



# SHORT-ACTING ADRENERGIC BRONCHODILATORS: EPINEPHRINE TO LEVALBUTEROL AND EVERYTHING IN BETWEEN

*By Doug Gardenhire EdD, MS, RRT-NPS*

**D**o you remember when, as a student, you were instructed to learn all of the different bronchodilating agents, but when you arrived at the hospital for clinical the therapists told you that all they used was Albuterol? Later, you discovered that someone was using a metroproterenol metered dose inhaler (MDI), and you asked "I thought everyone used albuterol?" Today, we have a number of agents to choose from, but which one should we choose?

The general indication for use of an adrenergic bronchodilator is relaxation of airway smooth muscle in the presence of reversible airflow obstruction associated with acute and chronic asthma (including exercise-induced asthma), bronchitis, emphysema,

bronchiectasis, and most other obstructive airway diseases. Differences in the rate of onset, peak effect, and duration led to a distinction in use between short-acting and long-acting agents. Short-acting  $\beta_2$  agonists such as albuterol, levalbuterol, or pirbuterol are indicated for relief of acute reversible airflow

**Today we have many short acting adrenergic bronchodilators.**

**Which one do we choose?**

obstruction in asthma or other obstructive airway diseases. Short-term acting agents may also be termed "relievers" as discussed in the Global Initiative for Asthma (GINA) guidelines.

Another category of adrenergic bronchodilators are ultra short-acting agents, such as epinephrine and racemic epinephrine. Epinephrine is a potent catecholamine bronchodilator that stimulates both  $\alpha$  and  $\beta$  receptors. Because epinephrine lacks  $\beta_2$ -receptor specificity, there is a high prevalence of side effects such as tachycardia, blood pressure increase, tremor, headache, and insomnia. Epinephrine occurs naturally in the adrenal medulla and has a rapid onset, but a short duration, because of metabolism by catechol O-methyltransferase (COMT). It has been administered both by inhalation and subcutaneous injection to treat patients with acute asthmatic episodes. It is also used as a cardiac stimulant, based on its strong  $\beta_1$  effects. Self-administered, intramuscular injectable doses of 0.3 and 0.15 mg are marketed to control systemic hypersensitivity (anaphylactoid) reactions. This drug is more useful for the management of acute asthma rather than for daily maintenance therapy because of its pharmacokinetics and side effect profile. Currently, epinephrine is available as a nebulizer solution and MDI. Racemic epinephrine is often used, either as

an inhaled aerosol or by direct lung instillation, for its strong  $\alpha$ -adrenergic vasoconstricting effect to reduce airway swelling after extubation or during epiglottitis, croup, or bronchiolitis, or to control airway bleeding during endoscopy. Racemic epinephrine is available as a nebulizer solution.

Sympathomimetic bronchodilators are all either catecholamines or derivatives of catecholamines. Catecholamines are a group of similar compounds having a sympathomimetic action, and a chemical structure consisting of an aromatic catechol nucleus and a dialiphatic amine side chain. Examples of catecholamines are dopamine, epinephrine, norepinephrine, isoproterenol, and isoetharine. The first three occur naturally in the body. Catecholamines, or sympathomimetic amines, mimic the actions of epinephrine more or less 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.

Adrenergic bronchodilators can exist in two different spatial arrangements, producing isomers. Rotation about the  $\beta$  carbon on the ethylamine side chain of the basic molecular structure produces two nonsuperimposable mirror images, termed enantiomers or simply isomers. The (R)- and (S)- isomers as the mirror image of each other. Enantiomers have similar physical and chemical properties, but not the same physiological effects. The (R)-isomer, or levo isomer, is active on airway  $\beta$  receptors, producing bronchodilation, and on extrapulmonary adrenergic receptors. The (S)-isomer, or dextro isomer, is not active on adrenergic receptors such as  $\beta$  receptors, and until recently the (S)-isomer was considered physiologically inert. Using their actual spatial configuration, the levo isomer and dextro isomer are referred to as the (R)-isomer (for rectus, right) and (S)-isomer (for sinister, left), respectively. Adrenergic bronchodilators such as epinephrine, albuterol, or salmeterol have been produced synthetically as racemic mixtures, or 50:50 equimolar mixes of the (R)-isomers and (S)-isomers. Natural epinephrine found in the adrenal gland occurs as the (R, or levo)-isomer only. Levalbuterol, released in 1999, represents the first synthetic inhaled solution available as the single (R)-isomer of racemic albuterol.

The three catecholamine drugs described earlier differ in their receptor preference, ranging from  $\alpha$  and  $\beta$  (epinephrine), to  $\beta$  nonspecific (isoproterenol), and finally to  $\beta_2$  specific

(isoetharine). The theory that explains the shift from a activity to b2 specificity has been termed the keyhole theory of b sympathomimetic receptors: The larger the side-chain attachment to a catechol base, the greater the b2 specificity. If the catecholamine structural pattern is seen as a keylike shape, then the larger the "key" (side chain), the more b2 specific the drug. Epinephrine has a methyl group attached to the terminal amine group and activates a and b receptors equally. Isoproterenol adds an additional methyl group with strong b stimulation and little a stimulation. Isoetharine further increases the bulk of the amine side chain and adds an ethyl group, modifying the structure of isoproterenol and producing b2-preferential activity. Currently, only isoetharine is available as a nebulizer solution. Isoproterenol is available as an injection.

Catecholamines are unsuitable for oral administration because they are inactivated in the gut and liver by conjugation with sulfate or glucuronide at the carbon-4 site. Because of this action, they have no effect when taken by mouth, limiting their route of administration to inhalation or injection. Catecholamines are also readily inactivated to inert adrenochromes by heat, light, or air. For this reason, racemic epinephrine, isoetharine, and isoproterenol are stored in amber-colored bottles. Nebulizer rainout (i.e., nebulized particles that condense and fall, under the influence of gravity) in the tubing may appear pinkish after treatment, and a patient's sputum may even appear pink-tinged after using aerosols of catecholamines.

Because the limited duration of action with catecholamines is hardly suitable for maintenance therapy of bronchospastic airways, drug researchers sought to modify the catechol nucleus, which is so vulnerable to inactivation. As a result, the hydroxyl attachment at the carbon-4 site was shifted to the carbon-5 position, producing a resorcinol nucleus. This change resulted in metaproterenol (named for the 3,5-attachments in the meta position) and terbutaline (for the tertiary butyl group). Because neither drug is acted on by COMT, both have a significantly longer duration of action of 4 to 6 hours compared with the short-acting catecholamine bronchodilators. Because of its bulky side chain, terbutaline is b2-preferential, thus possessing minimal cardiac (b1) effects. Both drugs can be taken orally because they resist inactivation by enzymes in the gastrointestinal tract and liver. For these reasons, the newer generation of resorcinols and other catecholamine derivatives was much better suited for maintenance therapy than the older catecholamine agents. Metaproterenol and terbutaline are slower to reach a peak effect (30 to 60 minutes) than epinephrine, isoproterenol, or isoetharine. Of these two agents only metaproterenol is available for inhalation, as a nebulizer solution or MDI. Terbutaline is available as a tablet to be taken by mouth or parenterally.

The trend in adrenergic bronchodilators has been toward development from nonspecific, short-acting agents, such as epinephrine, to b2-specific agents with action lasting up to 6 hours, such as albuterol and levalbuterol. A major limitation of b-adrenergic bronchodilators developed after isoproterenol and isoetharine was their 4- to 6-hour duration of action, which limited their usefulness in controlling nocturnal asthma symptoms and necessitated a less convenient, four-times-daily dosing schedule. Longer acting agents offer the advantages of less frequent dosing and protection through the night for asthmatic patients.

Dr. Douglas S. Gardenhire is a veteran therapist, author, educator and lecturer and the Director of Clinical Education in the Respiratory Care Program at Georgia State University.

**Why use 2\***

**When one will do.**

**StatCO<sub>2</sub> and Mini StatCO<sub>2</sub> ... provide enhanced economy.**

The AHA guidelines state, "An end tidal CO<sub>2</sub> detector placed on the ET tube ... can alert the clinician to tube dislodgements during transport."

How often have you successfully completed initial positive ET tube placement verification with an end tidal CO<sub>2</sub> detector only to find that the intubated patient needs to be moved or transported?

Some CO<sub>2</sub> detectors are only active for 2 hours. To stay within the guidelines that can often mean having to open another device each time a patient is moved. One StatCO<sub>2</sub> or Mini StatCO<sub>2</sub> provides 24 hour performance. With one StatCO<sub>2</sub> or Mini StatCO<sub>2</sub> you can monitor proper ET tube placement initially and as often as necessary within a 24 hour period. So StatCO<sub>2</sub> and Mini StatCO<sub>2</sub> are significantly more economical to use than some other CO<sub>2</sub> detectors!

But economy isn't the only advantage. Both also provide enhanced reliability and convenience.

**StatCO<sub>2</sub> and Mini StatCO<sub>2</sub> ... Verification with Enhanced Economy, Reliability and Convenience.**

\* or more.

**MERCURY RESPIRATORY**

Toll Free: (800) 237-6418  
www.mercurymed.com

StatCO<sub>2</sub> over 18 lbs body weight  
Mini StatCO<sub>2</sub> 7-15 lbs body weight

Printed 8/02 © 2002 Mercury Medical  
1. All guidelines 2001 for Endotracheal Resuscitation and Intubation, Guidelines for ET, p. 1-10

**CIRCLE READER ACTION CARD # 17**

Continuing Education... continued from page 22

It's unfair to paint the industry leaders as "bad guys". We educators remember that so many of the early respiratory therapy learning materials were actually developed and freely distributed by our equipment manufacturers. It's also a fact of life that most advances in patient management actually come from drug and/or equipment manufacturers. Any actions then, that might stifle that inventiveness would surely be counter-productive.

The relationships between MDs and pharmaceutical companies and the relationships between respiratory therapists and their equipment providers have traditionally been good ones. Evidently there are some in government who feel these relationships have crossed a line. Keeping continuing education on the up and up relies on voluntary commitment of all parties involved. We all want to preserve the integrity of continuing education. We want it to be objective and independent. And we want it to stay free of outside interference.

Sandra McCleaster, MA, RRT is a veteran therapist, author, lecturer and educator. She is also an adjunct faculty member at Bergen Community College in Paramus, NJ.