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Use of oral corticosteroids in the United Kingdom

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Summary

Administration of oral corticosteroids is associated with the development of osteoporosis and an increased risk of fractures. However, the size of the treated sub-population who would benefit from preventive therapy remains uncertain. The objective of this study was to investigate the usage pattern of oral corticosteroids in a large sample representative of the general population in England and Wales. Information was obtained from the General Practice Research Database (GPRD) which contains medical records of general practitioners. Oral corticosteroid users were patients aged 18 years or older who received one or more prescriptions for oral corticosteroids. Over 1.6 million oral corticosteroid prescriptions were issued to the cohort of 244 235 oral corticosteroid users. At any point in time, oral corticosteroids were being used by 0.9% of the total adult GPRD population. The highest use (2.5%) was by people between 70 and 79 years of age. Respiratory disease was the most frequently recorded indication for oral corticosteroid treatment (40%). Patients with arthropathies were most likely to use long-term, continuous treatment, and patients with chronic obstructive pulmonary disease least likely (19.3% and 6.1%, respectively, used oral corticosteroids for more than 2 years). The overall use of bone-active medication (oestrogens, bisphosphonates, vitamin D, and calcitonin) during oral corticosteroid treatment was low (between 4.0% and 5.5%). The current population in the UK at risk of developing corticosteroid-induced fractures might be as large as 350 000. Identification of these patients will be important for implementing preventive strategies in a cost-effective manner.

Introduction

Administration of oral corticosteroids has been associated with the development of osteoporosis and an increased risk of fracture. In a large population-based case-control study, it was found that the risk of hip fracture doubled during oral corticosteroid treatment when compared with age- and sex-matched non-fracture controls.[1] Hip fracture is the most severe of the fractures related to osteoporosis, and around 20% of all hip fracture patients die within 6 months after suffering the fracture.[2] Despite the increased recent awareness of corticosteroid-induced osteoporosis,[3–15] the size of this population at risk remains unclear. The objective of this study was to investigate the usage patterns of oral corticosteroids in a large sample representative of the general population in England and Wales; information was obtained from the General Practice Research Database (GPRD) which contains the computerized medical records of

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a large group of medical practices in England and Wales. There was particular interest in estimating the prevalence of oral corticosteroid usage, as well as the dose and natural history of utilization.

Methods

The General Practice Research Database

The current study included 683 practices from different geographic areas in the UK, registered with the General Practice Research Database (GPRD). The data recorded in the GPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes.[16–21] Clinical data are stored and retrieved by means of OXMIS codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9).[17,20] Each entry into GPRD is internally validated by cross-checking within the practice and by comparisons with external statistics.[16–21] Only data from practices that pass this quality control are compiled within the GPRD database. Several independent validation studies have confirmed a high level of completeness and validity of GPRD,[22–25] which is owned by the Department of Health in the UK.

Study population and methods

The study sample was selected from the GPRD to comprise a large retrospective cohort study aiming to evaluate the relationship between oral corticosteroid use and fracture risk.[26] Oral corticosteroid users were defined as permanently registered patients aged 18 years or older who received one or more prescriptions for oral corticosteroids during the period of time from the enrolment date of their practice in GPRD up to the end of data collection (December 1997). The average for this time period was 4.7 years. For each oral corticosteroid user, the daily corticosteroid dose over the total treatment period was estimated by dividing the total amount of prescribed prednisolone (or equivalent dose) in milligrams by the treatment time.[27] The treatment time was taken as the time from the first oral corticosteroid prescription until 31 days after the last prescription. Three dose categories were assigned: low dose (2.5 mg per day), medium (2.5–7.5 mg per day) and high dose (7.5 mg per day or more).

The indication for oral corticosteroid treatment was obtained by reviewing the morbidity recorded at the date on which a new course of treatment was started. At the commencement of new drug treatment, the general practitioners are required to record the indication for treatment on the same date in the medical record. Patients who received their first oral corticosteroid prescription at least 6 months after they were registered at the practice or after the practice enrolled in GPRD were considered to have started a new course of treatment. The morbidity recorded at the date of starting the oral corticosteroids was categorized according to the International Classification of Diseases (9th revision) categories. Patients were also classified according to the presence of concomitant disease. This classification was based on the clinical details recorded during the period from 6 months before commencing treatment until the cessation of oral corticosteroid treatment. These concomitant disorders included chronic obstructive pulmonary disease (ICD codes 490–496), inflammatory skin disorders (690–698), arthropathies (710–719), peripheral nervous system disorders (350–359) and non-infectious enteritis/colitis (555–558).

Statistical methods

A point prevalence estimate for oral corticosteroid use in the total adult GPRD population was estimated by dividing the total duration of oral corticosteroid use by the total observation time of GPRD. This prevalence estimate provides a cross-sectional measure of oral corticosteroid use. The total duration of oral corticosteroid use for this analysis was based on the length of use with each individual prescription. Kaplan-Meier survival analysis was conducted in order to estimate the duration of a course of oral corticosteroid treatment. Patients were considered to have discontinued treatment if they did not receive a repeat prescription within 3 months after the last oral corticosteroid prescription. Patients who transferred out, who died within 3 months of their last prescription, or who received their last prescription in the last 3 months of the study were censored.

Results

We identified 244 235 oral corticosteroid users in GPRD. Over 1.6 million oral corticosteroid prescriptions were issued to these 244 235 oral corticosteroid users. Within this cohort, 103 008 people received one prescription during follow-up, 37 424 people received two prescriptions and 103 803 people received three or more prescriptions. The mean and median numbers of prescriptions were 6.8 and 2.0 prescriptions, respectively. Prednisolone was the most frequently prescribed oral corticosteroid (90.8% of all prescriptions). Hydrocortisone and dexamethasone were given in 3.1% and 2.0% of prescriptions, respectively. The average dose over the follow-up period (from first prescription to last prescription) was 8.1 mg/day.

The prevalence of oral corticosteroid use in the total adult GPRD population is shown in Figure 1. The use of oral corticosteroids varied substantively over age, but was similar between males and females. At any point in time, oral corticosteroids were being used by 0.9% of the GPRD population (females and males combined). The highest use was by patients between 70 and 79 years of age (2.5%) and the lowest among patients between 20 and 29 years of age (0.2%). Of the three dose categories, the intermediate dose (2.5–7.5 mg daily) was used most frequently (0.4% of the population). The prevalence of higher-dose therapy (>7.5 mg daily) was 0.3%, and that of lower-dose treatment (<2.5 mg daily) was 0.1%. For all three dose categories, patients aged 70–79 years were using oral corticosteroids most frequently (0.9% in the high-, 1.3% in the intermediate- and 0.3% in the low-dose group). The lowest use was found in patients aged 20 to 29 years (0.08% in the high-, 0.09% in the intermediate- and 0.05% in the low-dose group).

The most frequently recorded indication for oral corticosteroid treatment was respiratory disease: around 40% of the patients had respiratory diseases recorded (Table 1) and 13% had associated respiratory symptoms. Cutaneous or musculoskeletal disorders were recorded in around 6% of the oral corticosteroid users.

Most patients received corticosteroid treatment for a short period of time. Treatment was continued for >6 months in only 22.1% of patients and for >5 years in only 4.3%. The utilization pattern was similar for both sexes, but elderly patients used oral corticosteroids for longer periods than younger patients. Oral corticosteroid treatment was continued for over 2 years by 20.0% of the oldest men and 20.1% of the oldest women, compared to 2.8% of the youngest men and 2.0% of the youngest women. In a separate analysis, we examined the impact of dose on the continuation of oral corticosteroid treatment. Patients on higher doses of oral corticosteroids were more likely to continue treatment for longer periods of time: 17.5% of these patients continued treatment for >2 years compared to only 1.1% of the low-dose patients.

Figure 2 shows the percentage of people who continued oral corticosteroid treatment stratified by concomitant disease. Patients with arthropathies were most likely to continue treatment: 19.3% used oral corticosteroids for >2 years. Patients with chronic obstructive pulmonary disease were least likely to continue treatment (6.1% for >2 years).

The concomitant use of bone-active treatments (hormone replacement therapy, bisphosphonates, vitamin D, and calcitonin) was also examined. The overall use of bone-active medication (any type) during oral corticosteroid treatment was very low, ranging from 4.0% to 5.5%. As shown in Figure 3,

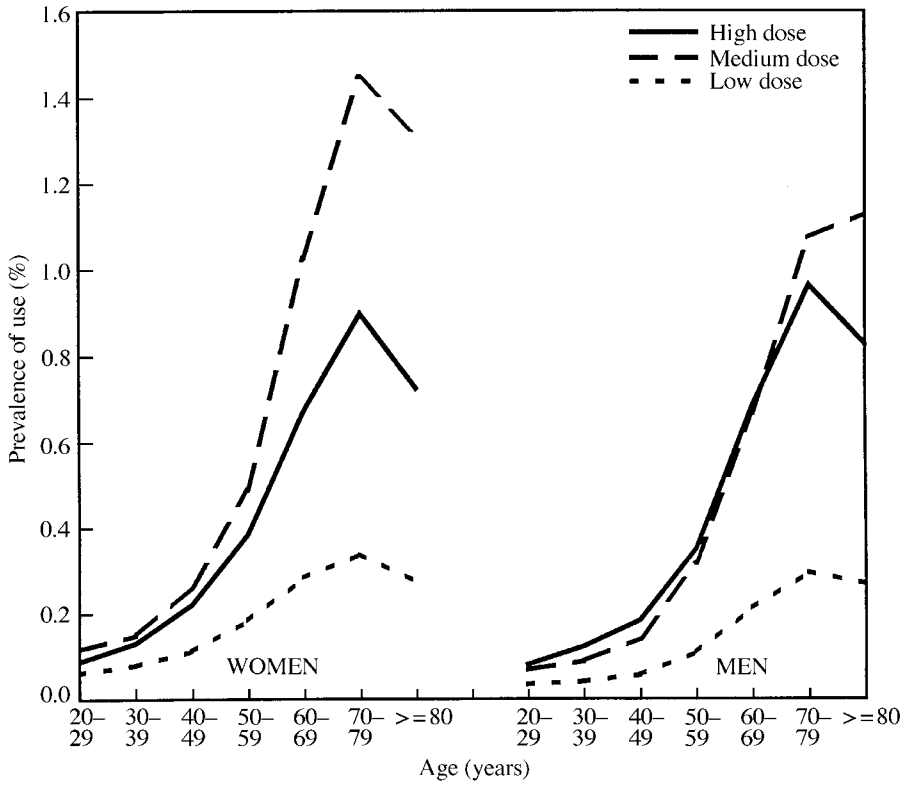

Figure 1. Use of oral corticosteroids in the total GPRD population, stratified by dose, age and gender.

Table 1 Indication for oral corticosteroid treatment

Indication	ICD code	No. of people (%)
Respiratory system	460–519	64 377 (39.9%)
Chronic obstructive pulmonary disease	490–496	49 273 (30.5%)
Other disease respiratory system	510–519	10 914 (6.8%)
Acute respiratory infection	460–466	4050 (2.5%)
Disease skin and subcutaneous tissue	680–709	10 084 (6.2%)
Other inflammatory disease skin	690–698	5685 (3.5%)
Other disease skin	700–709	4136 (2.6%)
Disease musculoskeletal and connective tissue	710–739	9967 (6.2%)
Rheumatism excluding back	725–729	6502 (4.0%)
Arthropathies	710–719	2861 (1.8%)
Disease nervous system	320–389	5553 (3.4%)
Peripheral nervous disease	350–359	2972 (1.8%)
Eye/adnexa disorders	360–379	1117 (0.7%)
Digestive system	520–579	4568 (2.8%)
Non-infectious enteritis and colitis	555–558	2467 (1.5%)
Neoplasms	140–239	3644 (2.3%)
Diseases circulatory system	390–459	3113 (1.9%)
Disease arteries/capillaries	440–448	1572 (1.0%)
Injury and poisoning	800–999	2115 (1.3%)
Unknown		32 901 (20.4%)
Total number of persons ($\geqslant$6 months retrospective information)		161 522

bisphosphonate and vitamin D use became more prevalent over the duration of oral corticosteroid treatment, particularly in the intermediate corticosteroid dose categories. The use of bisphosphonates increased among users of high doses of oral corticosteroids from 0.6% in the first 3 months to 2.4% at 5 years of treatment. At 5 years, the highest use of bisphosphonates was observed among the women aged 45–84 years using high doses of oral corticosteroids (6.4%, 8.4%, 9.8% and 5.9% in the women aged 45 to 54, 55 to 64, 65 to 74, and 75 to 84 years, respectively). Similarly, the use of vitamin D increased from 0.4% at the beginning to 1.1% at 5 years of high-dose oral corticosteroid treatment. The women aged 45 to 84 years showed the highest use (2.7%, 2.9%, 1.7% and 2.6% in the women aged 45 to 54, 55 to 64, 65 to 74, and 75 to 84 years, respectively). Concomitant use of calcitonin was very low in all three dose groups. The use of HRT did not change substantially over duration of oral corticosteroid treatment. The low-dose group had the highest HRT use compared to the high-dose group, an observation accounted for by the different proportions of women in each of the three dose groups, and the use of HRT for non-osteoporosis indications. HRT use was the highest among the women aged 45–64 years. Of the women aged 45–54 years, 30.2% received one or more HRT prescriptions during oral corticosteroid treatment. For the women aged 55–64 years, this figure was 15.9%.

Discussion

We have evaluated the utilization patterns of oral corticosteroids in a large cohort representative of the general population of England and Wales. Oral corticosteroids are used frequently, especially by the elderly. The likelihood of long-term oral corticosteroid use was related to age and concomitant disease. High doses of oral corticosteroids, which have the largest associated fracture risk, were used by 0.9% of the people aged 70 years or older. The use of bone-active treatments to prevent or treat the adverse skeletal effects of oral corticosteroids was, however, very low.

The widespread use of oral corticosteroids, particularly in the elderly population, indicates the need to quantify precisely the risk of corticosteroid-induced fractures and to identify the patients at highest risk of developing such fractures. Although oral corticosteroids have been used for the last 5 decades, there are few data on the magnitude of risk of corticosteroid-induced fractures and the determinants of this risk. Most information on the adverse bone effects of oral corticosteroids has been obtained from studies that evaluated changes in bone density during oral corticosteroid treatment.[10,11] There has been only one large study focusing on hip fracture, and it was not able to provide information on the relationship of fracture risk to dose or duration of oral corticosteroid use.[1] In our study, all oral

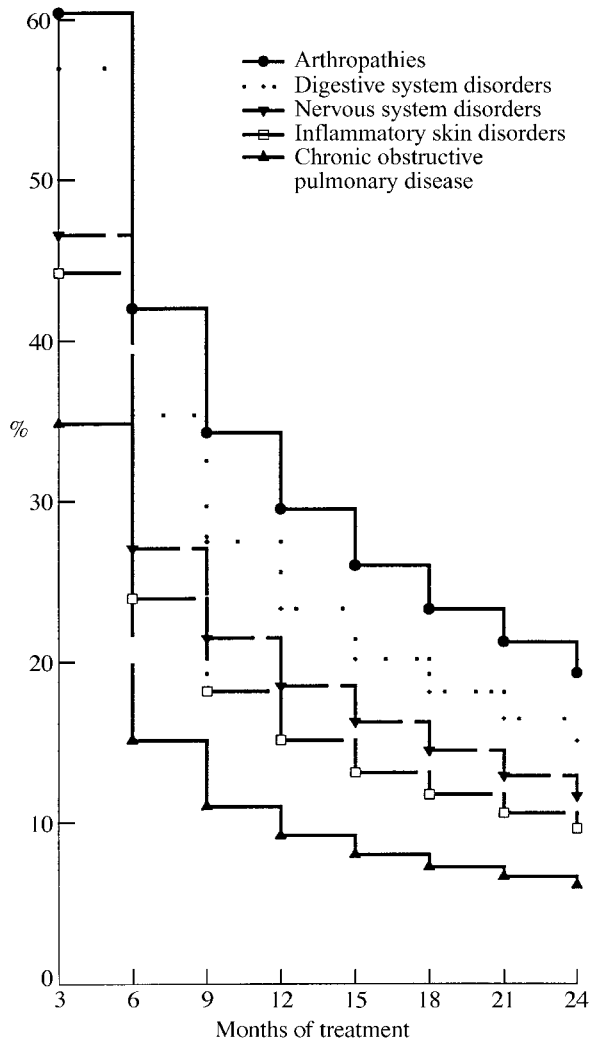

Figure 2. Percentage of patients who continued oral corticosteroid treatment over time, stratified by concomitant disease.

corticosteroid users had a significantly increased risk of hip fracture (OR = 1.61) relative to controls.[26] The risk of hip fracture was not significantly elevated among low-dose oral corticosteroid users, increased (OR = 1.77) with a daily prednisolone dose of 2.5–7.5 mg, and was highest (OR = 2.27) with doses of 7.5 mg daily or higher.[26]

Of the adult GPRD population, 0.9% were using oral corticosteroids. Extrapolation of these figures to the UK population as a whole (approximately 44.4 million adults in 1996) suggests that around 409 000 people currently use corticosteroids; 93 000 are taking doses >7.5 mg prednisolone daily, and have done so for >6 months; 350 000 are using corticosteroids at doses >2.5 mg prednisolone or equivalent daily. Fracture rates appear to increase even for those using lower doses of oral corticosteroids (at doses between 2.5–7.5 mg) and also increase shortly after commencement of oral corticosteroid treatment.[26] To quantify more precisely the number of patients at risk of developing corticosteroid-induced fractures, these findings will need to be confirmed.

Recent UK guidelines indicate that treatment for corticosteroid-induced osteoporosis should be considered if oral corticosteroids are to be used for >6 months at doses of 7.5 mg per day or more.[28] It is unclear whether other characteristics predispose patients to increased risks of corticosteroid-induced fracture. Three small studies have evaluated fractures rates in subgroups of oral corticosteroid users. These studies only evaluated age and gender and had inconsistent results, possibly due to the small numbers of patients.[29–31] Our results indicate great heterogeneity in the population using oral corticosteroids. They were used for a broad range of indications, at different doses, for varying durations and by patients of different age, gender and medical histories. In order to individualize and target preventive therapy with bone-active drugs, identification of patients at high risk for corticosteroid-induced fractures is needed. Given this widespread use in different patient groups, there is a need for further studies on the individual susceptibility to corticosteroid-induced fractures.

The use of oral corticosteroids in the UK has been addressed in two previous studies. These were cross-sectional surveys which included only a few hundred patients, one conducted in a hospital and the other in eight general practices of a single region.[32,33] The hospital study reported that the most common indications for oral corticosteroids were chest disease (39.2%) and neoplasm (7.9%).[32] The results of the primary-care study were different: here the most frequent indications were rheumatoid arthritis (23.1%) and polymyalgia rheumatica (21.7%); chest disease accounted for 19.5% of oral corticosteroid use.[33] Comparison with the results of our study is difficult given the differences in design and setting. Our study used a large longitudinal cohort with accrual of the study population over several years of observation. When weighting patients according to duration of use, respiratory disease accounted for 26.0% of oral corticosteroid use and musculoskeletal disease for 15.7% in our study. Patients with short-term exposure are more likely to be included in such longitudinal studies compared with cross-sectional studies. The greater frequency of pulmonary disease in our study is most likely to be explained by this difference in study design. Furthermore, our study was conducted in a large group of general practices which have registered a patient population that is known to be broadly representative of the population of England and Wales.[17,19,21]

Our classification of the indication was limited by the observation that the indication for oral corticosteroid treatment was not specified in the medical

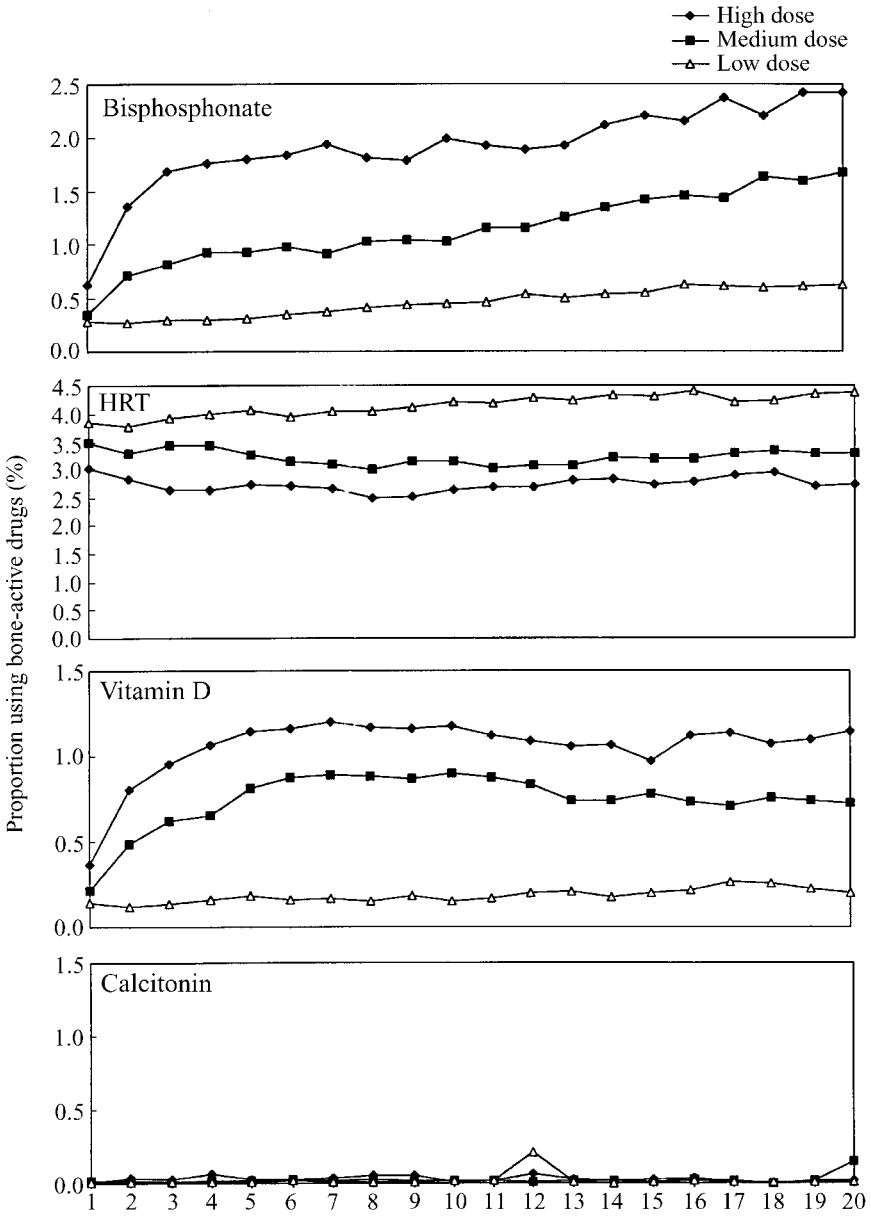

Figure 3. Trends in bone-active treatments over duration of oral corticosteroid use.

records of 20% of the patients. The physicians of GPRD are expected to record the indication on the date of starting the treatment. For repeat prescriptions, it is normally only necessary to enter the indication the first time the drug is being used. The reason for not specifying the indication for treatment in 20% of the patients is unknown. One possible explanation may be that oral corticosteroids may have already been previously prescribed, prior to the start of data collection for GPRD. Consistent with our results on indication for treatment, respiratory disease was the most frequently recorded condition (in the 6 months prior to start of oral corticosteroids) among the 20% of the patients who did not have their indication specified.

In conclusion, we have shown that oral corticosteroids are widely used over a broad range of indications for varying durations of time. The current population at risk of developing corticosteroid-induced fractures in the UK might be as large as 350 000 individuals. Bone-active drugs are used infrequently among oral corticosteroid users. Further studies to characterize the risk factors for fracture in corticosteroid users, and measures to identify and treat those subjects at the highest risk of future fracture, are urgently required.

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