Exposure to Allopurinol and the Risk of Cataract Extraction in Elderly Patients

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Objective: To determine whether exposure to allopurinol is associated with an increased risk of cataract extraction in elderly patients.

Methods: We conducted a case-control study using data from the Quebec universal health insurance program for all elderly patients. The 3677 cases were patients with a cataract extraction between 1992 and 1994. The 21,868 controls were randomly selected among patients not diagnosed with cataract and matched to cases on the date of the extraction. We determined the odds ratio of cataract extraction according to the cumulative dose and duration of allopurinol use relative to nonusers, using conditional logistic regression analysis. The analysis was adjusted for the effects of age, sex, diabetes mellitus, hypertension, glaucoma, and ophthalmic and oral corticosteroid exposure.

Results: A cumulative dose of allopurinol of more than 400 g or a duration of use of longer than 3 years were associated with an increased risk of cataract extraction, with odds ratios of 1.82 (95% confidence interval [CI], 1.18-2.80) and 1.53 (95% CI, 1.12-2.08), respectively. No increase in risk was observed for lower cumulative doses or shorter exposure periods.

Conclusion: Long-term administration of allopurinol increases the risk of cataract extraction in elderly patients.


ALLOPURINOL is an antihyperuricemic drug widely used for the treatment of hyperuricemia and chronic gout. It inhibits the terminal step in uric acid synthesis, which results in a reduction of uric acid concentrations in both serum and urine. In about 85% of patients with gout, serum urate concentrations can be normalized by an allopurinol dose of 300 mg/d, and in some patients a dose of 100 to 200 mg/d is sufficient. Treatment with allopurinol is usually well tolerated, with hypersensitivity reactions constituting the most common adverse effects.

In 1982, Fraunfelder et al reported 30 cases of cortical and subcapsular cataracts associated with long-term use of allopurinol that had been reported to the National Registry of Drug-Induced Ocular Side Effects (Oregon Health Sciences University, Portland). The observed lens changes appeared to have the characteristics of early age-related cataracts. At about the same time, Lerman et al used phosphorescence spectroscopy to demonstrate in vitro the probable presence of allopurinol in cataractous lenses that had been extracted from patients treated with allopurinol. The phosphorescence peaks characteristic of allopurinol could not be demonstrated in lenses from patients who had not ingested allopurinol.

Evidence from epidemiologic studies on the possible cataractogenic effects of allopurinol is inconclusive. Three epidemiologic studies did not show an increased risk. Another study reported an unusual morphologic thinning of the anterior clear zone of the lens in patients receiving long-term treatment with allopurinol. In the Lens Opacities Case-Control Study, wherein gout medications were found to be associated with a 2.5-fold increased risk of mixed cataract, no distinction was made between allopurinol and other medications for gout.

In this study, we investigate whether exposure to allopurinol is associated with an increased risk of cataract extraction in elderly patients and whether the risk varies according to the dose and duration of allopurinol use.

RESULTS

Of the 10,214 patients with cataract extractions, 6,735 patients did not meet...
POPTATION, MATERIALS, AND METHODS

SOURCE OF DATA

We conducted a case-control study among the elderly population of Quebec for the years 1987 to 1994, using data from the provincial health insurance plan database, which contains information about medical services and prescription drugs for all persons aged 65 years or older. Data in the records include information on the patient's age and sex, diagnoses, medical procedures, all filled prescriptions, and the specialty of the treating physician. Diagnoses are coded according to the International Classification of Diseases, Ninth Revision (ICD-9).9 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 recorded in the database. A high level of reliability and validity of the prescription data has been demonstrated.10

The base population from which the study was conducted consisted of a 10% random sample of the database, which covered the years 1987 to 1994.

CASE AND CONTROL SELECTION

Cases were subjects with a cataract extraction between 1992 and 1994 who had been enrolled in the base population for at least 5 years. The first date of surgery for cataract was set as the index date for the case. Controls were selected among all patients in the database who did not have a diagnosis of cataract or cataract extraction. Each potential control was randomly assigned an index date that corresponded to the first date of cataract surgery for one of the cases. Like cases, controls were required to have been enrolled in the database for at least 5 years prior to the assigned index date to become eligible. Potential controls were matched to each case on the index date of the case. Up to 6 controls per case were then randomly selected from these matched sets.

EXPOSURE TO ALLOPURINOL

All dispensations of allopurinol for cases and controls before the index date were identified. We defined “current exposure” as a dispensation of allopurinol that lasted into the 14-day period before the index date and “ever exposure” as any dispensation of allopurinol that had been recorded since the patient enrolled in the base population.

We determined the cumulative allopurinol dose for each patient by calculating the product of the dose and quantity of tablets dispensed for each allopurinol prescription since the patient’s enrollment in the base population, and by adding the respective allopurinol amounts of all these prescriptions. We defined the following cumulative dose categories: 0 mg, 1 to 100 000 mg, 100 001 to 200 000 mg, 200 001 to 400 000 mg, and more than 400 000 mg.

We ascertained the cumulative duration of exposure to allopurinol for each patient since enrollment in the base population. For the duration of exposure, we defined the following categories: no exposure, exposure for up to 1 year, exposure longer than 1 year to 3 years, and exposure for longer than 3 years.

Because drug dispensations to patients younger than 65 years are not recorded in the database and no data were available before 1987, the cumulative duration of exposure may actually be longer or the cumulative dose may be higher in cases where allopurinol was already dispensed to patients before these time points. We therefore defined the same cumulative dose and duration categories in allopurinol users who had not filled prescriptions for allopurinol during their first year after enrollment in the base population, because this group of patients more likely represents “new” users of allopurinol.

COVARIATES

Covariates included age, sex, systemic hypertension, diabetes mellitus, glaucoma, and previous use of oral or ophthalmic glucocorticoids. Systemic hypertension was defined by at least 1 diagnosis and diabetes mellitus by at least 1 dispensation of an oral hypoglycemic drug or insulin before the index date. We classified patients according to previous oral and ophthalmic corticosteroid use before the index date. Glaucoma was defined by a diagnosis of glaucoma or medical treatment for this condition, including ocular β-blockers, ocular parasympathomimetics, ocular α-agonists, and carbonic anhydrase inhibitors. Because of coding in the database, this definition also includes patients with ocular hypertension without manifest glaucoma.

STATISTICAL ANALYSIS

The rate ratio of cataract extraction for allopurinol was estimated from odds ratios (ORs) calculated by conditional logistic regression using the SAS PHREG program (SAS Institute, Cary, NC).11 We constructed individual models characterizing patients according to the cumulative dose or cumulative duration of allopurinol use, in some models also excluding patients who had not received any allopurinol dispensations during their first year after entry into the base population. For all these analyses, the reference category was the absence of exposure to allopurinol after enrollment in the base population. All models simultaneously controlled for all covariates listed above. P<.05, 2 tailed, was considered significant and 95% confidence intervals (CIs) were calculated for all relative risks.

Characteristics of cases and controls are summarized in Table 1. The risk of cataract extraction increased with age and was elevated in women and in patients with systemic hypertension, diabetes mellitus, or glaucoma. In patients with diabetes mellitus, the risk of cataract extraction was particularly increased in patients treated with insulin. More cases than controls had received dispensations of ophthalmic or oral corticosteroids before the index date.
The results of our study suggest that long-term use of allopurinol increases the risk of cataract extraction in elderly patients. An elevated risk has been indicated equally by some clinical and experimental observations, whereas most epidemiologic studies failed to find an increased risk. One of these studies had a limited sample size and may therefore have lacked power to detect an increased risk. In the larger studies, the measurement of allopurinol exposure has been criticized as not sufficiently distinguishing between short-term and long-term allopurinol use. Another epidemiologic study demonstrated an increased risk of cataract associated with gout medications, but could not distinguish between allopurinol and other medications for gout.

We observed an increased risk only in patients who had received allopurinol dispensations for a cumulative treatment period of longer than 3 years. Shorter cumulative treatment durations were not associated with an elevated risk. Lerman et al similarly reported that allopurinol had to be given for longer than 2 years to increase the risk. In the case series reported by Fraunfelder et al, cataract developed in about half of the cases after longer than 3 years of allopurinol exposure, while in the others shorter treatment durations were associated with an increased risk.

Eighty-nine cases and 384 controls were exposed to allopurinol, yielding an adjusted OR of 1.41 (95% CI, 1.10-1.79). One hundred sixty-nine cases and 851 controls had used allopurinol at any time after their enrollment in the base population, with an adjusted OR of 1.17 (95% CI, 1.08-1.27). Restricting the analysis to patients who had not been exposed to allopurinol during their first year in the base population resulted in an increased risk of 2.18 (95% CI, 1.18-4.00) for a cumulative treatment duration of longer than 3 years.

Table 1 shows the ORs of cataract extraction according to the cumulative dose of allopurinol since the patient’s enrollment in the base population. We did not observe an elevated risk for cumulative doses of up to 400 000 mg of allopurinol. For a cumulative dose of more than 400 000 mg the risk was increased, with an OR of 1.82 (95% CI, 1.18-2.80). Restricting the analysis to patients who had not had any dispensation of allopurinol during their first year after enrollment in the base population resulted in a somewhat higher risk estimate, with an adjusted OR of 3.29 (95% CI, 1.34-7.79) for a cumulative dose of more than 400 000 mg of allopurinol.

### Table 1. Characteristics of Cases and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 3677)</th>
<th>Controls (n = 21 868)</th>
<th>Adjusted† Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>21.0</td>
<td>36.6</td>
<td>1.00</td>
</tr>
<tr>
<td>75-84</td>
<td>41.3</td>
<td>37.4</td>
<td>1.9 (1.7-2.1)</td>
</tr>
<tr>
<td>≥85</td>
<td>37.8</td>
<td>25.9</td>
<td>2.4 (2.1-2.8)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>67.4</td>
<td>57.1</td>
<td>1.4 (1.3-1.5)</td>
</tr>
<tr>
<td>Diabetes mellitus treated with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral antidiabetics</td>
<td>11.3</td>
<td>8.7</td>
<td>1.3 (1.1-1.4)</td>
</tr>
<tr>
<td>Insulin</td>
<td>2.9</td>
<td>1.6</td>
<td>1.7 (1.4-2.2)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>47.1</td>
<td>37.9</td>
<td>1.3 (1.2-1.4)</td>
</tr>
<tr>
<td>Previous use of ocular corticosteroids</td>
<td>10.4</td>
<td>5.0</td>
<td>1.4 (1.2-1.6)</td>
</tr>
<tr>
<td>Previous use of oral corticosteroids</td>
<td>3.1</td>
<td>1.1</td>
<td>2.6 (2.1-3.4)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>21.8</td>
<td>7.2</td>
<td>3.1 (2.8-3.4)</td>
</tr>
</tbody>
</table>

*All data are presented as percentage unless otherwise indicated. †Adjusted for one another (all variables in table).

### Table 2. Odds Ratios of Cataract Extraction According to Cumulative Treatment Duration With Allopurinol

<table>
<thead>
<tr>
<th>Cumulative Treatment Duration</th>
<th>No. of Cases/Controls</th>
<th>Crude Odds Ratio</th>
<th>Adjusted* Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>3508/21 017</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Up to 1 y</td>
<td>71/297</td>
<td>1.07</td>
<td>1.07 (0.82-1.40)</td>
</tr>
<tr>
<td>1-3 y</td>
<td>42/242</td>
<td>1.04</td>
<td>1.02 (0.72-1.43)</td>
</tr>
<tr>
<td>&gt;3 y</td>
<td>56/212</td>
<td>1.58</td>
<td>1.53 (1.12-2.08)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, diabetes mellitus, systemic hypertension, previous ocular and oral corticosteroid use, and glaucoma.

### Table 3. Odds Ratios of Cataract Extraction According to Cumulative Dose of Allopurinol

<table>
<thead>
<tr>
<th>Cumulative Dose, mg</th>
<th>No. of Cases/Controls</th>
<th>Crude Odds Ratio</th>
<th>Adjusted* Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>3508/21 017</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1-100 000</td>
<td>87/460</td>
<td>1.14</td>
<td>1.13 (0.89-1.44)</td>
</tr>
<tr>
<td>100 001-200 000</td>
<td>27/139</td>
<td>1.17</td>
<td>1.12 (0.73-1.72)</td>
</tr>
<tr>
<td>200 001-400 000</td>
<td>26/153</td>
<td>1.02</td>
<td>0.96 (0.63-1.48)</td>
</tr>
<tr>
<td>≥400 000</td>
<td>29/99</td>
<td>1.74</td>
<td>1.82 (1.18-2.80)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, diabetes mellitus, systemic hypertension, previous ocular and oral corticosteroid use, and glaucoma.

†Excluding patients with allopurinol use during their first year in the base population.

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Because the daily dose of allopurinol may vary and is not considered when measuring the duration of use, we also investigated the risk according to the cumulative dose of allopurinol. A cumulative dose of more than 400 g of allopurinol, which roughly corresponds to 3½ years of treatment with 300 mg daily, was associated with an almost 2-fold increase in risk.

We also observed an increased risk for various previously described risk factors for cataract, among them old age, female sex, diabetes mellitus, systemic hypertension, glaucoma, and systemic or ophthalmic corticosteroid use.13-20 Except for old age and corticosteroid treatment, these risk factors are, however, not undisputed, because they could not be confirmed in all studies that were conducted.12 The increase in risk observed for glaucoma is, strictly speaking, that for ocular hypertension or glaucoma, because diagnostic coding in the database is not accurate enough to reliably distinguish between both conditions.

Some limitations of the study design need to be addressed. Cases were defined by cataract extraction, an end point that has often been used in studies of risk factors for cataract.5,20-27 Cataracts that are sufficiently severe to require extraction are the ones with the greatest clinical and public health effects. Referral for cataract surgery may, however, be more likely in patients who are under the care of a physician, such as users of allopurinol. If this accounted for the elevated risk for allopurinol, we would have expected to observe an increased risk similarly in patients using other drugs long term. This was not the case; we did not observe an elevated risk for HMG-CoA reductase inhibitors when we investigated the risk according to their duration of use.

In defining cases by cataract extraction, we treated all different subtypes of cataract as a single disease entity, because we did not have information on the specific subtype leading to the surgical procedure. We therefore do not know whether the risk of cataract associated with allopurinol varies by cataract subtype. Lack of classification by subtype, however, cannot account for the observed risk increase. If the risk is only for a single subtype, then the subtype-specific risk will yield even a higher point estimate than the combined one presented in our study.

Although we had at least 5 years of detailed drug exposure information for each patient before the index date, we did not have information on the patients’ drug use before 1987. The cumulative doses and durations of use we calculated may therefore actually be greater if patients had used allopurinol before these times. To address this limitation, we further examined the risk according to the cumulative dose and duration of allopurinol use by restricting our analysis to patients who had not filled prescriptions for allopurinol during their first year after enrollment in the base population. This group of patients more likely represents “new” users of allopurinol. In this restricted analysis, the risk estimates for the cumulative duration of use did not substantially change, thereby suggesting that exposure to allopurinol for longer than 3 years may be sufficient to increase the risk of cataract. This has also been suggested by clinical observations.2,4

Although we controlled in our analysis for several potential risk factors for cataract, we did not have information on others, most importantly exposure to UV radiation. Lerman et al11 suggested that allopurinol can be photobound to human lens proteins by UV radiation and that the drug has a cataractogenic action only in patients in whom such photobinding has occurred. They suggested that the photobound allopurinol acts as an additional photosensitizer within the lens, thereby enhancing the age-related photochemical changes that usually take place. Owing to the missing information, we could not further study the effect of UV light on the risk of cataract in allopurinol users. If UV light has an additive or synergistic effect on the risk of cataract in allopurinol users, the risk might even be greater in areas that have higher levels of UV radiation than Quebec.

We also did not have information on other potential risk factors for cataract such as trauma, alcohol use, and smoking. We have no reason to believe that trauma or smoking are independently related to allopurinol exposure and therefore do not expect confounding due to missing information on these variables. Although alcohol use is usually discussed among the potential risk factors for cataract, its role in cataractogenesis is inconclusive.11 Because patients with gout should avoid alcohol, alcohol intake may be less prevalent in allopurinol users. Assuming that alcohol intake leads to an elevated risk, failing to adjust for it would lead to a decrease in the risk estimates, but would not account for the observed increase in risk.

In summary, the results of our large-scale population-based epidemiologic study are in agreement with isolated clinical and experimental observations that suggest an increased risk of cataract for long-term allopurinol administration. Whereas the case reports indicated an increased risk of cataract predominantly for young patients receiving allopurinol,28 our study findings suggest that elderly patients are also at an increased risk when receiving long-term allopurinol treatment. Periodic lens evaluations in allopurinol-treated patients have occasionally been recommended.8,20 Further studies are needed that examine the relationship between the level of UV radiation exposure and the dose of allopurinol on the risk of cataract.

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A look at the past . . .

While it is neither advisable nor possible to force by legislation any one method of preventive treatment upon physicians in private practice, on the other hand it is the right and duty of the State to provide, for children born in almshouses, the best treatment thus far known, and to require for them the use of the silver-nitrate solution or of any other prophylaxis which may, in the future, prove to be equally efficacious."

After the reading of his paper, Dr. Howe recommended the adoption of the majority report submitted to the society at the meeting of 1897, which reads as follows:

We approve of the legislation which would result in the invariable use of this method (Crede’s) or any other equally safe and efficient, in almshouses, whereby the loss of vision from this disease would be lessened.

The elaborate minority report (of Dr. Jackson) was read. It dwells particularly on the argument that a good many of the statistics given by Dr. Howe and taken from European authors, were not in harmony with those found in this country.

Discussion—Dr. Prout against, Dr. Kipp for the majority report if it were made obligatory only to almshouses. With this restriction the majority report was adopted.