Association of Inhaled Corticosteroid Use With Cataract Extraction in Elderly Patients

Edeltraut Garbe, MD, MSc; Samy Suissa, PhD; Jacques LeLorier, MD, PhD, FRCPC

Context.—The use of systemic corticosteroids is a known risk factor for the development of cataracts. Objective.—To determine whether treatment with inhaled corticosteroids is associated with cataract extraction in the elderly.

Design.—Case-control study.

Setting.—Quebec universal health insurance program for all elderly (provincial health insurance plan database [RAMQ database]).

Patients.—RAMQ enrollees 70 years and older. The 3677 cases who underwent cataract extraction between 1992 and 1994. The 21,868 controls were randomly selected from patients who did not have a diagnosis of cataract and matched to cases on the index date of the case.

Main Outcome Measures.—Odds ratio of cataract extraction in patients with prolonged cumulative exposure to inhaled corticosteroids compared with nonusers.

Results.—Excluding patients with systemic steroid treatment and after adjusting for age, sex, diabetes, systemic hypertension, glaucoma, ophthalmic steroids, and the number of physician claims for services, use of inhaled corticosteroids for more than 3 years was associated with undergoing cataract extraction (odds ratio [OR], 3.06; 95% confidence interval [CI], 1.53-6.13). For high average daily doses of beclomethasone or budesonide (≥1 mg), the OR was elevated after more than 2 years of treatment (OR, 3.40; 95% CI, 1.49-7.76), whereas for low to medium doses (<1 mg) of these drugs, the OR was 1.63 (95% CI, 0.85-3.13) after 2 years.

Conclusion.—Prolonged administration of high doses of inhaled corticosteroids increases the likelihood of undergoing cataract extraction in elderly patients. Further studies are needed to investigate the risk of developing cataracts for low to medium doses over longer periods.

From the Potsdam Institute of Pharmacoepidemiology and Technology Assessment, Potsdam, Germany (Dr Garbe); the Division of Clinical Epidemiology, Royal Victoria Hospital and the Department of Epidemiology and Biostatistics, McGill University (Dr Suissa) and the Centre de Recherche, Hôtel-Dieu de Montréal, Université de Montréal (Dr LeLorier), Montreal, Quebec.

Reprints: Edeltraut Garbe, MD, MSc, Director, Potsdam Institute of Pharmacoepidemiology and Technology Assessment, Otto-Erich-Str 7, 14482 Potsdam, Germany (e-mail: 106700.3205@compuserve.com).
The prescription data include the drug name, dispensation date, dose, dosage form, treatment duration, and quantity of drug dispensed. Drugs dispensed to patients during stays in hospitals or nursing homes are not included in the database. Diagnoses are coded according to the International Classification of Diseases, Ninth Revision (ICD-9). The study was conducted using a 10% random sample of the database covering the years 1987 to 1994.

### Case and Control Selection

Cases were subjects with a cataract extraction between 1992 and 1994. All had at least 5 years of prior follow-up logged in the database. The date of the cataract extraction was set as the index date for the case. If a patient had surgery for cataract on more than one occasion, the date of the first cataract extraction was set as the index date. Controls were randomly selected among all patients in the database who did not have a diagnosis of cataract or had a cataract extraction. Like the cases, to be eligible controls were required to have been enrolled in the database for at least 5 years before a randomly assigned index date. Potential controls were matched to each case on the index date of the case to account for seasonal and secular trends in medication use. Up to 6 controls per case were then randomly selected from these matched sets.

### Corticosteroid Exposure

We identified all dispensed prescriptions for inhaled and oral corticosteroids for cases and controls before the index date. The following inhaled corticosteroids are listed on the Quebec provincial drug formulary and were included in the exposure definition (ie, beclomethasone, budesonide, flunisolide, and triamcinolone). Oral corticosteroids on the drug formulary included cortisone, hydrocortisone, prednisone, prednisolone, triamcinolone, methylprednisolone, dexamethasone, and betamethasone.

We defined recent exposure to inhaled corticosteroids as a drug dispensation that lasted into the 14-day period before the index date. We determined the influence of prolonged treatment with inhaled or oral corticosteroids by calculating the cumulative treatment duration with these drugs for each patient since entry into the database. For this calculation, we added the treatment durations of all dispensations of either inhaled or oral corticosteroids that were filled before the index date. For both groups of drugs, we defined the following categories of exposure duration: "no exposure," "exposure of 1 year or less," “between 1 to 3 years,” and “more than 3 years.” To eliminate confounding by concurrent oral corticosteroid use, we identified all patients who had not had systemic steroids dispensed before the index date. To reduce contamination by oral or inhaled corticosteroid use that could have taken place before the patient entered the database, we identified all patients who had not used inhaled or systemic steroids during their first year after entry into the database.

To investigate the influence of the daily dose of beclomethasone and/or budesonide, we determined for all patients the cumulative dose and cumulative duration of treatment with these drugs from the patients’ entry into the database until the index date. We calculated the average daily dose for each patient by dividing the cumulative dose of beclomethasone and/or budesonide by the cumulative treatment duration with these substances. We categorized this measure of the average daily dose into “1 mg or less” or “more than 1 mg” of beclomethasone and/or budesonide per day, since doses of beclomethasone and budesonide below 1 mg/d have been suggested to be free of systemic adverse effects in adults. To investigate the influence of the dose according to the duration of use, we categorized the cumulative duration of use of beclomethasone and/or budesonide into “1 year or less of treatment,” “1 to 2 years of treatment,” and “more than 2 years of treatment.”

### Covariates

Covariates included age, sex, systemic hypertension, diabetes mellitus, glaucoma, the number of physician claims for services in the year before the index date, and previous use of oral or ophthalmic corticosteroids. Systemic hypertension was defined by a diagnosis of hypertension before the index date. Diabetes mellitus was defined by an oral hypoglycemic drug or insulin being dispensed before the index date. We defined glaucoma by either a diagnosis of or medical treatment for glaucoma, including therapy with ocular beta-blockers, ocular parasympathomimetics, ocular alpha-agonists, and carbonic anhydrase inhibitors. Because of coding in the database, this definition also includes patients with ocular hypertension without manifest glaucoma. We classified patients according to ophthalmic steroid use (any previous use vs no use) and oral steroid use (use of oral steroids for more than 365 days vs 365 days or less). We categorized the number of physician claims for services into 10 claims or less vs more than 10 claims in the year before the index date.

### Statistical Analysis

The rate ratio of cataract extraction for each exposure group was estimated from odds ratios (ORs) calculated by conditional logistic regression using the SAS PHREG program (SAS Institute Inc, Cary, NC). We constructed individual models characterizing patients according to recent exposure to inhaled corticosteroids, the cumulative duration of inhaled corticosteroid treatment, and the dose and duration of beclomethasone and/or budesonide treatment. These analyses were either adjusted for oral corticosteroid use or restricted to patients who had not used oral corticosteroids before the index date. In some analyses, we also excluded patients who had used inhaled corticosteroids during their first year after entry into the database.

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Table 1.—Characteristics of Cases and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases, No. (%) (n = 3677)</th>
<th>Controls, No. (%) (n = 21 668)</th>
<th>Adjusted Odds Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>770 (21.0)</td>
<td>8013 (36.6)</td>
<td>1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>75-84</td>
<td>1518 (41.3)</td>
<td>8176 (37.4)</td>
<td>1.8 (1.6-2.0)</td>
</tr>
<tr>
<td>≥85</td>
<td>1389 (37.8)</td>
<td>5668 (25.9)</td>
<td>2.2 (2.0-2.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2479 (67.4)</td>
<td>12 495 (57.1)</td>
<td>1.5 (1.4-1.6)</td>
</tr>
<tr>
<td>Diabetes mellitus treated with oral antidiabetics</td>
<td>415 (11.3)</td>
<td>1908 (8.7)</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Insulin</td>
<td>105 (2.9)</td>
<td>357 (1.6)</td>
<td>1.4 (1.1-1.7)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>1730 (47.1)</td>
<td>8288 (37.9)</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Previous use of ocular steroids</td>
<td>383 (10.4)</td>
<td>1099 (5.0)</td>
<td>1.3 (1.1-1.5)</td>
</tr>
<tr>
<td>Previous use of oral steroids</td>
<td>112 (3.1)</td>
<td>245 (1.1)</td>
<td>2.1 (1.7-2.7)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>800 (21.8)</td>
<td>1574 (7.2)</td>
<td>2.7 (2.4-3.0)</td>
</tr>
<tr>
<td>&gt;10 Physician claims†</td>
<td>2727 (74.2)</td>
<td>8561 (39.2)</td>
<td>4.0 (3.7-4.3)</td>
</tr>
</tbody>
</table>

*Adjusted for all other variables in the table. CI indicates confidence interval.
†In year before the index date.

Table 2.—Exposure to Different Substances of Inhaled Corticosteroids by Cases and Controls

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Cases</th>
<th>No. of Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>377</td>
<td>1655</td>
</tr>
<tr>
<td>Budesonide</td>
<td>120</td>
<td>531</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>120</td>
<td>1655</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Subjects may have been exposed to more than 1 corticosteroid preparation.
we also analyzed the risk for systemic corticosteroids, using the same cumulative exposure periods as for inhaled corticosteroids, while in one analysis, we excluded patients treated with systemic corticosteroids during their first year in the database. For all these analyses, the reference category was the absence of exposure to the respective form of corticosteroid after entry into the database. All models simultaneously controlled for all covariates listed above. Two-tailed \( P \) values less than .05 were considered significant and 95% confidence intervals (CIs) were calculated for all relative risks. We further calculated the excess risk (ER) of cataract extraction by determining the baseline incidence rate (IR) in our study sample and applying the OR as an estimator of the risk ratio (RR) to this rate by using the following formula: \( \text{ER} = (\text{RR} - 1)I_0 \).

**RESULTS**

We identified 10,214 patients with cataract extractions, of whom 6,537 patients did not meet the eligibility criterion of being in the database for at least 5 years before the index event, leaving a group of 3,677 cases. We selected 21,868 controls who fulfilled the matching and eligibility criteria, that is, an average of 5.9 controls per case. The mean (SD) follow-up period in the database was similar for cases and controls, with 2,354 days (SD, 309) for cases and 2,308 days (SD, 305) for controls.

Characteristics of cases and controls are summarized in Table 1. The risk of cataract extraction increased with age and was elevated in women, in patients with diabetes, in patients with glaucoma, and in patients who had been dispensed ophthalmic or oral steroids before the index date. For patients who had more than 10 physician claims for services in the year before the index date, the risk was increased 4-fold compared with patients who had 10 or fewer physician claims.

Table 2 shows that, anytime during the observation period, 428 cases and 1,946 controls were exposed to inhaled corticosteroids. Budesonide and budesonide accounted for the majority of prescriptions. Seventy-six cases and 278 controls had used more than 1 type of inhaled corticosteroid. A total of 163 cases and 581 controls had been exposed recently to inhaled glucocorticoids, yielding an adjusted OR of 1.28 (95% CI, 1.00-1.65). Table 3 displays the risk estimates for inhaled corticosteroids associated with different cumulative periods of use. Excluding patients with systemic corticosteroid use, there was no increase in risk observed in patients who had used inhaled glucocorticoids for 1 year or less and in patients whose cumulative treatment duration ranged from 1 to 3 years. Patients who had used inhaled steroids for more than 3 years had an elevated risk with an adjusted OR of 3.06 (95% CI, 1.53-6.13). A further slight increase in risk was observed when the analysis excluded patients who had used inhaled steroids during their first year after entry into the database. After excluding patients with systemic steroid use, we identified 227 cases and 1,202 controls who had beclomethasone and/or budesonide dispensed (Table 4).
After patients were stratified by the cumulative treatment duration, cataract extraction was more frequent among patients who had received high doses of beclomethasone or budesonide for more than 2 years (adjusted OR, 3.40; 95% CI, 1.49-7.76). The OR for low to medium doses of beclomethasone or budesonide given for more than 2 years was 1.63 (95% CI, 0.85-3.13). For less than 2 years of treatment, there was no increase in risk seen for either low or high doses.

A total of 416 cases and 1724 controls were exposed to oral glucocorticoids before the index date. Table 5 shows the risk estimates for oral corticosteroids associated with different cumulative treatment durations. In comparison with inhaled corticosteroids, the risk of cataract extraction was already increased after more than 1 year of oral steroid use. A further increase in risk was observed for a cumulative exposure of more than 3 years. Excluding patients from the analysis who had used oral corticosteroids during their first year after entry into the database, as we did in the analysis for inhaled corticosteroids, did not result in important changes of these risk estimates.

In our study sample, the baseline incidence of cataract extraction was 1.75% per year. Applying our estimate of the rate ratio 3.06 for more than 3 years of inhaled steroid use to this baseline incidence, we calculated an ER of 3.61% per year, or 361 additional cases per 10,000 elderly persons per year.

**COMMENT**

The results of our study suggest that prolonged use of inhaled corticosteroids increases the risk of cataract extraction in the elderly. Patients who had no use of oral corticosteroids recorded for at least 5 years, but had been treated with inhaled corticosteroids for more than 3 years, had a 3-fold increased risk of cataract extraction compared with patients not treated with inhaled steroids. Based on this risk estimate, we calculated that such extended use of inhaled corticosteroids would give rise to 361 additional cases of cataract extraction per 10,000 elderly patients per year. Our findings are consistent with the known relation between use of systemic steroids and cataract formation and confirm the results of a recent study from Australia. Previous studies investigating this association did not find an increased risk, which may have resulted from insufficient power of these studies.

In a retrospective study, Cumming et al suggested an increased risk of posterior subcapsular cataract with increasing lifetime doses of inhaled corticosteroids. Due to the limited sample size in their study, they could not investigate the risk according to the daily dose of inhaled steroid and its duration of use.

In a review of clinical pharmacological studies, it has been suggested that both beclomethasone and budesonide in doses less than 1 mg/d were free of systemic adverse effects in adults, while in doses more than 1 mg/d, there was a potential for systemic effects. Classifying the average daily dose of beclomethasone and budesonide in study patients according to this cut point into “low to medium” or “high” doses, we did not observe an increased risk of cataract for either dose category for a treatment duration of up to 2 years. After more than 2 years of treatment, the risk was elevated more than 3-fold for high doses, whereas a much smaller and statistically not significant increase in risk was seen for low to medium doses.

Our study also confirmed an increased risk for various previously described risk factors for cataract, among them old age, female sex, diabetes mellitus, glaucoma, and systemic and ophthalmic steroid use. For systemic corticosteroids, we observed an increasing risk with increasing cumulative duration of treatment that already became apparent after treatment exceeded 1 year. The risk was also considerably elevated for patients with a higher number of physician encounters, which may reflect an increased risk of cataract extraction in patients with higher comorbidity. Also, cataract extraction is an elective procedure, and its timing will also depend on the physician’s advice.

Some limitations of the study design need to be considered. We defined cases by cataract extraction, an end point that has often been used in the investigation of risk factors for cataract. Cataracts requiring extraction are those sufficiently severe to affect vision and, therefore, are of greatest clinical and public health impact. It would have been desirable to investigate the risk also according to the subtype of cataract leading to the surgical procedure, but this information was not available to us. Lack of classification by subtype, however, cannot explain any of the positive associations we observed. If an association is not common to all cataract subtypes, then an examination of the subtype-specific risk will yield even a higher point estimate of the risk than the one presented in our study.

Although we had for each patient at least 5 years of detailed drug exposure information preceding the index date, we did not have information on the patients’ drug use before the age of 65 years. The different exposure durations we calculated may therefore actually be longer when the patients used the medications also before they entered the database. We also cannot rule out that among the patients with no systemic corticosteroid use some had used oral glucocorticoids before the age of 65 years. To address this concern of confounding by previous oral corticosteroid use, we investigated the risk of cataract extraction in patients who had not used oral corticosteroids and, in addition, had not used inhaled corticosteroids during their first year in the database. Since the risk estimate did not substantially change in this group of patients, which more likely represents new users of inhaled corticosteroids, confounding by previous systemic corticosteroid use appears to be of less concern.

Since the database does not contain information about drugs dispensed in hospitals, we cannot exclude that some patients may have received systemic corticosteroids while hospitalized. Short treatment courses with systemic corticosteroids in the hospital will be of minor importance for the development of cataract, since longer treatment periods with systemic corticosteroids are usually needed to increase the risk. In patients treated with systemic corticosteroids for an extended period, the corticosteroid is usually tapered and is likely to be continued after discharge from the hospital and will, therefore, also appear in the ambulatory records of drug dispensations.

In our analysis, we controlled for several factors that have been discussed as risk factors for cataract; however, we did not have information on others, such as trauma, UV radiation, alcohol, and smoking. We have no reason to believe that trauma, UV radiation, or alcohol intake are related to exposure with inhaled corticosteroids and, therefore, do not expect confounding by these variables. Smoking, described as a risk factor for cataract in some studies, but not in others, is a known risk factor for respiratory diseases. Although it has been suggested that smokers who develop respiratory symptoms for any reason tend to quit smoking, this may not necessarily be the case. However, since the risk of cataract in smokers is not high, failing to adjust for smoking should not affect the risk estimates in an important way.

In summary, the results of our study demonstrate an increased risk of cataract for prolonged use of high doses of inhaled corticosteroids. Further studies are needed to investigate the risk according to the dose over more extended treatment periods, since an increased risk also for lower doses of inhaled steroids cannot be ruled out by our study findings. In addition, in vitro studies...
have demonstrated different ratios of topical to systemic activity for different inhaled steroids\(^4\); therefore, studies are also needed that investigate the risk according to the steroid substance.

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References


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An HIV-Resistant Allele Is Exceptionally Frequent in New Guinean Highlanders

To the Editor.—Stromal-derived factor (SDF-1) is the natural ligand for CXCR4, a coreceptor with CD4 for T-lymphocyte cell line–tropic human immunodeficiency virus 1 (HIV-1). Recently, a common variant, SDF1-3′-A, was identified in SDF-1, and an SDF1-3′-A homozygous state was shown to delay the onset of acquired immunodeficiency syndrome (AIDS) in an association study involving 2857 patients. The recessive protection of the SDF1-1-3′-A allele was pronounced to be twice as effective as the dominant genetic restriction of AIDS conferred by CCR5 and CCR2 chemokine receptor variants.

Using a polymerase chain reaction–restriction fragment length polymorphism assay, we investigated the distribution of the SDF1-3′-A allele in 16 worldwide representative populations. Our results showed that the SDF1-3′-A allele frequencies vary drastically among the populations surveyed, ranging from 2.9% to 71.4% (Table). African populations exhibit the lowest frequencies (2.9%-9.1%), rates that agree with the reported frequency in African Americans. No SDF1-3′-A homozygous individuals were found in African samples in this study. The frequency of the allele increases in American Indians, Europeans, and Asians, ranging from 12.2% to 36.6%.

However, exceptionally high frequencies were found in 4 non–Austronesian-speaking populations, especially in 2 New Guinean highlander populations (66.7%-71.4%). The frequency of homozygotes in those populations can be as high as 47.6%. The frequency of the allele increases in American Indians, Europeans, and Asians, ranging from 12.2% to 36.6%.

In addition, no significant deviation from Hardy-Weinberg equilibrium was detected in each population studied, implying the absence of detectable selection differentials between the individuals with and without the SDF1-3′-A allele and population substructure in those samples. Our data indicate that the SDF1-3′-A allele is distributed across all continents, which contrasts with the predominant presence of the HIV-resistant allele CCR5-Δ32 (at the CCR5 locus) in only white populations. Thus, the global presence of the SDF1-3′-A allele together with its rareness in African populations (near absence of homozygotes in Africa) implies that the mutation originally occurred in Africa, and the frequency of the mutant alleles was elevated in non-African populations because of the subsequent bottleneck events during the migration of modern humans from Africa.