WHICH DRUGS ARE CONTRAINDICATED FOR ASTHMA PATIENTS?

One person in every five households in the UK is receiving treatment for asthma, according to latest figures. As well as treatment for asthma, many of these individuals also self-medicate for minor illnesses or require prescribed medication for other conditions. It is important that the drugs they take do not adversely affect their asthma control. In this article we review which drugs might cause problems in patients also taking treatment for asthma.

There are two groups of drug in common use that have the potential to cause problems for patients with asthma: beta-blockers and non-steroidal anti-inflammatory drugs (NSAIDs).

BETA-BLOCKERS

The usefulness of beta-blocking drugs in cardiovascular disease is well established. They are indicated for the management of patients with angina pectoris, myocardial infarction, congestive heart failure, hypertension, arrhythmias and thyrotoxicosis. Topical beta-blockade is also indicated for the treatment of glaucoma, a common and preventable cause of blindness.

Systemic beta-blockade

James Black, the discoverer of the first beta-blocking drug, was awarded a Nobel Prize for his work. His commendation described these agents as “the greatest breakthrough when it comes to pharmaceuticals against heart illness since the discovery of digitalis 200 years ago.”

Extensive trials have confirmed their worth. Beta-blockers have a significant impact on the prognosis of patients with coronary artery disease and heart failure and they have a fundamental role in the management of these conditions. Beta-blockade can, however, cause bronchoconstriction, and patients with obstructive airways diseases are frequently denied treatment with these life-saving drugs for fear of provoking acute, and possibly life-threatening, bronchospasm.1

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The basis for withholding beta-blockers from these patients is open to question. There are case reports of high doses of non-cardioselective beta-blockers precipitating acute bronchospasm and it is these reports that have guided recommendations to prescribe beta-blockers with caution, or to withhold them from patients with obstructive airways disease.

A meta-analysis of randomised, blinded, placebo-controlled studies examining the effect of beta-blockers on airway function, respiratory symptoms and beta2-agonist use in subjects with mild to moderate reversible airways disease, provides us with an evidence base for our prescribing decisions and our assessment of risk to our asthma patients from these agents.

It is important to bear in mind that beta-blockers vary in their selectivity for beta-receptors in the cardiovascular system. Non-cardioselective beta-blockers may have greater propensity to cause bronchospasm, because they tend to bind to beta2-receptors in the lungs, as well as beta1-receptors in the cardiovascular system. The pooled results of 16 trials of non-cardioselective beta-blockers demonstrated that, in comparison to placebo, regular use of these drugs causes a 13.5% decrease in the forced expiratory volume in one second (FEV1). Cardioselective beta-blockers do not appear to carry the same risk.

An initial dose of a cardioselective beta-blocker can produce a decrease in the FEV1. However, the reduction in the FEV1 is small and is not associated with any increase in respiratory symptoms. A patient would be unlikely to perceive a problem. In the longer term, when treatment is continued for more than a few days or weeks, there is no difference in the FEV1 or the use of beta2-agonists between the treatment and the placebo group. The incidence of respiratory symptoms is also similar.

A further concern about the use of beta-blockers in asthma patients is that they reduce response to beta2-agonist bronchodilators by blocking the receptor sites. Any decrease in this response may significantly increase the risk of treatment failure in an exacerbation and could potentially be dangerous. A meta-analysis found this to be true of non-cardioselective beta-blockers, but the opposite to be the case with cardioselective drugs. Non-cardioselective drugs produced a 22.5% decrease in the FEV1 response to beta2-agonists. Cardioselective beta-blockade was associated with an increased response to beta2-agonists in comparison to placebo, possibly because of upregulation of beta2-receptors in the lungs.

The incidence of cardiovascular disease in older subjects, and particularly in those with a degree of chronic airway obstruction, is high. The limitation of this meta-analysis is that study subjects tended to be young with mild to moderate airway obstruction. Extrapolation of the results to older patients with more severe disease may not be appropriate. In addition, some studies excluded patients who had had a recent exacerbation. The short duration of some of the studies means that the effects of long-term administration of beta-blockers on the frequency and severity of exacerbations is not known.

A later meta-analysis looked at the effects of cardioselective beta-blockers on patients with COPD. Reassuringly, it found no reduction in FEV1 or increase in respiratory symptoms with either initial or long-term use of these drugs.

In summary, the benefits of using cardioselective beta-blockers in patients with asthma (or COPD) and concomitant cardiovascular disease outweigh the risks. The guidelines that suggest caution were produced before the meta-analyses and the evidence suggests that these drugs should not be withheld. Cardioselective agents should be used in preference to non-cardioselective preparations (see Box). The starting dose should be low and the dose titrated slowly upward, monitoring the patient for lung function decline and respiratory symptoms.

### Cardioselective and non-cardioselective beta-blockers

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### Topical beta-blockers

Glucoma affects more than 5% of people over 75 years of age and topical non-selective beta-blockers are frequently used to reduce intraocular pressure. Drug is absorbed into the systemic circulation through the nasopharyngeal mucosa and this may be in sufficient quantity to cause systemic effects. Bronchospasm may be a clinically significant problem as many elderly people have undiagnosed reversible or irreversible obstructive airways disease.
A prospective 12-month study comparing the effects of four different topical agents (latanoprost, timolol, brimonidine and betaxolol) in 134 patients with open-angle and normal tension glaucoma suggests that some beta-blocking eye drops have the potential to cause respiratory side-effects. People taking part in the study had intraocular pressures, spirometry and ECGs performed at baseline and after three months’ treatment. A quarter of the patients given timolol reported systemic side-effects, notably shortness of breath. Peak expiratory flow (PEF) rates fell by 7% of the original value and five patients had a fall of 15% in both PEF and FEV1. The drug least likely to have a detrimental effect on lung function was latanoprost.

The researchers suggest that spirometry should be performed on all glaucoma patients before commencing topical beta-blockers. They considered that latanoprost is an effective therapy for glaucoma and seemed to have the least potential for systemic side-effects.

**ASPIRIN AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)**

Aspirin and NSAIDs are extremely useful drugs, but they have caused severe bronchospasm and death in asthmatic patients sensitive to them. Aspirin sensitivity is thought to affect between 5 and 20% of asthma patients. A systematic review of studies using oral provocation tests suggests that the prevalence is 21% of adults and 5% of children; a higher prevalence in adults than had been previously recognised. It is thought that aspirin-induced asthma involves inhibition of the enzyme cyclo-oxygenase (COX)-1. NSAIDs also inhibit COX-1 and cross-sensitivity to other NSAIDs was present in most of the aspirin sensitive subjects in the systematic review. Cross-sensitivity to paracetamol occurred in only 7%. Fewer than 2% of asthmatic patients were sensitive to both aspirin and paracetamol and reactions to paracetamol, if they occurred, were generally less severe. It is possible that paracetamol inhibits COX-3 and this may explain the lack of cross-reactivity with aspirin and the other NSAIDs. There is also a low risk of cross-sensitivity with the new generation of COX-2 inhibitors.

NSAIDs and aspirin are commonly used antipyretic, anti-inflammatory medications. Many are also available over the counter. They are present in many cold and flu remedies, obtainable in places such as supermarkets and corner shops, without the advice of a pharmacist. Although there are warnings on package inserts and labels, there is a danger that asthmatic patients will fail to read them.

It is wise to alert all asthma patients to the possibility of aspirin-induced asthma. Paracetamol is a safe alternative self-medication for minor illness and injury, but patients should also be advised to report any respiratory reaction to therapy, to stop treatment immediately and seek help.

Any asthma patient who has been positively identified as having aspirin-induced asthma or has experienced an asthmatic reaction to aspirin or NSAIDs must be advised to avoid all products containing these drugs. Aspirin sensitivity can develop in adult life in a patient who has previously used this drug without a problem. It is therefore wise to advise any young patient under the age of 40 years, or a patient who has not taken these drugs recently, of the risks. Suggest that they use an alternative drug, ie paracetamol. If aspirin or NSAIDs are positively indicated and you are in any doubt, a first dose can be taken under supervision. However, you will need to bear in mind that a reaction may not occur for up to three hours.

**SUMMING UP**

Asthma is a common condition and many patients, particularly as they age, will require therapy for other conditions, as well as their asthma. The incidence of cardiovascular disease rises with age and there is overwhelming evidence for the benefits of beta-blocking drugs and aspirin. Evidence has now emerged that, contrary to previous belief, cardioselective agents are safe for asthmatic patients. There is a realisation that sensitivity to aspirin in asthma patients is more common than previously thought and an increasing variety of drugs are available without prescription.

It is therefore important that health professionals with responsibility for the care of patients with long-term conditions such as asthma are aware of the risks and benefits of these drugs and are able to give appropriate advice.