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Review Article

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Ipratropium Bromide Respules: A review of its use in Asthma and COPD

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Abstract:
Inhalation therapy is the preferred route for managing asthma and chronic obstructive pulmonary disease (COPD) due to its rapid onset of action, lower systemic side effects, and reduced required drug doses. While pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers have shown comparable efficacy when used correctly, misuse—especially among elderly COPD patients—can lead to suboptimal treatment outcomes. Nebulizers, despite their limitations, have gained increasing support for maintenance and exacerbation management in stable COPD. Ipratropium bromide, a widely used anticholinergic bronchodilator, functions by antagonizing muscarinic receptors to induce bronchodilation. Often used in combination with beta-agonists, it enhances therapeutic outcomes in conditions like asthma, COPD, and bronchopulmonary dysplasia, although its long-term utility remains limited. Advances in inhalation device technology and deeper insights into disease mechanisms present opportunities for the development of targeted, disease-modifying therapies. Future strategies aim to address airway remodeling and structural lung damage to improve long-term outcomes and reduce exacerbations in both asthma and COPD.

Keywords: COPD, Nebulizers, Bronchodilator, Exacerbation

1. Introduction

National and international guidelines highlight inhalation therapy as the preferred method for administering drugs to treat asthma (1,2) and chronic obstructive pulmonary disease (COPD) (3–5), due to its several advantages over oral or parenteral treatments, including faster onset, lower required doses, and reduced systemic side effects (6). Previous systematic reviews have concluded that the three most commonly used inhalation devices—pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers—offer similar efficacy in managing asthma and COPD, provided they are used correctly (7–9).

However, in clinical practice, patients who use these inhalers incorrectly often experience less symptom relief compared to those who use the devices properly (10,11). This issue is particularly common among elderly COPD patients, many of whom struggle with optimal use of pMDIs and DPIs (10–12). Additionally, some drug formulations are not available for certain devices—such as the absence of an approved pMDI formulation for long-acting beta-agonists in the United States—which limits the options for drug/device combinations.

In recent years, new devices and drug formulations have entered the market, prompting further investigation into the benefits of different drug/device combinations for specific patient populations. The ERS/ISAM Task Force Report offers a comprehensive review of aerosol delivery devices and their appropriate use in clinical practice (13).

Despite certain limitations, such as reduced portability, longer administration times, variable drug output, and the need for cleaning, a growing body of evidence supports the use of nebulizers for maintenance therapy in outpatient settings (14). This article primarily focuses on the role of nebulizers in treating stable COPD and managing exacerbations of the disease. Issues related to aerosol delivery devices for patients on noninvasive or invasive mechanical ventilation are addressed elsewhere (15).

Asthma

Asthma is a chronic condition marked by variable airflow obstruction and heightened bronchial sensitivity. It is a common disease that can lead to significant morbidity and mortality (16, 17). This disorder causes inflammation and hyperreactivity in the airways, making them more susceptible to bronchoconstrictor stimuli (as reviewed by Grootendorst and Rabe in this issue (18).

During an acute asthma exacerbation, patients experience airway obstruction due to various triggers, which lead to limited airflow. The obstruction results from bronchoconstriction, mucus buildup, edema, and heightened inflammation. Common triggers for asthma exacerbations include viral infections, allergens (such as pet dander, cockroaches, dust mites, pollen, and mold), air pollution, tobacco smoke, exercise, and chemical exposure. Although asthma attacks occur in episodic bursts, the underlying inflammation of the airways persists chronically (19).

Asthma requires ongoing management, often involving daily medication use to prevent symptoms and maintain control of the condition.

Ipratropium Bromide

Ipratropium bromide is a quaternary ammonium derivative of atropine, which acts as a potent inhibitor of acetylcholine, a substance that causes bronchoconstriction and stimulates airway mucin production. As an anticholinergic bronchodilator, ipratropium is sometimes used in neonatal intensive care units (NICUs) as an adjunctive therapy for acute bronchospasm (20). When inhaled, ipratropium is poorly absorbed into the bloodstream and specifically targets the lungs to promote bronchodilation.

In combination with a beta-agonist, ipratropium enhances bronchodilation more effectively than either drug used alone. This combination therapy has been applied in infants with bronchopulmonary dysplasia (BPD). However, there is no evidence supporting long-term benefits of ipratropium bromide use in BPD patients (21). Ipratropium bromide is not recommended for treating acute bronchiolitis.

Ipratropium is a quaternary ammonium derivative of atropine that functions as an anticholinergic agent. Typically administered via inhalation, it delivers a localized effect with minimal systemic absorption (22). Developed by Boehringer Ingelheim, ipratropium's first monotherapy product received FDA approval in 1986. The combination product of ipratropium and albuterol followed, gaining FDA approval in 1996(23).

Ipratropium bromide is an anticholinergic (parasympatholytic) agent that, according to animal studies, inhibits vagally-mediated reflexes by blocking the action of acetylcholine, the neurotransmitter released from the vagus nerve. Anticholinergics prevent the increase in intracellular cyclic guanosine monophosphate (cyclic GMP) levels, which typically occurs when acetylcholine interacts with muscarinic receptors on bronchial smooth muscle.

Ipratropium bromide has low binding affinity to plasma albumin and α-acid glycoproteins, and it is partially metabolized. Autoradiographic studies in rats have indicated that it does not cross the blood-brain barrier. Although ipratropium bromide inhalation solution has not been specifically studied in patients with hepatic or renal insufficiency, caution is advised when using it in these populations.

Pharmacodynamics Ipratropium

Ipratropium is a short-acting agent that works by inhibiting the parasympathetic nervous system in the airways, leading to bronchodilation (24). Its effects begin within 1 to 2 hours and typically last for 4 to 6 hours. By relaxing the bronchial airways, ipratropium helps reverse the narrowing associated with symptoms like wheezing, chest tightness, cough, and impaired gas exchange (25,26).

In clinical trials involving the initial management of status asthmaticus, ipratropium showed clear benefits in improving pulmonary function in both children and adults. However, continued use of ipratropium following an acute asthma attack has not demonstrated significant advantages, nor has its prophylactic use been proven beneficial (27).

Mechanism of action: Ipratropium

Ipratropium functions as an antagonist to the muscarinic acetylcholine receptor, which leads to the suppression of the parasympathetic nervous system in the airways, thereby inhibiting its activity. The parasympathetic system typically triggers bronchial constriction and secretion in the airways. By blocking this action, ipratropium promotes bronchodilation and reduces secretion production (28).

On a cellular level, acetylcholine is released into muscle cells, causing contraction and narrowing of the airways. By administering ipratropium, acetylcholine's activity in the smooth muscle is inhibited, preventing contraction and resulting in relaxed, wider airways (29).

Molecular Mechanism of Ipratropium

Ipratropium is an acetylcholine antagonist that works by blocking muscarinic cholinergic receptors. This blockage reduces the production of cyclic guanosine monophosphate (cGMP), leading to decreased contraction of smooth muscles in the lung airways. The M2 receptors, located at the terminals of cholinergic nerve endings, typically serve as feedback regulators that inhibit acetylcholine release. When these receptors are blocked, acetylcholine release increases, which can enhance the bronchoconstrictor response to cholinergic nerve stimulation (30).

As a nonselective blocker, ipratropium also inhibits M2 receptors, resulting in an increased release of acetylcholine and potentially reducing the duration and extent of its effect on M3 receptors. This mechanism may contribute to the paradoxical bronchoconstriction sometimes observed following ipratropium use (31).

Intranasal ipratropium mimics the effects of atropine by inhibiting secretions from salivary and mucous glands and dilating bronchial smooth muscle. Compared to atropine, ipratropium is a more potent antimuscarinic agent and bronchial smooth muscle relaxant when inhaled (32).

Intranasal ipratropium also produces a localized parasympathetic effect, reducing water secretion from the nasal mucosal glands and providing relief from rhinorrhea, whether allergic or non-allergic. Clinical studies have shown that oral inhalation of ipratropium in COPD patients increases FEV1 by 24% to 25% above baseline, with similar improvements in forced vital capacity (FVC). Moreover, when used via a metered-dose inhaler, the combination of ipratropium and albuterol is more effective in managing COPD than either drug alone (33,34)

Ipratropium effects on muscarinic cholinergic receptors

Airway smooth muscle contains a high density of muscarinic M2 and M3 receptors, with a roughly 4:1 ratio (35). Although the M3 receptor, which is Gq-coupled, is expressed at lower levels, it plays a dominant role in inducing bronchial and tracheal smooth muscle contraction. This is supported by the functional affinities of various subtype-selective antagonists in airway tissues across multiple species, including humans (36-37). Furthermore, mice lacking muscarinic M3 receptors, but not M2 receptors, fail to exhibit bronchoconstriction induced by methacholine or vagal stimulation in vivo (38). However, some pharmacological studies have suggested that Gi-coupled M2 receptors may also contribute to airway smooth muscle contraction in the peripheral airways (39,40). In conditions like asthma and COPD, the regulation of airway smooth muscle tone by muscarinic receptors is exacerbated by two key mechanisms: increased expression and enhanced function of signaling molecules critical for muscarinic receptor-mediated contraction, and the heightened release of neuronal acetylcholine due to inflammatory-associated neuronal changes.

2. Future Therapeutic Targets and Strategies in Exacerbation of Asthma and COPD

In the future, there may be opportunities for innovative therapies that could alter the pathogenesis and progression of both asthma and COPD. For asthma, new treatments targeting upstream immunologic pathways or aiming to prevent or reverse the immune abnormalities seen in atopy could potentially lead to drugs that are genuinely “disease-modifying” or even offer a cure. However, the long-term effects of modifying the immune response remain uncertain, and conducting extensive clinical trials to assess these impacts may pose significant challenges.

Asthma's pathogenesis also involves chronic inflammation and structural changes in airway cells and tissues, such as smooth muscle, fibroblasts, and the epithelium. This phenomenon, known as "airway remodeling," can occur early in the disease and may contribute to its progressive nature in many patients. Gaining a deeper understanding of airway remodeling could open the door to new therapeutic targets, leading to more effective treatments for asthma (41-43).

Similarly, in COPD, the airways and lungs undergo substantial structural alterations, including goblet cell hyperplasia, mucous gland hypertrophy, chronic inflammation, small airway plugging (bronchiolitis), and extensive destruction of lung tissue (emphysema) (44). These areas remain key focuses of research for potential new therapies. Emerging drugs that repair or "restore" the abnormal structural changes in the respiratory system in both asthma and COPD could help slow or even reverse the progressive decline in lung function and overall health. These therapies might also reduce individuals' increased vulnerability to infections and, as a result, lessen the frequency of exacerbations in asthma and COPD patients. This could, in turn, slow disease progression and reduce mortality, representing a significant achievement in the search for therapies to manage chronicity and exacerbations in these diseases. Tackling these challenges will require concerted effort from both the scientific and medical communities, including academia and the pharmaceutical industry (45).

Conclusion

Inhalation therapy remains central to the management of asthma and COPD, offering significant advantages over systemic treatments. The choice of device and patient proficiency in its use are critical determinants of therapeutic success. Ipratropium bromide plays an important role in acute bronchodilation, especially when used in combination therapies, although its impact on long-term disease progression is limited. Future directions in treatment should focus on reversing airway remodeling and mitigating structural changes to reduce exacerbations and slow disease progression. Continued research and innovation in drug delivery systems and molecular therapies are essential for advancing care and improving outcomes for patients with chronic respiratory diseases.

References

[1]. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. Chest 2000;117:398S–401S.
[2]. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57:847–852.
[3]. Wedzicha JA. Exacerbations: etiology and pathophysiologic mechanisms. Chest 2002;121:136S–141S.
[4]. Schwartz J. Air pollution and hospital admissions for the elderly in Detroit, Michigan. Am J Respir Crit Care Med 1994;150:648–655.
[5]. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. Eur Respir J 2003;Suppl 41:46S–53S.
[6]. Voelkel NF, Tuder R. COPD: exacerbation. Chest 2000;117:376S–379S.
[7]. Pauwels RA. Similarities and differences in asthma and chronic obstructive pulmonary disease exacerbations. Proc Am Thorac Soc 2004;1: 73–76.
[8]. McCrory DC, Brown C, Gelfand SE, Bach PB. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Chest 2001;119:1190–1209.
[9]. Tobin MJ. Asthma, airway biology, and nasal disorders in AJRCCM 2002. Am J Respir Crit Care Med 2003;167:319–332.
[10]. Beeh KM, Beier J, Kornmann O, Buhl R. Sputum matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1, and their molar ratio in patients with chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and healthy subjects. Respir Med 2003;97:634639.
[11]. McFadden ER Jr. Acute severe asthma. Am J Respir Crit Care Med 2003;168:740–759
[12]. Wedzicha JA. Role of viruses in exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2004;1:115–120

[13]. Cazzola M, Di Perna F, D'Amato M, Califano C, Matera MG, D'Amato G. Formoterol Turbuhaler for as-needed therapy in patients with mild acute exacerbations of COPD. Respir Med 2001;95:917–921.
[14]. Murciano D, Auclair MH, Pariente R, Aubier M. A randomised, controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. N Engl J Med 1989;320:1521–1525.
[15]. Karpel JP, Pesin J, Greenberg D, Gentry E. A comparison on the effects of ipratropium bromide and metaproterenol sulfate in acute exacerbations of COPD. Chest 1990;98:835–839.
[16]. Pauwels R, Buist AS, Calverley PMA, Jenkins CR, Hurd SS, on behalf of the GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. Am J Respir Crit Care Med 2001; 163:1256–1276.
[17]. Rennard SI, Farmer SG. Exacerbations and progression of disease in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc 2004;1:88–92.
[18]. Kellerman DJ. P2Y(2) receptor agonists: a new class of medication targeted at improved mucociliary clearance. Chest 2002;121:201S– 205S.
[19]. Grootendorst DC, Rabe KF. Mechanisms of bronchial hyperreactivity in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc 2004;1:77–87.
[20]. Handley DA, Anderson AJ, Koester J, Snider ME. New millennium bronchodilators for asthma: single-isomer beta agonists. Curr Opin Pulm Med 2000;6:43–49.
[21]. Ruggiero A, Ariano A, Triarico S et al. Neonatal pharmacology and clinical implications. Drugs Context. 2019;8:212608.
[22]. Osmond MH, Klassen TP: Efficacy of ipratropium bromide in acute childhood asthma: a meta-analysis. Acad Emerg Med. 1995 Jul;2(7):651-6.
[23]. Almadhoun K, Sharma S: Bronchodilators .
[24]. Barnes P., Drazen J., Rennard S. and Thomson N. (2002). Asthma and COPD.
[25]. Hale T. and Rowe H. (2017). MEdications & mothers' milk (17th ed.). Springer publishing company.
[26]. Ng GY, da Silva O, Ohlsson A. Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants. Cochrane Database Syst Rev. 2001;3:CD003214.
[27]. Bhandari V. Postnatal inflammation in the pathogenesis of bronchopulmonary dysplasia. Birth Defects Res A. 2014;100(3):189-201.
[28]. Young TE, Magnum B, eds. Micormedex NeoFax Essentials. NJ: Thomson Reuters; 2020.
[29]. Rehder KJ: Adjunct Therapies for Refractory Status Asthmaticus in Children. Respir Care. 2017 Jun;62(6):849-865.
[30]. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. Thorax. 2005 Sep;60(9):740-6.
[31]. Reddel HK, Bacharier LB, Bateman ED, Brightling CE et al,. Global Initiative for Asthma Strategy 2021: Executive Summary and Rationale for Key Changes. Am J Respir Crit Care Med. 2022 Jan 01;205(1):17-35.
[32]. Couillard S, Connolly C, Borg C, Pavord I. Asthma in pregnancy: An update. Obstet Med. 2021 Sep;14(3):135-144.
[33]. Thornton CS, Haws JT. Bromism in the Modern Day: Case Report and Canadian Review of Bromide Intoxication. J Gen Intern Med. 2020 Aug;35(8):2459-2461.
[34]. Ajimura CM, Jagan N, Morrow LE, Malesker MA. Drug Interactions With Oral Inhaled Medications. J Pharm Technol. 2018 Dec;34(6):273-280.
[35]. Roffel AF, Elzinga CR, Van Amsterdam RG, De Zeeuw RA, Zaagsma J: Muscarinic M2 receptors in bovine tracheal smooth muscle: discrepancies between binding and function. Eur J Pharmacol 1988, 153:73-82.
[36]. van Nieuwstadt RA, Henricks PA, Hajer R, van der Meer van Roomen WA, Breukink HJ, Nijkamp FP: Characterization of muscarinic receptors in equine tracheal smooth muscle in vitro. Vet Q 1997, 19:54-57.

[37]. Fisher JT, Vincent SG, Gomeza J, Yamada M, Wess J: Loss of vagally mediated bradycardia and bronchoconstriction in mice lacking M2 or M3 muscarinic acetylcholine receptors. FASEB J 2004, 18:711-713.

[38]. Roffel AF, Elzinga CR, Zaagsma J: Muscarinic M3 receptors mediate contraction of human central and peripheral airway smooth muscle. Pulm Pharmacol 1990, 3:47-51.

[39]. Fisher JT, Vincent SG, Gomeza J, Yamada M, Wess J: Loss of vagally mediated bradycardia and bronchoconstriction in mice lacking M2 or M3 muscarinic acetylcholine receptors. FASEB J 2004, 18:711-713.

[40]. Roffel AF, Elzinga CR, Zaagsma J: Cholinergic contraction of the guinea pig lung strip is mediated by muscarinic M2-like receptors. Eur J Pharmacol 1993, 250:267-27.

[41]. Kumar SD, Brieva JL, Danta I, Wanner A. Transient effect of inhaled fluticasone on airway mucosal blood flow in subjects with and without asthma. Am J Respir Crit Care Med 2000;161:918–921.

[42]. Belvisi MG, Bottomley KM. The role of matrix metalloproteinases (MMPs) in the pathophysiology of chronic obstructive pulmonary disease (COPD): a therapeutic role for inhibitors of MMPs? Inflamm Res 2003;52:95100.

[43]. Tobin MJ. Asthma, airway biology, and nasal disorders in AJRCCM 2002. Am J Respir Crit Care Med 2003;167:319–332.

[44]. Handley DA, Anderson AJ, Koester J, Snider ME. New millennium bronchodilators for asthma: single-isomer beta agonists. Curr Opin Pulm Med 2000;6:43–49.

[45]. Kips JC, Pauwels RA. Long-acting inhaled beta(2)-agonist therapy in asthma. Am J Respir Crit Care Med 2001;164:923–932.