Eur Respir J, 1996, 9, 226–231
DOI: 10.1183/09031936.96.09020226
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

Skin bruising in asthmatic subjects treated with high doses of inhaled steroids: frequency and association with adrenal function

A. Roy, C. Leblanc, L. Paquette, H. Ghezzo, J. Côté, A. Cartier, J-L. Malo

Skin bruising in asthmatic subjects treated with high doses of inhaled steroids: frequency and association with adrenal function. A. Roy, C. Leblanc, L. Paquette, H. Ghezzo, J. Côté, A. Cartier, J-L. Malo. ©ERS Journals Ltd 1996.

ABSTRACT: High doses of inhaled corticosteroids (ICS) (budesonide and beclomethasone ≥800 µg·day^{-1}) are commonly used in the treatment of asthma. Some investigators have presented evidence for cutaneous effects (bruising), which suggests systemic absorption. This study aimed to assess the prevalence of skin bruising, relate the occurrence of skin bruising to adrenocortical function, and determine the risk factors for skin bruising.

One hundred adult asthmatic subjects taking high doses (800–2,000 µg·day^{-1}) of ICS for 3 months or more were recruited in an asthma clinic, and 100 control subjects paired for sex and age were recruited from an ophthalmology out-patient clinic. A detailed questionnaire on asthma, general habits and cutaneous lesions was administered. A cutaneous examination was performed. Urine cortisol levels were assessed on two consecutive days. Blood cortisol level and the response to Cortrosyn injection (60 min test) were evaluated.

One hundred adult asthmatics (66 females and 34 males), 73 on beclomethasone and 27 on budesonide, were included. The prevalence of skin bruising was 71% based on the questionnaire (32% in controls) and 48% (39 out of 81 subjects) based on direct examination of the skin. We found a satisfactory association between the response to questionnaire and examination of the skin. Adrenocortical function testing showed that a minority of subjects (14 with at least one abnormal test) had lower urinary or blood cortisol levels. These low cortisol levels occurred in subjects who reported skin bruising. By multiple logistic regression, being a female (odds ratio (OR)=20; 95% confidence interval (95% CI)=13–33) and taking ICS for asthma (OR=12; 95% CI=8–18) were significantly (t=5.4) related to the likelihood of developing skin bruising. In addition, among the asthmatic subjects, being older (OR=1.6; 95% CI=1.1–2.4/10 yrs interval) (t=2.3) and being a female (OR=22; 95% CI=7–75) (t=5.0) influenced the occurrence of skin bruising as documented by questionnaire.

In asthmatic subjects, taking high doses of ICS is associated with: 1) increased occurrence of skin bruising by comparison with controls, particularly in older subjects; and 2) a generally normal adrenocortical function, although this function is significantly lower in subjects reporting skin bruising.

Eur Respir J., 1996, 9, 226–231.

Dept of Chest Medicine and Dermatology, Sacré-Coeur Hospital, Montréal, Canada.

Correspondence: J-L. Malo
Dept of Chest Medicine
Sacré Coeur Hospital
5400 West Gouin
Montreal
Canada H4J 1C5

Keywords: Asthma
beclomethasone
bronchi
glucocorticoids

Received: February 14 1995
Accepted after revision October 10 1995

This work was partly funded by the Centre québécois d'excellence en santé respiratoire and by the McAbbie Foundation, Université de Montréal School of Medicine.

The use of inhaled corticosteroids (ICS) has represented a major breakthrough in the treatment of asthma since their introduction in the 1970s. Betamethasone and beclomethasone were the first ICS to be used. Multiple studies carried out in approximately 20,00 subjects and summarized previously have shown that these preparations cause few systemic side-effects provided that the dose is kept low [1, 2]. The few systemic side-effects demonstrated are more marked in children [3–8]. In the case of inhaled beclomethasone in adults, the threshold dose is close to 1 mg daily. Other ICS have since been developed for topical use in asthma (budesonide, flunisolide, fluticasone). The efficacy and side-effects of inhaled budesonide seem comparable to beclomethasone on a mg-per-mg basis [9].

In recent years, high doses of ICS have been advocated for the treatment of asthma. Doses of beclomethasone from 1–2 mg daily, and of budesonide from 0.8–1.6 mg daily are now frequently used in treating asthma [10]. Some suppression of the hypothalamo-pituitary-adrenal (HPA) axis has been described when such doses are used [1], but this blockade does not seem to have clinical implications [12] except in rare cases [5, 6]. Chronic use of ICS by adults, does not seem to be associated with

posterior capsular cataracts, a complication of oral steroids used [13]. However, conflicting findings have been reported with respect to the effects of ICS on bone [2, 14].

Steroid use may have other side-effects, primarily affecting the skin. Acne [15], skin-thinning and bruising have been associated with the use of ICS. Two reports describe the occurrence of skin bruising in adult asthmatic subjects using ICS [16, 17]. CAPEWELL *et al*. [17] found that 10 out of 21 subjects (48%) treated with high-dose ICS had skin bruising as compared to 2 out of 17 (12%) controls. In a survey carried out by questionnaire, MAK *et al*. [16] found that 47% of 202 adult asthmatic subjects taking ICS had bruising, as compared to 22% of asthmatic subjects not on ICS. Older male subjects on higher doses of ICS had a greater tendency to develop skin bruising. In these studies, the frequency of skin bruising was not compared by questionnaire and direct examination of the skin, nor was the severity of this phenomenon graded. Finally, the presence of skin bruising was not related to the HPA function. It is suspected that the mechanism of skin bruising is related to more systemic absorption of ICS.

We carried out a prospective study of the occurrence of skin bruising lesions in adult asthmatic subjects on high doses of ICS in order to: 1) assess the prevalence of this condition by comparison with a control group paired for sex and age; 2) related this side-effect to the possible systemic absorbtion by assessing HPA function; and 3) determine risk factors for bruising. The hypothesis is that skin bruising is more common in subjects taking inhaled steroids in comparison to control subjects and that subjects with skin bruising lesions have lower HPA function.

Subjects and methods

Subjects

We recruited one hundred asthmatic subjects on high daily doses of ICS (beclomethasone ≥1 mg; budesonide ≥800 μg) prospectively from an out-patient asthma clinic of a tertiary care hospital. They had to have taken ICS daily at the same dose for at least 3 months. Subjects were not to have taken oral steroids on a continuous basis for 1 year or more in the past 5 yrs. They were eligible if they had required short courses of oral steroids, but not if they had needed more than three courses per year, and not if these had been required during the 3 months preceding the study.

Control subjects (n=100) were recruited from a specialized out-patient clinic of the same hospital (ophthalmology). They were paired for sex and age (same decade) with every asthmatic subject. None of them suffered from asthma and none took or had ever taken ICS. None of the asthmatic or control subjects reported bleeding disorders, took aspirin or nonsteroidal anti-inflammatory drugs or anticoagulants.

Questionnaire

A trained nurse administered an asthma questionnaire requesting information on: duration, treatment, dose and duration of treatment with ICS, and oral steroid courses. In addition, questions were included on the severity, frequency and distribution of skin bruising lesions, and on exposure to sun.

Skin examination

Skin was examined in order to determine the presence or absence of skin bruising lesions. In addition, the Hess test was carried out in the following way: a pressure superior to the patient's systolic pressure by 10 mmHg was applied for 5 min with a sphygmomanometer; thereafter, the number of petechiae on the forearm was documented.

Hypothalamo-pituitary-adrenal function

A blood sample was taken in the afternoon for cortisol prior to and 30 and 60 min after intramuscular injection of Cortrosyn (25 IU). The best of the 30 or 60 min values was kept for analysis. Twenty four hour collections of urine were obtained on two consecutive days.

Table 1. – Baseline anthropometric, clinical and functional results of the asthmatic group

Sex M/F		34/66
Age# yrs		52±14
Age group n	≤30 yrs	8
	31–40 yrs	14
	41–50 yrs	20
	51–60 yrs	25
	61–70 yrs	25
	≥71 yrs	8
Atopy* n		72
Duration of asthma# yrs		21.1±16.3
Inhaled steroids (daily dose)**		
Beclomethasone (n=73)		1 mg, n=37; 1.5 mg, n=15; 2.0 mg, n=21
Budesonide (n=27)		0.8 mg, n=18; 1.2 mg, n=4; 1.6 mg, n=5
Total duration of treatment with inhaled steroids# yrs		6.8±6.1
Duration of current treatment with inhaled steroids (Bec or Bud)# months		36.9±28.3
Subjects who took one short course or more of oral steroids in the previous year excluding previous 3 months n		34
FEV_1# % pred		77±20
<80% pred n		37
FVC# % pred		89±20
<80% pred n		38

#: mean±SD; *: defined as at least one immediate skin reaction to a battery of 15 common inhalants, administered by the prick method; **: budesonide (Bud) was taken with the Turbuhaler®; in the case of subjects on beclomethasone (Bec), 33 used an Aerochamber® (MDI with spacer). M: male; F: female; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; % pred: percentage of predicted value; MDI: metered-dose inhaler.

If urinary creatinine levels were adequate and reflected complete collections in the two samples, the mean of the two urinary cortisol values was kept in the analysis of results. If one or other of the two urinary creatinine levels reflected incomplete collection of the total urine, the corresponding urinary cortisol value was discarded. Baseline cortisol levels were defined as normal if they were above 55 nmol·L^{-1}. A satisfactory response to Cortrosyn injection corresponded to a postinjection value ≥530 nmol·L^{-1}. Normal levels of 24 h urinary cortisol were above 130 nmol·day^{-1}.

Analysis of results

Chi-squared analysis, Student's unpaired t-test, one-way analysis of variance (ANOVA) and multinomial logistic analysis were used to analyse results as appropriate.

Results

In the prospective recruitment of subjects, 11 control subjects and 17 asthmatic subjects who were recruited refused to answer the questionnaire. Eighty one subjects underwent direct examination of the skin and urinary cortisol assessments, whilst in 76 subjects baseline cortisol levels were measured, and in 74 an assessment of response to Cortrosyn injection. Table 1 shows some baseline results of the asthmatic group. There were approximately twice as many females as males. The mean age was 52 yrs, and the duration of treatment with ICS was 37 months. Fifty five asthmatic subjects took beclomethasone, 1 mg·day^{-1}, or budesonide, 0.8 mg·day^{-1}. Slightly more than one third of subjects had significant baseline airway obstruction, with a forced expiratory volume in one second (FEV1) <80% predicted value.

Table 2 gives information on the features of skin bruising. More than twice as many asthmatic subjects as controls reported skin bruising. Females reported it more frequently than males both in the asthmatic and the control group. There was no significant difference between the two treatment groups (beclomethasone and budesonide) for bruising. The frequency of occurrence of skin bruising was significantly lower in the control subjects. In addition, the severity of skin bruising was significantly more pronounced in the asthmatic group. Whilst asthmatic subjects reported skin bruising on the superior and inferior limbs with approximately equal frequency, normal subjects had more skin bruising on the inferior limb. There were no differences in type of work, solar protection or artificial ultraviolet exposure in the two groups of subjects.

There was a significant association between the presence of skin bruising reported on the questionnaire and that found by physical examination ($p<0.001$): 35 subjects had skin bruising on both questionnaire and examination, and 18 had no skin bruising with either assessment. However, 24 did not have skin bruising on direct examination but did report some on the questionnaire. The Hess test was performed in 46 subjects. We found no significant association between results of the Hess test

Table 2. – Ecchymosis in asthmatic and control subjects

Presence of ecchymosis on questionnaire				
Asthmatic subjects	71/100			
Controls	32/100			p<0.001
Ecchymosis according to sex	Males	Females		
Asthmatic subjects	13	58		
Controls	2	30		p<0.001
Ecchymosis according to type of inhaled steroids	BEC	BUD		
With ecchymosis	52	19		
Without ecchymosis	21	8		NS
Frequency of ecchymosis	1–2 per month	1–2 per week	Daily	
Asthmatic subjects	31	28	12	
Controls	22	8	2	p=0.05
Severity of ecchymosis	Major trauma	Moderate trauma	Minor trauma	Spontaneous
Asthmatic subjects	14	13	23	21
Controls	22	0	3	7
				p<0.001
Site of ecchymosis (examination)	Inferior limbs	Face	Trunk	Superior limbs
Asthmatic subjects	6	1	2	58
Controls	14	1	2	30
	p<0.01			NS
Type of work	Indoor	Outdoor	Retired	
Asthmatic subjects	76	5	19	
Controls	73	6	21	NS
Solar protection	Yes	No		
Asthmatic subjects	67	33		
Controls	57	43		NS
Ultraviolet artificial exposure	Yes	No		
Asthmatic subjects	15	85		
Controls	19	81		NS

BEC: beclomethasone; BUD: budesonide; NS: nonsignificant.

and the reporting of skin bruising on the questionnaire: only 10 subjects had a positive test and reported bruising on the questionnaire, while 24 reported bruising but had a negative test. The dose and the duration of current or total treatment with ICS were no different in those reporting or those having skin bruising on examination. However, asthmatic subjects who reported skin bruising were significantly older (54±14 yrs as opposed to 48±15 yrs; $p<0.05$), but this difference was not significant on physical examination. Taking the inhaler with or without an Aerochamber did not affect reports of bruising. Indeed, of the 71 subjects with ecchymosis, 24 (34%) used an Aerochamber; of the 29 subjects without ecchymosis, nine (31%) also used in Aerochamber.

Six subjects had an abnormal 24 h urinary cortisol level, six an abnormal baseline cortisol, and 11 an abnormal response to Cortrosyn injection. Fourteen subjects had either abnormal urinary or plasma cortisol levels. Two subjects had three abnormal tests, whereas six other subjects had lower than predicted values in two of three tests. The other subjects (n=6) had only one abnormal test each, one with abnormal baseline plasma cortisol, four with lower than predicted response to Cortrosyn injection, and one subject with abnormal urinary cortisol levels. Only two of the 14 subjects with one or more abnormal tests reported having taken oral steroids on a regular basis (for 1 year or more) in the past. However, seven of the eight subjects with two or more abnormal tests were on daily doses of ICS ≥1,500 µg, whilst this was the case for only two of the six subjects with only one abnormal test. Urinary cortisol was significantly higher in those who did not report skin bruising (fig. 1), but this was not the case for blood cortisol values. Urinary cortisol was lower in those with increased occurrence of skin bruising on direct examination (fig. 1). However, we could not detect significant differences in urinary or blood cortisol levels according to the frequency or severity of skin bruising reported on questionnaire.

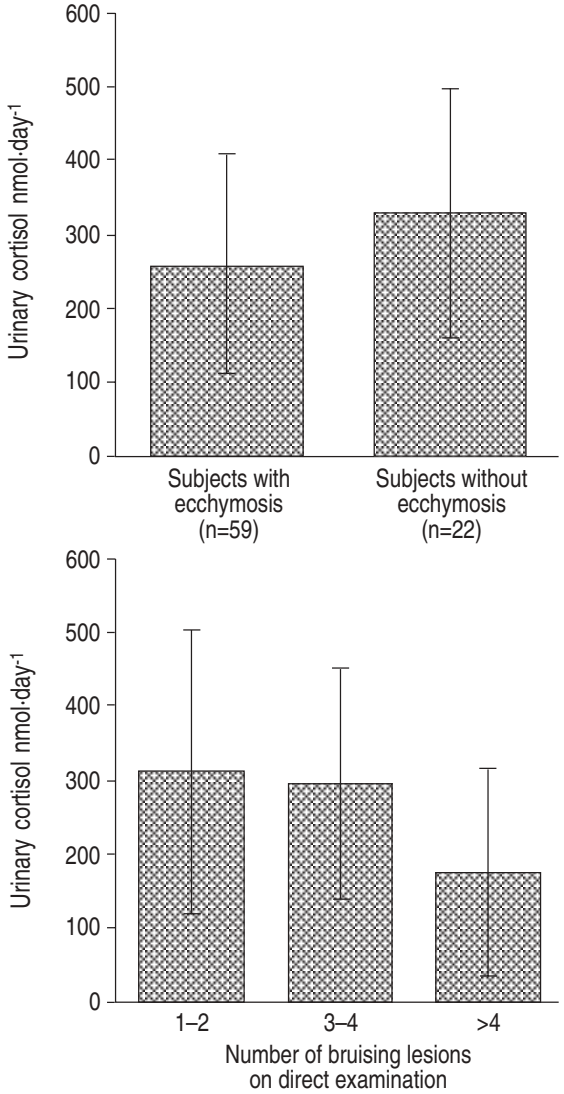

Fig. 1. – Twenty four hour urinary cortisol values in subjects with and without ecchymosis (upper panel) and according to the number of bruising lesions on direct examination of the skin. Values are presented as mean±SD.

Logistic regression performed in the two groups of subjects showed that being a female (OR=20; 95% CI=13–33) and taking ICS for asthma (OR=12; 95% CI=7.5–18.4), but not age, were determinants of the likelihood of having skin bruising on questionnaire (t=5.4). When we examined the asthmatic group only, we found that being a female (OR=22.3; 95% CI=6.7–74.7) (t=5.0) and being older (OR=1.6; 95% CI=1.1–2.4/10 yrs interval) (t=2.3), but not the type or dose of steroids; influenced the occurrence of skin bruising as documented by questionnaire.

Discussion

Anti-inflammatory treatment by inhalation, in particular of steroids, is currently the mainstay of asthma treatment [10]. Introduction, in recent years, of high-dose ICS (beclomethasone >1,000 µg or budesonide >800 µg daily) has raised concerns, especially regarding children, as to potential systemic side-effects, which could be mediated through absorption of these preparations in the systemic circulation [18, 19]. Although serum osteocalcin and other indices of bone metabolism can be altered by inhaling high doses of steroids [20], the relationship of this to increased bone loss and, more importantly, to bone fractures is speculative [21]. It seems clear that ICS, even at relatively high doses and for long intervals, do not enhance the development of cataracts in adults [13]. The risk of glaucoma formation has also been suggested [22], although this needs a prospective trial. Paradoxically, KIVIRANTA and TURPEINEN [23] have recently shown a beneficial effect of ICS on carbohydrate metabolism, insulin sensitivity and glucose tolerance.

ICS can also cause significant skin side-effects. Acne has been found in three interesting cases presented by MONK *et al.* [15]. Easy bruising and skin thinning have also been documented [16, 17]. The mean relative risk (OR of 12) in this study is higher than the risk of 2.2 reported by MAK *et al.* [16]. This can be explained by the fact that the definition of "bruising" was different in the two studies. MAK *et al.* [16] included only subjects who reported "bruising resulting from slight knock or

without apparent cause". The frequency of bruising assessed by direct examination was lower (10 out of 21 subjects) in the study carried out by CAPEWELL *et al*. [17] but the sample was small, making comparison difficult. Like MAK *et al*. [16], in the group of asthmatic subjects taking high doses of ICS, we found that age was a significant determinant of bruising. This was not the case for the control group, so we can speculate that age can potentiate the effect of ICS in the asthmatic group. As MAK *et al*. [16] found, females seemed more likely to develop skin bruising both in our asthmatic and control groups. MAK *et al*. [16] were able to detect a dose-dependent effect. This was not found in our study, probably because all of our subjects took high-dose ICS, this being one of the selection criteria. The range of dose was, therefore, limited (800–2,000 μg), which precluded documentation of a dose-dependent effect. As in the study by MAK *et al.* [16], taking oral steroids prior to the study was not a determinant of the likelihood of developing skin bruising.

We found no association between the Hess test and bruising. This suggests that the mechanism of the skin lesions in association with the intake of inhaled corticosteroids is different from purpura secondary to capillary fragility.

Plasma cortisol levels, before or after Cortrosyn injection, were less sensitive than 24 h urinary cortisol in identifying subjects who presented skin bruising. This can be related to the timing of plasma cortisol assessments, which was in the afternoon in our study. Morning plasma cortisol might have proved more sensitive, although this latter test still seems less satisfactory than 24 h urinary cortisol and the cortisol response to Cortrosyn injection [24].

Approximately one quarter of our asthma subjects were on inhaled budesonide and the rest on beclomethasone. We were unable to detect significant differences in the frequency of side-effects according to the type of ICS. In subjects using beclomethasone, the proportion of skin bruising was comparable with those taking budesonide, even though Turbuhaler® delivers a higher dose to the lung. These data warrant confirmation, as the number of subjects is still too limited to allow for sufficient discriminant power of analysis. As the difference between the two drugs was marginal (1%), this means that many more subjects would have to be included to detect a significant difference. In the two previously quoted studies on the same topics [16, 17], HPA function was not assessed in relation to the occurrence of skin bruising. We found that 14 subjects had at least one abnormal test reflecting HPA function; two subjects had three abnormal tests and six had two abnormal tests. In only two subjects can these abnormal tests by explained by previous continuous use of oral steroids. Although many indices can reflect adrenal suppression [2], BROWN *et al.* [25] used baseline cortisol, response to Cortrosyn and 24 h cortisol levels and selected lower normal limits close to the figures proposed in our work [25]. These authors identified significant suppression of adrenal function (defined as at least 2 out of 3 abnormal tests) in 20% (n=14) of 71 subjects taking 1,200 to 2,000 μg of ICS daily. The corresponding figure in our study was 8 out of 74 subjects (11%) having at least 2 out of 3 abnormal tests. It is reasonable to assume that administration of high dose ICS was responsible for this subclinical impairment of HPA function. Although we do not feel that these abnormalities warrant the use of oral short-acting corticosteroids, it probably justifies the administration of such preparations in some situations related to stress. Interestingly, we found that some indices were related to indices reflecting the presence and the severity of skin bruising, which might suggest that both phenomena, *i.e*. bruising and impaired HPA function, are mediated through systemic absorption of ICS at that dose. Firstly, urinary cortisol was lower in those who presented skin bruising. Secondly, at least one index of severity - the number of bruises on direct examination - was related to the level of urinary cortisol. This absorption is obviously minimal, but it is present, as a minority of subjects had significantly abnormal HPA function.

Although easy bruising causes more aesthetic than really meaningful side-effects, it is of concern especially since it affects the upper limbs. Some patients have to wear long sleeves because of it and may be referred to specialists for investigation of possible bleeding disorders. Although adequate control of asthma is paramount, keeping the dose of ICS as low as possible is desirable, as stressed by MONSON [20].

It would be interesting to relate this side-effect, skin bruising, to the occurrence of other side-effects possibly related to the use of inhaled corticosteroids. It would be valuable to know whether skin bruising can be used as a marker of impaired bone metabolism or other side-effects in subjects taking high-dose steroids.

Acknowledgements: The authors thank C. Hinse (Department of Biochemistry) for assessing cortisol levels and L. Schubert for reviewing the manuscript.

References

1. Huskisson SC, Meades CR, Cuss FM, Palmer JBD. Inhaled beclomethasone dipropionate. Castle Press Abertwyth, Glaxo Group Research Ltd, Greenford, England, 1987.
2. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. *Am J Med* 1995; 98: 196–208.
3. Nygind N, Hansen IB. Beclomethasone dipropionate aerosol effect on the adrenals in normal persons. *Acta Allergol* 1973; 28: 211–218.
4. Toogood JH, Crilly RG, Jones G, Nadeau J, Wells GA. Effect of high-dose inhaled budesonide on calcium and phosphate metabolism and the risk of osteoporosis. *Am Rev Respir Dis* 1988; 138: 57–61.
5. Hollman GA, Allen DB. Overt glucocorticoid excess due to inhaled corticosteroid therapy. *Pediatrics* 1988; 81: 452–455.
6. Zwaan CM, Odink RJH, Delamarre-Van de Waal HA, Dankert-Roelse JE. Acute adrenal insufficiency after discontinuation of inhaled corticosteroid therapy. *Lancet* 1992; 340: 1289–1290.
7. Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993; 92: 64–77.

8. Thomas BC, Stanhope R, Grant DB. Impaired growth in children with asthma during treatment with conventional doses of inhaled corticosteroids. *Acta Paediatr* 1994; 83: 196–199.
9. Toogood JH. Potential adverse effects of inhaled steroids. Parts 1 and 2. Contemporary Allergies 1993–1994; December 1993 and March 1994: pp. 12–16 and 12–16.
10. International Consensus Report on the Diagnosis and Management of Asthma. *Clin Exp Allergy* 1992; 22 (Suppl. 1): 1–44.
11. Smith MJ, Hodson ME. Effects of long-term inhaled high-dose beclomethasone dipropionate on adrenal function. *Thorax* 1983; 38: 676–681.
12. Toogood JH. Complications of topical steroid therapy for asthma. *Am Rev Respir Dis* 1990; 141: S89–S96.
13. 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.
14. Jennings BH, Andersson KE, Johansson SA. Assessment of 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.
15. Monk B, Cunliffe WJ, Layton AM, Rhodes DJ. Acne induced by inhaled corticosteroids. *Clin Exp Dermatol* 1993; 18: 148–150.
16. Mak VHF, Melchor R, Spiro SG. Easy bruising as a side-effect of inhaled corticosteroids. *Eur Respir J* 1992; 5: 1068–1074.
17. Capewell S, Reynolds S, Shuttleworth D, Edwards C, Finlay AY. Purpura and dermal thinning associated with high-dose inhaled corticosteroids. *Br Med J* 1990; 300: 1548–1551.
18. National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892. International consensus report on diagnosis and treatment of asthma. *Eur Respir J* 1992; 5: 601–641.
19. Barnes NC. Safety of high-dose inhaled corticosteroids. *Respir Med* 1993; 87 (Suppl. A): 27–31.
20. Monson JP. Systemic effects of inhaled corticosteroids. *Thorax* 1993; 48: 955–956.
21. Boulet LP, Giguère MC, Milot J, Brown J. Effects of long-term use of high-dose inhaled steroids on bone density and calcium metabolism. *J Allergy Clin Immunol* 1994; 94: 796–803.
22. Dreyer EB. Inhaled steroid use and glaucoma. *N Engl J Med* 1993; 329: 1822.
23. Kiviranta K, Turpeinen M. Effect of eight months of inhaled beclomethasone dipropionate and budesonide on carbohydrate metabolism in adults with asthma. *Thorax* 1993; 48: 974–978.
24. Brown PH, Blundell G, Greening AP, Crompton GK. Screening for hypothalamo-pituitary-adrenal axis suppression in asthmatics taking high-dose inhaled corticosteroids. *Respir Med* 1991; 85: 511–516.
25. 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.