Anticholinergic bronchodilators

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SYNOPSIS

Inhaled atropine causes bronchodilatation, but systemic absorption via the lung results in unwanted adverse effects. Ipratropium bromide and tiotropium bromide are structural analogues of atropine which have minimal systemic absorption following inhalation because of their quaternary ammonium structure. These anticholinergic drugs are useful bronchodilators in chronic obstructive pulmonary disease. They are rarely indicated in asthma. Bronchodilators provide symptomatic relief and improve health-related quality of life in patients with chronic obstructive pulmonary disease, but they do not influence the decline in lung function. The only measure currently known to halt this decline is stopping cigarette smoking.

Index words: chronic obstructive pulmonary disease, ipratropium bromide, tiotropium bromide.

(Aust Prescr 2003;26:33–5)

Introduction

The pharmacological properties of anticholinergic drugs have been recognised for over 100 years. Stramonium, a member of the Datura genus of plants, is a commonly mentioned source of anticholinergic bronchodilator therapy in 19th century medical literature. Burning the roots, stems and seeds of these plants created an aerosol of potent alkaloids, particularly atropine, which is the prototype of the currently used anticholinergic drugs. In the 1950s asthma cigarettes, made from stramonium, were widely used. With the subsequent availability of preparations of pure atropine sulfate for nebulisation, there was no further use of stramonium.

The popularity of these treatments declined with the advent of inhaled beta adrenoceptor agonists and because of the systemic anticholinergic adverse effects of nebulised atropine. More recently, structural analogues of atropine, such as ipratropium and tiotropium (which are not readily absorbed via the lung), have been developed as inhaled bronchodilators.

Vagal innervation of the lung

Cholinergic nerve fibres arise in the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve in the brainstem. They travel down the vagus nerve to parasympathetic ganglia within the walls of the airways. From these ganglia, short postganglionic fibres innervate airway smooth muscle and the submucosal glands in the lung. Activation of motor vagal nerve fibres releases acetylcholine at the neuro-effector junctions, where it binds to postsynaptic receptors, resulting in bronchoconstriction. Stimulation of the vagal nerve fibres innervating submucosal glands leads to an increase in mucus secretion.

Animal studies show that cholinergic innervation is greatest in larger airways and diminishes peripherally. Studies in humans have shown that cholinergic bronchoconstriction occurs mainly in larger airways whereas bronchodilatation induced by beta adrenergic drugs occurs in both large and small airways. The resting bronchomotor tone in normal airways has a cholinergic component, because giving an anticholinergic drug such as atropine causes bronchodilatation while the inhalation of edrophonium, an acetylcholinesterase inhibitor, results in bronchoconstriction.

Muscarinic receptors

The effects of vagal stimulation in the lung are mediated via muscarinic receptors. These receptors mediate the mucus secretory response to vagal nerve activation. Cholinergic agonists will stimulate mucus secretion from both submucosal glands and from goblet cells within the epithelium. These goblet cells are a major source of mucus in peripheral airways.

There are several different subtypes of muscarinic receptor. The muscarinic receptors on airway smooth muscle belong to the M_3 subtype and the presynaptic muscarinic receptors on vagal motor nerve fibres belong to the M_2 subtype. These M_2 receptors are called autoreceptors because their activation by acetylcholine inhibits further release of acetylcholine from the nerve terminals.

Anticholinergic bronchodilators

Atropine

Giving atropine, either systemically or as a nebulised solution, results in bronchodilatation. Inhaled doses of 2.5 mg atropine are associated with adverse effects such as dryness of the mouth, tachycardia, palpitations and blurred vision. With higher inhaled doses, systemic absorption can result in urinary retention (particularly in the elderly), headache and changes in mental status. Atropine is therefore no longer given as a nebulised solution.

Ipratropium bromide

Ipratropium bromide is a structural analogue of atropine, with a quaternary nitrogen structure. This structure reduces the ability of the molecule to cross cell membranes. There is, therefore, less systemic absorption with nebulised ipratropium than with nebulised atropine. Ipratropium blocks methacholine-induced bronchoconstriction, and induces bronchodilatation

in patients with asthma and patients with chronic obstructive pulmonary disease (COPD). There are no measurable effects on sputum volume, sputum viscosity or mucociliary clearance with clinically recommended doses of ipratropium.

The maximal bronchodilatation with ipratropium, inhaled from a metered-dose inhaler, occurs with a dose of 40–80 microgram. Although some bronchodilatation is evident soon after inhalation the maximal response occurs 1.5–2.0 hours afterwards. The duration of significant bronchodilatation after a standard dose of ipratropium is 4–6 hours.

Ipratropium cannot be detected in the blood after an inhalation. In experimental studies, where it has been given parenterally, its half-life has been estimated to be three hours. Long-term studies have shown no evidence of diminished responsiveness (tachyphylaxis) with regular therapy.

The main adverse effects of ipratropium relate to its anticholinergic activity. Up to 15% of patients will report transient dryness of the mouth and 'scratchiness' in the throat. In some studies up to 30% of patients have reported a bitter taste. These adverse effects rarely lead to patients discontinuing the drug if they perceive that it is helping them. Cardiovascular effects (tachycardia and increased cardiac output), which are typical of beta agonists (if taken in sufficient doses to result in systemic absorption) are not seen with the usual doses of ipratropium.

The main clinical indication for ipratropium bromide is the symptomatic relief of breathlessness in patients with COPD. It is rarely required for the treatment of patients with asthma because proper treatment of asthmatic patients with inhaled corticosteroids and long-acting beta agonists provides good control for the majority of patients. The extent of bronchodilatation with ipratropium in patients with COPD is similar to that achieved with inhaled beta agonists. The choice between ipratropium and beta agonists for a patient with COPD is determined by the patient's tolerance of the drug, rather than its efficacy. If troublesome adverse effects are encountered with either ipratropium or with beta agonists, the patient may well tolerate the other drug because the adverse effect profile for each drug is quite different.

Tiotropium bromide

Tiotropium bromide is a structural analogue of ipratropium. *In vitro* studies have shown that tiotropium has a half-life on the M_3 receptor of approximately 36 hours, whereas the receptor binding half-life of ipratropium is three hours. The duration of this binding to M_3 receptors may explain why a single inhaled dose of tiotropium results in bronchodilatation which lasts for approximately 24 hours. Large-scale clinical trials have shown that tiotropium inhaled once daily increases the forced expiratory volume (FEV_1) and quality of life in patients with COPD.

In comparative studies patients took tiotropium once daily, or ipratropium four times daily, for one year. Both drugs improved quality of life, but tiotropium resulted in a higher FEV_1 at the end of the dose interval.[1] Tiotropium also lengthened the time to first exacerbation and the time to first hospital admission due to an exacerbation of COPD. The number of patients who need to be treated with tiotropium for one year to prevent one exacerbation is nine, and 23 need to be treated to prevent one admission due to COPD.

Inhaled tiotropium is an effective once-daily anticholinergic bronchodilator in patients with COPD. There are no long-term studies of tiotropium in asthma so it is not indicated for patients with asthma.

Combination therapy

Anticholinergic drugs and beta adrenoceptor agonists produce bronchodilatation via separate mechanisms so there are theoretical reasons why they may be used in combination. Several studies have shown that the combination of ipratropium with a beta adrenoceptor agonist (either fenoterol or salbutamol) produces greater bronchodilatation than either drug alone.[2] None of these studies has investigated whether a higher dose of the single drug (either ipratropium or beta agonist) would have achieved the same result as the combination. However, a higher dose of either drug would carry with it the greater risk of unwanted adverse effects. Both beta agonists and ipratropium are therefore frequently used in combination to treat inpatients with acute exacerbations of COPD. There is also a place for the combination of beta agonists and ipratropium in maintenance therapy for COPD, primarily to minimise the risk of adverse effects with higher doses of either ipratropium or the beta agonist.

Delivery devices

Anticholinergic drugs are available as metered-dose inhalers or as solutions for nebulisation. Provided that patients use metered-dose aerosols properly, they are just as effective as nebulisers. Clinical studies in asthma in which bronchodilator administration by metered-dose inhalers (plus large volume spacer devices) has been compared with administration via nebulisers, show that the resultant bronchodilatation is comparable. Similar small studies in patients with COPD have shown that good inhaler techniques with metered-dose aerosols should be as effective as nebulised solutions in regular long-term therapy.[3] Large volume spacers and metered-dose aerosols are therefore the preferred method of drug delivery because they are cheaper than nebulisers and just as effective. The costs involved with nebulisers include both the purchase of the machine and the cost of the unit dose vials. This more expensive method of drug delivery should be reserved for patients who are unable to use a metered-dose aerosol and a large volume spacer.

Long-term outcomes

Although bronchodilators offer symptomatic relief in patients with COPD, no bronchodilators have been found to affect the annual decline in FEV_1. Smoking cessation is the only measure which is known to reduce the decline of FEV_1. Hence, the most important step that can be taken with patients with COPD is to stop smoking.

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Conflict of interest: Professor Seale has served on the advisory groups of several pharmaceutical companies which produce respiratory drugs, including GlaxoSmithKline and Boehringer Ingelheim.

Self-test questions

The following statements are either true or false *(answers on page 47)*

3. Anticholinergic bronchodilators are more effective than beta agonists.
4. Anticholinergic bronchodilators do not prevent the decline of lung function in patients with chronic obstructive pulmonary disease.

Medicinal mishap

Topical drug with systemic risk

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Case

A 75-year-old woman with hypertension and diabetes was prescribed warfarin for atrial fibrillation. During three and a half years of treatment her INR was 2.3–2.5.

When her INR rose to 14.1 on 27 February I thought it was a laboratory error (she displayed no bleeding) but told her to stop the warfarin. On 2 March the INR was 12.0, but she had developed huge bruises on all limbs and carpal tunnel pain. By 6 March the INR was 6.2, but the woman had bigger thigh and cheek haematomas. On 10 March the ecchymoses were subsiding and warfarin was resumed when the INR fell to 1.7.

Comment

The cause of this patient's problems was probably an interaction with an antifungal drug. Her dentist had prescribed amphotericin lozenges and miconazole oral gel on 9 February. She asked me on 13 February if these products might affect her warfarin, but as they were topical preparations I ignorantly reassured her.

Her dentist was also unaware of the potential interaction when the patient asked him about her warfarin. He may have been alerted had she been a surgical case rather than someone having her dentures fixed. The hospital pharmacy computer was not linked to her community pharmacist so there was no warning of the interaction between warfarin and miconazole.

Warfarin interacts with several antifungals including itraconazole, fluconazole and ketoconazole. The interaction may be mediated through the cytochrome P450 system.[1] Miconazole can inhibit the metabolism of drugs by cytochrome P450 3A and 2C9 and this is probably how it increases the effect of warfarin.

Although miconazole oral gel has a low bioavailability some is absorbed into the systemic circulation. This may be sufficient to cause a significant interaction with warfarin. Several reported cases involved bleeding.[2,3] As the consequences of bleeding can be catastrophic, high INR may require more intense treatment than this patient received.[4]

The interaction can also occur with other formulations of miconazole but may not be mentioned in the product information. There have been reports with topical cream[5] and vaginal pessaries.[6]

Conclusion

Topical medications can have systemic effects including drug interactions. As miconazole oral gel is available without a prescription, the public as well as health professionals need to be warned about the potential interaction with warfarin.

The case also serves as a reminder not to dismiss patients' concerns too quickly. A check of the product information would have alerted me to the interaction between miconazole oral gel and warfarin.

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