Pharmacology of bronchodilators

Action of $\beta_2$ agonists These work by binding to $\beta_2$ receptors in airway smooth muscle. Once bound to the receptor, they set in progress a complicated chain of events, similar to that produced by the action of the natural neurotransmitters.

There is an increase in cyclic adenosine monophosphate (cyclic AMP) in the cells. Through the action of an enzyme – protein kinase A – cyclic AMP activates target enzymes in the cells and opens ion channels in the cell membrane. The end result is muscle relaxation and bronchodilation.

Side-effects $\beta_2$ agonist bronchodilators are designed to bind selectively to $\beta_2$ receptors in the lungs. However, no drug is completely selective and it can bind to other sympathetic receptors in other organs, particularly when high doses of a drug, such as those given orally, intravenously or via nebuliser, are used.

It is this unwanted binding to receptors at other sites that causes side-effects. Stimulation of sympathetic receptors in the heart can cause tachycardia or arrhythmia, and stimulation of receptors in skeletal muscle can result in tremor. Other possible side-effects include muscle cramp and headache.

Generally, $\beta_2$ agonists are well tolerated and cause few problems when used in standard doses. Tremor can be problematic when the drugs are first introduced, but this tends to resolve with continued use. Some patients may be more susceptible than others: for example, those with ischaemic heart disease may be particularly susceptible to cardiac arrhythmia, while tachycardia may precipitate angina.

$\beta_2$ agonists can lead to depletion of serum potassium ($K^+$), resulting in hypokalaemia. This is a potentially serious side-effect, although it appears to be dose-related and is rare when drugs are given in standard doses.

It is largely a theoretical problem in asthma, but in the treatment of COPD the doses tend to be higher, the patients are usually older and frequently have co-morbidities that render them more susceptible.

Older patients may have a poor tolerance of biochemical disturbances and may also take diuretics that deplete serum potassium levels. It is therefore wise to check these levels in such patients and to consider using potassium-sparing diuretics, such as spironolactone.

It is impossible to predict what a ‘safe’ dose for any particular case might be, and a few susceptible patients may experience side-effects at comparatively low doses. In such cases, switching to a different $\beta_2$ agonist is rarely effective.

Anticholinergic bronchodilators Increased bronchomotor tone is thought to be an important component of airflow obstruction in COPD. Anticholinergic bronchodilators are therefore most useful in patients with COPD. Two anticholinergic bronchodilators are currently available.

Ipratropium bromide is the short-acting form. It takes 30–45 minutes to reach maximum effect so is not suitable for rapid symptom relief. Its effects last six to eight hours and it is generally used regularly three to four times a day.

Tiotropium is a new anticholinergic agent and has a 24-hour duration of action. In clinical trials involving patients with COPD, it was shown to have a number of advantages.

Tiotropium produced sustained improvements in lung function and reduced frequency of exacerbations; there were also fewer hospital admissions and reduced inpatient bed days (Casaburi et al, 2002). It has been available in the UK since September 2002 and promises to be an extremely useful drug for treating COPD. Further evaluation of its long-term effectiveness is awaited.
In the UK, diseases that cause airflow obstruction are common. About 5.1 million people receive treatment for asthma and about 600,000 people are diagnosed as having chronic obstructive pulmonary disease (COPD), although this is likely to be an underestimate (British Thoracic Society, 2001).

Constriction of airway smooth muscle gives rise to symptoms such as chest tightness, wheezing and breathlessness, and is an important component of airflow obstruction in both asthma and COPD. Bronchodilators, by relaxing smooth muscle, relieve these symptoms. There are three main forms:

- **Beta₂ agonist bronchodilators**;
- **Anticholinergic bronchodilators**;
- **Theophyllines**.

**Beta₂ agonists** come in a range of formulations: inhaled, oral and intravenous. Anticholinergics can be given by the inhaled route only, while theophyllines can be given by oral or intravenous routes only.

**Autonomic nervous system** It is vital to understand the basic physiology of the autonomic nervous system to appreciate the actions of beta₂ agonists and anticholinergics, and their potential to cause side-effects.

The autonomic nervous system consists of the sympathetic and parasympathetic nervous systems. The sympathetic nervous system prepares the body for ‘flight, fright or fight’. The parasympathetic nervous system provides a counterbalance by maintaining the equilibrium to ensure the body is not in a permanent state of readiness for ‘flight, fright or fight’.

The neurotransmitters for the sympathetic nervous system are noradrenaline and adrenaline. There are no sympathetic nerve fibres in the lungs and stimulation of the sympathetic receptors relies on circulating adrenaline and noradrenaline.

There is a range of sympathetic receptors throughout the body — for example, beta₁ and alpha receptors are found in the cardiovascular system. The receptors in the airway smooth muscle are beta₂ receptors.

The parasympathetic nerve supply to the lungs comes via the 10th cranial nerve — the vagus nerve. The neurotransmitter is acetylcholine and the lung receptors are known as muscarinic receptors. In a healthy person, stimulation of these receptors by acetylcholine produces a normal state of airway smooth muscle — that is, resting bronchomotor tone (Fig 1).

**Agonists and antagonists** Drugs described as agonists work by binding to a receptor and stimulating it to produce the desired therapeutic effect. They are sometimes referred to as stimulants and they work by mimicking the natural neurotransmitter.

As a result, beta₂ agonists are sometimes called beta₂ stimulants and are described as sympathomimetic or adrenergic agents. In other words, they mimic adrenaline and normal sympathetic nervous system response.

An antagonist drug also binds to a receptor, but does not stimulate it to produce a response. In effect, it blocks the receptor and prevents it from binding to its normal neurotransmitter. These drugs are sometimes described as blockers: for example, beta-blockers prevent adrenaline and noradrenaline from binding to beta receptors.

**Beta₂ agonist bronchodilators** These come in both short-acting and long-acting inhaled forms. The most familiar short-acting beta₂ agonists are:

- **Salbutamol**;
- **Terbutaline**.

They start to work within a few minutes of being inhaled and last for four to six hours. They are used for rapid symptom relief and are given in high doses in cases of acute, severe asthma.

The two long-acting beta₂ agonists available are salmeterol and formoterol. The action of these drugs has a duration of 12 hours, making them suitable for twice-daily use. Salmeterol has a slower onset of action than formoterol, making it unsuitable for rapid symptom relief.

In the treatment of asthma these drugs are used in addition to moderate to high doses of inhaled corticosteroids and short-acting beta₂ agonists, when these drugs have failed to give complete symptom control (British Thoracic Society/Scottish Intercollegiate Guideline Network, 2003).

In the treatment of COPD, long-acting beta₂ agonists have been shown to give prolonged symptom control and to improve health status (National Institutes of Health/National Heart, Lung, and Blood Institute, 2003). They may also reduce the frequency of exacerbations of moderate to severe COPD, particularly when given in combination with high doses of inhaled corticosteroids (Calverley et al, 2003; Szafranski et al, 2003).

Oral formulations of beta₂ agonist bronchodilators include sustained-release salbutamol, salbutamol syrup, and bambuterol (a precursor of terbutaline). These drugs may be used with patients who have difficulties with inhalers but they are not ideal — the high doses required tend to have side-effects and they have a slow onset of action.

Salbutamol can be given intravenously, although there is little evidence that this method is more effective than nebulised therapy (BTS/SIGN, 2003). Terbutaline can also be given as a continuous subcutaneous infusion in a small number of patients with very severe asthma.
in some patients, they are now rarely used in the UK owing to difficulties with their use.

**Action of theophyllines** One theory on the action of theophyllines is that they increase cyclic AMP levels. Increased levels of cyclic AMP leads to bronchodilation. There is also interest in possible anti-inflammatory actions. Theophyllines non-selectively inhibit a group of enzymes called phosphodiesterases (PDEs), which appear to be involved in inflammatory processes in both asthma and COPD.

Work is in progress to develop selective PDE-inhibitors to treat COPD. In asthma, they appear to have some beneficial, anti-inflammatory effects at low doses. However, little is understood about this possible action of theophyllines and they are not recommended for use in this way (BTS/SIGN, 2003).

**Monitoring** Theophyllines are given as sustained-release tablets and may be given by controlled intravenous infusion in cases of life-threatening asthma. A serum level of 10–20mg per litre is necessary to produce bronchodilation (the therapeutic window) but this gives little margin for error.

Worthwhile bronchodilation may require a level as high as 17mg/l, but side-effects may occur at levels as low as 24mg/l. Serum levels should therefore be within the therapeutic range, though side-effects may still occur within these parameters. Patients whose condition is maintained on theophyllines may need their serum levels checked more often if events or activities occur that may effect the stability of theophylline levels (Table 1).

**Side-effects** The main problems with theophylline use are toxicity and potential interactions. The most common side-effects are gastrointestinal, such as nausea and vomiting. Cardiovascular and neurological side-effects are more serious. Theophylline can produce cardiac arrhythmias and, when given in overdose, has been associated with sudden death. Neurological problems include sleep disturbance and seizure.

Theophyllines interact with many commonly used drugs. Appendix 1 of the British National Formulary gives a comprehensive list of interactions. There are also many commonly encountered conditions and factors that affect theophylline levels (Table 1).

The absorption rates of different formulations vary, so it is important that they are prescribed by trade name and patients are not switched from one brand to another, as this will destabilise serum levels.

**Inhaled therapy** Bronchodilators are best given by

**Action of anticholinergic bronchodilators** These work by binding to muscarinic receptors and blocking the action of acetylcholine. They reduce bronchomotor tone, which effectively leads to bronchodilation. Systemic absorption of the drugs is minimal, making them well tolerated with few side-effects.

**Side-effects** The most common is dryness in the mouth. There have also been reports of acute closed-angle glaucoma when anticholinergic and beta2 agonists are given together in a nebuliser (Shah et al, 1992). It is therefore good practice to use a mouthpiece, rather than a mask, when nebulising these drugs.

This will prevent the drug ‘mist’ coming into contact with the surface of the eye and should prevent the problem from occurring.

It may also be necessary to exercise caution when treating patients with prostatism. Anticholinergic agents could potentially precipitate acute urinary retention, although this appears to be largely a theoretical problem.

**Combined beta2 agonists and anticholinergics** These two classes of drug work on different nervous pathways. They appear to work well in combination and may produce better bronchodilation than either agent alone in COPD (NIH/NHLBI, 2003).

The drawback of combination inhalers of beta2 agonists and anticholinergics is the loss of flexibility in dosing of component drugs in the inhaler.

**Theophyllines** These have been available since the beginning of the 20th century, so it is perhaps surprising that their mode of action is poorly understood. Although they are cheap and can provide useful bronchodilation

<table>
<thead>
<tr>
<th>Situations that raise theophylline levels</th>
<th>Situations that lower theophylline levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stopping smoking</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Increasing age</td>
<td>Alcohol consumption</td>
</tr>
<tr>
<td>Liver congestion</td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td></td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Viral infections/influenza vaccine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs that raise theophylline levels</th>
<th>Drugs that lower theophylline levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinolone antibiotics</td>
<td>Furosemide (formerly frusemide)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Cimetidine</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 1. THEOPHYLLINE INTERACTIONS**
the inhaled route for the following reasons:

- The drug is delivered directly to the lungs where it is needed;
- Low doses can produce the desired effect;
- The onset of action is quicker;
- There is a lower incidence of side-effects.

However, tablets and syrups are easy to take and can be done so discreetly, and are more acceptable to some patients. Inhalers require a degree of manual dexterity and some require good coordination. Since low doses of drug are used, good inhaler technique is essential. The drug will not work if most of it is deposited in the mouth.

In order to reach peripheral airways, particles of 2–5 microns need to be produced. There is a bewildering choice of devices to produce particles of this size, but they can be usefully divided into four main groups:

- Pressurised metered-dose inhalers (pMDIs);
- Breath-activated pMDIs;
- Dry-powder inhalers (DPIs);
- Nebulisers.

The most widely prescribed inhalers are pMDIs, but they are also the most difficult to use effectively. Since the drug leaves the actuator at about 70mph, good ‘hand/breath’ coordination is vital to prevent it being deposited in the mouth or at the back of the throat and swallowed.

Holding chambers (spacers) overcome problems with coordination but can be bulky and not very portable. This usually makes them impractical for use outside the home. But there is evidence that high doses of bronchodilators, given through a spacer in an emergency, are as effective as those administered through a nebuliser (Fig 2).

Breath-activated pMDIs and DPIs overcome coordination problems. Breath-activated pMDIs only ‘fire’ when the patient breathes in, while DPIs use the patient’s inspiratory flow to lift the drug powder out of the inhaler and carry it into the lungs.

Some DPIs require the patient to generate higher inspiratory flow rates than others. If the patient cannot generate sufficient flow, the drug powder will not be broken down into small enough particles. Similarly, if the patient generates too high a flow rate, the drug will impact at the back of the throat or in the large airways.

Nebulisers do not require the patient to coordinate and deliver high doses of drugs. However, the drugs are extremely expensive, and the systems currently in use tend to be bulky and reliant on a power source. This makes nebulised therapy restrictive.

Nebuliser equipment is not available on prescription and requires careful maintenance. Guidelines suggest patients should be thoroughly assessed by a specialist before long-term use is recommended (BTS, 1997).

**Conclusion** Bronchodilators form the mainstay of therapy for symptomatic relief in obstructive airways disease. They are effective and well tolerated. They are best given by inhaler and correct technique is vital if the patient is to get the best possible benefit. Technique needs to be taught and checked regularly.

---

**FIG 2. EMERGENCY TREATMENT USING A SPACER DEVICE**

1. Put two parts of the spacer together.
2. Remove the mouthpiece cap from the metered dose inhaler.
3. Shake inhaler and insert into flat end of spacer.
4. Place spacer mouthpiece in patient’s mouth and press inhaler canister once to release a dose of the short-acting bronchodilator medication. (If unable to use the mouthpiece, attach facemask to the mouthpiece end and place over nose and mouth ensuring a good seal).
5. Only one dose of medication should be actuated at a time.
6. Ask the patient to breathe in and out through the spacer device for four or five breaths.
7. Remove the mouthpiece from the patient’s mouth.
8. For effective relief of symptoms in acute asthma, repeat steps 4–7. Up to 20 puffs (actuations) of a short-acting bronchodilator may be required for adult patients (up to 10 puffs for children).
9. Shake the inhaler gently between actuations. This can be done with the canister still inserted in the spacer device.

If there is no immediate improvement or the patient’s condition continues to deteriorate, seek urgent medical help. While waiting for emergency assistance, repeat the above steps.