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Inhaled Corticosteroids and Cataract

Prevalence, Prevention and Management

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Abstract

Oral and topical (ocular) corticosteroids are known to have the potential to cause cataracts, but inhaled corticosteroids have generally been considered to be free of this adverse effect. However, a large epidemiological study has recently found a strong association in adults between use of inhaled corticosteroids and risk of posterior subcapsular cataract, the most serious type of cataract. This is likely to be a causal association as the association was strong (odds ratio of 10 for heavy users of corticosteroids compared with nonusers); in addition, there was a dose-response relationship and the association is biologically plausible.

For people with asthma, the benefits of inhaled corticosteroids for management of their respiratory symptoms will be much greater than the risk of cataract. This is particularly true for children, in whom the risk of cataract is extremely low. Nevertheless, the existence of serious adverse effects of inhaled corticosteroids means they should be used for the shortest duration, and in the lowest dose, compatible with effective asthma management.

It has long been known that oral and topical (ocular) corticosteroids can cause cataracts.[1] Inhaled corticosteroids have generally been considered to be free of this adverse effect. However, a recent epidemiological study involving over 3500 older Australians has found a strong association between use of inhaled corticosteroids and risk of cataract.[2] In this article, we review the evidence link-

ing inhaled corticosteroids with cataract, and suggest ways in which this problem might be minimised. The paper begins with a summary of what is known about the epidemiology of cataract and about the non-ocular adverse effects of inhaled corticosteroids.

1. Epidemiology of Cataract

1.1 Prevalence of Cataract

Cataracts are an enormous clinical and public health problem. In developing countries, cataracts are the major cause of blindness.[3] In more developed countries, cataract surgery is one of the most frequently performed operations and accounts for a significant proportion of healthcare costs.[4]

A cataract is an opacity that forms somewhere in the lens of the eye. Cataracts are very rare in children, where they are often inherited (sometimes as part of a more general genetic disorder) or are caused by an intrauterine infection such as rubella.[5] Cataracts become increasingly common with age.[6,7] The 3 main types of age-related cataract are nuclear cataract, cortical cataract, and posterior subcapsular cataract. Nuclear cataract involves the nucleus of the lens and progressively increases the density, and hence opacity, of this part of the lens. Cortical cataract involves the surface of the lens, beginning at the periphery and then extending as 'spokes' towards the visual axis. Posterior subcapsular cataracts arise just under the capsule of the lens, usually in the centre of this area and so tend to be directly on the visual axis. Posterior subcapsular cataracts are the most visually disabling type of cataract and account for most cataract surgery.[8]

Two recent studies of cataract prevalence, 1 from the US and 1 from Australia,[6,7] suggest that about 30% of people over the age of 50 years have significant cortical cataract, about 20% have advanced nuclear cataract and about 5% have some evidence of posterior subcapsular cataract. The prevalence of cataract increases with age. In the Australian Blue Mountains Eye Study,[6] the prevalence of any type of severe cataract was 5% in people aged 55 to 64 years, 22% in people aged 65 to 74 years, 52% in people aged 75 to 84 years and 68% in people aged 85 years and over.

1.2 Risk Factors for Cataract

Established risk factors for cataract include increasing age, cigarette smoking, diabetes mellitus and use of systemic and topical (ocular) corticosteroids.[1] Hypertension and ultraviolet B radiation are probably also associated with increased risk of cataract. Whether or not antioxidant vitamins are associated with reduced risk of cataract remains unclear.[1] Although once believed to have a role in cataract prevention, recent evidence suggests that use of aspirin (acetylsalicylic acid) is not associated with cataract.[1]

1.3 Oral and Topical (Ocular) Corticosteroids and Cataract

Use of oral and topical (ocular) corticosteroids are established risk factors for development of posterior subcapsular cataract.[1,9] The association between oral corticosteroids and cataract was first reported in 1960,[10] and the appearance of cataract in patients treated with topical (ocular) corticosteroids was noted in 1963.[11] In 38 studies of people treated with oral corticosteroids reviewed by Urban and Cotlier,[9] posterior subcapsular cataract was present in between 0% (in a study of patients with asthma) and 90% (in a study of renal transplant patients) of recipients, with an overall prevalence of 22% across all 38 studies.

It has been suggested that the lens in children might be more sensitive to the effects of corticosteroids than the lens in adults.[9,12,13] This might be explained by the large doses, relative to body size, of oral corticosteroids received by children in many of the published reports.

Biological explanations for the effect of corticosteroids on the lens include inhibition of sodium-potassium pumps in the lens epithelium, leading to accumulation of water within lens fibres, and agglutination of lens proteins.[9,14]

2. Systemic Effects of Inhaled Corticosteroids

Systemic effects of inhaled corticosteroids at sites other than the eye are being increasingly recognised.[15,16] In high doses, they cause suppression of the hypothalamic-pituitary-adrenal axis. There is also evidence that inhaled corticosteroids may cause osteoporosis in older people.[17-19] Less certain is the effect of inhaled corticosteroids on growth in children.

Several studies have found that users of inhaled corticosteroids have lower bone density than nonusers.[17-19] For example, Marystone et al.[17] found that elderly people using inhaled corticosteroids had lower bone density at the hip, spine and distal radius than nonusers, but their bone density was still higher than in users of oral corticosteroids. Calcium supplements have been advocated for prevention of this complication of inhaled corticosteroids.[19]

There has been concern that use of inhaled corticosteroids by children with asthma may lead to growth retardation. However, chronic illnesses like asthma can lead to growth retardation even if corticosteroids are not used.[15,16] Growth retardation might also be explained by the delayed puberty seen in some children with asthma.[15,16] Allen et al.[20] conducted a systematic review of 21 studies of the association between corticosteroids and height and found that oral corticosteroids (mainly prednisone) were associated with reduced height but that inhaled corticosteroids (mainly beclomethasone) were not.

Several more recent studies, however, are not so reassuring.[21-23] Two randomised trials have found that asthmatic children treated with inhaled beclomethasone 200μg twice daily gained less height than children receiving placebo.[21,22] In a retrospective cohort study, Saha et al.[23] investigated the growth of 200 children with asthma who were aged 1 to 11 years. Prior to commencement of inhaled corticosteroids, these children gained height at the same rate as children without asthma. However, growth retardation occurred after they started treatment with inhaled corticosteroids, particularly in the first year of use.

In addition to an effect on the lens, there is some evidence that use of inhaled corticosteroids may be a cause of glaucoma.[24] In a recent Canadian case-control study of people aged over 65 years, Garbe et al.[24] compared use of inhaled corticosteroids in 9793 people with newly diagnosed open-angle glaucoma or ocular hypertension with use of these drugs in 38 325 people who had visited ophthalmologists for other reasons. While there was no association overall, people who had used high doses of inhaled corticosteroids for >3 months had a 44% increased risk of glaucoma. In this study, 'high dose' was defined as ≥1600 μg/day of beclomethasone, budesonide or triamcinolone. Flaws in this study include reliance on an insurance plan database for information on confounders and possible selection bias due to participants in the control group all being ophthalmology patients. Although the study by Garbe et al.[24] is not conclusive, an association between inhaled corticosteroids and glaucoma is in accord with the known effects of oral and topical (ocular) corticosteroids on intraocular pressure.[25]

3. Inhaled Corticosteroids and Cataract

A case report in 1980 suggested that inhaled corticosteroids might cause cataracts.[26] Studies published since this case report was published are summarised in table I. Most of these studies have involved patients attending specialist asthma clinics and have found no association between inhaled corticosteroids and cataract.[27-31] The problem with the studies of people with asthma is that nearly all participants have also used oral corticosteroids, making it difficult to disentangle the effects of inhaled corticosteroids from the effects of oral corticosteroids. Further, most studies have involved only children. Because cataracts are extremely rare in children, even quite large increases in relative risk might have been missed.

Table I. Studies of the frequency of posterior subcapsular cataract (PSC) among users of inhaled corticosteroids

Reference	Setting	Mean age (y)	No. of inhaled corticosteroid users	Dosage (μg/day)	No. of PSCs
Nassif et al.[27]	Asthma clinic	13	32	532	1
Simons et al.[28]	Asthma clinic	14	95	750	0
Tinkelman et al.[29]	Asthma clinic	12	108	336	0
Toogood et al.[30]	Asthma clinic	61	48	1500	15
Abuekteish et al.[31]	Asthma clinic	12	140	592	1
Cumming et al.[2]	Community	65	158	486	22

3.1 The Blue Mountains Eye Study

By far the largest study of inhaled corticosteroids and cataract is the recently published Blue Mountains Eye Study.[2] This study is described in detail because it is the only study to date that has been able to clearly distinguish between the effects of oral and inhaled corticosteroids.

Cross-sectional data from the study were collected from 1992 to 1993, from 3654 people aged 49 to 97 years living in the Blue Mountains west of Sydney, Australia. Lens photographs were taken and the photographs were then assessed by trained, masked graders for presence and severity of nuclear, cortical and posterior subcapsular cataract. A detailed history of use of oral, ocular and inhaled corticosteroids was taken at the clinic visit. Of the study participants, 11% reported that they were current (5%) or past (6%) users of inhaled corticosteroids.

The Blue Mountains Eye Study found a strong association between use of inhaled corticosteroids and posterior subcapsular cataract, as shown in detail in table II. Of people who reported using inhaled corticosteroids at the time the study was done, 14% had posterior subcapsular cataract, compared with 6% of people who had never used inhaled corticosteroids. Nuclear cataract, but not cortical cataract, was also more common in people who used inhaled corticosteroids (see table II).

At the time the data were collected, beclomethasone was by far the most commonly used inhaled corticosteroid in Australia. People who had inhaled more than 2g of beclomethasone during their lifetime (calculated by multiplying the number of years of use by the usual number of puffs per day, assuming 100μg per puff) were at particularly high risk of having a posterior subcapsular or nuclear cataract (see table II). Of these heavy users, 27% had at least some posterior subcapsular cataract and 40% had advanced nuclear cataract.

The design of the Blue Mountains Eye Study allowed the effect of inhaled corticosteroids to be examined separately from that of oral corticosteroids, because the study involved a large number of people from the general population, not just people with asthma attending specialist clinics. The strong association between use of inhaled corticosteroids and posterior subcapsular and nuclear cataract persisted when the analysis was restricted to those participants who had never used oral corticosteroids.

In the Blue Mountains Eye Study, the association between inhaled corticosteroids and cataract was as strong, if not stronger, than the association between oral corticosteroids and cataract. This raises the possibility that at least some of the effect of inhaled corticosteroids might be due to direct entry of corticosteroid into the eye because of poor inhaler technique. This hypothesis deserves careful study.

3.2 Other Studies

The only other study of inhaled corticosteroids and cataract in older adults involved only 48 people (mean age 61 years) attending a specialist asthma clinic.[30] There was no comparison group of nonusers of inhaled corticosteroids. Slit-lamp examination revealed posterior subcapsular cataract in 14 participants, but all these individuals had also used oral corticosteroids. The study found no associa-

tion between duration of use or dose of inhaled corticosteroids and presence of cataract.

Several relevant studies have been conducted in children. Nassif et al.[27] identified 1 posterior subcapsular cataract among 32 children treated with inhaled corticosteroids for an average of 1.3 years; all participants in this study had used oral corticosteroids in the past. In this study, there were 20 children with asthma who used neither oral nor inhaled corticosteroids; none of these 20 children had a cataract. Simons and colleagues[28] conducted slit-lamp examinations of the lenses of 96 young people with asthma who had used inhaled corticosteroids for an average of 5 years and none had any evidence of cataract. Tinkelman et al.[29] did not find any cataracts in 108 children treated with inhaled beclomethasone for 1 year. Abuekteish et al.[31] examined 140 young people with asthma who used inhaled corticosteroids and found a 13-year-old girl with bilateral posterior subcapsular cataracts: this girl had received treatment with numerous courses of oral corticosteroids.

3.3 Discussion

Criteria have been developed for assessing whether or not an association found in observational epidemiological studies is likely to represent a true causal relationship.[32] The association between inhaled corticosteroids and posterior subcapsular cataract, as described in the Blue Mountains Eye Study, fulfils most of these criteria. The association was quite strong, with 3 times higher prevalence of posterior subcapsular cataract in users than in nonusers of inhaled corticosteroids. There was a clear dose-response relationship, with heavier users of inhaled corticosteroids being much more likely to have posterior subcapsular cataract than less frequent users. The relationship is biologically plausible and, indeed, makes good sense, given the known causal association between oral and topical (ocular) corticosteroids and posterior subcapsular cataract.

The 1 causal criterion that is not fulfilled is consistency of findings across several studies, as only the Blue Mountains Eye Study has found a clear relationship between use of inhaled corticosteroids and posterior subcapsular cataract. The failure of other studies to find an association is probably explained by their small sample sizes and the fact that most participants had also used oral corticosteroids. Nevertheless, the results of the Blue Mountains Eye Study need to be replicated before concluding with absolute certainty that inhaled corticosteroids can cause cataracts.

The evidence from the Blue Mountains Eye Study for a causal association between inhaled corticosteroids and nuclear cataract is not as strong as for posterior subcapsular cataract. The magnitude of the association was smaller; there was no dose-response relationship; and there is no analogous association between oral corticosteroids and nuclear cataract.

Table II. Results of the Blue Mountains Eye Study[2]

Use of inhaled corticosteroids	Posterior subcapsular cataract		Nuclear cataract	
	prevalence (%)	odds ratio (95% CI)[a]	prevalence (%)	odds ratio (95% CI)[a]
Never	6	1.0 (referent)	18	1.0 (referent)
Current	14	3.0 (1.7-5.1)	23	1.7 (1.1-2.5)
Lifetime dose of beclomethasone[b]				
<1000mg	13	2.5 (0.9-7.4)	9	1.0 (0.5-2)
1000-1999mg	20	5.1 (1.3-19.8)	10	1.0 (0.3-3.7)
>2000mg	27	10.0 (3-33.2)	40	5.4 (1.5-9.1)

a Odds ratios are adjusted for age, gender, education, smoking, diabetes mellitus, hypertension, sun-related skin damage and use of oral corticosteroids.

b Lifetime dose = number of years of use of beclomethasone × 52 × usual number of puffs per week × 0.1 (100μg per puff).

CI = confidence interval.

Two important unanswered questions are the nature of the dose-response relationship between inhaled corticosteroids and cataract and whether the effect of inhaled corticosteroids on the lens differs in different age groups. Although the data from the Blue Mountains Eye Study suggest that even relatively low doses of beclomethasone can be harmful, much more work is needed before any statement could be made about the amount of inhaled corticosteroid (in terms of daily dose and duration of use) that is needed to cause a cataract.

The Blue Mountains Eye Study provides reasonable evidence that inhaled corticosteroids can cause posterior subcapsular cataracts in people aged 50 years and over. What about children and young adults? Oral and topical (ocular) corticosteroids are known to cause cataracts in children and so it is plausible that inhaled corticosteroids could have the same effect. The small studies of children with asthma done to date have not found any association, but this may be false reassurance. The incidence of cataract in children is unknown but it is certainly very low. Even if the incidence were as high as 1 in 1000 per year, a study would need to include at least 2200 children to detect even a 10-fold increase in cataract incidence due to inhaled corticosteroids (assuming that 50% of the children used inhaled corticosteroids and 50% did not). Such a study may never be done. Based on current evidence, the clinically prudent conclusion should be that inhaled corticosteroids have the potential to cause cataracts in children, as well as adults. However, for most children, the tiny risk of cataract will be vastly outweighed by the benefits of better control of their asthma symptoms.

4. Prevention and Management

The obvious way to prevent corticosteroid-associated cataracts is to use these medications only in people who really need them. However, this paper is not the place for consideration of alternative methods of treatment of asthma and other respiratory conditions.

For those who need inhaled corticosteroids, it is important to avoid direct application of corticosteroid from the inhaler into the eye. This route of entry to the lens is possible if patients have poor inhaler technique. Although unproven at present, it seems likely that use of spacers and other innovative delivery systems will reduce the incidence of cataract in people who need to use inhaled corticosteroids for management of their asthma. It is interesting that in a study of adults with asthma which found no association between inhaled corticosteroids and cataract most participants used spacers.[30]

The various inhaled corticosteroids (beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone) differ in their topical and systemic potencies;[16] hence, it might be expected that their potential for causing cataracts might also vary. However, the relative ocular potency of the different inhaled corticosteroids has not been studied to date.

Methods for preventing cataract are not yet proven, but it would be sensible to advise users (and nonusers) of inhaled corticosteroids to stop smoking and wear a hat with a wide brim when outdoors. In the future, it may be possible to make dietary recommendations aimed at reducing the risk of cataract.

Regular screening for cataract in people using inhaled corticosteroids is not recommended, as there is no evidence that treatment of cataract at an early stage is any more effective than treatment when the cataract causes visual impairment. On the other hand, people using inhaled corticosteroids who notice difficulties with their vision should be referred to an eye specialist, who can check for the presence of cataract or glaucoma. Those people found to have a cataract causing substantial visual disability can be offered cataract surgery. The operation will usually comprise extracapsular extraction of the lens and insertion of an intraocular lens implant. A later capsulotomy procedure is frequently needed. Cataract surgery is often done on a day only basis, and rarely requires more than an overnight stay in hospital. Although the operation is highly successful, there is a small risk of serious

complications, either from the surgery itself or from the subsequent capsulotomy.[33-35]

5. Conclusions

Current evidence suggests that people who use inhaled corticosteroids are at increased risk of developing posterior subcapsular cataract, the most visually disabling type of cataract, However, for people with asthma, the benefits of inhaled corticosteroids for management of their respiratory symptoms will usually be much greater than the risk of cataract. This is particularly true for children, in whom the risk of cataract is extremely low. Nevertheless, the existence of some serious adverse effects of inhaled corticosteroids means they should be used for the shortest duration, and in the lowest dose, compatible with effective asthma management.

Addendum

A second population-based study has found that inhaled corticosteroids increase the risk of cataract. Garbe et al.[36] compared past inhaled corticosteroid use among 3677 people who had cataract surgery with use among 21 868 control patients. All study participants were aged 70 years or older. In this large study, use of >1000 μg/day of budesonide or beclomethasone for more than 2 years was associated with a 3-fold increased risk of cataract surgery.

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