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Drugs, including alcohol, that act as risk factors for cataract, and possible protection against cataract by aspirin-like analgesics and cyclopenthiazide

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SUMMARY A case-control study of cataract in Oxfordshire explored the risks and benefits associated with a variety of drugs. Steroids including the diuretic spironolactone, nifedipine, heavy smoking, and beer drinking were associated with a raised risk. On the other hand aspirin-like analgesics (paracetamol, ibuprofen, aspirin, etc.) appeared to protect against cataract. Cyclopenthiazide appeared to provide a similar protection.

Cataract is the major cause of blindness worldwide, but only recently have some major risk factors in cataract been elucidated in different countries.[1-5] We conducted a case-control study of cataract in Oxford and have reported on the risks associated with diabetes, myopia, severe diarrhoea, glaucoma, and employment on a military base.[3 5] Here we report on drugs that appear to be risk factors for cataract in Oxford, and on drugs that appear to have protected against cataract.

Material and methods

Three hundred cases and 609 controls aged 50–79 were interviewed for this study. Cases were those patients aged between 50 and 79 having cataract extracted in the Oxford Eye Hospital. Cases and controls had the same age-sex distribution.[5] Details of the recruitment, questionnaire, and data analysis have been reported.[5] The subjects were asked what drugs they had taken regularly for at least four months at any time in the past. They were also asked about their current and past smoking and drinking habits. In the analysis of the data odds ratios were computed from contingency tables and are reported as valid estimates of relative risk. Thus a reported relative risk of 2 for a particular factor implies that the group exposed to that factor are twice as likely to be admitted for cataract extraction as those not exposed to that factor. Conversely a relative risk of 0·5 implies that the group exposed to the factor are protected against cataract, being only half as likely to have a cataract extracted as the unexposed group.

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Results

STEROIDS

Long-term steroid therapy causes posterior subcapsular cataract,[6] but in the present study consumption for as little as four months was scored. Nevertheless steroids emerged as a significant risk (Table 1). The steroids most commonly reported were prednisolone and spironolactone with a risk

Table 1 *Steroids as a risk factor for cataract*

	Controls	*Cases*	*Total*
Steroid	38	32	70
No steroid	571	268	839
Total	609	300	909
Percentage positive	6·2	10·7	

χ^2 test, $p<0·025$; relative risk=1·79; 95% confidence limits=1·09 to 2·93.

Table 2 *Diuretics and cataract*

	Controls	*Cases*	*Total*
Reporting diuretics	155	57	212
No diuretics	454	243	697
Total	609	300	909
Percentage positive	25·5	19·0	

χ^2 test, $p<0·031$; relative risk=0·69; 95% confidence limits=0·49 to 0·97.

Table 3 *Diuretics as protective agents in older patients (aged 70–79)*

	Controls	*Cases*	*Total*
Reporting diuretics	99	27	126
No diuretics	183	110	293
Total	282	137	419
Percentage positive	35·1	19·7	

χ^2 test, $p<0.001$; relative risk=0·45; 95% confidence limits=0·28 to 0·74.

Table 4 *Percentage of cases and controls reporting different diuretics*

	Present study		*Edinburgh**	
	Control	*Cases*	*Control*	*Cases*
Amiloride	3·9	3·3	2·8	3·5
Bumetanide	1·3	3·0	0·9	1·2
Bendrofluazide	3·3	1·7	4·9	6·6
Cyclopenthiazide	10·8	3·7	3·7	2·7
Frusemide	3·9	3·7	3·1	6·5
Hydrochlorthiazide	4·8	4·0	–	–
Spironolactone	1·8	4·0	–	–
Triamterene	1·2	0·7	–	–
Other	1·8	2·7	–	–

*from Clayton *et al.*[1]

Table 5 *Cyclopenthiazide as a protective factor for cataract—contingency table*

	Controls	*Cases*	*Total*
+Cyclopenthiazide	66	11	77
−Cyclopenthiazide	543	289	832
Total	609	300	909
Percentage positive	10·8	3·7	

χ^2 test, $p<0.001$; relative risk=0·31; 95% confidence limits=0·16 to 0·60.

attached to each. The risk associated with spironolactone is discussed under diuretics.

DIURETICS

Diuretics have been reported as a risk factor in the Edinburgh study,[1] but this did not emerge from our results. In fact diuretics appeared to provide some protection (Table 2), especially in older patients (Table 3). The imbalance between cases and controls differed for different diuretics, with an excess of cases for bumetanide and spironolactone contrasting with an excess of controls reporting bendrofluazide and cyclopenthiazide (Table 4). The Edinburgh study found excess reports of every diuretic except cyclopenthiazide in cases, whereas we found several diuretics with an excess in controls (Table 4). The age-sex distributions of our cases and controls were almost identical, whereas the Edinburgh study had

Table 6 *Spironolactone as a risk factor for cataract*

	Controls	*Cases*	*Total*
Spironolactone	11	12	23
Without spironolactone	598	288	886
Total	609	300	909
Percentage positive	1·8	4·0	

χ^2 test, $p<0.05$; relative risk=2·3; 95% confidence limits=1·002 to 5·28.

an excess of older cataract patients, who would increase the score for all diuretics. We analysed the data for each diuretic by χ^2 test: only two produced significant results. Cyclopenthiazide (Navidrex K) appeared to be protective, decreasing the risk of cataract by a factor of nearly 3 (Table 5). The proportion of subjects reporting cyclopenthiazide was greater in each of the four control groups than in the cases. The only diuretic found to be a significant risk factor was spironolactone, with a relative risk of 2·3 (Table 6). This drug is a steroid, and the associated risk of cataract seems to be similar to that for the other steroids (Table 1). When subjects reporting spironolactone (a risk factor) and/or cyclopenthiazide (a protective factor) were removed from the data, patients reporting other diuretics were equally distributed between the cases (12·0%) and controls (13·0%), so that the apparent protective effect of diuretics (Table 2) was entirely due to cyclopenthiazide.

NIFEDIPINE

Nifedipine has not been mentioned as a possible risk factor for cataract but it appeared to be so in our study (Table 7). The cases reporting nifedipine had no striking common feature except as expected for angina (5 out of 9) and hypertension (8 out of 9). This risk may be related to hypertension, which others have reported as a risk factor.[1]

CIGARETTES

Subjects were asked about their past and present use of cigarettes and number of years as a smoker. Daily cigarette consumption multiplied by years as a smoker gave a cigarette-year value which was used to group subjects. The highest group was more common among cases, and so a contingency table was drawn up comparing these 'heavy smokers'—that is, those whose cigarette-year score exceeded 1500—with non-smokers (Table 8). Only 2·8% of the controls reported this level of smoking compared with 7% of cases. By our definition 'heavy smoking' of cigarettes was associated with a doubling of the risk of cataract. A similar increase was reported from Edinburgh.[1]

Table 7 *Nifedipine as a risk factor for cataract*

	Controls	*Cases*	*Total*
Nifedipine	7	9	16
Without nifedipine	602	291	893
Total	609	300	909
Percentage positive	1·2	3·0	

χ^2 test, $p<0·05$; relative risk=2·7; 95% confidence limits=1·00 to 7·32.

Table 8 *Cigarette smoking and cataract*

	Controls	*Cases*	*Total*
'Heavy smoker'*	25	21	46
Non-smoker	241	103	344
Total	266	124	390
Percentage positive†	2·8	7·0	

χ^2 test, p=0·032; relative risk=1·97; 95% confidence limits=1·05 to 3·67.
*'Heavy smoker' means subjects with cigarette-year score >1500—e.g. subject who smoked more than 30 cigarettes/day for 50 years or 40 cigarettes/day for 37·5 years, etc.
†Percentage of the total in the study.

Table 9 *Beer drinking and cataract*

	Controls	*Cases*	*Total*
More than 2 pints/day	15	15	30
Nil to 2 pints/day	594	285	879
Total	609	300	909
Percentage 'heavy'	2·5	5·0	

χ^2 test, p=0·044; relative risk=2·08; 95% confidence limits=1·005 to 4·32.
2 Pints=1136 ml.

ALCOHOL

Subjects were asked about their consumption of beer, wines, and spirits separately. The score for all three was added to give a total alcohol score. Those reporting higher scores for total alcohol, past and present, were overrepresented among cases, indicating a possible risk, but comparison of those consuming 10 or more units of alcohol per day with those consuming less did not reveal a significant difference by the χ^2 test (one unit of alcohol is half a pint (284 ml) of beer, or one glass of wine, or a single whisky). For individual beverages 'heavy drinkers' (more than 4 units per day) of either spirits or beer were overrepresented among cases. The difference for spirits was not statistically significant, but 'heavy' beer drinkers appeared to double their risk of cataract (Table 9). The cataract group had a greater proportion of subjects reporting a high beer consumption than any of the four control groups. All but one of the 'heavy' beer drinkers were male, and in males alone the risk was similar to the overall risk: relative risk=2·2 (95% confidence limits 1·02 to 4·66), p=0·041. An association between cataract and high alcohol consumption was reported by Clayton *et al.*[1]

Table 10 *Contingency table for aspirin as a possible protective agent against cataract*

	Controls	*Cases*	*Total*
Aspirin	44	15	59
No aspirin	565	285	850
Total	609	300	909
Percentage positive	7·2	5·0	

χ^2 test, p=0·2, not significant.

Table 11 *Paracetamol (acetaminophen) as a protective factor against cataract—contingency table*

	Controls	*Cases*	*Total*
Paracetamol	107	26	133
No paracetamol	502	274	776
Total	609	300	909
Percentage positive	17·6	8·7	

χ^2 test, $p<0·001$; relative risk=0·45; 95% confidence limits=0·29 to 0·71.

Table 12 *Aspirin-like analgesics as protective factors against cataract*

	Controls	*Cases*	*Total*
Aspirin-like analgesics	185	51	236
No aspirin-like analgesics	424	249	673
Total	609	300	909
Percentage positive	30·4	17·0	

χ^2 test, $p<<0·001$; relative risk=0·47; 95% confidence limits=0·33 to 0·66.

ASPIRIN-LIKE ANALGESICS: PROTECTIVE FACTORS?

Risk factors are those factors experienced by a significantly greater proportion of cases than of controls. To our surprise some drugs were reported by a greater proportion of controls than of cataract patients, indicating a possible anticataract effect. These drugs were the aspirin-like analgesics (non-narcotic analgesics). Aspirin was reported by 7·2% of controls and 5·0% of cases, but this difference was not statistically significant (Table 10). Paracetamol (acetaminophen) was reported by twice as many controls as cases and emerged as a highly significant protective factor, with a relative risk of 0·45 (Table 11). The 95% confidence limits for this relative risk are 0·29 to 0·71. Consumption of paracetamol for at least four months is associated with a significant protection against cataract. The proportion of subjects reporting other aspirin-like analgesics was also greater among controls than cases, so we analysed

Table 13 *Protection by aspirin-like analgesics in those not reporting steroids*

	Controls	*Cases*	*Total*
Aspirin-like analgesics	172	42	214
No aspirin-like analgesics	399	226	625
Total	571	268	839
Percentage positive	30·1	15·7	

χ^2 test, $p<<0.001$; relative risk=0·43; 95% confidence limits=0·30 to 0·63.

Table 14 *Protection by paracetamol in those not reporting steroids*

	Controls	*Cases*	*Total*
Paracetamol	100	22	122
No paracetamol	471	246	717
Total	571	268	839
Percentage positive	17·5	8·2	

χ^2 test, $p<0.001$; relative risk=0·42; 95% confidence limits=0·26 to 0·68.

Table 15 *Protection by ibuprofen in those not reporting steroids*

	Controls	*Cases*	*Total*
Ibuprofen	40	8	48
No ibuprofen	531	260	791
Total	571	268	839
Percentage positive	7·0	3·1	

χ^2 test, $p<0.025$; relative risk=0·41; 95% confidence limits=0·19 to 0·89.

the data for these drugs as a whole (Table 12). The relative risk was very similar for the entire group, again indicating that either taking aspirin-like analgesics or something closely associated with taking these analgesics had halved the risk of cataract. The extent of protection was very similar in males and females.[4] The term 'aspirin-like analgesics' includes aspirin, paracetamol, ibuprofen and similar drugs, naproxen, benorylate, mefenamic acid, and flufenamic acid. The proportions of total controls reporting these drugs were 7·2% aspirin, 17·6% paracetamol, 7·2% ibuprofen family, 4·1% for the rest.

As the implications of the association between these drugs and protection against cataract are so important, it is necessary to be sure that the association is real. It is useful therefore to compare the different control groups lest the result be due to a single group, perhaps the hospital controls, being major consumers of analgesics. In fact aspirin-like analgesics were reported by 29·9%, 32·1%, 32·3%, and 27·0% of the hospital controls and three community control groups respectively compared with only 17% of cataract patients.[4] The close comparability of the four different control groups, all of them differing widely from the cases, enhances our confidence that the association between aspirin-like analgesics and protection against cataract is real. The low p value adds further support to that view. Many of the subjects reporting aspirin-like analgesics also reported arthritis (42% of cases and 36% of controls), and some of these had also reported taking steroids, a known risk factor for cataract in our population (Table 1). It seemed useful therefore to exclude those reporting steroids from the analysis. On doing so the apparent protection by aspirin-like analgesics increased slightly (Table 13). The apparent protection by paracetamol increased slightly, remaining highly significant (Table 14). Without the steroid takers ibuprofen emerged as a significant protective factor (Table 15).

Discussion

It appears from these results that a variety of drugs affect lens opacification but most surprisingly that some, the aspirin-like analgesics, may exert a protective effect. We did not attempt to validate drug consumption. The usual method by blood and urine tests is not possible, because our interest extended to drugs taken in the past. Validation from hospital notes or general practitioner notes would not be useful, as they are not comparable, and some drugs that were most interesting are over-the-counter drugs. However, most patients seem confident in remembering drugs they have taken regularly for at least four months, and any lack of recall should be the same in all groups. Comparisons we have made between the five groups[5] indicate that the powers of recollection of the different groups are comparable.

STEROIDS

Steroids were associated with an 80% increase in the risk of cataract. There are several ways in which steroids could cause cataract. They can increase glucose levels in plasma and aqueous humour, increase cation permeability, inhibit Na-K-ATPase and glucose 6-phosphate dehydrogenase and RNA synthesis[6] and can bind to lens proteins.[7] The steroids previously associated with cataract have a side chain structure that permits reaction with amino groups to form a stable adduct. Spironolactone does not have this side chain, but both spironolactone and prednisolone have a carbonyl function on the A ring where protein binding could occur. Prenisolone-protein adducts were identified in rat lenses opacified by incubation in prednisolone and in cataracts removed from patients who had received prolonged steroid therapy.[8]

DIURETICS

From our results we conclude that spironolactone, a steroid diuretic, is a risk factor for cataract and that other diuretics have little effect either way, except for the apparent protection by cyclopenthiazide. This contrasts with the conclusion from the Edinburgh study that all diuretics are risk factors for cataract, some worse than others, with the degree of risk related to the elevation of plasma urea.[1]

CIGARETTES AND ALCOHOL

Both 'heavy smoking' and 'heavy beer drinking' appeared as risk factors in this study (Tables 8 and 9). Cigarette smoking was the only factor where the data were stratified after all the interviews had been completed. No close relationship was observed, and comparison of all smokers with non-smokers did not reveal a risk. Furthermore there is a possibility of confounding between cigarette smoking, beer drinking, and work on a military base, which was reported as a risk factor in the preceding paper,[5] but analysis for interaction between risk factors by means of GLIM (Royal Statistical Society, Edinburgh) indicated that these three risk factors are independent.

ASPIRIN-LIKE ANALGESICS: PROTECTIVE FACTORS?

The protective effects of aspirin-like analgesics (non-narcotic analgesics[9]) have been reported briefly by us,[4] but here we present the contingency tables for individual members of this family. Earlier studies indicating that aspirin protected against cataract in rheumatoid arthritis and diabetic patients[10 11] were criticised.[12] Subsequently we showed that aspirin could prevent the cyanate-induced opacification of incubated rat lenses.[13] The strong association between consumption of aspirin, paracetamol, ibuprofen, and similar drugs and protection against cataract in this study does not establish a causal relationship, but if these drugs are not responsible for the protective effect it means that those subjects taking them are protected in some other way, perhaps by the condition for which they took the drugs. However, the drugs were taken for a variety of reasons—about 40% for arthritis. It seems unlikely that arthritis protects against cataract, and it would have to be an extremely powerful effect fully to explain the results, because only 36% of the controls reporting these drugs had also reported arthritis. It is no more likely that suffering pain protects against cataract. We can think of no explanation other than a direct protection against cataract by aspirin-like analgesics. Most of the standard criteria for a causal relationship[14] are satisfied in this study. The only previous link between the aspirin-like analgesics and cataract was in the studies of aspirin. Before our study there was no suggestion that paracetamol, ibuprofen, and the other drugs might have any protective effect.

Various mechanisms have been proposed for the apparent protective effect of aspirin, but most recently we have favoured the view that acetylation of the lens proteins served to protect them against chemical insults such as cyanate, glucose, glucose 6-phosphate, and prednisolone that are associated with cataract.[13] This mechanism received further support from laboratory studies of Rao *et al.*[15] This explanation cannot be extended to the other aspirin-like analgesics, because most of them lack an acetyl group and therefore cannot acetylate proteins. A mechanism involving prostaglandins is superficially attractive, but paracetamol, which is a feeble inhibitor of prostaglandin synthesis, appears strongly protective against cataract, whereas indomethacin, a powerful inhibitor of prostaglandin synthesis, is not protective, being reported by 3·1% of controls and 3·3% of cases. They may act by lowering blood glucose levels.[4] Aspirin-like analgesics lower fasting blood glucose levels in diabetics and non-diabetics[16 17] and improve glucose tolerance[16 18 19] and the insulin response to glucose.[17 19] These properties are shared by aspirin, salicylates, and ibuprofen but not by indomethacin.[20–22]

If aspirin-like analgesics are protective because they lower blood glucose, it would imply that the level in many subjects aged 50 to 79 is higher than is healthy for the lens. There is some evidence to support that notion. First, diabetes is such a powerful risk factor[3] that any elevation of blood glucose could be harmful. Indeed, it was shown in the Edinburgh survey that the mean glucose level in cataract patients exceeded that of controls even when diabetics were excluded from the analysis.[23] Secondly, it has been reported that 44% of cataract patients have an abnormal glucose tolerance curve.[24] A moderate but chronic elevation of glucose concentration is unlikely to have any osmotic effect and is more likely to act through non-enzymic glycosylation of lens proteins. This reaction occurs to most proteins, notably to long-lived proteins found in the tissues that are damaged in diabetes.[25] If the aspirin-like analgesics protect against cataract by lowering blood glucose levels, it is possible that they give some protection against other glucose-induced damage—perhaps retinopathy, neuropathy, and basement membrane damage. An apparent protection by aspirin against diabetic retinopathy has been noted.[26 27]

A second case control study in Oxford that incorporates more detailed questions on analgesics has been started so that the dosage required of a protective effect can be elucidated. There are studies indicating that low-dose aspirin protects against

myocardial infarction, unstable angina, and strokes. Additional protection against cataract would be a great bonus, although some might prefer paracetamol as a potential anticataract drug. Indeed, it is possible that paracetamol is also effective against the above life-threatening conditions.

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