

Risk of cataract among users of intranasal corticosteroids

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Background: Oral corticosteroid users are at increased risk of cataract, but the risk among intranasal corticosteroids users is unknown.

Objective: Our purpose was to describe the risk of cataract among users of intranasal steroids.

Methods: A retrospective observational cohort study of cataract incidence was conducted among users of oral and intranasal steroids identified from the United Kingdom-based General Practice Research Database with a nested case-control analysis to control for confounding factors. The study population included 286,078 subjects aged less than 70 years old drawn from 350 general practices in England and Wales. Patients were classified as users of only intranasal corticosteroids, users of only oral corticosteroids, and nonusers of either medication. Computerized medical records were used to identify cases of cataract. Two hundred twenty-five cases were randomly selected for validation against general practitioners' held referral and hospitalization letters.

Results: The incidence rate of cataract (1.0/1000 person-years) among users of intranasal corticosteroids was similar to the incidence rate among nonusers. However, oral corticosteroid users were at higher risk of cataract (2.2/1000 person-years). Approximately 70% of intranasal corticosteroid exposure was to beclomethasone dipropionate only; the event rate in this group was similar to that in the unexposed group. Cataract risk did not increase with the number of prior prescriptions for intranasal corticosteroids.

Conclusion: The use of intranasal corticosteroids was not associated with an increased risk of cataracts in this study population. (*J Allergy Clin Immunol* 2000;105:912-6.)

Key words: *Intranasal corticosteroids, cataract, beclomethasone dipropionate*

Over the past decade the use of intranasally administered corticosteroids has become increasingly common in

Abbreviations used

CI:	Confidence interval
COPD:	Chronic obstructive pulmonary disease
GP:	General practitioner
GPRD:	General Practice Research Database
ICD:	International Classification of Diseases
OXMIS:	Oxford Medical Information System
RR:	Relative risk

the treatment of allergic rhinitis. Intranasally administered corticosteroids act topically on the nasal mucosa to reduce inflammation by reducing the cell-mediated immune response. A large proportion of topical corticosteroids administered intranasally may be cleared by mucociliary action and swallowed. The earliest corticosteroids used intranasally (hydrocortisone, betamethasone, and dexamethasone) led to systemic exposure, causing adrenal suppression.¹ The discovery of synthetic corticosteroids with high topical and low systemic activity relative to the earlier compounds has reduced the systemic exposure associated with the use of intranasal corticosteroids.²

Long-term oral corticosteroid^{3,4} use has previously been linked to an increased risk of ocular side effects. Recently the results from 2 large observational studies have suggested that inhaled corticosteroid use may also increase the risk of cataract. A study of adults by Cumming et al⁵ found a dose-response-related increase in posterior subcapsular cataracts among users of inhaled corticosteroids. However, the findings of this study were limited by low sample size, the uncertain accuracy of subject recall of drug use, and the inability to ensure that drug use preceded the development of the cataract. Garbe et al⁶ found an increase in cataract risk with 3 or more years of inhaled corticosteroid use among a small group of individuals more than 70 years old.

It is possible that systemic exposure may result from use of the newer types of intranasal corticosteroids. One small case series has suggested that intranasal corticosteroid use may be associated with the development of cataracts.⁷ However, no study results have been presented to describe the incidence rate of cataract among users of intranasal corticosteroids. Specifically, there is no information on the risk of cataracts in users of intranasal corticosteroids younger than 65 years of age.

We present here the results of a large-scale retrospective observational study conducted in 286,078 patients, aged less than 70 years, identified from the United Kingdom-based General Practice Research Database (GPRD)

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to describe the incidence rate of cataract among new users of intranasal corticosteroids without other prior oral or inhaled steroid use relative to individuals without a history of corticosteroid use. Incidence rates are also presented for users of oral corticosteroids relative to the same control population to compare our study results with those of previously published literature describing an increased risk of cataracts among users of oral corticosteroids.

METHODS

Data source

This study was based on information derived from the GPRD. Since 1987, more than 4 million residents in the United Kingdom have been enrolled with selected general practitioners (GPs) who use office computers provided by Value Added Medical Products to provide data for research purposes to the GPRD. The database is currently administered by the Medicines Control Agency of the United Kingdom. The GPs received instruction on the standardized recording of medical information and they agreed to supply anonymous information to academic researchers on a continuing basis. The information recorded in the database includes patient characteristics, drugs dispensed, clinical diagnoses, notation of referrals to consultants, hospitalizations, certain historic information and other findings (eg, smoking status, blood pressure, height, and weight). The GPs generate prescriptions directly from the computer, and these are automatically transcribed into the patient's computer record. The details of each prescription including dose, instructions, and quantity are automatically recorded on computer and can be used to determine dose and duration of drug exposure. A modification of the Oxford Medical Information System (OXMIS) classification is used to enter medical diagnoses, and a coded drug dictionary based on the Prescription Pricing Authority's dictionary is used for the recording of prescriptions. (OXMIS codes were mapped onto International Classification of Diseases [ICD] codes for the purpose of this study.) Two large validation studies determined that information on all patient referrals and hospitalizations present in the manual medical records in the general practitioners' offices was recorded on the computer more than 90% of the time.^{8,9}

Study design

The current study was conducted within 3 retrospectively identified treatment cohorts from the GPRD with use of data from 1991 to 1996. To be eligible, subjects had to be aged less than 70 years in 1993 without a history of asthma or chronic obstructive pulmonary disease (COPD) (except for the oral corticosteroid cohort). The 3 cohorts were (1) subjects exposed to intranasal corticosteroids only (beclomethasone, fluticasone, budesonide), (2) subjects exposed to oral corticosteroids only (prednisolone, prednisone, methylprednisolone, dexamethasone, betamethasone), and (3) subjects not exposed to any corticosteroids. The intranasal corticosteroid cohort included all subjects in the database who received at least one prescription for an intranasal corticosteroid, and who had, before their first intranasal corticosteroid prescription, at least 1 year of valid computer-recorded information. Subjects with a history of inhaled corticosteroid use on the basis of database records were excluded from the intranasal corticosteroid cohort. Subjects who had received prescriptions for oral corticosteroids after their first intranasal corticosteroid prescriptions were included in the appropriate cohort until a prescription for the oral corticosteroid was issued, at which point they were excluded from further study. These subjects were included to allow more comparability of health status with the oral corticosteroid cohort. The oral corticosteroid cohort included all subjects who had at least one recorded prescription for oral corticosteroids.

TABLE I. Diagnoses that resulted in subjects being excluded as cases

Retinitis pigmentosa
Heterochromic cyclitis
Corneal graft
Subconjunctival hemorrhage
Dystrophy Fuchs endothelial eye
Macular degeneration
Episcleritis
Uveitis/iritis
Corneal abrasion
Keratitis
Blepharitis
Diabetic retinopathy
Vasculitis
Uremia

Subjects with any prescriptions for intranasal corticosteroids were excluded from this cohort. The untreated population was a random sample of subjects who had no recorded prescriptions for oral, inhaled, or intranasal corticosteroids. Each unexposed subject's cohort entry date was a randomly selected date at least 1 year after first recorded database activity.

We estimated the incidence of cataracts among each exposure cohort and performed 2 nested case-control studies to assess the influence of confounding factors. For the cohort analysis we ascertained all first cataracts (ICD 374x) recorded in the database. Table I describes diagnoses that were excluded from this study to avoid confounding bias attributable to the cataract resulting from an underlying pathologic condition. We accumulated person-time exposure for each group as follows: from the first prescription for a nasal corticosteroid in the nasal corticosteroid cohort, from the first oral corticosteroid prescription for the oral corticosteroid group, and from a random date in the unexposed cohort until the end of the study period, the subject transferred out, died, or a cataract was diagnosed, or an oral steroid was received. The nested case-control studies were conducted to estimate the dose response adjusted for potential confounders. Cases were all subjects with a diagnosis of cataract from among the study cohorts. We matched 4 controls without a diagnosis of cataract from these cohorts to each case on age, sex, general practice, and index date of case.

Case validation

Clinical records were received for 225 cases of cataract selected at random from the cases identified in the cohort study. The clinical records included GP records, referral letters from ophthalmic specialists, and hospital discharge summaries from cataract surgery. Ninety-seven percent of the cataracts mentioned in the database were confirmed in the medical records.

Statistical analysis

In the cohort study the incidence rates of each ocular event were compared across the 3 treatment groups. The incidence rate of cataract for each treatment group was equal to the number of events divided by the cumulative number of prescriptions for each group; the number of prescriptions for each patient was calculated from the study entry until the subject transferred out, died, or a cataract was diagnosed. Relative risk (RR) and 95% confidence intervals (CI) were performed to compare the incidence rates in the intranasal and oral corticosteroid groups to those found in the unexposed population. The presence of a potential drug dose-response effect on the occurrence of each outcome was estimated by stratifying drug-specific cataract risks according to number of prescriptions a patient

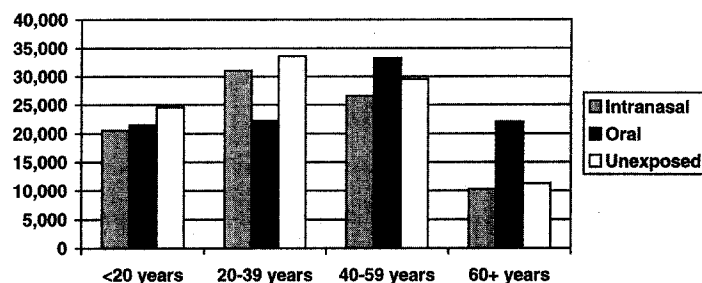


FIG 1. Distribution of person-years of follow-up by age and treatment cohort.

TABLE II. Incidence rates and relative risks of cataract (cohort study)

Exposure	Person-years	Cases	Incidence rate/1000 person-years	95% CI	RR	95% CI
Nonexposed	206,560	213	1.0	0.9-1.1	Reference	
Intranasal corticosteroids						
All	208,753	217	1.0	0.9-1.2	1.0	0.8-1.2
Beclomethasone only	140,831	140	0.9	0.7-1.0	1.0	0.8-1.2
Oral corticosteroids						
All	289,371	629	2.2	2.0-2.3	2.1	1.8-2.5
Subjects without asthma	91,064	274	3.0	2.7-3.4	2.9	2.4-3.5

received during the study period. RR estimates and 95% CIs were calculated to compare each stratified group with the group receiving only a single prescription during the study period.¹⁰

Because experimental evidence from animals suggests that beclomethasone dipropionate may have an increased potential for systemic effects relative to the other intranasal corticosteroids,^{11,12} we performed all analyses twice, inclusive of any intranasal corticosteroid use and restricted to beclomethasone dipropionate use only. It was possible that patients may have been misclassified with respect to beclomethasone dipropionate exposure during the study period because intranasal beclomethasone dipropionate was approved for over-the-counter use in the United Kingdom in 1994. To describe the influence of this effect, we conducted all the analyses twice: first for the entire time period and then for the time period ending December 31, 1993. We also performed all analyses limited to individuals aged 55 years and older to describe and compare our population rates with the rates found by Walker et al⁴ in a different health care database.

In the nested case-control study, we estimated the association between cataract and oral or intranasal corticosteroids (with unexposed subjects as the referent) with use of conditional logistic regression to estimate the odds ratios adjusted for age, sex, general practice, calendar time, prior patient history of hypertension, diabetes, renal failure and tobacco smoking, with SAS statistical software (version 6.12, SAS Institute, Cary, NC).

RESULTS

The total study population consisted of 286,078 patients. There were 88,301 intranasal corticosteroid users; 70% of these used only nasal beclomethasone dipropionate. The oral corticosteroid cohort contained 98,901 subjects; 41% had no previous database evidence of either asthma or COPD. Approximately 56% of both cohorts were female. We identified 98,876 subjects in the unexposed cohort, 51% of whom were female. Fig 1 describes the age distribution in all 3 patient cohorts.

Oral corticosteroid users were substantially older; approximately 50% were 50 years old or older. The age range in the unexposed cohort closely resembled that of the intranasal corticosteroid cohort, with 25% aged 50 years or older.

We identified 1059 cases of first-time cataract after review of the computer profiles, 217 in the intranasal corticosteroid cohort, 629 in the oral corticosteroid cohort, and 213 in the unexposed cohort. Table II presents the incidence rates for each of these cohorts. The incidence rates for all intranasal corticosteroids (1.0/1000 person-years) and nasal beclomethasone only (0.9/1000 person-years) are similar to those in the unexposed cohort (1.0/1000 person-years). The rates in the oral corticosteroid cohort are significantly higher in both the total oral corticosteroid cohort and the subset of subjects without asthma. These results were essentially unchanged when the population was restricted to database information available before 1994. There was no increase in the RR of cataract among all users of intranasal corticosteroids (RR 1.0, 95% CI 0.6-1.4) nor among beclomethasone dipropionate users alone compared with the unexposed (RR 0.8, 95% CI 0.5-1.2). The results of the other analyses also remained unaffected by this restriction. Although the rate of cataract was higher among unexposed patients aged 55 years and older (4.4/1000 person-years) compared with the rate in younger subjects, there was no increased risk of cataract with use of any intranasal corticosteroid (RR 1.1, 95% CI 0.9-1.4) or beclomethasone only (RR 1.0, 95% CI 0.8-1.3) in the older group. However, among this older age group use of oral corticosteroids was associated with a significantly increased risk of cataract (RR 1.4, 95% CI 1.2-1.7); this was also true for oral corticosteroid users without a history of asthma (RR 1.6, 95% CI 1.3-2.0).

TABLE III. RR of cataract according to number of intranasal, beclomethasone, and oral corticosteroid prescriptions

Cataract	No (No. [%])	Yes (No. [%])	Crude RR	95% CI
Any intranasal corticosteroid prescriptions				
1	52,352 (99.7)	133 (0.3)	Reference	—
2-4	25,895 (99.8)	61 (0.2)	0.9	0.7-1.3
5-9	6,776 (99.8)	15 (0.2)	0.9	0.5-1.5
10+	3,061 (99.7)	8 (0.3)	1.0	0.5-2.1
Beclomethasone only prescriptions				
1	39,825 (99.7)	97 (0.2)	Reference	—
2-4	15,985 (99.8)	31 (0.2)	0.8	0.5-1.2
5-9	3,860 (99.7)	7 (0.2)	0.7	0.3-1.6
10+	1,613 (99.7)	5 (0.3)	1.3	0.5-3.1
Oral corticosteroid prescriptions				
1	56,378 (99.5)	273 (0.5)	Reference	—
2-4	29,669 (99.4)	171 (0.6)	1.2	1.0-1.4
5-9	7,245 (99.0)	74 (1.0)	2.1	1.6-2.7
10+	4,980 (97.8)	111 (2.2)	4.6	3.7-5.7
Oral corticosteroid prescriptions among patients without asthma				
1	25,086 (99.5)	126 (0.5)	Reference	—
2-4	10,136 (99.5)	48 (0.5)	1.0	0.7-1.3
5-9	2,616 (98.9)	29 (1.1)	2.2	1.5-3.3
10+	2,888 (97.6)	71 (2.4)	4.9	3.7-6.5
Total	40,726 (99.3)	274 (0.7)	—	—

Table III presents an estimate of the effect of cumulative exposure on the risk of cataract. For all intranasal corticosteroids and for beclomethasone only, there is no difference in the rate of cataract between the different levels of prescriptions issued. When we examined this effect within the oral corticosteroid cohort, we found a clear indication of increased cataract risk with increasing duration of exposure, both in the total cohort and in subjects without asthma (Table III). This effect remained when a nested case-control analysis of oral steroid users was conducted controlling for the influence of age, sex, diabetes, hypertension, and smoking status. Similar patterns were found in the restricted sample of subjects aged 55 years or older.

The results of the nested case-control study among intranasal steroid users and steroid naive patients found no evidence of any association between intranasal steroid use and cataracts after controlling for age, sex, diabetes, hypertension, or smoking status. There was no meaningful difference between the adjusted and crude estimates. The adjusted odds ratio also did not vary by number of intranasal corticosteroid prescriptions. Relative to patients with no history of intranasal corticosteroid use, the risk of cataract was similar for patients who received 1 (odds ratio 1.1, 95% CI 0.8-1.3), 2 to 4 (odds ratio 1.1, 95% CI 0.8-1.3), 5 to 9 (odds ratio 0.9, 95% CI 0.5-1.5), 10 to 24 (odds ratio 1.0, 95% CI 0.4-2.3), or 25 or more (odds ratio 1.3, 95% CI 0.3-5.3) prescriptions for intranasal corticosteroids.

DISCUSSION

This study is the first large-scale retrospective study conducted to estimate the incidence rate of cataract

among users of intranasal corticosteroids aged less than 70 years. We found no increased risk of cataract associated with the use of intranasal corticosteroids or among a restricted sample using only beclomethasone dipropionate compared with nonusers. When we examined the effect of cumulative intranasal exposure in relation to cataract, the RRs did not change with increasing number of prescriptions issued. By contrast, oral corticosteroid use was associated with an increased risk of cataract, and this risk increased with the number of oral corticosteroid prescriptions issued.

The overall incidence of cataracts in the unexposed and intranasal cohorts of our study was 1.0/1000 person-years. We estimated the incidence of cataracts among oral corticosteroid users aged 55 and older to compare our results with previously published estimates. The incidence in this age group in the current study (4.4/1000 person-years) is essentially identical to that found at Group Health Cooperative (4.7/1000 person-years) in a prior study.⁴ Our findings agree with previous research from an observational study indicating an increased risk of cataract³ with greater oral corticosteroid exposure. Because our study was conducted in a population that was younger, the results of our study extend these findings into patients who are less than 66 years old. Our finding of no association between the use of intranasal corticosteroid and cataract has not been previously reported.

The limitations of this study are related to the information obtainable from the GPRD. It is possible that misclassification of the exposures and outcomes could have biased our study results. A significant number of study members may have had undiagnosed cataracts. However, because systemic corticosteroid use is an identified risk

factor for adverse ocular events, it is reasonable to conclude that individuals taking any form of corticosteroids may be more likely than patients without prior corticosteroid use to report their eye problems and be diagnosed, regardless of any actual drug effect. This type of differential diagnostic bias would be expected to spuriously inflate the association between intranasal corticosteroid use and our outcomes of interest. The lack of any association, despite the possible presence of this diagnostic bias, provides confidence in the validity of our results. It is also possible that the diagnosis recorded in the database did not correspond well to the actual diagnosis given by the physician. The results of our validation study found, however, a very high concordance (97%) between the database and clinical records for diagnosis of cataract, indicating no real presence of an information bias.

It is also possible that our study may have misclassified exposure to intranasal corticosteroids. Assuming a negative effect of intranasal corticosteroid use, misclassification of intranasal corticosteroid users as noncorticosteroid users could cause a spurious null association between intranasal corticosteroids and ocular events. It was unlikely, however, that we misclassified drug exposure on the basis of the database record. Prescriptions are automatically recorded because the physician uses the computer system to provide the drug prescription. It is possible that the number of prescriptions may be a poor surrogate for the drug dosage. We chose not to use prescription information to calculate dose because we felt it would not accurately represent actual drug exposure because of the high likelihood of these drugs being used only in response to symptoms. Our surrogate for cumulative dose was crude, but we would have expected people with more prescriptions to be diagnosed more frequently. The lack of any association between cataract risk and number of intranasal corticosteroid prescriptions suggests both no drug effect and no substantial effect of misclassification bias. It is possible that unknown use of intranasal beclomethasone (Beconase OTC) could have occurred in our study population because this treatment has been approved for sale in the United Kingdom since 1994. Our analyses restricted to the period of time prior to 1994, however, were essentially the same as those

from the entire study period. These results suggest that the effect of exposure misclassification did not substantially affect the results of our study.

In conclusion, the results of our study provide additional reassurance about the safety of intranasal corticosteroid use in relation to cataract. The lack of any increased risk for cataract has not been previously demonstrated. Additional studies are needed to confirm this finding in other populations. However, given the size of our study population, it is likely that the results of our study will be generalizable to other patient populations outside the United Kingdom. With the results of this study, physicians have additional information to help them decide about the relative value of intranasal corticosteroids in the treatment of their patients with allergic rhinitis.

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