



TODAY'S VERSATILE HAND-HELD NEBULIZERS

By Stephanie Richardson

Respiratory therapists are always seeking ways to achieve better therapy compliance in their asthma and chronic obstructive pulmonary disease patients. Because many of their patients are children and geriatrics that may have trouble using traditional metered dose inhalers, therapists often turn to nebulizers to provide efficient drug delivery.

Today, technological advances are giving patients and respiratory therapists more efficient and convenient options for aerosol therapy. Nebulizers are more versatile than metered dose inhalers

and can be used to generate aerosols of bronchodilators, corticosteroids, antibiotics, surfactant and mucolytic agents.

In addition, new devices such as breath-actuated and vibrating mesh nebulizers grant patients faster treatment times than standard nebulizers

and MDIs. They also generate a more uniform particle size of medications, which promotes better delivery to the lungs and small airways where aerosol delivery counts the most.

Therapy on-demand

Although they've been slower to catch on due to their high cost, breath-actuated nebulizers are revolutionizing aerosol therapy by speeding up drug delivery and delivering a more effective dose. Unlike their continuous flow counterparts, breath-actuated nebulizers generate aerosol in response to a patient's inspiratory flow. This on-demand therapy is a significant advance in small volume nebulization. A patient must exert a specific force on the mouthpiece of a breath-actuated nebulizer for it to deliver medication. This guarantees a patient will receive more medication in his or her lungs when a strong enough breath is taken to trigger the device. It also won't try to deliver medication, thus wasting it, when a patient is coughing or resting. So, these devices provided the highest inhaled drug mass and the lowest loss to the room.

To maximize respirable dose, the device delivers high emitted dose and high respirable fraction. Emitted dose is the total amount of drug delivered to the patient; respirable fraction is the amount that will reach the small airways to produce the desired therapy. The high output rate of breath-actuated nebulizers, combined with more than 78 percent respirable fraction, translates into a very high respirable dose. Increased drug deposition quickens the onset of therapy, helping patients breathe better, faster. All in all, this means

shorter treatment times with the likelihood of better patient outcomes and reduced costs

So to re-cap, breath-actuated aerosol therapy means less wasted medication, high efficiency, better patient compliance and clinical dose assurance. But breath-actuated nebulizers offer benefits to respiratory therapists, too. With low environmental loss of medication, these devices help provide a safer work environment for therapists. Conversion to these devices is cost-effective due to decrease administration time. This increases therapist availability, contributing to a reduction in missed treatments. And, if more respiratory therapists are available, this helps address the problem of staffing shortages.

Vibrating mesh technology

New, electronic nebulizers are quickly getting approval from patients due to their smaller size, lack of noise, and super-fast delivery. Vibrating mesh nebulizers are some of the smallest high-tech devices now on the market. What differentiates vibrating mesh nebulizers from others is their ability to generate aerosols with high fine-particle fractions. This means they are more efficient at delivering drugs to the lungs than traditional jet nebulizers, and higher particle deposition means less medication is left in the device. Some of these devices are also breath-actuated, further improving their efficiency.

In 2005, one manufacturer patented an aerosol mixing chamber for its device for its vibrating mesh device. The chamber decreases the amount of drug needed to deliver an efficient dose to a patient. It works by suspending a cloud of aerosolized medicine in the chamber until the patient takes a normal breath. It has been shown to achieve a delivered dose of 65 - 75%, where some other nebulizers only deliver up to 40% of medication.

Another benefit of vibrating mesh technology is it permits drugs to be optimized for the device. For example, an aerosol medicine can be customized based on droplet size, delivery speed, patient interface and chamber design. These advancements give therapists the opportunity to improve patient compliance and change the way aerosol treatments are taken in the future. Beyond traditional aerosol therapy, the Food and Drug Administration has taken a look at how these devices can be used to deliver medications that are usually injected at the bedside. It's believed vibrating mesh nebulizers may be able to effectively deliver drugs for diabetes, as well as asthma, COPD, cystic fibrosis and avian flu.

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Improvements in drug formulations and the design and efficiency of nebulizers have led to the increased use of inhaled therapies in ventilator patients. In many intensive care units, respiratory therapists use nebulizers for aerosol therapy because they don't require continuous attendance by the therapist. However, several factors affect aerosol therapy in ventilator patients, including the choice of nebulizer, its gas flow rate and the position of the nebulizer in the ventilator circuit.

For critical care patients, aerosol delivery systems include the ventilator, its tubing, and the endotracheal or tracheostomy tube. ICU patients may require a nebulizer that operates inline with standard ventilator circuits and mechanical ventilators. Recent studies have shown that certain nebulizers have increased the efficiency of inhaled drug delivery in ventilator patients to a level comparable to their ambulatory counterparts. They do this by producing a precisely defined particle size to create a fine particle, low-velocity aerosol.

Because integrating a nebulizer into a ventilator patient's care can be tricky, some parameters should be followed:

- Make sure the device produces an acceptable median mass aerodynamic diameter (MMAD) for aerosol particles.
- Use high-compressed flow rates less than 6 Lpm.
- Use ventilators that nebulize on inspiration.
- Do not use ventilator humidification during nebulizer administration.
- Fill the device's reservoir to maximum capacity with drug solution. Add saline if necessary for extra volume.

A new Do you remember when you were a student and 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 use is albuterol. Later, you discover someone is using metroproterenol metered dose inhaler (MDI), and you asked "I thought everyone used albuterol?" Today as a respiratory therapist we have a number of agents to choose from, but which one should we choose. This article will review the short acting adrenergic bronchodilator agents available and their indication for use.

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 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 b2 agonists such as albuterol, levalbuterol, or pirbuterol are indicated for relief of acute reversible airflow obstruction in asthma or other obstructive airway diseases.

Short-acting agents are termed "rescue" agents in the 2007 National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPP EPR 3) guidelines. Short-term acting agents may also be termed "relievers" as discussed in the Global Initiative for Asthma (GINA) guidelines. Bronchodilators are key to the management of chronic obstructive pulmonary disease (COPD) symptoms.

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 a and b receptors. Because epinephrine lacks b2-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

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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 β_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 α -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 β 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 β receptors, producing bronchodilation, and on extrapulmonary adrenergic receptors. The (S)-isomer, or dextro isomer, is not active on adrenergic receptors such as β receptors, and until recently the (S)-isomer was considered physiologically inert. The two mirror images of the isomers rotate light in opposite directions, and this is the basis for designating them as dextrorotatory (d, +) or levorotatory (l, -). 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 α and β (epinephrine), to β non-specific (isoproterenol), and finally to β_2 specific (isoetharine). The theory that explains the shift from α activity to β_2 specificity has been termed the keyhole theory of β sympathomimetic receptors: The larger the side-chain attachment to a catechol base, the greater the β_2 specificity. If the catecholamine structural pattern is seen as a keylike shape, then the larger the "key" (side chain), the more β_2 specific the drug. Epinephrine has a methyl group attached to the terminal amine group and activates α and β receptors equally. Isoproterenol adds an additional methyl group with strong β stimu-

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lation and very 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. nebulization method integrates ventilator operations and a single-patient use nebulizer to conduct respiratory therapy. It's approved for use in all patient groups from neonates through adults and operates in continuous and intermittent modes. The device works without changing ventilator parameters and can be refilled without interrupting ventilation. More importantly, the nebulizer doesn't add airflow to the ventilator circuit, so it doesn't trigger false or unnecessary alarms. It also doesn't heat, degrade or shear medication.

A nebulizer's location within the ventilator circuit affects drug deposition. Optimal placement is in the inspiratory limb

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