EXTENDED REPORT

Prevalence of long term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice

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Ann Rheum Dis 2002;**61**:32–36

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Accepted 5 July 2001

Background: The use of oral corticosteroids (CS) is one of the most common causes of iatrogenic osteoporosis. Recently, therapeutic guidelines dealing with the skeletal complication of CS have been published.
Objective: To evaluate how CS are used in the community and the frequency of active intervention against corticosteroid induced osteoporosis in daily clinical practice.
Material and methods: After approval by the Committee on Medical Ethics and the Data Protection Commission all prescriptions for CS which were filled by pharmacies in the northeast area of Iceland (population 26 664) during a two year period were collected. Thereafter, clinical information was obtained from medical records at the healthcare centres and from the local hospital. Patients who were taking CS for at least three months a year or for repeated periods (for a total of three months annually) were included in the study. These patients also received a questionnaire about hormone replacement therapy, bisphosphonates, and dietary consumption of calcium and vitamin D.
Results: A total of 191 patients were included in the study or 0.7% of the population. Their mean age was 66 years (17–93) and 106/191 (55%) were women. Only 63 (33%) patients had no registered complication due to the treatment, according their medical records. Thirty nine (20%) patients had had an osteoporosis related fracture and 50 (26%) of the patients had presumed CS induced osteoporosis. A total of 52% patients were receiving supplementary vitamin D (fish liver oil) and 37% were taking calcium tablets regularly, while 91% of the patient group were consuming milk products regularly. Only 17 (9%) patients were taking bisphosphonates and 18/81 (22%) of the postmenopausal women were receiving hormone replacement therapy.
Conclusions: Relatively few patients receiving long term treatment with CS are also receiving primary prevention against CS induced osteoporosis, although several patients are taking vitamin D and calcium tablets. Specific treatment against osteoporosis was in most cases instituted secondary to osteoporotic complications. Thus although there are available treatment alternatives against CS induced osteoporosis, the doctors who prescribed CS did not make use of this form of treatment for their patients.

On 21 September 1948 Philip Showalter Hench, a rheumatologist working at the Mayo Clinic in Rochester, Minnesota, in the USA, treated a patient with rheumatoid arthritis with an extract which his colleague Edward Calvin Kendall, a biochemist, had managed to isolate from adrenal gland cortex. Initially they referred to this extract as compound E,[1] which later became known as cortisone. This first patient, a 29 year old woman with a history of four and a half years of polyarthritis, demonstrated remarkable improvement during the days following treatment. In 1950, only two years later, Hench and Kendall, together with a biochemist from Switzerland, Tadeus Reichstein, were awarded the Nobel prize for their discovery.[2]

Half a century later, glucocorticosteroids (CS) are still used for several acute and chronic disorders.[3 4] CS have a prompt anti-inflammatory effect and are relatively safe for short term use. On the other hand, serious complications have often been reported in long term users.[4 5] The most serious complication associated with long term use of CS is probably steroid induced osteoporosis; thus CS are the most common cause of iatrogenic osteoporosis in the younger age group.[6] In addition, patients with rheumatoid arthritis who have been treated with CS have a significantly increased risk of fragility fractures.[7]

In Iceland, 1.3 million tablets of prednisolone (5 mg) and 200 000 tablets of dexamethasone (0.5 mg) are used annually in a population of 270 000 (personal communication with Delta hf and Farmasia ehf). There is little reported information about how and why CS are used in the general population. Only two studies have focused on this subject, both conducted in England.[8 9] These studies demonstrate that 0.5–0.9% of the population in England are receiving long term treatment with CS.[8 9] Furthermore, other studies indicate that prophylactic treatment against steroid induced osteoporosis is not given enough attention.[5 10] No population based epidemiological information is available on the use of CS in the Scandinavian countries.

Recently, both the British Association for Rheumatology and the American College of Rheumatology published consensus papers on prophylactic measures against steroid induced osteoporosis in rheumatic patients who are in need of CS.[11 12] Similar recommendations are being developed in Iceland and other northern countries. At this point, it is of interest to analyse the use of CS in an unselected population and to evaluate the prevalence of decision making by doctors for the prevention of corticosteroid induced osteoporosis.

Abbreviations: CS, corticosteroids; DEXA, dual *x* ray absorption; HRT, hormone replacement therapy

MATERIAL AND METHODS

Patient selection

All prescriptions for oral prednisolone (H02AB06) during the 24 month period January 1995 to December 1996 which were filled by pharmacies in northeast Iceland were included in this study. Subjects who received at least two prescriptions for prednisolone during this period were informed by letter and asked for permission to review their medical records, both at their respective healthcare centre and the outpatient clinic at the Akureyri Central Hospital. Those patients who did not respond were sent a reminder two weeks later.

All patients who were taking prednisolone before January 1995 and cumulatively after treatment that lasted for more than three months were included in the study, as well as those patients who received repeated treatment that lasted for more than three months annually.

Questionnaire and collection of data

All participants sent the letter requesting participation in the study also received a questionnaire asking about consumption of milk and milk products, vitamins, calcium tablets, and the use of Icelandic fish liver oil—Lysi (containing 11–22 μg of vitamin D per 5 ml (440–880 i.a.), depending on the type of fish liver (cod, shark, or coalfish)), as well as questions about drug consumption—for example, bisphosphonates, calcitonin, and hormone replacement therapy (HRT).

Information was collected from the patients' records on indications for the treatment and the initial dose of prednisolone, and the mean dose of prednisolone was calculated. Symptoms and signs which the doctor responsible registered as possible complications due to the treatment were also recorded.

Demographic data

During the study period, six full time practising internists were present in the area: a cardiologist, a gastroenterologist, a geriatrist, a lung specialist, and two rheumatologists. In addition, consultants in oncology were contacted regularly. Of 22 doctors working as general practitioners in the healthcare centres in the study area, one was an internist and lung specialist, another was a specialist in dermatology and venereal diseases, and the third was a paediatrician. Almost all outpatient specialist services were provided at the local hospital, where 48 specialists in different fields of medicine provided consultations. About 26 700 inhabitants were living in the area during the time of the study.

Statistics

The data were coded and entered in an Excel program and further analysed, using a PC. The study protocol was approved by the Committee on Medical Ethics at the Akureyri Central Hospital and the Data Protection Commission.

RESULTS

Use of glucocorticosteroids

During the study 1977 prescriptions for prednisolone were filled for 748 subjects. A total of 349 patients received two or more prescriptions for prednisolone during the study period, and of these, 191 fulfilled the criteria for inclusion in the study. Thus 0.72% of the inhabitants were receiving long term treatment with prednisolone.

The mean age of the participants (106 (55%) women, 85 (45%) men) was 66 years (17–93); 64 for women and 68 for men. Figure 1 shows the female/male ratio in the different age groups.

In 163/191 (85%) cases which were initially included in the study, it was possible to estimate the length of time for which the treatment was continued; the average was 47 months, with a range of 3–300 months (fig 2). In these cases the mean initial dose of prednisolone was 24 mg/day (range 5–80); the average continuous dose was 6 mg/day (2–15). There was no difference in these values between men and women.

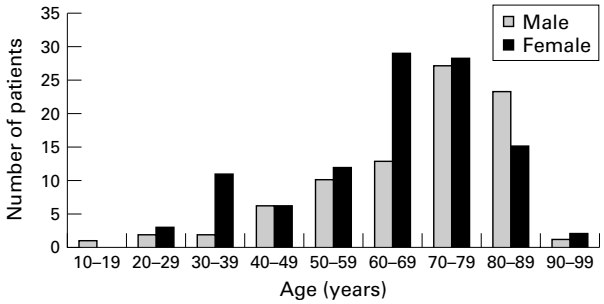

Figure 1 Age and sex distribution of 191 patients taking continuous oral corticosteroids for at least three months.

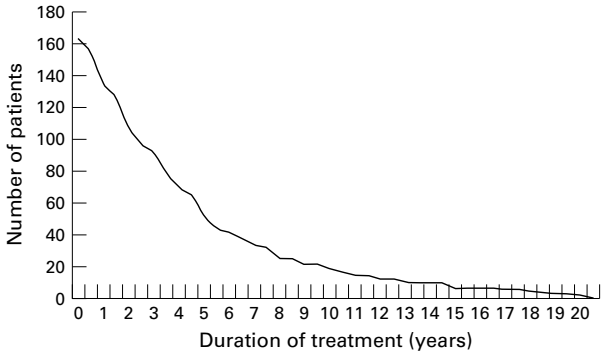

Figure 2 Duration in years of continuous oral corticosteroid treatment in 163 patients. The length of time was calculated from the start of the treatment to the end of the treatment or to the date of the study.

Rheumatic disorders were the most common indication for long term use of prednisolone (44%), followed by pulmonary diseases (table 1).

Complications

Cushing's syndrome (26%), osteoporosis or osteopenia (26%), and fragility fractures (20%) were frequently reported in patient records as a possible complication due to the CS treatment (table 2). In 33% of the records no complication associated with CS was recorded.

Only two women had undergone a bone density measurement with the dual *x* ray absorption technique (DEXA). One had osteoporosis (T score: L2–4 –3.53SD; femoral neck

Table 1 Medical disorders for which oral corticosteroids were prescribed for 191 patients receiving long term treatment

Disorder	No of patients	%
Chronic pulmonary disease*	59	31
Polymyalgia rheumatica	54	28
Rheumatoid arthritis	20	10
Inflammatory bowel disease	15	8
Poststatus organ transplantation	8	4
Temporal arteritis (biopsy proven)	6	3
Neoplasm	6	3
Dermatological disorders	5	3
Pulmonary fibrosis	4	2
Connective tissue diseases	4	2
Other disorders	10	5
Total number of patients	191	100

*Chronic obstructive lung disease and emphysema.

Table 2 Complications due to long term treatment with glucocorticosteroids, diagnosed by the clinicians and registered in the records for 191 patients. No complication which could be related to corticosteroid treatment was recorded in 63 of the 191 patient records (33%)

Complication	No of patients	%
Osteoporosis	50	26
Cushingoid changes	49	26
Fractures (assumed osteoporosis related*)	39	20
Oedema	37	19
Infection problems	24	13
Gastrointestinal complaints	20	10
Cataract/glaucoma	18	9
Hypertension	16	8
Hyperglycaemia/diabetes mellitus	15	8
Dermal atrophy	14	7
Mental symptoms	11	6
Muscular atrophy	4	2
Thrombosis	4	2
Oral mucosal symptoms	1	0.5

*32 compression fractures in vertebral column; three fractures of the distal ulna; and one fracture each of the following: collum femoris, subtrochanter, tibia, and fibula.

–3.20SD) while the other had normal bone density (T score: L2–4 +0.36SD; femoral neck +0.84SD). At the time of the study no DEXA instrument was available in the study area.

Fractures

Of the 191 subjects, 39 patients (25 female, 14 male) experienced a fragility fracture after the beginning of the CS treatment. Most common were vertebral fractures (32 subjects) and three patients had a fracture of the forearm. One patient had a history of fracture of the femoral neck, another of the trochanter area of the hip, and two patients had fracture of the distal tibia. One patient had both vertebral fracture and fracture of the wrist, and the patient who had a hip fracture also had a fractured pelvis.

The mean age of the patients who had fractures was 75 (62–90) or nine years older than the average for the patient group as a whole ($p<0.0001$). However, there was no difference in the initial doses (26 mg *v* 24 mg) or the mean doses of prednisolone (6.3 mg *v* 6.0 mg) in those patients who had a fragility fracture and those who did not. The treatment duration—that is, from the start of the treatment to the time of the fracture, which could be calculated in 23 of these cases was an average of 31 months (range 3–168).

Mortality

Twenty seven patients died during the study period; their mean age was 74. Of these, 10 patients died owing to respiratory failure and three owing to pneumonia. Another 8 patients died because of cardiac failure, five from malignancy, and one patient died owing to cerebral vascular accident. Nine of these patients had had a fracture.

Decision making to prevent corticosteroid induced osteoporosis

According to the patient records, active intervention against steroid induced osteoporosis was carried out in 61/191 (32%) cases. The mean age of these 61 patients (45 female, 15 male) was the same as for the whole group—namely, 66 years (23–93).

Calcium and vitamin D

Of the 164 patients who were alive when the study ended, 132 (80%) returned the questionnaire. According to the answers to the questionnaire, 93% of patients regularly consumed milk products. In addition, 37% of patients were taking calcium tablets and 52% were taking Lysi (fish liver oil), which is rich in vitamin D. At the same time, 38 (29%) patients were taking both calcium tablets and Lysi.

Hormone replacement therapy

Of the 106 female patients, 81 (76%) were menopausal or postmenopausal with a mean age of 64. Only 18 of these women (22%) were receiving HRT. No male patient had been treated with testosterone.

Bisphosphonates

Seventeen patients (9%), nine women and eight men, were receiving bisphosphonates. Of these, 14 subjects received this treatment after they had experienced osteoporosis related fractures, one patient had osteoporosis according to a DEXA measurement, and another patient was assumed to have osteoporosis. In addition, one male patient with diabetes mellitus and recently diagnosed with polymyalgia rheumatica was receiving bisphosphonate as primary prevention against steroid induced osteoporosis.

Of the 39 patients who had a history of fragility bone fractures, 14 (36%) were being treated with bisphosphonates.

Calcitonin

Two patients with major pain problems due to multiple compression fractures of the spine were treated with calcitonin for a short time when they were admitted to hospital.

The 29 patients with assumed osteoporosis (58%) according to the patient records received neither HRT nor treatment with bisphosphonates. On the other hand, 44% of these patients were taking calcium tablets regularly and 58% were receiving supplementary vitamin D (Lysi).

DISCUSSION

This study includes all prescriptions for prednisolone given by general practitioners and specialists in different fields of medicine during a two year period in a well defined area that represents one tenth of the Icelandic population. Thus the results reflect the prescription of CS in an unselected community, where 0.7% of the inhabitants were deemed in need of long term treatment with CS. Furthermore, one fifth of the subjects who needed CS had fragility fractures.

During the study period about 700 subjects received a prescription for CS. In most cases, the treatment was only for a short time. However, one quarter of the patients had been judged in need of treatment for more than three months. These results are similar to those reported for the UK, where 20% of patients who received a prescription for CS were still taking them six months later.[8 9] The mean dose of prednisolone and the length of the treatment in our study were also similar to the figures for the two studies in the UK. The indications for long term treatment with CS both in Iceland and in the UK were in most cases rheumatic and pulmonary diseases. However, inflammatory bowel diseases were seen more frequently in Iceland than in the UK. A recent study showed that specialists in pulmonary medicine and gastroenterology used higher doses of CS than rheumatologists (13.8 mg, 12.7 mg, 8.0 mg prednisolone, respectively), but the rheumatic patients continued the treatment for a longer period—that is, 85 months in comparison with 41 and 61 months in the other two patient groups.[13]

Our study underlines the point that doctors have various problems to deal with when treating patients with CS. Osteoporosis was reported in a quarter of the cases and almost one sixth of the patients had had a spinal fracture. In addition, several other problems were reported. However, caution is necessary in interpreting the results as this study was a retrospective analysis. On the other hand, a prospective study of 128 asthmatic patients showed that 11% of patients who were

receiving oral CS had vertebral fracture(s), whereas none of the patients who were not taking CS orally had such fractures.[14] Osteoporotic fractures give rise to pain problems, disturb daily activity, and profoundly influence the quality of life. Furthermore, they decrease life expectancy,[15] especially for male patients.[16] In addition, fractures due to osteoporosis greatly increase the cost to the healthcare system.[17]

The first report by Cushing illustrated the connection between hypercortisolaemia and osteoporosis[18]; moreover, osteoporosis can even be the first sign of Cushing's syndrome.[19] Shortly after the introduction of "compound E", it was realised that treatment with CS would result in iatrogenic osteoporosis. The negative effect on the bone metabolism by CS is complex and not fully understood. CS influence both the formation of the bone stroma by osteoblasts[20] and the microarchitecture of the bone.[7] Furthermore, CS have a negative effect on the production of sex hormones,[21] which may have a further negative influence on bone turnover. Earlier, influence on the parathyroid hormone by CS was thought to be the major reason for osteoporosis in patients receiving long term CS treatment. However, this theory has recently been questioned.[20] On the other hand, CS disturb the effect of vitamin D on the gastrointestinal mucosa, resulting in an imbalance in the metabolism of calcium[22] and secondary hyperparathyroidism, but even this mechanism is also questioned today.[23] In this context it is right to point out that calcium and vitamin D supplements only inhibit the bone loss associated with CS treatment in a minor fashion during the first year of treatment,[23] but not during the following years, as measured by bone density in the femoral neck.[24] However, although no studies indicate that vitamin D or calcium reduce the incidence of fractures in patients receiving long term treatment with CS, it is generally agreed that the daily requirement of both calcium and vitamin D in such patients should be assured, because it is an inexpensive primary prevention.

The bone loss associated with CS is most rapid early in the treatment phase.[24] Thus 15% of those subjects who are in need of long term treatment with CS can expect a vertebral fracture in their first year of treatment.[25] CS not only reduce the bone mineral density but also influence the microarchitecture of the bone, which results in a further increase of the risk of fracture.[7 26 27] In this context, it has been proposed that patients receiving CS who have a bone density with a T score value of less than −1.5SD (the difference in standard deviation (SD) with respect to the peak bone mass in a young adult of the same race and sex), as measured by DEXA, should be classified as having osteoporosis, instead of a T score of less than −2.5SD, as currently recommended for the diagnosis of postmenopausal osteoporosis.[28]

Most patients in our study took calcium and vitamin D supplements. On the other hand, only 22% of the postmenopausal women used HRT. This percentage was twice as high as that reported for the British population[8] and was also higher than for 64–69 year old Icelandic women in general.[29] Thus our Icelandic patients who are receiving CS more often take calcium and vitamin D, and our female patients more frequently use HRT, than women in the population as a whole.

Only one patient received bisphosphonate as a primary prevention. However, one third of the patients who had a history of fragility fracture were already following this regimen. In the British population only 0.6–2.4% were treated with bisphosphonates. Our study was carried out based on the prescriptions for CS in 1995 and 1996. It should be noted that bisphosphonates were released for general use in Iceland in 1996; thus the percentage of patients with manifest osteoporosis who were taking this drug was acceptable at that time. However, increased use of this regimen and other treatment alternatives for primary prevention of corticosteroid induced osteoporosis is necessary in daily clinical practice.

Steroid induced osteoporosis can partly be prevented and treated. For this it is necessary to start primary prevention at the same time as the CS treatment is begun or to offer active treatment against osteoporosis if the patient already has a history of manifest osteoporosis—that is, the patient has previously had a fragility fracture, or has low bone density (T score <−1.5SD) as evaluated by DEXA. Repeated evaluation by DEXA, to determine the efficacy of the intervention, is advised six or 12 months after the start of the CS treatment. If the T score has decreased more than 3–5% from baseline, the anti-osteoporosis drug should be changed or some other drug added to the present treatment. The different treatment alternatives have been summarised in several reviews recently,[30 31] and both the British and the American Associations of Rheumatology have published consensus reports on this issue.[11 12]

In summary, CS are often used over the long term in the Icelandic community—that is, by about 0.7% of the general population at any given time, mostly patients with various pulmonary and rheumatic chronic disorders. In addition, complications due to the treatment often need to be dealt with by the healthcare system; one fifth of the CS users in the present study experienced fragility fractures. Furthermore, although several patients were receiving active treatment owing to manifest osteoporosis, few patients were receiving optimal primary prevention against corticosteroid induced osteoporosis. Thus for the sake of those patients who require long term treatment with CS, all those in the healthcare system, including the doctors who write the prescriptions, need to make certain that they keep abreast of information and education about treatment and prophylaxis alternatives for corticosteroid induced osteoporosis.

ACKNOWLEDGMENTS

The authors are grateful to the doctors in northeast Iceland who made this study possible and also thank the secretarial staff at the Akureyri Central Hospital and at all healthcare centres in the study area for their assistance. The study was supported by a grant from the research fund of the Akureyri Central Hospital.

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