Primary Care Respiratory Journal (2007); **16**(3): 149-154

Primary Care RESPIRATORY JOURNAL
www.thepcrj.org

REVIEW

The properties of inhaled corticosteroids: similarities and differences

***Neil C Barnes**

Professor of Respiratory Medicine, Barts and The London NHS Trust School of Medicine and Dentistry, London, UK

Received 16th April 2007; accepted 18th April 2007

Summary

Inhaled corticosteroids remain the most important therapy for chronic asthma in both adults and children. As all inhaled corticosteroids act by binding to a common glucocorticoid receptor there is little evidence of any real difference in clinical efficacy between the different inhaled corticosteroids. The main potential differences are in their propensity to cause side effects. Local side effects such as a hoarse voice do occur in a proportion of adults and there is some limited evidence that ciclesonide may cause less local side effects. In adults there is little evidence for clinically important systemic side effects from doses of inhaled steroids below 800 mcg/day (beclomethasone equivalent). Above this dose a proportion of patients may show some adrenocortical suppression, though it is unlikely to be of clinical importance. Data on bone mineral density and fracture rates is discrepant, but an overview would suggest that below 800 mcg/day there is no increase in fracture risk whereas above this dose there might be an increased fracture risk. The properties of ciclesonide would suggest that it has less propensity for systemic side effects, but large long-term studies are needed to confirm this. In children using inhaled steroids at above-licensed doses reductions in short-term growth can occur, but there is little evidence for reductions in long-term growth at normal doses. At above-licensed doses, biochemical adrenocortical suppression can occur with some unusual but documented cases of clinical Addisonian crisis. Limited evidence in paediatric age groups would suggest that ciclesonide may have some advantage although it is not as yet licensed in all countries for paediatric use. Data on differences in side effects between normal and asthmatic patients, and between asthmatic patients with near-normal lung function compared to those with impaired lung function, indicate that inhaled corticosteroids (particularly fluticasone) are absorbed more in those with normal lung function; this strongly supports stepping down the inhaled steroid dose when asthma is controlled – as is recommended in asthma guidelines.

NC Barnes. *Prim Care Resp J* 2007; **16**(3): 149-154.
doi:10.3132/pcrj.2007.00038

Keywords inhaled corticosteroids, efficacy, properties, side effects, comparison

Contents

Introduction

In adults and children inhaled corticosteroids are the most important treatment for chronic asthma. This is because their clinical effects are essential in achieving the goals of asthma management as set out in national and international guidelines: eliminating or reducing chronic symptoms of asthma; preventing exacerbations; maximising lung function; reducing the need for rescue beta$_2$-agonist treatment; enabling normal activity including

*** Corresponding author:** The London Chest Hospital, Bonner Road, London, E2 9JX, UK
Tel: +44 (0)20 8983 2406 Fax: +44 (0)20 8983 2279 E-mail: neil.barnes@bartsandthelondon.nhs.uk

exercise; and doing so in a safe manner.[1,2] These attributes have been demonstrated in numerous well conducted controlled clinical trials. In addition, there is evidence from a limited number of clinical trials and a huge number of database studies that inhaled corticosteroids reduce hospitalisations due to asthma.[3] Database and ecological studies strongly indicate that inhaled corticosteroids markedly reduce the asthma death rate.[4] In this regard they are the only treatment for chronic asthma which has been shown to reduce asthma deaths.

There are five inhaled steroids currently available in the UK: beclomethasone dipropionate (BDP), budesonide (Bud), fluticasone dipropionate (FP), mometasone furoate (MF) and ciclesonide (CIC). A sixth inhaled steroid, triamcinolone acetate (TAA), is available in the USA and a number of other countries but is not available in the UK. Triamcinolone is less potent than the other inhaled corticosteroids and is less specific for the glucocorticoid receptor: it will not be considered further in this review.

Mode of action of inhaled steroids

All inhaled steroids work by binding to a common glucocorticoid receptor – so the basic pharmacology and clinical studies would indicate that the same clinical effect can be achieved with all inhaled steroids though not at the same microgramme dose; i.e. if given at a high enough dose, all inhaled corticosteroids can potentially achieve the same clinical activity. In addition, the equitherapeutic dose of different inhaled steroids varies depending on the delivery device used. However, at doses of inhaled steroids with equal clinical effect there are differences in their side effect profiles, the importance of which is a subject of considerable controversy. Therefore, the main variation between the different inhaled steroids is in their side effect profiles at clinically equivalent doses.

Relative potency of the different inhaled steroids

The relative potency of different inhaled corticosteroids has been the subject of considerable dispute and debate. This is due to a number of factors. Firstly, doing robust studies which can accurately determine relative potencies in clinical trials is fraught with difficulties – frequently, claims are made about relative potency based on inadequate study design. Secondly, efficacy is affected by the delivery device, which brings another level of complication. Thirdly, whereas fluticasone, budesonide and mometasone are active drugs in their own right, BDP and ciclesonide are pro-drugs. BDP has relatively poor activity and is metabolised to 17-beclomethasone monoproprionate (17-BMP) which is the main active constituent. Ciclesonide again has low activity and is metabolised into its active constituent des-ciclesonide.[5] Although *in vitro* potency is often a poor guide to *in vivo* effects, this is not the case with inhaled corticosteroids; broadly speaking the drug's activity at the glucocorticoid receptor *in vitro* is predictive of the *in vivo* potency. Using different methodologies the Pharmacology Section of the UK BTS/SIGN Asthma Guidelines group and the Cochrane collaboration have tried to determine the relative microgramme potency of commonly used inhaled steroids.[2,6] Using these different methodologies they came to the conclusion that BDP and budesonide were approximately equiactive, whereas fluticasone is equally active at half the microgramme dose. Equiactive doses for the newer inhaled steroids are more difficult to determine. Available evidence would suggest that mometasone is approximately equipotent to FP and that ciclesonide falls somewhere between the potency of BDP and fluticasone.[5] A further complication is the introduction of CFC-free inhalers – see below.

Local side effects of inhaled corticosteroids

The main local side effects of inhaled corticosteroids are oral candidiasis, cough at the time of inhalation, hoarse voice and dysphonia. Cough is a local irritant effect and can usually be overcome by a change in the delivery device; when using a metered dose inhaler (MDI) the addition of a large volume spacer reduces cough. Oral candidiasis is dose-related; it is not frequently a major problem and can usually be prevented by gargling, washing and spitting out after taking the inhaler. In some cases, local antifungal treatment may be needed. There are some individuals who are exquisitely sensitive to even small doses of inhaled steroids and get oral thrush despite all preventative measures.

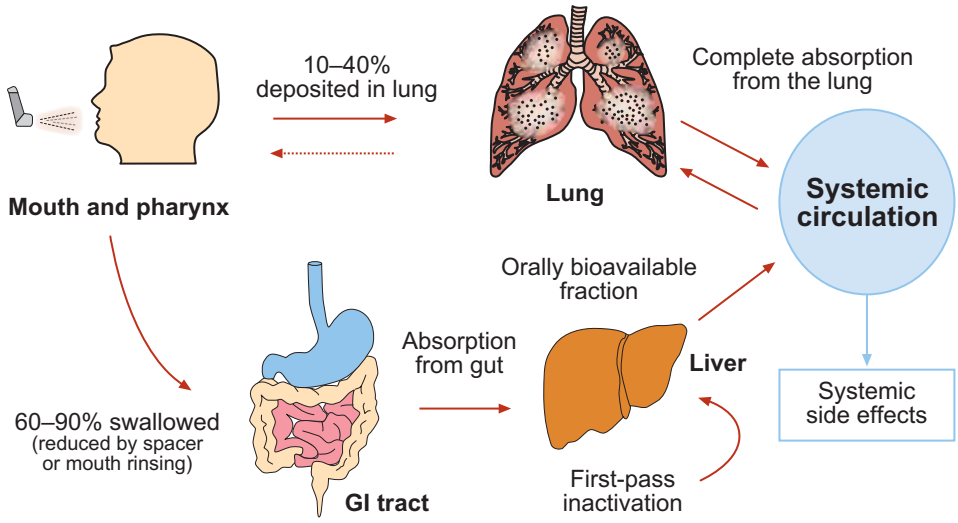
The most difficult local side effect to manage is hoarse voice and dysphonia. This is caused by the inhaled steroid being deposited on the vocal cord and causing a myopathy of the arytenoid muscles. Since all inhaled steroids have to cross the vocal cords to be active this is the most difficult side effect to overcome and it is not helped by gargling and spitting out after inhaler use. It tends to be worse with the dry powder inhalers than MDIs (where the effect can be decreased by using a large volume spacer). Dysphonia and hoarse voice are dose-related, and are not usually a problem at low doses except in those who use their voice professionally such as actors or singers. At higher doses dysphonia can be troublesome for any individual. There is some evidence that ciclesonide has less propensity for causing upper airways problems.[7] This is thought to be due to ciclesonide being a pro-drug; the esters which convert ciclesonide into the active moiety des-ciclesonide are not present in high enough concentrations in the upper airways to cause enough conversion to cause myopathy.

Systemic effects of inhaled corticosteroids

The systemic effects of inhaled corticosteroids are caused by their absorption into the systemic circulation. The fate of inhaled steroids in the body is shown in Figure 1.

When a steroid is inhaled a proportion of the drug is deposited in the mouth and swallowed; it may then be absorbed in the gastrointestinal tract where it is subject to first-past metabolism in

Figure 1. The fate of inhaled corticosteroids.



the liver. Fluticasone, ciclesonide and mometasone are subject to almost complete first-pass metabolism, whereas only approximately 85% of BDP undergoes first-pass metabolism. Therefore, for fluticasone, mometasone and ciclesonide the gut-absorbed drug can cause very little systemic activity, and even for BDP the systemic activity due to gut absorption is low.

Inhaled steroid deposited in the lung is the main source for systemic absorption. The more drug deposited in the lung the more the clinical activity increases but also the more the systemic absorption increases. The main site of absorption of inhaled corticosteroids is from the alveoli and therefore smaller particles which tend to penetrate better into the alveoli are more likely to be absorbed and cause systemic side effects. Impaired lung function also has an effect on absorption of inhaled corticosteroids. A number of studies have shown – particularly for fluticasone propionate – that absorption is higher in normal individuals than in asthmatics with airflow obstruction.[8-10] Further studies have shown that when asthmatic patients with airflow obstruction improve, their absorption of fluticasone increases. This is probably because in the obstructed asthmatic airway the drug impacts in the bronchi where there is little absorption, whereas in normal individuals or asthmatics with only minor airflow obstruction more drug reaches the alveoli and is absorbed. This effect – of differential absorption between normal subjects and asthmatic patients – is less marked for budesonide and ciclesonide.[9-11] The demonstration that absorption of inhaled corticosteroids is greater in individuals with normal lung function is a strong argument for stepping down the dosage once asthma is controlled, particularly if lung function is normal or near normal.

The potential or actual side effects of inhaled steroids are listed in Table 1. The side effect which has been most widely studied (as it is readily amenable to testing) is adrenocortical suppression. Adrenocortical suppression is dose-related though there do seem to be certain individuals, both among adults and children, who are particularly sensitive to the adrenocortical suppressive effect of steroids. In adults biochemical adrenocortical suppression only seems to occur at doses of inhaled steroids above 800 mcg/day (BDP equivalent). There are very few case reports of clinically important adrenocortical suppression occurring in adults.[12] In children there are fewer controlled studies of the adrenocortical suppressive effects of inhaled steroids but there are case series' indicating that clinically important adrenocortical suppression may occur at doses of inhaled corticosteroids above the licensed dose.[12,13] Fluticasone is the commonest inhaled corticosteroid

Table 1. Potential systemic side effects of the inhaled corticosteroids.

Adrenocortical suppression
Increased osteoporosis and bone fractures
Skin thinning and purpura
Weight gain
Cataracts
Glaucoma
Diabetes mellitus
Increased pulmonary infections
Growth retardation in children

reported to show adrenocortical suppression in children in these case series', but this may be because of preferential prescribing of the drug at higher doses to those with more difficult asthma. There is some evidence that ciclesonide may have less adrenocortical suppressive activity than conventional inhaled corticosteroids.[14]

Easy bruising has been shown to be a side effect of inhaled corticosteroids. The best controlled study demonstrating this was the EUROSCOP Study in COPD patients which showed a higher rate of bruising in those treated with budesonide 800 mcg/day than those treated with placebo.[15] The relative propensity for different inhaled corticosteroids to cause bruising has not been formally studied.

In adults one of the main concerns with inhaled corticosteroids is their potential for decreasing bone mineral density and causing osteoporosis. A number of studies have shown the effects of inhaled corticosteroids on markers of bone metabolism but the relevance of these markers to the risk of reduced bone mineral densisty or osteporosis is unclear. Using triamcinolone at 1200 mcg/day over a three-year period in the Lung Health 2 study there was a statistically significant reduction in bone mineral density at the neck of the femur over a three-year period.[16,17] This study demonstrates that inhaled corticosteroids may cause reductions in bone mineral density, but the extrapolation of results with triamcinolone to other inhaled steroids is inappropriate since triamcinolone has greater systemic bioavailability. A Cochrane review of controlled trials on the effect of inhaled corticosteroids on bone mineral density and fracture rate showed no effect, but the studies were probably too short-term to give a definitive answer.[18] The best controlled trial data comes from two studies in COPD: in the EUROSCOP study budesonide 800 mcg/day over a three-year period showed no detrimental effect on bone mineral density – indeed, at the femoral trochanter there was an increase in bone mineral density in the budesonide-treated group compared with placebo;[16] and in the recently published TORCH study, measurement of bone mineral density was performed in a subset of patients and showed that there was no difference in bone mineral density in the group treated with fluticasone 1000 mcg/day compared with placebo.[19] Furthermore, the TORCH study showed no increase in fracture rate over the three years of the study. Database studies have produced conflicting results. Wong *et al*, in a cross sectional study of bone mineral density, reported an increased fracture rate risk related to the cumulative dose of inhaled corticosteroids.[20] However, such cross sectional studies are difficult to control for prescription of systemic steroids which are known to cause reduced bone mineral density. Database studies of fracture risk have produced conflicting results. Hubbard *et al*, using a primary care database in the UK, reported a dose-dependent increase in fractures with daily doses of inhaled corticosteroids of above 600 mcg/day leading to a 2.5-fold increase in fractures.[21] In contrast, Suissa *et al*, using a large database in Quebec, showed an increase in hip fractures only in those patients on >2000 mcg/day BDP equivalent and, slightly oddly, an increased risk of upper limb fractures of 12% for every 1000 mcg/day BDP equivalent.[22] In all of these studies, controlling for confounding variables such as previous courses of oral steroids, smoking, and differences in exercise (which can all influence bone mineral density) is difficult. Overall, the evidence would suggest that at doses under 800-1000 mcg/day of BDP equivalence there is no increased risk of reduction in bone mineral density or fracture risk, and above 1000 mcg/day it is possible that an increased risk occurs.

Data on cataracts are again discordant. A prospective study of 95 patients aged 5-25 years on a median dose of BDP or budesonide of 750 mcg/day over a five-year period showed no occurrence of posterior subcapsular cataracts.[23] In contrast a database study reported by Cummings *et al* showed the relative risk of cataracts was increased by inhaled corticosteroids.[24] The TORCH study, in a very limited subset of patients, showed no increase in cataract risk.[19] Overall the data on cataracts is too limited to determine if there is an increased risk or not and there is no data to indicate that there are differences between different inhaled corticosteroids.

With regard to other potential side effects such as weight gain, hypertension and diabetes, there is really little evidence for this in adults and no evidence of differences between different inhaled corticosteroids. With regard to infection risk, there is no evidence in asthmatic individuals of an increased risk of infection; however, somewhat surprisingly, in the TORCH study there was an increase in physician-reported pneumonia.[19] This may be because there is chronic bronchial sepsis in 30-40% of COPD patients. There is again no evidence of differences between different inhaled corticosteroids. Small observational studies show no evidence of an increased risk of reactivation of tuberculosis, and again there is no evidence of a difference between different inhaled corticosteroids.[25]

The major concern in paediatric practice is the potential for inhaled corticosteroids to cause growth suppression. Short term studies using knemometry, a technique which very accurately measures the growth of the lower leg, has shown effects with FP above 200 mcg/day and budesonide above 400 mcg/day.[26] Longer term studies of the effects of inhaled corticosteroids on growth are complicated by the fact that asthma itself can decrease growth, particularly if it is poorly controlled.[27] In longer term studies over several years, a small effect on growth is seen in the first year with the effect diminishing over time. In the CAMP study, budesonide 200 mcg/day over a 4-6 year time period caused a 1.1 cm decrease in growth compared to placebo; however, this group of children had very mild asthma.[28] In the START study, budesonide 200 mcg/day over a three-year period caused a 1.34 cm decrease in growth in the first year but this diminished to only 0.33 cm by the third year.[29] Sorkness *et al* showed no effect of fluticasone 200 mcg/day on growth.[30] Ferguson *et al* compared fluticasone 200 mcg/day with budesonide 400 mcg/day; they showed equivalent

asthma control but growth was 0.9 cm per year less with budesonide than with fluticasone.[31] The data would suggest that budesonide and BDP cause growth suppression at doses above 400 mcg/day and fluticasone above 200 mcg/day. Data on ciclesonide is limited but at a dose of 160 mcg/day no effect on cortisol was seen in a paediatric study.[32] The basic pharmacology of ciclesonide would suggest that it may have less growth suppressant effect, but this needs to be confirmed in larger long-term studies and at higher doses.

CFC-free inhalers

Chlorofluorocarbon (CFC) propellant inhalers may have different particle size characteristics to CFC-free inhalers. This does not seem to be a problem with fluticasone, where the CFC and hydrofluoroalkane (HFA) preparations have similar efficacy and side effects. However, for BDP, one CFC-free preparation has a smaller particle size, thereby increasing the deposition of the drug in the lung and the propensity for absorption from the alveoli, and at the same microgramme doses there is evidence of an increase in systemic side effects.[33] Although there is a theoretical argument that deposition of particles in smaller airways may be beneficial there is little hard clinical evidence to support this notion.

Conclusion

Inhaled corticosteroids are the most important treatment for asthma. There is little evidence for any difference in clinical efficacy between the different inhaled steroids. The main potential difference between inhaled steroids is in their propensity to cause local and systemic side effects. There is some limited evidence that ciclesonide may cause less local side effects. In adults, there is little evidence for any systemic side effects at doses below 800mcg/day BDP equivalent. In children, there is little evidence for reduction in long-term growth at normal licensed doses. The properties of ciclesonide would suggest that it has less propensity for systemic side effects, but large long-term studies are needed to confirm this.

Conflict of interest declaration

The author has lectured for or received consulting fees from GlaxoSmithKline, AstraZeneca, Altana, Merck, Generics and TEVA. He has received research funding from GlaxoSmithKline and AstraZeneca which has gone into departmental funds. Neither he nor his family own shares in any pharmaceutical company.

References

1. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline for management of asthma. *Thorax* 2003;**58**(suppl 1):1-94.
2. Global Initiative for Asthma (GINA). Global Strategy for Asthma management and Prevention: NHLBI/WHO Workshop Report. Bethesda: National Institutes of Health, National Heart, Lung and Blood Institute, 2002. Publication no. 02-3659.
3. Suissa S, Ernst P, Kezouh A. Regular use of inhaled coritcosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002;**57**:880-4.
4. Ernst P, Spritzer WD, Suissa S *et al.* Risk of fatal and near fatal asthma in relation to inhaled corticosteroid use. *JAMA* 1992;**268**:3462-4.
5. Belvisi MG, Bundschuh DS, Stoeck M, *et al*. Preclinical profile of ciclesonide, a novel corticosteroid for the treatment of asthma. *J Pharmacol Exp Ther* 2005; **314**:568-74.
6. Adams N, Bestall JM, Lasserson TJ, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. The Cochrane Library (ISSN 1464-780X).
7. Kalliner MA. Pharmacological characteristics and adrenal suppression with newer inhaled corticosteroids: A comparison of ciclesonide and fluticasone propionate. *Clin Ther* 2006;**28**:319-31.
8. Brutsche MH, Brutsche IC, Munawar M *et al*. A Comparison of pharmacokinetics and systemic effects of inhaled fluticasone a propionate in patients with asthma and healthy volunteers: a randomised crossover study. *Lancet* 2000;**356**:556-61.
9. Harrison TW, Wisniewski A, Honour J, Tattersfield AE. Comparison of the systemic effects of fluticasone propionate and budesonide given by dry powder inhaler in healthy and asthmatic subjects. *Thorax* 2001;**56**:186-91.
10. Harrison TW, Tattersfield AE. Plasma concentration of fluticasone propionate and budesonide following inhalation from dry powder inhalers by healthy and asthmatic subjects. *Thorax* 2003;**58**:258-60.
11. Nave R, Gunawardena KA, Zech K, Bethke TD. Pharmacokinetic disposition of inhaled ciclesonide and its metabolite desisobutyryl-ciclesonide in healthy subjects and patients with asthma are similar. *Int J Clin Pharmacol Ther* 2006;**44**:1-7.
12. Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002;**87**:457-61.
13. Mortimer KJ, Tata LJ, Smith CJ *et al*. Oral and inhaled corticosteroids and adrenal insufficiency: a case-control study. *Thorax* 2006;**61**:405-08.
14. Weinbrenner A, Huneke D, Zschiesche M *et al*. Circadian rhythm of serum cortisol after repeated inhalation of the new topical steroid ciclesonide. *J Clin Endocrinol Metab* 2002;**87**:2160-3.
15. Pauwels RA, Lofdahl CG, Laitinen LA *et al*. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med* 1999;**340**:1948-53.
16. Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;**343**:1902-09.
17. Scanlon, PD. Connett JE, Wise RA *et al* and the Lung Health Research Group. Loss of Bone Density with inhaled Triamcinolone in Lung Health Study II. *Am J Respir Crit Care Med* 2004;**170**:1302-09.
18. Jones A, Fay JK, Burr M, Stone M, Hood K, Roberts G. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. The Cochrane Library (ISSN 1464-780X).
19. Calverley PM, Anderson JA, Celli B *et al*; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;**356**:775-89.
20. Wong CA, Walsh LJ, Smith CJ *et al*. Inhaled corticosteroids use and bone-mineral density in patients with asthma. *Lancet* 2000;**355**:1399-403.
21. Hubbard R, Tattersfield A, Smith C, West J, Smeeth L, Fletcher A. Use of inhaled corticosteroids and the risk of bone fracture. *Chest* 2006;**130**:1082-8.
22. Suissa S, Baltzan M, Kremer R, Ernst P. Inhaled and nasal corticosteroid use and the risk of fracture. *Am J Respir Crit Care Med* 2004;**169**:83-6.
23. Simons FER, Persuad MP, Gillespie CA, Cheang M, Shuckett EP. Absence of posterior subcapsular cataracts in young patients treated with inhaled glucorticosteroids. *Lancet* 1993;**342**:776-8.
24. Cumming RG, Mitchell P, Leeder SR. Use of Inhaled Corticosteroids and the Risk of Cataracts. *N Engl J Med* 1997;**337**:8-14.
25. Bahceclier NN, Nuhoglu Y, Nursoy MA, Kodalli N, Barlan IB, Basaran MM. Inhaled corticosteroid therapy is safe in tuberculin-positive asthmatic children. *Pediatr Infect Dis J* 2000;**19**:215-18.
26. Agertoft L, Pederson S. Short-term knemometry and urine cortisol excretion in

children treated with fluticasone propionate and budesonide: a close-response study. *Eur Resp J* 1997;**10**:1507-12.
27. Balfour-Lynn L. Growth and childhood asthma. *Arch Dis Child* 1986;**61**:1049-55.
28. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;**343**:1054-63.
29. Pauwels RA, Pedersen S, Busse WW *et al*, START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;**361**:1071-6.
30. Sorkness CA, Lemanske RF Jr, Mauger DT, *et al*; The Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. *J Allergy Clin Immunol* 2007;**119**:64-72.
31. Ferguson AC, Van Bever HO, Teper AM, Lasytsya O, Goldfrad CH, Whitehead PJ. A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma. *Respir Med* 2007;**101**:118-29.
32. Pedersen S, Garcia-Garcia ML, Manjra A, Theron I, Engelstatter R. A comparative study of inhaled ciclesonide 160 microg/day and fluticasone propionate 176 microg/day in children with asthma. *Pediatr Pulmonol* 2006;**41**:954-61.
33. Lipworth BJ, Jackson CM. Pharmacokinetics of Chlorofluorocarbon and hydrofluoroalkane metered-dose inhaler formulations of beclamethasone dipropionate. *Br J Clin Pharmacol* 1999;**48**:866-8.