Starting steroids for asthma

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Summary

Inhaled corticosteroids are indicated for everyone with persistent asthma. For most patients low doses are sufficient to improve clinical outcomes. Increasing the dose may not cause a proportionate improvement in the patient's symptoms and lung function. After the patient's asthma has been well controlled and stable for six to eight weeks, the dose of inhaled corticosteroid should be gradually decreased. The aim is to find the lowest dose that maintains asthma control. Inhaled corticosteroids may slow the rate of growth in children, but they do not appear to have a significant effect on their final height.

Key words: beclomethasone, budesonide, ciclesonide, corticosteroids, fluticasone.

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Introduction

The indications for inhaled corticosteroids and the choice of dose are two of the most important questions in asthma management today. In the past asthma management guidelines have given conflicting advice, but new data have now enabled a more consistent approach. Underpinning the recommendations in guidelines is the acknowledgement that even seemingly mild asthma can be associated with serious morbidity and even death.

The case for commencing corticosteroids

One reason why there is uncertainty regarding optimal treatment is that the natural history of mild asthma in adults is not well documented. The Global INitiative for Asthma (GINA) guidelines define patients with mild asthma as those who experience symptoms at least once a week but less than once a day over a three-month period, including exacerbations which may affect sleep and activity.[1] Australian mortality studies from almost 20 years ago suggest that some people with apparently mild asthma can have fatal attacks, although there are no longitudinal prospective studies of mild asthma to confirm this.[2]

Several recent, shorter studies shed light on the consequences of untreated asthma and the relative merits of treatment.[3,4,5] These suggest that some untreated patients with mild asthma have a frequency of severe exacerbations approaching that for moderate to severe asthma. Their symptoms will improve with low-dose inhaled corticosteroids, but if left untreated some patients will have significantly poorer lung function over time.[6]

Inhaled corticosteroids vs placebo

The largest study of asthma treatment ever undertaken[7] involved 7241 patients who had not received regular inhaled corticosteroids. These patients had mild asthma (wheeze, cough, dyspnoea or chest tightness at least once a week but less frequently than daily) of less than two years' duration. The active treatment group received either budesonide 400 microgram daily (or 200 microgram daily if aged under 11 years) for three years. Approximately 5% of the patients taking placebo and 3% of the patients taking budesonide had at least one severe asthma exacerbation (hazard ratio of 0.56 (95% CI 0.45–0.71%)). There were also fewer courses of oral corticosteroids and better lung function in the budesonide group. However, in children under 11 years old, three-year growth was reduced by 1.34 cm compared to placebo, although the magnitude of this difference decreased over each of the three years.

In another comparative study in children[8], budesonide (400 microgram daily) was compared to nedocromil sodium or placebo over 4–6 years. Budesonide again resulted in better lung function than placebo and was superior to nedocromil and placebo in symptom control and prevention of exacerbations. There was an effect on height, but only at 12 months and not subsequently.

Inhaled corticosteroids vs short-acting bronchodilators

In an early study of patients with newly diagnosed asthma[3], an inhaled corticosteroid (budesonide 1200 microgram daily) was compared to a short-acting beta$_2$ agonist (terbutaline 500 microgram twice a day). After two years, patients given budesonide had better lung function, symptom control and airway responsiveness. Twelve months after patients taking terbutaline were changed over to budesonide, their lung function had not caught up to that of the patients who had taken budesonide continuously. In addition, improvement was maintained in only 33% of the patients who ceased budesonide after two years.[4] This shows that in some patients the improvements achieved by taking a low daily dose of

budesonide for two years may be temporary. However, improvement in airway responsiveness was maintained suggesting that inhaled corticosteroids may have a disease-modifying effect at least in some patients. This study has also been interpreted as indicating that failure to use inhaled corticosteroids in asthma may permit airway remodelling which is not fully reversible, although it must be remembered that the control group received regular beta agonist, not placebo.[3]

Inhaled corticosteroids vs inhaled corticosteroids plus long-acting bronchodilators in mild asthma

A large study compared the effects of adding formoterol to low doses of budesonide over one year. It included 698 people with mild asthma who had not previously taken corticosteroids. They were assigned to twice-daily treatment with 100 microgram budesonide, 100 microgram of budesonide plus 4.5 microgram of formoterol, or placebo.[5] Budesonide alone reduced the risk of severe exacerbations by 60% and the number of poorly-controlled asthma days by 48%. Adding formoterol increased lung function but had no effect on other end points. By contrast, in the 1272 patients who had previously received inhaled corticosteroid, adding formoterol was more effective than doubling the corticosteroid dose.

The case against inhaled corticosteroids

The evidence suggests that inhaled corticosteroids confer important benefits in mild persistent asthma. Although in children this may be at the price of some initial growth slowing, studies show that children taking inhaled corticosteroids over longer periods attain their predicted adult height. However, a recent multicentre study appears to challenge the role of regular inhaled corticosteroids.[9]

In this study, patients with mild persistent asthma received either budesonide 200 microgram twice a day, zafirlukast 20 mg twice a day or placebo. All patients had monthly telephone contact with the study nurse, a detailed written action plan, and were advised to use inhaled or oral corticosteroids if their asthma symptoms worsened. After one year, the group on placebo had neither significantly poorer morning peak flows nor a greater frequency of asthma exacerbations than those receiving regular corticosteroids. The authors estimated that the only treatment required was a 10-day course of inhaled budesonide on average every two years and oral corticosteroids on average every eight years. However, patients receiving intermittent inhaled corticosteroids had 26 more days of asthma symptoms over a year, and less improvement in their asthma control scores and airway hyperresponsiveness than patients taking regular budesonide.[9]

The findings of this study must be interpreted with great care because the selection criteria and an initial period of intense treatment may make the population unrepresentative of that seen in general practice.

What do asthma management guidelines currently say?

The Australian Asthma Management Handbook recommends inhaled corticosteroids for patients with mild asthma characterised by occasional symptoms, exacerbations more than 6–8 weeks apart and a normal forced expiratory volume in one second (FEV_1) when asymptomatic.[10] It also states that preventive treatment is indicated if patients require reliever medication 3–4 times a week or more.

The British Thoracic Society guidelines advise starting inhaled corticosteroids when a reliever is taken three or more times a week, exacerbations of asthma have occurred in the last two years, symptoms are occurring three or more times a week, or are causing night waking one night a week.[11] Although the British guidelines state that a threshold for introducing inhaled steroids has never been firmly established, in recent years several large studies and meta-analyses have been published. These enable firmer recommendations and an assessment of the strength of evidence supporting the guidelines.

Who should be treated?

All the large randomised controlled trials provide strong evidence that patients with mild persistent asthma achieve and maintain control of their asthma more effectively on inhaled corticosteroids than on no treatment. These trials support the current recommendations in guidelines, that patients who are symptomatic or needing a reliever three or more times a week should receive low-dose inhaled corticosteroids, at doses up to the equivalent of budesonide 400 microgram daily or fluticasone 250 microgram daily.

The assessment of severity is important. Some patients who present with symptoms suggestive of mild asthma may have more severe disease on objective measures. By contrast, many patients who present with poor control or acute severe symptoms actually have untreated mild–moderate asthma. In patients with moderate to severe asthma, combination therapy with long-acting bronchodilators achieves greater and more rapid asthma control than inhaled corticosteroids alone.

Which starting doses should be used?

All guidelines agree that inhaled corticosteroids are the first choice preventer for adults with asthma and that the starting dose should be appropriate to the severity of the disease. For mild persistent asthma, they advise starting with low doses of inhaled corticosteroids, up to 250 microgram daily of fluticasone or beclomethasone, or 400 microgram daily of budesonide. An equivalent dose of the halogenated inhaled corticosteroid ciclesonide is 160 microgram daily.

In moderate to severe asthma, the GINA guidelines and the British Thoracic Society guidelines, based on evidence from several large trials, advocate commencing treatment with an

inhaled corticosteroid (budesonide 400–1000 microgram or fluticasone 250–500 microgram daily) and a long-acting bronchodilator.

The question of whether to start with a low dose or a higher dose has been partly answered by a recent systematic review of 13 clinical trials of inhaled corticosteroids.[12] The trials compared different starting doses in adults who had not previously taken inhaled corticosteroids for asthma of varying severity. Meta-analysis showed that there was no significant difference between high or moderate doses of inhaled corticosteroids for day and night symptom scores, and reliever use. Comparison of studies using a step-down approach versus constant low–moderate doses of inhaled corticosteroid showed no difference in lung function, symptoms or reliever medication use. Meta-analysis of the change in peak expiratory flow showed no significant difference in morning values.

The same review compared low doses (beclomethasone less than 400 microgram daily) with moderate doses (beclomethasone 400–800 microgram daily). It showed that while moderate doses improved morning peak expiratory flow and night symptom scores, there was no difference in daytime symptom scores, symptom-free days or reliever use. This review did not analyse exacerbations as the studies were relatively short (average 4–12 weeks) and did not always report exacerbations as an end point.

Reduce the dose of any inhaled corticosteroid when the patient's asthma is stable

It is important to note that several studies show smokers with mild persistent asthma have a poor response to low-dose inhaled corticosteroids, but may respond to higher doses.[13]

Is increasing the dose of inhaled corticosteroids worthwhile?

Clinical trials and a meta-analysis show that the dose-response curve for inhaled corticosteroids is relatively flat. In a meta-analysis of eight studies in 2324 adults and adolescents, the fluticasone dose-response curve began to flatten out at 100–200 microgram a day[14] with 90% of the ultimate benefit of fluticasone 1000 microgram a day achieved, on average, at 100–250 microgram a day. Therefore, in the majority of patients there is little benefit in increasing the dose above 250 microgram daily for a range of outcomes including lung function, symptom scores and reliever use.[12,14,15,16]

Some caution should be exercised here as these studies were all of 6–12 weeks duration and were also primarily undertaken in people with sub-optimally controlled asthma who were already receiving inhaled corticosteroids. Some studies suggest this is a less steroid-responsive population than those who receive inhaled corticosteroids for the first time.[17] A meta-analysis of the dose-response curve for budesonide found similar results with 90% of the maximum response being achieved with 300–600 microgram daily.[18]

In all these studies it is clear that a minority of patients do respond to higher doses. Importantly, the relationship between dose and adverse effects shows a much stronger dose-response effect. High doses are associated with a steep rise in the risk of adverse effects, both local and systemic.[15]

All guidelines emphasise the importance of ensuring good device use and checking compliance, inhaler technique and reviewing trigger factors before considering further increases in treatment if patients have not achieved good asthma control. Reduce the dose of any inhaled corticosteroid when the patient's asthma is stable to the lowest clinically effective dose that maintains good control. If good asthma control is not achieved by low-dose inhaled corticosteroids, a long-acting bronchodilator should be added.

Comparative efficacy of different inhaled corticosteroids

When an appropriate dose is chosen (see Table 1), the available inhaled corticosteroids are of similar efficacy so the choice of steroid may depend on delivery device. There is inadequate evidence to draw firm conclusions about the relative safety of each of the inhaled corticosteroids and the comparative risks of systemic adverse effects in relation to their clinical effects.

Should inhaled corticosteroids always be used alone as first-line therapy for mild asthma?

A recent meta-analysis undertaken for the National Asthma Campaign in preparation for the revised Asthma Management Handbook showed that combination therapy with an inhaled corticosteroid and a long-acting beta agonist achieved statistically greater improvements in lung function tests than inhaled corticosteroids alone in patients aged 4–80 years who had previously not received corticosteroids. These improvements may not always be of clinical importance, but combination therapy also resulted in fewer exacerbations in patients who were symptomatic on inhaled corticosteroids alone.

Conclusion

Mild persistent asthma in adults and children has better outcomes if it is treated with low-dose inhaled corticosteroids. These doses have an extremely low risk of adverse effects

Table 1

Approximate dose equivalence of inhaled corticosteroids

Inhaled corticosteroid	Dose (microgram)
Beclomethasone CFC-free	100
Fluticasone	100
Budesonide	200
Ciclesonide	80

in adults. They may slow growth in children, but do not affect the attainment of final predicted height. The benefits of protection against symptoms, exacerbations and impaired lung function are strongly in favour of treatment, but this should always be considered in the context of each individual patient's needs. Low-dose inhaled corticosteroids alone achieve excellent outcomes in mild asthma, but adding a long-acting bronchodilator is indicated if optimal control is not achieved.

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Professor Jenkins has received honoraria for presentations at educational meetings and membership of advisory boards from GlaxoSmithKline, AstraZeneca and Altana, all manufacturers of respiratory drugs, including inhaled corticosteroids. The Woolcock Institute of Medical Research also receives research funding from these companies to perform clinical trials in asthma.

Self-test questions

The following statements are either true or false (answers on page 87)

1. The dose of inhaled corticosteroid should be gradually reduced after a patient's asthma has been stable for several weeks.
2. A large increase in the dose of an inhaled corticosteroid is unlikely to have a proportionate effect on lung function.