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.1 Treatment with allopurinol is usually well tolerated, with hypersensitivity reactions constituting the most common adverse effects.

In 1982, Fraunfelder et al2 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 al3,4 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.5,6 Another study reported an unusual morphologic thinning of the anterior clear zone of the lens in patients receiving long-term treatment with allopurinol.7 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.8

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.

Of the 10,214 patients with cataract extractions, 6735 patients did not meet...
POPULATION, 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). 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. 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 b-blockers, ocular parasympathomimetics, ocular a-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). 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 dispensions 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.
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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79). 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, 1.10–1.79).

In Table 2, we display the ORs of cataract extraction according to the cumulative duration of allopurinol use. The risk was not increased in patients who had been exposed to allopurinol for up to 3 years. Patients who had received dispensations of allopurinol for longer than 3 years exhibited an elevated risk, with an adjusted OR of 1.53 (95% CI, 1.12–2.08). Restricting the analysis to patients who had not been exposed to allopurinol during their first year in the base population resulted in an increase of the risk estimate, with an adjusted OR of 2.34 (95% CI, 1.37–4.00) for a treatment duration of longer than 3 years.

Table 3 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.

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 described.
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 cumula-
tive 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 previ-
ously described risk factors for cataract, among them
old age, female sex, diabetes mellitus, systemic hyper-
tension, glaucoma, and systemic or ophthalmic cortico-
steroid use.13-20 Except for old age and corticosteroid
treatment, these risk factors are, however, not undis-
puted, because they could not be confirmed in all stud-
ies that were conducted.12 The increase in risk observed
for glaucoma is, strictly speaking, that for ocular hyper-
tension 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 ad-
dressed. 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 ac-
cording 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 spe-
cific subtype leading to the surgical procedure. We
therefore do not know whether the risk of cataract asso-
ciated 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 allo-
purinol 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 infor-
mation on others, most importantly exposure to UV ra-
diation. Lerman et al8 suggested that allopurinol can be
photobound to human lens proteins by UV radiation and
that the drug has a cataractogenic action only in pa-

ers, 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 poten-
tial 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 ex-
pose and therefore do not expect confounding due to
missing information on these variables. Although alco-
hol use is usually discussed among the potential risk fac-
tors for cataract, its role in cataractogenesis is inconclu-
sive.13 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 ob-
erved 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 sug-
gest an increased risk of cataract for long-term allopurinol
administration. Whereas the case reports indicated an in-
creased risk of cataract predominantly for young patients
receiving allopurinol,28 our study findings suggest that el-
derly patients are also at an increased risk when receiving
long-term allopurinol treatment. Periodic lens evalua-
tions in allopurinol-treated patients have occasionally been
recommended.8,20 Further studies are needed that exa-
mine the relationship between the level of UV radiation ex-
posure and the dose of allopurinol on the risk of cataract.

Accepted for publication August 14, 1998.

The Pharmacoepidemiology Research Units of the
Centre Hospitalier de l’Université de Montreal, Campus
Hôtel-Dieu, and of the Royal Victoria Hospital, McGill Uni-
versity, Montreal, Quebec, are funded in part by the Fonds
de la Recherche en Santé du Québec. Dr Suissa is the re-
cipient of a Senior Scientist Award from the Medical Re-
cearch Council of Canada. Cooperation on this project was
supported by the Association of Clinical Pharmacology, Ber-
lín/Brandenburg, Germany.

We thank Annemarie Castilloux from the Pharmaco-
epidemiology Research Unit of the Centre Hospitalier de l’Uni-
versité de Montreal, Université de Montreal, Campus
Hôtel-Dieu, for her assistance in data management.

Reprints: Edeltraut Garbe, MD, MSc, Potsdam Insti-
tute of Pharmacoepidemiology and Technology Assess-
ment, Otto-Erich-Str 7, 14482 Potsdam, Germany (e-mail:
106700.3205@compuserve.com).

©1998 American Medical Association. All rights reserved.

Downloaded From: on 03/02/2018
REFERENCES