Inhaled steroids in asthma

Should the doses be reduced?

BACKGROUND Since their introduction in the 1970s, unit doses of inhaled corticosteroids (ICS) have increased exponentially (a twenty-fold rise from beclomethasone 50 µg through fluticasone 500 µg). Current prescription data suggests that in Australia more than 50% of all dispensed fluticasone/salmeterol dry powder units are the 500/50 µg combination.[1]
OBJECTIVE To discuss the efficiency of doses currently used in Australia.
DISCUSSION The use of both single drug ICS therapy alone or in conjunction with a long acting beta agonist (LABA) may be too high. The additional therapeutic effects of such doses are likely to be of minimal benefit (if any at all) and expose patients to unnecessary long term side effects.

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Asthma remains significantly under treated in Australia with up to 40% of patients who need regular preventive therapy not receiving it.[2] Inhaled corticosteroids are a key to asthma management in both adults and children and are first line therapy for anything more than trivial asthma.[3] Inhaled corticosteroids usage reduces airway inflammation; improves lung function and quality of life; and reduces exacerbations.

The 3 Plus Plan

As the 3 Plus Plan for asthma management gains momentum in Australia, hopefully more people with previously under treated asthma will be on regular inhaled steroids. Such medication usage will often be prolonged (frequently lifelong) and it is important that doses used in treatment are reviewed critically.

Most people with nonacute asthma will respond to relatively small doses of ICS. Figure 1 shows a series of response curves to increasing doses of inhaled budesonide. Most of the benefit in terms of improving morning peak flow is obtained with 400 µg of budesonide a day. A marginal increase occurs with a doubling of the daily dose to 800 µg and no extra benefit is obtained by a further doubling to 1600 µg a day.[4] The dose response curve is thus very flat above a daily dose of 400 µg.

A recent meta-analysis reviewed similar data for fluticasone (Table 1). A daily dose of 250 µg (equivalent to 400-500 µg budesonide) provided 90% of the theoretical maximal benefit.[5] These data and those from other studies are remarkably consistent and indicate there is little advantage to be obtained by prescribing daily doses in excess of 800 µg of budesonide or 500 µg of fluticasone in the maintenance treatment of asthma. These doses are approximately half those previously recommended and a fraction of the advised maximum daily doses.

Should the initial dose be high and then reduced or low and increased?

Few studies have explored this question but evidence suggests that high doses (up to 1200 µg budesonide a day) are better than lower doses.[6,7] Either way, when asthma control has been satisfactory for 6-8 weeks, dose reduction should be attempted. For a significant number of patients, especially children, this will mean cessation of therapy.

Few data exists to guide dose effectiveness in exacerbations of asthma. Very high inhaled doses (greater than 2000 µg of fluticasone or 4000 µg of budesonide) may be as effective as systemic steroid[8] but confirmatory studies are needed. Systemic corticosteroids remain essential in the management of acute severe asthma.

The theoretical effects of delivery device and differences in local biotransformation/retention within the lung complicate consideration of efficacy and systemic dose but the significance of these factors is uncertain and no substantive data exists to allow meaningful comparison between ICS products and delivery devices.

Certainly, modern ICS are notable for the completeness of their removal in the liver making the swallowed part of any inhaled dose relatively unimportant in the overall systemic effect. Therefore, it is the dose directly delivered and absorbed through the lung that is likely to be asso-

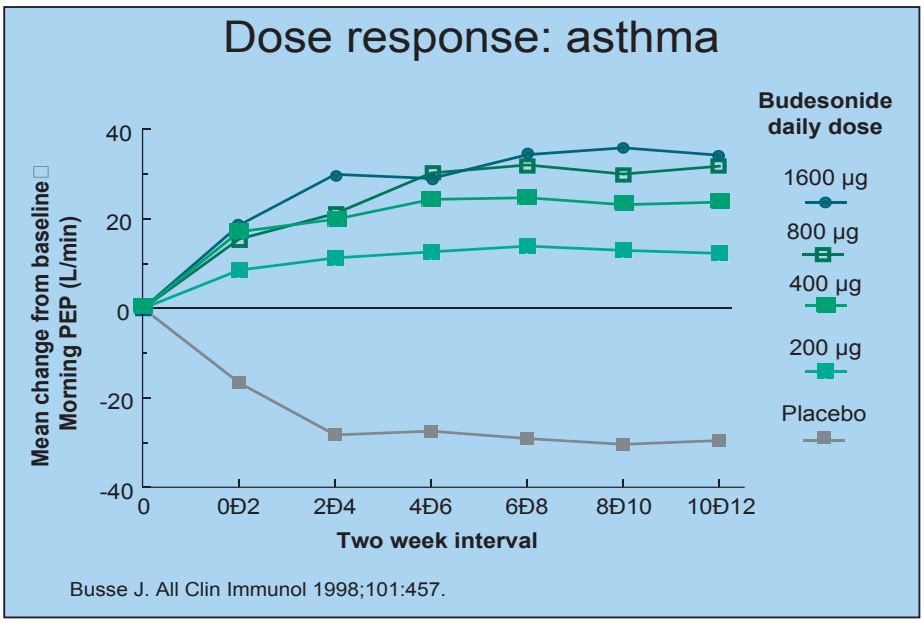

Figure 1. Response to increasing doses of inhaled budesonide

ciated with systemic side effects.

What evidence is there that inhaled steroids may constitute a risk to health?

Systemic steroids have a clearly defined side effect profile that is well understood. With inhaled steroids, measurable effects inhibiting endogenous cortisol production are evident in nonasthmatic subjects in daily doses above 800 µg beclomethasone.[9] In patients with asthma, higher doses are necessary to affect cortisol output, and the significance of cortisol inhibition is less clear.

There have been recent case reports of high doses of fluticasone producing sufficient cortisol inhibition to induce Addisonian hypoglycemia (on occasion with fitting) in children[10] and in some cases growth inhibition.[11] However, in adults a study showed no evidence of cortisol under production during the stress of acute, severe asthma, even in subjects maintained on quite large doses of ICS.[12]

Other studies have observed the relationship between inhaled steroids and skin fragility[13] and ICS and both raised intra-ocular pressure[14] and post-subcapsular lens opacities.[15] The strength of these associations and their clinical significance remains to be fully established however.

More concern exists relating to the negative effects of ICS on bone mineral density (BMD). Although a recent Cochrane Collaboration meta-analyses[16] could find no evidence of BMD loss or fracture for 'conventional doses' taken for 2-3 years there is abundant evidence of a relationship between ICS dose and loss of BMD in cross sectional analyses.[17] A recent paper documented prospectively significant loss of BMD associated with the use of inhaled triamcinolone[18] (not used in Australia). The impact of such reductions in BMD is not merely theoretical. Wong et al calculate for example that taking beclomethasone 2000 µg daily for seven years versus 200 µg daily for one year would result in a 1 standard deviation fall in BMD. At menopause such differences in BMD in women have been associated with a doubling of fracture risk.

Given the numbers of people taking ICS, small changes in BMD may have large impacts on public health. It would seem there is little room for complacency.

Clearly there is an imperative to prescribe ICS in doses that are effective but minimise the potential for side effects. In our current understanding, this implies a total daily dose in the long term of less than 1000 µg of budesonide or beclomethasone or less than 500 µg of fluticasone or Qvar form of beclomethasone. For children the respective doses are less clear but may be at least half this daily dose.

How do long acting beta agonists (LABA) and in particular combination LABA and ICS therapy influence required daily doses?

Although inflammatory processes underlie the pathology of asthma, smooth muscle abnormalities are also important and LABA substantially augment the clinical control of asthma offered by ICS. Combination therapy with ICS and LABA is more effective in controlling asthma than doubling the ICS dose[19,20] and in addition to improving symptoms reduces the number of asthma exacerbations suffered.[21] Long acting beta agonists/inhaled corticosteroids combination thus offer clinicians the opportunity to keep daily steroid doses low, while improving asthma control.

With combined ICS and LABA therapies, asthma control is often the best patients have ever experienced and without active encouragement to consider dosage reduction many people will happily continue to take very large

Table 1. Outcome measure vs daily fluticasone dose

Measure	80% max effect	90% max effect
FEV1	146 µg/d	209 µg/d
AM PEF	172 µg/d	247 µg/d
Rescue Rx	71 µg/d	102 µg/d
Major exacerbation	108 µg/d	155 µg/d
Night awakening	135 µg/d	193 µg/d

amounts of ICS unmindful of potential long term side effects. Back titration from high doses of ICS is essential. A suggested regimen for back titrating is to reduce the dose by 25% or nearest equivalent at each visit reviewing the patient in six weeks. An alternative strategy may be to begin with relatively low doses.

Is there a role for very high unit dose ICS dispensers?

I believe there is little place for very high dose combination therapy. This includes the 500 µg fluticasone or fluticasone/salmeterol dry powder devices and the 250 µg metered dose inhaler (MDI) equivalent. Given the available data, the maximum strength units readily available should probably be 250 µg and 125 µg respectively. Perhaps higher doses should have an authority listing on the Pharmaceutical Benefits Scheme.

These limits recognise the extra asthma control available in combination treatment and limit the side effects likely to occur through prolonged high dose therapy. Although poor patient compliance with therapy undoubtedly 'protects' some patients to some extent against long term side effects, poor compliance is associated with greater morbidity from asthma[22] and is an unacceptable outcome. With combination ICS/LABA therapy this is likely to be substantially less since the symptom relief offered by LABA component is an active cue to reinforce medication use.

Regular use of ICS offers patients the best way to control asthma. If symptoms and frequent short acting beta agonist use persists despite doses of 1000 µg of beclomethasone/budesonide or half this of fluticasone or Qvar beclomethasone, a LABA probably in combination therapy should be added. Once control is obtained the dose of medication should be reduced to the minimum controlling symptoms.

Conclusion

The therapeutic goal, established and reached in cooperation with the patient, should be to control asthma on low doses of ICS (alone or with LABA) taken once or twice daily in a consistent and reliable fashion. For most patients this should be achievable in daily doses less than or equal to 500-1000 µg of beclomethasone/budesonide or 250-500 µg of fluticasone/Qvar beclomethasone.

The 3 Plus Visit Plan offers financial incentives to better asthma management and has the potential to substantially improve the morbidity (and probably mortality) of Australians with asthma. By ensuring doses of ICS used in association with this program are appropriate we can achieve these goals without imposing longer term problems of steroid side effects.

Conflict of interest

Dr Bowler has received sponsorship to attend meetings from GlaxoSmithKline, and AstraZeneca and has received consultancy payments from both companies and Merck Sharp Dohme.

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