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Can cataract be prevented?

JOHN J. HARDING

Abstract

The feasibility of preventing cataract by elimination of risk factors or by anti-cataract therapy is reviewed. Elimination of the major risk factors in Western countries would be difficult, although it has potential in the developing world. Various approaches to drug therapy have been made but ran into problems. The development of aldose reductase inhibitors received by far the greatest financial support but problems with toxicity were rapidly followed by the collapse of the original hypothesis. The case of aspirin, paracetamol and ibuprofen built up more slowly with no encouragement from the pharmaceutical industry. Positive results have been achieved *in vitro*, and in the prevention of diabetic cataract in rats, as well as the identification of an association with a protective effect against cataract in human patients. A clinical trial of these compounds is required. Other anti-cataract agents are also being investigated.

Key words Aldose reductase inhibitors, Anti-cataract therapy, Aspirin, Cataract, Ibuprofen, Paracetamol

It has been suggested that there is no need to prevent cataract because there is a perfectly good surgical procedure to deal with it as and when it arises. Cataract surgery has not, however, eliminated the problem; indeed cataract remains the major cause of blindness and visual impairment world-wide. In India alone there are almost 4 million people newly blind from cataract every year[1] in spite of enormous efforts from Indian ophthalmologists and the government. A 15-year eye care programme in Nepal, with emphasis on cataract surgery, has not decreased the prevalence of cataract blindness significantly.[2] Closer to home there are waiting lists, with an 18-month wait being commonplace after being listed. Most patients will spend more than a tenth of their remaining life expectancy visually impaired on the list; some die with their cataracts. The cost of cataract surgery is a worry to some authorities, accounting for 12% of the Medicare budget in the United States.

The other major drawback of surgery is the risk of complications. In percentage terms the risk of most complications is small, but given the enormous number of procedures – about 2 million per annum in both the United States and India, for example – the overall number of even serious complications is great. One complication, posterior capsular opacification (PCO), occurs in up to 50% of patients but in younger patients it affects almost 100%.[3] In many of the countries with the greatest cataract problems the equipment to deal with this complication is a rarity, a point which is ignored by those advocating greater use of the latest Western surgical techniques in developing countries.[4] In Nepal the outcome of surgery with intraocular lenses was no better than that without; and 50% of the impaired vision in operated eyes was attributed to surgical complications including PCO.[5]

Accepting that prevention of cataract is desirable, the next question is how to achieve this objective. There would seem to be two major possibilities: elimination of risk factors and an anti-cataract drug. Abandoning the use of phospholine iodide for the treatment of glaucoma has prevented tens of thousands of cataracts.[6,7] The scope for further prevention in Western countries is limited because there is not a single predominant cause of cataract and even the major causes are somewhat intractable (Table 1). If diabetes accounts for about 12% of cataract in the West, only that proportion could be eliminated by wiping out diabetes. Of course it is likely that steps that fall short of elimination could provide tangible benefits. Better control of blood sugar levels would probably decrease the amount of cataract in the following decades.

Table 1. *Attributable risks for the risk factors for cataract identified in Oxfordshire*

Factor	Attributable risk (%)
Diabetes	12
Myopia	7
Glaucoma	6
Steroids	5
Severe diarrhoea	4
Heavy smoking	3
Heavy drinking	3
Military work	3
Spironolactone	2
Renal failure	2

Adapted from Harding and van Heyningen.[8]

John J. Harding ✉
Nuffield Laboratory of Ophthalmology
University of Oxford
Oxford OX2 6AW, UK

Table 2. *Problems with the aldose reductase (AR) hypothesis*[11]

AR has never been shown to convert glucose stoichiometrically to sorbitol using only NADPH
The usual assay with glyceraldehyde is invalid
AR is remarkably inefficient
AR is extremely sluggish
AR is remarkably non-specific
Different preparations have markedly different patterns of relative activities with different substrates
AR activity is very low in human lens
Osmotically significant levels of sorbitol have never been found in human lens
Adult human lens placed in high-glucose medium does not accumulate sorbitol
The X-ray structure of AR has no binding site for glucose

Developing countries have different risk factors and there is evidence that 50% of the cataract may be attributable to life-threatening diarrhoea.[9] In this case the possibility of eliminating this proportion by prevention of diarrhoea arises. The great advantage of elimination of risk factors is that this would not normally lead to side-effects. Indeed better control of diabetes, and elimination of diarrhoea, heavy drinking and smoking could only bring additional benefits.

Anti-cataract drugs are the alternative option for cataract prevention and have been investigated for many years, but as yet none is licensed for use in the United Kingdom or the United States. Drugs to prevent cataract are sold in many countries. Some are known to be ineffective, while for others there is no evidence either way. The first compounds to be studied systematically were the aldose reductase inhibitors, or ARIs.[10] However, they have not proved very successful and the hypothetical basis for their use has been undermined.[10,11] The most serious problem with the sorbitol/osmotic stress hypothesis for cataractogenesis is that the pure enzyme, isolated or recombinant, has never been shown to convert glucose stoichiometrically to sorbitol (Table 2). That is, the 'enzyme' cannot perform the reaction that gave it its name. It is not a reductase for aldoses.

The next group of potential anti-cataract drugs – aspirin, paracetamol (acetaminophen) and ibuprofen – arrived on the scene by a series of fortuitous observations.[12] Cotlier and Sharma[13] first suggested that aspirin might be the cause of the decreased lens opacification in rheumatoid arthritis patients. One important mechanism for cataractogenesis is by chemical modification of lens proteins,[12] so it seemed at first unlikely that aspirin would protect because it is known to acetylate proteins. Very recently acetylation of a single amino group of a major human lens protein was demonstrated.[14] However, it was shown that aspirin can protect lens proteins against attack by other modifiers, such as cyanate,[15] prednisolone,[16] glucose and other sugars.[17–19] Ibuprofen also protected lens crystallins against attack by sugars and cyanate.[19–21]

The reason for looking at ibuprofen was because it, together with aspirin and paracetamol, had been associated with a protective effect against cataract in a population in Oxfordshire.[22] This result came from a case–control study of 300 cataract patients and 609 controls,[23] and was confirmed in a second case–control study in Oxfordshire[24] and two others in Germany and India.[25,26] At this stage a carefully controlled randomised clinical trial of these drugs against early cataract was required but none has been carried out. Aspirin, paracetamol and ibuprofen are out of patent and cheap. Population studies attempting to test the hypothesis have mostly been add-ons to other studies and have been too small with subjects too young for a worthwhile cataract study. A trial is necessary because case–control studies cannot prove a causal relationship, only demonstrate associations.

Causal relationships can be demonstrated in animal experiments and these have established the beneficial effects of these three drugs. Aspirin appears to delay cataract in naphthalene- and galactose-fed rats and in diabetic rats.[27,28] Paracetamol and ibuprofen, as well as aspirin, protected against diabetic cataract in rats.[29] The drugs were given in the drinking solution and protected for up to 160 days. They decreased glycation of lens proteins and maintained glutathione levels.

The potential of the aspirin-like drugs to prevent cataract is summarised in Table 3. Clinical trials would be the logical next step.

Other agents have been studied as potential anti-cataract therapy and some have come to human studies. These include bendazac, pantethine and vitamins A, C and E. In general the results have been disappointing. However a recent report indicates that poor nutrition in early life could enhance the risk of lens opacities six or seven decades later.[30] The results of a full clinical trial conducted on the vitamins are awaited with diminishing patience.

Prevention of cataract has been achieved in many animal models by different chemical compounds, showing the possibilities of prevention.[12] Only a few of

Table 3. *Anti-cataract potential of the aspirin-like drugs*

Aspirin and ibuprofen decrease the binding of harmful sugars, steroids and cyanate to lens proteins
Aspirin and ibuprofen protect some enzymes against chemically induced inactivation
Aspirin and ibuprofen protect incubated rat lenses against cyanate-induced opacification
Aspirin, paracetamol and ibuprofen prevent cataract in diabetic rats
Aspirin, paracetamol and ibuprofen were all associated with a protective effect against cataract in human populations in case–control studies in Oxford (UK), Germany and India

these molecules have been taken into clinical trials designed to test whether or not they can prevent cataract in man. There is the opportunity to test others now the laboratory studies have shown what is possible. Preventing 50% of cataract would be a wonderful achievement but would not eliminate the need for cataract surgery.

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