Easy bruising as a side-effect of inhaled corticosteroids

V.H.F. Mak, R. Melchor, S.G. Spiro

ABSTRACT: We wished to determine the prevalence of easy bruising in patients taking inhaled corticosteroids (ICS) compared with those who did not. Differences in age, dosage and duration of use of ICS between patients who bruised and those who did not were also investigated.

Confidential questionnaire surveys were conducted over a 6 month study period amongst patients attending a respiratory out-patient clinic and taking regular ICS, and a control group of patients attending non-respiratory clinics and not taking any form of corticosteroids. Patients with bleeding disorders or taking oral steroids, non-steroidal anti-inflammatory drugs or anticoagulants were excluded from the study.

Questionnaires from 202 respiratory patients using ICS (group A) were compared with 204 non-ICS patients (Group B) of similar age and sex distribution. Significantly more patients in Group A reported easy bruising than in group B (47 vs 22%, relative risk 2.18, 95% confidence interval (95% CI) 1.62–2.94), and it was the commonest reported symptom. In Group A, the patients that reported easy bruising tended to be older (61 vs 52 yrs), on higher daily dosages (1,388 vs 1,067 μg) and had been taking inhaled corticosteroids for longer (55 vs 43 months) than non-bruisers.

Overall, females reported easy bruising more frequently than males in both groups. However, comparing Group A with Group B, males taking ICS had a higher relative risk for bruising than females (males, relative risk 5.80, 95% CI 2.38–14.13; females, relative risk 1.80, 95% CI 1.32–2.44). The prevalence of easy bruising increased significantly with increasing dosage and increasing duration of use of ICS. Also, the prevalence of easy bruising increased significantly with age in Group A but not in Group B. However, this effect of age was not significant in patients taking <1,000 μg·day⁻¹. There was no difference in the proportion of bruisers and non-bruisers who had previously been treated with continuous oral steroids, nor in the number of courses of oral corticosteroids taken over the previous year.

Easy bruising should be recognized as a frequent side-effect of inhaled corticosteroids, which increases in prevalence with increasing age, dosage and duration of use.

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Inhaled corticosteroids (ICS) are widely used in the treatment of asthma [1–3]. The advantage of using inhaled rather than oral corticosteroids is that side-effects are reduced for the equivalent therapeutic effect because they rely more on topical action than systemic activity. Common side-effects of systemic or oral corticosteroids include weight gain, glucose intolerance, adrenocortical suppression, cataract formation, proximal myopathy, dermal thinning with easy bruising and osteoporosis. However, ICS are thought to have a low incidence of serious systemic side-effects. Known local side-effects of ICS include dysphonia, hoarseness, sore throat and oropharyngeal candida infection; less specific symptoms include nausea, headache, dry throat, rashes and impaired taste or smell [4, 5] and are not dose related. The most important clinical systemic side-effect of ICS is adrenocortical suppression, which has been reported when the total daily dosage of ICS exceeds about 1,500 μg [6, 7]. Other systemic side-effects that have recently been reported include increased bone turnover [8], impaired glucose and lipid metabolism [9] and cataract formation [10], although this last effect is not well-established.

Many respiratory physicians have noticed that some patients with asthma or obstructive airways disease complain of easy bruising after starting treatment with ICS. Easy bruising can also occur in Cushing's disease, patients on long-term oral corticosteroids, bleeding disorders and collagen-related syndromes such as
Ehlers-Danlos. Spontaneous and easy bruising has been described during therapy with high dose inhaled beclomethasone dipropionate in relation to skin thinning [11, 12].

If easy bruising is related to high dose ICS treatment, this may imply significant systemic absorption of ICS in these patients and they may be at risk of other systemic effects of corticosteroids. However, the exact prevalence of easy bruising and the dosage and duration of therapy at which it occurs is not known. The aim of this study was to establish the prevalence of easy bruising by conducting a survey amongst patients using ICS compared to other hospital patients not using ICS nor systemic corticosteroids.

Methods

We surveyed two sample populations of patients attending out-patient clinics using questionnaires. Group A consisted of all patients attending a respiratory out-patient clinic during a 6 month study period (February to July 1990), who had been taking ICS for more than one year. Group B comprised patients of similar age and sex distribution attending general medical, neurological, gastroenterological or endocrine out-patient clinics and not taking ICS. Any patients in either group who were taking long-term oral or topical corticosteroids, non-steroidal anti-inflammatory drugs or anticoagulants were excluded from the study. We also excluded patients who were taking low dose aspirin and those taking sulphasalazine or mesalazine as these are non-steroidal anti-inflammatory drugs and may have an effect on platelet function.

Patients in Group A answered a questionnaire concerning their asthma medications, including the dosage, type of ICS (beclomethasone or budesonide, aerosol or powder), duration of therapy and the number of courses of steroids taken over the previous year (a course being defined as 5–14 days of high dose oral corticosteroids). Compliance was assessed by asking patients whether they "never", "rarely", "occasionally" or "frequently" forgot to take their medications. Side-effects noticed and other medications taken were also recorded. Any patients who admitted that they "occasionally" or "frequently" forgot to take their medication were excluded from the study. The question concerning easy bruising was included amongst a list of other recognized side-effects of ICS that they may have noticed since starting their treatment (see Appendix). If a patient requested clarification, "easy-bruising" was defined for them as "bruising resulting from a slight knock or without apparent cause". The notes of all patients were studied from the time of original referral to the clinic until the time of the study, to see if the patient had at any time taken continuous oral corticosteroids for more than two consecutive months, or had had depot steroid injections.

Patients in group B answered a questionnaire on their reasons for attending a clinic, the medications they were using and symptoms noticed within the last two years since starting any of their medications, with easy bruising included in a list of possible side-effects (see Appendix). The list of possible side-effects differed in the two groups because our objective was to compare the prevalence of easy bruising with other known side-effects of ICS in Group A, which would not necessarily have been present in patients in Group B. Therefore, a list of side-effects common to all types of medication was used for Group B. In neither questionnaire was it obvious that easy bruising was of special interest.

All questionnaires were distributed, checked and clarified by one of the authors. If any patient reported easy bruising in either of the two groups, the patient was asked if they had any history of bleeding disorders, such as prolonged bleeding after tooth extraction, and, if so, were excluded from the study.

The study was approved by the local Ethics Committee.

Statistics

Data were analysed using SPSS/PC+ version 3.0 on a personal computer. Tests used included calculation of group means, standard deviations and Student's t-test. Differences between group proportions were analysed using Chi-squared (χ²) tests with Yates' continuity correction for 2×2 tables, and relative risk was calculated with 95% confidence intervals (95% CI) using standard techniques [13].

Results

There were 202 patients in Group A (ICS-users) and 204 in Group B (no corticosteroids). There were no significant differences between the two groups for age (yrs; mean±sd) (Group A 56±19; Group B 53±17, p>0.05) or sex distribution (males/females: Group A, 95/107; Group B, 81/123, χ² 1.93, d.f. 1, p>0.05).

Other respiratory drugs taken by patients in Group A included: inhaled β₂-agonists, inhaled ipratropium bromide, oral sustained release β₂-agonists, oral theophylline preparations. No patients in Group A were taking sodium cromoglycate or nedocromil sodium. Patients in Group B had a wide variety of conditions: cardiovascular (mostly hypertension and heart failure), respiratory (e.g. chronic obstructive Airways disease (COAD) not taking ICS and mild asthma not taking ICS), gastrointestinal, neurological, endocrine and metabolic disorders. They were on a variety of commonly used medications, none of which have been associated with easy bruising.

In Group A, easy bruising was the most frequent symptom noticed since ICS usage started, being reported in 47% of questionnaires. Hoarseness was reported in 41%, sore throat in 28%, headaches in 13% and rashes in 6% of questionnaires.

Significantly, more patients in Group A (95 out of 202) reported easy bruising compared to Group B (44 out of 204 χ² 28.1, d.f. 1, p<0.0001), with a increased relative risk of 2.18 (table 1). There was no
significant difference in age (mean±SD) between patients who reported easy bruising in Group A and Group B (61±15 yrs vs 56±17 yrs, p>0.05). Significantly, more females than males bruised in both groups (Group A: 36 out of 95 males vs 61 out of 107 females, χ² 8.26, d.f. 1, p<0.005; Group B: 5 out of 89 males vs 39 out of 115 females, χ² 17.3, d.f. 1, p<0.0001). However, significantly more males reported easy bruising in Group A (36 out of 95) than in Group B (5 out of 89), with the relative risk for easy bruising for males in Group A compared with Group B being 5.80 (χ² 20.5, d.f. 1, p<0.0001, table 1). Similarly, significantly more females reported easy bruising in group A (61 out of 107) compared with group B (39 out of 115), but the relative risk was lower than for males being 1.80 (χ² 13.9, d.f. 1, p<0.001, table 1).

Group A was divided into two subgroups: patients on ICS who reported easy bruising and those who did not. A significant difference between the two subgroups was found for mean age (bruisers 61±15 yrs; non-bruisers 52±21 yrs, p<0.0001), mean daily dosage (bruisers 1,388±659 µg·day⁻¹; non-bruisers 1,067±690 µg·day⁻¹, p<0.001) and mean duration of ICS usage (bruisers 55±40 months; non-bruisers 43±33 months, p<0.05).

No significant difference was found in the number of courses of oral steroids taken over the last year; 36% of patients in the subgroup of easy bruisers had received one or more courses of oral steroids over the past year compared with 35% in the subgroup of non-bruisers. There was also no significant difference in the number of patients who had had previous treatment with continuous oral steroids (9 out of 95 of easy bruisers and 7 out of 107 of non-bruisers, χ² 0.26, d.f. 1, p>0.05), and none had been on continuous oral steroids for at least 2 yrs prior to the study.

The prevalence of easy bruising increased significantly with increasing daily dosage of ICS. Of 105 patients taking ≤1,000 µg·day⁻¹ of ICS, 41 patients reported easy bruising. In patients taking 1,001-1,999 µg·day⁻¹, 21 out of 43 reported easy bruising and in those taking ≥2,000 µg·day⁻¹, 33 out of 52 reported easy bruising (χ² 8.95, d.f. 2, p<0.05) (fig. 1).

We also arbitrarily divided Group A into three groups for duration of ICS usage; <36 months, 36-60 months and >60 months. The prevalence of easy bruising increased significantly with increasing duration of use of ICS. Of 83 patients taking ICS for <36 months, 36-60 months and >60 months, 36, 33 and 33 patients reported easy bruising, respectively (χ² 8.95, d.f. 2, p<0.05).

Table 1. Summary of relative risk with 95% confidence intervals (95% CI) in parenthesis for different groups of patients

<table>
<thead>
<tr>
<th>Therapeutic groups</th>
<th>Relative risk of bruising (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (ICS users) vs Group B (non-ICS users)</td>
<td>2.18 (1.62-2.94)</td>
</tr>
<tr>
<td>Group A females vs Group A males</td>
<td>1.59 (1.18-2.16)</td>
</tr>
<tr>
<td>Group B females vs Group B males</td>
<td>6.04 (2.48-14.68)</td>
</tr>
<tr>
<td>Group A females vs Group B females</td>
<td>1.80 (1.32-2.44)</td>
</tr>
<tr>
<td>Group A males vs Group B males</td>
<td>5.80 (2.36-14.13)</td>
</tr>
<tr>
<td>Group A 1001-1999 µg·day⁻¹ vs &lt;1000 µg·day⁻¹</td>
<td>1.25 (0.85-1.84)</td>
</tr>
<tr>
<td>Group A &gt;2000 µg·day⁻¹ vs &lt;1000 µg·day⁻¹</td>
<td>1.63 (1.19-2.23)</td>
</tr>
<tr>
<td>Group A 36-60 vs &lt;36 months of ICS usage</td>
<td>1.65 (1.08-2.53)</td>
</tr>
<tr>
<td>Group A &gt;60 vs &lt;36 months of ICS usage</td>
<td>1.47 (1.02-2.11)</td>
</tr>
</tbody>
</table>

ICS: inhaled corticosteroids.

Fig. 1. Percentage of patients defined as bruisers and non-bruisers grouped by total daily dosage of inhaled corticosteroids. [ ] bruisers; [ ] non-bruisers.
months, 30 reported easy bruising. In patients using ICS for 36–60 months, the prevalence of easy bruising was 30 out of 53, and in patients that had been taking ICS for >60 months, the prevalence was 35 out of 66 ($\chi^2$ 6.85, d.f. 2, $p<0.05$) (fig. 2). A summary of the relative risk of bruising between groups is shown in table 1.

Dividing the patients in Group A and Group B into three arbitrary age groups (<40 yrs, 40–65 yrs and >65 yrs), the prevalence of easy bruising was found to increase significantly with age in Group A ($\chi^2$ 12.26, d.f. 2, $p<0.005$) (fig. 3a), but not in Group B ($\chi^2$ 1.67, d.f. 2, $p>0.05$) (fig. 3b). Analysing each age group separately, no significant difference was found in the prevalence of easy bruising between Group A and Group B in the <40 age group (Group A 9 out of 39 vs Group B 9 out of 54, $\chi^2$ 0.26, d.f. 1, $p>0.05$). However, there was a significant difference between Group A and Group B for both the 40–65 yrs (Group A 42 out of 86 vs Group B 20 out of 94, $\chi^2$ 13.91, d.f. 1, $p<0.0005$) and >65 yrs (Group A 44 out of 77 vs Group B 15 out of 56, $\chi^2$ 10.96, d.f. 1, $p<0.001$) age groups. This effect was not due to an excess of females in the older age groups in Group A as the proportion of males to females in the three age groups was similar between Group A and Group B (table 2, for each 2x2 table comparing proportion of males and females between Group A and Group B in the three age groups, $\chi^2$ <1, d.f. 1, $p>0.05$).

The increased prevalence of easy bruising with age in Group A was not significant if only patients taking ≤1,000 $\mu$g·day$^{-1}$ were considered ($\chi^2$ 5.05, d.f. 2, $p>0.05$) (fig. 4a), but the effect of age was significant when the dose exceeded 1,000 $\mu$g·day ($\chi^2$ 6.30, d.f. 2, $p<0.05$) (fig. 4b).

In Group A, 180 patients were using metered dose inhalers and 22 were using powder delivery systems. Eighty four (48%) of those using metered dose inhalers and 11 (50%) of those using powder delivery systems reported easy bruising ($\chi^2$ <0.1, d.f. 1, $p>0.05$). Only 4% of the patients were using budesonide, therefore, no comparison could be made on possible differences between budesonide and beclometasone dipropionate.

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Table 2. Proportion of males and females in Group A and Group B divided into three age groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>&lt;40 yrs</th>
<th>40-65 yrs</th>
<th>&gt;65 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Males</td>
<td>16 (41%)</td>
<td>44 (51%)</td>
<td>35 (48%)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>23 (59%)</td>
<td>43 (49%)</td>
<td>41 (52%)</td>
</tr>
<tr>
<td>B</td>
<td>Males</td>
<td>16 (30%)</td>
<td>41 (43%)</td>
<td>24 (43%)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>37 (70%)</td>
<td>54 (57%)</td>
<td>32 (57%)</td>
</tr>
</tbody>
</table>

Fig. 4. - a) Number of bruisers and non-bruisers grouped by age in patients taking $\leq 1,000 \mu g \cdot day^{-1}$ of inhaled corticosteroids. b) Number of bruisers and non-bruisers grouped by age in patients taking $>1,000 \mu g \cdot day^{-1}$ of inhaled corticosteroids. ICS: inhaled corticosteroids. ☒: bruisers; ☐: non-bruisers.

Discussion

Inhaled corticosteroids have been highly effective in the treatment of asthma for nearly 20 yrs. Previously, the most commonly reported side-effects were hoarseness and sore throat [4, 5]. However, in our survey, easy bruising was the commonest reported symptom, occurring in almost half of the patients who were using ICS. The relative risk of easy bruising in patients using ICS was more than double that of a population of patients of similar age and sex distribution but not using ICS. In both groups, females reported easy bruising more often than males, but the proportion of male bruisers was significantly higher in the group of ICS users. The increased relative risk of easy bruising in male users of ICS was nearly six times that of male non-ICS users (although the 95% CI is quite wide), whereas in female users of ICS the increased risk was less than double.

Patients who bruised tended to be older than the non-bruisers in both groups. Also, patients who bruised were, on average, using larger doses of ICS and for a longer period of time, but the range for these two parameters was large, and there was considerable overlap with the non-bruisers. However, the prevalence of easy bruising increased with increasing dosage and with increasing duration of therapy, with similar prevalence in the groups having used ICS for 36-60 months and for >60 months, suggesting that, if a patient is going to bruise on ICS therapy, they will do so within the first 5 yrs of treatment.

Reports of easy bruising in patients taking ICS have been few [11, 12]. Recent reviews of systemic side-effects of ICS have not mentioned easy bruising [4, 5], emphasis being placed on adrenocortical suppression. However, CAPEWELL et al. [12] described easy bruising or purpura associated with dermal thinning in a small group of patients taking high dose ICS ($>1,500 \mu g \cdot day^{-1}$). Ten out of 21 patients on high dose ICS were found to have purpura compared with 5 out of 15 patients on lower doses of ICS and 2 out of 17 controls. Effects on the skin in patients taking high dose ICS were found to be similar to those seen in patients taking oral corticosteroid therapy, but ICS produced more dermal thinning in women than in men. They concluded that skin thinning and purpura are important systemic side-effects of high dose ICS.

There are several factors that may affect our analysis. The questionnaires used in the two groups of patients were not identical. The objectives of the study were to compare the prevalence of easy bruising with other known side-effects of ICS, and to compare the prevalence of easy bruising in a hospital out-patient population not taking ICS. Questions relating to side-effects of ICS such as hoarseness and sore throat were felt not to be relevant for Group B, therefore, side-effects common to many medications were used in the questionnaire instead. However, the question relating to easy bruising was in the middle of both lists so that it was not prominent in either questionnaire and the results are unlikely to
be biased in favour of ICS users. Also, it is unlikely that patients in Group A were aware that easy bruising was a possible side-effect of ICS treatment, as the present study was conducted before any other study on this association was published.

Several patients in Group A were taking medications for other conditions and patients in Group B were also on a large variety of medications. However, any patients that were taking medication known to induce bruising were excluded in both groups. One major difference between the two groups is that all patients in Group A were being treated for reversible airways obstruction. Therefore, it is possible that the disease itself produces bruising, although this is unlikely. The number of patients who had taken courses of oral corticosteroids and the number of courses taken over the last year was similar between the bruisers and the non-bruisers. We had no information on the number of steroid courses before that time. It is possible that, since bruising is associated with a higher maintenance dose of ICS, these patients have more severe disease, and may have required more frequent courses of oral steroids in the past than the non-bruising group. Many patients now start themselves on courses of steroids at home or are given them by their general practitioner, and a detailed past steroid history would be difficult to obtain.

We did not allow for differences in effective dosage between aerosol and powder delivery systems, nor did we allow for the use of spacer devices. However, the proportion of patients using either aerosol or powdered delivery systems amongst the bruisers and non-bruisers in Group A was the same.

There may be a difference in the incidence of bruising between the type of ICS used. The majority of patients in the present study were taking beclomethasone dipropionate (BDP). However, BDP is metabolized into an active metabolite, beclomethasone monopropionate which is cleared only slowly [14]. Budesonide is cleared much faster than BDP in vitro [15], and, therefore, may produce less systemic effects. When the systemic effects of budesonide and BDP have been directly compared, budesonide has been found to produce less adrenocortical suppression [16] and less effect on bone metabolism [8] at equivalent doses. Therefore, the prevalence of easy bruising in patients taking budesonide may be lower than the prevalence found in the present study and needs further investigation.

The clinical significance of easy bruising is not yet certain. Since easy bruising is seen in systemic corticosteroid therapy and the pattern of dermal thinning in patients that bruise on ICS has been reported to be similar to that of patients taking oral corticosteroids [12], this would suggest that there is significant systemic absorption of ICS in many patients. However, the use of high dose ICS therapy for asthma is common and very few serious systemic complications have been reported [5]. Whether easy bruising is associated with other systemic side-effects such as adrenocortical suppression or increased bone metabolism needs further investigation. However, at present, the proven benefits of ICS therapy outweigh the disadvantages, and so they remain the treatment of choice in asthma.

Appendix

Question concerning symptoms noticed for patients using inhaled corticosteroids:

Have you noticed any of the following since you started taking Becotide/Becloforte/Pulmicort? (please tick)

- Sore throat: Yes ... No ...
- Hoarseness: Yes ... No ...
- Easy bruising: Yes ... No ...
- More wheeze: Yes ... No ...
- Headaches: Yes ... No ...
- Rashes: Yes ... No ...

Question concerning symptoms noticed for patients not using inhaled corticosteroids:

Have you noticed any of the following since starting your medication or in the last 2 years?

- Headaches: Yes ... No ...
- Difficulty sleeping: Yes ... No ...
- Itching: Yes ... No ...
- Dry skin: Yes ... No ...
- Headaches: Yes ... No ...
- Nausea: Yes ... No ...
- Rashes: Yes ... No ...
- Dizziness: Yes ... No ...

References

7. Gordon ACH, McDonald CF, Thomson SA, Frame MH, Pottage A, Crompton GK. - Dose of inhaled...