



ANTICHOLINERGIC BRONCHODILATORS: DIFFERENT SOLUTION TO THE SAME PROBLEM

By Doug Gardenhire EdD, MS, RRT-NPS

Anticholinergic agents work on the parasympathetic nervous system. In the lung agents given by inhaled aerosol can block cholinergic-induced airway constriction. This article will review anticholinergic bronchodilator agents available and their indication for use. I will also discuss the benefits anticholinergic bronchodilators have when used in combination with adrenergic bronchodilators.

Anticholinergic (Parasympatholytic) Agents

Parasympatholytic (anticholinergic, or antimuscarinic) agents that are given by aerosol include ipratropium, a combination of ipratropium and albuterol, and tiotropium. However, other anticholinergic agents such as atropine have been used in the past to achieve the desired pulmonary effect.

Are the bronchodilator effects of β agonists increased by adding anticholinergic agents?

Ipratropium bromide (Atrovent) is a nonselective antagonist of M1, M2, and M3 receptors. Ipratropium is currently available in three formulations for bronchodilator use: as a chlorofluorocarbon-propelled metered dose inhaler (CFC MDI) with 18 $\mu\text{g}/\text{puff}$, a hydrofluoroalkane-propelled MDI (HFA MDI) with 17 $\mu\text{g}/\text{puff}$, and a nebulizer solution of 0.02% concentration in a 2.5-ml vial, giving a 500- μg dose per treatment. This agent is an N-isopropyl derivative of atropine. As a quaternary ammonium derivative of atropine, ipratropium is fully ionized and does not distribute well across lipid membranes, limiting its distribution more to the lung when inhaled.

The profile of clinical effect for ipratropium differs from that of inhaled β -adrenergic agonists. The onset of bronchodilation begins within minutes but proceeds more slowly to a peak effect 1 to 2 hours after inhalation. The β agonists can peak between 20 and 30 minutes depending on the agent. In asthma, the duration of bronchodilator effect is about the same for ipratropium as for β agonists.

Ipratropium bromide (Atrovent nasal spray) is available for treatment of rhinopathies and rhinorrhea, including nonallergic perennial rhinitis, viral infectious rhinitis, and allergic rhinitis, if intranasal corticosteroids fail to control symptoms. The nasal spray is available in two strengths, with a 0.03% solution delivering 21 $\mu\text{g}/\text{spray}$ and the 0.06% solution delivering 42 $\mu\text{g}/\text{spray}$. The 0.03% strength is given as two sprays per nostril two or three times daily, and the

0.06% strength is given as two sprays per nostril three or four times daily. Intranasal ipratropium has been shown to significantly reduce the volume of nasal secretions and symptoms in patients with allergic rhinitis and in those with nonallergic rhinitis. Side effects with the nasal spray are largely local and have included nasal dryness, itching, and epistaxis in a few patients. Dry mouth and dry throat have also occurred. Systemic symptoms such as blurred vision or urinary hesitancy are rare.

Ipratropium and albuterol (Combivent) is a combination MDI product, with the usual doses of each agent (18 $\mu\text{g}/\text{puff}$ of ipratropium, 90 $\mu\text{g}/\text{puff}$ of albuterol). The combination therapy has been shown to be more effective in stable COPD than either agent alone. Another agent, DuoNeb, is available as a combination of ipratropium (0.5 mg) and albuterol base (2.5 mg).

Tiotropium bromide (Spiriva), a muscarinic receptor antagonist, is a long-acting bronchodilator. It is a quaternary ammonium compound structurally related to ipratropium. Like ipratropium, tiotropium is poorly absorbed after inhalation. Inhalation of a single dose gives a peak plasma level within 5 minutes, with a rapid decline to very low levels within 1 hour. Tiotropium exhibits receptor subtype selectivity for M1 and M3 receptors. The drug binds to all three muscarinic receptors (M1, M2, and M3) but dissociates much more slowly than ipratropium from the M1 and M3 receptors. This results in a selectivity of action on M1 and M3 receptors. In patients with COPD, tiotropium gives a bronchodilating effect for up to 24 hours, with adequate dose. The drug also gives a prolonged, dose-dependent protection against inhaled methacholine challenge.

Use in Chronic Obstructive Pulmonary Disease

Anticholinergic agents were found to be more potent bronchodilators than β -adrenergic agents in bronchitis-emphysema, and this is likely to be their primary clinical application. In a 90-day, multicenter study, the investigation compared 40 μg of ipratropium with 1.5 mg of metaproterenol, both given by MDI, in a population

continued on next page



Join us May 14-16, 2009 in Orlando for the 9th Annual Focus Conference at Disney's Coronado Springs Resort

of patients with COPD. Explanations for the superiority of anticholinergic action in COPD are debated but may relate to the complicated, inflammatory, noncholinergic pathways seen in asthma, especially due vagally mediated reflex bronchoconstriction. Conversely, the pathology of COPD may reveal the reason for the superior effect of anticholinergic over β -adrenergic drugs. Ipratropium has been approved by the U.S. Food and Drug Administration (FDA) specifically for use in the treatment of COPD, although the drug is also prescribed for treatment of asthma.

Tiotropium, an antimuscarinic bronchodilator, offers a prolonged duration of action of up to 24 hours with a single daily inhalation. In dose-ranging trials an inhaled dose of 18 μ g once per day has been found to give significant bronchodilation in patients with COPD with few side effects. Perhaps one of the more important effects of a long-acting drug such as tiotropium is the elevation in baseline, predose FEV1. Unlike ipratropium, lung function is maintained more consistently at a higher level throughout the day with tiotropium. This may have a significant effect on quality of life and reduction of breathlessness in patients with COPD.

Current COPD guidelines do not dictate the use of any one specific bronchodilator. However, it is noted that the use of a short-term β_2 agonist and an anticholinergic, such as ipratropium, improves the forced expiratory volume in 1 second (FEV1) in patients with COPD. The use of a long-term anticholinergic, such as tiotropium, improves the health of patients with COPD. The use of a single agent or combination will be dictated by the patient's response.

Use in Asthma

Anticholinergic agents such as ipratropium do not have a labeled indication for asthma in the United States. Current asthma guidelines state that ipratropium may have some additive benefit when given with inhaled β agonists. Antimuscarinic bronchodilators are not clearly superior to β -adrenergic agents in treating asthma. Antimuscarinic and β -adrenergic agents have an approximately equal effect on flow rates in many patients. These agents may be especially useful in the following applications when prescribed for asthmatic patients:

- Nocturnal asthma, in which the slightly longer duration of action may protect against nocturnal deterioration of flow rates
- Psychogenic asthma, which may be mediated through vagal parasympathetic fibers
- Asthmatic patients with glaucoma, angina, or hypertension who require treatment with β -blocking agents
- As an alternative to theophylline in patients with notable side effects from that drug
- Acute, severe episodes of asthma not responding well to β agonists

Combination Therapy: β -Adrenergic and Anticholinergic Agents in Chronic Obstructive Pulmonary Disease

Theoretically, a combination of β -adrenergic and anticholinergic agents should offer advantages in the treatment of COPD and asthma, based on the following considerations:

- Complimentarily of sites of action exists, with anticholinergic effect seen in the more central airways and β -agonist effect in the smaller, more peripheral airways.
- Mechanisms of action from anticholinergic and β -adrenergic agents are separate and complementary.

continued on page 80

MVAP
MEDICAL SUPPLIES, INC.

The MVAP 2008 Sleep Testing Supplies catalog is filled with new and exciting products at fantastic prices! Call today to request our free catalog.

Our ecommerce website is loaded with new products and bargains, which are updated daily! Check-out our MVAP Q&A forum, too! Log on today to request our free catalog.

MVAP Medical Supplies
1415 Lawrence Drive, Newbury Park, CA 91320
Toll Free: 1-877-735-MVAP (68271) | Toll Free Fax: 1-877-735-7213 | www.mvapmed.com

CIRCLE READER ACTION CARD # 40

Therapeutic Humidification
Anything less is.....¹

ThermoFlo™ System
ARC Medical, Inc.
Changing Humidification Since 1990.
322 Patterson Ave. • Scottsdale, GA 30079
Phone (404) 373-8311 • FAX (404) 373-8385
Order Toll Free (800) 950-ARC1 (2721)
arcmedical.com

1. No reported incidences of ET tube occlusions since 1990.

CIRCLE READER ACTION CARD # 41

We offer a complete line of Breathing Filters, HMEs and HMEFs to meet your needs. From quality 99.9% efficient options to our premium quality 99.999% range; whatever your needs we have a solution.

INTERSURGICAL
INCORPORATED

support@intersurgicalinc.com
T: (315) 451 2900

CIRCLE READER ACTION CARD # 95

Respiratory Pharmacology... Continued from page 69

Additive Effect of β Agonists and Anticholinergic Agents

Conflicting results have been found on the question of whether the bronchodilator effect of β agonists is increased by adding an anticholinergic agent, in either COPD or asthma. Many of the studies performed with combined anticholinergic and β -agonist bronchodilator therapy suffer from small sample sizes and poor statistical power. Before the approval of combined albuterol and ipratropium (Combivent), a large, well-controlled study was conducted over 85 days with 462 patients at 24 centers. Patients represented stable COPD. The study showed superior efficacy of the combination therapy of ipratropium and albuterol compared with either agent alone. Another study with ipratropium plus albuterol with albuterol or ipratropium alone on the percentage change in FEV1 showed a mean peak increases in FEV1 were 31 to 33% for combined drug therapy, compared with 24 to 25% for ipratropium alone and 24 to 27% for albuterol alone. Flow rates were significantly better on all test days. Symptom scores did not differ among the three groups, however. As a large, well-designed study, these results support combination anticholinergic and β -agonist therapy in COPD.

Anticholinergics are another solution to the fight to relieve air flow obstruction. These agents work well with beta agonists as well as on their own. The next time a patient is in distress the use of an anticholinergic may be needed.

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.

Managing Generational Differences... Continued from page 51

ing to change them unless you're willing to punish noncompliance. If you get a few members to cooperate, peer pressure will work better than your attempts at coercion. In the meantime, what tasks can most effectively be assigned to individuals?

Make learning the centerpiece. Gen Xers are hooked on email so use it liberally but judiciously: Save some important information for distribution exclusively during a team meeting and make sure team members know that is what's on the agenda. Like it or not, meetings are important so members can get feedback from others that's friendly and helpful — including from the boss who should always attend and participate.

Keep rethinking your goals. Is total participation really necessary except when strategic decisions are being made? If you're not going to change courses no matter what, don't demand an opinion from everyone. Gen Xers hate being lashed into discussion even when they know the boss has already decided the outcome.

Compensate only those who exhibit the desirable behavior even if that means some high performers don't get the reward they might have had if they'd been team-minded. They'll probably move on, but that's exactly what the reward system is meant to facilitate. As part of your evaluation, ask your direct reports, "What have you done (initiated) that has enhanced the productivity, effectiveness, and satisfaction of co-workers, especially your teammates?" Unless compensation reflects the individual's contribution to the team, teamwork is doomed. (It may be anyhow: As younger workers take over from the forty- and fiftysomethings they are much more likely to reward individual efforts and breakthroughs. That will doom teams no matter what top management wants or thinks.)

Understand the importance of lifestyle.

You will never get 100 percent commitment from Gen Xers. The word "loyalty" doesn't mean what it meant to their parents, many of whom were rewarded for their loyalty with serial layoffs in the 80s. As often as possible, make allowances for family or personal needs of employees. They will put family and friends before the organization regardless. In deference to family time, consider moving meetings to early morning. Schedule working lunches instead of keeping people late.

If an activity is not a command performance and you want cross-generational participation, understand that lifestyle rules. Make the meeting short. Provide an agenda for every meeting and stick to it. Make sure there some sort of a welcoming committee. Gen Xers will not work a room like their elders. If no one talks to them, they just won't come back. And don't expect 100 percent turnout even at an organizational social function that's free to all.

The goal of cross-generational harmony in the workplace is not impossible. Boomers can learn to manage, motivate, and retain Gen Xers. Gen Xers can learn to appreciate the Boomers' knowledge of organizational history and culture — and yes, their work ethic. As Boomers retire, Gen Xers may end up managing older workers — an excellent reason for them to develop an understanding of that generation's values and styles.

Marilyn Moats Kennedy is founder and managing partner of Career Strategies, a 34-year old management consulting firm in Illinois. Kennedy holds a MSJ from Northwestern University and is a regular columnist in Focus. MMKcareer@aol.com