



# Combination inhalers for asthma

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## Summary

**Patients whose asthma is not well controlled by inhaled corticosteroids may benefit from the addition of a long-acting beta<sub>2</sub> agonist. The effects of inhaling a corticosteroid and a long-acting beta<sub>2</sub> agonist can reduce symptoms, improve lung function and prevent exacerbations. Once the patient's asthma is controlled it may be appropriate for them to use one of the combination inhalers which contain both types of drug. These combination inhalers may not be more efficacious than inhaling the drugs separately, but they are more convenient.**

Key words: budesonide, eformoterol, fluticasone, salmeterol.

(*Aust Prescr* 2005;28:26–8)

## Introduction

Combination inhalers that include both a corticosteroid and a long-acting beta<sub>2</sub> agonist are now available for the treatment of asthma. There are currently two combinations in Australia and they have a variety of doses and inhaler devices.

## The rationale for the use of combination therapy<sup>1</sup>

Asthma is a chronic inflammatory condition of the airways in which the predominant inflammatory cells are eosinophils.

### In this issue...

Drugs for asthma and hypertension always appear in the Top 10 drugs. Although the charts contain several new antihypertensives, Suzanne Hill and Tony Smith remind us that older drugs still have a role. Many patients with hypertension need more than one drug and there is also an increased use of combined therapy in asthma. Christopher Worsnop discusses whether combination inhalers have any advantage over the separate administration of the drugs they contain.

Patients may need a combination of antibiotics if they are at risk of surgical infection. Overuse of antibiotics leads to resistance, so Wendy Munckhof advises on when prophylaxis is indicated.

Surgical patients may need a blood transfusion. As supplies are scarce, James Isbister reviews the factors which need be addressed before blood is ordered.

Inhaled preparations of corticosteroids have become the standard treatment for asthma as these cells are sensitive to their effects.<sup>1,2</sup>

The airway inflammation also produces increased reactivity in bronchial smooth muscle, leading to bronchoconstriction. Stimulation of beta<sub>2</sub> adrenergic receptors on smooth muscle cells causes relaxation of bronchial smooth muscle. Beta<sub>2</sub> agonists are therefore used for quick relief of bronchospasm. Patients with persistent asthmatic symptoms used to take regular doses of short-acting beta<sub>2</sub> agonists, but there was concern that such regular use may worsen asthma and increase asthma deaths. When long-acting beta<sub>2</sub> agonists were developed, there were similar concerns. However, it is now clear that they are of benefit, although they should not be used without an inhaled corticosteroid to treat asthma.<sup>1,2</sup>

## The interaction between corticosteroids and beta<sub>2</sub> agonists

In addition to bronchial smooth muscle, beta<sub>2</sub> adrenergic receptors are also present on other cells in the airways including mast cells and vascular endothelium. With chronic use of beta<sub>2</sub> agonists, these receptors become down-regulated. However, this can be balanced by the concurrent use of corticosteroids because corticosteroids can interact with the beta<sub>2</sub> receptor gene to increase the production of beta<sub>2</sub> receptors *in vitro*.<sup>1,2</sup> Inflammation can desensitise beta<sub>2</sub> receptors, and beta<sub>2</sub> stimulation can inhibit some aspects of inflammation, such as mast cell mediator release, and plasma exudation from post-capillary venules. Both of these effects can be prevented by corticosteroids. In turn, beta<sub>2</sub> agonists can increase the actions of corticosteroids by interacting with glucocorticoid receptors in the nucleus and enhancing their binding to DNA.<sup>1,2</sup>

## The appropriate dose of corticosteroids

It has been difficult to demonstrate the dose-response characteristics of inhaled corticosteroids in asthma because the improvement in asthma with steroids takes time and is variable across individuals. However, it is apparent that there is a relatively flat dose-response curve above 1000 microgram per day of beclomethasone or equivalent (1000 microgram per day of budesonide or 500 microgram per day of fluticasone). This means that most control of the airway inflammation is achieved with a low dose of inhaled corticosteroids. Systemic effects can occur at doses at or above 1000 microgram per day of beclomethasone or equivalent. The addition of long-acting beta<sub>2</sub>

agonists shifts the dose-response curve to the left, so the same benefit is achieved with lower daily doses of the steroid.

Once a patient's asthma is controlled, consideration should be given to reducing the dose of inhaled corticosteroid. Exactly when and how this should be done is not clear as there is insufficient evidence. However, the Global Initiative for Asthma (GINA) guidelines<sup>3</sup> suggest that the patient should be stable for at least three months, and the Australian National Asthma Council guidelines state that dose reduction should be considered after asthma has been stable for 6–12 weeks.<sup>4</sup> Leaving patients on high doses of inhaled corticosteroids can lead to systemic adverse effects, and is not appropriate. Adding a long-acting beta<sub>2</sub> agonist may enable a reduction in the dose of corticosteroid.

## Clinical data

There have now been many good quality studies showing that the control of moderate or severe asthma can be improved by adding a long-acting beta<sub>2</sub> agonist to therapy with inhaled corticosteroids. Adding a long-acting beta<sub>2</sub> agonist is superior to doubling the dose of inhaled corticosteroid, or increasing the steroid even further, in gaining control of asthma which is not well controlled. This has been demonstrated across a range of outcomes including asthma symptoms, nocturnal awakenings, use of short-acting beta<sub>2</sub> agonist medication, asthma free days, health-related quality of life, asthma exacerbations, spirometry and expiratory peak flows. When attempts are made to reduce the dose of inhaled corticosteroid in patients with stable asthma, the addition of a long-acting beta<sub>2</sub> agonist allows a greater reduction in the steroid dose than can be achieved with placebo.

Long-acting beta<sub>2</sub> agonists have also been compared with placebo, theophylline and leukotriene receptor antagonists, such as montelukast or zafirlukast, in patients with asthma that is not well controlled with inhaled corticosteroids. They are superior to placebo and theophylline, and have produced similar or better outcomes when compared with adding a leukotriene receptor antagonist to inhaled corticosteroids.

A meta-analysis (called 'MIASMA') of nine parallel group trials compared increasing the dose of inhaled corticosteroids with the addition of salmeterol to inhaled corticosteroids in patients with symptomatic asthma.<sup>5</sup> The daily doses of steroids in patients at the time of randomisation in these trials were 200–1000 microgram of beclomethasone, or 200–500 microgram of fluticasone. Adding salmeterol had benefits which included greater morning peak flows, increased FEV<sub>1</sub><sup>\*</sup>, a higher percentage of days and nights without asthma symptoms, and a higher percentage of days and nights without a need for rescue medication with short-acting beta<sub>2</sub> agonists. These benefits were present at three months and six months. There were also fewer

\* forced expiratory volume in one second

exacerbations in patients who added salmeterol. To prevent one exacerbation, 40 patients need to be treated with salmeterol compared with increasing the inhaled corticosteroid dose. The number needed to treat to prevent an asthma exacerbation with inhaled fluticasone varies from 2.1 to 2.9 with daily doses from 1000 microgram to 100 microgram.<sup>6</sup>

With such evidence supporting the combined use of both types of drugs in asthma, it was logical to combine them into one inhaler. Studies comparing single inhalers with inhaling the drugs from separate inhalers have found no disadvantage with the combination products.

The Gaining Optimal Asthma control (GOAL) study compared a combination of fluticasone/salmeterol with fluticasone alone in 3500 patients with asthma that was not well controlled. A step-up approach was used, with patients starting on a lower dose, and then increasing it after 12 weeks if their asthma was not totally controlled. The fluticasone/salmeterol combination led to a greater proportion of patients having totally or well controlled asthma, with fewer exacerbations, and better health-related quality of life than those receiving fluticasone alone. These benefits were seen in patients who had already been taking inhaled corticosteroids before entering the trial, as well as in those who had not taken steroids before.<sup>7</sup>

## Advantages of combination inhalers

It is more convenient for patients who require two asthma drugs to use one, rather than two, inhalers. Another advantage is that it is not possible to stop the steroid if both drugs are given in a single inhaler. This addresses the concern that patients using two inhalers would be tempted to use just the long-acting beta<sub>2</sub> agonist, as it produces a symptomatic improvement faster than steroids can. There is a cost advantage in using a combination inhaler instead of two separate inhalers and there is the possibility that indirect costs may also be reduced. The patient's asthma may be better controlled with the combination and, as a lower dose of inhaled corticosteroid may be needed, the adverse effects can be minimised.

## Potential limitations of combination inhalers

A possible limitation with any combination preparation is the lack of flexibility in dosing. This is not such an issue with combination inhalers as there are six different strengths of the fluticasone/salmeterol products and two of the budesonide/eformoterol products (Table 1). The eformoterol dose can be increased as the dose in these products is below the maximum that can be used, so patients can vary their dose during exacerbations.

Another limitation is that patients may use the inhaler to relieve bronchospasm and get much higher doses of inhaled steroid than intended, particularly if they have an inhaler that contains a high dose of steroid. To avoid this, judicious prescribing is required with some thought given to the dose of steroid that

Table 1

### Combinations of inhaled corticosteroids and long-acting beta<sub>2</sub> agonists available in Australia

Combination	Device	Dose delivered (microgram)
budesonide/eformoterol (dry powder)	Turbuhaler	200/6
		400/12
fluticasone/salmeterol (dry powder)	Accuhaler	100/50
		250/50
		500/50
(aerosol)	Metered dose inhaler	50/25
		125/25
		250/25

each patient needs. Certainly, prescribing the maximum dose for all is not appropriate. If a patient is on a high dose of inhaled corticosteroid, whether in a single drug inhaler or a combination inhaler, the need for the high dose should be reviewed regularly, and the dose reduced if the patient's asthma has been stable for several months at least. Patients also need to be well educated about how to deal with any deterioration in their asthma. In some circumstances, increasing the dose of the combination inhaler would be appropriate, but in others, alternative strategies may be required.

The inhalers are simple and easy to use so there is a temptation to prescribe them to anyone with respiratory problems, including patients with chronic obstructive pulmonary disease. This temptation should be resisted, as the combination inhalers are primarily indicated for asthma. The diagnosis of asthma should not be taken lightly as it usually commits patients to long-term medication. This means that patients must change their attitude to their health as they should monitor their asthma regularly with expiratory peak flow charts, and have plans to enable them to deal with exacerbations.

### When to use combination inhalers

The Australian National Asthma Council guidelines suggest adding a long-acting beta<sub>2</sub> agonist to inhaled steroids if the patient requires a short-acting beta<sub>2</sub> agonist more than once daily in moderate asthma. Combination therapy is recommended for all patients with severe asthma. The GINA guidelines suggest that both moderate and severe persistent asthma should be treated with inhaled corticosteroids and a long-acting beta<sub>2</sub> agonist. When starting treatment, the Australian guidelines begin with a higher dose of inhaled steroids. The GINA guidelines suggest starting intensive treatment including combination therapy to get asthma under control quickly and then reducing the dose when the asthma is stable, or starting with lower doses in less severe asthma

and increasing treatment if needed. As there is no evidence comparing the different approaches, the options remain open.

### Prescribing restrictions on combination therapy

Combination inhalers are a restricted benefit if they are prescribed under the Pharmaceutical Benefits Scheme. They are restricted to patients who have previously had frequent episodes of asthma while receiving optimal doses of inhaled corticosteroids, or oral corticosteroids, and who have been stabilised on the relevant inhaled corticosteroid used concomitantly with the relevant long-acting beta<sub>2</sub> agonist.

### References

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*Conflict of interest: none declared*

### Self-test questions

*The following statements are either true or false (answers on page 51)*

1. The efficacy of asthma treatment with a long-acting beta<sub>2</sub> agonist and a corticosteroid is significantly enhanced if they are combined in a single inhaler.
2. Patients inhaling a corticosteroid for their asthma may be able to reduce the dose if a long-acting beta<sub>2</sub> agonist is added to their therapy.