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Children and the Risk of Fractures Caused by Oral Corticosteroids

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ABSTRACT

Oral corticosteroids are known to increase the risk of fracture in adults, but their effects in children remain uncertain. The medical records of general practitioners in the United Kingdom (from the General Practice Research Database) were used to estimate the incidence rates of fracture of children ages 4–17 years taking oral corticosteroids (n = 37,562) and of control children taking nonsystemic corticosteroids (n = 345,748). Each child with a fracture (n = 22,846) was subsequently matched by age, sex, practice, and calendar time to one child without a fracture. The average duration of treatment was 6.4 days (median, 5 days). The risk of fracture was increased in children with a history of frequent use of oral corticosteroids; children who received four or more courses of oral corticosteroids had an adjusted odds ratio (OR) for fracture of 1.32 (95% CI, 1.03–1.69). Of the various fracture types, the risk of humerus fracture was doubled in children who received four or more courses of oral corticosteroids (adjusted OR, 2.17 [1.01–4.67]). Fracture risk was also increased among children using 30 mg prednisolone or more each day (adjusted OR for fracture, 1.24 [1.00–1.52]) and among those receiving four or more courses of oral corticosteroids (OR, 1.32 [1.03–1.69]). Children who stopped taking oral corticosteroids had a comparable risk of fracture to those in the control group. Our findings suggest that children who require more than four courses of oral corticosteroid as treatment for underlying disease are at increased risk of fracture. It is not entirely clear whether this relates directly to oral corticosteroid use or the underlying disease and its severity. Irrespective of these issues, this group of children is at increased risk of fracture. (J Bone Miner Res 2003;18:913–918)

Key words: osteoporosis, glucocorticoid, epidemiology, childhood

INTRODUCTION

ORAL CORTICOSTEROIDS PLAY a major role in the treatment of diseases such as asthma and inflammatory joint disorders. In adults, osteoporosis is a well-known and major complication of oral corticosteroid treatment. A recent study reported that the risk of hip fracture was doubled in adults using higher doses of oral corticosteroids and the risk of vertebral fractures increased 4-fold. Its findings suggested that the adverse skeletal effects of oral corticosteroids manifest rapidly.[1] Several studies have reported decreased bone density in children taking oral corticosteroids.[2–12] Few details, however, were provided on the relationship between bone density and daily dose and duration of oral corticosteroid treatment. No studies have evaluated the risk of fracture in children taking oral corticosteroids. Thus, the threshold for adverse skeletal effects of oral corticosteroids still remains to be defined in children.

Children are frequently prescribed oral corticosteroids. In our study population, representative of the general population in England and Wales, 1.2% of the children received a course of oral corticosteroids during 1 year. Given this widespread use, our study was carried out to evaluate whether the use of oral corticosteroids increases the risk of fracture in children.

MATERIALS AND METHODS

Data source

In the United Kingdom, health care delivery is centered on the general practitioners (GPs), who are responsible for

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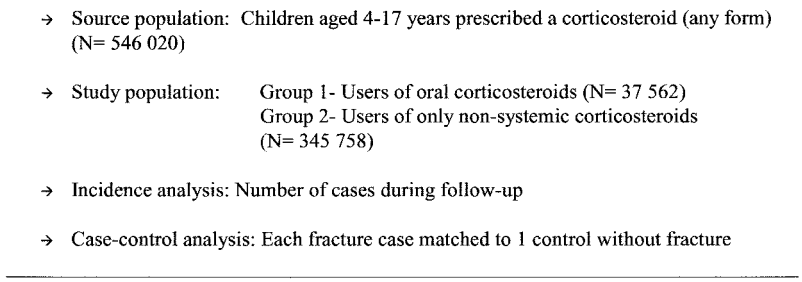

FIG. 1. Flowchart showing selection of the study population.

primary health care and specialist referrals. The information in this study was obtained from the General Practice Research Database (GPRD), which contains computerized medical records of 683 general practices in the United Kingdom.[13] Approximately 6% of the total registered population of England and Wales is represented in the database. The age and sex distributions of the enrolled patients are representative of the population in England and Wales. The data accrued in the GPRD include demographic information (including sex and year of birth), prescription details, clinical events, preventive care, referrals to specialist care, and hospital admissions and their major outcomes.[13] The data quality of each entry into GPRD is measured against specific targets, developed by comparisons with external statistics, to ensure research standards are met. Only data from practices that pass this quality control check are compiled to form the GPRD database. Several independent validation studies have shown that the GPRD database has a high level of completeness and validity, specifically with regard to recording of fractures.[14,15] The GPRD is owned by the UK Department of Health and managed by the Medicines Control Agency.

Study population

Figure 1 shows an outline of the selection of the study population. We screened the GPRD for all permanently registered children ages 4–17 years who were prescribed a corticosteroid (oral, injections, suppositories, inhaled, skin creams, and ear, eye or nose drops). Of this population, two study groups were formed.

- Group 1: cohort of users of oral corticosteroids comprised of children prescribed one or more courses of oral corticosteroids.
- Group 2: reference cohort comprised of children prescribed nonsystemic corticosteroids (topical, aural, ophthalmic, or nasal) but *not* oral, inhaled, injectable, or suppository corticosteroids.

Selecting a study population based on corticosteroid prescription records ensured active registration of the children at the general practice. The most frequently used nonsystemic corticosteroids in group 2 were skin creams (79.1% of the children). Children were followed from the start of data collection (1987 onward) or from age 4 years (whichever date came last) until the end of data collection (December 1997) or to age 18 years (whichever date came first).

The indication for oral corticosteroid treatment was obtained by reviewing the morbidity recorded on the date at the start of a new course of treatment. At the start of a new course of treatment, the general practitioners are required to record the indication for treatment. Children 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.

Incidence analysis

We estimated the incidence rate of fracture during exposure to oral corticosteroid treatment. The period of exposure was taken as the time period from start of oral corticosteroid treatment up to 91 days after the last prescription for group 1. For group 2, the incidence rate of fracture was based on the total follow-up period.

Nested case-control analysis

We used a nested case-control analysis to evaluate any effect of corticosteroid dose on fracture risk. Using this design, corticosteroid exposure was measured relative to a single point in time—the date of first fracture during follow-up (index date). The fracture cases were children in group 1 or 2 who experienced a fracture. For each case, one control patient was randomly selected, matched by age (same birth year), sex, GP practice, and calendar time (by using the same index date as for cases). If no control patient was found, the age criterion was expanded by 1 year to match patients and controls within the same practice; otherwise, children of the same age were randomly selected as controls from other practices. A total of 99.1% of the cases were matched by practice, sex, calendar time, and year of birth.

The exposure to oral corticosteroids was based on the prescription information before the index date. Current users were children who had received their last oral corticosteroid prescription in the 3 months preceding the index date; recent users, within 3–12 months; and past users, more than 12 months before the index date. The daily dose of oral corticosteroid was obtained from the written dosage instructions for the last prescription before the index date and the strength of the tablets (milligrams of prednisolone or equiv-

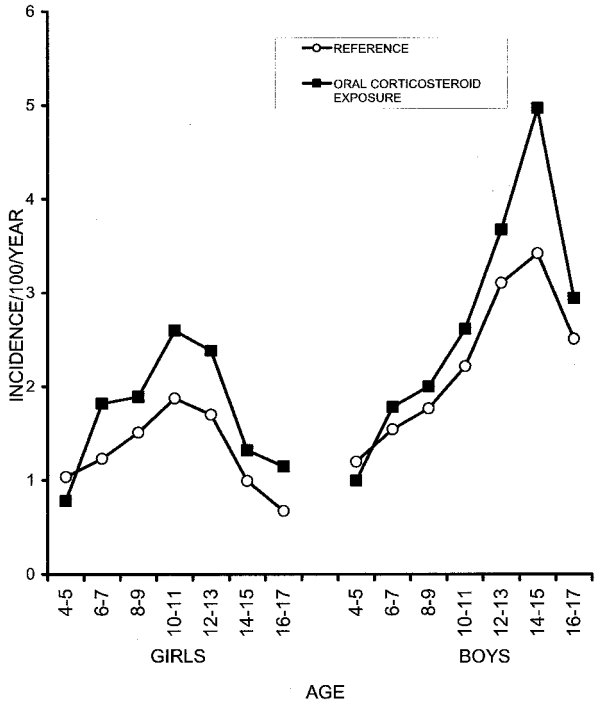

FIG. 2. Incidence of fractures during oral corticosteroid exposure and in the reference group stratified by age and sex.

alent).[16] Three dose categories were assigned: low dose (less than 10 mg/day), medium (10–30 mg/day), and high dose (30 mg/day or more). The duration of oral corticosteroid treatment was based on the number of prescriptions before the index date.

As part of the case-control study, the general practitioners were requested to confirm the diagnosis of fracture and provide discharge summaries or diagnostic reports. Children who left the practice were excluded, because their medical notes were no longer present at the practice. Also, the validation was restricted to the practices that were still registered with GPRD at the time of the validation. Fifty randomly selected children of each group with questionnaires returned were analyzed. The diagnosis of fracture was confirmed by the GP in 95.0% of the cases. Four children (4.0%) had a suspected fracture that was not confirmed after further investigation. There were no differences between groups in the percentages of fractures confirmed (group 1, 96.0%; group 2, 94.0%)

Statistical analysis

In the incidence analysis, rates of fractures were calculated by dividing the number of cases by the total number of person-years of follow-up.[17] The adjusted relative rate (RR) was estimated using a Poisson regression model that included age and sex. In the case-control analysis, the odds ratio (OR) of fracture in children with oral corticosteroid use compared with those without was calculated. Adjusted ORs for fractures in oral corticosteroid users compared with non-users of oral corticosteroids were estimated using conditional logistic regression. Models included current, recent, and past use of oral corticosteroids. The analysis was controlled for clinical variables and drug use that have been associated in adults with the risk of fractures.[1] Only risk factors that occurred in at least 1% of the cases and controls were included (i.e., history of seizures, use in the 6 months before the index date of nonsteroidal anti-inflammatory drugs [NSAIDs] and bronchodilators). The analysis was also controlled for a history of diseases that were frequently treated with oral corticosteroids in the study population. These included facial nerve disorders (ICD-9 category 351), nonsuppurative otitis media (381), acute respiratory infection (465), allergic rhinitis (477), bronchitis (490), asthma (493), other diseases of the respiratory system (519), regional enteritis/ulcerative colitis (555 and556), dermatitis (692 and 693), urticaria (708), and arthropathies (710–719). Final regression models were determined by backward elimination using a significance level of 0.25. The impact of variable elimination on the magnitude of the effect estimate was checked.

RESULTS

A total of 37,562 children (41.7% girls, mean age 9 years) were prescribed an oral corticosteroid preparation. The children were followed for an average of 2.7 years (median, 2.3 years) after the start of oral corticosteroid treatment. They received, on average, 2.4 oral corticosteroid prescriptions during this follow-up period. The majority of children only received one oral corticosteroid prescription (59.0%), while 14.7% of the children received four or more prescriptions. The indication for oral corticosteroid treatment mostly concerned respiratory disease. Asthma was recorded at the start of treatment in 57.2% of the children, acute respiratory infection in 2.5%, bronchitis in 2.4%, and respiratory symptoms in 15.7%. Less frequent indications for treatment concerned urticaria (1.5%), dermatitis (1.5%), facial nerve disorder (0.7%), and nonsuppurative otitis media (0.5%). A total of 345,758 children were prescribed a nonsystemic corticosteroid (52.9% girls, mean age of 8 years). They were followed for an average of 3.7 and median of 3.5 years.

In the oral corticosteroid cohort, 746 children suffered a fracture during the oral corticosteroid treatment (rate of 2.2 fractures per 100 person-years). Figure 2 shows the fracture incidence in the reference cohort and in the oral corticosteroid cohort during oral corticosteroid exposure. It shows that fractures rise in incidence before puberty, with the largest incidence around puberty, followed by decreasing fracture incidence. The risk of fracture for boys was generally higher than that for girls. The age- and sex-adjusted relative risk (RR) of fracture in the oral corticosteroid cohort was 1.20 (95% CI, 1.12–1.29) compared with the reference cohort. The excess fracture incidence in the oral corticosteroid group was apparent in both boys and girls and at most ages.

The case-control analysis included 22,846 cases and 22,846 controls. The control patients had similar age and sex distributions (Table 1). There were 4100 children who received an oral corticosteroid prescription before the index date. The average daily dose was 22.0 mg prednisolone or equivalent per day (median of 20 mg/day). A total of 347

Table 1. Characteristics of Fracture Cases and Controls

	Cases (n = *22,846*)	*Controls* (n = *22,846*)
Age (years)		
4–9	8702 (38.1%)	8705 (38.1%)
10–13	8045 (35.2%)	8048 (35.2%)
14–17	6099 (26.7%)	6093 (26.7%)
Sex		
Girls	8956 (39.2%)	8956 (39.2%)
Boys	13,890 (60.8%)	13,890 (60.8%)
Medical history		
Asthma	3815 (16.7%)	3571 (15.6%)
Arthropathies	746 (3.3%)	584 (2.6%)
Seizures	646 (2.8%)	570 (2.5%)
Drug use in the prior 6 months		
Bronchodilators	2383 (10.4%)	2060 (9.0%)
NSAIDs	509 (2.2%)	341 (1.5%)

children (8.5%) received a daily dose of less than 10 mg/day, 1953 (47.6%) received 10–30 mg/day, and 1169 (28.5%) received 30 mg/day or more. No information on daily dose was available for 631 children (15.4%). The average treatment duration was for 6.4 days (median, 5 days). Prednisolone was the most frequently used type of oral corticosteroid (95.3%), prescribed mainly in 5-mg tablets (97.4% of all prednisolone prescriptions).

Table 2 shows the ORs of fracture according to oral corticosteroid usage. The risk of fractures was increased in children with a history of frequent use (four or more oral corticosteroid prescriptions before the index date): the adjusted OR for fracture in the 3–12 months after the last prescription was 1.32 (95% CI, 1.03–1.69). Compared with non-users, the OR for fracture was 1.36 (95% CI, 0.96–1.93) in children with a prior exposure of 4–5 oral corticosteroid prescriptions; 1.27 (95% CI, 0.83–1.92) with 6–9 prescriptions previously; and 1.30 (95% CI, 0.73–2.31) with $\geq$10 prescriptions previously. The adjusted OR for fracture was 1.24 (95% CI, 1.00–1.52) in children using 30 mg prednisolone or more per day. Children who stopped oral corticosteroids did not have an increased risk of fracture (adjusted OR for past use 0.96 [95% CI, 0.87–1.06]).

In children with recent use of oral corticosteroids at a daily dose of 30 mg prednisolone or more, the adjusted OR for fracture was 1.05 (95% CI, 0.78–1.42) in those with a history of one prior prescription, 1.36 (95% CI, 0.93–1.99) with two to three prior prescriptions, and 1.44 (95% CI, 0.95–2.18) with four or more prior prescriptions. A test for linear trend across these categories of prior exposure was statistically significant in these children with high daily doses. No statistically significant trend with prior oral corticosteroid exposure was found in the lower dose groups.

The most frequent types of fractures in the study population were radius/ulna (8024 children), followed by carpal (4547 children), humerus (2205 children), and foot (1835 children). As shown in Table 3, recent use of oral corticosteroids was associated with an increased risk of humerus fractures (adjusted OR of 1.74 [95% CI, 1.20–2.53]). There was also a dose response with humerus fracture. The OR of humerus fracture increased from 1.44 in the group of children with a history of only one oral corticosteroid prescription to 1.99 in the intermediate group and to 2.17 in the group of children with four or more prior oral corticosteroid prescriptions. Recent use of oral corticosteroids did not increase the risk of radius/ulna fractures (adjusted OR of 1.00), carpal fractures (adjusted OR, 0.88), or foot fractures (adjusted OR, 1.35).

DISCUSSION

We found that children who frequently used oral corticosteroids had an increased risk of fracture, particularly that of the humerus. Most children received oral corticosteroids for short periods at high doses. Children who had discontinued oral corticosteroid treatment had fracture risks that were comparable with non-users.

It is known that oral corticosteroids can lead to a decrease in bone density in children. This decreased bone density has been found to occur irrespective of the underlying disease.[2–12] It is not yet clear what dose and duration of oral corticosteroid treatment is needed for the development of osteoporosis in children. A study in 55 children with Crohn's disease or ulcerative colitis found that the cumulative dose of prednisolone correlated negatively with lumbar spine bone density.[3] A similar relationship between low bone density and cumulative corticosteroid dose was found in a study of 119 children and young adults with Crohn's disease.[2] Our data suggest that children using repeated courses of high doses of oral corticosteroids have an increased risk of fracture. This study could not address whether long-term continuous treatment with lower doses of oral corticosteroids is also associated with an increased fracture risk. The reason is that only a few children in our study population used oral corticosteroids in this manner.

Short courses of oral corticosteroids are routinely used in the management of a severe asthma attack.[18] One study has evaluated the effects of repeated courses of short-term high-dose prednisolone on the hypothalamic-pituitary-adrenal axis. It found that children receiving no more than four courses per year of high-dose, systemic corticosteroid do not have a compromised hypothalamic-pituitary-adrenal axis. However, among children who received four or more courses of systemic corticosteroid per year, some were found to have a subnormal response to hypoglycemia and adrenocorticotrophic hormone (ACTH).[19] Our results show an increased risk of fracture for children who received four or more courses of oral corticosteroid treatment and no effect for children receiving less than four courses. Although the direct relationship between inhibition of the hypothalamic-pituitary-adrenal axis and risk of fracture is not established, these findings suggest that the threshold of an increased fracture risk in children may be four courses of oral corticosteroid treatment.

The largest increase in fracture risk in children using oral corticosteroids was seen at the humerus. The risk of humerus fracture was found to increase with high cumulative doses of oral corticosteroids. These results are similar to those found in adults. The OR of humerus fracture in adult oral corticosteroid users was 1.63.[1] No information was

TABLE 2. OR FOR FRACTURE ACCORDING TO ORAL CORTICOSTEROID EXPOSURE

	No. of cases	*No. of controls*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)**
Use of oral corticosteroids				
Non-use	20,716	20,876	Reference	Reference
Current use	342	314	1.10 (0.95–1.29)	0.98 (0.83–1.15)
Recent use	715	609	1.19 (1.06–1.33)	1.05 (0.93–1.19)
Number of prior prescriptions				
1	316	291	1.10 (0.93–1.29)	0.98 (0.83–1.16)
2–3	227	202	1.14 (0.94–1.38)	1.01 (0.83–1.24)
≥4	172	116	1.52 (1.19–1.93)	1.32 (1.03–1.69)
Daily dose (mg prednisolone or equivalent)				
<10	58	51	1.15 (0.79–1.67)	1.03 (0.71–1.51)
10–29	329	291	1.14 (0.98–1.34)	1.02 (0.87–1.21)
≥30	224	167	1.37 (1.11–1.68)	1.24 (1.00–1.52)
Past use	1,073	1,047	1.04 (0.95–1.14)	0.96 (0.87–1.06)

* Adjusted ORs are based on multivariate logistic regression models including past use of NSAIDs and bronchodilators, history of seizures, arthropathies, nonsuppurative otitis media, acute respiratory infection, or urticaria.

TABLE 3. ORS FOR DIFFERENT TYPES OF FRACTURE WITH RECENT ORAL CORTICOSTEROID EXPOSURE STRATIFIED BY THE NUMBER OF PRIOR PRESCRIPTIONS

			No. of prior prescriptions		
	No. of cases	*Overall [Adjusted OR (95% CI)]*	*1 [Adjusted OR (95% CI)]*	*2/3 [Adjusted OR (95% CI)]*	*≥4 [Adjusted OR (95% CI)]*
Radius/ulna	8024	1.00 (0.82–1.23)	1.03 (0.77–1.37)	0.85 (0.62–1.18)	1.24 (0.83–1.86)
Carpal	4547	0.88 (0.68–1.15)	0.74 (0.52–1.06)	1.24 (0.79–1.93)	0.79 (0.46–1.35)
Humerus	2205	1.74 (1.20–2.53)	1.44 (0.85–2.44)	1.99 (0.99–4.02)	2.17 (1.01–4.67)
Foot	1835	1.35 (0.87–2.08)	1.25 (0.69–2.28)	1.32 (0.67–2.58)	1.68 (0.69–4.13)

available in this study on the exact location of the humerus fracture. Trabecular bone is present in the supracondylar region of the humerus, and oral corticosteroid therapy could possibly affect this region. Further research is needed to confirm this hypothesis. In adults, hip and vertebrae are sites that are typically affected by oral corticosteroid treatment. In children, fractures at these sites occur very rarely. There were 221 children with a femur fracture (including hip) and 77 children with a clinically symptomatic vertebral fracture.

A weakness of our study was that control for confounding was restricted to age, sex, a variety of medical diagnoses, and treatments. There were no data on the nutritional status of the children or on their physical activity. Also, no detailed information was available on the severity of the underlying disease, and the statistical adjustment was limited to presence or absence of disease or drug use. Cases and controls were not matched for disease severity, and children using oral corticosteroids may have had more severe disease activity. The most plausible effect of these limitations was that we were more likely to observe an increased risk of fracture in children using oral corticosteroids. The reference group in our study consisted of children prescribed nonsystemic corticosteroids. Documented prescription was a means for ensuring active registration at the practice. Users of nonsystemic corticosteroids were selected because this would conservatively (downward) bias any estimate of risk associated with oral corticosteroids. Exclusion of children with frequent use of nonsystemic corticosteroids before the reference date did not modify the results. Finally, the number of children using high daily doses for prolonged periods of time was relatively small; this is the most likely reason for the borderline statistical significance of the fracture effect of doses more than 30 mg daily.

In conclusion, children who require more than four courses of oral corticosteroid as treatment for underlying disease are at increased risk of fracture, particularly at the humerus. It is not entirely clear whether this relates directly to oral corticosteroid use or the underlying disease and its severity. Irrespective of these issues, this group of children is at increased risk of fracture.

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