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Risk of Cataracts in the Childhood Asthma Management Program Cohort

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To the editor:

Use of systemic corticosteroids is a well established risk factor for the development of posterior subcapsular cataracts (PSCs) in both children and adults.¹ Dose and duration of inhaled corticosteroids (ICSs) have been reported to be independent risk factors for the development of PSCs in older patients.² Occurrence of PSCs is rare in children, and studies of children treated with ICSs have not found an increased risk of PSCs.^{3–5} We previously reported no risk of cataracts in 955 children in the Childhood Asthma Management Program (CAMP) assessed by lens photography after 4–6 years (mean 4.3 years) of budesonide 400

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Conflict of interest:

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µg/day by Turbuhaler™, nedocromil 16 mg/day or placebo. However, one child in the budesonide group was diagnosed as having a barely measurable PSC on slit lamp exam 5 months after the photography.⁸

The CAMP cohort has been followed continuously since closure of the trial in 1999. In 2005, two additional participants (both from the budesonide arm) reported PSCs, with one requiring surgery. In response to these reports and in consultation with the CAMP Data and Safety Monitoring Board, all CAMP participants were urged to obtain a dilated slit lamp examination specifically for the presence of cataracts (Supplementary Appendices E1 and E2). The findings from the resulting exams plus the 3 reports of cataracts obtained previously form the basis of this report.

Three outcomes were defined for each participant: examination for cataract, any cataract finding, and any posterior finding. Covariates included cumulative doses of ICSs and oral corticosteroid for asthma to the date of the cataract exam. The ICSs included the blinded budesonide and unblinded ICSs prescribed during the trial and ICS self-reported as taken for asthma during the observational post-trial follow-up. Prednisone bursts during the post trial follow-up were assumed to conform to the CAMP trial regimen (up to 60 mg for each of 2 days, followed by up to 30 mg for each of 2 days).

The association of each outcome with randomized treatment group and with inhaled and oral corticosteroid use for asthma categorized as ever versus never was assessed by chi square analysis and logistic regression. Association of cataract posterior finding with the cumulative dose of ICS and cumulative dose of oral corticosteroid was assessed by logistic regression. Each cumulative dose was modeled first as a continuous variable and then as three indicator variables corresponding to tertiles of increasing dose. Lastly, each cumulative dose was modeled as a score based on the tertiles as a test for a dose-response effect. Analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC) or STATA 9.2 (StataCorp, College Station, TX).

232 participants aged 15 to 26 years were examined, 22.3% of the original CAMP cohort (N=1041). Median duration from randomization to exam was 12 years (range 4–14 years), and median duration from lens photography to exam was 8 years (range 0.4–9 years). Median duration of ICS use among those using ICSs was 4.0 years (range 0–13) and median 4-day dose (per burst) of prednisone during CAMP, for those ever taking prednisone for asthma during CAMP, was 150 mg range (15–180).

Sixteen participants were assessed as having cataract findings, of whom 12 were classified as having posterior findings (Table E1). The percentage of participants obtaining exams was similar across randomized treatment groups (22.8% budesonide, 22.1% nedocromil, 22.0% placebo, $P=0.96$; Table 1, Panel A). Among those examined, there was no evidence of increased cataracts in the budesonide compared to the placebo group (odds ratio (OR) = 1.6, 95% CI=(0.5, 4.9), $P=0.44$), nor any evidence of increased posterior findings (OR=1.3, 95% CI=(0.4, 4.7), $P=0.67$) (Table 1, Panel A).

Participants ever using corticosteroids for asthma were more likely to obtain a cataract exam (25.8% ever using ICS versus 12.8% never using ICS, $P<0.0001$, Table 1, Panel B; 23.6% ever using oral corticosteroid versus 16.4% never using oral corticosteroid, $P=0.03$, Table 1, Panel C). However, in those examined, the risk of cataract finding did not differ by ICS use (OR=0.8, ever versus never, 95% CI=(0.2, 2.9), $P=0.71$) nor by oral corticosteroid use (OR=1.1, ever versus never, 95% CI=(0.2, 5.2), $P=0.88$) (Table 1, Panels B and C). Similar results were obtained for the risk of posterior finding. There was no association of cataract or posterior finding with cumulative ICS dose or cumulative oral corticosteroid dose (Table 2).

Our findings suggest that long-term administration of ICS in the recommended low to medium doses is not a significant risk factor for the development of PSCs in children, adolescents and young adults. We did not find an association of cataracts or specifically PSCs with ICS use. These findings are consistent with the initial CAMP report based on evaluation of lens photographs of 92% of the participants after 4–6 years of treatment.⁵ This now becomes the longest study to date for the development of cataracts in children treated with ICS, and our findings are consistent with 3 other non-randomized studies of long-term ICS therapy in children.^{3,4,6}

Chronic systemic corticosteroids are associated with a risk of developing PSCs in children as well as adults. Reports in the literature vary widely but indicate that 15–35% of children on daily oral corticosteroids for at least 1 year develop PSCs.⁷⁻⁸ Risk factors for development of PSCs include: daily dose (> 10 mg/day); duration (> 2 years); and method of administration (daily versus every other day). It is possible that some children with multiple courses of oral prednisone per year developed PSCs that then regressed, as this has been previously reported.⁹

We report a 5.2% prevalence of posterior findings in our participants which is much higher than the 0.2% in healthy young adults quoted from population based studies.^{1,2} However, these studies used reports of clinically significant cataracts. In that regard, our finding of one patient requiring surgery for cataract is not significantly different from that reported in the NHANES 2007–2008 vision questionnaire database for participants 14–25 years old (1/232 versus 2/1621, $p=0.33$ Fisher's exact test).¹⁰ Our high prevalence could be a consequence of our specific request that the eye care provider to look for cataracts. Additionally the finding of more cataracts on slit-lamp exam than on lens photography was recently reported.¹¹

A weakness of our report is that only 22.3% of the CAMP population obtained a dilated slit lamp examination; our power to detect a difference in risk is very low, as indicated by the broad 95% confidence limits on our risk estimates. Nevertheless, ours is one of the largest studies in children with asthma to date, and despite those who had greater corticosteroid exposure being more likely to have obtained an exam, we did not find any association between cataract findings and exposure to corticosteroids for asthma (Tables 1 and 2). Another weakness was lack of standardization in the ophthalmic exam and the prompt to eye care providers to look specifically for evidence of cataracts. However, this represents what happens in the real world outside of standardized clinical trials. Additionally, our dose data are a mix of prescribed dose (during the trial) and reported dose taken (during the follow-up phases). Finally, we did not include use of nasal and topical corticosteroids in the analysis, nor use of corticosteroids for conditions other than asthma. However, in a population based case-control study, exposure to topical corticosteroids did not affect the association between cataract and use of inhaled corticosteroids.²

Our findings of a lack of cumulative effect of ICSs and short bursts of oral corticosteroids does not rule out the possibility that high daily doses of ICSs will contribute to cataract formation, particularly in patients with other risk factors.³⁻⁵

In conclusion, the long-term use of ICSs in the recommended ranges in combination with occasional bursts of oral prednisone during childhood was not associated with an increased risk of cataracts. Thus, regular monitoring for cataracts does not appear to be warranted in children, adolescents and young adults with asthma being treated with low-medium dose ICS without other significant risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PSCs	posterior subcapsular cataracts
ICS	inhaled corticosteroid
CAMP	Childhood Asthma Management Program
OR	odds ratio
CI	confidence interval

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Examination for cataracts and cataract findings by randomized treatment and ever versus never use of corticosteroids for asthma

Table 1

Examined				Cataract findings [*] in those examined				Posterior findings ^H in those examined					
No.	No.	(%)		No.	%	OR ^I	95% CI	P'	No.	%	OR ^I	95% CI	P'
A. Randomized treatment group													
Budesonide	311	71	(22.8%)	7	9.9%	1.6	(0.5, 4.9)	0.44	5	7.0%	1.3	(0.4, 4.7)	0.67
Nedocromil	312	69	(22.1%)	3	4.4%	0.7	(0.2, 2.7)	0.56	3	2.9%	0.5	(0.1, 2.8)	0.44
Placebo	418	92	(22.0%)	6	6.5%				5	5.4%			
Total	1041	232	(22.3%)	16	6.9%				12	5.2%			
p&			0.96		0.43				0.54				
B. Use of inhaled corticosteroid in CAMP trial or observational study													
Ever	760	196	(25.8%)	13	6.6%	0.8	(0.2, 2.9)	0.71	9	4.6%	0.5	(0.1, 2.1)	0.36
Never	281	36	(12.8%)	3	8.3%				3	8.3%			
Total	1041	232	(22.3%)	16	6.9%				12	5.2%			
p&			<0.0001		0.71				0.35				
C. Use of oral corticosteroid in CAMP trial or observational study													
Ever	846	200	(23.6%)	14	7.0%	1.1	(0.2, 5.2)	0.88	10	5.0%	0.8	(0.2, 3.8)	0.77
Never	195	32	(16.4%)	2	6.3%				2	6.3%			
Total	1041	232	(22.3%)	16	6.9%				12	5.2%			
p&			0.03		0.88				0.77				

CAMP=Childhood Asthma Management Program, OR=odds ratio, CI=Confidence interval

* Cataract findings include: dense PSC, mild PSC, radial cataract, congenital, nuclear cataract, cortical spokes, flecks, lamellar and post subcapsular haze, sutural opacities, etc.

^H Posterior findings include: PSC, posterior subcapsular opacity, hint of PSC, posterior opacity, very early posterior subcapsular change, posterior opacity, trace PSC, post subcapsular haze on any examination.

^I Odds ratio: Bud/Ned vs Plbo (Panel A), Ever vs Never (Panels B and C)

^J Wald chi square for odds ratio different from 1

^K Chi square for difference in proportion amongst treatment groups

Table 2

Cataracts and cataract findings by cumulative ICS dose and prednisone dose in 232 participants who obtained a dilated slit lamp examination*

	Cataract findings				Posterior findings			
	Odds ratio	95% CI	P	p ^H	Odds ratio	95% CI	P	p ^H
A. Continuous cumulative ICS and prednisone dose								
Male	0.73	(0.3, 2.1)	0.56		0.29	(0.1, 1.1)	0.08	
Age at rz (per yr)	1.12	(0.9, 1.4)	0.38		1.02	(0.8, 1.4)	0.86	
ICS (per mg)	1.00	(1.0, 1.0)	0.52		1.00	(1.0, 1.0)	0.82	
Prednisone (per mg)	1.00	(1.0, 1.0)	0.50		1.00	(1.0, 1.0)	0.40	
B. Tertiles of cumulative ICS and prednisone dose								
Male	0.74	(0.3, 2.2)	0.58		0.28	(0.1, 1.1)	0.07	
Age at rz (per yr)	1.12	(0.9, 1.4)	0.40		1.02	(0.8, 1.4)	0.88	
ICS:								
1–408 mg (vs none)	0.18	(0.2, 1.9)	0.15	0.20	0.79	(0.2, 1.8)	0.14	0.46
409–897 mg (vs none)	1.56	(0.4, 6.6)	0.55		0.83	(0.2, 4.1)	0.82	
>=898 mg (vs none)	0.71	(0.1, 3.8)	0.69		0.48	(0.1, 3.1)	0.44	
Prednisone:								
1–465 mg (vs none)	1.33	(0.2, 7.7)	0.75	0.95	0.62	(0.1, 6.0)	0.96	0.92
466–1440 mg (vs none)	1.30	(0.2, 8.2)	0.78		0.71	(0.1, 6.0)	0.75	
>=1441 mg (vs none)	1.69	(0.3, 10.8)	0.58		1.34	(0.2, 10.0)	0.77	

* Dose is cumulative through date of exam for cataract

^HP for all 3 categorical terms combined

^IP for linear trend across 3 categories