNase is the first new drug for CF to be approved in more than three decades, which helps explain why it moved from the laboratory to the market in record time.

In a National Institutes of Health placebo-controlled, crossover study, aerosolized DNase in various dosage regimens -- 10 mg three times daily, 20 mg once daily, and 20 mg twice daily -- improved lung function by 10% to 20% in 16 CF patients. The drug consistently elevated forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV1) compared with baseline values and values after the placebo period. No associated adverse effects were noted 3 months after therapy, nor were any anti-DNase antibodies detected. (Hubbard RC *et al*. *N Engl J Med.* 1992; **326**: 812-815.) In a larger 6- month study of 968 young CF patients (aged 5-20 years) with mild or moderate disease, a 5% improvement in lung function measurements was noted, along with substantial subjective improvement. Patients reported less shortness of breath, significantly fewer lung infections, less need for intravenous antibiotics, reduced hospital stays, better sleep, less wracking coughs, and less loss of voice. Side effects included hoarseness, throat irritation, and rash. Approximately 5% of patients developed antibodies against DNase. At the completion of the trial, the 968 participants either continued DNase therapy or started therapy if they were in the placebo group.

DNase administration is by inhalation via a plastic tube extending from a hand-held canister. Genentech has priced therapy at $9,855 per patient per year, wholesale. The retail price of Pulmozyme DNase is expected to reach $13,000 per year, although Genentech plans to make the

drug available to indigent patients. Even though therapy is costly, Genentech hopes to generate $500 million in annual sales within 3 years from the estimated 50,000 or more CF patients in the United States and Western Europe (where the drug will be marketed jointly with Genentech's Swiss parent, Roche Holding Ltd.). The drug may also benefit patients with other types of lung diseases, such as severe bronchitis and asthma.

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Additional information from Genentech and the FDA.

flunisolide

Tradename AeroBid
Manufacturer Forest Pharmaceuticals
Treatment Class Respiratory
Indication Asthma

Asthma Inhalation Therapy

From the January 1994 issue [*Med Sci Bull*. 1996;19(3):1] of *Medical Sciences Bulletin*

Up to 5% of the US population suffers from asthma, a respiratory condition characterized by airway inflammation, airway obstruction (at least partially reversible), and airway hyperresponsiveness to such stimuli as environmental allergens, viral respiratory-tract infections, irritants, drugs, food additives, exercise, and cold air. The major underlying pathology in asthma is airway inflammation. Inflammatory cell -- eosinophils, CD4+ lymphocytes, macrophages, and mast cells -- release a broad range of mediators, including interleukins, leukotrienes, histamine, granulocyte-colony-stimulating factor, and platelet aggregating factor. These mediators are responsible for the bronchial hyperreactivity, bronchoconstriction, mucus secretion, and sloughing of endothelial cells. Because asthma is an inflammatory disease, early treatment with **inhaled glucocorticoids** is recommended for optimum long-term control. **Beta-agonists**, while effective for symptomatic control in the short term, do not control

the inflammation; indeed, there is evidence that excessive use may exacerbate asthma and contribute to its worldwide increase in prevalence, morbidity, and mortality. (Barnes PJ. *Br Med J*. 1993; **307**: 815-816. Kemp JP. *Arch Intern Med*. 1993; **153**: 805- 812.)

Glucocorticoid Therapy: Inhalation vs Oral

Inhalation therapy with **anti-inflammatory glucocorticoids** is recommended for the initial treatment of asthma, with the addition of beta-agonists as needed. Glucocorticoids reduce the risk of fatal and near fatal asthma in both children and adults, and administration by inhalation (compared with oral administration) reduces the risk of systemic side effects. This is because the glucocorticoids available for inhalation therapy are highly active topically and only weakly active systemically, which minimizes effects on the pituitary-adrenal axis, the skin, and the eye. Side effects associated with inhalation therapy are primarily oropharyngeal candidiasis and dysphonia (due to atrophy of laryngeal muscles). Both side effects are less common when a spacer is used because less drug is deposited in the oropharynx and larynx. Oral glucocorticoids cause atrophy of the dermis -- with thin skin, striae, and ecchymoses -- but inhaled glucocorticoids do not cause similar changes in the respiratory tract.

Another advantage of inhaled over oral administration is that the direct deposition of steroid in the airways generally provides more predictable administration. The oral doses required for adequate control vary substantially, whereas inhaled glucocorticoids are usually effective within a narrower range. There are, however, a number of factors that influence the availability of inhaled glucocorticoids: extent of airway inflammation; degree of lung metabolism; amount of drug swallowed and metabolized in the GI tract; the patient's ability to coordinate the release and inspiration of the medication; type of glucocorticoid; and the delivery system. (When a spacer is used between the inhaler and the mouth, the inhaler is easier to manipulate and more drug reaches the lungs.)

The most widely used aerosol glucocorticoids are beclomethasone dipropionate (**Vanceril/Schering**) and budesonide (**Rhinocort/Astra**, similar to beclomethasone). These agents have a high affinity for intracellular glucocorticoid receptors but are rapidly metabolized to biologically inactive compounds. In one study comparing the efficacy of inhaled versus oral therapy for reducing respiratory symptoms and improving airway function, the ratio of the potency of inhaled budesonide versus oral prednisone was about 40 to 1. There is no evidence that efficacy diminishes with time. Asthma can usually be controlled with beclomethasone or budesonide 200 to 800 microgram inhaled daily. Doses up to 1000 microgram daily have little effect on pituitary-adrenal secretion in adults; larger doses may cause some (variable) dose-dependent suppression of secretion. Doses of 2000 microgram/day in adults have been associated with thinning of the skin, slight glucose intolerance, psychiatric disturbances (rarely), and cataracts (with long-term therapy). Beclomethasone in doses of 1000 to 2000

microgram/day (long term) has been associated with decreases in bone density. Flunisolide (AeroBid/Forest) and triamcinolone (Azmacort/Rorer) are also available for inhalation therapy in the United States, but they haven't been studied as extensively. (Utiger RD. *N Engl J Med*. 1993; **329**: 1731-1733.)

Inhaled Glucocorticoids in Young Children

Early treatment with inhaled glucocorticoids gives optimal long-term control of asthma. In children, there is some evidence that delaying the initiation of such therapy may result in irreversible changes in the airways. Moderate doses of glucocorticoids by inhalation have proved to be safe for children, even young children, and even when given over long periods of time. In their study of 15 children aged 2 to 7 years given budesonide 200 microgram/day by inhalation, Volovitz et al. found the drug to be remarkably safe and effective for up to 5 years. The severity of asthma decreased in the first month of therapy (58% reduction in the number of days with asthma symptoms and 75% reduction in use of bronchodilators), and improvement was maintained. At the end of the trial, asthma recurred in 13 of the 15 patients enrolled, and budesonide was required to control the symptoms.

Budesonide did not suppress pituitary-adrenal function; there was no documented effect on 24-hour serum cortisol concentration, serum cortisol responses to corticotropin, or urinary cortisol excretion. Growth patterns -- height, weight, and bone age -- were normal throughout the treatment period for all patients. Larger doses have been shown to delay growth and skeletal maturation, but then so can asthma. No cataracts were seen (although cataracts have been reported with glucocorticoid inhalation therapy). The investigators concluded that "prolonged administration of budesonide in a relatively low dose of 200 microgram per day to young children with severe asthma is not only effective but also safe, as demonstrated by their normal linear growth and normal pituitary-adrenal function." (Utiger RD. *N Engl J Med*. 1993; **329**: 1731-1733. Volovitz B *et al. N Engl J Med*. 1993; **329**: 1703- 1708.)

The Problem with Metered-dose Inhalers

The standard device for asthma inhalation therapy is the **metered-dose aerosol inhaler (MDI)**. One problem with these devices is the difficulty of determining when the inhaler is out of medication. Williams *et al*. interviewed 51 asthmatic patients and examined their inhalers to see whether the patients were using their inhalers appropriately.

They found that in this particular group of patients, the correct protocol was often ignored. Of the 81 inhalers assessed, 21 were at their "floating weight" (that is, the canisters had delivered the licensed number of doses) and 12 were at their "red weight" (canisters had enough expellent left for only 48 hours). Nineteen patients had no inhaler in reserve. During the interview, 37 of the 51 patients admitted to

using an inhaler until it was almost or completely empty, and 36 occasionally or frequently ran out of inhalant (33 of whom became moderately or severely wheezy).

Only three assessed their inhalers by flotation, and none asked to float their canister when given a nearly empty canister to use. Almost all the patients continued to use their inhalers after the canisters had delivered the licensed number of doses. Running out of medication unawares may provoke rebound bronchospasm and increase the risk of morbidity and even mortality, said the investigators. They concluded that "aerosol metered dose inhalers give insufficient information about the drug remaining in the inhaler and are therefore unsafe. A counter mechanism could rectify the problem." (Williams DJ *et al. Br Med J*. 1993; **307**: 771-772.)

Bergner *et al*. also believe that some exacerbations of asthma occur when patients continue to use MDIs beyond the specified number of sprays. The problem is that patients are unable to tell by sight, sound, or taste when the dose is no longer adequate, so they generally continue to use their inhalers until the canister is exhausted. "Our own unpublished trial indicated that the 'sink or float' test that some pharmaceutical companies recommend does not accurately reveal when the specified number of sprays has been actuated. When metered dose medications are taken at a regularly scheduled frequency, patients should calculate the finish date and mark their calendars. When an MDI is used 'as needed,' patients should keep a written tally, although this is cumbersome and unlikely to occur." (Bergner A *et al. JAMA*. 1993; **269**: 1506.)

A second problem with canisters is the tendency for some inhalers to deliver less than promised. Bergner et al. noted that many of their patients claim that some inhaler sprays decline in force, volume, or effectiveness before the specified number has been used, even though the device is shaken before use. (Bergner A *et al. JAMA*. 1993; **269**: 2051.) Weiss noted that a decline in the force of spray may occur long before the end of the life of the canister as specified by the manufacturer. An asthmatic himself, Weiss has noted that his flunisolide (**AeroBid**) inhaler loses spray strength after the 17th day of use, even though the product should last for 25 days. Weiss wrote to the manufacturer (**Forest Pharmaceuticals**), but his request for information was ignored. He wrote to the FDA, but waited 8 months before getting some (incomplete) information. He concluded that, "(1) the failure of MDIs to deliver the specified number of specified doses may be a cause of asthmatic exacerbations; (2) drug delivery by MDIs as a function of the number of inhalations used needs documentation and should be required by the FDA; and (3) it may be impossible to get desired information out of a pharmaceutical company and a long time to get a response of any sort from the FDA." (Weiss W. *JAMA*. 1993; **270**: 2050.)

A Forest Pharmaceuticals spokesperson replied that failure to clean the inhaler system may have caused the "perceived" loss of efficacy. Cleaning involves

removing the metal cartridge, rinsing the plastic inhaler and cap with briskly running warm water, drying thoroughly, and replacing cartridge and cap. Failure to clean the inhaler system properly may result in medication clogging the delivery system, which could lead to a decrease in the dose delivered. The FDA also commented that a number of factors may be involved in spray decrease, including priming (priming an inhaler before use is counted as one spray), temperature (the inhaler should be at room temperature), and agitation (the inhaler should be well shaken). (Bodenheimer S. *JAMA*. 1993; **270**: 2050. Nightingale SL. *JAMA*. 1993; **270**: 2051.)

One reason for diminished dose administration is the design of the MDI itself. When only 15% or so of the original amount of suspension is left in the MDI, the meter chamber does not fill uniformly and the doses left are below acceptable levels. Manufacturers of some inhalers warn patients of this fact. However, "Patients generally do not count sprays and are not aware of how close they are to the end of the specified number of sprays," said Bergner. "Therefore, when their asthma exacerbates, they do not make the association between the exacerbation and the diminishing doses that may be delivered toward the end of the canister's 'life.'" Either they use more beta-agonist if the efficacy of the glucocorticoid is diminished, or vice versa, or they just assume their asthma got worse. Physicians donate usually ask how close patients are to the end of their inhalers but just assume that an asthma exacerbation is due to other causes (viral infection, pollen count, weather change, etc.). "It is our concern that the asthma patients most likely to be seriously affected by diminished doses are those with the most continuous, severe, and disabling asthma," said Bergner, and "the insidious reduction in doses delivered at the end of metered dose inhalers may be contributing, in part, to the increased mortality, hospitalizations, and morbidity of asthma in spite of the great advances made in our understanding and therapy of this common disorder." (Bergner A *et al. JAMA*. 1993; **270**: 2051.)

fluticasone propionate

Tradename Flonase
Manufacturer Allen & Hanburys
Treatment Class Anti-Inflammatory, Antiallergic, and Immunologic
Indication Seasonal and perennial allergic rhinitis

Advances in the Pharmacotherapy of Allergies and Asthma

As the pathogenesis of asthma becomes better understood, the drug therapies that are emerging to combat the symptoms of this disease are more effective and have safety profiles superior to those of existing drug therapies.

Among the therapies described at the recent annual meeting of the American Academy of Allergy, Asthma, and Immunology were:

Salmeterol: Patients who use salmeterol 42 mcg bid or other asthma therapies such as prn beta-agonists did not have a higher-than-expected incidence of cardiac arrhythmias (Poster 1333).

Fluticasone: Novel dosage forms called the Diskhaler and the Diskus have been found to effectively deliver therapeutic doses of the drug to asthmatic patients (Poster 2041).

Triamcinolone: This drug has been reformulated with a non-CFC inhalant propellant and has been found to be effective and well tolerated in pediatric asthmatic patients (Poster 1328).

Pranlukast: This orally active, investigational leukotriene receptor antagonist improved pulmonary function and asthma symptoms; it simultaneously reduced the use of rescue albuterol. The improvements were noted to occur as quickly as within 1 week and were sustained for the 12 weeks of the study (Poster 1305).

(AAAAI, February 1997, San Francisco, CA)

Using Corticosteroids to Treat the Common Cold

From issue No. 248-249 (May/June, 1998) of *Medical Sciences Bulletin*

Recently, corticosteroids have been used as adjunctive therapy in certain infectious diseases, including acute viral laryngitis and *H. influenzae meningitis*. A study was conducted to determine if intranasal corticosteroids would decrease the duration and the severity of the symptoms of the common cold by lessening inflammation in the nasal cavity during the infection.

Two hundred adults, average age of 24 years, participated in this double-blind study. They were instructed to begin treatment with fluticasone propionate, a corticosteroid with broad antiinflammatory activity, or placebo, between 24 to 48 hours after cold symptoms appeared. The daily dose consisted of two puffs per nostril four times a day at equal intervals while they were awake, totaling 800 mg/day for 6 days. During the 21 days of the study, they kept a diary of the symptoms they were experiencing by assigning each a number representing its severity (0=absent, 3=severe). They also recorded adverse effects, time off from work or school due to the illness, and body temperature.

In general, fluticasone propionate treatment had no clinically recognizable effects on cold symptoms, although it significantly reduced nasal congestion and cough on some study days. For those infected with rhinoviruses, the treatment caused shedding of viable rhinoviruses, and viruses were found more often in the treated group then the placebo group (37% vs. 14%, $p < 0.001$). However, this did not impact the symptoms of the illness. This study showed that the symptoms were more severe in those subjects with positive cultures for S. pneumoniae, H. influenzae, or M. catarrhalis in the nasopharynx. No changes were observed in the colonization of these bacteria, and the subjects experienced no effect on the severity of their symptoms.

The study determined that using high doses of intranasal fluticasone propionate has no effect on the symptoms or duration of the common cold. In some cases, especially in patients with certain concomitant bacterial infections, symptoms were worse with treatment compared to placebo.

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Corticosteroids Studied For COPD, RA

Mar. 27, 1998: Two studies published in British weekly medical journals present data on use of corticosteroids in chronic obstructive pulmonary disease and rheumatoid arthritis.

Inhaled fluticasone was compared with placebo in 281 COPD patients over a six-month period in a Lancet article (1998; 351: 773-80). Slightly more patients receiving placebo (37% vs. 32%) had at least one exacerbation, but exacerbations were classified as moderate or severe more frequently in the placebo group (86% vs. 60%). The authors conclude that inhaled corticosteroids may have a role in long-term treatment of COPD.

Reprints: J. Efthimiou, Glaxo Wellcome Research and Development, Greenford, Middlesex UB6 0HE, U.K.

An editorialist, commenting on the study (pp. 766-7), agreed that patients whose peak expiratory flow responds to steroids with increases of 15 L/min or more should be continued on such therapy.

Reprints: N. C. Barnes, Resp. Med., London Chest Hosp., London E2 9JX, U.K.

A meta-analysis in the British Medical Journal (1998; 316: 811-8) explores the utility of short-term, low-dose prednisolone in treatment of rheumatoid arthritis. Based on data from 10 published trials, the authors found that oral prednisolone had a marked effect over placebo on joint tenderness, pain, and grip strength. Compared with NSAIDs, prednisolone had a greater effect on joint tenderness and pain but not on grip strength. The group concludes that prednisolone doses of 15 mg or less per day may be used intermittently, especially when symptoms of rheumatoid arthritis are not otherwise controlled.

Reprints: P. C. Gotzsche, Nordic Cochrane Ctr., Rigshospitalet, Dept. 7112, Tagensvej 18 B, DK-2200 Copenhagen N., Denmark; p.c.gotzsche@cochrane.dk.

Accompanying editorialists were unconvinced (pp. 789-90) by the authors' recommendations for more use of prednisolone. Explaining that the authors did not give full weight to the possibility of adverse drug reactions with steroids, the editorialists conclude, "Clinicians who encounter these adverse effects in day to day practice might be forgiven for adopting a more cautious stance than that adopted by the authors from the Nordic Cochrane Centre."

Reprints: C. Cooper, U. Southampton, Southampton Genl. Hosp., Southampton, S016 6YD, U.K.

Apr. 21, 1999: Pharmacotherapy of asthma is addressed in several reports in the Journal of Allergy and Clinical Immunology (1999; 103; www1.mosby.com).

Therapeutic doses of fluticasone had little effect on the hypothalamic-pituitary-adrenal axis in a 28-day study (pp. 622-8). Mean plasma cortisol response to cosyntropin was similar among fluticasone, triamcinolone, and placebo and significantly less than in patients taking prednisone. Triamcinolone was statistically similar to placebo on most measures but reduced the area under the cortisol concentration time curve.

Reprints: J. T. C. Li, Mayo Clinic Foundation, 200 1st St. SW, Rochester, MN 55905.

montelukast

Tradename Singulair
Manufacturer Merck & Co., Inc
Treatment Class Anti-Inflammatory, Antiallergic, and Immunologic
Indication Asthma

Montelukast Approved for Asthma in Adults and Children

From issue No. 246 (March, 1998) of *Medical Sciences Bulletin*

Montelukast was recently approved by the FDA for the prevention and chronic treatment of asthma in adults and children aged 6 years and older. It is the third anti-leukotriene agent (the first two being zafirlukast and zileuton) to be approved for treatment of asthma and the only anti-leukotriene approved for use in children.

The prevalence of asthma, a serious and common chronic disease, is increasing worldwide, especially among children. Asthma is defined as a chronic inflammatory disorder of the airways, marked by reversible airway narrowing and increased airway responsiveness to a variety of stimuli. The recommended therapy for asthma, as outlined in the guidelines of the National Asthma Education and Prevention Program, varies according to asthma severity. In all but mild intermittent asthma, for which the recommended therapy is a short-acting inhaled beta2 agonist for exacerbations, the cornerstone of asthma treatment is anti-inflammatory therapy.

How It Works
Montelukast is a potent and specific antagonist of the cysteinyl leukotriene receptor, known as the CysLT1 receptor, and thus inhibits the physiologic action of leukotriene D4 at this receptor. The cysteinyl leukotrienes B4, C4, and D4 were formerly known collectively as the slow-reacting substance of anaphylaxis (SRS-A). These compounds are released from inflammatory cells, including mast cells and eosinophils, and contribute in several ways to the pathophysiology of asthma. Their effects include bronchoconstriction, increased airway responsiveness, enhanced mucus secretion, increased vascular permeability leading to airway edema, and decreased action of respiratory cilia.

After oral administration, montelukast is rapidly absorbed, with mean oral bioavailability of 64%. The absorption of montelukast is not influenced by the ingestion of food. Maximum plasma concentrations are reached 3 to 4 hours after administration of a 10-mg film-coated tablet and 2 to 2.5 hours after administration of a 5-mg chewable tablet. Montelukast is eliminated predominantly by metabolism followed by biliary excretion. The mean plasma half-life in young adults ranges from 2.7 to 5.5 hours. There is minimal accumulation of parent drug at steady state.

Clinical Tips
The clinical utility and safety of montelukast have been studied in large American and multinational clinical trials. Montelukast has been evaluated in adult patients with asthma of varying severity, including mild and moderate asthma, in addition to exercise-induced bronchospasm and aspirin-sensitive asthma. Clinical trials in children 6 to 14 years of age have assessed the efficacy and safety of montelukast in pediatric patients with mild to moderate asthma and those with exercise-induced bronchospasm.

Endpoints examined in large-scale clinical trials enrolling adult patients with mild persistent asthma not controlled with beta agonist included both objective and subjective asthma parameters as well as asthma outcomes such as frequency of asthma exacerbations and attacks and the need for rescue corticosteroid therapy. Montelukast produced rapid improvements in asthma signs and symptoms, with decreases in beta-agonist use and improved asthma symptoms evident after the first dose. After 12 weeks of therapy with montelukast 10 mg once daily at bedtime, forced expiratory volume in 1 second (FEV1) had improved significantly and beta-agonist use had fallen significantly as compared with results for patients receiving placebo. In addition, significant improvements relative to placebo were recorded for montelukast-treated patients in daytime symptom scores, frequency of nocturnal awakenings, quality-of-life measures, and several asthma outcomes, notably frequency of asthma exacerbations and attacks and the need for oral corticosteroid rescue therapy. No tolerance to the treatment effect of montelukast has been noted in non placebo-controlled extension studies of up to 1 year in duration.

The suitability of once-daily administration of montelukast 10 mg was evaluated in a small group of patients with exercise-induced bronchospasm. Compared with patients receiving placebo, patients treated with montelukast showed significant reductions in the fall in FEV1 after exercise. This protection was present at the end of the dosing interval, namely 20 hours after the previous day's bedtime dose of montelukast, and persisted throughout the 12-week treatment

period, with no evidence of tolerance developing. Among children, montelukast 5 mg once daily also inhibited exercise-induced bronchoconstriction at the end of the dosing interval.

In patients receiving an inhaled corticosteroid, the addition of montelukast to the treatment regimen produced additional benefit, as measured by significant improvement in FEV1 relative to patients receiving inhaled beclomethasone alone. In another double-blind, placebo-controlled trial, addition of montelukast permitted tapering of the inhaled corticosteroid dose by a mean of 47% over 12 weeks of treatment compared with 30% in the placebo group. Fully 40% of montelukast-treated patients were able to taper completely off corticosteroids during the treatment period, more than in the placebo group (29%).

In a 4-week study of aspirin-sensitive asthmatics, 87% of whom were receiving oral or inhaled corticosteroids or both, the addition of montelukast to treatment caused significant improvements in FEV1 and beta-agonist use. Moreover, patients in the montelukast group had fewer days with asthma exacerbations than those in the placebo group and reported significant improvement in global evaluations and quality-of-life assessments.

Montelukast has been studied in one large, double-blind, placebo-controlled clinical trial of children aged 6 to 14 years. Results for pediatric patients receiving 5 mg montelukast once daily were similar to those for adult asthmatics, with significant improvement recorded in both objective and subjective asthma parameters, as well as improvement in parental global evaluations and asthma exacerbation rates. Merck has committed to study the effect of chronic, long-term administration of montelukast on linear growth among pediatric patients.

Clinical trial results suggest that montelukast can be administered as controller therapy for patients with mild, persistent asthma whose symptoms are not controlled with as-needed beta agonist. In addition, patients with moderate to severe asthma who are receiving inhaled or oral corticosteroids, or both, may benefit from addition of montelukast to the treatment regimen. However, at present, insufficient data are available for the manufacturer to make specific recommendations for these uses.

Adverse events among patients receiving montelukast occurred with frequency similar to that among patients in the placebo groups. Montelukast use does not appear to be associated with rises in serum transaminase levels, as has been reported for other anti-leukotriene agents.

Montelukast shows a dose response, with the 10-mg dose identified as the minimal dose producing maximum clinical response in adults. There is no evidence of dose-related toxicity, as early studies assessed doses as high as 200 mg daily for several weeks without evidence of tolerability or safety problems. The recommended dose in adolescents and adults 15 years of age and older is 10 mg once daily in the evening. The pediatric dose for patients 6 to 14 years of age is 5 mg once daily in the evening, administered as a chewable tablet.

What the Patient Should Know

1. Patients should be advised to take montelukast daily as prescribed, even when they are asymptomatic.

2. Montelukast is not indicated for the treatment of acute asthma attacks. Short-acting inhaled beta agonist should be used to treat acute attacks.
3. Phenylketonuric patients should be informed that the 5-mg chewable tablet contains phenylalanine.

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Exercise-Induced Asthma: Effects of Salmeterol and Montelukast

July 16, 1998: This morning's New England Journal of Medicine (1998; 339) sheds light on appropriate therapy of exercise-induced asthma.

Long-term treatment with salmeterol protected against exercise-induced asthma, but continued administration reduced the length of time for which the drug is effective (pp. 141-6).

In patients performing cycle ergometry while breathing frigid air, salmeterol's effectiveness at 30 minutes after an inhaled dose was maintained throughout a one-month study. However, the drug's effect at nine hours after a dose declined over the 30-day period.

Reprints: E. R. McFadden, Jr., Pulmonary and Critical Care Medicine, U. Hosp. of Cleveland, 11100 Euclid Ave., Cleveland, OH 44106.

In 110 patients ages 15-45 years with mild asthma, montelukast 10 mg daily at bedtime protected against exercise-induced asthma over a 12-week study period. Compared with placebo, the leukotriene modifier improved the area under the FEV1 curve, the maximal decrease in FEV1 after exercise, and the time to return from the maximal decrease in FEV1 to pre-exercise levels. Adverse effects were similar between the groups, and patients receiving montelukast did not experience tolerance to the medication or rebound worsening of lung function after discontinuation. However, one fourth of the patients did not respond to montelukast therapy.

Reprints: T. F. Reiss, Merck and Company, P.O. Box 2000, Rahway, NJ 07065.

Editorialists commenting on the studies warn that more head-to-head comparisons of active asthma therapies are needed. "Only patients with easily controlled, stable asthma were studied," they explain. "Whether the long-term control of exercise-induced symptoms provided by montelukast is similar or superior to that provided by other leukotriene modifiers or an optimally administered inhaled glucocorticoid remains to be tested in patients with mild, moderate, or severe asthma. Until more direct comparisons are available, physicians and their patients must decide for themselves which among an expanding range of therapeutic options to use."

Reprints: J. Hansen-Flaschen, U. Pennsylvania Sch. of Med., Philadelphia, PA 19104.

Comparison of drug therapies for exercise-induced asthma

January 18, 2000:

A new study concludes that Merck & Co.'s drug Singulair (montelukast) offers longer-lasting protection against exercise-induced asthma flare-ups, compared to the commonly used, and older, drug Serevent (salmeterol), from Glaxo Wellcome.

- researchers randomized 191 people with exercise-induced asthma to treatment with either once-daily montelukast or twice-daily salmeterol to collect data.
- found that both medications were effective at reducing exercise-induced asthma within three days of treatment onset, but that the benefits of salmeterol diminished after four weeks of treatment, and even further after eight weeks of treatment.

- salmeterol recipients also resorted to other medications to control asthma symptoms more often than montelukast-treated patients.
- authors note that while montelukast appeared to be more effective than salmeterol, neither drug completely eliminated exercise-induced asthma.
- note: Merck & Co. funded the study, the makers of montelukast.

The study is in the Annals of Internal Medicine (2000;132:97-104).

pranlukast

Tradename Ultair
Manufacturer SmithKline Beecham
Treatment Class Respiratory
Indication Asthma

Focus On: New Receptor Antagonists

From the November 1996 issue [*Med Sci Bull*. 1996;19(3):8] of *Medical Sciences Bulletin*

Asthma and the leukotriene receptor: new options for therapy

Asthma is a chronic inflammatory disease of the airways that is complicated by episodes of acute inflammation. Even patients with mild disease show airways inflammation, including infiltration of the mucosa and epithelium with activated T cells, mast cells, and eosinophils. T cells and mast cells release cytokines that promote eosinophil growth and maturation and the production of IgE antibodies, and these, in turn, increase microvascular permeability, disrupt the epithelium, and stimulate neural reflexes and mucus- secreting glands. The result is airways hyperreactivity, bronchoconstriction, and hypersecretion, manifested by wheezing, coughing, and dyspnea.

Traditionally, asthma has been treated with oral and inhaled bronchodilators. These agents help the symptoms of asthma, but do nothing for the underlying inflammation. Recognition during the last 10 years of the importance of inflammation in the etiology of asthma has led to the increased use of corticosteroids, but many patients continue to suffer from uncontrolled asthma. Now the FDA has approved the first of a new class of antiasthma drugs -- the leukotriene inhibitors and antagonists -- with the potential to interfere with the initial steps in the inflammatory cascade.

We first reported on leukotrienes in MSB back in 1979, when the so-called "slow reacting substance of anaphylaxis" was identified as an arachidonic acid derivative and given the name "leukotriene C." Since that time, scientists have determined that the leukotrienes (of which there are A, B, C, D, and E subtypes) play a crucial role in asthma. They cause airways smooth muscle spasm, increased

vascular permeability, edema, enhanced mucus production, reduced mucociliary transport, and leukocyte chemotaxis.

Like the related prostaglandins, leukotrienes are synthesized from arachidonic acid in the cell membrane. Arachidonic acid in mast cells, macrophages, monocytes, eosinophils, and basophils is released from membrane phospholipids by the activation of phospholipase A2. After its release, arachidonic acid undergoes metabolism via two major pathways: the cyclooxygenase pathway (which produces various prostaglandins and]xanes) and the 5-lipoxygenase pathway (which produces leukotrienes). The prostaglandins, thromboxanes, and leukotrienes are known collectively as eicosanoids.

There are a number of anti-leukotrienes under investigation that either block leukotriene receptors or prevent leukotriene synthesis by blocking the enzyme 5-lipoxygenase (just as aspirin and the nonsteroidal anti-inflammatory agents block the other enzyme -- cyclooxygenase -- involved in arachidonic acid metabolism). The leukotriene inhibitors are a varied lot: some block 5-lipoxygenase directly, some inhibit the protein that "presents" arachidonate to 5- lipoxygenase, and some displace arachidonate from its binding site on the protein. The leukotriene antagonists, by contrast, block the receptors themselves that mediate airways hyperreactivity, bronchoconstriction, and hypersecretion.

The market for the new leukotriene inhibitors and antagonists is in the billions of dollars. An estimated 13 million Americans have asthma, and many are not controlled with available bronchodilators and corticosteroids. Indeed, asthma mortality has risen 40% since 1982. Abbott, Merck, and SmithKline Beecham all have anti-leukotrienes in final clinical trial, and Zeneca's **zafirlukast** (*Accolate*) was approved in late September. Abbott's **zileuton** (*Zyflo*) was the first leukotriene to be reviewed by the FDA. It was rejected in October 1995 because of adverse effects on liver function tests, but Abbott refilled an application in June, and an FDA advisory committee has recommended the drug for approval with the suggestion that liver function be carefully monitored. SmithKline Beecham's **pranlukast** (*Ultair*) is a leukotriene receptor antagonist licensed from Ono Pharmaceutical and approved for marketing in Japan. Merck's **montelukast** (*Singulair*) is a long-acting agent that will be the subject of an NDA filing during the first part of 1997. A number of additional drugs are under investigation, including the leukotriene antagonists **pobilukast**, **tomelukast**, and **verlukast**, and several inhibitors of leukotriene synthesis. (Holgate ST et al. J Allergy Clin Immunol. 1996;98:1-13. Spector SL. Annals of Allergy, Asthma, Immunol. 1995;75:473- 474. Additional information from the manufacturers.)

Where Do Leukotriene Modifiers Fit in Therapy?

Aug 28, 1998: An editorial in the Journal of Allergy and Clinical Immunology (1998; 102: 170-2) assesses the place of leukotriene modifiers in asthma therapy. Responding to research indicating that the investigational agent pranlukast may

attenuate allergen-induced early- and late-phase pulmonary responses, the editorialist notes, "The challenge for the future will be to show that the leukotriene modifiers have significant effects on reducing airway inflammation and disease progression.... If this is accomplished, the leukotriene modifiers may become one of the preferred long-term controller therapies for asthma."

The author names these potential applications of the orally administered agents:

- Alternatives to inhaled glucocorticoid therapy in patients with mild persistent asthma who cannot take the inhaled medication
- Alternatives to high-dose inhaled glucocorticoid therapy
- Addition to therapy, taking advantage of the leukotriene modifiers different mechanisms of action
- Alternative medications in patients with aspirin sensitivity
- Opportunity to improve understanding of asthma and perhaps identify patient subgroups with a primary leukotriene-modified process

New Asthma Drugs Produce Reactions

Mar. 19, 1999: Two case reports of adverse reactions to leukotriene modifiers prompt an editorialist in the Journal of Allergy and Clinical Immunology (1999; 103) to warn of idiosyncratic reactions to these new asthma agents.

Drug-induced lupus was associated with zafirlukast therapy in the first case (pp. 533-4). A nine-year-old girl received the agent for eight days when symptoms began. The agent was continued for two months, during which symptoms continued. Following drug discontinuance, symptoms gradually resolved over the following two months.

Reprints: T. H. Finkel, Natl. Jewish Med. Res. Ctr., 1400 S. Jackson St., Denver, CO 80206.

A leukotriene modifier approved for marketing in Japan, pranlukast, produced Churg-Strauss syndrome after corticosteroid withdrawal (pp. 534-5). Previously associated only with zafirlukast therapy, Churg-Strauss has usually occurred in patients with histories of chronic sinusitis and may be unmask by corticosteroid withdrawal.

Reprints: M. Kinoshita, Medicine, Kurume U. Sch. of Med., 67 Asahi-machi, Kurume 830-0011, Japan.

The editorialist explores the link between leukotriene modifier therapy and hypersensitivity/ autoimmune reactions such as these (pp. 374-5). Since the conditions occur rarely, they could not have easily been detected during clinical testing, he notes. "Further immunopathogenetic study of the association of

leukotriene modifiers and eosinophilia and Churg-Strauss syndrome in the small number of patients may highlight new mechanisms of the disease," he concludes.

Reprints: www.mosby.com/jaci.

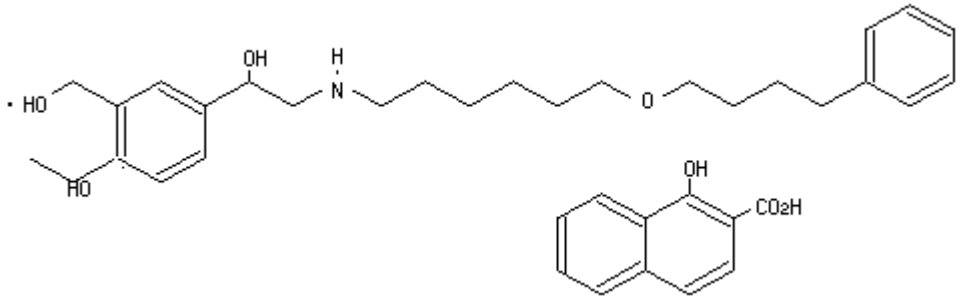
salmeterol

Tradename Serevent Inhalation Aerosol
Manufacturer Glaxo Wellcome
Treatment Class Respiratory
Indication Asthma

Serevent Long-acting Inhaler for Asthma

From the June 1994 issue of *Medical Sciences Bulletin*, published by Pharmaceutical Information Associates, Ltd.

The Food and Drug Administration (FDA) recently granted marketing approval for salmeterol xinafoate (**Serevent Inhalation Aerosol/Glaxo**). The product is the first long-acting inhaled bronchodilator to reach the US market. It is indicated for twice-daily use in maintenance treatment of asthma and prevention of bronchoconstriction in patients aged 12 years or older who have obstructive airway disease.



Potentially Large Market

Serevent has a large potential market: an estimated 12 million Americans have asthma. A chronic condition, asthma is characterized by symptoms ranging from occasional wheezing and coughing to severe shortness of breath and tightening in the chest. Asthma sufferers often wake up during the night because of nocturnal symptoms. Until now, bronchodilator therapy meant having to inhale doses every 4 to 6 hours; thus, it was not possible get a full night's protection. Serevent represents a significant advance, because a single dose provides 12-hour protection.

Chemically, Serevent is a racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol, a highly selective beta2-adrenergic bronchodilator. The aerosol formulation consists of the active drug in a mixture of trichlorofluoromethane and dichlorofluoromethane with lecithin.

Mode of Action

Salmeterol is at least 50 times as selective for beta2-adrenoceptors as albuterol. Like other beta2-adrenoceptor agonists, salmeterol stimulates the intracellular enzyme adenyl cyclase, which catalyzes the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP). Accumulation of cAMP relaxes bronchial smooth muscle and inhibits the release of mediators of immediate hypersensitivity, especially from mast cells. In humans, salmeterol inhibits early- and late-phase responses to inhaled allergens, an effect that lasts more than 30 hours. Single doses of the drug attenuate allergen-induced bronchial hyperresponsiveness; however, the clinical relevance of this anti-inflammatory action has not been established.

Because salmeterol acts locally in the lungs, plasma drug concentrations are not clinically relevant. After administration of therapeutic doses, systemic concentrations may be very low or non-detectable. Nevertheless, in healthy volunteers administration of 1 mg of drug produced peak plasma concentrations of about 650 pg/mL at about 45 minutes. The estimated terminal elimination half-life was 5.5 hours.

Salmeterol undergoes extensive hydroxylation and is eliminated primarily in the feces. The drug is 94% to 98% bound to plasma proteins.

Clinical Data

In single-dose trials, salmeterol produced effective bronchodilation, defined as an increase of more than 15% in 1-second forced expiratory volume (FEV1), within 10 to 20 minutes after administration of a 42-µg dose. Peak therapeutic improvement occurred about 180 minutes after administration, and in most cases the improvement remained clinically significant for 12 hours.

Serevent has been used in more than 50 countries. Clinical trials have tested the product in more than 35,000 patients. It has been shown to significantly increase mean morning peak expiratory flow rate and the mean percentages of days without symptoms and of nights without awakenings and to decrease the need for rescue medications.

In maintenance therapy, the recommended dosage is 42 µg (two inhalations) of drug twice a day (morning and evening). For prevention of exercise-induced bronchoconstriction, patients should take two inhalations 30 to 60 minutes before exercising. (Note: patients using Serevent for maintenance therapy should not take additional doses to prevent exercise-induced bronchoconstriction, and the drug should not be used to treat acute symptoms of asthma). Serevent may be used with or without concomitant corticosteroid therapy.

However, if patients are using corticosteroids, they should not stop or reduce that medication just because they feel better -- salmeterol and corticosteroids have different actions, salmeterol inhibiting airway constriction and corticosteroids suppressing inflammation. Patients may use short-acting beta-agonists intermittently while receiving Serevent maintenance therapy, but they should discontinue maintenance use of any short-acting bronchodilators. They should also be alert for an increasing need for short-acting drugs, which may be a sign of destabilized asthma.

Side Effects

Side effects are similar to those reported for other widely used inhaled bronchodilators. The most frequently reported are tremors, headaches, and coughs. Other possible adverse reactions include tachycardia, palpitations, immediate hypersensitivity reactions, nervousness, and paradoxical bronchospasm. Use of Serevent is contraindicated for patients with hypersensitivity to any component of the product. Current evidence indicates that dose alteration is not necessary for elderly patients. Use in infants or children less than 12 years old or in pregnant or nursing women has not been studied. Concomitant use of monoamine oxidase (MAO) inhibitors may potentiate the effects of Serevent.

Important concerns regarding the safety of salmeterol have been raised internationally. There was a small, statistically nonsignificant increase in asthma-related deaths among patients treated with salmeterol compared with those taking albuterol. (Castle W *et al. Br Med J*. 1993; **306**: 1034- 1037.) Others have reported cases of sudden respiratory arrest in otherwise healthy young asthmatics treated with salmeterol. (Clark CE *et al. Respir Med*. 1993; **87**: 227-228.) Further experience with the drug is needed to confirm whether this is a clinically important problem with salmeterol.

How Supplied

Serevent Inhalation Aerosol is available in 13-g canisters containing 120-metered actuations (each delivering 25 µg salmeterol base from the valve and 21 µg from the actuator). Also available are 6.5-g canisters containing 60 metered actuations. (*FDC Reports*. Feb. 14, 1994, pp.23-24. Brogden RN & Faulds D. *Drugs*. 1991; **42**: 895-912; additional information from the manufacturer.)

Improving lung function in patients with chronic bronchitis and emphysema

> **April 19, 1999:** A recent study concludes that Glaxo Wellcome Inc.'s Serevent(R) (salmeterol xinafoate) Inhalation Aerosol is effective in improving lung function in patients with chronic bronchitis and emphysema (chronic obstructive pulmonary disease (COPD)).

- researchers at the University of North Carolina at Chapel Hill School of Medicine compared twice-daily treatment with Serevent to four-times-daily treatment with the anticholinergic bronchodilator Atrovent(R) (ipratropium bromide) in 411 COPD patients, all of whom had at least a 10-year history of smoking.
- found that, compared to placebo, Serevent therapy resulted in significant improvements in lung function, as evidenced by FEV1 (the volume of air exhaled in one second) and that the effectiveness of the therapy was maintained throughout the 12-week study period.
- authors note that patients treated with Serevent also showed significant decreases in the need for beta2-agonist therapy for the relief of COPD symptoms.
- adverse effects associated with the use of Serevent included: headache (12%), upper respiratory tract infection (9%), sore throat (8%) and diarrhea (5%).

- the study suggests that Serevent may be preferable to other therapies, including Atrovent, due to its longer- lasting effects that make it necessary to take the drug only twice a day.

  The study is in the journal Chest (April, 1999).

Tolerance Develops to Salmeterol with Two Doses

Feb. 17, 1998: Tolerance to the broncho-protective effect of salmeterol against methacholine- induced bronchoconstriction develops after only the second dose of the long- acting beta-2 agonist. The study of 10 patients with mild asthma is in Annals of Allergy, Asthma, and Immunology (1998; 80: 31-4).

Concerns about regular use of beta agonists in patients with asthma have led researchers to analyze methacholine-induced bronchoconstriction in patients taking salmeterol. The current study indicates that, after one dose of salmeterol, the amount of methacholine needed to produce a 20% fall in FEV1 was significantly greater than the amount required after two doses, indicating development of tolerance.

Reprints: D. E. Drotar, Dept. of Med., Royal U. Hosp., Saskatoon, SK S7N 0W8, Canada.

Salmeterol Improves QOL In Refractory Asthma

Mar. 16, 1998: In the Journal of Allergy and Clinical Immunology (1998; 101: 188-95), researchers report that salmeterol improved quality of life indicators in patients whose conditions were not well controlled with daily-inhaled corticosteroids. On the disease-specific Asthma Quality of Life Questionnaire, global scores improved, as did individual domains (activity limitations, asthma symptoms, emotional function, and environmental exposure).

Patients taking salmeterol had improved clinical measures of efficacy, the paper reports, as well as a decreased requirement for as-needed albuterol. The 506 patients were randomly assigned to salmeterol 42 mcg or placebo delivered using a metered dose inhaler. Improvements were found in FEV1, morning and evening expiratory flow, and asthma symptoms.

Reprints: J. P. Kemp, Allergy & Asthma Med. Grp. and Res. Ctr., APC, 9610 Granite Ridge Dr., Suite B, San Diego, CA 92123.

terbutaline sulfate

Tradename Brethine (CibaGeneva Pharmaceuticals), Bricanyl (Aventis)
Manufacturer Ciba Geneva Pharmaceuticals, Aventis
Treatment Class Respiratory
Indication bronchospasm due to asthma, bronchitis

MedWatch News
Letter on an Unapproved Use of Terbutaline Sulfate

FOR IMMEDIATE RELEASE	**FOOD AND DRUG ADMINISTRATION**
November 13, 1997	**Broadcast Media: (301) 827-3434**
	Consumer Hotline: (800) 532-4440

Source: FDA MedWatch Program

Dear Colleague:

The Food and Drug Administration (FDA) would like to call to your attention concerns about subcutaneous administration, via infusion pump, of terbutaline sulfate for the treatment and prevention of preterm labor (tocolytic therapy).

Terbutaline sulfate, in various dosage forms, has been approved by FDA for the treatment of asthma. Adequate data establishing the safety and effectiveness of the use of terbutaline as a tocolytic agent have not been submitted to FDA. Thus, the use of terbutaline sulfate to treat preterm labor is an unapproved or "off-label" use. The only drug product currently approved for tocolytic therapy is ritodrine hydrochloride injection (Yutopar Intravenous Injection, manufactured by Astra), and it is approved for intravenous use only.

FDA is concerned about the promotion and increasingly widespread use of subcutaneous terbutaline delivered by infusion pump for the treatment/prevention of preterm labor. The approved labeling for terbutaline sulfate injection (Brethine, manufactured by Ciba Geneva Pharmaceuticals, and Bricanyl, marketed by Hoechst Marion Roussel), states that the drug should not be used for the management of preterm labor. FDA separately reviews infusion pumps, and they are not labeled for subcutaneous administration of terbutaline.

Based on information available to the Agency, as well as a review of the published literature, it is clear that the demonstrated value of tocolytics in general is limited to an initial, brief period of treatment, probably no more than 48-72 hours. No benefit from prolonged treatment has been documented. In addition, the safety of long-term subcutaneous administration of terbutaline sulfate, especially on an outpatient basis, has not been adequately addressed.

Published reports on the safety of this use are seriously hampered by methodologic inadequacies. It appears that women receiving continuous subcutaneous terbutaline sulfate infusions experience side effects and complications similar to those experienced by women receiving terbutaline and other beta-sympathomimetics intravenously. Complications include chest pain, tachycardia, dyspnea, and pulmonary edema. At least one maternal death occurred during outpatient use of a continuous infusion of terbutaline sulfate by subcutaneous pump. The impact

of long-term use on maternal glucose metabolism and the risks of prolonged exposure of the fetus are largely unknown.

In June 1995, the American College of Obstetrics and Gynecology (ACOG) issued Technical Bulletin Number 206, which addresses preterm labor and, specifically, the use of tocolytic agents to manage uterine contractions. This bulletin notes that intermittent administration of subcutaneous terbutaline has been proposed as an alternative to oral maintenance therapy in certain patients. As stated in the Technical Bulletin, the ACOG found no clinical evidence to support the efficacy of this approach. Further, the bulletin states, "To date, no studies have convincingly demonstrated an improvement in survival or any index of long-term neonatal outcome with the use of tocolytic therapy. On the other hand, the potential damages of tocolytic therapy to the mother and neonate are well documented."

In the absence of data establishing the effectiveness and safety of the drug/device, FDA is alerting practitioners, home health care agencies, insurance carriers, and others that continuous subcutaneous administration of terbutaline sulfate has not been demonstrated to be effective and is potentially dangerous. FDA is investigating the promotional activities of companies providing tocolytic therapy services. We encourage health care professionals to report adverse events associated with the use of terbutaline sulfate as a tocolytic agent to the FDA's MedWatch program at 1-800-FDA-1088/FAX 1-800-FDA-0178. This is a voluntary system of reporting adverse events and product problems to FDA.

If you have comments and concerns about this issue, please contact the FDA Office of Health Affairs, Medicine Staff, telephone number (301) 443-5470.

Sincerely yours,

Stuart L. Nightingale, M.D.
Associate Commissioner for Health Affairs

Theophylline

Tradename Various
Manufacturer Various
Treatment Class Respiratory
Indication Asthma

Behavioral and Cognitive Effects of Theophylline Discounted

From *Medical Sciences Bulletin*, published by Pharmaceutical Information Associates, Ltd

Theophylline is a common treatment for asthma, which affects 5% of the US population. There is, however, a controversy over the possible effects of theophylline on behavior, attention, and

school performance among children. Some data indicate that adverse effects may be linked to elevated theophylline blood levels.

In response to an FDA call for further research, a double blind, crossover study examined the dose-response relationship between serum theophylline concentrations and reported behavioral and cognitive effects.

Fifteen mildly to moderately asthmatic children between the ages of 4.5 and 8 years were randomized to receive either low- dose (8.4 mg/kg/day) or high-dose (19.4 mg/kg/day) theophylline. After a 36-hour washout period, patients were switched to the other study arm. One low-dose patient withdrew after the first dose because of insomnia. Psychological testing was accomplished using the Peabody Picture Vocabulary Test-Revised, a Child Behavior Check List completed by the child's mother, the Sequential Processing Scale of the Kaufman Assessment Battery for Children, and the Continuous Performance Test. The CPT was not given to children younger than five years.

The results were encouraging for parents of children with asthma. Theophylline had no discernible effect on learning. As a group, the children in the study did exhibit an increase in behavioral and emotional problems. One low-dose and one high-dose child who were initially hyperactive, however, improved with treatment. Although one patient showed no behavioral changes at the theophylline level of 23.4 micro/mL, one child became hyperactive at the 22.6 ML/mL level. Side effects, e.g., parent- reported impulsivity and psychosomatic complaints, occurred mainly during the first week of treatment, with significant improvement by the second week. Since three hyperactive children improved with theophylline treatment, children displaying symptoms of attention deficit hyperactivity disorder should not be arbitrarily excluded from theophylline therapy. Formal evaluation of cognitive functioning and behavior should be made if problems persist after several weeks of therapy. Furthermore, physicians must be aware of different dose-response curves for bronchodilation, cognition, and behavior. (Stein MA & Lerner CA. *Ann Allergy* 1993; **70**: 135-140.)

Triamcinolone

Tradename Azmacort
Manufacturer Rhone-Poulenc Rorer
Treatment Class Respiratory
Indication Asthma

Triamcinolone OK in High Doses for Rhinitis

Mar. 16, 1998: Triamcinolone aqueous nasal spray has no measurable effect on adrenocortical function in pediatric patients with allergic rhinitis, even at the highest recommended doses (440 mcg/day), report authors in the Journal of Allergy and Clinical Immunology (1998; 101: 157-62). The small amounts of

drug absorbed were shown in pharmacokinetic studies to decline rapidly, with little or no drug accumulation.

Some 80 children ages 6-12 years received placebo or one of two doses of triamcinolone (220 or 440 mcg/day) for six weeks. No effects on adrenocortical function were reflected in plasma cortisol concentrations following a cosyntropin stimulation test, nor did the drug accumulate during six hours of testing following the final triamcinolone dose after the six weeks of therapy.

Reprints: A. S. Nayak, 130 Franklin Ave., Normal, IL 61761.

Viozan

Generic Name NA
Manufacturer AstraZeneca Pharmaceuticals
Treatment Class Respiratory
Indication Reduce the symptoms of breathlessness, cough, and sputum production that plague sufferers of chronic obstructive pulmonary disease (investigational; not approved in US)

Studies Show Viozan Reduces COPD Symptoms

by Rosemarie Foster, BA, MA

Viozan	
Brand Name:	Viozan
Active Ingredient:	NA
Indication:	Reduce the symptoms of breathlessness, cough, and sputum production that plague sufferers of chronic obstructive pulmonary disease (investigational; not approved in US)
Company Name:	AstraZeneca Pharmaceuticals
Availability:	investigational; not approved in US

Introduction

Patients with chronic obstructive pulmonary disease (COPD, including chronic bronchitis and emphysema) have relied on drugs such as inhaled salbutamol and ipratropium bromide, oral theophylline, and corticosteroids to deal with the muscle spasms,

inflammation, and increased secretions associated with their disease. But for many patients, these agents do not do enough.

A new alternative is currently under investigation. Several presentations made at the American Thoracic Society annual meeting in Toronto in May supported the efficacy of the drug Viozan (AR-C68397AA) for reducing the symptoms of breathlessness, cough, and sputum production that plague COPD sufferers.

The drug is delivered via a pressurized metered dose inhaler and is manufactured by AstraZeneca. AstraZeneca anticipates filing a new drug application in the US by the latter part of 2001.

How It Works
Viozan acts as a dual D2 dopamine receptor agonist and a beta-2-adrenoreceptor agonist. It was designed to inhibit sensory nerve activity in the lung and produces bronchodilation.

Clinical Study Results
Two phase II randomized, double blind, placebo-controlled studies have been completed to evaluate the efficacy of Viozan. In the first study, the efficacy and tolerability of Viozan were compared to that of placebo as well as salbutamol and ipratropium bromide. In a 4-week study, 701 COPD patients were randomized to receive one of three Viozan doses (400 mcg, 600 mcg, or 1000 mcg), salbutamol (200 mcg), ipratropium bromide (40 mcg), or placebo 3 times daily. The 600-mcg dose of Viozan produced a significant reduction in COPD symptoms compared to placebo. At the dose regimens tested, salbutamol and ipratropium bromide showed only limited efficacy.

In the second study, the efficacy and tolerability of Viozan were investigated in a 6-week trial of 872 COPD patients who were randomized to receive one of three Viozan doses (45 mcg, 270 mcg, or 495 mcg) or placebo 3 times daily. Viozan reduced COPD symptoms in a dose-dependent manner, these differences being statistically significant with the two higher doses. At the two higher doses the improvement in symptoms was accompanied by a significant reduction in use of rescue bronchodilator as well as increases in patients' health-related quality of life as measured using the St. Georges Respiratory Questionnaire.

Adverse Events
Safety and tolerability data indicated that Viozan was generally well tolerated. Adverse events that were more common in the

Viozan group compared to placebo included reported in the groups studied included tremor, nausea, and taste of treatment.

References

1. Laitinen, LA, et al. "Efficacy of Viozan (AR-C68397AA) versus salbutamol and ipratropium bromide in the management of COPD." Presented at the 96th meeting of the American Thoracic Society, May 2000.
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5. Merck Manual, Home Edition, 1997 edition, page 179.

Zafirlukast

Tradename Accolate
Manufacturer AstraZeneca
Treatment Class Respiratory
Indication Asthma

News from 1995 AAAI Meeting: Accolate for Asthma

August, 1995: Special to the *Medical Sciences Bulletin*

A variety of novel approaches are being investigated to control the symptoms of asthma. One interesting approach is the administration of drugs that block the inflammatory component of asthma. Leukotrienes have been known to play a role in the inflammatory cascade and one new agent designed to block the activity of leukotrienes, Accolate, has shown significant clinical promise. The following research results were presented at a recent scientific meeting and highlight the activity of this therapeutic agent.

Two New Studies Provide Further Evidence for Effectiveness of Accolate
The results of two new studies on the efficacy and safety of the leukotriene-receptor antagonist **Accolate (tm)** (also known as ICI 204,219) were presented at the recent annual meeting of the American Academy of Allergy and Immunology in New York.

Each study was 13 weeks in length, multicenter, double blind, and involved patients with self-assessed mild-to-moderate asthma. The first study (Lockey RF et al, Abstract), which involved 762 patients compared the effects of Accolate with those of placebo. Patients treated with Accolate had improvements compared to placebo in daytime asthma symptom scores (p less than 0.01), nighttime awakenings (p less than 0.05), mornings with asthma (p less than 0.01) beta-agonist use (p less than 0.01) and morning PEFR (+14 L/min, p less than 0.01). FEV1 percent predicted increased to >80% in the active treatment group, which was significant (p less than 0.01) compared to placebo.

In the second study, (Nathan RA et al, Abstract) 287 patients with mild to moderate asthma were randomized to receive Accolate (20 mg bid), cromolyn sodium (2 puffs qid) or placebo. More patients responded to treatment with Accolate (64%) and cromolyn (68%) than with placebo (46%, p less than 0.05); no difference was observed between the active treatment groups. Treatments were as well tolerated as placebo.

Accolate is an oral tablet product being developed by **Zeneca** for first-line chronic prophylaxis and treatment of adult and adolescent asthma. The compound is a highly selective and potent antagonist of leukotrienes. These compounds are important mediators of inflammatory bronchospastic diseases and blocking their activity results in the control of inflammatory symptoms of asthma. Accolate is currently undergoing Phase III investigations.

Zafirlukast Approved for Asthma

From the November 1996 issue [*Med Sci Bull*. 1996;19(3):1] of *Medical Sciences Bulletin*

The FDA has approved the leukotriene receptor antagonist **zafirlukast** (*Accolate*/Zeneca), the first truly new asthma drug to hit the market in 25 years. Zafirlukast blocks receptors for the cysteinyl leukotrienes C4, D4, and E4 (that is, leukotrienes bound to the amino acid cysteine). The cysteinyl leukotrienes are potent bronchoconstrictors, approximately 100 to 1,000 times more potent than histamine. By blocking receptors that mediate bronchoconstriction, vascular permeability, and mucous secretion, zafirlukast significantly improves the wheezing, coughing, and dyspneic symptoms of asthma. The drug is indicated for chronic asthma therapy; it is not a bronchodilator and should not be used to reverse bronchospasm, although therapy can be continued during acute attacks.

In randomized double blind clinical trials involving 1,380 patients with mild-to-moderate asthma, zafirlukast improved daytime asthma symptoms, nighttime awakenings,

mornings with asthma symptoms, rescue beta2-agonist use, forced expiratory volume, and morning peak expiratory flow rate. Safety trials involving more than 4,000 patients, some of whom took zafirlukast for more than one year, indicate that zafirlukast is generally safe and well tolerated.

Side Effects

- headache (12.9% vs. 11.7% for placebo)
- infection, nausea, and diarrhea (3% vs. 2% for placebo)

The most common side effect reported in clinical trials was headache, which occurred in 12.9% of zafirlukast patients and 11.7% of placebo patients. Approximately 3% of zafirlukast patients and 2% of placebo patients reported infection, nausea, and diarrhea. All other side effects were reported with the same frequency (less than 2%) by both groups.

Interaction with Other Drugs

- warfarin
- terfenadine
- erythromycin
- theophylline
- aspirin

Zafirlukast is rapidly absorbed orally; peak plasma concentrations are achieved at three hours after dosing. Administration with food reduces mean bioavailability by about 40%. Zafirlukast is 99% protein bound and is extensively metabolized in the liver (cytochrome P450-2C9 system); 10% of the dose is excreted in the urine and the rest in the feces. Mean terminal elimination half-life is approximately 10 hours. Clearance is reduced in the elderly and in patients with hepatic impairment. Because zafirlukast is metabolized by the P450 system, there is the potential for interaction with other drugs metabolized by the same system. Studies conducted so far show that zafirlukast prolongs the half-life of warfarin, and that zafirlukast pharmacokinetics are altered by concomitant administration of terfenadine, erythromycin, theophylline, and aspirin.

Precautions

Zafirlukast should not be used in pregnancy (unless clearly needed) and should not be

used during breast-feeding. Safety and efficacy have not been established in children younger than age 10. Available in 20-mg tablets, zafirlukast is administered 20 mg twice daily on an empty stomach (one hour before or two hours after meals). (Holgate ST et al. J Allergy Clin Immunol. 1996;98:1-13. Spector SL. Annals of Allergy, Asthma, Immunol. 1995;75:473-474. Spector SL et al. Am J Respir Crit Care Med 1994;150:618-623. Additional information from the manufacturer.)

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Pharmacology Examination

Select the ***best*** answer to each of the following questions.

1. Epinephrine, isoproterenol, and isoetharine are part of which class of Beta-adrenergic medication.

a) resorcinols
b) saligenins
c) catecholamines
c) none of the above

2. _____ is the only major side effect of aerosolized steroids.
a) tachycardia
b) occasional renal failure in elderly patients
c) a fungal infection of the oropharynx
d) transient tachypnea

3. _____ is the actual content of water vapor in a gas measured in milligrams per liter.
a) absolute humidity
b) potential humidity
c) relative humidity
d) effective humidity

4. Stimulation of _____ causes increased myocardial conductivity, increased heart rate, and increased contractile force.
.
a) Alpha receptors
b) Beta1 receptors
c) Beta2 receptors
d) all Beta receptors

5. The primary use for _____ is for vasoconstriction and upper airway decongestion, to relieve airway edema with specific indications for use being laryngeal edema, laryngotracheobronchitis, croup, and for post-extubation glottic edema.
a) ephedrine
b) theophylline
c) racemic epinephrine
d) epinephrine

6. Bronchodilation can be accomplished by _____.
a) through SNS stimulation and increased production of cAMP
b) by decreasing the destruction of cAMP through inhibition of phosphodiesterase
c) by decreasing the bronchoconstricting influence of the PNS
d) all of the above

7. An advantage of _____ is that dose delivery occurs over sixty to ninety breaths, rather than in one or two inhalations.

a. DPIs
b. MDIs
c. SPAGs
d. SVNs

8. If the upper airway were bypassed or dry gases were inhaled, a chain reaction of events would take place causing adverse reactions such as _____.

a) impairment of ciliary activity
b) slowing of mucus movement
c) atelectasis
d) all of the above

9. Isoproterenol is a very strong Beta1 and Beta2 stimulant and an effective bronchodilator, but _____, it is rarely used for bronchodilation today.

a) due to its cost
b) because it can cause kidney failure
c) because of the probability of tachycardia
d) because effective use requires such high doses

10. _____ belongs to a group of vegetable organic compounds known as xanthines and is commonly used for the relief and prevention of bronchospasm.

a) Theophylline
b) Fenoterol
c) Pirbuterol
d) Bitolterol

11. Metaproterenol, terbutaline, and fenoterol are all part of which class of Beta Adrenergic medications?

a) catecholamines
b) resorcinols
c) saligenins
d) none of the above

12. Which of the following is a side effect of Beta-adrenergic agonists?

a) tachyphylaxis
b) skeletal muscle tremor
c) increase in heart rate and force of contraction
d) all the above

13. Prednisolone is a _____ that is rarely aerosolized, has anti-inflammatory potency 3-4 times that of hydrocortisone but it takes longer to reach its peak effect, so the route of administration is oral or parenteral.

a) beta adrenergic bronchodilator
b) xanthine
c) steroid
d) synthetic steroid

14. With prolonged use, steroids _____, so patients have to be weaned slowly to begin proper functioning again.

a) lead to suppression of the adrenal cortex and adrenal insufficiency
b) activate circulating antibodies which can cause dire circumstances
c) cause lowered blood pressure
d) all the above

15. Cromolyn sodium and nedocromil sodium are prophylactic drugs known as _____.

a) mediator modifiers
b) mucolytics
c) proteolytics
d) xanthines

16. _____ cause contraction of the muscle fibers of the arterioles and small arteries, triggering a reduction of blood flow to the affected area and lowering of hydrostatic pressure that permits fluid to move into the tissues.

a) bronchodilators
b) decongestants
c) mucokinetics
d) none of the above

17. Particles between _____ microns are optimal in size for depositing in the bronchi, trachea and pharynx.

a) .005 and .5
b) .5 and 1.5
c) 2 and 5
d) 6 and 10

18. _____ is the maximum amount of water vapor that a gas can hold at a given temperature.

a) absolute humidity
b) potential humidity
c) relative humidity
d) effective humidity

19. The normal fluctuation of _____ is the basis of the circadian rhythm, or diurnal variation.
    a) liver enzymes
    b) platelets
    c) red blood cell count
    d) cortisol

20. _____ are useful in the treatment of thick secretions that are difficult to expectorate, and they can help to stimulate a cough.
    a) Corticosteroids
    b) MDIs
    c) Ultrasonic nebulizers
    d) Wetting agents

21. _____ is a topically active inhaled corticosteroid less potent than fluticasone, but greater than beclomethasone.
    a) Prednisone
    b) Budesonide
    c) Theophylline
    d) DPI

22. _____ inactivates cAMP thereby removing its bronchodilating influence.
    a) aerosolizing
    b) the enzyme adenylate cyclase
    c) the enzyme phosphodiesterase
    d) Theophylline

23. _____ is considered to be the most useful narcotic antitussive agent.
    a) Theophylline
    b) Prednisone
    c) Budesonide
    d) Codeine

24. A _____ is a humidification device that uses a conduction system that allows the gas to be introduced into the water below its surface.
    a) bubble diffusion device
    b) blow–by humidifier
    c) jet humidifier
    d) heated humidifier

25. _____, like leukotrienes, are arachidonic acid derivatives that cause bronchospasm.
    a) Prostaglandins
    b) Xanthines
    c) Thromboxanes
    d) Antimuscarinics

26. _____ is recommended for use with COPD patients having a bronchospastic component to their disease, and should be delivered prior to a Beta agonist for best results.

a) Albuterol
b) Pirbuterol
c) Ipratropium
d) Budesonide

27. _____, through stimulation of receptors, cause vasoconstriction and decrease fluid in the airway.

a) mucolytics
b) decongestants
c) expectorants
d) Xanthines

28. _____ is a physiologically inert substance found in many aerosol preparations, and it is used as a solvent and stabilizing agent.

a) propylene glycol
b) Cytokine
c) antioxidant
d) nitric oxide

29. _____ is an orally administered expectorant that achieves its action through stimulation of the vagus nerve, which, in turn, stimulates the submucosal bronchial glands to produce more serous fluid.

a) Hydrocodone
b) Diphenhydramine
c) Super Saturated Potassium Iodide (SSKI)
d) Codeine

30.Cloxacillin. dicloxacillin. methicillin. nafcillin. and oxacillin are all _____.

a) “broad-spectrum” semisynthetic penicillin derivatives that are given for gram negative microorganisms
b) part of a subgroup of the penicillins that is resistant to penicillinase
c) substitutes for penicillin G when it has been proven effective
d) all the above

31. _____ have become increasingly popular because this delivery system is relatively inexpensive, and does not require the hand-breath coordination required of metered dose inhalers.

a) SPAGs
b) DPIs
c) SVNs
d) USNs

32. Agitation can cause catecholamine release and produces auto-PEEP in ventilator patients, but the problem of imbalance between 02 deliveries and 02 consumption can be prevented by administering ____.

a) Haloperidol (Haldol)
b) Progesterone
c) Doxapram
d) all the above

33. The safest and most common mucokinctic is _____.

a) Xanthine
b) Propylene Glycol
c) Saline (NaCl)
d) water

34. _____ delivery is reserved for the patient who is not capable of taking deep, coordinated breaths.

a) IPPB
b) centrifugal room nebulizer
c) USN
d) Babbington nebulizer

35. _____ is the amount of water vapor in a gas as compared to the maximum amount possible, expressed as a percentage.

a) absolute humidity
b) potential humidity
c) relative humidity
d) effective humidity

36. According to _____, the volume of a gas increases as its temperature increases.

a) the law of gravity
b) Charles' law
c) Moles' law
d) the Joule–Thompson effect

37. _____ significantly decreases pulmonary artery pressure, decreases shunting and improves PaO2, however, it can be lethal being a toxic component of air pollution.

a) Alveolate
b) Virazole
c) Pentamidine
d) Nitric oxide

38. _____ is the drug of choice for aspergillosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, North American blastomycosis, and sporotrichosis.

a) Gentamicin
b) Kanamycin
c) Amphotericin B
d) Tobramycin

39. _____ is a highly specialized jet-type aerosol generator designed to for administering ribavirin (Virazole)

a) centrifugal room nebulizer
b) USN
c) SPAG
d) the Babbington nebulizer

40. _____ decreases systemic and pulmonary vascular resistance, decreases blood pressure, increases stroke volume, increases cardiac output, and increases heart rate.

a) Prostaglandin E1
b) Pentamidine Isethionate
c) Amphotericin B
d) Dextromethorphan

41. A patient has bronchospasm and thick, tenacious secretions. The physician asks the caregiver to deliver an aerosolized bronchodilator. Which of the following bronchodilators would **NOT BE INDICATED** in this situation?

a) Isoproterenol
b) Epinephrine
c) Atropine
d) Metaproterenol

42. A patient is receiving isoproterenol to treat his bronchospasm. Two hours after his aerosol treatment, the bronchospasm returns. Which bronchodilator should the caregiver suggest?

a) Isoetharine
b) Racemic epinephrine
c) Epinephrine
d) Metaproterenol

43. A patient is receiving ultrasonic therapy. The caregiver is asked to recommend the solution for nebulization, which will cause the least amount of mucosal irritation. Which fluid should the therapist suggest?

a) Half-normal saline (0.45%)
b) Hypertonic saline (10%)
c) Propylene glycol 10%
d) Sterile water

44. _____ is used to reverse ventilatory depression as a result of opiate administration (morphine, methadone, heroin).

a) Pancuronium
b) Progesterone
c) Naloxone
d) Xanthine

45. Drugs for Ards include:

a) Dopamine
b) Antioxidants
c) Digitalis
d) Atropine

46. The goal of all _____drugs is to enhance secretion mobilization, and all should be re-evaluated after therapy has been administered for about 24-48 hours to determine if the goals of therapy (i.e., increased secretion mobilization and elimination) have been achieved.

a) bronchodilating
b) mucokinetic
c) Beta-adrenergic
d) Vasoactive

47. The disadvantages encountered when relying on DPIs for drug administration include:

a) Potential adverse reaction to lactose or glucose carrier substance
b) Dose inhaled is not as obvious as it is with MDIs, causing patients to distrust that they've received a treatment
c) Capsules must be loaded into the devices prior to use
d) All of the above

48. How many milliliters of solution must be given if an order is for 4 drops of 2.25 Vapo Ephrine?

a) 0.5 ml
b) 0.2 ml
c) 0.01 ml
d) 0.15 ml

49. Which of the following statements best describes the term *aerosol*?

a) particulate matter suspended in a gas
b) particulate matter vaporized into a gas
c) particulate molecules in a gaseous form
d) molecular particles of hygroscopic substances

50. A piezoelectric transducer _____.

a) measures % relative humidity
b) is an efficient heating element for producing a heated aerosol
c) is part of a Babington nebulizer
d) transforms electrical impulses to sound waves

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