

INHALED CORTICOSTEROIDS IN CHILDHOOD ASTHMA

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SUMMARY

Inhaled corticosteroids (ICS) have become the cornerstone of the treatment of persistent asthma in children, but uncertainty exists regarding various aspects of their use, including safety concerns.

ICS should be used in children who have symptoms of persistent asthma, irrespective of age. The safe dose of ICS is regarded as 400 µg/day of budesonide equivalent; side-effects are associated with increasing doses. Current evidence suggests that this dose is safe in long-term growth studies in children with asthma, but growth monitoring should take place at each visit. Adding other controllers to ICS should be considered preferable to increasing ICS doses above 400 µg/day of budesonide equivalent.

Inhaled corticosteroids (ICS) have become the cornerstone of treatment of asthma in adults and children. The first published report of their beneficial use in children appeared in 1973,¹ and since then they have been recommended for the management of persistent asthma, particularly in the moderate and severe categories.

The clinical efficacy of ICS has been demonstrated in mild, moderate and severe asthma in several studies. ICS reduce symptoms and improve quality of life in children who have asthma; they reduce airway inflammation and improve lung function and bronchial hyperresponsiveness. The sale of ICS has increased worldwide since the late 1980s and their use is widely advocated in international asthma guidelines.

The increased use of ICS has been accompanied by concerns regarding side-effects in children. These relate particularly to growth, but there are also concerns regarding possible effects on lung development in young children.

Many issues surrounding the use of ICS in childhood asthma remain contentious, and we shall attempt to address some of them.

HOW EARLY SHOULD ICS BE INTRODUCED?

A study done by Agertoft and Pedersen² suggested that the improvement in lung function was significantly greater in children who started budesonide treatment early (within 2 years of onset of asthma) than in children who did not start the treatment until a few years after onset of asthma symptoms. This has been inter-

preted to suggest that ICS should be introduced early in the treatment of childhood asthma to prevent irreversible airway obstruction and loss of lung function.

The CAMP study³ compared the use of budesonide to nedocromil and placebo in 1 041 children aged 5 - 12 years who had mild to moderate asthma, and followed them up for 4 - 6 years. Their primary outcome measure was the degree of change in the forced expiratory volume in one second (FEV₁) measured post bronchodilator. This has been used as a surrogate measure for lung growth. There was no significant difference between either of the treatment or placebo groups, suggesting that airway remodelling was not an issue in these children.

The Expert Panel Report⁴ (EPR) of the National Asthma Education and Prevention Program (NAEPP) Science Base Committee recently published updated recommendations on the guidelines for the diagnosis and treatment of asthma. The panel stated that ICS are the preferred treatment for initiating therapy in children of all ages with persistent asthma. It is also their opinion that long-term-control therapy (preferably with ICS) should be strongly considered in infants and young children who in the past year had more than three episodes of wheezing that lasted longer than 1 day and affected sleep, particularly if they are considered at high risk of developing persistent asthma.

The balance of opinion would appear to be that ICS should be started in asthmatics who have persistent symptoms, irrespective of their age, and the response carefully assessed.

LOW VERSUS HIGH DOSE?

Two schools of thought exist regarding dose: 'hit early, hit hard' versus 'start low and step up'. In the majority of children and adolescents with asthma, satisfactory control can be achieved with low doses of ICS. The doses recommended in the South African guidelines⁵ are lower than those suggested by the Global Initiative for Asthma (GINA)⁶ and the British Thoracic Society.⁷ The CAMP study³ data suggest that 400 µg/day of budesonide is effective in mild to moderate asthma. Dose-response studies reveal that the dose-response curve is relatively flat, with most benefit obtained at the lowest ICS doses.⁸ Once the daily dose of 400 µg/day of budesonide equivalent is exceeded, the incidence of side-effects rises steeply. The recommendation is therefore to start at the appropriate dose for the severity of the asthma, and then step down once control is achieved. Even low-dose ICS are efficacious in controlling asthma in children.

HOW DOES ONE CHOOSE BETWEEN ICS?

Direct comparisons between the available ICS are very difficult. The newer ICS have excellent first-pass metabolism and therefore negligible absorption from oral deposition of the drug. However, most of the systemic effects of the ICS result from the fraction deposited in and absorbed from the lung. Improved drug delivery has resulted in potentially increased systemic availability. Other factors that need to be considered are the physicochemical properties (such as lipophilicity and receptor residency time) and different

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deposition characteristics from the inhaler and delivery devices.

There are currently four ICS available in South Africa: beclomethasone, budesonide, fluticasone and triamcinolone. They are available in a variety of formulations and delivery devices. Selecting the most appropriate ICS for the patient includes the availability of the preparation, patient preference, age of the patient, ease of administration and cost. Patients in the public sector are far more limited in terms of choice than those in the private sector.

Fluticasone may be used at half the dose equivalent of budesonide, as it is twice as potent. However, the delivery device and the drug formulation should also be taken into account in determining the dose of ICS.

HOW FREQUENTLY SHOULD THE ICS BE ADMINISTERED?

The recommended dosing frequency is twice daily, but budesonide, because of its reversible fatty acid conjugation, has been shown to be effective when used once a day in mild asthma.⁹

IS THE DELIVERY SYSTEM IMPORTANT?

The dose of drug inhaled into the airways is influenced by a number of factors, including inhaler design, formulation of the drug, quality of the aerosol produced from the inhaler, inhalation technique, and airway/lung disease status. The delivery of ICS to the intra-thoracic airways is improved from 10% with a pressurised metered dose inhaler (pMDI) to 20% with a pMDI/spacer combination. Dry powder inhalers have varying efficacy. Budesonide via Turbuhaler was found to be as effective as twice the dose given via a pMDI with Nebuhaler in asthmatic children¹⁰ and this must be taken into account when deciding on the ICS dose. The fine-particle ICS delivered by the hydrofluoroalkane pMDIs improve delivery of the drug to the small airways and may increase the amount of drug available for absorption. Fig. 1 illustrates where ICS are deposited and transported.

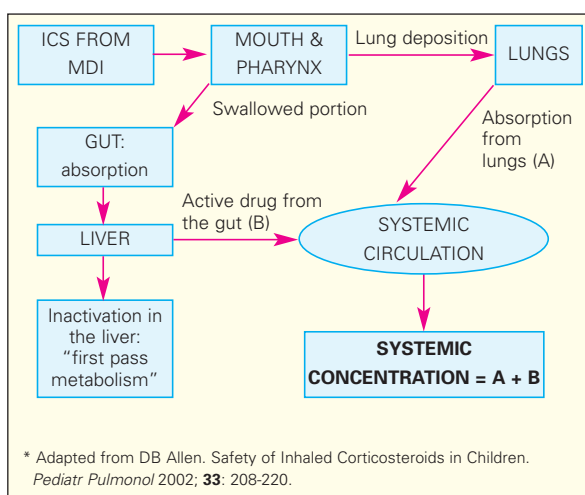


Fig. 1. What happens to inhaled corticosteroids (ICS)

DO ICS INFLUENCE LONG-TERM OUTCOME?

No study has ever established that ICS cure asthma. Lung function reverts to pre-ICS values after they have been stopped. As mentioned previously, some studies suggest that earlier introduction of ICS may prevent irreversible airway inflammation with remodelling. The

problem is that there is no single short-term surrogate marker for the best asthma outcome. However, lung function in mid-adult life has been found to be normal if asthma had been mild during childhood, even if no ICS had been taken.¹¹ The only adults who showed evidence of airway obstruction were those who had had moderately severe asthma in childhood.

HOW SAFE ARE ICS IN CHILDREN?

ICS may have local and systemic side-effects. The local side-effects include peri-oral dermatitis, oral candidiasis, hoarseness, dysphonia and coughing during inhalation.

Much more attention has been paid to systemic side-effects. These include hypothalamic-pituitary-adrenal (HPA) axis suppression, reduction in growth velocity, effects on bone structure, mass and turnover, and Cushing's syndrome. Marked individual variation in the degree of adrenal suppression by ICS occurs. A recent study in the UK identified 33 patients (28 children) who developed acute adrenal crisis associated with ICS.¹² Thirty-one (94%) of the cases were associated with fluticasone, despite its being the least prescribed ICS. The authors advise that a fluticasone dose of 400 µg/day in children should not be exceeded unless the child is being managed by a specialist in paediatric asthma.

A twofold increase in the prevalence of posterior sub-capsular cataracts in patients on ICS has been reported.¹³ The degree of risk is related to both the current and the cumulative lifetime dose of ICS. The CAMP study³ reported the formation of a tiny cataract in one child, but that child had received supplementary systemic steroids for asthma exacerbations and poor control.

Many studies of growth in asthmatic children on ICS have demonstrated some impairment in short-term growth as measured by knemometry (lower leg growth). In the CAMP study³ the mean increase in height of the budesonide group was 1.1 cm less than the placebo group with a reduction in growth velocity during the first year of the study. Estimation of final adult height was comparable for all three treatment groups. Agertoft and Pedersen¹⁴ analysed the growth of the children in their study after a mean duration of 9.2 years and also found transient growth suppression in the first year of the study, but this was not significant after 2 years of treatment and the final adult height of their subjects was 0.3 cm greater than expected.

The CAMP study³ found no difference in bone density or body growth and development in children on budesonide when compared with nedocromil or placebo.

CONCLUSION

ICS are highly effective in the control of persistent asthma. Small doses of ICS pose no significant risk for systemic side-effects, but the therapeutic to systemic effect should be reassessed if they are used at higher doses for prolonged periods. HPA axis suppression is rare, but idiosyncratic responses may occur even at conventional doses of ICS. Growth suppression is detectable if ICS with poor first-pass inactivation are used at doses exceeding 400 µg/day, but ICS alone have no effect on final adult height and remain much safer than oral steroids.

Strategies for the use of ICS in children include:

- Start at the appropriate age in children who have persistent symptoms
- Start with an appropriate (rather than high) dose
- Step down to the lowest dose which controls the symptoms once asthma control has been achieved
- Step down to a once-daily dose, preferably administered in the morning

- Choose an appropriate delivery system
- Utilise the most cost-effective therapy
- Limit steroid therapy for co-morbid conditions
- Monitor the growth of the children
- Utilise low-to-medium-dose ICS and supplement with non-steroid controllers such as leukotriene receptor antagonists, long acting β_2 -agonists, or theophylline where appropriate.

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