

Review article

Anticholinergic antimuscarinic agents in the treatment of airways bronchoconstriction in children

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Autonomic nerves regulate airway muscle tone, secretions, blood flow, microvascular permeability, and the migration of inflammatory cells. Cholinergic nerves, the dominant bronchoconstrictor pathway in airways, derive from the vagus nerve, enter the lung at the hilum, travel along the posterior walls of the airways, and reach synapse in parasympathetic ganglia which are located within the airway wall. Short postganglionic fibers go from these ganglia to airway smooth muscle and mucous glands (1). The activation of the vagus causes the release of acetylcholine from cholinergic nerve terminals with stimulation of muscarinic cholinergic receptors. At least three sub-types of muscarinic receptor have been identified (2). M1 receptors are excitatory; they are present in parasympathetic ganglia and facilitate cholinergic reflexes. M2 receptors located prejunctionally on postganglionic parasympathetic nerves inhibit acetylcholine release and may limit vagal bronchoconstriction. M3 receptors are localized on airway smooth muscle and on airway glands; their stimulation is associated with bronchoconstriction and mucus secretion.

The mechanisms that might contribute to cholinergic bronchoconstriction in asthma include increased vagal tone, increased reflex bronchoconstriction due to stimulation of sensory receptors in the airway (irritant receptors and C-fiber endings), and increased acetylcholine release induced by inflammatory mediators (3). Anticholinergic agents affect only the cholinergic reflex component

of bronchoconstriction, antagonizing the actions of acetylcholine at parasympathetic, postganglionic, effector-cell junctions by competing with acetylcholine for receptor sites (4).

Atropine is the prototype muscarinic cholinergic antagonist, but because of its absorption from alimentary and respiratory tracts into the systemic circulation and the capacity to cross the blood-brain barrier, with inevitable appearance of side-effects such as dry mouth, tachycardia, and hallucinations, its use in the treatment of airways disease has been restricted. Chemical alteration of atropine to produce ipratropium bromide (IB) and oxitropium bromide (OB) had little effect on the anticholinergic efficacy of the drugs, but it effectively reduced lipid solubility and decreased absorption across cell membranes, thereby increasing and prolonging the bronchodilator efficacy and virtually abolishing the side-effects (4, 5). IB is a synthetic quaternary ammonium salt, is derived from hyoscyne (scopolamine), which is structurally related to ipratropium, and is as active as IB in the degree of bronchodilation observed after inhalation (7).

Bronchodilator therapy with anticholinergic agents

Acute asthma

A number of studies have demonstrated that inhaled anticholinergic agents produce dose-related bronchodilation in children with acute asthma. IB has

bronchodilator properties in childhood asthma when given by nebulized solution in doses of 75–250 µg. Higher doses do not produce greater bronchodilator effects (8, 9). The bronchodilating effect of 40 µg IB delivered by a powder-device system or by metered-dose inhaler (MDI) has been shown to be equivalent in two studies (10, 11). However, one study showed that only 21% of patients had a substantial bronchial response (i.e., at least 15% increase in FEV₁ 30 min after inhalation) to inhalation of 40 µg of IB by MDI (11). Studies of OB in childhood asthma are few (12–14). It has been shown that OB administered by MDI at a dose of 200 µg is as effective as fenoterol administered at the same dose in children with mild bronchoconstriction (12). In this study, both the drugs induced submaximal bronchodilation, as demonstrated by further improvement in lung function after administration of a double dose of the β_2 agonist (12). No comparison has been performed in children between IB and OB. However, in adult asthmatic patients, it has been shown that both drugs are active for 10 h, with 200 µg of OB equivalent in effectiveness to 80 µg of IB administered by MDI (15) and that OB is as active as IB in the degree of bronchodilation achieved 15 min after dosing (7).

The maximum effect achieved with anticholinergic drugs is lower than that achieved with maximum doses of inhaled β_2 agonists, and the time taken to achieve maximum bronchodilation may be delayed for up to 90 min. For these reasons, there is little indication for their use as a first-line, single drug in the therapy of acute asthma (16). However, there have been a large number of studies focusing on the combined use of anticholinergic drugs with β_2 agonists. The effect is additive or less than additive. Most of these studies have concluded that the addition of IB or OB to inhaled β_2 agonists enhances the degree and duration of bronchodilation without the expected increases in heart rate and tremor associated with high doses of β_2 agonists (12, 16–21). Furthermore, frequent administration by inhalation of salbutamol and IB was recently recommended in the initial management of severe acute asthma in children (17). It appears that anticholinergics should be considered in all patients refractory to other medications (22), and in patients who tolerate β_2 agonist poorly, resulting in muscle tremor, tachycardia, or idiosyncratic sensitivity (17). Because side-effects of β_2 agonists are most likely to occur in acutely ill patients treated with aerosol therapy every 2–3 h, the use of alternating therapy with β_2 -adrenergic and anticholinergic agents is an attractive option.

Paradoxical bronchoconstriction has been reported with nebulized inhaled IB solution. This was due to the hypotonicity of the solution as well

as to the presence of bacteriostatic and preservative agents such as ethylenediamine tetracetic acid and benzalkonium chloride, which are potent bronchoconstrictor stimuli (23). The reformulation of the commercially available solution as an isotonic preparation and the removal of these bacteriostatic and preservative agents have largely resolved the problem which may occasionally be seen when large doses of the solution are nebulized to the patients (23).

Chronic asthma

Conflicting results have been obtained in patients with chronic asthma requiring regular treatment with bronchodilators. The use of IB given by MDI 40 µg t.i.d. compared with placebo was associated with an improvement of symptoms and peak-flow rates in a study (24), an effect which was not confirmed by two additional studies evaluating the addition of IB to the regimen commonly used such as inhaled salbutamol and/or inhaled corticosteroids and/or theophylline (25, 26). In one study, maintenance treatment with IB (40 µg t.i.d.) did not diminish the diurnal variation in airway caliber nor did it reduce symptom scores or decrease the use of additional doses of salbutamol (26). IB may have failed to reduce diurnal variation in airway caliber because anticholinergic action at this dose does not last long enough to be effective in an 8-h regimen. Since regular treatment with IB 40 µg t.i.d. for 4 months had no effect on bronchial hyperreactivity (BHR) in children with mild stable asthma (27) and was not associated with significant side-effects, higher doses of the drug could be studied in children with chronic asthma.

In adults with chronic asthma, a high-dose inhaled IB, 160 µg taken at night, reduced the morning "dip" of peak expiratory flow rate (28). Thus, anticholinergic agents have been shown to have a useful and a rather prolonged bronchodilator action which approaches that achieved by therapeutic doses of beta adrenergic drugs, whereas in younger asthmatic patients β_2 agonists are more effective (29).

Bronchial challenge studies

With the exception of cholinergic challenges in other bronchial challenge studies, anticholinergic agents have been invariably demonstrated to be weaker in their protective effect than β_2 agonists and often weaker than sodium cromoglycate (4). Furthermore, studies on exercise, isocapnic hyperventilation, cold air, and distilled water challenges have shown heterogeneous effects of anticholinergic agents in protecting against bronchoconstriction

(30–36). Nebulized IB has been shown to provide about 50% protection against exercise-induced bronchoconstriction (30). The protection observed in the exercise challenge cannot be ascribed solely to the bronchodilation produced by IB since no correlation was observed between bronchodilation and protection. Moreover, a study has shown the dose of IB (500 µg) that produced the greatest bronchodilation had the least effect on exercise-induced bronchoconstriction (30).

In challenge studies excluding methacholine-induced bronchoconstriction in which the patients are fully protected (30), individual analyses of patients' responses to the drug show large inter-individual variations: some patients fail to respond whereas others have their bronchoconstriction markedly attenuated. This indicates that the contribution of the cholinergic component to airflow limitations differs between asthmatic patients, and that it may change from time to time in the same patients. In challenge studies, the protection was observed with doses ranging from 200 to 300 µg of nebulized IB, and there was no additional benefit from higher doses (30–36). The protection in cholinergic challenge has been shown to last for at least 6 h after administration of 200 µg OB by MDI (36). In this study, we postulated that a more prolonged action against methacholine challenge would have been possible with the use of a higher dose.

Asthma in pre-school children and in infants

Some infants and pre-school children with wheezing disease do not respond to nebulized salbutamol, and this treatment may lead to hypoxemia in some patients (37). IB administered as nebulized solution at the dose of 250 µg was associated with a reduction of airways resistance, specific conductance, and total respiratory resistance, and with an improvement in clinical conditions in approximately 40% of asthmatic children aged 3–32 months (38). Two months of regular treatment with nebulized IB was associated with an immediate improvement in 30% of wheezing toddlers although symptom scores during the IB and placebo periods were virtually identical (39). Subsequent studies showed that pre-school children respond well to nebulized IB with an improvement more evident in large airways (40) and associated with an increase in oxygen saturation, in contrast to the hypoxemia that accompanies the administration of salbutamol (41). The metered-dose aerosol plus spacer and mask (MDA) delivery of IB was as effective as nebulization in wheezing in infants aged less than 25 months. The MDA was more convenient, required less time and equipment, and was well accepted by the small patients (42).

Acute bronchiolitis

Nebulized IB is frequently administered to infants suffering from acute bronchiolitis. However, studies have produced conflicting results. An improvement was observed in the work of breathing during the acute phase of the disease (43), but no significant changes in the rate of resolution of the illness have been reported (44). More recently, treatment with either nebulized salbutamol (0.15 mg/kg per dose) or IB (250 µg per dose) resulted in clinically significant improvement in infants between 6 weeks and 24 months of age who were exhibiting the first episode of acute bronchiolitis. However, the combined therapy with the two drugs resulted in no additional benefit with respect to decrease in the respiratory rate, accessory muscle score, wheeze score, oxygen saturation, or hospitalization rate (45).

Respiratory distress syndrome and bronchopulmonary dysplasia (BPD)

Preliminary studies suggest a role for nebulized IB in the neonatal intensive care unit. A fall in rate of breathing has been reported in preterm babies ventilated for respiratory distress syndrome after receiving 20 µg of IB down the endotracheal tube (46). A reduction in pulmonary resistance and an increase in compliance have been observed in ventilator-dependent premature infants with BPD after a single dose of nebulized IB (25 µg/kg) (47). Similarly, a reduction in airways resistance and an increase in forced expiratory flow rates have been observed after nebulized atropine in BPD infants after extubation (48).

Conclusions

The newer preparations of muscarinic cholinergic antagonists have an undoubted therapeutic role in the management of airflow obstruction in acute asthma, but they should be considered an adjunct therapy rather than first-line drugs (16, 49–51). The duration of bronchodilation is usually 4–6 h with a delay in maximum reactive effect of up to about 1 h. The optimum dose of IB is 250 µg by nebulizer and 40–80 µg by MDI. More protective effect in challenge studies was observed with higher doses, which are also associated with longer lasting significant bronchodilator effect and frequently with a larger area under the bronchodilation curves (52, 53).

OB has not been extensively studied in children with asthma. The recommended dosage is 100–200 µg by MDI. Higher doses than those usually administered have been recently recommended

in children, in order to obtain a rapid and perhaps more prolonged bronchodilation (12).

In consideration of the fact that the therapeutic index (maximum tolerated dose divided by the minimum curative dose) of anticholinergic agents is high, it seems appropriate to give larger doses when the recommended one does not produce symptomatic relief. As demonstrated in animal studies, >500 times the inhaled bronchodilating dose can be administered before side-effects are observed (54), and the erroneous administration of a massive overdose (32 mg atropine methonitrate) was associated with only slightly untoward side-effects in one patient (55).

In children, there are no dose-response studies with OB nebulized solution. The recommended dosage, in adults with chronic obstructive pulmonary disease, is between 1500 and 2000 μg (56). This is probably true also for children since the suggested dosage for nebulizer therapy may be up to 10 times that delivered by MDI containing the same drug (57). Only 20% of the dose present in the nebulizer reaches the patient and only 10–20% of this reaches the lung. So if, for example, a 500- μg dose is nebulized, only approximately 20 μg may reach the airways (58).

Anticholinergic agents may be almost as effective as β_2 agonists in some children with asthma; however, there is no evidence that anticholinergic muscarinic receptor antagonists are actually better in terms of peak responses. Furthermore, the effectiveness of muscarinic antagonists is quite variable among patients with asthma. It has been suggested that before starting treatment with this class of drugs, asthmatic patients should be tested to find out whether they are responders or nonresponders (11). A routine assessment must be performed in each patient before giving these agents since it is not possible to detect any differences clinically, in baseline reactivity, or in the symptoms or medication use of the subjects, which can help to identify the patients who respond to the cholinergic antagonists.

Another question with anticholinergic agents is whether these agents act primarily on the large airways or whether they have an effect also on small airways. Autoradiographic mapping has demonstrated high densities of muscarinic receptors in large airways and a diminishing density of receptors in smaller airways (59). This is consistent with the observation that vagal stimulation has a marked effect on medium-sized bronchi but little effect on bronchioles (60), and that cholinergic antagonists have a preferential effect on large airways. In contrast, beta agonists affect both central and peripheral airways equally (61). Since peripheral airways obstruction is particularly important in the

production of dyspneic symptoms, cholinergic antagonists could be less effective than adrenergic agents in symptom relief. However, other studies performed in children (18, 62) or in adults (63) demonstrated that IB caused bronchodilation of both large and small airways. Therefore, future studies on anticholinergic agents should carefully evaluate the ability of these compounds not only to improve lung functions, but also to relieve symptoms.

Although an addictive effect of IB and β_2 agonists has been shown in many trials (12, 16–21), there is no clear evidence of any true synergism between the two classes of bronchodilators. In chronic asthma, anticholinergic agents are more effective in older patients (over the age of 40–45) than in younger, more acute asthmatics. The use of this class of bronchodilators has not been associated with a rebound increase in bronchial hyperresponsiveness in asthmatic children nor with a reduction in efficacy over a period of time (27). In adult patients, it has been shown that, after regular treatment, four times daily IB showed persistence of bronchodilator effect for at least 1 year (64).

The particular efficacy of these agents in wheezy infants and in adult patients with chronic obstructive pulmonary disease may suggest a link between these two diseases (49), and prospective studies will reveal whether responsiveness to anticholinergic agents in wheezing diseases of infancy can be considered a marker for the risk of developing chronic bronchitis in adult life.

The available anticholinergic agents IB and OB are nonselective agents: they block both facilitative (M1 and M3 receptor-mediated) and inhibitory (M2 receptor-mediated) effects. OB is claimed to have a longer duration of action than IB, enabling twice, rather than 3–4 times, daily dosing (65). It has been observed, however, that "this apparent difference almost certainly reflects the higher relative dose of oxitropium delivered by the standard inhaler, rather than an intrinsically longer clinical action" (65). In the future, increasingly better insight into the structure of muscarinic acetylcholine receptors, including definition of the amino-acid sequences of the receptor subtypes, as well as the development of modeling of the ligand binding sites, will facilitate the production of new and more selective anticholinergic drugs. A muscarinic antagonist which selectively blocks postjunctional receptors will presumably be more effective since the feedback effect of endogenous acetylcholine will still operate.

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