

Purpura and dermal thinning associated with high dose inhaled corticosteroids

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Abstract

Objective—To assess the effect of high dose inhaled corticosteroids on skin.

Design—Cross sectional study of patients receiving treatment for chest diseases.

Setting—Outpatient chest clinic in a teaching hospital.

Patients—68 Patients divided into four groups of similar age—namely, 15 receiving long term oral prednisolone, 21 receiving high dose inhaled corticosteroids, 15 receiving low dose inhaled corticosteroids, and 17 controls.

Main outcome measures—Skin thickness at three sites measured by A scan ultrasound and clinical assessment of purpura.

Results—Compared with controls patients in both the oral prednisolone treated group and the high dose inhaled corticosteroid treated group had significantly thinner skin at all three sites (group median thicknesses: prednisolone treated group 28-33% less than controls; high dose inhaled corticosteroid treated group 15-19% less than controls). Differences in skin thicknesses between the low dose inhaled corticosteroid treated group and the controls were trivial. The prevalence of purpura was significantly greater in patients receiving oral prednisolone (12/15 patients) and high dose inhaled corticosteroids (10/21) than in controls (2/17).

Conclusion—Skin thinning and purpura represent further evidence of systemic effects of high dose inhaled corticosteroids.

Introduction

The introduction of inhaled corticosteroids revolutionised the treatment of bronchial asthma in the 1960s.¹ High dose inhaled corticosteroids, either 1000-2000 µg beclomethasone dipropionate or 800-1600 µg budesonide, have recently produced further benefits in chronic severe asthma²⁻⁴ and possibly chronic bronchitis.^{5,6} Such treatment is not without problems. Locally, oropharyngeal candidiasis or dysphonia may occur, as with low dose inhaled corticosteroids.⁷ Systemically, adrenal suppression is common when daily doses exceed 1500 µg.^{3,4,8} More recently, evidence of other systemic effects has been reviewed, including altered glucose and lipid metabolism and impairment of growth in children.⁹ This raises the possibility of other potentially serious consequences previously associated with systemic corticosteroid treatment, such as cutaneous atrophy.

Clinicians here and elsewhere have suspected

that "typical steroid skin changes" of purpura and cutaneous thinning may occur in patients receiving high dose inhaled corticosteroids alone¹⁰ (G K Crompton, personal communication). These clinical observations required objective evaluation. This study therefore aimed at determining whether there was any objective evidence of thinner skin or purpura in patients taking high dose inhaled corticosteroids. A cross sectional study was conducted in an outpatient chest clinic population, comparing patients receiving high dose inhaled corticosteroids with a control group. Patients receiving low dose inhaled corticosteroids and patients receiving long term systemic prednisolone were also compared with the control group.

Patients and methods

Seventy six outpatients attending a chest clinic were invited to take part. All patients had either asthma or chronic bronchitis with some reversibility of airways obstruction and were aged 18 or over. All patients had received a constant dose and regimen of inhaled or systemic treatment for at least six months. No patient taking inhaled corticosteroids had previously received long term (more than one month) continuous systemic corticosteroid treatment. Patients who had taken various types of corticosteroid treatment were excluded from the study.

Eight of the 76 patients were subsequently excluded: two declined, two failed to attend the study session, and four had been taking various corticosteroid treatments. Sixty eight patients were therefore studied, comprising four distinct groups. These were 15 patients receiving long term systemic corticosteroid treatment (prednisolone 5-20 mg/day); 21 patients receiving high dose inhaled corticosteroids (beclomethasone dipropionate 1000-2250 µg/day) who had never received long term systemic corticosteroid treatment; 15 patients using low dose corticosteroid inhalers (beclomethasone dipropionate 200-800 µg/day) who had never received either long term high dose inhaled treatment or long term prednisolone; and 17 control patients, who had never received inhaled or systemic corticosteroids (table I).

Skin thickness is related to both age and sex.^{11,12} Change in skin thickness with age is small,¹² and furthermore there was good comparability for age between each patient group and the control group (table I). Female skin is thinner than male skin by a factor of 0.8.¹¹ All analyses were therefore performed after adjustment of the raw data for sex by using the correction factor: female skin thickness × 1.25 = male skin thickness. All groups were well matched for sex,

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TABLE I—Clinical details of the four groups of patients

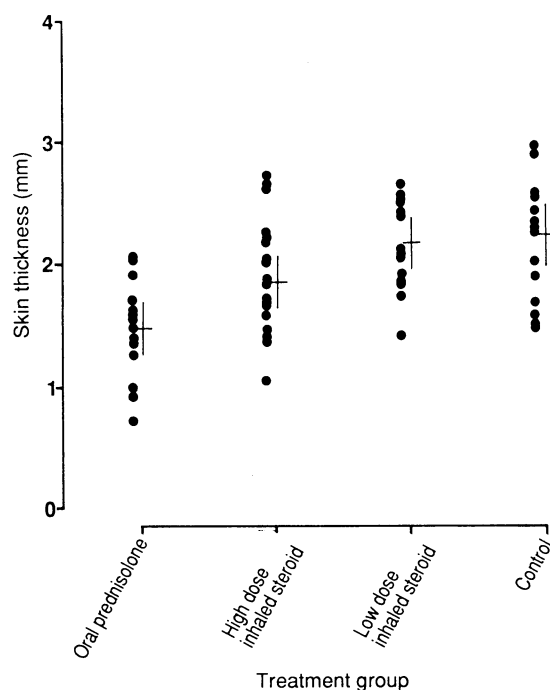
Group	No	Median age (years) (range)	M:F ratio	No suffering with asthma/bronchitis/other	Median daily dose of steroid (range)	Median duration of steroid treatment (months) (range)	Median lifetime dose of short course prednisolone (range)
Patients receiving oral prednisolone	15	59 (26-73)	9:6	13/1/1	10 mg Prednisolone (5-20)	102 (30-3600)	9500 mg (360-38 000)
Patients receiving high dose inhaled steroid	21	55 (21-69)	13:8	16/5/0	2 mg Beclomethasone dipropionate (1.0-2.25)	48 (6-72)	200 mg (0-4200)
Patients receiving low dose inhaled steroid	15	55 (29-75)	9:6	14/1/0	0.4 mg Beclomethasone dipropionate (0.2-0.8)	18 (6-105)	0 (0-1620 mg)
Controls	17	55 (38-63)	9:8	7/5/5	None	None	None

although there was a slightly higher male to female ratio in the group receiving high dose inhaled corticosteroids (13:8) compared with controls (9:8) (table I). Details of the patients' diseases and corticosteroid treatment were obtained from the patients, cross checked with the case notes, and recorded on a standardised form. The patients' "total lifetime dose" of prednisolone, given in short courses for exacerbations of asthma, was calculated in milligrams by using the formula: patient's usual short course dosage regimen \times average number of short courses a year \times number of years' receiving short courses.

Each patient was examined by an experienced dermatologist (AF or DS) without knowledge of the patient's disease or corticosteroid treatment. Purpura was assessed by noting the presence or absence of purpuric or ecchymotic lesions on the face, neck, and limbs, and using a four point scoring system from zero (none) to 3 (severe) with the theoretical maximum individual score of 9. Striae were likewise graded from zero (none) to 3 (severe). Solar exposure was classified as "high" if patients had worked in an outdoor occupation for more than five years or had spent more than three months in a tropical or subtropical region.^{13 14} The presence or absence of solar keratoses was noted. Solar elastosis of the face and dorsum of the right hand was separately assessed using a 10 cm visual analogue scale from zero to 100. An "elastosis score" was calculated for each patient by taking the mean of the two observations. After this examination details of topical corticosteroid treatment and patient's awareness of increased skin bruising and fragility were recorded.

Skin thickness was measured by pulsed A scan ultrasound using a dermal depth detector (Cutech Ltd, United Kingdom).^{11 12} Transit time measurements were converted to skin thickness in millimetres on the basis that the ultrasound velocity in skin is 1580 m/s, so that one microsecond equals 0.79 mm.¹² This technique does not differentiate between epidermis and dermis and the measurement is therefore total skin thickness—that is, dermal plus epidermal thickness. The epidermis contributes roughly 5% of the total. Five ultrasound measurements were taken from the dorsum of the right hand (a solar exposed site) and from the medial aspect of the upper right arm and the upper outer quadrant of the left buttock (both non-solar exposed sites). The individual mean value at each site was then calculated.

To account for the fact that we were carrying out repeated tests across three sites, only results significant at the 1% level were considered notable, hence maintaining an approximate overall 5% level of significance. To assess whether there was any difference among the groups a Kruskal-Wallis test was performed on all the data at each site. If this test result was significant then it remained to determine between which groups the differences were significant. The three steroid treated groups were to be compared with the control group, so that multiple comparisons were to be made. The non-parametric test chosen for this analysis was the Nemenyi extension of the Kruskal-Wallis ranking technique,¹⁵ which allows multiple comparisons among groups of different sizes. For this test the χ^2 approximation to the specified



Individual skin thicknesses over buttock in the four groups of patients. Horizontal and vertical bars are medians and 95% confidence intervals¹⁶

distribution function was made as sufficient data points were available.

Differences in the prevalences of purpura and striae were assessed by the χ^2 test with Yates's correction. The purpura and striae scores were dichotomised into a group with a score of zero and a group with scores of 1 or more—that is, the presence or absence of these features was tested.

The study was approved by the local medical ethics committee, and witnessed and written informed consent was obtained from every patient.

Results

Table II summarises the skin thickness measurements of each group at each site investigated, and the figure shows the individual measurements over the buttock. Unless stated otherwise all results given below are significant at the 1% level.

In the group taking long term prednisolone skin thickness was substantially less than that in the control group at all sites (median thicknesses over hand, arm, and buttock 33%, 28%, and 32% less than in control group). In the group taking long term high dose inhaled corticosteroids skin thickness was also less than that in the control group at all sites (median thicknesses over hand, arm, and buttock 15%, 17%, and 19% less than in control group). In the group taking long term low dose inhaled corticosteroids no significant differences in skin thickness compared with control values were found at any site.

In the group taking long term high dose inhaled corticosteroids there was a negative correlation between duration of treatment and skin thickness which was significant at two of the three sites (hand: $r_s = -0.18$, $p = 0.2$; arm: $r_s = -0.37$, $p = 0.01$; buttock: $r_s = -0.42$, $p = 0.004$ (Spearman's rank correlation corrected for ties)).

The prevalence of purpura as noted by the clinician was lowest in the control group (2/17 patients) and increased across the low dose inhaled steroid (5/15), high dose inhaled steroid (10/21), and prednisolone treated groups (12/15 patients) (χ^2 for trend = 15.93, $df = 3$, $p < 0.01$; table III). Comparing each drug treatment group separately with the controls suggested significant differences in respect of the prednisolone

TABLE II—Skin thicknesses (millimetres) in the four groups of patients. Figures are median values (interquartile ranges in parentheses)

Group	No	Hand	Arm	Buttock
Patients receiving oral prednisolone	15	0.84 (0.23)	0.79 (0.32)	1.58 (0.44)
Patients receiving high dose inhaled steroid	21	1.07 (0.27)	0.91 (0.28)	1.88 (0.71)
Patients receiving low dose inhaled steroid	15	1.26 (0.33)	1.03 (0.17)	2.17 (0.64)
Controls	17	1.26 (0.28)	1.09 (0.25)	2.33 (0.63)

Skin thicknesses in women multiplied by 1.25 and combined with values in men.

TABLE III—Solar elastosis score and prevalence of high sun exposure, striae, and awareness of purpura or skin fragility in the four groups

Group	No	Mean (SD) solar elastosis score	No with history of high sun exposure	No aware of purpura/fragility	No with striae	No with purpura
Patients receiving oral prednisolone	15	42 (19.6)	2	13	2	12
Patients receiving high dose inhaled steroid	21	40 (25.3)	9	8	4	10
Patients receiving low dose inhaled steroid	15	43 (23.9)	6	8	5	5
Controls	17	39 (21.6)	6	3	6	2

and high dose inhaled steroid treated groups, although in the case of this second group the difference was marginal. Comparing patients' awareness of bruising or skin fragility gave the four proportions as three of 17 patients, eight of 15, eight of 21, and 13 of 15 ($\chi^2=15.63$, $df=3$, $p<0.01$; table III). Comparing individual groups with the control group showed only the prednisolone treated group to be significantly different.

There was no evidence of any difference in the prevalence of striae noted by the clinician among the four groups (6/17 patients, 5/15, 4/21, 2/15; $\chi^2=3.00$, $df=3$, $p>0.1$). When compared with the control group the three treatment groups were found to be very similar in terms of sun exposure, except that slightly fewer patients taking prednisolone were in the high exposure group (NS). The degree of solar elastosis was also similar in all four groups (table III).

Discussion

In this study treatment with high dose inhaled corticosteroids was associated with skin thinning and increased purpura. This phenomenon is supported by clinical observations elsewhere in Britain, including two reports to the Committee on Safety of Medicines (S Wood, personal communication, 1989). There were no commensurate differences in solar exposure and the changes were equally apparent in sites not exposed to the sun. The four groups of patients were also similar in age. As there is a consistent relation between male and female skin thickness¹¹ we were able to apply a correction factor to overcome the difference. With use of the adjusted data the non-parametric tests showed significant differences in skin thickness at all sites in the high dose inhaled corticosteroid and systemic steroid treated groups.

There are potential problems inherent in all cross sectional studies of patients with asthma. The corticosteroid treatment given to the individual patients in this study was determined on clinical criteria only, reducing comparability among the four groups. Furthermore, as in the assessment of bone mass¹⁷ the possible confounding influence of previous short courses of prednisolone must be considered.¹⁸ Such treatment is a cornerstone in the management of patients with chronic severe asthma. Thus it is extremely difficult to find patients for study who are taking high dose inhaled corticosteroids and have not at some time had short courses of prednisolone. The median lifetime dose of prednisolone was only 200 mg in the 21 patients using high dose inhaled corticosteroids, and none had received short courses of prednisolone within the preceding six months. It remains possible that the skin changes seen with high dose inhaled corticosteroids may also reflect a synergistic effect of previous courses of prednisolone.

Dermal thinning may be measured by xeroradiography, skinfold callipers, biopsy, or ultrasound.^{11 19} Pulsed A scan ultrasound is rapid, non-invasive, reproducible, and sensitive and will detect dermal thinning within days of the patient beginning topical corticosteroids.^{11 12 19 20} Results correlate highly with those of xeroradiography and epidermal biopsy.²⁰

It is well known that topical or systemic corticosteroids can produce both macroscopic and microscopic skin changes. Clinically the skin becomes

thin, fragile, and transparent with loss of subcutaneous tissue, increased mobility, and purpura—"blot haemorrhages."^{21 22} The skin is less resistant to trauma, and trivial injuries may cause surprisingly extensive tears.^{23 24} Cutaneous atrophy with systemic treatment tends to be dose related and is more common in older patients after prolonged use of prednisolone or triamcinolone acetonide.^{23 25} Effects similar to those caused by topical and systemic corticosteroids were seen in patients taking high dose inhaled corticosteroids, presumably from systemic absorption. There is a growing awareness that high dose inhaled corticosteroids may cause a variety of systemic effects.⁹ Suppression of the hypothalamic-pituitary-adrenal axis has been recognised for years.^{4 8 26} Insulin and lipid metabolism are altered,²⁷ bone resorption is increased,²⁸ and osteoporosis may occur.¹⁷ Growth in children may be impaired, although this is controversial.^{9 29} Cataracts have also been reported.³⁰

In general, women have thinner skin than men.¹¹ In this study there was generally more pronounced thinning of female than male skin among patients taking steroids. In the prednisolone treated group median skin thickness was 33% less in men and 44% less in women when compared with the respective male and female control groups. Likewise, in the high dose inhaled corticosteroid treated group skin thickness was 20% less in men and 23% less in women. Furthermore, changes in skin thickness are associated with changes in bone density in postmenopausal women.³¹ This may have implications for assessing long term risks of osteoporosis with inhaled corticosteroids.

High dose inhaled corticosteroids remain the preferred treatment in moderate and severe chronic asthma. Clinicians, however, should take note of cutaneous changes seen in such patients and be aware of this potential side effect. Clearly, on the basis of our findings a prospective study of patients beginning high dose inhaled corticosteroid treatment is warranted.

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A randomised controlled trial of surgery for glue ear

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Abstract

Objective—To assess the effect of five different surgical treatments for glue ear (secretory otitis media) on improvement in hearing and, assuming one or more treatments to be effective, to identify the appropriate indications for surgery.

Design—Randomised controlled trial of children receiving (a) adenoidectomy, bilateral myringotomy, and insertion of a unilateral grommet; (b) adenoidectomy, unilateral myringotomy, and insertion of a unilateral grommet; (c) bilateral myringotomy and insertion of a unilateral grommet; and (d) unilateral myringotomy and insertion of a grommet. Children were followed up at seven weeks, six months, 12 months, and 24 months by symptom history and clinical investigations.

Setting—Otolaryngology department in an urban hospital.

Patients—149 Children aged 4-9 years who were admitted for surgery for glue ear and who had no history of previous operations on tonsils, adenoids, or ears and no evidence of sensorineural deafness. Inadequate follow up information on levels of hearing and on middle ear function was obtained from 22.

Main outcome measures—Mean hearing loss (dB) of the three worst heard frequencies between 250 and 4000 Hz, results of impedance tympanometry, and parental views on their child's progress.

Results—In the 127 children for whom adequate information was available ears in which a grommet had been inserted performed better in the short term (for at least six months) than those in which no grommet had been inserted, irrespective of any accompanying procedure. Most of the benefit had disappeared by 12 months. Adenoidectomy produced a slight improvement that was not significant, though was sustained for at least two years. The ears of children who had had an adenoidectomy with myringotomy and grommet insertion, however, continued to improve so that two years after surgery about 50% had abnormal tympanometry compared with 83% of those who had had only myringotomy and grommet insertion, and 93% of the group that had had no treatment. Logistic regression analyses identified preoperative hearing

level as the single best predictor of good outcome from surgery. Other variables contributed little additional predictive power.

Conclusions—If the principal objective of surgery for glue ear is to restore hearing then our study shows that insertion of grommets is the treatment of choice. The addition of an adenoidectomy will increase the likelihood of restoration of normal function of the middle ear but will not improve hearing. When deciding appropriate indications for surgery, a balance has to be made between performing unnecessary operations and failing to treat patients who might benefit from surgical intervention. Preoperative audiometry scores might be the best predictor in helping to make this decision.

Introduction

Glue ear, or otitis media with effusion, is the commonest reason for elective surgery in childhood.¹ In England and Wales in 1986 about 73 000 operations were carried out in NHS hospitals (based on hospital activity analyses for Oxford and for East Anglian regional health authorities) and a further 18 000 are estimated to have been performed in independent hospitals (J P Nicholl, personal communication). Despite the popularity of these operations considerable uncertainty exists about their efficacy and the appropriate indications for their use. Although the results of 15 randomised controlled trials concerning a total of 1549 children have been published since 1967, few of the studies can easily be compared.²⁻¹⁶ Variations of case definition, exclusion criteria, case severity, outcome measures, duration of follow up, and method of analysis have all contributed to the difficulty in achieving consensus. A further complication is that a variety of operative procedures in different combinations have been studied: adenoidectomy, myringotomy, and grommet (tympanostomy tube) insertion (table I).

Despite the difficulties entailed in making detailed comparisons between the trials it is possible to identify some consistent findings. Firstly, myringotomy results in little or no benefit.^{14,16} Secondly, myringotomy plus grommet insertion is effective for up to 12 months,^{2,3,14} though two studies found that this procedure was not

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