Adverse effects of oral corticosteroids in relation to dose in patients with lung disease

L J Walsh, C A Wong, J Oborne, S Cooper, S A Lewis, M Pringle, R Hubbard, A E Tattersfield

Abstract

Background—The adverse effects of oral corticosteroids are widely recognised but there are few quantitative data on which to base advice to patients. In a two part cross sectional study we compared adverse effects in patients with lung disease taking oral corticosteroids and control subjects and related the adverse effects to corticosteroid dose in the patient group.

Methods—Data on oral corticosteroid use, lifestyle, fractures, and other possible adverse effects were collected by questionnaire and compared between a community based cohort of patients taking continuous or frequent intermittent oral corticosteroids for asthma, chronic obstructive pulmonary disease, or alveolitis and age and sex matched control subjects. Dose related effects were explored in the corticosteroid group using cumulative dose quartiles and multiple logistic regression.

Results—A total of 367 patients (≥50 years, 48% female) and 734 control subjects completed the questionnaire. The cumulative incidence of fractures since the time of diagnosis was 23% for patients taking oral corticosteroids and 15% in the control group (odds ratio (OR) 1.8; 95% confidence interval (CI) 1.3 to 2.6). Patients were more likely to have had a fracture of the vertebrae (OR 10; 95% CI 2.9 to 34), hip (OR 6; 95% CI 1.2 to 30), and ribs or sternum (OR 3.2, 95% CI 1.6 to 6.6) than control subjects. They also reported a significant increase in cataracts, use of antacids, muscle weakness, back pain, bruising, oral candidiasis, and having fewer teeth. The effects of oral corticosteroids were dose related: the odds ratio for patients in the highest compared with the lowest cumulative dose quartile (median prednisolone dose 61 g versus 5 g) ranged from 2 for all fractures to 9 for vertebral fractures and bruising.

Conclusions—By quantifying the morbidity associated with the use of oral corticosteroids, this study should help to rationalise their long term use.

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Keywords: oral corticosteroids; dosage; adverse effects; fractures; osteoporosis

Oral corticosteroids are the most effective treatment available for many medical conditions including severe chronic asthma. Following their introduction 50 years ago their use has escalated and, despite the widespread use of inhaled corticosteroids, some 50 000 patients with asthma and chronic obstructive pulmonary disease (COPD) in the UK take oral corticosteroids regularly. Adverse effects such as osteoporosis, cataract, and muscle weakness are widely recognised and have considerable public health implications. They are also of concern to patients who need to balance the beneficial and adverse consequences of corticosteroid therapy. One difficulty when trying to address both public health issues and patient concerns is the lack of quantitative data on which to base advice.

Osteoporosis is probably the adverse effect of greatest concern and one that is amenable to prophylactic intervention. Most studies that have attempted to assess fracture risk in patients taking oral corticosteroids have been small or confounded by the underlying disease such as rheumatoid arthritis. In a recent study the risk of hip fracture over 4 years was doubled in patients taking oral corticosteroids compared with a control population. There are, however, no data on the risk of fracture or other adverse effects in relation to dose or duration of oral corticosteroid therapy after allowing for confounding influences. We have addressed this by using computerised general practice records to identify patients over the age of 50 who are taking oral corticosteroids for obstructive airways disease or alveolitis, two conditions that do not cause symptoms that could easily be attributed to oral corticosteroids. The first study provides information on the prevalence of fracture and other adverse effects compared with an age and sex matched control population. The second looks at how the incidence of fractures and other adverse effects relate to cumulative prednisolone dose.
ENTRY CRITERIA
Men and women aged 50 years or more with a diagnosis of asthma, COPD, or fibrosing alveo-

tis were included if they required either (a) continuous oral corticosteroids, defined as
daily or alternate day oral corticosteroid therapy for at least the last 6 months or (b) fre-
quent intermittent courses of oral cortico-
steroids, defined as a mean daily dose of 5 mg
prednisolone (or equivalent dose of other
corticosteroid) over the previous 6 months.
Patients receiving oral corticosteroids for other
conditions were excluded.

Control subjects had never had oral cortico-
steroid treatment or a diagnosis or treatment for lung disease. Patients and control subjects
were excluded if they had a metabolic disease
known to affect bone metabolism such as thy-
rotoxicosis or were not well enough to take
part.

STUDY PROTOCOL
A questionnaire with an explanation of the
study and a personal letter signed by the
general practitioner was sent to each patient
and three age and sex matched control
subjects. Subjects were asked to complete the
questionnaire or contact us if help was needed. If
no reply was received after 3 weeks the
patient was contacted by telephone and assist-
ance offered. If two control subjects had not
replied after a repeat mailing further control
subjects were approached; if all three replied
the first two identified were used.

STUDY 1: QUESTIONNAIRE STUDY
The questionnaire asked for details, including
duration or timing, of the main end points: fractures, back pain, bruising, muscle weak-
ness, the presence and condition of teeth, and a
diagnosis of cataract, diabetes, hypertension,
herpes zoster, and oral thrush. All fractures
except those of the skull, facial bones, fingers,
and toes were included. Information from the
control subjects was obtained for the same time
period or, for premenopausal patients having a
menopause (age at last menstrual
period), and height loss (cm) was recorded.

The questionnaire also asked for information
on lifetime cigarette consumption in pack
years, alcohol intake (classified as <10, 10–30
or >30 units/week), weekly consumption of
milk, cheese and yoghurt to estimate mean
daily calcium intake (mg/day) using dietary
tables,5 age at menopause (age at last menstrual
period or, for premenopausal patients having a
hysterectomy but no oophorectomy, when
menopausal symptoms commenced), and exer-
cise determined from regular sporting activity
between ages 15 and 25 years and at present on
a five point scale (1 = none to 5 = more than
three times per week). Patients were also asked
to grade their most strenuous daily activity as
light, moderate, heavy, or very heavy. Drug use,
including hormone replacement therapy, vita-
min D, calcium supplements, thiazide diuret-
ics, bisphosphonates, other treatment for oste-
oporosis, and any family history of osteoporosis
or height loss was recorded.

The general practice computerised and writ-
ten records were studied for subjects in both
groups to confirm the presence or absence of a
respiratory diagnosis and use of cortico-
steroids.

STUDY 2: DOSE RESPONSE STUDY
The relationship between oral corticosteroid
dose and fracture in the past 30 years, cataract
ever, current bruising, and muscle weakness
was assessed in the patients taking oral cortico-
steroids. The total cumulative dose and dura-
tion of oral corticosteroid therapy was esti-

cated from the questionnaire and
corroborated against the general practice
record, without knowledge of the main out-
come measures. The questionnaire provided
information on the corticosteroid used, daily
cumulative dose, duration of treatment, mean number of
booster courses per year, and the dose
prescribed for a typical course. The computer-
ised record provided information on daily dose,
number of tablets prescribed, dose per tablet,
and duration of treatment while the paper
record provided data prior to the computer
record.

For the primary analysis we calculated the
patient’s total lifetime dose as the total dose of
prednisolone (g) or equivalent taken at any
time—that is, continuous plus previous
courses. Oral corticosteroids other than pred-

disolone were converted to prednisolone equiv-

alent doses.6 In a secondary analysis we looked at
the relation between duration of treatment
(total time that continuous or frequent inter-
mittent corticosteroids had been taken) and
mean daily dose during the 6 months before
the questionnaire on adverse effects (including
any additional treatment for exacerbations).
The use of inhaled corticosteroids was
measured as a total lifetime dose (mg).

ANALYSIS OF DATA
Demographic, lifestyle, and all outcome mea-

ures were compared between the corticosteroid
and matched control groups. The independent
effect of corticosteroids on adverse effects was
assessed using conditional logistic regression
with appropriate interaction terms to assess
any modifying effect of sex. Odds ratios were
calculated to give an estimate of the rate ratio.5

For the dose response study patients taking
oral corticosteroids were grouped into quar-
tiles according to their total cumulative dose of
prednisolone. Significant adverse effects of
interest identified in study 1 were then

pared in the different quartiles using mul-
tiple logistic regression analysis; p values refer
to a test of linear trend in odds ratios across
quartiles. The analysis controlled for sex, age

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Table 1: Demographic data for patients with obstructive airways disease or alveolitis taking oral corticosteroids and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Corticosteroid patients</th>
<th>Control subjects</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>177</td>
<td>268.9 (7.5)</td>
<td>354</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>171</td>
<td>26.5 (6.9)</td>
<td>338</td>
</tr>
<tr>
<td>Age at menopause</td>
<td>167</td>
<td>47.0 (4.9)</td>
<td>292</td>
</tr>
<tr>
<td>HRT (number of years)</td>
<td>36</td>
<td>2.7 (3.0)</td>
<td>82</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>112</td>
<td>20 (0.09-114)*</td>
<td>179</td>
</tr>
<tr>
<td>Calcium from dairy produce (mg)</td>
<td>172</td>
<td>631 (25-1198)*</td>
<td>354</td>
</tr>
<tr>
<td>Bisphosphonate/calcitonin</td>
<td>20</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium supplement</td>
<td>25</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

Men

<table>
<thead>
<tr>
<th></th>
<th>Corticosteroid patients</th>
<th>Control subjects</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>190</td>
<td>69.6 (9.1)</td>
<td>380</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>181</td>
<td>25.8 (6.0)</td>
<td>364</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>164</td>
<td>29.9 (0.2-150)*</td>
<td>293</td>
</tr>
<tr>
<td>Calcium from dairy produce (mg)</td>
<td>183</td>
<td>614 (25-1070)*</td>
<td>380</td>
</tr>
<tr>
<td>Bisphosphonate/calcitonin</td>
<td>4</td>
<td>1</td>
<td>0.12</td>
</tr>
<tr>
<td>Calcium supplement</td>
<td>13</td>
<td>6</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values are mean (SD) or *median (range).

All p values obtained by conditional logistic regression.

Results

We identified 452 patients taking oral corticosteroids who fulfilled the entry criteria; 367 (81%) completed the questionnaire of whom 48% were female. Of the 85 who did not respond, 15 were too unwell, one had moved, 48% were female. Of the 85 who did not respond, 15 were too unwell, one had moved, and the remainder did not wish to participate. Two control subjects were identified from the same practice for each patient; the response rate for the control subjects was 61% but this will be a conservative estimate as no allowance was made for patients who had died or moved (21% of patients in a comparable study in Nottingham(3)).

Among the 367 patients taking oral corticosteroids 162 (44%) had a recorded diagnosis of asthma, 111 (30%) had asthma and COPD, 82 (22%) had COPD alone, and 12 (3%) had fibrosing alveolitis. For most patients (98%) the corticosteroid taken was prednisolone with a median total lifetime dose of 16.3 g (range 1.1–186 g) over a median of 5.5 years (range 0.5–46 years). Women had a higher median cumulative lifetime dose than men (20 g vs 15.3 g) and a higher median duration of steroid use (6.4 years vs 4.5 years). A quarter of the patients had taken frequent intermittent oral corticosteroids in the previous 6 months and 89% were taking an inhaled steroid regularly.

Table 2: Fractures and other adverse effects in patients taking oral corticosteroids compared with the control population

<table>
<thead>
<tr>
<th></th>
<th>Steroid patients (%)</th>
<th>Control group (%)</th>
<th>No of case control sets</th>
<th>Unadjusted odds ratio (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any “osteoporotic”   fracture</td>
<td>23.2</td>
<td>14.7</td>
<td>367</td>
<td>1.8 (1.3 to 2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 or more fractures</td>
<td>7.4</td>
<td>3.1</td>
<td>367</td>
<td>2.5 (1.4 to 4.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Vertebral</td>
<td>4.1</td>
<td>0.4</td>
<td>367</td>
<td>10.0 (2.9 to 34.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip</td>
<td>1.6</td>
<td>0.3</td>
<td>367</td>
<td>6.0 (1.2 to 29.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ribs/sternum</td>
<td>5.4</td>
<td>1.8</td>
<td>367</td>
<td>3.2 (1.6 to 6.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Wrist</td>
<td>5.7</td>
<td>6.1</td>
<td>367</td>
<td>0.9 (0.5 to 1.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Upper limb (not wrist)</td>
<td>4.4</td>
<td>2.0</td>
<td>367</td>
<td>2.1 (1.1 to 4.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lower limb</td>
<td>5.7</td>
<td>4.5</td>
<td>367</td>
<td>1.3 (0.7 to 2.3)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain in past year</td>
<td>54.3</td>
<td>48.2</td>
<td>362</td>
<td>1.3 (1 to 1.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Bruising</td>
<td>72.9</td>
<td>10.9</td>
<td>362</td>
<td>21.9 (13.9 to 34.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>59.8</td>
<td>19.3</td>
<td>360</td>
<td>6.7 (4.8 to 9.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height loss of 2.5cm  (since age 25)</td>
<td>37.6</td>
<td>26.3</td>
<td>367</td>
<td>1.7 (1.3 to 2.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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<th>Control group (%)</th>
<th>No of case control sets</th>
<th>Unadjusted odds ratio (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataracts</td>
<td>18.4</td>
<td>8.6</td>
<td>365</td>
<td>2.6 (1.8 to 3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.5</td>
<td>4.6</td>
<td>364</td>
<td>1.4 (0.8 to 2.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17.8</td>
<td>23.5</td>
<td>356</td>
<td>0.7 (0.5 to 1.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>29.7</td>
<td>2.7</td>
<td>364</td>
<td>15.5 (8.7 to 27.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of H₂ antagonists</td>
<td>22.6</td>
<td>7.8</td>
<td>367</td>
<td>3.5 (2.4 to 5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shingles (since)</td>
<td>12.5</td>
<td>9.4</td>
<td>367</td>
<td>1.4 (0.94 to 2.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Respiratory diagnosis</td>
<td>29.2</td>
<td>9.2</td>
<td>367</td>
<td>3.2 (1.6 to 6.6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Obtained by conditional logistic regression.

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Fracture risk

Patients taking oral corticosteroids had significantly more fractures than the control group (odds ratio 1.8) and were more likely to have had two or more fractures (OR 2.5) and fractures of the vertebrae (OR 10), hip (OR 6), and ribs or sternum (OR 3.2; table 2). Corticosteroid use did not affect the prevalence of fractures of the wrist, clavicle, or scapula. Adjustment for the differences between the steroid and control group in smoking, current regular exercise, and most strenuous daily activity had little effect on the size of the odds ratios (adjusted OR for total fractures 1.75, 95% CI 1.1 to 2.7). The only modifying effect of sex was in relation to having two or more fractures (pinteraction = 0.03) which was increased in women (12% v 4%) but not in men taking corticosteroids. Height loss of 2.5 cm or more was more common in women taking corticosteroids (45% v 28%) but not in men.

Other adverse effects

The problems reported most frequently by patients taking oral corticosteroids include bruising (73%), muscle weakness (60%), back pain (54%), oral candidiasis (30%), indigestion (23%), and a diagnosis of cataract (18%). All occurred significantly more frequently in the patients on oral corticosteroids than in the control population with odds ratios ranging from 1.3 for back pain to 21 for bruising (table 2). Diagnoses of diabetes and herpes zoster were slightly more common in the corticosteroid group but the differences from control were not significant. More control subjects reported a diagnosis of hypertension. Half the patients taking oral corticosteroids had no natural teeth compared with 39% in the control population (p<0.001) and, of those with teeth, twice as many reported that they were in poor condition.

STUDY 2: ORAL CORTICOSTEROID DOSE RESPONSE STUDY

Demographic data for the patients according to quartiles based on their cumulative dose of prednisolone are shown in table 3. The dose of prednisolone approximately doubled for each successive quartile with a slightly greater increase in the highest quartile. There was little difference in mean age between quartiles but there were more women in the highest dose quartile. After allowing for confounding variables there was a dose related increase in all fractures, vertebral fractures, and two or more fractures. The odds ratio for risk of fracture in the highest compared with the lowest quartile ranged from 2.2 for any fracture to 9 for vertebral fractures (table 4, fig 1). All hip fractures occurred in the two highest dose quartiles. There was also a highly significant dose relationship between oral corticosteroid use and cataract, bruising, and muscle weakness after allowing for confounding variables with odds ratios for the highest compared with the lowest quartile of 3 for cataract and muscle weakness

| Table 3 Demographic data for the corticosteroid quartiles (total cumulative dose of prednisolone) |
|---------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Corticosteroid quartile         | 1     | 2      | 3      | 4      |
| Mean (SD) demographic data     |        |        |        |        |
| Age                            | 71 (9.0) | 68 (9.4) | 71 (8.7) | 67 (9.4) |
| Women (%)                      | 47     | 39     | 47     | 60     |
| Age at menopause               | 46 (4.5) | 48 (4.7) | 47 (5.5) | 47 (4.7) |
| Dose of prednisolone           | 5.1    | 11.7   | 23.6   | 60.6   |
| Median cumulative (g)          | 1.1–7.7 | 7.8–16.3 | 16.4–37.4 | 37.6–186 |

| Table 4 Relationship of 30 year cumulative incidence of fracture, cataract, ever and current bruising, and muscle weakness with total cumulative corticosteroid dose quartiles |
|---------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Corticosteroid quartile         | 1     | 2      | 3      | 4      |
| Analysis OR 95%CI               |        |        |        |        |
| All fracture UV                 | 1.0   | 1.5    | 1.8    | 1.9    |
|                  MV               | 1.0   | 1.96   | 0.95 to 4.0 | 2.13  | 2.04 to 4.4 | 2.22  | 1.04 to 4.8 | 0.04 |
| Vertebras UV                    | 1.0   | 1.0    | 3.3    | 4.4    |
|                  MV               | 1.0   | 1.4    | 0.31 to 6.7 | 4    | 1.06 to 15 | 9.2   | 2.4 to 36 | <0.001 |
| Ribs/sternum UV                 | 1.0   | 5.6    | 5.5    | 3.8    |
|                  MV               | 1.0   | 6.3    | 1.23 to 33 | 5.9  | 1.14 to 31 | 5.4   | 0.94 to 31 | 0.1   |
| 2 or more fractures UV          | 1.0   | 1.2    | 1.8    | 2.5    |
|                  MV               | 1.0   | 1.9    | 0.61 to 5.7 | 2.4  | 0.83 to 7.1 | 4.1   | 1.4 to 12 | <0.01 |
| Cataract UV                     | 1.0   | 0.7    | 2      | 1.6    |
|                  MV               | 1.0   | 0.9    | 0.36 to 2.3 | 2.5  | 1.1 to 5.6 | 3.1   | 1.3 to 7.5 | 0.002 |
| Bruising UV                     | 1.0   | 1.5    | 2.8    | 4.2    |
|                  MV               | 1.0   | 2.2    | 1.03 to 4.6 | 3.9  | 1.7 to 8.6 | 9.4   | 3.6 to 25 | <0.001 |
| Muscle weakness UV              | 1.0   | 1.3    | 1.9    | 2.1    |
|                  MV               | 1.0   | 1.5    | 0.79 to 3 | 2.5  | 1.2 to 5 | 3.3   | 1.5 to 7 | <0.001 |

Odds ratios are given using multiple logistic regression analysis in relation to the first quartile in a univariate (UV) and multivariate (MV) analysis with 95% confidence intervals for the latter.
and 9 for bruising. There was no significant difference in any outcome measure between patients taking continuous oral corticosteroids and those receiving frequent intermittent courses after allowing for total cumulative prednisolone dose and other variables.

The effects of duration of oral corticosteroid use and mean dose over the previous 6 months were less marked than the effects of cumulative oral corticosteroid dose. Nevertheless, duration of treatment was significantly related to vertebral fracture (adjusted OR for highest v lowest quartile = 4.3) and bruising (OR 4.7) whereas mean dose over the previous 6 months was related to all fractures (OR 2.3), vertebral fracture (OR 5.0), two or more fractures (OR 5.6), bruising (OR 2.0), and cataract (OR 2.6).

Discussion

Oral corticosteroids are of great benefit in many conditions and can be life saving. Adverse effects were noted shortly after their introduction11–13 but the extent and magnitude of these adverse effects in relation to dose are not well documented. We have looked at adverse effects in a large community population of patients compared with control subjects and have related the incidence of adverse effects to the total dose of oral corticosteroids used.

Our main end point was the cumulative incidence of fractures since osteoporosis and the associated risk of fracture is a major concern with oral corticosteroid use and has considerable public health implications.14

We compared adverse effects in each patient with two age and sex matched control subjects from the same general practice over the same time period. Our questionnaire response rate for both cases and controls was reasonable, considering the delays that arise in updating general practice lists. The case response rate exceeded that for the control subjects as expected, since the steroid group was identified from recent prescriptions. It is possible that the lower response rate in the control subjects led to an overestimate of fracture rate in this group, since subjects with a fracture may be more likely to respond to the questionnaire than those without. This would cause the impact of oral corticosteroids on fracture to be underestimated. On the other hand, we cannot exclude a possible effect of recall bias on some end points since patients taking oral corticosteroids may be aware of potential adverse effects and more likely to report bruising and back pain, and antacids may be prescribed more readily. It seems unlikely, however, that this bias will extend to the reporting of major events such as fracture and cataract, with the possible exception of vertebral fractures. In the event, the size of the effects we observed for the main end points was large and consistent between the case-control and dose response studies.

The first study confirmed the increased risk of fracture in patients taking oral corticosteroids seen in previous studies.2–6 The greatest effect was seen with vertebral fracture where the odds ratio was 10 compared with the control subjects. These figures are higher than most previous estimates but comparison between studies is difficult due to different methods of ascertainment of vertebral fractures, small size of previous studies, and confounding by diseases such as rheumatoid arthritis which affect fracture risk independently.15 Our figures will underestimate the true incidence of vertebral fracture since they refer to the number of patients who were aware that they had had a vertebral fracture and did not assess the number of vertebral fractures that a patient might have had. Although the major effect of corticosteroids is on trabecular bone, hip fracture was increased among the patients which is in keeping with previous findings.16, 17 The increased risk of fractures with oral corticosteroids was seen in both sexes although loss of height was greater in women.

In study 2 we analysed the cumulative incidence of fractures in the last 30 years to ensure comparable time periods of observation for each dose quartile while minimising the number related to sport and accidents in young adults. The risk of having a fracture was closely related to dose and again the largest effect was seen with vertebral fractures where the odds ratio for patients in the highest dose quartile compared with those in the lowest quartile was 9. The dose related effects of corticosteroids on fracture may be an underestimate since some fractures would have occurred prior to corticosteroid use and the steroid dose refers to the total dose before and after the fracture occurred. Most of the corticosteroid and fracture data were derived from the questionnaire and computerised records so the opportunity for observer bias was minimal. The study had limited power to look at the shape of the dose response relation to oral corticosteroid use but there was no evidence of a plateauing of effect with higher doses.

A wide range of other adverse effects of oral corticosteroids has been documented previously although the incidence of specific complications has varied considerably11–15 because of small numbers and differences in the patients studied. Our study confirmed the association of oral corticosteroids with bruising, muscle weakness, oral candidiasis, use of antacids, and cataracts. We also found that patients taking oral corticosteroids were more likely to have no natural teeth or teeth in poor condition, although whether this is due to oral corticosteroids or to the concomitant use of inhaled drugs by these patients is uncertain.19, 20

The outcome measures which showed the largest difference between patients and control subjects in study 1 (vertebral fractures and bruising) also showed the greatest dose related effects in study 2.

This study has shown substantial differences in the risk of fractures and other adverse effects between a community based population of patients with lung disease taking oral corticosteroids and an individually matched control group. The adverse effects were strongly related to the total cumulative dose of prednisolone taken. Many of these adverse effects cause considerable morbidity to patients. The extent to which the adverse effects could have
been avoided or prevented by lower doses of prednisolone or by preventative therapy is uncertain, but the low incidence of treatment to prevent osteoporosis is notable. Quantifying the morbidity from oral corticosteroids in the community and knowing the extent to which their adverse effects are dose related should encourage policies to prevent adverse effects and help rational prescribing of these valuable and widely used drugs.

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