On the use of selected bronchodilators* in the asthmatic and non-asthmatic patient

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Acute and chronic bronchospasm can pose a serious, if not life-threatening problem to the anesthetist in the operating room situation. The patient with an irritable airway requires special treatment. In this article, the author reviews aspects of respiratory anatomy and physiology, and discusses some of the drug choices available to the anesthetist—including some of the newer beta-2 specific types.

The uses and indications for various bronchodilators in the control of bronchospasm are many and varied. With the numerous drugs on the market today, the practitioner is faced with a variety of drugs from which to choose. What would truly be the best drug to use in a given situation? It is the purpose of this article to communicate some basic facts about the more common types of bronchodilators as well as several of the newer types, and their relationship to bronchospasm.

Etiology of bronchospasm

When discussing the etiology of bronchospasm, the first consideration is the anatomy of the bronchi. The trachea and bronchi are a framework of incomplete rings of hyaline united by fibrous tissue and nonstriated muscle. Below the larynx and progressing into the bronchi is mucous membrane which contains pseudostratified ciliated epithelium interspersed with goblet cells.

The cilia beat the overlying layers of mucous upwards toward the larynx. The epithelial surface of the bronchi contain cuboidal secretory cells. The bronchial surface is folded into longitudinal ridges which allow for changes in passage diameter. This elastic framework is responsible for the elastic recoil of the lung during expiration.

Non-striated muscle fibers form two helical tracts which run in opposite directions through the entire tracheobronchial tree. These fibers become gradually thinner until they finally terminate as they reach the alveolar level.

These muscles and indeed, the bronchiolar passageways themselves are under nervous and hormonal control. Muscle contraction narrows the airway diameter and muscle relaxation results in bronchial dilation. There is a small degree of tone to this bronchiolar musculature; it relaxes slightly on inspiration and constricts slightly on expiration.

Abnormal constriction of these tiny passageways may result from muscle stimulants in the circulatory system or local release of excitants such as serotonin or histamine.

Nerves supplying these air passages are an extensive mingling of vagal and sympathetic fibers. The parasympathetic

*Ephedrine sulfate, isoproterenol, aminophylline, racemic epinephrine isoetharine, terbutaline.
fibers run from the parasympathetic ganglia in the peribronchial tissue and consist of afferent and efferent fibers. There are also efferent sympathetic ganglia, primarily of the beta-2 type. The mechanism of bronchospasm is complex and all the causes and parameters are not known. By definition, bronchospasm is simply a spasm of the bronchial wall musculature resulting in dyspnea, wheezing-type rales and decreased pulmonary compliance.

During forced expiration, intrapleural pressure is transmitted directly to the outer wall of the main and lobar bronchi which lie outside the parenchyma of the lungs. The collapse of these bronchi limits the expiratory flow of air.

The extent of bronchospasm is determined by the degree of resistance of all airways. Bronchospasm is often quickly and dramatically reversed by the administration of various bronchodilator agents. Airway narrowing can also be caused by edema and inflammation of the bronchial walls—either due to infection or irritation.

During bronchospasm, Gold has determined that eight things happen: (1) the vital capacity and FEV₁ are decreased, (2) residual volume decreases, (3) compliance decreases and frictional resistance increases, (4) ABG’s at this time show a lowered PaO₂, (5) Dead space to tidal volume ratio increases and venous admixture increases, (6) O₂ uptake increases, cardiac output increases and CO₂ production increases, (7) O₂ diffusing capacity increases, and (8) pulmonary blood flow abnormalities exist.

The incidence of bronchospasm intraoperatively is surprisingly low; Shnider found an incidence of only 6% of asthmatic patients who went into bronchospasm and most of these were with intubation, which is in itself, a powerful irritant. One of the most common factors associated with the precipitation of bronchospasm was the presence of an endotracheal tube. The individual with an irritable tracheobronchial tree due to allergies or smoking, as well as those at extremes in age, are patients at risk.

Some other causes of bronchospasm postulated include irritation due to inhaled allergens, inhalation of toxic vapors, respiratory infections, air pollution, carcinoid syndrome, pulmonary vascular congestion, acute pulmonary embolism and drugs such as Pentothal® and Anectine® which stimulate the release of humoral substances (serotonin, acetylcholine and histamine).

Understanding the etiology of bronchospasm must also include a knowledge of the innervation of the tracheobronchial tree. The smooth muscle around the airways is arranged in a geodesic type of configuration. The role of the autonomic nervous system in the innervation of the tracheobronchial tree is primary. According to Collins, the tone of the smooth muscle fibers in the walls of the airways is mediated and regulated by the autonomic system. Parasympathetic efferent fibers arise from the dorsal motor nucleus of the vagus where they run to the chest and form plexuses on the main pulmonary artery.

These plexuses communicate with hilar parasympathetic ganglia and intermingle with the sympathetic and hilar plexuses. The parasympathetic fibers are distributed mostly in the bronchi, blood vessels and mucous glands, while the sympathetic fibers are found mostly in the pulmonary and bronchial vessels.

Stimulation of the sympathetic afferents will cause relaxation of the bronchial wall musculature while stimulation of the parasympathetic fibers will cause constriction. Sympathetic stimulation will elicit the “fight or flight” response and logically that would include bronchodilation, enabling the individual to get more air. Since parasympathetic fibers are found in the bronchi and small blood vessels, local irritation or histamine release could cause stimulation of these fibers resulting in bronchial constriction.

There are three types of sympa-
thetic nerve receptors found in the body, but only two will be considered in any detail here. The alpha receptors are found primarily in the peripheral blood vessels and stimulation of these will cause a generalized peripheral vasoconstriction. There are two types of Beta receptors.

The beta-1 type are found primarily in the myocardium and intestinal smooth muscle, and stimulation of these causes myocardial stimulation. The beta-2 type receptors are found in the bronchioles, uterus and skeletal muscle arteries. Stimulation of these will cause a bronchodilation.\(^3\)

In treating bronchospasm, stimulation of these beta-2 receptors is required. This will impart a bronchodilation without the cardiac stimulation associated with generalized beta stimulation. There are a number of new drugs that are beta-2 specific, but many of these are not available for use in the acute situation, so often we are forced to rely on drugs that are less selective in their beta-adrenergic activity.

**Discussion of drugs**

In discussing the following six drugs, an effort was made to review them relative to their capacity to bronchodilate. More important side effects will be mentioned, but it is beyond the scope of this article to discuss them in relation to their other uses and purposes.

The following are the three major classifications of bronchodilators: (1) Adrenergics or sympathomimetics; (2) Xanthine derivatives whose prototype is theophylline; and (3) Corticosteroids that are used when the aforementioned bronchodilators are not effective or when the bronchospasm is caused by an acute allergic response. These last mentioned presumably work to decrease edema and inflammation.

The adrenergic group is the most effective one, and drugs from this group to be discussed include ephedrine, isoproterenol, racemic epinephrine, terbutaline sulfate and isoetharine.

The xanthine derivatives are effective in patients who, for some reason cannot tolerate the adrenergic drugs. The example discussed is aminophylline. The xanthine derivatives not only bronchodilate, but also produce a mild diuretic effect. They are often used in the treatment of pulmonary edema. They also include a medullary stimulating action.\(^1\)

The corticosteroids are valuable in the patient with chronic respiratory problems when most of the more rapidly acting bronchodilators are ineffective. They are best at suppressing allergic responses and will potentiate the effects of the adrenergic bronchodilators. They are often used in status asthmaticus or acute bronchial asthma in the patient who has chronic problems of this nature.\(^1\)

Each category of drugs, and actually each drug has its own advantages and disadvantages. Generally speaking, the adrenergic bronchodilators have many central nervous system and cardiovascular side effects, unless they are beta-2 agonists.

The nonspecific beta stimulators can precipitate episodes of coronary ischemia and insufficiency due to myocardial stimulation in a heart that does not have the reserves to tolerate such stimulation. Their rapid absorption can cause hypertension, CNS stimulation, excitability and even cerebral hemorrhage. Caution must be exercised in the administration of these medications to the individual with hyperthyroidism or ischemic heart disease.

The xanthine derivatives have many drawbacks. They can cause GI disturbances and CNS stimulation. The primary GI disturbances include nausea and vomiting. These drugs have also been associated with agitation, hyperreflexia and myoclonic seizures. It has also been noted that too rapid IV injection of these drugs can precipitate a cardiac arrest.\(^1\) Ironically, inhalation of xanthine derivatives can also be a causative factor in bronchospasm.

Consideration was given to the
utilization of antihistaminic drugs in the treatment of bronchospasm, and it was ascertained that they really have no place in the treatment of bronchospasm. Their action is relatively weak and can produce a drying effect of the mucosa that can further perpetuate the problem.\(^1\)

Specifically, the first drug considered is ephedrine sulfate:

\[
\text{\begin{array}{c}
\text{O} \\
\text{C} - \text{C} - \text{NH}_3 \\
\text{H}_2\text{SO}_4 \\
\text{CH}_3 \\
\end{array}} \times 2
\]

It is an adrenergic sympathomimetic that lacks a catechol nucleus. It occurs naturally in various plants and has been used in China for more than five thousand years. It was first prepared synthetically in 1927 and is a levo-isomer.

Ephedrine acts similarly to epinephrine, although the effects are longer lasting and may be present for several hours. It also has a weaker bronchodilating action than epinephrine, but may be the agent of choice for mild bronchospasm or for patients requiring continuous medication.

Its principal action in bronchodilation is produced by beta stimulation of bronchial smooth muscle, vasoconstriction and relief of bronchial mucosal edema. It does have alpha receptor activity as well as both direct and indirect sympathomimetic activity. The indirect activity is a release of norepinephrine from sympathetic receptor sites and/or impairment of norepinephrine uptake by storage granules.\(^5\)

It has a positive inotropic effect and chronotropic effect on the heart thereby causing cardiac stimulation and a rise in blood pressure. Its CNS stimulation occurs primarily in the cortex and medulla and it is often used in the treatment of narcolepsy. It stimulates the respiratory centers in the medulla and relaxes the hypotonic muscle of the bronchial muscle and GI tract. Its effects depend upon the release of norepinephrine from the adrenergic nerve terminal stores, and also a direct action on effector cells.

Repeated doses become less and less effective as norepinephrine stores become depleted. Too frequent inhalation of ephedrine can lead to overdose and drying of the airway, and can even precipitate a bronchospasm and inflammation if used over a prolonged period of time.

Side effects of ephedrine administration include CNS stimulation and urinary retention by relaxation of the sphincter muscle of the bladder. Caution must be exercised when using this drug in the elderly male with preexisting prostate problems.

Avoidance of the use of this drug in the individual with poor myocardial reserve is important. In the patient where myocardial stimulation, tachycardia and hypertension are undesirable, this drug should be used carefully, if at all. The patient with hyperthyroidism, ischemic heart disease or myocardial infarct may not tolerate this drug. Care must also be taken in the patient with renal disease.

Ephedrine is somewhat resistant to the action of monamine oxidase, thus it has a somewhat longer duration of action than epinephrine. Ephedrine easily crosses the blood-brain barrier, hence its powerful CNS activity. It does undergo hydroxylation and deamination in the liver. There it is conjugated then excreted in the urine. Ephedrine's excretion is dependent upon the urinary pH and it will be reabsorbed in alkaline urine.

Care must also be taken if this drug is used in conjunction with halothane or cyclopropane as these agents have been found to sensitize the heart to catecholamines and life-threatening ventricular arrhythmias can develop.

Ephedrine also has some important drug interactions. In the patient on monamine oxidase inhibitors, ephedrine should be avoided. Monamine oxidase within the nerve ending is primarily responsible for the inactivation of norepinephrine after its release from the
synaptic vesicles. Administration of monamine oxidase inhibitors will increase the level of norepinephrine at the receptors thereby precipitating a hypertensive crisis when ephedrine is administered. Ephedrine is not a drug to be used when CNS stimulation, cardiac stimulation and hypertension are undesirable.

Another adrenergic drug often used is isoproterenol. It is a sympathomimetic amine with a predominant beta-adrenergic action. It is also a sympathethic catecholamine with little alpha stimulation, so its main actions deal with cardiac stimulation and bronchial smooth muscle relaxation.

It has a positive inotropic and chronotropic effect, greater than that of epinephrine and increases the stroke volume, cardiac output and coronary blood flow. It can improve A-V conduction and enhance the rhythmicity of the S-A node. It is the treatment of choice in heart blocks as it suppresses arrhythmias and ectopies.

It relaxes bronchial and arterial smooth muscle, decreases vascular resistance and can cause hypotension as well. It relieves bronchoconstriction, relaxes smooth muscle of the GI tract and has been found to be a more potent bronchodilator than epinephrine. It is chemically similar to ephedrine:

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{CH}_3 \\
\text{CH}_2 \text{NH} \quad \text{CH}_3 \\
\text{HCl}
\end{align*}
\]

Isoproterenol is also a better choice for the hypertensive patient because of its vasodilator action. If it is inhaled, it causes a liquefaction of tenacious secretions, shrinks swollen mucous membranes and relaxes bronchial wall musculature. Hence, it is quite useful in the treatment of bronchospasm. Patients can develop a tolerance to isoproterenol, however, and overuse can lead to CNS stimulation.

Isuprel® is a generalized beta stimulator and bronchodilation is usually accompanied by cardiac stimulation and vasodilation. Some of this can be avoided with the use of metered aerosols. It does lose its effectiveness after about 40 minutes. Increased work of the heart can, in turn, cause episodes of angina. Also, palpitations, tremor and tachycardia are seen as well as headaches and bouts of hypotension.

Isoproterenol is contraindicated in patients with decreased coronary blood flow, myocardial infarcts by history, vascular stenosis and digital-induced heart block. It can also precipitate cardiac arrhythmias, so care must be taken in the patient anesthetized with halothane, ethrane or cyclopropane.

Isoproterenol interacts with several drugs in potentially dangerous ways. In the digitalis-toxic patient, dangerous ventricular arrhythmias can be produced as its automaticity effects are negated and the myocardium is stimulated. If it is used concurrently with another myocardial stimulant, fatal arrhythmias can result. In the patient on Inderal®, Isuprel® will increase the heart rate while Inderal® blocks beta stimulation. A fall in peripheral resistance with a sudden, dramatic decrease in blood pressure results. Though isoproterenol is a relatively good bronchodilator, it is a generalized beta stimulator and must be avoided in the patient with a low cardiovascular reserve and/or hypotensive state. Isoproterenol is readily absorbed and metabolized by monamine oxidase and catecholomethyltransferase. It is conjugated in the liver and the metabolites are excreted in the urine.

When considering the xanthine derivatives, aminophylline was chosen as it is the one used most commonly. The xanthines are weakly basic alkaloids, and aminophylline is a preparation of theophylline and ethyl enediamine.

Aminophylline's pharmacological activity includes direct beta action resulting in cardiac stimulation, coronary dilation, smooth muscle relaxation, diuresis, mild skeletal muscle stimulation and mild CNS and respiratory stimulation. Its cardiac effects are more potent.
than most of the other bronchodilators used. It can potentiate the cardiac inotropic response to beta adrenergic agonists and stimulate the release of catecholamines from the adrenal medulla.

\[
\begin{align*}
\text{CH}_3 & \quad \text{N} & \quad \text{H} \\
\text{O} & \quad \text{N} & \quad \text{N} \\
\text{CH}_3 & \quad \text{2-} & \quad \text{CH}_2 & \quad \text{NH}_2 \\
\end{align*}
\]

The use of halothane or ethrane along with aminophylline can precipitate ventricular arrhythmias if the practitioner is not aware of what can happen and intervene appropriately. It can also stimulate the release of norepinephrine from receptor sites.

Aminophylline’s cellular basis for action is as follows: It is a competitive inhibitor of certain forms of the cyclic nucleotide phosphodiesterase. These are enzymes that catalyze and increase the AMP levels so that concurrent use or release of catecholamines will potentiate the xanthines. Calcium and cyclic AMP are regulators of cell function and interact to modulate cellular function, so when the xanthines are used, the enzymes responsible for the regulation of AMP are inhibited and there are intracellular translocations of calcium.

Aminophylline is an excellent bronchodilator—especially in relieving bronchospasm caused by histamine release. It can overcome biliary spasm, is a mild diuretic and causes a prolonged augmentation of gastric secretion. It can also decrease the clotting time as well as increase the basal metabolic rate.

Some of the other effects include GI irritation, nausea and vomiting. If it is administered intraoperatively, the patient should be intubated to avoid possible silent aspiration. Powerful CNS stimulation has been noted with clonic and fascicular muscle contractions.

In patients with severe MI or ischemic heart disease, xanthines not only beta stimulate, but they may also precipitate free alkaloids when they are exposed to the blood pH. The result could be ventricular arrhythmias due to myocardial stimulation and sensitization to catecholamines. Rapid injection increases this effect and the result is often cardiac arrest. Aminophylline is partially demethylated and oxidized and then excreted in the urine as methyluric acid and methylxanthines. Approximately 10% is excreted unchanged.1

There are also varied drug interactions with aminophylline. In the patient exposed to organophosphate pesticides, the ability to metabolize acetylcholine is lost due to the reduction of the enzyme acetylcholinesterase. Because aminophylline also interferes with normal cell function, this disruptive effect can be potentiated by its use in these patients. If aminophylline is given concurrently with another cardiac stimulant, or if the patient has poor cardiovascular reserve, a cardiac arrest can occur. Though aminophylline seems to be the favorite choice of many practitioners, it is a general beta stimulant, and is not the best choice for the patient with compromised cardiac function.

Several newer drugs with specific beta-2 type action are now being tested. Although racemic epinephrine or Vaponefrin® is not really beta-2 specific, it does avoid many of the cardiovascular effects of the other drugs when it is given correctly.

Racemic epinephrine is a mixture of the dextro and levo isomers of epinephrine. It is pictured here:

\[
\begin{align*}
\text{OH} & \\
\text{CH}_2 & \quad \text{NH}_2 & \quad \text{CH}_3 & \quad \text{HCl} \\
\text{OH} & \\
\end{align*}
\]

The levo isomer is the one we are the most familiar with, and it is 15 to 20 times more active than the dextro isomer. Most of the activity in the racemic mixture is due to the levo isomer. This mixture is essentially half the strength of epinephrine HCl and is supplied as a 2.20% solution in a metered nebulized container. It is for inhalation purposes only and must never be injected IV. The normal dose is one or two puffs through a nebulizer metered to deliver 0.3 mg per puff.
Racemic epinephrine has minimal cardiac side effects because it is approximately half strength, but it is not indicated for long term use since it will cause the same kind of cardiac stimulation and side effects seen with epinephrine. It is excellent in the acute situation but for longer term bronchodilation, another choice would have to be made.

Other drawbacks are that in various tests, many physicians found no indications for using racemic epinephrine in preference to epinephrine. Since, if you use enough of it, you will get the same effects. There were also studies in which there was a small incidence of toxicity in a ciliated epithelial organ culture, so prolonged use is not recommended.

In use, racemic epinephrine has benefited the patient in an acute situation with an immediate improvement in signs and symptoms, but it was noted that the natural history of the disease was not altered by racemic epinephrine therapy. It was also noted that there was no increase in PaO₂ values.

Racemic epinephrine is half the strength of epinephrine, but is supplied at twice the concentration. Its administration would deliver almost the same concentration of the levoisomer as if epinephrine itself were being given.

The redeeming factor here is that doses are metered and only a very small amount of the levoisomer is delivered, thereby drastically reducing the undesired side effects. Racemic epinephrine is used primarily for its topical vasoconstrictive action when applied to mucous membrane.

Two new beta specific drugs are also available for limited use. The first is isetharine, a structural analog of isoproterenol:

\[
\text{OH} \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{CH} \\
\text{OH} \quad \text{OH} \quad \text{CH}_2 \quad \text{CH}_3 \quad \text{CH}_3
\]

It, too is a sympathomimetic and differs from all the others mentioned in that it is beta-2 specific. It has an affinity for beta-2 receptors and by stimulating these only, the cardiovascular effects of beta-1 stimulation are avoided.

Isoetharine has a rapid onset and a short duration of action. It is a catechol and is inactivated by catecholomethyltransferase. It is best administered by metered dose nebulization since this allows for small doses and minimal systemic absorption. In this way, many of the cardiac side effects seen even with slight beta stimulation are avoided.

Isoetharine works to relax bronchial smooth muscle, uterine muscle, and vascular supply to the skeletal muscle. Tests with isetharine have shown that, after its use, there has been an increased FEV₁ with no changes in either pulse or blood pressure. Again, it must be mentioned that this drug is relatively new and not readily available. Still, it would seem an ideal drug to administer to the cardiac patient or patient with poor vascular, neurological or neuromuscular status, thus avoiding many of the detrimental beta-1 effects.

Another beta-2 specific drug is known as terbutaline sulfate or Brethine®. It is pictured below:

\[
\text{OH} \quad \text{OH} \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{H}_2\text{SO}_4
\]

Terbutaline has a beta-2 action and its administration results primarily in bronchodilation due to relaxation of the bronchial wall musculature. Its molecular configuration protects it from two inactivating enzymes in the body: monamine oxidase and catecholomethyltransferase.

If it is administered orally, it will have a more prolonged effect. Patients can still have subjective side effects with terbutaline sulfate, and studies have shown that they have experienced some dizziness, palpitations and flushing. This, too, is another fairly new drug and it is not readily available in the acute situation. It would seem to be a good

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choice when cardiovascular effects are undesirable and the patient is not in an acute state of bronchospasm. However, it would seem that isoetharine might be slightly superior to terbutaline sulfate in this regard.3

Corticosteroids are also used in the treatment of bronchospasm. Their importance is their potent anti-inflammatory effect. They are useful in the treatment of chronic and prolonged asthma where the previously mentioned agents have no effects. Nevertheless, they are a possibility and should be mentioned since they are used infrequently in the operating room for the purpose of bronchodilation, decreasing inflammation and decreasing edema.

Conclusion

In conclusion, the drugs used in the treatment of bronchospasm must be divided into those used in the acute and chronic clinical situation. The major determinant in the use of these specific drugs is the severity of side effects and individual patient ability to tolerate them.

It would seem that one of the safest drugs in terms of known side effects is isoetharine. Next would come terbutaline sulfate followed by racemic epinephrine. Although the newer beta-2 specific bronchodilators would seem to be good choices in the treatment of bronchospasm, they are not currently in use in the acute situation. Choices are limited to the catechols and xanthine derivatives. Steroids are important in acute allergic responses and in the chronic problems of bronchospasm. A thorough knowledge of the better known drugs would aid the practitioner in the choice of one for a given patient and specific set of circumstances.

REFERENCES


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