

SAFER MEDICATION USE

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INHALED CORTICOSTEROIDS

Inhaled corticosteroids are generally considered to be safe when used at low doses. Patients who require high dose inhaled steroids, particularly for prolonged periods, are at risk of systemic side effects including adrenal suppression, reduced bone mineral density, cataract, glaucoma, growth restriction in children and pneumonia in patients with chronic obstructive pulmonary disease. It is important to review inhaled corticosteroid therapy regularly, particularly in children and when high doses are being used over extended periods, ensuring the lowest effective dose is used, considering add-on therapies and specialist referral as appropriate. Patients at risk of systemic adverse effects should be issued with a steroid treatment card.

Background

There are five inhaled corticosteroids (beclometasone, budesonide, ciclesonide, fluticasone, and mometasone) licensed in the UK for the management of asthma.¹ When prescribed at equivalent doses (both low and high) there is no difference in efficacy.^{2,3} They are available individually or as part of a combination, as pressurised metered dose inhalers (pMDIs) or as dry powder devices. Budesonide and fluticasone are licensed in combination with long-acting beta-2-agonists for chronic obstructive pulmonary disease (COPD).¹

Those pMDIs containing chlorofluorocarbon (CFC) propellants are expected to be phased out in the near future as hydrofluoroalkane containing pMDIs become available. A recent Drug Update (No. 59) provides guidance on switching to CFC-free beclometasone, as doses may be different from those containing CFCs.⁴

Oropharyngeal effects

Local adverse effects are common and whilst seldom serious they may deter adherence to therapy.⁵ The occurrence of oropharyngeal candidiasis is dose related and can be reduced by rinsing the mouth and/or cleaning the teeth after inhalation, and by the use of spacer devices, which reduces oral deposition; anti-fungal lozenges or mouthwash are occasionally required.^{1,5} Hoarseness resulting from a localised corticosteroid-induced myopathy has been reported. Cough and mild bronchospasm may be associated with pMDI propellants or dry powder inhalation; these can be eased by pre-treatment with an inhaled short acting beta-2-agonist.¹

Systemic effects

Inhaled corticosteroids are safest when used in low

doses.⁶ However, prolonged treatment, particularly at high doses (>800micrograms per day of beclometasone or equivalent, in adults) carries a greater risk of systemic effects, including adrenal suppression, reduction in bone mineral density, cataract and glaucoma.⁵ In children, administration of inhaled corticosteroid at doses ≥ 400 micrograms per day of beclometasone or equivalent may be associated with systemic adverse effects which include growth failure.⁷

Adrenal suppression

Adrenal suppression is a dose-related class effect of all inhaled corticosteroids, which occurs as a result of systemic absorption of the corticosteroid and on rare occasions has led to adrenal crisis.⁸ Signs and symptoms associated with adrenal suppression are detailed in the practice point below. As of the 26th February 2008, the Medicines and Healthcare products Regulatory Authority (MHRA) had received 90 reports of adrenal suppression or insufficiency with inhaled beclometasone (12 reports), budesonide (11) and fluticasone (67); in addition there has been one case of adrenal crisis reported with budesonide and seven cases with fluticasone.⁹

Practice point – MHRA advice^{1,8}

Prescribers are reminded that the presenting symptoms of adrenal suppression and crisis are non-specific and include

- Anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, hypoglycaemia and seizures.
- Situations which may trigger acute adrenal crisis include infection, trauma, surgery or any rapid reduction in dosage.
- Additional systemic corticosteroids should be considered during such periods of stress.

Clinical adrenal insufficiency has been identified in a small number of children who have become acutely unwell at the time of intercurrent illness. Most were treated with high doses of inhaled corticosteroids and include a fatal case in a 5 year old caused by prolonged use of an exceptionally high dose of fluticasone (exceeding the licensed maximum).^{7,10}

Practice point – guidance for children⁷

- The dose or duration of inhaled steroid treatment required to place a child at risk of clinical adrenal insufficiency is unknown, but is likely to be at least 1000 microgram per day of beclometasone or equivalent.
- Whilst regular monitoring of the child's height is recommended, isolated growth failure is not a reliable indicator of adrenal suppression and monitoring growth cannot be used as a screening test of adrenal function.
- It is not known how frequently tests of adrenal function would need to be repeated if a child remains on a high dose of inhaled corticosteroid.

Growth

In children, although growth restriction is well established with systemic corticosteroid therapy, it does not seem to occur with recommended doses of inhaled therapy.¹ Even when used at higher than licensed doses the long-term evidence for an impact on growth and final height is inconclusive.^{2,3} In clinical practice, when selecting an inhaled corticosteroid, other factors, such as the most appropriate device, are considered to be more important than possible differences in the impact on growth.^{2,3} The height of children receiving prolonged treatment with inhaled corticosteroids should be monitored.^{1,7} If growth is slowed, ensure the lowest effective dose is prescribed and consider referral to a paediatrician.¹

Bone mineral density

Treatment with inhaled corticosteroids at recommended doses over two to three years has not shown a significant effect on bone mineral density or an increased risk of fracture in younger adults with asthma or mild COPD.¹¹ These patients are at a lower risk of osteoporosis and fractures, the implications in higher risk patients has not been established, nor has the effect of long-term treatment. A recent 3 year study of fluticasone alone or in combination with salmeterol, in patients with COPD (FEV₁ <60%), reported a non-significant increase in the incidence of fractures compared with placebo (5.4 %, 6.3% and 5.1% respectively) and no significant change in bone mineral density.¹² Higher doses of inhaled corticosteroids have been associated with increased bone turnover, but data on bone mineral density and fractures at these doses are not available.¹¹ At present, current evidence does not support the use of biochemical markers to monitor for any effects on bone mineral density in the clinical setting.¹¹

Ocular effects

A small risk of glaucoma with prolonged, high doses of inhaled corticosteroids has been reported.¹ It has been suggested that monitoring of intraocular pressure in such circumstances may be warranted.¹³ Inhaled corticosteroids are associated with a risk of cataract (number needed to harm is 16 [95% CI 13-19]).¹⁴ The risk appears greatest with high doses of inhaled corticosteroid for prolonged periods, which is consistent with the known risk of cataract associated with systemic corticosteroids.¹⁵

Pneumonia

Inhaled steroids have a role in the management of patients with more advanced COPD or repeated exacerbations, however long-term safety has not been fully established.¹⁶ Inhaled steroids either alone or in combination with long-acting beta-2-agonists increase the likelihood of pneumonia.¹² Fluticasone either alone or in combination with salmeterol, significantly increased the risk of pneumonia (18.3% and 19.6% respectively vs. placebo 12.3% p<0.001); however, no statistically significant effects on overall mortality were demonstrated.¹² Older patients, those with lower body mass index and patients with very severe disease are at highest risk of pneumonia irrespective of treatment.¹⁷

Practice point – MHRA advice¹⁷

- Physicians should remain vigilant for pneumonia and other infections of the lower respiratory tract (i.e. bronchitis) in patients with COPD who are treated with inhaled products that contain steroids, as clinical features of such infections and exacerbations frequently overlap.
- Any patient with severe COPD who has pneumonia during treatment with inhaled steroids should have their treatment reconsidered.

Is there any comparative safety data?

There is limited data on the comparative safety of different inhaled corticosteroids. Beclometasone and budesonide appear approximately equivalent.⁷ Fluticasone, whilst providing equal clinical activity to beclometasone (CFC-containing) and budesonide at half the dosage, has little evidence of improved safety.⁷ When fluticasone pMDI is compared to beclometasone CFC-free pMDI (QVAR[®]), the dose ratio is 1:1 and where reported the incidence of local adverse effects is similar.¹⁸ Fluticasone may be associated with less impact on growth than other inhaled corticosteroids, however, this has not been shown consistently across studies.²

The relative safety of the newer inhaled corticosteroids, mometasone and ciclesonide, are not fully established.⁷ A recent systematic review of ciclesonide found adverse events occurred with similar frequency to beclometasone and budesonide.¹⁹ A reduced incidence of candidiasis compared to fluticasone, may be of importance to people who find this to be problematic.¹⁹

Guidance from the National Institute for Health and Clinical Excellence has been issued on the management of chronic asthma in all age groups. This recommends that when an inhaled corticosteroid is considered appropriate, the least costly product suitable for the individual should be prescribed.^{2,3} In adults and children over 12 years old, there is little difference in the adverse effect profiles of the available inhaled corticosteroids.³

How can adverse effects be minimised?

The British Guideline on the Management of Asthma recommends titrating the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained, to minimise systemic adverse effects. In both adults and children where higher doses of inhaled corticosteroids are required, add-on agents such as long acting beta-2-agonists should be actively considered.⁷ Where necessary in difficult to treat children, the use of daily doses of ≥ 800 mcg beclometasone dipropionate (CFC-containing) or equivalent, should be under the care of a specialist paediatrician for the duration of the treatment. Specific written advice about steroid replacement, in the event of severe intercurrent illness, should be part of the management plan for children on high doses of inhaled corticosteroid.⁷

When should steroid cards be issued?

The MHRA advise that steroid treatment cards are provided for all patients (or their parents/carers) who require prolonged treatment with high doses of inhaled steroids.^{1,6} These serve to educate patients about their treatment and alert clinicians to the possibility of adrenal suppression and the need for steroid therapy. Further guidance from the MHRA regarding the supply of steroid cards is available at [link](#).⁶

When should adverse reactions be reported to the MHRA?

All serious suspected adverse reactions to any inhaled corticosteroid should be reported to the MHRA via the Yellow Card Scheme www.yellowcard.gov.uk. This includes adrenal suppression, growth retardation, decrease in bone mineral density, cataract and glaucoma suspected to be related to inhaled corticosteroid use. All suspected adverse reactions to black triangle drugs (which include ciclesonide, mometasone, and Clenil Modulite[®] and Fostair[®] CFC-free brands of beclometasone¹) should be reported, as should all suspected serious reactions to any drug, herbal or OTC medicine. The Yellow Card Centre Northern and Yorkshire can provide support and guidance on any adverse reaction related enquiry or completion of a Yellow Card. Information is available via our website [link](#).

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KEY – Randomised Controlled Trial (RCT), Meta-analysis (MA), Guideline (G), Review (R)

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