

Allopurinol use and the risk of cataract formation

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SUMMARY Several reports have suggested an association between chronic allopurinol ingestion and cortical and subcapsular cataract formation. To examine this possibility we identified 51 allopurinol users and compared their lenses with those of 76 patients who did not use allopurinol. The existence of lens opacities and the level of visual acuity were assessed by review of medical records or by prospective ophthalmic examinations; in both phases of the study the examiners were blinded as to the patient's use or non-use of allopurinol. Three different outcomes were considered: formation of any cataract, formation of a posterior subcapsular cataract, and formation of a cataract contributing to a corrected visual acuity of 20/30 or worse. The risk ratio for the formation of any cataract was 1.3 (95% confidence interval: 0.8, 2.0), the risk ratio for the formation of a posterior subcapsular cataract was 0.9 (0.3, 2.0), and the risk ratio for the formation of a cataract contributing to a loss of visual acuity was 1.3 (0.6, 2.9). None of these risk ratios was changed appreciably after controlling for age, sex, hypertension, or diabetes. Thus, after a mean of 6.9 years of allopurinol use, we found no evidence to confirm that allopurinol users were at higher risk of acquiring cataracts.

Cases reported to the National Registry of Drug-Induced Ocular Side Effects¹ have suggested an association between allopurinol use and cortical and subcapsular cataract formation. Lerman *et al.*² demonstrated that allopurinol is photobound in the human lens and suggested that it is cataractogenic in patients in whom this photobinding has occurred. Although Jick and Brandt³ found no association between allopurinol use and cataract surgery, their study did not include ophthalmic examinations. To find out whether allopurinol use increases the risk of cataract formation we designed a study that included ophthalmic examinations.

Patients and methods

RETROSPECTIVE PHASE

From hospital pharmacy records we identified 457 allopurinol users without concomitant chemotherapy, including 56 who had received an ophthalmic examination at our institution. After excluding

patients whose examinations preceded allopurinol use, or whose records suggested a history of congenital cataracts, ocular disease, ocular trauma, or exposure to toxic cataractogenic agents (n=26), or whose examinations did not include a lens examination (n=6), we had 24 allopurinol users for this phase of the study. By the same exclusion criteria we identified 54 allopurinol non-users from among all patients who had been referred for ophthalmic examination prior to the initiation of amiodarone or hydroxychloroquine therapy.

PROSPECTIVE PHASE

Of the 401 allopurinol users without ophthalmic examinations in the retrospective review 193 who were known to be alive and in the proximity of our hospital were invited to receive a free examination: 159 declined, six did not keep a scheduled appointment, and one was excluded by the same criteria used in the retrospective phase, leaving 27 allopurinol users in the prospective phase. Ophthalmic examinations to assess visual acuity and lens opacities were also performed on 22 non-users of allopurinol who were recruited from our hospital based internal medicine practice.

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BASELINE INFORMATION

By medical record review (retrospective phase) or patient interview (prospective phase) we obtained each patient's sex; age at the ophthalmic examination; history of diabetes, hypertension, or glaucoma; use of birth control pills, oestrogens, miotic medications, or phenothiazines; and occupation. No records or interviews suggested congenital cataracts, ocular disease, ocular trauma, or exposure to cataractogenic agents.

OPHTHALMIC EXAMINATION INFORMATION

From the medical records in the retrospective phase and the detailed ophthalmic examinations in the prospective phase we recorded each patient's initial, corrected, and best corrected Snellen visual acuity; nuclear colour as pale yellow, yellow, dark yellow, or brown/black; existence or previous removal of cataracts; evidence of injury or inflammation; and presence of retinopathy (diabetic retinopathy or maculopathy).

Cataracts were divided into four major classes—nuclear, cortical, supranuclear, and posterior subcapsular. Age related changes such as cortical flecks and isolated vacuoles, lamellar separations, and sutural prominence were not classified as cataracts, nor were Mittendorf dots. If the cortical, supranuclear, or subcapsular opacity was visible at the slit-lamp against the red reflex, and if it consisted at least of linear or clustered aggregates of the flecks, vacuoles, and lamellar separations, it was designated a cataract. Patients with a best corrected Snellen visual acuity of 20/30 or worse as a result of retinal disease were excluded. Retrospective information was obtained from medical records without any knowledge of allopurinol use. Similarly, information obtained from all prospective ophthalmic examinations was determined without knowledge of allopurinol use.

Three aspects of cataract existence were considered as possible outcomes: the development of any cataract, posterior subcapsular cataracts, or cataracts that contributed to a best corrected visual acuity of 20/30 or worse. Because of inadequate medical record information, five allopurinol users and four non-users in the retrospective phase could not be classified as to their best corrected visual acuity and were eliminated in the analyses for this outcome.

STATISTICAL METHODS

All numbers and analyses were based on patients, not individual eyes. Estimated risks for cataract development were compared by the χ^2 test.⁴ Risk ratios and corresponding 95% confidence intervals were constructed.⁵ In the one instance where an estimated risk

Table 1 *Distribution of age, sex, diabetes, and hypertension for allopurinol users and non-users*

	<i>Allopurinol users (n=51)</i>	<i>Non-users (n=76)</i>
Age		
Mean (years)	61.8	57.6
Standard deviation	12.4	12.2
Male sex	38 (75%)	27 (34%)
Diabetes	13 (25%)	5 (7%)
Hypertension	27 (53%)	26 (34%)

for non-users equalled 0.0, 0.5 was added to the numerator of this risk.⁵ Potential confounding by age, sex, diabetes, and hypertension was controlled by two methods: a logistic regression model that expressed each outcome as a function of allopurinol use and the potential confounders⁵; and a propensity score analysis,⁶ by which patients were stratified by their likelihood for allopurinol use, according to subranges of a logistic regression model that expressed allopurinol use as a function of the confounders. Power calculations for detecting relevant values for the risk ratio were based on the non-null distribution of the test statistic in the usual χ^2 test of association.⁴ Increased risk for cataract formation with increased duration of allopurinol use was examined by a χ^2 test for trend.⁷

Results

Allopurinol users were older and contained more males, more diabetics, and more hypertensives than non-users (Table 1). Estimated risk ratios were similar for the two phases of the study, except for the formation of a posterior subcapsular cataract (Table 2), where these estimated risk ratios had the widest confidence intervals. Therefore, because of the strong similarities of results in the two data sets, all further analyses were based on the single combined data set.

Compared with non-users the allopurinol users did not appear to have an excess risk for any of the three outcomes. Adequate data on the exact duration of allopurinol use were available for 37 of the 51 allopurinol users. The mean duration of use was 6.9 years, standard deviation 6.9 years. Only seven patients had used allopurinol for more than 10 years. No tendency for increased risk of cataract formation with increased duration of allopurinol use was observed for any of the three outcomes. When potential confounding by age, sex, diabetes, and hypertension was controlled both by logistic regression and by propensity score analyses, the adjusted risk ratios remained non-significant and were very similar to the crude estimates. Our sample size is

Table 2 Estimated risks and risk ratios for the formation of any cataract, of a posterior subcapsular cataract, or of a cataract contributing to loss of visual acuity* for allopurinol users compared with non-users in retrospective, prospective, and combined data sets

Data set	Number of subjects	Any cataract		Posterior subcapsular cataract		Cataract leading to loss of visual acuity	
		Risk	Risk ratio	Risk	Risk ratio	Risk	Risk ratio
Retrospective							
Users	24	0.33		0.17		0.32	
Non-users	54	0.31	1.1 (0.5, 2.1)†	0.19	0.9 (0.3, 2.6)†	0.20	1.6 (0.7, 3.8)†
Prospective							
Users	27	0.52		0.04		0.11	
Non-users	22	0.41	1.3 (0.7, 2.4)	0.00	2.5 (0.3, 21.6)	0.05	2.4 (0.3, 20.4)
Combined							
Users	51	0.43		0.10		0.20	
Non-users	76	0.34	1.3 (0.8, 2.0)	0.13	0.9 (0.3, 2.0)	0.15	1.3 (0.6, 2.9)

*Cataract contributing to corrected visual acuity 20/30 or worse. †95% Confidence interval.

sufficient for detecting large effects of allopurinol on all three outcomes (for example, RR=3.0) and small effects (for example, RR=1.5) for any cataract (Table 3) but insufficient for detecting small effects for posterior subcapsular cataracts or cataracts contributing to a best corrected visual acuity of 20/30 or worse.

Discussion

March *et al.*⁸ demonstrated that oxipurinol, an allopurinol metabolite, enters the human lens. Using high-resolution phosphorescence spectroscopy, Lerman *et al.*²⁹ showed that allopurinol is photo-bound in the human lens. They have suggested that this leads to photosensitisation and subsequent cataract formation. Our study differs from the report by Jick and Brandt,³ who found no association between allopurinol use and surgery for cataract extraction, because our patients had full ophthalmic examinations by methods shown to be valid, reproducible, and sufficiently sensitive.

We did not find evidence of a major increase in risk

for any of three types of cataracts among users of allopurinol. One potential problem is possible misclassification of the presence or absence of a cataract in our retrospective phase. However, all determinations of outcome obtained from medical records were obtained without knowledge of allopurinol use, and therefore any misclassification would be expected to be random, that is, independent of allopurinol use. The strong similarities in results from both study phases, despite different methods for detecting outcomes, makes it unlikely that there was any substantial random misclassification bias, especially since the prospective phase strictly followed a valid and reproducible classification system.¹⁰⁻¹⁴

Another possible explanation for the negative results is a selection bias by which either our allopurinol users or non-users do not reflect the true risks for cataract formation. For example, our non-users with rheumatic conditions may have used aspirin, which may be protective against cataract formation.¹⁵ However, this potential bias would tend to overstate the association between allopurinol use and cataract formation rather than bias it towards the null value. Although our low recruitment rate could potentially introduce bias, we considered it was imperative to include a detailed ophthalmic examination to eliminate an ascertainment bias that might have existed in a study that relied on cataract surgery,³ rather than on the presence of a cataract. Although it is possible that our negative results are due to an insufficient period of allopurinol use, there was no increased risk for cataract formation with increased duration of allopurinol use.

Finally, our study has a limited ability to identify a true but relatively weak association. Nevertheless, the consistency of the results with those of the prior study³ argue against a strong association between allopurinol and cataracts.

Table 3 Power of test of significance for our data set to detect risk ratios of 1.5, 2.0, and 3.0 for the formation of any cataract, of a posterior subcapsular cataract, or of a cataract contributing to loss of visual acuity*

Risk ratio to be detected	Any cataract	Posterior subcapsular cataract	Cataract contributing to loss of visual acuity
1.5	0.52	0.17	0.19
2.0	0.97	0.46	0.50
3.0	0.99	0.92	0.94

*Cataract contributing to corrected visual acuity of 20/30 or worse.

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References

- 1 Fraunfelder FT, Hanna C, Dreis MW, Cosgrove KW. Cataracts associated with allopurinol therapy. *Am J Ophthalmol* 1982; **94**: 137-40.
- 2 Lerman S, Megaw JM, Gardner K. Allopurinol therapy and cataractogenesis in humans. *Am J Ophthalmol* 1982; **94**: 141-6.
- 3 Jick H, Brandt DE. Allopurinol and cataracts. *Am J Ophthalmol* 1984; **98**: 355-8.
- 4 Colton T. *Statistics in medicine*. Boston: Little, Brown, 1974: 163-81.
- 5 Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research: principles and quantitative methods*. Belmont: Wadsworth, 1982: 320-456.
- 6 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effect. *Biometrika* 1983; **70**: 41-55.
- 7 Brown BW, Hollander M. *Statistics: a biomedical introduction*. New York: Wiley, 1977: 211-5.
- 8 March WF, Goren S, Shoch D. Action of allopurinol on the lens. In: Leopold IH, ed. *Symposium on ocular therapy*. St Louis: Mosby, 1974: 83-95.
- 9 Lerman S, Megaw JM, Fraunfelder FT. Further studies on allopurinol therapy and human cataractogenesis. *Am J Ophthalmol* 1984; **97**: 205-9.
- 10 Chylack LT Jr. Classification of human cataracts. *Arch Ophthalmol* 1978; **96**: 888-92.
- 11 Chylack LT Jr, Lee MR, Tung WH, Chang HM. Classification of human senile cataractous change by the American Cooperative Cataract Research Group (CCRG) Method: I. Instrumentation and technique. *Invest Ophthalmol Vis Sci* 1983; **24**: 424-31.
- 12 Chylack LT Jr, White O, Tung WH. Classification of human senile cataractous change by the American Cooperative Cataract Research Group (CCRG) Method: II. Staged simplification of cataract classification. *Invest Ophthalmol Vis Sci* 1984; **25**: 166-73.
- 13 Chylack LT Jr, Ranoil BJ, White O. Classification of human senile cataractous change by the American Cooperative Cataract Research Group Method: III. The association of nuclear color (sclerosis) with extent of cataract formation, age and visual acuity. *Invest Ophthalmol Vis Sci* 1984; **25**: 174-80.
- 14 Chylack LT Jr, Rosner B, Garner W, et al. Validity and reproducibility of the Cooperative Cataract Research Group (CCRG) cataract classification system. *Exp Eye Res* 1985; **40**: 135-47.
- 15 Cottier E, Sharma YR, Niven T, Brescia M. Distribution of salicylate in lens and intraocular fluids and its effect on cataract formation. *Am J Med* 1983; **74**: 83-90.

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