CLINICAL PRACTICE

SYSTEMIC EFFECTS OF INHALED STEROIDS AND THEIR RELEVANCE IN CHILDREN WITH ASTHMA

Robin J Green

Asthma is a common condition with a well-described pathology and consequent treatment principles. Some therapies are very effective in controlling not only symptoms of the disease but also the disease itself, and yet in children treatment of this condition remains contentious.

Asthma is defined by the National Heart, Lung and Blood Institute as 'a chronic inflammatory disorder of airways, in which many cells play a part, including mast cells and eosinophils in susceptible individuals. This causes symptoms which are usually widespread but variable, airflow obstruction that is often, but not always, reversible spontaneously or with treatment, and causes an associated increase in airway responsiveness to a variety of stimuli'.[1] The implication of this definition and most others is that asthma is an inflammatory disorder. This holds true for all forms of the disease, even when it is mild. Hence the most important treatment should be directed at inflammation[2] and the most effective anti-inflammatory agent is the corticosteroid,[3] both in adults and in children.

For many years oral corticosteroids controlled asthma very effectively but at huge cost in terms of unwanted side-effects. The introduction of inhaled corticosteroids (ICS) provided a safer alternative to oral steroids,[4] and their use has been shown to reduce the need for systemic steroids. ICS are successful in decreasing nonspecific bronchial hyperresponsiveness.[5,6] sufficiently to control asthma symptoms over a period of time.

Despite this apparent answer to the problem of asthma, many practitioners are reluctant to use ICS in children because of so-called 'adverse effects'. Drug effects, however, include both adverse (or undesired) effects and beneficial effects, and in addressing the role of ICS in the management of childhood asthma, some clarity is required on the balance between these two extremes.

Robin Green is a paediatric pulmonologist in private practice at Sunninghill Hospital in Johannesburg. He is active in the National Asthma Education Programme, the South African Allergic Rhinitis Working Group, the South African Pulmonology Society and the Allergy Society of South Africa.

ADVERSE EFFECTS OF ICS

At the outset it should be stated that measurable systemic effects are not equivalent to clinically relevant systemic side-effects. Simple detection of the drug in the blood or a measured change in a physiological variable does not necessarily denote an adverse event. In addition measurable systemic activity is dependent on the sensitivity of the method used. Few true studies have looked at the clinical relevance of adverse events, and most opponents of ICS have lumped all systemic activity under adverse events.

The systemic effect of ICS depends on the amount of drug systemically absorbed from both the gastro-intestinal tract (GIT) and the intrapulmonary airway. Factors influencing systemic activity include the amount swallowed (roughly 80% of a metered dose), the affinity of the drug for receptors, and especially selectivity for the glucocorticoid receptors, metabolism in the circulation and liver (oral bio-availability), activity of metabolites and systemic clearance. The fraction that is absorbed in the pulmonary circulation is also systemically active.

A number of strategies have been employed to minimise the systemic activity of ICS. These include reducing the amount swallowed, through manipulating the inhaler technique, or by using a spacer, or by mouth washing after use. The intrinsic structure of the ICS can be altered to increase receptor affinity, increase glucocorticoid receptor affinity, increase first-pass metabolism, reduce activity of metabolites and increase systemic clearance. These manouvres have been employed with the newer generation ICS. Spacer devices (Fig. 1) should be considered an integral part of ICS therapy in children, and the spacer used should be that recommended by the manufacturer for the particular drug, as mixing and matching delivers inconsistent dosages.

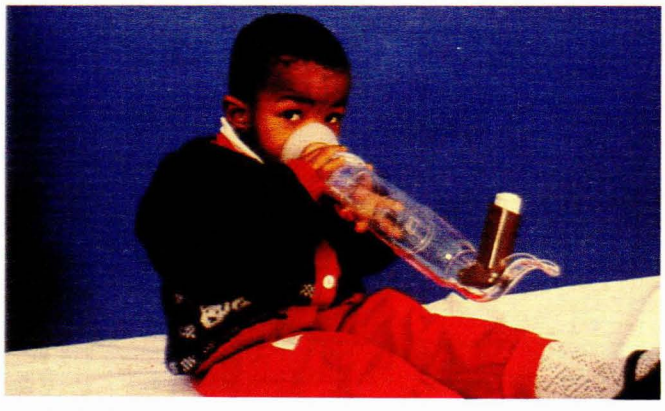

Fig. 1. Child using an inhaled steroid via a Babyhaler spacer.

It has largely been in children that adverse effects have been of concern to practitioners treating asthma, with growth the important variable. Surrogate markers for the systemic effects of ICS have included measures of hypothalamopituitary axis (HPA) activity, biochemical markers of bone mineralisation,

short-term growth, and of course growth over time. The degree of HPA axis suppression is dependent on a number of variables, including dose of ICS, duration of action, frequency of administration, time of day administered and route of administration.

A number of tests have been employed to 'measure' the systemic effect of ICS. These include both basal adrenal activity and the more sensitive stimulation tests. When interpreting such tests it must be remembered that normal cortisol secretion varies during the course of the day, that laboratory studies may not reflect physiological changes, that many tests are difficult to perform, and that often changes noted are within the normal range for a particular test.

With regard to the effect of ICS on the HPA axis, conflicting results[7] reported may be due to uncontrolled studies, previous use of oral steroids, variable duration of treatment, variable inhaler systems and different measuring methods. Some of these studies indicated that significant effects on basal adrenal function (cortisol secretion) can be detected at doses of ICS around 400 µg per day. However, no clinically relevant endocrine effects have been reported in children who have received such therapy for many years.

The mechanism of the effect of ICS on growth is not fully understood, but may involve both an indirect effect on growth hormone secretion, and a direct effect on bone metabolism. Important considerations in this regard are that the rate of growth in childhood and final height are determined by the impact of a range of environmental factors on genetic potential. In addition growth measurement is subject to error, especially when growth velocity is low (mid-childhood), where error in 3-monthly intervals may be as high as 50%. Compounding variables for height determination are seasonal changes, year-by-year changes, time of onset of puberty, effect of asthma (many asthmatic children have a slower growth rate than normal children and a physiological delay in puberty which does not affect final adult height), severity of asthma,[7] and lastly the effect of oral steroid use.

Although short-term growth studies, usually involving knemometry, report variable rates of lower limb growth with ICS, long-term follow-up studies have been few. Three such studies found no long-term effect (up to 6 years) on growth with variables doses of ICS (up to 1 100 µg/m^2/d).[8] In conclusion, it appears that knemometry (short-term) studies show effects of ICS on growth (of the lower leg) at doses from 400 µg/d, that long-term statural growth is not affected at this or higher doses, and that knemometry may be oversensitive for measurement of this sort.[7]

The use of bone turnover to reflect systemic adverse events is based on the understanding that systemic glucocorticoid therapy has a deleterious effect on the skeleton, leading to decreased bone mass and ultimately to osteoporotic fractures.[9] Thirty to fifty per cent of patients receiving long-term (over years) treatment with doses of prednisone of 7.5 - 10 mg per day would develop skeletal fractures.[10]

Numerous methods are available for assessing bone turnover, both biochemical and radiological. Bone densitometry is the latest and probably the most practical, but like the other tests described, it is associated with a number of problems. Bone metabolism (like asthma itself) is influenced by disease states, activity, diet and the confounding effect of oral steroids.

Although short-term studies in general have found ICS to have no effect on systemic measures of bone metabolism,[11,12] it is the long-term effects that would be more important. Few studies have been performed in children, but in one sentinel study Agertoft and Pedersen[13] found no change in bone density in children after 4.5 years (mean dose of ICS 691 µg/d) compared with steroid-naïve asthmatics.

In conclusion, while there is no indication of increased risk of osteoporosis or fractures in children on ICS, it is wise to aim for the lowest dose with long-term treatment. However, at the onset of treatment of asthma use of high-dose ICS is becoming a popular way of gaining initial control of the disease.

Beneficial effects of ICS

It has become common practice to discuss adverse events due to ICS as the sole manifestation of drug activity. This is not the case. Many beneficial systemic effects are known or becoming obvious.

As has been discussed, uncontrolled asthma can cause poor growth in childhood and delayed puberty, and this effect is magnified by the need for repeated courses of oral steroids. There is evidence that growth is improved with ICS. Short-term growth was marginally better in a fluticasone propionate-treated group than in a placebo control group ($N = 13$) (not statistically significant),[14] and this probably reflects an overall improvement in health.

Three studies comparing asthmatic patients given ICS early with patients in whom the introduction of ICS was delayed demonstrated increasing loss of lung function with increasing delay in introduction of ICS.[15-17] This would impact on cost and number of exacerbations, and could have future medicolegal implications.

An exacerbation of asthma, especially a severe exacerbation, is a serious illness. There is evidence that treatment with ICS (fluticasone propionate) results in fewer exacerbations than treatment with sodium cromoglycate[17] and has a significantly greater effect than treatment with β_2-agonists,[18] and together with the benefits of improved long-term control and quality of life, the cost of ICS is lower than that of some other agents, such as sodium cromoglycate.

Conclusion

Concerns about the systemic unwanted effects of ICS have greatly limited their use, especially in children. The adverse effects of inhaled glucocorticosteroids are dose-related, with

little or no evidence of clinically relevant systemic unwanted effects at doses of < 400 µg/d. In most patients optimal asthma control can be maintained with these or lower doses. There are currently no anti-inflammatory drugs that are as effective as inhaled glucocorticosteroids in the first-line treatment of asthma.

In children with asthma it is reassuring to note that guidelines for management now advocate the use of ICS in all severities of persistent disease[19] (and not just for severe asthma), and that with the newer inhaled corticosteroids and delivery devices (fluticasone propionate or budesonide turbuhaler) equal effect may be achieved at half the dose of both BDP and budesonide in a metered dose inhaler.[19,20]

1. National Heart Lung and Blood Institute. International Consensus Report on Diagnosis and Management of Asthma. *Clin Exp Allergy* 1992; **22:** suppl 1, 1-72.
2. Warner JO. Use of corticosteroids in children with asthma. *Eur Respir Rev* 1993; **3:** 326-328.
3. Barnes NC. Advances in inhaled steroid therapy. *Eur Respir Rev* 1994; **4:** 295-300.
4. Geddes DM. Inhaled corticosteroids: Benefits and risks. *Thorax* 1992; **47:** 404-407.
5. Clarke PS. The effect of beclomethasone dipropionate on bronchial hyperreactivity. *J Asthma* 1982; **19:** 91-93.
6. Ryan G, Latimer KM, Juniper EF, Roberts RS, Hargreave FE. Effect of beclomethasone dipropionate on bronchial responsiveness to histamine in controlled nonsteroid-dependent asthma. *J Allergy Clin Immunol* 1985; **75:** 25-30.
7. Pedersen S. Safety aspects of corticosteroids in children. *Eur Respir Rev* 1994; **4:** 33-43.
8. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994; **88:** 373-381.
9. Toogood JH, Hodsman AB. Effects of inhaled and oral corticosteroids on bone. *Ann Allergy* 1991; **67:** 87-90.
10. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990; **112:** 352-364.
11. Wolthers OD, Riss BJ, Pederson S. Bone turnover in asthmatic children treated with oral or inhaled budesonide. *Pediatr Pulmonol* 1993; **16:** 341-346.
12. Kinberg KA, Hopp RJ, Biven RE, Gallagher JC. Bone mineral density in normal and asthmatic children. *J Allergy Clin Immunol* 1994; **94:** 490-497.
13. Agertoft L, Pedersen S. Bone density in childhood during long-term treatment with budesonide. *Eur Respir J* 1993; **6:** 261s.
14. MacKenzie CA, Wales JKH. Growth in asthmatic children. *BMJ* 1991; **202:** 416.
15. Haahtela T, Alanko K, Muitari A, *et al*. The superiority of combination beclomethasone and salbutamol over standard dosing of salbutamol in the treatment of chronic asthma. *Ann Allergy* 1989; **62:** 63-66.
16. Selroos O, Pietinalho A, Lofroos A-B, Riska H. Effect of early versus late intervention with inhaled corticosteroids in asthma. *Chest* 1995; **108:** 1228-1234.
17. Price JF, Weller PH. Comparison of fluticasone propionate and sodium cromoglycate for the treatment of childhood asthma (an open parallel study). *Respir Med* 1995; **89:** 362-368.
18. Van Essen-Zandvliet EB, Hughes MD, Waalrens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or β_2-agonist on lung function, airway responsiveness and symptoms in children with asthma. *Am Rev Respir Dis* 1992; **146:** 547-554.
19. British Thoracic Society. The British Guidelines on asthma management. *Thorax* 1997; **52:** suppl 1, S1-S21.
20. Van Asperen P, Fitzgerald D, Mellis C, Honner M, Smith L, Ambler G. Fluticasone propionate (FP) 750 mcg/day is as effective as beclomethasone dipropionate (BDP) 1 500 mcg/day in paediatric asthma (Abstract). *Eur Respir J* 1996; **9:** 114s.

DRUG ALERT

ROCHE WITHDRAWS POSICOR

Roche announced on Monday 8 June 1998 the voluntary withdrawal of the antihypertensive and anti-anginal medication, Posicor (mibefradil), and is advising physicians to propose alternative therapies to their patients.

This action is based on evolving information concerning the potential for drug interactions, some of them serious, which may occur when Posicor is taken together with some other medications. The decision follows analysis of the preliminary results of a 3-year long-term study of Posicor in congestive heart failure — this demonstrated no significant difference between Posicor and placebo when added to standard therapy in this patient population, but did provide further information on drug interactions.

In both hypertension and chronic angina pectoris, Posicor has proved to be consistently effective and well tolerated when used appropriately. However, the combination of Posicor and some other commonly used drugs, among them cardiovascular agents, may increase the frequency of the side-effects of these other medications.

In principle, drug interactions can be addressed by appropriate labelling; however, in the case of Posicor, Roche believes that the complexity of such prescribing information would make it too difficult to implement. As patient well-being is of the highest priority to Roche, the company has preferred to voluntarily withdraw the compound from all markets.

The company is working closely with regulatory authorities to appropriately inform physicians and other health care professionals of its decision.

Patients should not simply discontinue treatment with Posicor; instead they should promptly consult their physicians about appropriate alternative therapy. In addition, patients should not add any new medication to their present treatment without consulting their physicians.

Enquiries: Kelvyn Henry, Public Affairs Director, tel (011) 928-8734 or (011) 974-5335.