THORAX

Editorials

Inhaled corticosteroid therapy in children: an assessment of the potential for side effects

Long before asthma was considered to be an inflammatory disorder, glucocorticosteroids were used in its management. It soon became apparent that a heavy price had to be paid for the success of this new treatment which was associated with significant side effects including, in children, growth impairment.[1] When inhaled corticosteroid therapy was introduced,[2] paediatricians welcomed its steroid-sparing properties and freedom from side effects,[3–5] and it is no exaggeration to say that it has transformed the lives of many asthmatic children. Nevertheless, there have always been anxieties about the potential side effects of inhaled corticosteroid therapy and, from an early stage, it was recommended that, in children, inhaled corticosteroids should be given only when treatment with sodium cromoglycate had failed,[6] a recommendation which persists in most published guidelines.[7 8]

Corticosteroids selected for administration by the inhaled route are chosen on the basis that they have high topical but minimal systemic potency, a high affinity for pulmonary epithelial tissue, and rapid hepatic destruction after absorption.[9] In the UK the first such drug to be introduced was beclomethasone dipropionate, closely followed by betamethasone-17-valerate (which is no longer available), and later by budesonide and fluticasone. Elsewhere other corticosteroids have been licensed for administration by the inhaled route – for example, triamcinolone acetonide and flunisolide.

In the UK both beclomethasone and budesonide are licensed for administration to children in doses of up to 400 μg daily, and numerous studies testify to the apparent safety of such doses.[10–12] However, childhood asthma is by no means always controlled by conventional doses of inhaled corticosteroid therapy, and higher doses may have to be used, especially in younger children with recurrent wheeze[13 14] and in children with otherwise intractable asthma. Moreover, recent publications have cast doubt on the safety of inhaled corticosteroid therapy even when given in conventional doses, and there has been widespread public anxiety, some of it shared by the medical profession, sometimes resulting in the undertreatment of childhood asthma.[15] This paper reviews the side effects of inhaled corticosteroid therapy in children.

Adrenal suppression

Early papers on adrenal function in children receiving inhaled corticosteroid therapy were reassuring, reporting either no adrenal suppression[16–18] or adrenal suppression only on high doses.[19 20] Most recent studies have continued to offer reassurance,[21 22] although caution has been advised in the use of higher doses.[23 24] Adrenal stimulation tests are by no means physiological,[25] but Law *et al*,[26] measuring nocturnal cortisol secretion in asthmatic children receiving inhaled corticosteroid therapy, reported reduced adrenal secretion, a delayed rise from the nocturnal nadir, and low early morning cortisol levels. Although these effects were more significant at higher doses, they occurred at all dosage levels, cortisol secretion being reduced on daily doses as low as 400 μg. Other authors have also found that relatively modest doses of inhaled corticosteroid therapy can cause adrenal suppression.[27–29]

There is therefore good evidence that inhaled corticosteroid therapy, even when given in normally recommended doses, can produce adrenal suppression. There is no firm evidence that any child has ever come to harm as a result of adrenal suppression induced by inhaled corticosteroid therapy and, in most stimulation studies, it has been notable that basal cortisol is much more sensitive than stimulated cortisol to the effects of inhaled corticosteroid therapy; this suggests that an adequate adrenal reserve is maintained in most cases, a suggestion which has been confirmed in adults with acute severe asthma.[30]

Bone metabolism

Inhaled corticosteroid therapy has been associated with corticosteroid-like effects on bone metabolism in adults, especially at higher doses.[31 32] Although these effects appear to be dependent on dose and duration of treatment, no precise safe cutoff point has been determined. The situation in children is also unclear; König *et al*[33] failed to demonstrate any adverse effect on bone metabolism, but papers presented at the recent meetings of the European Respiratory and American Thoracic Societies were divided between those reporting that inhaled corticosteroid therapy had no effect on bone metabolism[34–37] and those apparently demonstrating significant effects.[38 39] These inconsistent findings may reflect the imperfections of the markers of bone metabolism in common use. The development of improved methods such as the assay of collagen deoxypyridinoline crosslinks[40] offers the potential to study this aspect of inhaled corticosteroid therapy with a greater degree of accuracy than has been possible hitherto. Until more precise and consistent information is available it seems sensible to follow the advice of Toogood and Hodsman[41] to titrate the dose of inhaled corticosteroid therapy to the lowest level needed to maintain optimum control.

Growth

Following the introduction of inhaled corticosteroid therapy, several authors reported no adverse effect on

growth.[42 43] There was even evidence in some cases of catch-up growth when the asthma came under control,[44] an effect which is not altogether surprising given the growth-retarding effect of asthma.[45 46]

The mechanism by which asthma and other allergic diseases[47 48] affect growth is uncertain, but is not closely related to the severity of the disease, and even in mild asthmatics there may be pubertal delay with prolongation and depression of the prepubertal nadir in height velocity,[47 49] a combination which usually results in normal adult stature.[50]

Despite anxieties raised by the series reported in the letter by Littlewood *et al*,[51] which included older children in whom the effects of delayed puberty could not be excluded, studies of the effect of inhaled corticosteroid therapy on growth have generally continued to give reassuring results.[52–56] However, the introduction of knemometry,[57 58] a technique for measuring the length of the ulna or lower leg with great accuracy, has reopened the debate. Using knemometry, Wolthers and Pedersen[59 60] demonstrated a convincing dose-related suppression of short-term lower leg growth in children receiving inhaled corticosteroid therapy, and MacKenzie and Wales reported similar results.[61]

It is easy to dismiss the results of knemometry as academic findings of no clinical importance. However, using conventional height measurements, two recent studies have demonstrated that inhaled corticosteroid therapy affects growth. In one, a placebo-controlled study, there was significant slowing of the growth of prepubertal children given inhaled corticosteroid therapy in a daily dose of 400 μg,[62] an effect which was not associated with adrenal suppression as assessed by overnight urinary cortisol.[63] In the other, a study involving 162 prepubertal children, there was a dose-related reduction in mean height velocity in children on beclomethasone, although some of these children had had occasional systemic steroids for acute asthmatic exacerbations.[64]

Inhaled corticosteroid therapy therefore affects growth. The clinical implications of these findings are uncertain, and there is no reason to disbelieve previous findings that patients on inhaled corticosteroid therapy can expect to attain normal adult height, compatible with the height of their parents.[49]

Cataract

Systemic corticosteroid therapy is associated with the development of posterior subcapsular cataracts in asthmatic children[65] but, although several case reports have suggested that inhaled corticosteroid therapy might occasionally have a similar effect,[66 67] it is impossible from these reports to separate the effects of inhaled corticosteroid therapy from those of systemic therapy. Simons *et al*[68] found no evidence of cataract in 95 young asthmatics on inhaled corticosteroid therapy and concluded that "screening for this complication does not appear to be warranted". Our own results (unpublished) based on slit lamp ophthalmoscopy in 158 asthmatic children – in whom we found one case of cataract in a small group of three children who had been on continuous oral steroid therapy and none in the remaining children who had had steroids only by inhalation – support this view.

Diabetes and other metabolic effects

In adults inhaled corticosteroid therapy has been associated with decreased insulin sensitivity and rises in total and high density lipoprotein cholesterol.[69] The author is unaware of any similar metabolic studies in children.

Candidiasis and other infections

It became apparent soon after the introduction of inhaled corticosteroid therapy that it was associated with the occasional development of oral candidiasis, and more commonly with oropharyngeal colonisation with *Candida*.[17 70] These are seldom problematical in children, even in the absence of the usual preventive measures such as large spacers and mouth rinsing. Sore throat and hoarseness also occur, unrelated to *Candida* colonisation.[70]

Inhaled corticosteroid therapy does not produce immunosuppression in children[71] and, unlike systemic corticosteroid therapy, does not predispose to severe viral infections such as varicella; there is no good reason to warn parents of such hypothetical hazards.[72]

Dermal thinning and purpura

Cutaneous changes, absent in patients on conventional doses, have been reported in adults receiving high-dose inhaled corticosteroid therapy.[73] No comparable paediatric studies have been reported.

Idiosyncratic reactions

Most paediatric and thoracic physicians looking after asthmatic children will have encountered the occasional patient in whom significant systemic toxicity appears to occur on modest doses of inhaled corticosteroid therapy. This usually takes the form of increased weight with the development of Cushingoid facies,[74] but occasionally includes hirsutes and other effects.[75]

Rarely, a child is hypertensive to either inhaled corticosteroid therapy or the propellants used in its delivery. The usual reaction is bronchospasm, and the close temporal association between the administration of the drug and the onset of wheeze leaves the patient in no doubt as to the causal nature of this association, although the attending doctor is more often sceptical! More common is bronchospasm or cough precipitated by dry powder inhalers in which lactose is used as a carrier for the drug.

Occasionally inhaled corticosteroid therapy is associated with psychological effects.[76] Sometimes these amount to no more than childish *joie de vivre* as might be expected when a disabling disorder is controlled; in other cases inhaled corticosteroid therapy appears to unleash behavioural disturbance of such severity that treatment has to be stopped.

These idiosyncratic effects are sometimes specific to an individual drug and disappear when an alternative inhaled corticosteroid is used.

Differences between inhaled corticosteroids

Because beclomethasone was the first inhaled corticosteroid to be introduced, and it remains the most widely used drug, there are more published data on its side effects than on the two more recently introduced drugs. Where comparison has been made, and this has been mainly in adults, differences between the individual corticosteroids available for inhalation appear to be slight.[77] The potential benefits of fluticasone, which is almost completely metabolised on first pass metabolism through the liver, remain to be established in practice, although there is evidence that in normal doses it may have no effect on growth[78 79] and plasma cortisol levels remained normal in two series involving 300 children on this drug.[80 81]

Prevention of side effects

Topical, and possibly systemic, side effects of inhaled corticosteroid therapy can be reduced by meticulous attention to inhaler technique, including mouth washing

after inhalation[82 83] and the total dose to which the child is exposed may be reduced by selection of an appropriate inhalation device.[84]

Conclusions

In daily doses within the recommended range inhaled corticosteroid therapy has an excellent safety record in children. There is, however, increasing evidence of a variety of dose-related side effects. Whilst these may be of dubious clinical importance, until such time as we know more about their significance it seems reasonable to adhere to the current recommendations that inhaled corticosteroid therapy should be used only after prophylaxis with cromoglycate has failed and, before high-dose inhaled corticosteroid therapy is given, the introduction of alternative prophylactics such as salmeterol or sustained release theophylline should be considered. A possible exception is in young children[85] in whom the twice daily regimen of nebulised inhaled corticosteroid therapy is much less disruptive to family life than the more frequent dosage required for the administration of cromoglycate.

Inhaled corticosteroid therapy has improved the lives of countless asthmatic children over the past 20 years and, although we cannot ignore the potential of this form of treatment to produce side effects, we must not allow this to lead to the undertreatment of a common, sometimes disabling, and occasionally fatal, disease. Inhaled corticosteroid therapy may not be the elixir of life, but for most asthmatic children it is more panacea than poison, and is likely to remain a mainstay in their management for many years to come.

Consultant in Medical Paediatrics,
Royal Aberdeen Children's Hospital,
Aberdeen AB9 22G,
UK

GEORGE RUSSELL

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