Prevention of Corticosteroid Induced Osteoporosis in Inpatients Recently Discharged from a Tertiary Teaching Hospital

MALCOLM D. SMITH, SAU PENG CHEAH, KAREN TAYLOR, and MICHAEL J. AHERN

ABSTRACT. ***Objective.*** To determine the medical conditions for which oral corticosteroids are prescribed and to determine the frequency and type of osteoporosis prophylaxis offered to these patients.

Methods. Medical records of all inpatients for the period March to October 1999 who were documented in pharmacy records as either having received continuous oral steroids for at least 3 months or who had at least 4 courses of oral steroids per year were examined for the following data: age, sex, medical condition for which steroids were required, dose and duration of steroid therapy, whether they were offered bone mineral density (BMD) scans, and whether they were offered drug prophylaxis for steroid induced osteoporosis and the type of drug prophylaxis offered. Followup telephone calls were made to verify patients' use of prophylactic treatment and to validate the chronic use of oral corticosteroids. Use of BMD testing was also validated by comparing the list of patients in this study with the records of bone densitometer units in the area.

Results. A total of 189 medical records were examined: 38% were women (n = 72) and 62% were men (n = 117), with an age range of 19–91 years; 73% were taking continuous steroid therapy, the remaining 27% had multiple courses of prednisolone through the year. Steroids were prescribed for respiratory (n = 82, 43%), rheumatological (n = 74, 39%), hematological (n = 16, 8%), dermatological (n = 8, 4%), and gastrointestinal conditions (n = 7, 4%). Chronic obstructive airway disease was the most common respiratory condition for which steroids were prescribed (77, 94%), and polymyalgia rheumatica (36%) and inflammatory arthritis (41%) were the most common rheumatological conditions for which steroids were prescribed. In total, 47% (n = 89) were offered BMD scans while 53% (n = 100) were not. Of the 100 patients not offered BMD scans, 21 (21%) were receiving some form of drug prophylaxis, while 79% of patients were not taking any form of drug prophylaxis. Prophylaxis consisted of calcitriol (64%), alendronate (11%), calcitriol and calcium (7%), calcium alone (7%), alendronate and calcium (3%), etidronate and calcium (2%), alendronate, calcitriol and calcium (1%), alendronate and calcitriol (1%), and hormone replacement therapy (4%). Rheumatologists utilized both BMD testing and prophylactic treatment twice as often in patients taking chronic oral corticosteroid treatment than other specialty physicians.

Conclusion. Compared to literature reports, the use of prophylaxis for corticosteroid induced osteoporosis was relatively high at this teaching hospital, with a surprisingly large number of patients receiving this treatment with no monitoring by BMD measurements. (J Rheumatol 2001;28:566–70)

Key Indexing Terms:
OSTEOPOROSIS CORTICOSTEROIDS PROPHYLAXIS

While oral corticosteroids are an essential component in the management of many conditions, the chronic use of corticosteroids can be associated with a number of adverse effects including skin changes, truncal obesity, diabetes, hypertension, and osteoporosis[1]. Chronic oral corticosteroid use is one of the major iatrogenic causes of osteoporosis[2], which is still underdiagnosed and often inadequately treated[3]. A large cross sectional retrospective study[1] of 303 patients who were undergoing continuous corticosteroid treatment showed that only 14% had received prophylactic treatment to prevent bone loss. A telephone survey[4] showed that of 147 patients who were receiving a mean prednisolone dose of 10 mg per day, 42% were receiving no preventive treatment. Another study[5] of corticosteroid treated hospital inpatients reported that only 12 of 214 patients (5.6%) were receiving any form of osteoporosis prophylaxis. Considering that there is now a simple method to accurately measure bone density[6] and ample evidence that intervention can prevent bone loss and its associated morbidity[7-9], it seems appropriate that a more aggressive

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approach to the prevention of osteoporosis should be taken by medical practitioners who prescribe corticosteroids.

We investigated the prevalence of bone mineral density (BMD) testing and the use of treatment to prevent osteoporosis in a cohort of patients recently discharged from a tertiary referral teaching hospital who were prescribed oral corticosteroid treatment.

MATERIALS AND METHODS

A retrospective audit of inpatients admitted to an Australian teaching hospital over an 8 month period was performed to determine the conditions for which corticosteroids are prescribed, the use of BMD testing in this patient group, and the frequency and type of osteoporosis prophylaxis offered to these patients. A list of potentially eligible patients was obtained from the pharmacy computer records of patients discharged from the Repatriation General Hospital (RGH) over a 3 month period from August 16 to October 25, 1999, taking ≥ 5 mg prednisolone. This was supplemented by a manual search of all inpatient discharge prescriptions for the period from March 1 to August 15, 1999, and including any patient who was discharged taking ≥ 5 mg prednisolone.

The medical records for all patients identified in this audit (215 patients) were then retrieved and searched by one author (SPC). Subjects were considered eligible for this audit if they were either taking continuous oral corticosteroids for at least 3 months or had at least 4 courses of oral corticosteroids per year, with a dose of ≥ 5 mg prednisolone.

The following information was retrieved from the medical records of all eligible patients: age, sex, condition for which corticosteroids were prescribed, dose and duration of corticosteroid therapy, performance and result of a BMD test, whether they were offered drug prophylaxis and the type of drug prophylaxis, and whether the patient had had a fracture documented by radiograph at any time. Medical conditions for which corticosteroids were prescribed could be categorized under 5 main general headings: respiratory, rheumatological, hematological, dermatological, and gastrointestinal.

A followup telephone call to each patient was made (by KT), to validate the information extracted from the medical record, to establish the continuation of chronic corticosteroid usage and the compliance with any osteoporosis prophylactic treatment, and to enquire whether a BMD test had been performed since discharge from hospital. Twenty-six patients had died after discharge from hospital and telephone confirmation could not be undertaken. These patients were excluded from further data analysis. The performance of BMD tests on this group of patients was independently validated by screening the records of all BMD tests performed at 2 tertiary referral hospitals in the area, and only those patients with a record of having had BMD testing were included in the BMD data analysis.

Statistics. The number of patients offered BMD testing and prophylactic treatment who were managed by rheumatologists compared to those managed by other physicians was analyzed using 2 × 2 contingency tables, using a chi-squared approach with 2 degrees of freedom. A p value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 330 medical records were retrieved, with 215 patients fulfilling the entry criteria for this audit, but 26 patients could not be contacted by telephone for confirmation of the data. Therefore 189 patients were finally included; the demographic details of this patient group are presented in Table 1. About 73% were undergoing continuous corticosteroid therapy, while the remaining 27% had multiple courses of prednisolone through the year, predominantly for chronic airway obstruction (COAD). Duration of corticosteroid treatment was known for about 73% of subjects. There was variable duration of corticosteroid usage, with the majority of patients receiving corticosteroids for less than 3 years (Table 1). The main medical conditions for which corticosteroids were prescribed were respiratory conditions (n = 82, 43%), rheumatological conditions (n = 74, 39%), hematological conditions (n = 16, 8.5%), dermatological conditions (n = 8, 4.2%), and gastrointestinal conditions (n = 7, 3.7%) (Table 1). COAD was the most common respiratory condition for which corticosteroids were prescribed (77 patients, 94%), while polymyalgia rheumatica (36%) and inflammatory arthritis (41%) were the most common rheumatological conditions for which corticosteroids were prescribed.

Table 1. Demographic details of patient group studied in the audit.

Number	189
Sex, M:F	117:72
Age, mean ± SD yrs	75.2 ± 10.5
Age range, yrs	19–91
Duration of corticosteroid treatment, yrs (%)	
0–1	94 (49.7)
1–2	33 (17.4)
2–3	34 (18)
3–4	14 (7.4)
4–5	7 (3.7)
> 5	7 (3.7)
Condition treated (%)	
Respiratory	82 (43)
Musculoskeletal	74 (39)
Hematology/oncology	16 (8.5)
Dermatology	8 (4.2)
Gastroenterology	7 (3.7)
Other	2 (1.1)
Number discharged with prophylaxis	100 (53)
Number continuing prophylaxis on followup	90 (47.6)
Number of fractures	42

Of the 189 subjects, 47% (n = 89) were offered BMD scans, while 53% (100 patients) were not. Women were more likely to have a BMD performed (BMD group 45% female, non-BMD group 29% female). As almost all women in this group were postmenopausal, it was not possible to assess any effect of the menopausal state of the woman on the likelihood of a BMD test being performed. Of 100 patients not offered BMD scans, 21% were receiving some form of drug prophylaxis for corticosteroid induced osteoporosis compared to 67% of the patients offered BMD (chi-squared = 41.4, $p < 0.001$). In the total patient group (189 subjects), 47% were not prescribed any form of prophylactic therapy. For those who were taking prophylaxis for corticosteroid induced osteoporosis, the treatments offered were calcitriol (64%), alendronate (11%), calcitriol and calcium (7%), calcium alone (7%), alendronate and calcium (3%), sodium etidronate and calcium (2%), alendronate, calcitriol and calcium (1%), alendronate and calcitriol (1%), and hormone replacement therapy (4%) (Figure 1). Ten patients

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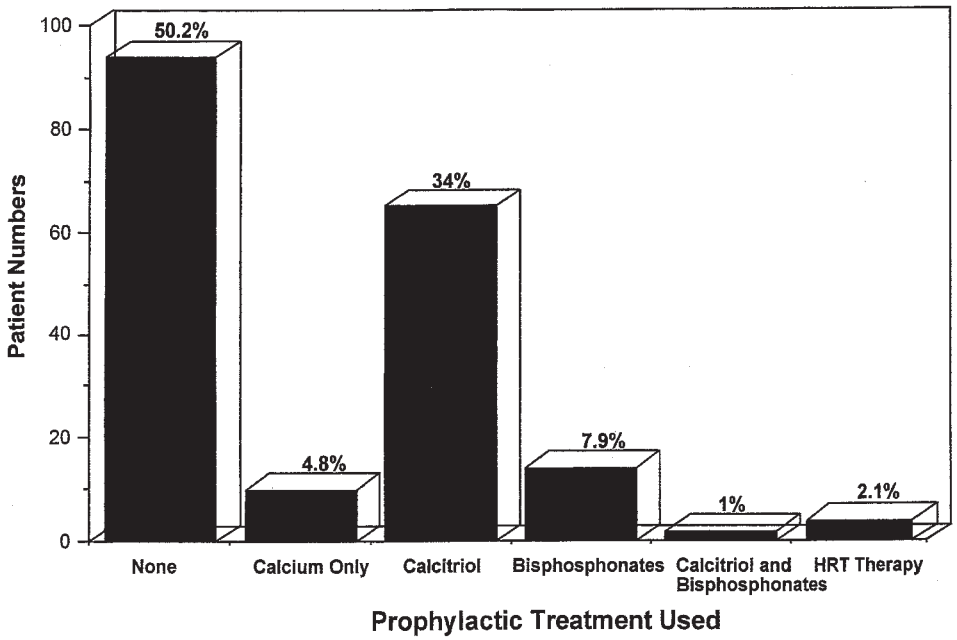

Figure 1. Prophylactic treatment offered to patients undergoing longterm oral corticosteroid treatment, at the time of discharge from hospital.

(10% of all patients prescribed prophylactic treatment) had ceased prophylaxis for corticosteroid induced osteoporosis after discharge from hospital, mainly due to costs of or difficulty obtaining the prescribed prophylactic treatment. Forty-two (22%) of this group of patients had sustained a fracture at some time (32 crush vertebral fractures, 6 fractures of the neck of femur, 3 rib fractures, one wrist fracture), confirmed radiologically. Patients managed by rheumatologists were more likely to be offered BMD testing (68%) and prophylactic treatment (59%) than those managed by other specialists (BMD testing 34%, prophylactic treatment 32%; chi-squared for BMD testing 20.47, $p < 0.001$, chi-squared for prophylactic treatment 13.69, $p < 0.001$). The patient group was analyzed according to the disease state for which oral corticosteroids were prescribed (COAD/asthma, nonmalignant non-COAD conditions, and malignant conditions), irrespective of the specialty of the treating physician. There were significant differences between the 3 disease groups (chi-squared 7.225, $df = 2$, $p < 0.05$ for BMD testing; chi-squared 6.395, $df = 2$, $p < 0.05$ for prophylactic treatment), but these differences were due to only 10% of patients with malignancy being offered BMD testing or prophylactic treatment. When the group of patients with malignancy was excluded from the analysis, there were no differences between the disease groups. Therefore, the more significant factor determining the use of BMD testing and prophylactic treatment was the type of specialist physician rather than the disease being treated with corticosteroids.

DISCUSSION

The pathogenesis of corticosteroid induced osteoporosis is complex and multifactorial[10,11]. The cellular mechanisms of corticosteroid induced bone loss have yet to be clearly defined. Preliminary studies showed that patients who have undergone longterm corticosteroid treatment have reduced bone turnover and decreased bone formation at the cellular level[12]. Supraphysiological concentrations of corticosteroids inhibit osteoblast proliferation and differentiation and stimulate osteoblast apoptosis. In addition, reduced expression of type I collagen, osteocalcin, insulin-like growth factor-1 (IGF-1), and IGF binding proteins 3 and 5 that enhance IGF-1 activity has been described. Corticosteroids also seem to decrease transforming growth factor-ß activity, resulting in an increase in binding to nonsignaling receptors. In addition to these direct suppressive actions on bone formation, bone resorption is increased predominantly by indirect means, including hyperparathyroidism secondary to reduced intestinal calcium absorption, increased calcium excretion in the urine, and hypogonadism resulting from corticosteroid induced effects on the hypothalamic-pituitary axis and gonads.

LoCascio, *et al*[13] found that bone loss occurs predominantly in the first 5–7 months of treatment with corticosteroids, with only minor changes observed after 12 months of treatment. However, the findings of this study are contrary to the general perception of chronic corticosteroid use, which is that higher doses and longterm therapy are

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more likely to be associated with greater bone loss[3]. The "safe" minimum dose below which there is likely to be no bone loss has yet to be established, with some evidence suggesting that daily doses of prednisolone lower than 7.5 mg have no longterm adverse effects[14]. However, this finding is controversial[15].

The level of prophylaxis for corticosteroid induced osteoporosis was unusually high in this patient group compared to that reported in previous studies. Peat, *et al*[5] showed in a survey of corticosteroid treated hospital inpatients that only 5.6% received any form of bone protection treatment. Other investigators[16] commented that in the UK over 25,000 patients take continuous oral corticosteroids and only 14% receive any therapy to prevent bone loss. This audit, however, showed that the treating medical practitioners at our hospital are active in prescribing prophylactic treatment for corticosteroid induced osteoporosis, with slightly more than half the patients undergoing chronic corticosteroid treatment receiving some form of bone protection. Interestingly, a large percentage of these patients were not offered BMD scans. BMD measured using dual energy x-ray absorptiometry (DEXA) is currently the single best estimate of bone strength[6]. While BMD scans are not essential in the prevention of corticosteroid induced osteoporosis, this test is useful for monitoring the effects of intervention and to aid treatment decisions in certain situations. One possible reason for the low number of BMD scans noted in this study could be the incomplete documentation in the medical record of the performance of BMD scans, as the lack of any documentation of a BMD scan result in the medical record was recorded as no BMD scan having been performed. However, an attempt was made to validate this result by searching the data base of BMD tests performed at the 2 major tertiary referral hospitals in the region.

Some patients in this audit were prescribed calcium alone as prophylaxis for corticosteroid induced osteoporosis, despite there being no good evidence that calcium supplementation alone has any efficacy[9,17]. Sixty-four percent of those offered drug prophylaxis were prescribed calcitriol. Two overlapping metaanalyses found that natural or synthetic vitamin D supplementation, along with calcium, produced a clinically and statistically significant reduction in bone loss at the lumbar spine and forearm, but not at the femoral neck[18,19]. Unfortunately, the tendency to reduce fracture incidence did not reach statistical significance. Bisphosphonate use is the only treatment to date that not only prevents bone loss but helps increase bone mass, as shown in a metaanalysis that pooled data from 13 studies where patients taking corticosteroids were treated with etidronate, alendronate, risedronate, or placebo[20]. BMD measurements at the lumbar spine were 4% higher (95% CI 2.5–5.5) in the bisphosphonate treated patients than in the controls after 12 months of treatment. Calcitriol was the main prophylactic treatment offered in this patient group, partly because until recently only vitamin D or its synthetic analogs (e.g., calcitriol) had evidence to support a role in prophylaxis for corticosteroid induced osteoporosis. In addition, calcitriol is often better tolerated by elderly patients than bisphosphonates and the longterm compliance with hormone replacement therapy has been shown to be low[21,22].

Guidelines for the prevention of corticosteroid induced osteoporosis have been published[23,24], with prophylactic treatment recommended for patients who are taking > 7.5 mg per day of prednisolone, but there may be a case for special consideration for the elderly population, such as our patients included in this audit, who are likely to be at risk of age related as well as corticosteroid induced osteoporosis. However, current government prescribing restrictions in Australia inhibit the use of calcitriol or bisphophonates in patients taking longterm corticosteroid therapy, except those who have already had an osteoporotic fracture. This results in many patients who require prophylactic treatment for either postmenopausal or corticosteroid induced osteoporosis being disadvantaged by the prohibitive cost of unsubsidized prophylactic treatments. A change in the government regulations in Australia will be necessary to allow effective primary prevention of corticosteroid induced osteoporosis for those patients receiving chronic corticosteroid treatment.

Another possible explanation for these results is that it reflects a greater awareness of the potential for osteoporosis in this relatively older age group of patients, which would be further exacerbated by chronic corticosteroid therapy. This might reflect a greater awareness of this potential health issue in the medical community, possibly enhanced by continuing medical education either at a local level or in recent medical publications. Buckley, *et al*[25] assessed the variations in physicians' judgments about risks and efficacy of treatment to prevent corticosteroid induced osteoporosis using a postal questionnaire sent to 425 physicians, 50% of whom were specialists. Only 50% of physicians responded to the survey. Most physicians rated osteoporosis one of the 3 most significant side effects of corticosteroid treatment; however, there was significant variation in physicians' judgments about the importance of corticosteroid induced osteoporosis. There was also significant variation in physicians' judgements about the importance of discussing osteoporosis as a side effect with patients and their use of prophylaxis. The physician characteristics most associated with these variations were physician specialty and experience with corticosteroid use. Primary care physicians and physicians who commonly prescribe corticosteroids were more likely to report that they would prescribe prophylaxis to prevent corticosteroid induced bone loss. Another study[4] reported that patients evaluated by primary care physicians and rheumatologists were more likely to have had bone density testing and to have received preventive treatments than were patients of other specialists. While 43% of the subjects in

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this study were treated with oral corticosteroids for respiratory conditions, only 34% were offered BMD testing, and 32% were offered prophylactic treatment if managed by a respiratory physician. This contrasted with patients managed by a rheumatologist, of whom 68% were offered BMD scans and 59% were receiving prophylaxis for corticosteroid induced osteoporosis.

The major influence on the use of BMD testing and prophylactic treatment appears to be an awareness of the potential for chronic low dose oral corticosteroid therapy to cause osteoporosis and the prophylactic treatment options available. This is clearly an area that can be significantly improved by further medical education.

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