RESPIRATORY MEDICINE (1998) 92 (SUPPLEMENT B), 15–23

RESPIRATORY MEDICINE

Effect of inhaled beclomethasone dipropionate and budesonide on adrenal function, skin changes and cataract formation

R. G. DLUHY

Endocrinology–Hypertension Division, Brigham & Womens Hospital, Boston, MA, U.S.A.

Introduction

Adrenocortical suppression as a consequence of corticosteroid therapy is a well-known and serious systemic adverse effect. Although the risk of adrenocortical suppression during the treatment of asthma is greatly decreased by administering corticosteroids via the inhaled compared with the oral route, some concern remains regarding the inhalation of high dosages. Other adverse effects that have been linked with corticosteroid use include skin changes (thinning, bruising) and cataract formation. Adverse effects in children are of particular importance because of the possibility that the individual will require many years of long-term treatment. This article will summarise the available literature regarding the potential for inhaled budesonide and beclomethasone dipropionate (BDP) to cause adrenal suppression, skin changes and cataracts.

Adrenocortical Suppression

Several tests are available to assess adrenocortical function. In studies of patients receiving inhaled steroids, morning plasma cortisol levels, 24 h urinary free cortisol levels and/or a short tetracosactrin test (plasma cortisol measured 30 min following an intramuscular injection of tetracosactrin 250 μg) have been used most commonly.

EXPERIENCE IN ADULTS

Standard dosage

The standard dosage for inhaled BDP and budesonide is considered to be between 200 and 800 μg daily. Three randomised, cross-over, comparative studies, each including ≤30 asthmatic patients, measured the impact of BDP and budesonide, both administered at 400 μg daily, on adrenal function (1–3). In one of the studies, morning plasma cortisol levels were slightly lower after the 2 week treatment period for each drug (1). In another, there was no effect of either inhaled corticosteroid on basal cortisol levels (2), and in the remaining study, more increases than decreases in basal cortisol levels were found following treatment (3). In two of these studies a tetracosactrin test was performed, and no significant effect was seen with either drug on the tetracosactrin-stimulated cortisol response (1–3). Thus, conventional dosages of inhaled BDP and budesonide do not appear to blunt adrenal function.

High dosage

The results of studies comparing high dosages of inhaled budesonide and BDP in adult volunteers and asthma patients are provided in Table 1 (4–11). Most studies reported evidence of adrenal suppression as indicated by one or more variables.

Normal volunteers

Johansson *et al.* (4) examined the effects of large single evening doses of both oral and inhaled budesonide and BDP in a cross-over study. Eight volunteers received oral BDP and budesonide 2, 4 and 8 mg. Twelve volunteers received, by inhalation, BDP 200, 800 and 3250 μg and budesonide 200, 800 and 3200 μg. BDP produced a larger reduction in plasma cortisol levels, measured the following day at 8 a.m., 10 a.m. and 12 noon, than budesonide. However, there are some possible drawbacks with this study. Although cortisol levels show great variability and have a wide normal range, the investigators reported no absolute values for cortisol or any indication of whether the values were outside the normal range. Significance calculations were based on the area under the plasma cortisol–time

Correspondence should be addressed to: R. G. Dluhy, Endocrinology–Hypertension Division, Brigham & Womens Hospital, 221 Longwood Avenue, Boston, MA 02115, U.S.A.

This supplement was sponsored by Glaxo Wellcome plc.

0954-6111/98/92B015+09 $12.00/0

TABLE 1. Results of studies comparing the effects of high dosages of inhaled budesonide and beclomethasone dipropionate in normal adult volunteers and adult asthma patients

Reference	No. of subjects	Study design	Duration of therapy	Budesonide total daily dosage (frequency)	BDP total daily dosage (frequency)	Assessment criteria	Overall results[a]
Normal volunteers							
Johansson *et al.* (4)	12	r,db,co,pc	1 dose	200 μg (o.d.)	200 μg (o.d.)	Cortisol 8 a.m., 10 a.m., 12 noon	Significant difference at highest dose, BDP > BUD
				800 μg (o.d.)	800 μg (o.d.)		
				3200 μg (o.d.)	3250 μg (o.d.)		
Lofdahl *et al.* (5)	12	co	2 days	2400 μg (b.i.d.)	1500 μg (b.i.d.)	Morning cortisol	BDP > BUD
				4800 μg (b.i.d.)	3000 μg (b.i.d.)		
				7200 μg (b.i.d.)	4500 μg (b.i.d.)		
Brown *et al.* (6)	9	r,db,co	6 days	2000 μg (b.i.d.)[b]	2000 μg (b.i.d)[b]	Serum cortisol 24 h UFC	With spacer, BUD=BDP Without spacer, BDP > BUD at suppressing cortisol
Jennings *et al.* (7)	39	co	2 weeks	800 μg (b.i.d.)	800 μg (b.i.d.)	Morning cortisol; 24 h UFC; DHEAS	Dose effect BDP = BUD 24 h UFC and DHEAS; BDP > BUD morning cortisol
				2500 μg (b.i.d.)	2500 μg (b.i.d.)		

TABLE 1. Continued

Reference	No. of subjects	Study design	Duration of therapy	Budesonide total daily dosage (frequency)	BDP total daily dosage (frequency)	Assessment criteria	Overall results[a]
Asthma patients							
Brown *et al.* (8)	78	cs	Median 56 days	1200–2650 μg (mean 1600 μg)	1200–2650 μg (mean 1600 μg)	Morning cortisol; 24 h UFC; tetracosactrin test	HPA suppression in 15/69 BDP and 1/9 budesonide patients
Ebden *et al.* (9)	28	r,db,co	6 weeks	1600 μg (b.i.d.)[c]	1500 μg (b.i.d.)	Basal cortisol Tetracosactrin test	Significantly reduced; BUD = BDP No effect; BUD = BDP
Selroos and Halme (10)	24 17	co	2 weeks 2 weeks	1200 μg (b.i.d.) 1600 μg (b.i.d.)	1000 μg (b.i.d.)[b] 1000 μg (b.i.d.)[c]	Morning cortisol; 24 h UFC	Shows effects of spacer and mouth rinsing (BUD > BDP)
Svendsen *et al* (11)	36	db,co	6 weeks	1600 μg (b.i.d.)	1500 μg (b.i.d.)	Plasma cortisol Tetracosactrin test	No effect; BUD = BDP No effect; BUD = BDP

b.i.d., twice daily; co, cross-over; cs, cross-sectional; db, double blind; DHEAS, dehydroepiandrosterone sulphate; HPA, hypothalamic – pituitary – adrenal; o.d., once daily; pc, placebo controlled; r, randomised; UFC, urinary free cortisol.

[a]BUD = BDP denotes that there was no significant difference between the two treatments. BUD > BDP signifies that budesonide had significantly greater effect on assessment criteria than BDP.

[b]Administered with and without a spacer.

[c]Administered with a spacer.

curve, although the curve had only three points. Lofdahl *et al.* (5) gave 19 healthy volunteers BDP 2250 μg inhaled three times daily for 2 days. Of these 19 individuals, the 12 who had decreases in plasma cortisol of >50% were then entered in a cross-over study and received daily doses of BDP 1500, 3000 and 4500 μg and budesonide 2400, 4800 and 7200 μg daily for 2 days. After the lowest dosage of both corticosteroids, serum cortisol levels decreased significantly compared with pre-treatment values. The authors reported that the dose–response curves were parallel but that budesonide was less potent in suppressing serum cortisol than BDP. The validity of this comparative study in a population selected for sensitivity to adrenal suppression by BDP may be questionable. In an open, cross-over study, 39 healthy volunteers received 800 or 2500 μg of budesonide or BDP daily for 2 weeks followed by a 2-week wash-out period before crossing over to the other treatment (7). There was a significantly greater fall in plasma cortisol with BDP compared with budesonide, but there were no treatment differences in terms of effects on urinary cortisol or DHEAS. Both budesonide and BDP had a significant dose-related effect on plasma and urinary cortisol and DHEAS. A further study by this group confirmed that increasing inhaled dosages of budesonide between 800 and 3200 μg daily in volunteers caused dose-related decreases in plasma cortisol and adrenal cortical androgen levels (12) (data are not shown in Table 1 because the study was not comparative).

Brown *et al.* (6) conducted a randomised, double-dummy, cross-over study in nine healthy adults. BDP or budesonide 1000 μg twice daily was administered, via a metered dose inhaler (MDI) with or without a spacer device, for 6 days and serum cortisol and 24 h urinary free cortisol levels were measured. When a spacer device was not used, the systemic effects observed with BDP (i.e. reductions in serum cortisol and 24 h urinary free cortisol levels) were greater than with budesonide; however, the use of an MDI with spacer device resulted in no difference for the two drugs in the reductions in serum cortisol and 24 h urinary free cortisol levels. The magnitudes of the changes in serum and urinary cortisol were small with both agents (with and without spacer), and the resulting levels remained within the normal range.

Asthma patients

Brown *et al.* (8) carried out a cross-sectional study in patients with asthma taking 1200–2650 μg (mean 1600 μg) daily of an inhaled steroid (BDP, $n = 69$; budesonide, $n = 9$). Basal morning plasma cortisol and 24 h urinary free cortisol levels were measured, and a short (60 min) tetracosactrin test was performed. If two of these three tests were below the normal range, the HPA axis was considered to be suppressed. On this basis, 16 patients had adrenal suppression (15/69 BDP; 1/9 budesonide). There was no clear relationship between adrenal function and the dosage of inhaled steroid. A later report by this group of investigators rated the relative merits of these three screening tests for adrenal suppression (13). The conclusion was that the short tetracosactrin test and measurement of 24 h urinary free cortisol were equally useful but that morning plasma cortisol was a less sensitive screening method.

In a double-blind, double-dummy, cross-over study in 36 asthma patients, neither budesonide 800 μg twice daily nor BDP 750 μg twice daily for 6 weeks had a significant effect on plasma cortisol levels or response to the short tetracosactrin test (11). Similarly, an earlier randomised, double-blind, cross-over study comparing 6-week treatment periods of budesonide 1600 μg daily via a spacer and BDP 1500 μg daily in 28 patients found no effect of either treatment on the short tetracosactrin test (9). However, in this study the mean basal cortisol levels were significantly lower after both treatments (budesonide $P < 0{\cdot}01$; BDP $P < 0{\cdot}05$), but there was no significant between-group difference in this parameter after 6 weeks of treatment.

Selroos and Halme (10) studied the effects of spacer devices and mouth rinsing on the systemic absorption of budesonide and BDP. Three cross-over studies, each involving a 2-week treatment period, were conducted, with morning serum cortisol and 24 h urinary free cortisol being measured at the end of each period. Study 1 examined 24 patients already taking BDP 500 μg twice daily (ten using a spacer device) who were switched to budesonide dry powder inhaler 600 μg twice daily without mouth rinsing. The results showed no significant change in serum or urinary cortisol levels for the patients switching from BDP without a spacer. However, a significant drop in levels of both parameters was observed in patients switching from BDP with a spacer to budesonide dry powder formulation. A second study, in ten patients taking budesonide 800 μg with and without swallowing the mouth-rinsing water, showed significantly higher serum cortisol levels in patients who mouth rinsed but did not swallow. In a third study 17 patients took budesonide 800 μg via a dry powder inhaler and BDP 500 μg via a spacer, both twice daily without mouth rinsing. No significant differences were detected in serum cortisol levels with either treatment. As expected, mouth rinsing with swallowing increased the systemic exposure to inhaled steroids but the design of this study made it impossible to differentiate the effects of the two drugs on adrenal function from the effects of the method of administration.

Roy *et al.* (14) found that 14 of 100 patients receiving inhaled budesonide or BDP (800–2000 μg daily for ≥3 months) had one or more abnormally low results for baseline cortisol, 24 h urinary free cortisol or response to the tetracosactrin test. Those who had more than one abnormal result were more likely to be receiving ≥1500 μg inhaled steroid daily. The study did not compare the incidence of abnormal results between budesonide and BDP. In a study in asthma patients who reported easy bruising after receiving inhaled steroids, Melchor *et al.* (15) found that of 32 patients receiving a mean dose of 1590 μg day^{-1} only two had evidence of adrenal suppression.

EXPERIENCE IN CHILDREN

Short-term studies (weeks–months)

Low to medium dosage

The results of comparative short-term studies of the effect of standard dosages (≤400 μg daily) of inhaled BDP and budesonide on adrenal function in children have been conflicting. In a randomised, double-blind, cross-over study in 21 children, Baran (16) found no abnormal morning plasma cortisol levels following 3 weeks of treatment with either budesonide 100 μg twice daily or BDP 100 μg twice daily. Similarly, two randomised, double-blind, cross-over studies comparing budesonide 400 μg daily and BDP 400 μg daily for 4 weeks reported no effect of either agent on adrenal function as measured by the tetracosactrin test (17) or by 24 h urinary cortisol metabolites (18). However, in the study of Springer *et al.* (18) a subnormal decrease in 11-deoxycortisol was detected after metyrapone challenge in 2/10 children while receiving budesonide and in 4/10 children while receiving BDP; cortisol responses were variable and adrenocorticotrophic hormone concentrations increased in most patients (18). In a randomised, cross-over study, 12 children received budesonide and BDP 400 μg daily, each for 2 weeks (19). Both budesonide and BDP significantly suppressed nocturnal cortisol levels, with the degree of suppression being greater after 4 weeks than after 2 weeks of treatment, regardless of sequence of treatment administration. In none of these short-term studies was a significant difference in plasma cortisol and in 24 h urinary cortisol detected between the two drugs.

High dosage

Dosages of inhaled BDP and budesonide >400 μg daily in children have been associated with adrenal suppression (20). This is supported by evidence from Bisgaard *et al.* (21), who compared budesonide and BDP in children with asthma in a randomised, double-blind, parallel-group study. Children received daily dosages of 200, 400 and 800 μg of either BDP (n = 30) or budesonide (n = 10) for three consecutive 4-week periods. Measurement of 24 h urinary free cortisol levels revealed significant dose-related decreases in the BDP and budesonide groups, with no significant treatment-related difference. There were no significant dose- or treatment-related effects for either BDP or budesonide according to the tetracosactrin test of adrenal function. Similarly, Prahl (22) conducted a study comparing BDP and budesonide (500–1800 μg daily) for 6-week periods in 16 children with asthma and 27 healthy, age- and sex-matched children as controls. Eleven of the treated children demonstrated no difference in 24 h urinary free cortisol with either treatment, three individuals had a reproducible decrease with BDP and two showed a reproducible decrease with budesonide. There was no significant difference between the effects of the two drugs.

In contrast to this observation of no difference in effect on adrenal function between the two steroids, a randomised, cross-over study comparing budesonide with BDP (dosage range 800–1200 μg, mean 900 μg day^{-1}) in 31 children with asthma found that the reduction in 24 h urinary free cortisol was significantly greater during the 6-week treatment period with BDP compared with budesonide (23). Moreover, this difference was greater in children receiving >1000 μg daily. However, most of the 24 h urinary free cortisol values of children receiving BDP continued to remain within the normal range during treatment. Russel *et al.* (24) conducted a cross-sectional study in children who had been receiving daily dosages of ≤800 μg and 34 children (21 receiving budesonide; 13 receiving BDP) who had been receiving dosages >800 μg daily for >3 months. Adrenal function was assessed by short tetracosactrin tests. All children receiving ≤800 μg daily had normal basal and stimulated cortisol levels. Some children in the >800 μg daily group with both treatments had evidence of suppression of either basal or stimulated cortisol levels, and four children (two receiving BDP and two receiving budesonide) had values below the normal reference range for both variables.

Long-term studies (≥1 yr)

No long-term, comparative studies of the impact of inhaled BDP and budesonide on adrenal function in children have been published. However, Bhan *et al.* (25) assessed adrenal function in 28 children with asthma who had received inhaled BDP for at least 1 yr. Eighteen children had previously received prednisolone and had received BDP (mean 500 μg daily) for an average of 3·2 yr, and the remaining ten had not received prednisolone but had received BDP (mean 420 μg daily) for an average of 3·5 yr. These 28 children were compared with 15 children with asthma who

had been treated without use of oral or inhaled corticosteroids. Morning cortisol and 24 h urinary free cortisol levels were measured and short tetracosactrin tests were performed. No child showed evidence of adrenal suppression. Although mean morning cortisol and 24 h urinary free cortisol values were slightly lower in children receiving BDP, particularly those who had received prior treatment with prednisolone, none was considered to be clinically important. Varsano *et al.* (26) conducted an open study in 16 children with severe asthma who had received budesonide 200 μg daily via an MDI with a spacer for 1 yr. Adrenal function was assessed by measuring morning plasma cortisol after 1, 3, 6 and 12 months of treatment and by performing short tetracosactrin tests before the study commenced and after 6 and 12 months of treatment. All individual serum cortisol levels were within the normal range at all time points. Results of the short tetracosactrin test after 6 and 12 months of budesonide treatment were also normal.

Thus, these two long-term, non-comparative studies in children with asthma treated for ≥1 yr with BDP (mean 500 μg daily) or budesonide (200 μg daily) found no evidence of adrenal suppression with either drug.

Skin Changes

The use of systemic corticosteroids has been implicated in dermal atrophy, fragility and striae. There is also some suggestion that high doses of inhaled corticosteroids can also cause skin changes. In a cross-sectional study of 68 patients with moderate to severe asthma, Capewell *et al.* (27) measured skin thickness by ultrasound and clinically assessed purpura. Patients had been receiving steroids for up to 30 yr and were divided into four groups: those on oral steroids, those on high-dose inhaled steroids (BDP 1000–2250 μg daily), those on low-dose inhaled steroids (BDP 200–800 μg daily) and controls (who received no steroids). Skin thickness was significantly decreased in the oral and the high-dose inhaled steroid groups compared with controls; there was no difference in thickness between the low-dose inhaled steroid group and the control group. The same pattern of results was reported for purpura. Because patients receiving high-dose inhaled steroids had also had a prior exposure to oral steroids (median lifetime prednisolone dose of 200 mg), the authors speculated that the skin changes in this group could reflect a synergistic effect of previous courses of prednisolone.

Using a questionnaire, Mak *et al.* (28) found that asthma patients taking inhaled steroids (n = 202) had more than twice the relative risk of easy bruising compared with a group of patients of similar age and sex distribution who were not using inhaled steroids (n = 204). The prevalence of easy bruising appeared to be related to increased age, dosage and duration of treatment. The two groups were well matched for courses of oral corticosteroids taken during the previous year but there was no information on the number of oral steroid courses before that time. These researchers subsequently conducted a prospective, open study in asthma patients who had reported easy bruising after beginning inhaled steroids (mean dose 1590 μg day^{-1}) and found that platelet count and bleeding times were within the normal ranges (15).

In agreement with this, in a study of 200 asthma patients receiving high-dose inhaled steroids, Roy *et al.* (14) found that twice as many of those receiving high-dose inhaled steroids reported skin bruising compared with non-asthmatic controls matched for age and sex (71% *vs.* 32% according to questionnaire). There was no difference in the incidence of bruising between patients receiving BDP and those receiving budesonide (21/73 and 8/27, respectively) but the numbers of these patients were too small to allow a meaningful comparison. Only 14 patients receiving inhaled steroids had one or more test results suggestive of impairment of adrenal function. Urinary cortisol levels, but not blood cortisol levels, were significantly higher in patients who did not report skin bruising. In addition, older patients (52 years of age) receiving inhaled steroids were more likely to report skin bruising than elderly patients (61 years of age) not receiving inhaled steroids. Unlike the study by Mak *et al.* (26), a dose–response effect was not seen in this study.

Other skin changes associated with the use of inhaled steroids include angina bullosa haemorrhagica (oral blood blister) (29,30). In addition, acne has been reported in four patients using inhaled corticosteroids and it appeared to be dose dependent in one of the individuals (31). However, these adverse skin effects are very rare.

Cataract Formation

Treatment with oral steroids is known to cause cataracts of a characteristic appearance, classically posterior subcapsular and beginning as a fine, granular and vacuolated opacity. The incidence of posterior subcapsular cataracts (PSCCs) associated with steroid use increases with increased dosage and duration of treatment, but there is considerable interindividual variation in susceptibility (32). PSCCs have been reported to develop following as little as 5 mg prednisolone daily and in as little as 2 months, although the usual time to onset is at least 1 yr with a dosage equivalent to prednisolone 10 mg daily. Visual impairment is usually minimal in PSCCs resulting from steroid use, although there have been rare reports of cataracts requiring surgical extraction.

Toogood *et al.* (33) studied the association between the occurrence of PSCCs and inhaled and oral steroid therapy in a cross-sectional study of 48 adults with asthma. Twenty-five patients had some type of lens opacity, 13 of whom had PSCCs. The occurrence of PSCCs correlated with the current daily prednisolone dosage and the duration of prednisolone use, but not with the dosage or duration of inhaled steroids (mean 1460 μg daily; mean duration 9·2 yr).

There have been a number of case reports of asthma patients treated with inhaled BDP who subsequently developed PSCCs, but almost all of these patients had also received oral steroids (34–37).

Sevel *et al.* (38) studied 42 asthmatic children who had received oral corticosteroids for a minimum of 3 yr. Twelve were treated with inhaled BDP. Only one child had cataracts concurrent with corticosteroid therapy, and this child was found to be steroid dependent and markedly growth stunted. Nassif *et al.* (39) performed slit-lamp examination of the eyes of 56 asthmatic children on steroid therapy followed up for at least 6 months. Small, clinically non-apparent, subcapsular cataracts were detected in 1/24 children treated with alternate-day oral prednisolone and in 1/32 treated with inhaled BDP (mean 500 μg daily). Simons *et al.* (40) conducted a cross-sectional study in 95 young patients (median age 13·8 years) taking inhaled BDP or budesonide (300–2000 μg daily for a median of 5 yr). No PSCCs were found and the authors concluded that routine screening for PSCCs in this patient population was not warranted.

A population-based, cross-sectional study of the prevalence of cataracts in 3654 people (aged 49–97 years; mean age 65 years) was conducted in Australia (41). In the 370 subjects reported using inhaled BDP, either currently or previously, there was a higher prevalence of PSCCs predominantly in subjects with a lifetime dose of >2000 mg. Adjusting for the use of systemic corticosteroids and other potential confounding factors had little effect on the magnitude of this association. The association with PSCCs was less marked when the analysis was restricted to subjects who had never used systemic corticosteroids. This study was conducted in 1992 and 1993, and because budesonide was approved for use in Australia in late 1991 BDP was the only inhaled corticosteroid used for any extended period. However, there is no reason to suspect that the effect of budesonide would be any different from that of BDP.

Conclusions

The majority of comparative studies suggest that low to medium dosages (≤400 μg day^{-1}) of inhaled BDP and budesonide have no effect on adrenal function in adults and children. Two non-comparative studies examining long-term use (≥1 yr) of inhaled BDP and budesonide in children support this conclusion. High dosages of BDP and budesonide (>1500 μg day^{-1} in adults and >400 μg day^{-1} in children) do appear to have an effect on adrenal function, but there is considerable interindividual variation. Moreover, the clinical significance of this effect is not known (for example, whether adrenal suppression will correlate with side-effects in other tissues). There is no convincing evidence of a statistically significant difference in effect on adrenal function between BDP and budesonide, but in many studies BDP appears to have greater HPA axis suppression than budesonide on a microgram-for-microgram basis (Table 1).

Skin thinning and bruising may be associated with the use of high dosages of inhaled steroids, especially in older subjects. However, individuals receiving such therapy often have a history of oral steroid treatment which is a confounding factor. Further studies are warranted to determine whether easy bruising correlates with adrenal suppression. It would appear to be prudent to be alert to easy bruising in elderly patients receiving long-term (years) high-dose inhaled steroids. There are no comparative data with respect to the relative incidence of skin changes with budesonide and BDP.

For some time now it has been known that systemic corticosteroids can cause PSCCs. However, it would now appear that long-term, high-dose (cumulative lifetime dose >2000 mg) inhaled corticosteroid treatment is also associated with an increased prevalence of PSCCs in adult patients. However, multiple risk factors are associated with the formation of cataracts, including use of inhaled or systemic steroids, smoking, diabetes mellitus, hypertension, sun exposure and age.

The risk:benefit ratio for inhaled corticosteroids is highly favourable compared with oral corticosteroids. As with any drug, in order to minimise the potential for adverse effects, the lowest dose of an inhaled corticosteroid that achieves the desired effect should be used.

References

1. Bjorkander J, Formgren H, Johansson SA *et al.* Methodological aspects on clinical trials with inhaled corticosteroids: results of two comparisons between two steroid aerosols in patients with asthma. *Eur J Respir Dis* 1982; **63** (Suppl. 122): 108–117.
2. Willey RF, Godden DJ, Carmichael J, Preston P, Frame M, Crompton GK. Comparison of twice daily administration of a new corticosteroid budesonide with beclomethasone dipropionate four times daily in the treatment of chronic asthma. *Br J Dis Chest* 1982; **76**: 61–68.

3. Keelan P, Gray P, Kelly P, Frame M. Comparison of a new corticosteroid aerosol, budesonide, with beclomethasone dipropionate in the treatment of chronic asthma. *Ir Med J* 1984; **77:** 244–247.
4. Johansson S-A, Andersson K-E, Brattsand R *et al.* Topical and systemic glucocorticoid potencies of budesonide, beclomethasone dipropionate and prednisolone in man. *Eur J Respir Dis* 1982; **63** (Suppl. 122): 74–82.
5. Lofdahl C-G, Mellstrand T, Svedmyr N. Glucocorticoids and asthma. Studies of resistance and systemic effects of glucocorticoids. *Eur J Respir Dis* 1984; **65** (Suppl. 136): 69–79.
6. Brown PH, Matusiewicz SP, Shearing C *et al.* Systemic effects of high dose inhaled steroids: comparison of beclomethasone dipropionate and budesonide in healthy subjects. *Thorax* 1993; **48:** 967–973.
7. Jennings BH, Larsson B, Andersson K-E *et al.* A comparison of budesonide and beclomethasone in healthy volunteers. The assessment of systemic effects of inhaled glucocorticosteroids. Univ Lund 1990; **11:** 1–14.
8. Brown PH, Blundell G, Greening AP, Crompton GK. Hypothalamo-pituitary-adrenal axis suppression in asthmatics inhaling high dose corticosteroids. *Respir Med* 1991; **85:** 501–510.
9. Ebden P, Jenkins A, Houston G, Davies BH. Comparison of two high dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 μg/day) and budesonide (1600 μg/day), for chronic asthma. *Thorax* 1986; **41:** 869–874.
10. Selroos O, Halme M. Effect of a volumatic spacer and mouth rinsing on systemic absorption of inhaled corticosteroids from a metered dose inhaler and dry powder inhaler. *Thorax* 1991; **46:** 891–894.
11. Svendsen UG, Frolund L, Heinig JH *et al.* High-dose inhaled steroids in the management of asthma. A comparison of the effects of budesonide and beclomethasone dipropionate on pulmonary function, symptoms, bronchial responsiveness and the adrenal function. *Allergy* 1992; **47:** 174–180.
12. Jennings BH, Andersson K-E, Johansson S-A. Assessment of the systemic effects of inhaled glucocorticosteroids: comparison of the effects of inhaled budesonide and oral prednisolone on adrenal function and markers of bone turnover. *Eur J Clin Pharmacol* 1991; **40:** 77–82.
13. Brown PH, Blundell G, Greening AP, Crompton GK. Screening for hypothalamo-pituitary-adrenal axis suppression in asthmatics inhaling high dose corticosteroids. *Respir Med* 1991; **85:** 511–516.
14. Roy A, Leblanc C, Paquette L *et al.* Skin bruising in asthmatic subjects treated with high doses of inhaled steroids: frequency and association with adrenal function. *Eur Respir J* 1996; **9:** 226–231.
15. Melchor R, Mak VHF, Spiro SG. Easy bruising and adrenocortical function in patients taking inhaled corticosteroids. *Thorax* 1994; **49:** 404P.
16. Baran D. A comparison of inhaled budesonide and beclomethasone dipropionate in childhood asthma. *Br J Dis Chest* 1987; **81:** 170–175.
17. Field HV, Jenkinson PMA, Frame MH *et al.* Asthma treatment with a new corticosteroid aerosol, budesonide, administered twice daily by spacer inhaler. *Arch Dis Child* 1982; **57:** 864–866.
18. Springer C, Avital A, Maayan CH *et al.* Comparison of budesonide and beclomethasone dipropionate for treatment of asthma. *Arch Dis Child* 1987; **62:** 815–819.
19. Nikolaizik WH, Marchant JL, Preece MA, Warner JO. Endocrine and lung function in asthmatic children on inhaled corticosteroids. *Am J Respir Crit Care Med* 1994; **150:** 624–628.
20. Ninan TK, Reid W, Carter PE *et al.* Effects of high doses of inhaled corticosteroids on adrenal function with severe persistent asthma. *Thorax* 1993; **48:** 599–602.
21. Bisgaard H, Nielsen MD, Andersen B *et al.* Adrenal function in children with bronchial asthma treated with beclomethasone dipropionate or budesonide. *J Allergy Clin Immunol* 1988; **81:** 1088–1095.
22. Prahl P. Adrenocortical suppression following treatment with beclomethasone and budesonide. *Clin Exp Allergy* 1991; **21:** 1145–1146.
23. Pederson S, Fuglsang G. Urine cortisol excretion in children treated with high doses of inhaled corticosteroids: a comparison of budesonide and beclomethasone. *Eur Respir J* 1988; **1:** 433–435.
24. Russell G, Ninan TK, Carter PE *et al.* Effects of inhaled corticosteroids on hypothalamo-pituitary-adrenal function and growth in children. *Res Clin Forums* 1989; **11:** 77–86.
25. Bhan GL, Gwynn CM, Morrison Smith J. Growth and adrenal function of children on prolonged beclomethasone dipropionate treatment. *Lancet* 1980; January 12: 96–97.
26. Varsano I, Volovitz B, Malik H, Amir Y. Safety of 1 year of treatment with budesonide in young children with asthma. *J Allergy Clin Immunol* 1990; **85:** 914–920.
27. Capewell S, Reynold S, Shuttleworth D *et al.* Purpura and dermal thinning associated with high dose inhaled corticosteroids. *Br Med J* 1990; **300:** 1548–1551.
28. Mak VHF, Melchor R, Spiro SG. Easy bruising as a side-effect of inhaled corticosteroids. *Eur Respir J* 1992; **5:** 1068–1074.
29. Higgins EM, du Vivier AWP. Angina bullosa haemorrhagica – a possible relation to steroid inhaler. *Clin Exp Dermatol* 1993; **16:** 244–246.
30. High AS, Main DMG. Angina bullosa haemorrhagica: a complication of long-term steroid inhaler use. *Br Dent J* 1988; **165:** 176–179.
31. Monk B, Cunliffe WJ, Layton AM, Rhoces DJ. Acne induced by inhaled corticosteroids. *Clin Exp Dermatol* 1993; **18:** 148–150.
32. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. *Am J Med* 1995; **98:** 196–208.
33. Toogood JH, Markov AE, Baskerville J, Dyson C. Association of ocular cataracts with inhaled and oral steroid therapy during long-term treatment of asthma. *J Allergy Clin Immunol* 1993; **91:** 571–579.
34. Allen MB, Ray SG, Leitch AG *et al.* Steroid aerosols and cataract formation. *Br Med J* 1989; **299:** 432–433.

35. Fraunfelder FT, Meyer SM. Posterior subcapsular cataracts associated with nasal or inhalation corticosteroids. *Am J Opthalmol* 1990; **109:** 489–490.
36. Karim AKA, Thompson GM, Jacob TJC. Steroid aerosols and cataract formation. *Br Med J* 1989; **299:** 918.
37. Kewley GD. Possible association between beclomethasone dipropionate aerosol and cataracts. *Aust Paediatr J* 1980; **16:** 117–118.
38. Sevel D, Weinberg EG, Van Niekerk CH. Lenticular complications of long-term steroid therapy in children with asthma and eczema. *J Allergy Clin Immunol* 1977; **60:** 215–217.
39. Nassif E, Weinberger M, Sherman B *et al.* Extrapulmonary effects of maintenance corticosteroid therapy with alternate-day prednisolone and inhaled beclomethasone in children with chronic asthma. *J Allergy Clin Immunol* 1987; **80:** 518–529.
40. Simons FER, Persaud MP, Gillespie CA *et al.* Absence of posterior subcapsular cataracts in young patients treated with inhaled glucocorticoids. *Lancet* 1993; **342:** 776–778.
41. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *New Engl J Med* 1997; **337:** 8–14.