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Adverse reactions following routine anticholinergic eye drops in a paediatric population: an observational cohort study.

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ABSTRACT

Objectives To investigate the presence, nature and relationship to age, sex, ethnicity and BMI of adverse reactions following routine cycloplegic eye drops in children.

Design Prospective observational cohort study.

Setting Ophthalmology outpatient clinic Dutch metropolitan hospital; February, March and April 2009.

Participants 3 to14 year old children receiving two drops of cyclopentolate 1% (C+C) or one drop of cyclopentolate 1% and one drop of tropicamide 1% (C+T). Patients were categorised by age (3 to 6, 7 to 10 and 11 to 14 years), sex, ethnicity and BMI (low, normal or high).

Outcome measures Rate and nature of adverse reactions reported at 45 minutes following treatment. Crude and adjusted OR for reporting an adverse reaction using stepwise regression analysis with BMI, age, ethnicity and sex.

Results 912 of 915 eligible patients participated (99.7%). Adverse reactions were reported for C+C in 10.4% and in C+T in 4.8% (42/408 and 24/ 504; p=0.002). Central effects were present in 95% (C+C) respectively 92% (C+T). Compared to C+T an increased risk was present in C+C (crude OR 2.3 [1.4 to 3.9], p=0.002). Forward adjustment showed BMI to be an influencing factor in treatment (OR 3.1 [1.7 to 5.6], p<0.001). In a multivariate model, dose of cyclopentolate remained associated with adverse reactions. Analysis per BMI- respectively age category and regime, indicated associations with low BMI (OR C+C 21.4 [6.7 to 67.96], p<0.001 respectively C+T 5.2 [2.1 to 12.8], p<0.001) and young age (OR C+C 8.1 [2.7 to 24.8], p<0.001).

Conclusions Adverse reactions were common and almost exclusively involved the central nervous system. Both presence and severity were associated with repeated installation of cyclopentolate 1%, low BMI and young age. In specific paediatric populations a single dose of cyclopentolate must be considered. Vital function monitoring facilities are advisable. Adjustment of guidelines is recommended.

Strengths and limitations of this study

- This study not only investigated presence and nature of adverse reactions after commonly used cycloplegic regimes but also determined risk factors.
- Strong evidence for a dose response relationship is provided.
- The study was not randomized neither blinded therefore observer bias could not be ruled out completely.
- Some sub-groups comprised a limited number of subjects.
- We encourage a critical approach to the use of cyclopentolate 1% in specific paediatric populations and propose adjustment of guidelines.

INTRODUCTION

Refractive errors can cause decreased visual acuity and problems in binocularity such as strabismus in children. Due to strong accommodative reflexes and the inability to respond reliably to subjective refraction, objective refraction in children is a necessity to assess their refractive state. Objective refraction can only be obtained in the absence of accommodation. Paralysis of accommodation, i.e. inhibition of the ciliary muscle, is achieved with anticholinergic eye drops. Cyclopentolate 1% and cyclopentolate 1% combined with tropicamide 1% are commonly used anticholinergic eye drops for objective refraction in the pediatric population. The use of anticholinergic eye drops is generally considered to be safe.[1,2] Severe adverse reactions following administration are very rare.[2] For tropicamide large surveys report an incidence of 0%.[3-5] Adverse reactions following cyclopentolate seem to be more common and dose related.[6] They occur between 15 to 60 minutes following administration. The adverse reactions often include the central nervous system (CNS), but subside within 2-6 hours with no permanent sequelae.[7-9] For reports on rates of the milder adverse reactions one can only refer to the rates encountered during surveys or efficacy studies. A study of Bagheri and colleagues[6] in 96 six to twenty year old subjects, reports an adverse reaction rate of 5%, 11% and 24% after one dose, a double dose and a triple dose of cyclopentolate 1%. In contrast, a smaller study of Mohan and Sharma[10] mentions the absence of ocular or systemic side effects in a similar population receiving the same treatment regimes. Although Bagheri and colleagues report adverse reaction rates, they do not specify the nature of these adverse reactions.[6]

In young children about 5 to 9% need objective refraction because of failure in vision screenings programs or refractive errors.[11,12] In older children and early puberty this increases up to 14%.[13-17] Depending on the health care arrangements of individual countries the measurement of objective refraction is performed in hospitals or health care centers, as well as in local optometric practices. The latter usually do not have facilities to monitor vital functions. In our clinic with an ethnically diverse population we use routinely either a double dose of cyclopentolate 1% (C+C) or cyclopentolate 1% combined with tropicamide 1% (C+T). Adverse reactions following both regimes are seen, but relatively more often encountered using C+C. Besides an apparent association with regime our observations also suggested a possible correlation with younger age and/or lower body mass index (BMI). Both suggest a dose response relationship. The literature does not provide sufficient knowledge on this subject. The purpose of this study was to gain more insight in the presence and nature of adverse reactions following administration of C+C and C+T for objective refraction assessment in children. A secondary aim was to investigate whether age and/or BMI are associated with adverse reactions.

METHODS

This study was designed as a prospective, single-centre, cross-sectional and observational cohort study. The study group investigators were research assistants and 4 orthoptists. The study population were all patients between 3 and 14 years requiring an objective refraction at an ophthalmology outpatient clinic of a metropolitan hospital, during February, March and April 2009. The recruitment period of three months was chosen because of the high return rate of our subjects after this period. The lower limit of 3 year was chosen because of cooperation problems with length and weight measurements below this age. Furthermore possible adverse reactions might not be distinguishable from common sleepiness or behavioural problems due to normal wake/sleep patterns below this age. The upper limit of 14 years was chosen because of the limited amount of patients needing an objective refraction after this age. All orthoptists used their normal individual regime to assess objective refraction with either C+C or C+T.

Procedures

Subjects were numbered consecutively. Length and weight were determined. BMI was calculated according to the formula: BMI= Weight/height. Subjects were allocated to three categories: low BMI, normal BMI or high BMI, according to the international cut off values for under- and overweight by sex between 2 and 18 years.[18,19] For South Asian subjects cut-off values according to the guidelines of Wilde et al[20] were used. Subjects were allocated to the following ethnic main groups: Dutch, Turkish, Moroccan, Indian-subcontinental (including Indian, Pakistani and Surinam-Hindoestani) or Black West-African (including Black African of the African Gold Coast, Black subjects from both the Dutch Antilles and Surinam). Remaining subjects were allocated to category “Other”. Subjects were also subdivided into three age categories; 3 to 6, 7 to10 or 11 to14 years. A case report form with the designated number of the subject was added to the outpatient chart. The examining orthoptist noted either no drops, C+C or C+T on this form. In children receiving eye drops the examining orthoptist made enquiries approximately 45 minutes following the first eye-drop. The parent(s) or guardian(s) and/or child were asked “did you notice anything different following the eye drops”. Responses concerning blurred vision and/or photophobia were excluded. All other responses where noted. Adverse reactions were clustered; e.g. severe to moderate drowsiness, mild drowsiness or apathy, excitation & hyperactivity and/or behavioral problems, dizziness, red face and/or cheeks and/or nose bleeding. Furthermore classified as being “central” or “peripheral”.

Bias

To avoid treatment bias the examining orthoptist was kept unware of the BMI status of the subjects. To avoid response bias from parents and/or children two procedures were followed. Firstly, the length and weight measurements were introduced as being part of a departmental pediatric population survey for development of

medicinal prescription guidelines. Secondly the inquiries about the adverse reactions were made with an open question technique.

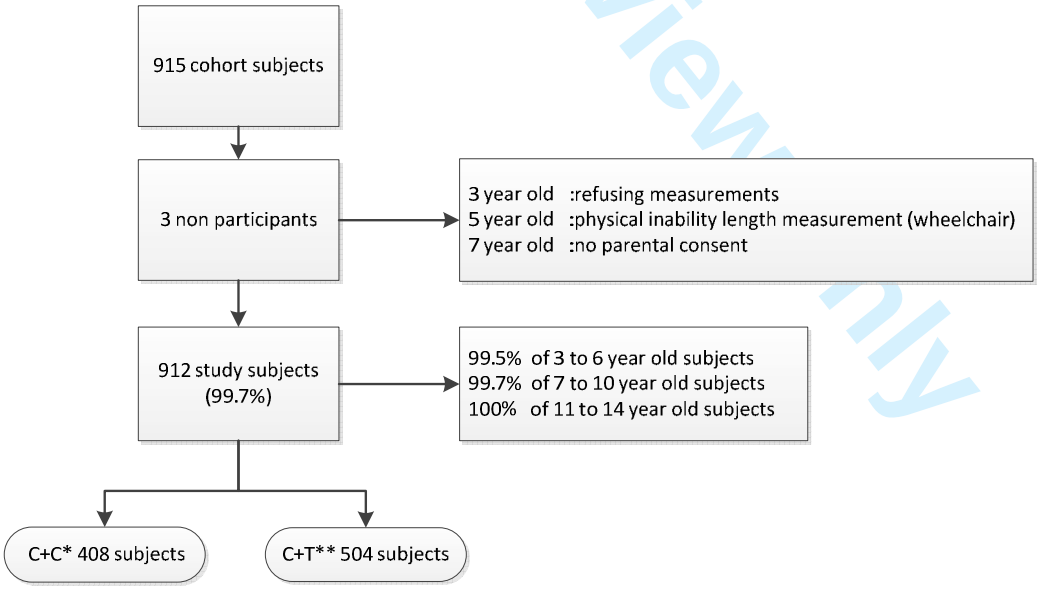
Data analysis

Data were analyzed in SPSS 22 for Windows. Differences were considered statistically significant if $p<0.05$; two-sided. A difference of 2% in reported adverse reactions was considered clinically significant. Variables were compared between the treatment C+C and C+T using the independent samples T-test or the X^2- test, as appropriate. Univariate stratified and multivariate logistic regression analyses were performed to assess the impact of variables on the likelihood that a subject would report an adverse reaction. Odds ratios for treatment were calculated without and with adjustment for BMI, age, ethnicity and sex in a forward model. Odds ratios for BMI; for treatment, with normal BMI subjects receiving C+C as reference group, and age; for treatment, with 6 to 10 year old subjects receiving C+C as reference group, unadjusted and adjusted for age, sex and ethnicity respectively sex, ethnicity and BMI were computed in a multivariate backwards model.

RESULTS

912 of 915 eligible patients participated (99.7%; figure 1). 408 received C+C and 504 received C+T (figure 1).

Figure 1 Flow chart diagram showing number of subjects in the cohort and number of subjects participating in the study



* C+C: Two drops of cyclopentolate 1%
** C+T: One drop of cyclopentolate 1% and one drop of tropicamide 1%

Table 1 reflects the baseline group characteristics stratified by regimes C+C and C+T.

Table 1 Baseline characteristics of children who underwent objective refraction assessment, stratified by cycloplegic eye drop treatment.

	C+C[a]		C+T[b]		p-value
	n (%)	mean	n (%)	mean	
Total	408		504		
Age in years	408	7.6 ± 3.1	504	7.6 ± 3.1	p=0.997[c]
Sex	408		504		p=0.85[d]
Male	207 (50.7)		260 (51.6)		
Female	201 (49.3)		244 (48.4)		
BMI	408		504		p=0.50[e]
Low BMI	18 (4.4)		29 (5.8)		
Normal BMI	292 (71.6)		366 (72.6)		
High BMI	98 (24)		109 (21.6)		
Ethnicity	408		504		p=0.95[e]
Moroccan	81 (19.9)		107 (21.2)		
Turkish	71 (17.4)		86 (17.1)		
Indian Sub-continent	68 (16.7)		73 (14.5)		
Dutch	110 (27.0)		137 (27.2)		
Chinese	9 (2.0)		12 (2.4)		
Black West-African	29 (7.1)		34 (6.7)		
Other	41 (10.0)		55 (10.9)		
Age category	408		504		p=0.92[e]
3 to 6 years	163 (40.0)		200 (39.7)		
7 to10 years	158 (38.7)		191 (37.9)		
11 to14 years	87 (21.3)		113 (22.4)		

[a]Two drops of cyclopentolate 1%

[b]One drop of cyclopentolate 1% and one drop of tropicamide 1%

[c]Independent Samples T-test

[d]X^2- test with Yates Continuity Correction

[e]X^2- test

Adverse reactions; presence and nature.

Adverse reactions were reported in 10.4% (42/408) of children following C+C administration and in 4.8% (22/504) of subjects following C+C administration (p=0.002). Central effects were present in 95.2% (C+C; 40/42) and 91.7% (C+T; 22/24, table 2). Severe drowsiness was the most frequently reported adverse reaction (5.4%) following C+C administration. It was most often present in children aged 3 to 6 years and predominantly present in children with low BMI (table 2). Reports of severe drowsiness and excitation, hyperactivity and/or behavioral problems were significantly less often present following C+T administration. Extreme excitation, hyperactivity and/or behavioral disorder was the only adverse reaction expressed in high BMI and only reported in the youngest age category following either treatment (table 2).

Table 2 Number and calculated percentage of clustered adverse reactions stratified by cycloplegic eye drop treatment, and their distribution across age- and BMI categories.

		C+C[a]							
				3 to 6 years		7 to10 years		11 to14 years	
Complaint		n	AR[c] n(%)	n	AR[c] n(%)	n	AR[c] n(%)	n	AR[c] n(%)
Severe or moderate drowsiness[d]		408	22 (5.4)	163	18 (11.0)	158	2 (1.3)	87	2 (2.3)
Mild drowsiness or apathy[d]		408	10 (2.5)	163	9 (5.5)	158	1 (0.6)	87	0
Excitation, hyperactivity and/or behavioral problems[d]		408	6 (1.5)	163	6 (3.7)	158	0	87	0
Dizzyness[d]		408	2 (0.5)	163	0	158	0	87	2 (2.3)
Red cheeks or face (feverish, flushing)[e]		408	2 (0.5)	163	1 (0.6)	158	1 (0.6)	87	0
Nose bleeding[e]		408	0	163	0	158	0	87	0
	BMI								
Severe or moderate drowsiness	Low BMI	18	13 (72.2)	13	11 (84.6)	3	1 (33.3)	2	1 (50.0)
	Normal BMI	292	9 (3.1)	125	7 (5.6)	104	1 (1.0)	63	1 (1.6)
	High BMI	98	0	25	0	51	0	22	0
Mild drowsiness or apathy	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	10 (3.4)	125	9 (7.2)	104	1 (1.0)	63	0
	High BMI	98	0	25	0	51	0	22	0
Excitation, hyperactivity and/or behavioral problems	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	5 (1.7)	125	5 (4.0)	104	0	63	0
	High BMI	98	1 (1.0)	25	1 (4.0)	51	0	22	0
Dizzyness	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	2 (2.0)	125	0	104	0	63	2 (3.2)
	High BMI	98	0	25	0	51	0	22	0
Red cheeks or face (feverish, flushing)	Low BMI	18	0	13	0	3	1 (33.3)	2	0
	Normal BMI	292	2 (2.0)	125	1 (0.8)	104	0	63	0
	High BMI	98	0	25	0	51	0	22	0
Nose bleeding	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	0	125	0	104	0	63	0
	High BMI	98	0	25	0	51	0	22	0
		C+T[b]							
				3 to 6 years		7 to10 years		11 to14 years	
Complaint		n	AR[c] n(%)	n	AR[c] n(%)	n	AR[c] n(%)	n	AR[c] n(%)
Severe or moderate drowsiness[d]		504	8 (1.6)	200	6 (3.0)	191	1 (0.5)	113	1 (0.9)
Mild drowsiness or apathy[d]		504	11 (2.2)	200	4 (2.0)	191	5 (2.6)	113	2 (1.8)
Excitation, hyperactivity and/or behavioral problems[d]		504	3 (0.6)	200	3 (1.5)	191	0	113	0
Dizzyness[d]		504	0	200	0	191	0	113	0
Red cheeks or face (feverish, flushing)[e]		504	1 (0.2)	200	1 (0.5)	191	0	113	0
Nose bleeding[e]		504	1 (0.2)	200	1 (0.5)	191	0	113	0
	BMI								
Severe or moderate drowsiness	Low BMI	29	5 (17.2)	14	3 (21.4)	9	1 (11.1)	6	1 (16.7)
	Normal BMI	366	3 (8.2)	157	3 (1.9)	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Mild drowsiness or apathy	Low BMI	29	5 (17.2)	14	1 (7.1)	9	2 (22.2)	6	2 (33.3)
	Normal BMI	366	6 (1.6)	157	3 (1.9)	129	3 (2.3)	80	0
	High BMI	109	0	29	0	53	0	27	0
Excitation, hyperactivity and/or behavioral problems	Low BMI	29	0	14	0	9	0	6	0
	Normal BMI	366	2 (0.6)	157	2 (1.3)	129	0	80	0
	High BMI	109	1 (0.9)	29	1 (3.0)	53	0	27	0
Dizzyness	Low BMI	29	0	14	0	9	0	6	0
	Normal BMI	366	0	157	0	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Red cheeks or face (feverish, flushing)	Low BMI	29	0	14	0	9	0	6	0
	Normal BMI	366	1 (0.3)	157	1 (0.6)	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Nose bleeding	L-BMI	29	0	14	0	9	0	6	0
	N-BMI	366	1 (0.3)	157	1 (0.6)	129	0	80	0
	H-BMI	109	0	29	0	53	0	27	0

[a]Two drops of cyclopentolate 1%

[b]One drop of cyclopentolate 1% and one drop of tropicamide 1%

[c]AR: Adverse reactions

[d]CNS adverse reaction

[e]Peripheral adverse reaction

Relation of adverse reactions with sex, BMI, ethnicity and age.

Low BMI was more strongly associated with adverse reactions in C+C than in C+T (table 3). In both treatment groups the frequency of adverse reactions was highest in the youngest age group. Only in C+C younger age was associated with a statistically significantly increased risk (table 3). A borderline value however was present in C+T (p=0.06; crude OR 95% CI 0.95-6.6). Furthermore, in both interventions for all age categories, adverse reactions were more frequently reported in children with low BMI compared to those with normal BMI (table 3).

Table 3 Frequencies, percentages and crude odds ratios of adverse reactions with respect to sex, BMI, ethnicity and age category stratified by cycloplegic eye drop treatment.

	C+C[a]				C+T[b]			
	n	n (%) AR[c]	Crude OR[d] 95% CI[e]	P value	n	n (%) AR[c]	Crude OR[d] 95% CI[e]	P value
	408	42 (10.3)			504	24 (4.8)		
Sex	408	42			504	24		
Male	207	25 (12.1)	1[f]		260	12 (4.6)	1[f]	
Female	201	17 (8.5)	0.7 (0.4 to1.3)	0.23	244	12 (4.9)	0.9 (0.4 to 2.1)	0.87
BMI category	408	42			504	24		
Low BMI	18	13 (72.2)	24.5 (8.1 to 73.8)	<0.001	29	10 (34.5)	14.3 (5.6 to 36.8)	<0.001
Normal BMI	292	28 (9.6)	1[f]		366	13 (3.6)	1[f]	
High BMI	98	1 (1.0)	0.1 (0.01 to 0.7)	0.02	109	1 (0.9)	0.3 (0.03 to 1.9)	0.19
Ethnic main group	359	39 (10.9)			437	21 (4.9)		
Dutch	110	13 (11.8)	1[f]		137	6 (4.4)	1[f]	
Moroccan	81	10 (12.3)	1.1 (0.4 to 2.5)	0.91	107	5 (4.7)	1.1 (0.3 to 3.6)	0.91
Turkey	71	5 (7.0)	0.6 (0.2 to 1.7)	0.30	86	4 (4.7)	1.1 (0.3 to 3.9)	0.92
Indian-subcontintent	68	10 (14.7)	1.3 (0.5 to 3.1)	0.58	73	5 (6.8)	1.6 (0.5 to 5.5)	0.45
Negro	29	1 (3.4)	0.3 (0.03 to 2.1)	0.21	34	1 (2.9)	0.7 (0.08 to 5.7)	0.71
Other	49	3 (6.1)	0.5 (0.1 to 1.8)	0.28	67	3 (4.5)	1.0 (0.3 to 4.2)	0.97
Age category	408	42			504	24		
3 to 6 year	163	34 (20.9)	10.2 (3.5 to 29.4)	<0.001	200	15 (7.5)	2.5 (0.95 to 6.6)	0.06
7 to10 year	158	4 (2.5)	1[f]		191	6 (3.1)	1[f]	
11 to14 year	87	4 (4.6)	1.9 (0.5 to 7.6)	0.39	113	3 (2.7)	0.8 (0.2 to 3.4)	0.81
Age category 3 to 6	163	34			200	15		
Low BMI	13	11 (84.6)			14	4 (28.6)		
Normal BMI	125	22 (17.6)			157	10 (6.4)		
High BMI	25	1 (4.0)			29	1 (3.4)		
Age category 7 to10	158	4			191	6		
Low BMI	3	1 (33.3)			9	3 (33.3)		
Normal BMI	104	3 (2.9)			129	3 (2.3)		
High BMI	51	0			53	0		
Age category 11 to14	87	4			113	3		
Low BMI	2	1 (50.0)			6	3 (50.0)		
Normal BMI	63	3 (4.8)			80	0		
High BMI	22	0			27	0		

[a]Two drops of cyclopentolate 1%

[b]One drop of cyclopentolate 1% and one drop of tropicamide 1%

[c]AR: Adverse reactions

[d]OR: Odds ratio

[e]CI: Confidence Interval

[f]1: Reference group

Relation of adverse reactions with dose of cyclopentolate, BMI and age.

In children receiving C+C there was a significantly increased overall risk for adverse reactions compared to those receiving C+T (OR 2.3 [1.4-3.9]; table 4). In a forward model we explored the influence of the variables BMI, age, ethnicity and sex on the odds ratio for treatment. Only BMI was found to have a significant influence (table 4).

Table 4 Odds ratio for reporting adverse reactions for treatment, and stepwise adjustment of this odds ratio with BMI, age, ethnicity and sex.

Step	Factors	OR[a] + 95% CI[b]	P value
1	Treatment	2.3 (1.4 to 3.9)	0.002
2	Treatment + BMI [cat]	3.1 (1.7 to 5.6)	<0.001
3	Treatment + BMI [cat] + Age [cat]	3.0 (1.6 to 5.5)	<0.001
4	Treatment + BMI [cat] + Age [cat] + Ethnicity [cat]	3.0 (1.6 to 5.5)	<0.001
5	Treatment + BMI [cat] + Age [cat] + Ethnicity [cat] + Sex [cat]	3.0 (1.5 to 5.4)	<0.001

[a]OR: Odds ratio

[b]CI: Confidence Interval

Our analysis indicated that dose of cyclopentolate, (low) BMI and (young) age were associated with adverse reactions. The apparent dose response relationship was explored in more detail. Table 5 shows the unadjusted, crude, odds ratios for reporting adverse reactions per BMI category and regime, with normal BMI subjects receiving C+C as reference group in a multivariate model. A strong dose response relationship was found. Following adjustment for gender, ethnicity and age, dose of cyclopentolate remained highly significantly associated with adverse reactions. We also explored age category and regime (table 5). In this model a dose response mechanism was also visible. Following adjustment for gender, ethnicity and BMI, dose of cyclopentolate was associated with adverse reactions in the youngest subjects.

Table 5 Odds ratios for reporting adverse reactions per BMI category respectively age category and regime, with normal BMI respectively 7 to 10 old children receiving C+C[a] as reference group; backwards analysis.

Regime	BMI	Crude Or[c] (95% CI)[d]	P value	Adjusted[f] OR[c] (95% CI)[d]	P value
C+C[a]	High	0.1 (0.01 to 0.7)	0.02	0.1 (0.02 to 0.9)	0.04
	Normal	1[e]		1[e]	
	Low	24.6 (8.2 to74.1)	<0.001	21.4 (6.7 to 67.96)	<0.001
C+T[b]	High	0.09 (0.01 to 0.7)	0.02	0.1 (0.01 to 0.8)	0.03
	Normal	0.35 (0.2 to 0.7)	0.02	0.34 (0.2 to 0.7)	0.002
	Low	4.98 (2.1 to 11.8)	<0.001	5.2 (2.1 to 12.8)	<0.001

Regime	Age	Crude OR[c] (95% CI)[d]	P value	Adjusted[g]OR[c] (95% CI)[d]	P value
C+C[a]	11 to 14	1.8 (0.4 to7.4)	0.41	1.7 (0.4 to 7.4)	0.48
	7 to 10	1[e]		1[e]	
	3 to 6	10.2 (3.5 to 29.5)	<0.001	8.1 (2.7 to 24.8)	<0.001
C+T[b]	11 to 14	1.1 (0.2 to 4.9)	0.92	0.7 (0.1 to 3.5)	0.66
	7 to 10	1.3 (0.4 to 4.6)	0.72	0.9 (0.2 to 3.5)	0.88
	3 to 6	3.1 (1.0 to 9.7)	0.046	1.97 (0.6 to 6.5)	0.26

[a]Two drops of cyclopentolate 1%

[b]One drop of cyclopentolate 1% and one drop of tropicamide 1%

[c]OR: Odds ratio

[d]CI: Confidence Interval

[e]1: Reference group

[f]Adjusted for sex (cat), age (cat) and ethnicity (cat)

[g]Adjusted for sex (cat), BMI (cat) and ethnicity (cat)

DISCUSSION

This study showed that mild adverse reactions following cycloplegic eye drops are common in children. Adverse reactions were highest following administration of a double dose of cyclopentolate, in low BMI subjects and in young age. Furthermore, adverse reactions were virtually absent in subjects with high BMI. Our data suggest a dose dependent increase of adverse reactions.

Interpretation of findings.

One objective of this study was to gain more insight in the nature of the adverse reactions. Drowsiness was the most frequently reported adverse reaction. According to the international guidelines of the Council of International Organizations of Medical Sciences the rate of both severe and mild drowsiness can be classified as “commonly present” (≥1% and <10%).[21] For a double dose of cyclopentolate 1%, the severe drowsiness rate as reported in the youngest age category, can even be classified as “very commonly” present (≥10%).[21] Furthermore, regardless the amount of cyclopentolate, severe drowsiness is very commonly present in low BMI subjects of all age categories. Worldwide only a limited number of companies produce cyclopentolate 1% and tropicamide 1%. In general manufacturers provide a summary of product characteristics for the individual countries. [22-35] The summaries of product characteristics give a wide variety of possible central effects. CNS involvement in children is mentioned as being uncommon[22,23] or rare[24]; e.g. present in >0.1% but <1%.[21] Drowsiness is mentioned in a few, however without any further specification of frequency[25,26] Although increased risk for adverse reactions is

described for infants and young children, no statements are made about risk for low weight subjects in the documents we studied.

The present study showed that adverse reactions were present in 4.8% and 10.4% of children receiving one dose versus two doses of cyclopentolate 1%. Both rates and the 2.2 fold difference in rate is in concordance with Bagheri and colleagues.[6] Our findings support their statement that the incidence of adverse reactions increases with repeated installation of cyclopentolate. The reported adverse reactions in our study almost exclusively involved the CNS. This is not in line with a report of Pi and colleagues.[36] Although not reporting actual rates, they mention eye irritation and conjunctival hyperemia as the most common side effects in a large cohort of six to fifteen year old subjects receiving 3 drops of cyclopentolate 1%. In our study we focused on all unwanted effects without influencing patients and/or parents beforehand by providing a specified list. This might have given an underestimation of minor unwanted effects. The complaints reported by Pi and colleagues[36] were expected effects immediately following eye drop application. They generally subside quite quickly and might have been forgotten at the time of our inquiry.

We believe that the adverse reactions can only be attributed to cyclopentolate. The frequent involvement of the CNS following instillation of cyclopentolate is in line with the literature.[7-9] Drowsiness was the most frequently reported side effect, followed by excitation and hyperactivity and/or behavioral changes. The factor 3.4 higher rate of moderate to severe drowsiness and the factor 2.5 higher rate of excitation and hyperactivity and/or behavioral problems in a double dose of cyclopentolate compared to a single dose of cyclopentolate are more evidence for the toxicity of cyclopentolate.

Our study shows that adverse reactions occurred most frequently in young, low BMI subjects. In general one can state that young children have an increased risk for drug related adverse events. The dose relative to blood volume and body weight is greater compared to adults.[8, 37-39] Children have a higher cutaneous blood flow and tissues are less dense; thus absorption may be more profound and rapid.[38,39] Children have a limited serum protein binding capacity.[38,39] The less a drug is bound to proteins, the greater is the availability of the drug in the blood plasma. Metabolic systems and organs are immature and clearing is slower, resulting in a prolonged half-life.[38,39] In subjects with low BMI the dose relative to blood volume and body weight is higher compared to subjects with normal and high BMI.

Children have a large brain mass in relation to body volume and a higher blood brain barrier permeability than adults, thereby facilitating CNS side effects.[39,40] The thalamus plays an important role in regulating states of sleep, wakefulness, attention and alertness. The hippocampus is involved in memory, spatial navigation and inhibition.

Hippocampal dysfunction is associated with poor impulse control, hyperactivity, behavioral changes and disorientation.[41] It seems likely that these areas play a role in the central effects of cyclopentolate. The high incidence of reported adverse reactions especially in the youngest children of our study supports the hypothesis that immaturity of the CNS plays a key role in cyclopentolate's potency for adverse reactions.

In this study adverse reactions were mostly present in the youngest children. However in the oldest children a considerable amount of adverse reactions were still reported. Although no longer immature, the hormonal changes, rapid restructuration of the brain and the increased physical growth might explain the relatively high susceptibility for cyclopentolate in puberty.[38-40]

Study limitations.

Our study has potential limitations. Firstly, the design of this study did not allow determination of the exact time of onset of the adverse reaction, but an onset of approximately 15 to 30 minutes after leaving the examining room was reported in both regimes. We did not gather information on the duration of the reported adverse reactions. However all effects were still present at departure of the subject from our department, indicating that side effects lasted at least 45 to 60 minutes after onset. All accompanying adults were instructed to contact us if adverse reactions did not disappear within 4 hours. We were not contacted. This could be considered an indication that all reactions had disappeared after this time period. Secondly, although the examiner was unaware of the BMI status of the subjects, clinical observations might unconsciously have influenced their inquiries, which might have resulted in an observer bias. However the open question technique should have eliminated such an effect. Thirdly, treatment with either a single or double dose of cyclopentolate was not randomized. However the individual orthoptists of this study had their preference for one of the two regimes, and subjects were planned for examination several weeks prior by administration staff who were unaware of the treatment regimes administered. As such, this can be considered as pseudo-randomisation.[42] Finally, some sub-groups comprised a limited amount of subjects. This could have influenced outcomes; both in rates and subsequent analyses.[43] The question technique used ensured prevention of provoked adverse reactions reports. The strong evidence for a dose response relationship and the results of the 95% CI limits enable generalization to the population.

Conclusions and implications for healthcare professional and policymakers.

Although cyclopentolate 1% generally can be considered to be a safe cycloplegic, the high incidence of adverse events following cyclopentolate in young, low BMI children poses the question whether it is acceptable to use cyclopentolate in a setting without facilities to monitor vital functions. This study shows the presence of a strong dose response relationship with occurrence of adverse reactions. Both presence and severity of adverse reactions increased in low BMI, in young age, and in repeated installation of cyclopentolate 1%. The results of this

study can be generalized to the population. We propose to make adjustments in the (inter)national guidelines for objective refraction in children. This advice would be especially applicable for settings without facilities to monitor vital functions. In young, low BMI subjects the increased risk for drowsiness should be taken into account. In this category of children assessment should be performed with use of a single dose of cyclopentolate, and if necessary combined with tropicamide 1%. Adverse reactions, especially severe drowsiness, were far less common following this regime. With increasing age and increasing BMI, a double dose of cyclopentolate can be administered safely. When a double dose of cyclopentolate 1% is necessary in young and/or low BMI subjects, the objective refraction should be performed in a hospital setting. Finally, we recommend general adjustment of product documentation.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The Medical Research Involving Human Subjects Act did not apply to this study according to the Dutch Central Committee on Research Involving Human Subjects (CCMO, The Hague). The study was conducted according to the principles of the Declaration of Helsinki (version 59th WMA General Assembly, Seoul, Republic of Korea, October 2008) the Dutch Agreement on Medical Treatment Act and the Dutch Personal Data Protection Act.

Data sharing: No additional data available.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Manuscript	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	X	Title; page 1 Abstract; page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	X	Page 2
Introduction				
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	X	Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses		Page 3
Methods				
Study design	4	Present key elements of study design early in the paper	X	Page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X	Page 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	X	Page 4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X	Page 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X	Page 4
Bias	9	Describe any efforts to address potential sources of bias	X	Page 4
Study size	10	Explain how the study size was arrived at	X	Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X	Page 5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	X	Page 5
		(*b*) Describe any methods used to examine subgroups and interactions	X	Page 5
		(*c*) Explain how missing data were addressed	n.a.	
		(*d*) If applicable, explain how loss to follow-up was addressed	n.a.	
		(*e*) Describe any sensitivity analyses	n.a.	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X	Page 5 and 6

		(b) Give reasons for non-participation at each stage	X	Page 4
		(c) Consider use of a flow diagram	X	Page 4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	X	Page 5
		(b) Indicate number of participants with missing data for each variable of interest	n.a.	
		(c) Summarise follow-up time (eg, average and total amount)	n.a.	
Outcome data	15*	Report numbers of outcome events or summary measures over time	X	Page 6-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X	Page 6-10
		(*b*) Report category boundaries when continuous variables were categorized	X	Page 6-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	X	Page 7-10
Discussion				
Key results	18	Summarise key results with reference to study objectives	X	Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X	Page 12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X	Page 10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	X	Page 12
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X	Page 13

*Give information separately for exposed and unexposed groups.

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Adverse reactions following routine anticholinergic eye drops in a paediatric population: an observational cohort study.

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Adverse reactions following routine anticholinergic eye drops in a paediatric population: an observational cohort study.

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ABSTRACT

Objectives To investigate the presence, nature and relationship to age, sex, ethnicity and body mass index (BMI) of adverse reactions following routine cycloplegic eye drops in children.

Design Prospective observational cohort study.

Setting Ophthalmology outpatient clinic Dutch metropolitan hospital; February, March and April 2009.

Participants 3 to14 year old children receiving two drops of cyclopentolate 1% (C+C) or one drop of cyclopentolate 1% and one drop of tropicamide 1% (C+T). Patients were categorised by age (3 to 6, 7 to 10 and 11 to 14 years), sex, ethnicity and BM (low, normal or high).

Outcome measures Rate and nature of adverse reactions reported at 45 minutes following treatment. Crude and adjusted odds ratios (OR) for reporting an adverse reaction using stepwise regression analysis with BMI, age, ethnicity and sex.

Results 912 of 915 eligible patients participated (99.7%). Adverse reactions were reported for C+C in 10.3% and in C+T in 4.8% (42/408 and 24/504, p=0.002). Central effects were present in 95% (C+C) respectively 92% (C+T). Compared to C+T an increased risk was present in C+C (crude OR 2.3 [1.4 to 3.9], p=0.002). Forward adjustment showed BMI to be an influencing factor in treatment (OR 3.1 [1.7 to 5.6], p<0.001). In a multivariate model, dose of cyclopentolate remained associated with adverse reactions. Analysis per BMI- respectively age category and regime, indicated associations with low BMI (OR C+C 21.4 [6.7 to 67.96], p<0.001 respectively C+T 5.2 [2.1 to 12.8], p<0.001) and young age (OR C+C 8.1 [2.7 to 24.8], p<0.001).

Conclusions Adverse reactions were common and almost exclusively involved the central nervous system. Both presence and severity were associated with repeated installation of cyclopentolate 1%, low BMI and young age. In specific paediatric populations a single dose of cyclopentolate must be considered. Vital function monitoring facilities are advisable. Adjustment of guidelines is recommended.

Strengths and limitations of this study

- This study investigated presence and nature of adverse reactions in commonly used cycloplegic regimes and determined risk factors.
- Evidence for a dose response mechanism is provided.
- Observer bias could not be ruled out completely.
- Some sub-groups comprised a limited number of subjects.
- This study warrants a critical approach to the use of cyclopentolate 1% in specific paediatric populations and adjustment of guidelines and product documentation.

INTRODUCTION

In children, refractive errors can cause decreased visual acuity and problems in binocularity such as strabismus. Due to strong accommodative reflexes and the inability to respond reliably to subjective refraction, objective refraction in children is required to assess their refractive state. Objective refraction can only be obtained with cycloplegia through anticholinergic eye drops. Cyclopentolate 1% and tropicamide 1% are both commonly used anticholinergic eye drops for objective refraction in the paediatric population. Depending on ocular alignment, the (expected) refractive error and iris colour, cyclopentolate will be applied once, twice or three times[1]. In subjects with darker irises a combination with tropicamide is often required.[1] The use of anticholinergic eye drops in children is generally considered to be safe.[1,2] Severe adverse reactions following administration are very rare.[2] With regards to tropicamide, the literature agrees that it provokes rarely adverse reactions.[1,3-5] Adverse reactions following the application of cyclopentolate are more common and could be dose related.[6] Young children are most at risk.[1] The adverse reactions occur between 15 to 60 minutes following on administration, often impact the central nervous system (CNS), but subside within 2-6 hours with no permanent sequelae.[7-9] Anticholinergic CNS adverse reactions include; psychotic reactions and behavioural disturbances, ataxia, incoherent speech, restlessness, hallucinations, hyperactivity or drowsiness, seizures, disorientations as to time and place and failure to recognize people.[1] Peripheral anticholinergic adverse reactions include; urinary retention, diminished gastrointestinal motility, tachycardia, hyperpyrexia, vasodilation, skin rash, decreased secretion in salivary and sweat glands, pharynx, bronchi and nasal passages.[1]

For reports on rates and nature of the milder adverse reactions one can only refer to the rates encountered during surveys or efficacy studies. For rates on adverse reactions we searched in larger sample sized studies since the rates of small sample sized studies cannot be extrapolated to the general population.[10] With regards to tropicamide, several very large surveys report an absence of adverse reactions.[3-5] A study of Bagheri and colleagues[6] involving 96 six to twenty year old subjects, reports an adverse reaction rate of 5%, 11% and 24% after one dose, a double dose and a triple dose of cyclopentolate 1%. In contrast, a smaller study of Mohan and Sharma[11] observed the absence of ocular or systemic side effects in a similar population receiving the same treatment regimes. Although Bagheri and colleagues[6] report adverse reaction rates, they do not specify the nature of these adverse reactions. A study of Egashira and colleagues[12] involving 20 six to twelve year old subjects, reports one subject with drowsiness and two subjects with hyperactivity, of whom one also suffered from visual hallucinations, following one dose of cyclopentolate 1%.

In young children, about 5 to 9% need objective refraction because of failure in vision screenings programs due to either strabismus or decreased visual acuity.[13,14] With older children and children in puberty visual acuity complaints increases up to 14%.[15-19] A relatively large part of this group requires objective refraction to assess their refraction.

Depending on the health care arrangements of individual countries the objective measurement of refraction is performed in hospitals or health care centers, as well as in local optometric practices. The latter usually do not have facilities to monitor vital functions. In our Dutch metropolitan hospital ophthalmology outpatient clinic with an ethnically diverse population we use routinely either a double dose of cyclopentolate 1% (C+C) or one dose of cyclopentolate 1% followed by one dose of tropicamide 1% (C+T). Adverse reactions following both regimes are seen, but a larger number of adverse reactions were encountered using C+C. Besides an apparent association with regime, our observations also suggested a possible correlation with younger age and/or lower body mass index (BMI). The available literature does not provide sufficient evidence to show the presence and nature of adverse reactions and relating factors. This survey does not address the reason for the choice of, or the effectiveness of, the departmental routinely used regimes. However both regimes are commonly used worldwide.[1] The purpose of this study was to gain more insight into the presence and nature of adverse reactions following administration of C+C and C+T for objective refraction assessment in children. A secondary aim was to investigate whether the frequency of adverse reactions was associated with age and/or BMI.

METHODS

This study was designed as a prospective, single-centre, cross-sectional and observational cohort study. The study group investigators were research assistants and 4 orthoptists. The study population were all patients between 3 and 14 years who required an objective refraction at our ophthalmology department during February, March and April 2009. The study period of three months was chosen because of the high return rate of our subjects after this three month period. The lower limit of 3 year was chosen because of cooperation problems associated with length and weight measurements below this 3 year age limit. Furthermore possible adverse reactions might not be distinguishable from common sleepiness or behavioural problems due to normal wake/sleep patterns seen in children below this age. The upper limit of 14 years was chosen because there are a limited number of patients requiring an objective refraction beyond this age. Treatment was given in accordance with standard departmental protocol. The orthoptists were not restricted in their choice of medication and used their normal individual regime to assess objective refraction with either C+C or C+T.

Procedures

The parents and children were asked if they would participate in a survey where length and weight measurements would be recorded to establish if there was the need to develop new departmental guidelines for the eye examination of children. The parents and children were free to refuse to participate in the survey. Both oral explanation and measurements were conducted upon arrival at our department. The participating subjects were numbered consecutively. Length and weight were determined. BMI was calculated according to the formula: BMI= Weight/height. Subjects were divided between three categories: low BMI, normal BMI or high BMI, according to the

international cut off values for under- and overweight by sex between 2 and 18 years.[20,21] For South Asian subjects cut-off values according to the guidelines of Wilde et al[22] were used. Subjects were allocated to the following ethnic main groups: Dutch, Turkish, Moroccan, Indian-subcontinental (including Indian, Pakistani and Surinam-Hindoestani) or Black West-African (including Black African of the African Gold Coast, Black subjects from both the Dutch Antilles and Surinam). Remaining subjects were assigned to category "Other". Subjects were also subdivided into three age categories; 3 to 6, 7 to10 or 11 to14 years. A case record form with the designated number of each subject was added to the outpatient chart. The examining orthoptist noted either no drops, C+C or C+T on this form. For children receiving eye drops the examining orthoptist made enquiries approximately 45 minutes following the first eye drop. The parents and children were asked "did you notice anything different following the eye drops". Any responses relating to blurred vision and/or photophobia were excluded. All other responses were noted. Adverse reactions were classified as, severe to moderate drowsiness, mild drowsiness or apathy, excitation & hyperactivity and/or behavioral problems, dizziness, red face and/or cheeks and/or nose bleeding. A further classification was recorded as being either a "central (CNS)" or "peripheral" adverse reaction in accordance with the list provided in the first paragraph of the introduction of this manuscript. Parents were instructed to contact us if adverse reactions did not disappear within 4 hours.

Bias

To avoid treatment bias the examining orthoptist was kept unware of the BMI status of the subjects. To avoid response bias from parents and/or children two procedures were followed. Firstly, the length and weight measurements were introduced as being part of a departmental paediatric population survey and this was done to establish if there was a requirement for the development of new departmental guidelines for the eye examination of children. Secondly the inquiries about the adverse reactions were made with an open question technique

Data analysis

Data were analyzed in SPSS 22 for Windows. Differences were considered statistically significant if $p<0.05$; two-sided. A difference of >2% in reported adverse reactions was considered clinically significant. Variables were compared between the treatment C+C and C+T using the independent samples T-test or the X^2- test, as appropriate. Univariate stratified and multivariate logistic regression analyses were performed to assess the impact of variables on the likelihood that a subject would report an adverse reaction. Odds ratios for treatment were calculated without and with adjustment for BMI, age, ethnicity and sex in a forward model. Odds ratios for BMI; for treatment, with normal BMI subjects receiving C+C as reference group, and age; for treatment, with 6 to 10 year old subjects receiving C+C as reference group, unadjusted and adjusted for age, sex and ethnicity respectively sex, ethnicity and BMI were computed in a multivariate backwards model.

RESULTS

912 of 915 eligible patients participated (99.7%; figure 1). 408 received C+C and 504 received C+T (figure 1).

Figure 1 Flow chart diagram showing number of subjects in the cohort and number of subjects participating in the study.

**C+C: Two drops of cyclopentolate 1%*

***C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

Table 1 reflects the baseline group characteristics stratified by regimes C+C and C+T.

Table 1 Baseline characteristics of children who underwent objective refraction assessment, stratified by cycloplegic eye drop treatment.

	C+C[a]		C+T[b]		p-value
	n (%)	mean	n (%)	mean	
Total	408 (44.7)		504		
Age in years	408	7.6 ± 3.1	504	7.6 ± 3.1	p=0.997[c]
Sex	408		504		p=0.85[d]
Male	207 (50.7)		260 (51.6)		
Female	201 (49.3)		244 (48.4)		
BMI	408		504		p=0.50[e]
Low BMI	18 (4.4)		29 (5.8)		
Normal BMI	292 (71.6)		366 (72.6)		
High BMI	98 (24)		109 (21.6)		
Ethnicity	408		504		p=0.95[e]
Moroccan	81 (19.9)		107 (21.2)		
Turkish	71 (17.4)		86 (17.1)		
Indian Sub-continent	68 (16.7)		73 (14.5)		
Dutch	110 (27.0)		137 (27.2)		
Chinese	9 (2.0)		12 (2.4)		
Black West-African	29 (7.1)		34 (6.7)		
Other	41 (10.0)		55 (10.9)		
Age category	408		504		p=0.92[e]
3 to 6 years	163 (40.0)		200 (39.7)		
7 to10 years	158 (38.7)		191 (37.9)		
11 to14 years	87 (21.3)		113 (22.4)		

[a]*C+C: Two drops of cyclopentolate 1%*

[b]*C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[c]*Independent Samples T-test*

[d]*X^2-test with Yates Continuity Correction*

[e]*X^2-test*

Adverse reactions; presence and nature.

Adverse reactions were reported in 10.3% (42/408) of children following C+C administration and in 4.8% (24/504) of subjects following C+T administration (p=0.002). Central effects were present in 95.2% (C+C; 40/42) and 91.7% (C+T; 22/24, table 2). Severe to moderate drowsiness was the most frequently reported adverse reaction (5.4%) following C+C administration. It was most often present in children aged 3 to 6 years and predominantly present in children with low BMI (table 2). Reports of severe to moderate drowsiness and excitation, hyperactivity and/or behavioral problems were significantly less often present following C+T administration. Excitation, hyperactivity and/or behavioral disorder was the only adverse reaction expressed in high BMI and only reported in the youngest age category following either treatment (table 2). None of the parents contacted us after leaving the outpatient clinic.

Table 2 Number and calculated percentages of clustered adverse reactions stratified by cycloplegic eye drop treatment, and their distribution across age- and BMI categories.

		C+C							
				3 to 6 years		7 to10 years		11 to14 years	
Complaint		n	AR[a] n(%)	n	AR[a] n(%)	n	AR[a] n(%)	n	AR[a] n(%)
Severe or moderate drowsiness[b]		408	22 (5.4)	163	18 (11.0)	158	2 (1.3)	87	2 (2.3)
Mild drowsiness or apathy[b]		408	10 (2.5)	163	9 (5.5)	158	1 (0.6)	87	0
Excitation, hyperactivity and/or behavioral problems[b]		408	6 (1.5)	163	6 (3.7)	158	0	87	0
Dizzyness[b]		408	2 (0.5)	163	0	158	0	87	2 (2.3)
Red cheeks or face (feverish, flushing)[c]		408	2 (0.5)	163	1 (0.6)	158	1 (0.6)	87	0
Nose bleeding[c]		408	0	163	0	158	0	87	0
	BMI								
Severe or moderate drowsiness	Low BMI	18	13 (72.2)	13	11 (84.6)	3	1 (33.3)	2	1 (50.0)
	Normal BMI	292	9 (3.1)	125	7 (5.6)	104	1 (1.0)	63	1 (1.6)
	High BMI	98	0	25	0	51	0	22	0
Mild drowsiness or apathy	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	10 (3.4)	125	9 (7.2)	104	1 (1.0)	63	0
	High BMI	98	0	25	0	51	0	22	0
Excitation, hyperactivity and/or behavioral problems	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	5 (1.7)	125	5 (4.0)	104	0	63	0
	High BMI	98	1 (1.0)	25	1 (4.0)	51	0	22	0
Dizzyness	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	2 (2.0)	125	0	104	0	63	2 (3.2)
	High BMI	98	0	25	0	51	0	22	0
Red cheeks or face (feverish, flushing)	Low BMI	18	0	13	0	3	1 (33.3)	2	0
	Normal BMI	292	2 (2.0)	125	1 (0.8)	104	0	63	0
	High BMI	98	0	25	0	51	0	22	0
Nose bleeding	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	0	125	0	104	0	63	0
	High BMI	98	0	25	0	51	0	22	0

		C+T							
				3 to 6 years		7 to10 years		11 to14 years	
Complaint		n	AR[c] n(%)	n	AR[c] n(%)	n	AR[c] n(%)	n	AR[c] n(%)
Severe or moderate drowsiness[d]		504	8 (1.6)	200	6 (3.0)	191	1 (0.5)	113	1 (0.9)
Mild drowsiness or apathy[d]		504	11 (2.2)	200	4 (2.0)	191	5 (2.6)	113	2 (1.8)
Excitation, hyperactivity and/or behavioral problems[d]		504	3 (0.6)	200	3 (1.5)	191	0	113	0
Dizzyness[d]		504	0	200	0	191	0	113	0
Red cheeks or face (feverish, flushing)[e]		504	1 (0.2)	200	1 (0.5)	191	0	113	0
Nose bleeding[e]		504	1 (0.2)	200	1 (0.5)	191	0	113	0
	BMI								
Severe or moderate drowsiness	Low BMI	29	5 (17.2)	14	3 (21.4)	9	1 (11.1)	6	1 (16.7)
	Normal BMI	366	3 (8.2)	157	3 (1.9)	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Mild drowsiness or apathy	Low BMI	29	5 (17.2)	14	1 (7.1)	9	2 (22.2)	6	2 (33.3)
	Normal BMI	366	6 (1.6)	157	3 (1.9)	129	3 (2.3)	80	0
	High BMI	109	0	29	0	53	0	27	0
Excitation, hyperactivity and/or	Low BMI	29	0	14	0	9	0	6	0
behavioral problems	Normal BMI	366	2 (0.6)	157	2 (1.3)	129	0	80	0
	High BMI	109	1 (0.9)	29	1 (3.0)	53	0	27	0
Dizzyness	Low BMI	29	0	14	0	9	0	6	0
	Normal BMI	366	0	157	0	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Red cheeks or face (feverish, flushing)	Low BMI	29	0	14	0	9	0	6	0
	Normal BMI	366	1 (0.3)	157	1 (0.6)	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Nose bleeding	L-BMI	29	0	14	0	9	0	6	0
	N-BMI	366	1 (0.3)	157	1 (0.6)	129	0	80	0
	H-BMI	109	0	29	0	53	0	27	0

[a] *C+C: Two drops of cyclopentolate 1%*

[b] *C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[c] *AR: Adverse reactions*

[d] *CNS adverse reactions*

[e] *Peripheral adverse reactions*

Relation of adverse reactions with sex, BMI, ethnicity and age.

Neither sex nor ethnicity was related with adverse reactions (table 3). In both interventions low BMI subjects had a statistically highly significantly increased risk for adverse reactions, however the odds ratio for adverse reactions was significantly higher in C+C compared to C+T (table 3). In both treatment groups the frequency of adverse reactions was highest in the youngest age group. Only in C+C younger age was associated with a statistically highly significantly increased risk for adverse reactions (table 3). A borderline significance; p=0.06 instead of p<0.05, however was present in C+T. Furthermore, in both interventions for all age categories, adverse reactions were more frequently reported in children with low BMI compared to those with normal BMI (table 3).

Table 3 Frequencies, percentages and crude odds ratios of adverse reactions with respect to sex, BMI, ethnicity and age category stratified by cycloplegic eye drop treatment.

	C+C[a]				C+T[b]			
	n	n (%) AR[c]	Crude OR[d] 95% CI[e]	P value	n	n (%) AR[c]	Crude OR[d] 95% CI[e]	P value
	408	42 (10.3)			504	24 (4.8)		
Sex	408	42			504	24		
Male	207	25 (12.1)	1[f]		260	12 (4.6)	1[f]	
Female	201	17 (8.5)	0.7 (0.4 to1.3)	0.23	244	12 (4.9)	0.9 (0.4 to 2.1)	0.87
BMI category	408	42			504	24		
Low BMI	18	13 (72.2)	24.5 (8.1 to 73.8)	<0.001	29	10 (34.5)	14.3 (5.6 to 36.8)	<0.001
Normal BMI	292	28 (9.6)	1[f]		366	13 (3.6)	1[f]	
High BMI	98	1 (1.0)	0.1 (0.01 to 0.7)	0.02	109	1 (0.9)	0.3 (0.03 to 1.9)	0.19
Ethnic main group	359	39 (10.9)			437	21 (4.9)		
Dutch	110	13 (11.8)	1[f]		137	6 (4.4)	1[f]	
Moroccan	81	10 (12.3)	1.1 (0.4 to 2.5)	0.91	107	5 (4.7)	1.1 (0.3 to 3.6)	0.91
Turkey	71	5 (7.0)	0.6 (0.2 to 1.7)	0.30	86	4 (4.7)	1.1 (0.3 to 3.9)	0.92
Indian-subcontintent	68	10 (14.7)	1.3 (0.5 to 3.1)	0.58	73	5 (6.8)	1.6 (0.5 to 5.5)	0.45
Negro	29	1 (3.4)	0.3 (0.03 to 2.1)	0.21	34	1 (2.9)	0.7 (0.08 to 5.7)	0.71
Other	49	3 (6.1)	0.5 (0.1 to 1.8)	0.28	67	3 (4.5)	1.0 (0.3 to 4.2)	0.97
Age category	408	42			504	24		
3 to 6 year	163	34 (20.9)	10.2 (3.5 to 29.4)	<0.001	200	15 (7.5)	2.5 (0.95 to 6.6)	0.06
7 to10 year	158	4 (2.5)	1[f]		191	6 (3.1)	1[f]	
11 to14 year	87	4 (4.6)	1.9 (0.5 to 7.6)	0.39	113	3 (2.7)	0.8 (0.2 to 3.4)	0.81
Age category 3 to 6	163	34			200	15		
Low BMI	13	11 (84.6)			14	4 (28.6)		
Normal BMI	125	22 (17.6)			157	10 (6.4)		
High BMI	25	1 (4.0)			29	1 (3.4)		
Age category 7 to10	158	4			191	6		
Low BMI	3	1 (33.3)			9	3 (33.3)		
Normal BMI	104	3 (2.9)			129	3 (2.3)		
High BMI	51	0			53	0		
Age category 11 to14	87	4			113	3		
Low BMI	2	1 (50.0)			6	3 (50.0)		
Normal BMI	63	3 (4.8)			80	0		
High BMI	22	0			27	0		

[a]*C+C: Two drops of cyclopentolate 1%*

[b]*C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[C]*AR: Adverse reactions*

[d]*OR: Odds ratio*

[e]*CI: Confidence Interval*

[f]*1: Reference group*

Relation of adverse reactions with dose of cyclopentolate, BMI and age.

For children receiving C+C there was a significantly increased overall risk for adverse reactions compared to those receiving C+T (OR 2.3 [1.4-3.9]; table 4). In a forward model we explored the influence of the variables BMI, age, ethnicity and sex on the odds ratio for treatment. Only BMI was found to have a significant influence (table 4).

Table 4 Odds ratio for reporting adverse reactions for treatment, and stepwise adjustment of this odds ratio with BMI, age, ethnicity and sex.

Step	Factors	OR[a] + 95% CI[b]	P value
1	Treatment	2.3 (1.4 to 3.9)	0.002
2	Treatment + BMI [cat]	3.1 (1.7 to 5.6)	<0.001
3	Treatment + BMI [cat] + Age [cat]	3.0 (1.6 to 5.5)	<0.001
4	Treatment + BMI [cat] + Age [cat] + Ethnicity [cat]	3.0 (1.6 to 5.5)	<0.001
5	Treatment + BMI [cat] + Age [cat] + Ethnicity [cat] + Sex [cat]	3.0 (1.5 to 5.4)	<0.001

[a]*OR: Odds ratio*

[b]*CI: Confidence Interval*

Our analysis indicated that the dosage of cyclopentolate saw the most adverse reactions when administered to young children with low BMI. These relations were explored in more detail. Table 5 shows the unadjusted, crude, odds ratios for reporting adverse reactions per BMI category and regime, with normal BMI subjects receiving C+C as reference group in a multivariate model. Following adjustment for gender, ethnicity and age, dose of cyclopentolate remained highly significantly associated with adverse reactions. We also explored age category and regime (table 5). Following adjustment for gender, ethnicity and BMI, dose of cyclopentolate was associated with adverse reactions in the youngest subjects.

Table 5 Odds ratios for reporting adverse reactions per BMI category respectively age category and regime, with normal BMI respectively 7 to 10 year old children receiving C+C[a] as reference group; backwards analysis.

Regime	BMI	Crude OR[c] (95% CI)[d]	P value	Adjusted[e] OR[c] (95% CI)[d]	P value
C+C[a]	High	0.1 (0.01 to 0.7)	0.02	0.1 (0.02 to 0.9)	0.04
	Normal	1[e]		1[e]	
	Low	24.6 (8.2 to74.1)	<0.001	21.4 (6.7 to 67.96)	<0.001
C+T[b]	High	0.09 (0.01 to 0.7)	0.02	0.1 (0.01 to 0.8)	0.03
	Normal	0.35 (0.2 to 0.7)	0.02	0.34 (0.2 to 0.7)	0.02
	Low	4.98 (2.1 to 11.8)	<0.001	5.2 (2.1 to 12.8)	<0.001

Regime	Age	Crude OR[c] (95% CI)[d]	P value	Adjusted[f] OR[c] (95% CI)[d]	P value
C+C[a]	11 to 14	1.8 (0.4 to 7.4)	0.41	0.17 (0.4 to 7.4)	0.48
	7 to 10	1[e]		1[e]	
	3 to 6	10.2 (3.5 to 29.5)	<0.001	8.1 (2.7 to 24.8)	<0.001
C+T[b]	11 to 14	1.1 (0.2 to 4.9)	0.92	0.7 (0.1 to 3.5)	0.66
	7 to 10	1.3 (0.4 to 4.6)	0.72	0.9 (0.2 to 3.5)	0.88
	3 to 6	3.1 (1.0 to 9.7)	0.046	1.97 (0.6 to 6.5)	0.26

[a]C+C: Two drops of cyclopentolate 1%
[b]C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%
[c]OR: Odds ratio
[d]CI: Confidence Interval
[e]1: Reference group
[f]Adjusted for sex (cat), age (cat) and ethnicity (cat)
[g]Adjusted for sex (cat), BMI (cat) and ethnicity (cat)

DISCUSSION

This study showed that adverse reactions following cycloplegic eye drops are common in children. Adverse reactions were highest following the administration of a double dose of cyclopentolate to young children with a low BMI. Adverse reactions were virtually absent in subjects with high BMI. Our data suggest a dose response mechanism.

Interpretation of findings.

One objective of this study was to gain more insight in the nature of the adverse reactions. All adverse reactions reported were expected adverse reactions; they were observed and documented previously. Drowsiness was the most frequently reported adverse reaction. According to the international guidelines of the Council of International Organizations of Medical Sciences the rate of both severe and mild drowsiness can be classified as “commonly present” (≥1% and <10%).[23] For a double dose of cyclopentolate 1%, the severe to moderate drowsiness rate as reported in the youngest age category, can even be classified as “very commonly” present (≥10%).[23] Furthermore, regardless the amount of cyclopentolate, severe to moderate drowsiness was very commonly present in low BMI subjects of all age categories. Worldwide only a limited number of companies produce cyclopentolate 1% and tropicamide 1%. In general manufacturers provide a summary of product characteristics for the individual countries.

[24-37] The summaries of product characteristics give a wide variety of possible central effects. CNS involvement in children is mentioned as being uncommon[24,25] or rare[24]; e.g. present in >0.1% but <1%.[23] Drowsiness is mentioned in few, but without any further reference to the frequency.[27,28] An increased risk for adverse reactions is identified for infants and young children, but no statements are made about the risks for low weight subjects in the documents we studied.

In addition to classification by frequency, adverse reactions can also be classified by severity. The Common Terminology Criteria for Adverse Events grades adverse reactions according to a System Organ Class.[38] This system has 5 levels of grading; where grade 1 represents mild symptoms, grade 2 represents moderate symptoms up to grade 5, representing death related to the adverse reaction. The adverse reactions reported in our survey mainly belong to the "nervous system disorders". Dizziness, hyperactivity and/or behavioral problems, and mild drowsiness or apathy are classified as grade 1 adverse reactions. Severe or moderate drowsiness are classified as grade 2 adverse reactions. The peripheral adverse reactions reported are all grade 1 adverse reactions. A significant difference between the interventions was present. A double dose of cyclopentolate had 52.4% grade 2 adverse reactions while one dose of cyclopentolate had 33.3%.

The present study showed that adverse reactions were present in 4.8% and 10.3% of children receiving one dose versus two doses of cyclopentolate 1%. Both rates and the 2.2 fold difference in rate is in concordance with Bagheri and colleagues.[6] Our findings support their statement that the incidence of adverse reactions increases with repeated installation of cyclopentolate. The reported adverse reactions in our study almost exclusively involved the CNS. This is not in line with a report of Pi and colleagues.[39] Although not reporting actual rates, they mention eye irritation and conjunctival hyperemia as the most common adverse reactions in a large cohort of six to fifteen year old subjects receiving 3 drops of cyclopentolate 1%. In our study we focused on all unwanted reactions without influencing patients and/or parents beforehand by providing a specified list. This might have given an underestimation of minor unwanted effects. The complaints reported by Pi and colleagues[39] were expected effects immediately following eye drop application. They generally subside quite quickly and might have been forgotten at the time of our inquiry.

Worldwide tropicamide and cyclopentolate have been used for decades. The lack of adverse reactions following tropicamide is acknowledged and well described. Although an effect of tropicamide on adverse reactions cannot be ruled out, we believe that the adverse reactions can only be attributed to cyclopentolate. The frequent involvement of the CNS following instillation of cyclopentolate is in line with the literature.[7-9] Drowsiness was the most frequently reported adverse reaction, followed by excitation and hyperactivity and/or behavioral changes. The factor 3.4 higher rate of severe to moderate drowsiness and the factor 2.5 higher rate of excitation and hyperactivity and/or behavioral problems

in a double dose of cyclopentolate compared to a single dose of cyclopentolate are more evidence for the impact of cyclopentolate.

Our study shows that adverse reactions occurred most frequently in young- and low BMI subjects. In general one can state that young children have an increased risk for drug related adverse events. The dose relative to blood volume and body weight is greater compared to adults.[8, 40-42] Children have a higher cutaneous blood flow and tissues are less dense; thus absorption may be more profound and rapid.[41,42] Children have a limited serum protein binding capacity.[41,42] The smaller the protein binding capacity, the greater the availability of the drug in the blood plasma. Metabolic systems and organs are immature and clearing is slower, resulting in a prolonged half-life.[41,42] In subjects with low BMI the dose relative to blood volume and body weight is higher compared to subjects with normal and high BMI.

Children have a large brain mass in relation to body volume and a higher blood brain barrier permeability than adults, thereby facilitating CNS adverse reactions.[42,43] The thalamus plays an important role in regulating states of sleep, wakefulness, attention and alertness. The hippocampus is involved in memory, spatial navigation and inhibition. Hippocampal dysfunction is associated with poor impulse control, hyperactivity, behavioral changes and disorientation.[44] It seems likely that these areas play a role in the central effects of cyclopentolate. The high incidence of reported adverse reactions especially in the youngest children of our study supports the hypothesis that immaturity of the CNS plays a key role in cyclopentolate's potency for adverse reactions.
In this study adverse reactions were mostly present in the youngest children. However in the children in puberty a considerable amount of adverse reactions were still reported. Although no longer immature, the hormonal changes, rapid restructuration of the brain and the increased physical growth might explain the relatively high susceptibility for cyclopentolate in puberty.[39-41]

Study limitations.

Our observational study has several potential limitations.1) We realize that an actual dose response relationship could only be determined with plasma concentrations using intravenous measurements of the dose. But this is not feasible in an observational design and more importantly to invasive for children. If a regime with one dose and three doses of cyclopentolate were added to this observational study we might have established a dose response relationship in the more true sense. These regimes however are infrequently used by our staff. Despite the limitations, we feel we have found enough evidence to state there is an indication of "a dose response mechanism". 2) Despite the apparent lack of adverse reactions with regards to tropicamide in the literature, a tropicamide effect could only have been ruled out if a regime using one drop of tropicamide 1% was admitted in this survey. Again, such a regime in infrequently used. 3) The design of this study did not allow determination of the exact time of onset

of the adverse reaction, but an onset of approximately 15 to 30 minutes after leaving the examining room was reported in both regimes. We did not gather information on the duration of the reported adverse reactions. However all effects were still present at departure of the subject from our department, indicating that the adverse reactions lasted at least 45 to 60 minutes after onset. None of the parents contacted us after leaving the outpatient clinic. This could be considered an indication that all adverse reactions had disappeared after this time period. 4) Although the examiner was unaware of the BMI status of the subjects, clinical observations might unconsciously have influenced their inquiries, which might have resulted in an observer bias. However the open question technique should have eliminated such an effect. 5) Besides age and BMI there are more variables influencing the amount of active compound a subject might receive; such as firmly squeezing the eyelids or crying of the subject, thereby reducing the amount of active compound one receives. We did not take these variables into account. 6) Treatment with either a single or double dose of cyclopentolate was not randomized. However the individual orthoptists of this study had their fixed preference for one of the two regimes, and subjects were planned for examination several weeks prior by administration staff who were unaware of the treatment regimes administered. As such, this can be considered as pseudo-randomisation.[45] 7) Finally, some sub-groups comprised a limited amount of subjects. This could have influenced outcomes; both in rates and subsequent analyses.[10] The questioning technique used ensured prevention of provoked adverse reactions reports. Furthermore, the results of the 95% CI limits enable generalisation to the population.

Conclusions and implications for healthcare professional and policymakers.

Although cyclopentolate 1% generally can be considered to be a safe cycloplegic, the high incidence of adverse events following cyclopentolate in young, low BMI children poses the question whether it is acceptable to use cyclopentolate in a setting without facilities to monitor vital functions. This study provides evidence for a dose response mechanism with the occurrence of adverse reactions. Both presence and severity of adverse reactions are increased in low BMI, young age and in repeated installation of cyclopentolate 1%. The results of this survey can be generalized to the population. We propose to make adjustments in the (inter)national guidelines for objective refraction in children. This advice would be especially applicable for settings without facilities to monitor vital functions. In young, low BMI subjects the increased risk for drowsiness should be taken into account. In this category of children assessment should be performed with use of a single dose of cyclopentolate, and if necessary combined with tropicamide 1%. Adverse reactions, especially severe drowsiness, were far less common following this regime. With increasing age and increasing BMI, a double dose of cyclopentolate can be administered safely. When a double dose of cyclopentolate 1% is necessary in young and/or low BMI subjects, e.g. children up to at least 6 years of age and low BMI subjects of all ages, the objective refraction should be performed in a hospital setting, or at least in a location where vital functions can be monitored. This survey shows once again that cyclopentolate is a potent drug that can cause moderate adverse reactions to the CNS in children. For young children and children with a low

BMI, the risk of a seriously adverse reaction is rare; however the possibility of an occurrence should always be taken into consideration. Finally, we recommend general adjustment of product documentation.

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Contributors: HMvM was involved at every stage from the literature search, planning and design of the study, data abstraction, data analysis, data interpretation, and writing. MVJ was involved with the study plan and design and writing. DG was involved with data abstraction, data analysis and especially in data interpretation and writing. NESD was involved with data interpretation and editing the manuscript for important intellectual content. She is the guarantor. All authors had full access to the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis prepared the initial manuscript drafts, which were subsequently edited by all authors. All authors agreed to submission.

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Ethical approval: The Medical Research Involving Human Subjects Act did not apply to this study according to the Dutch Central Committee on Research Involving Human Subjects (CCMO, The Hague). A written CCMO statement is present. The study was conducted according to the principles of the Declaration of Helsinki (version 59th WMA General Assembly, Seoul, Republic of Korea, October 2008) the Dutch Agreement on Medical Treatment Act and the Dutch Personal Data Protection Act.

Data sharing: No additional data available.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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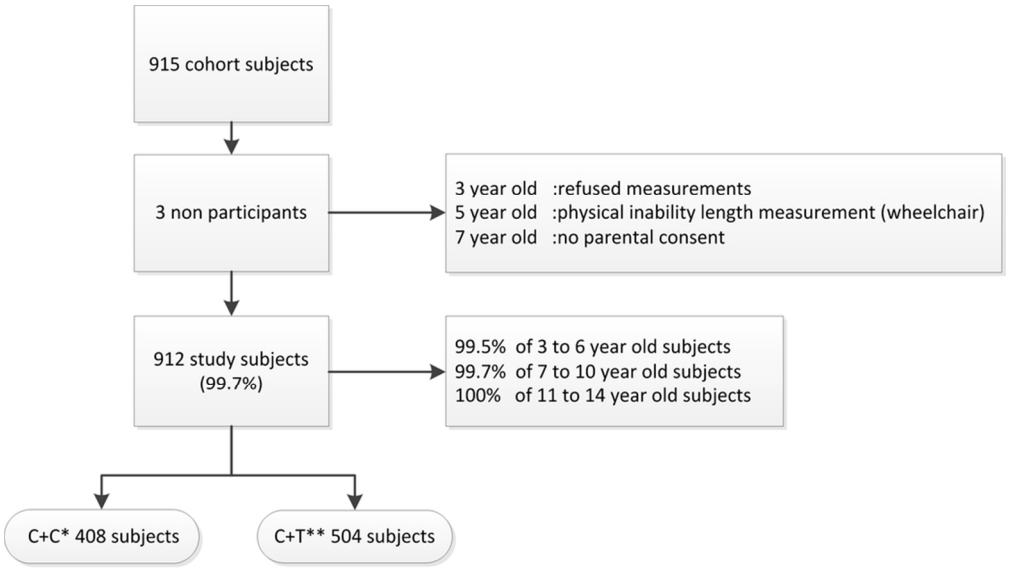

*C+C: Two drops of cyclopentolate 1%
**C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%

87x49mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Manuscript	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	X	Title; page 1 Abstract; page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	X	Page 2
Introduction				
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	X	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses		Page 4
Methods				
Study design	4	Present key elements of study design early in the paper	X	Page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X	Page 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	X	Page 4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X	Page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X	Page 5
Bias	9	Describe any efforts to address potential sources of bias	X	Page 5
Study size	10	Explain how the study size was arrived at	X	Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X	Page 5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	X	Page 5
		(*b*) Describe any methods used to examine subgroups and interactions	X	Page 5
		(*c*) Explain how missing data were addressed	n.a.	
		(*d*) If applicable, explain how loss to follow-up was addressed	n.a.	
		(*e*) Describe any sensitivity analyses	n.a.	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X	Page 5 and 6

		(b) Give reasons for non-participation at each stage	X	Page 6
		(c) Consider use of a flow diagram	X	Page 6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	X	Page 6
		(b) Indicate number of participants with missing data for each variable of interest	n.a.	
		(c) Summarise follow-up time (eg, average and total amount)	n.a.	
Outcome data	15*	Report numbers of outcome events or summary measures over time	X	Page 7-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X	Page 7-10
		(*b*) Report category boundaries when continuous variables were categorized	X	Page 7-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	X	Page 7-10
Discussion				
Key results	18	Summarise key results with reference to study objectives	X	Page 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X	Page 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X	Page 10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	X	Page 13
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X	Page 14

*Give information separately for exposed and unexposed groups.

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Adverse reactions following routine anticholinergic eye drops in a paediatric population: an observational cohort study.

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Adverse reactions following routine anticholinergic eye drops in a paediatric population: an observational cohort study.

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ABSTRACT

Objectives To investigate the presence, nature and relationship to age, sex, ethnicity and body mass index (BMI) of adverse reactions following routine cycloplegic eye drops in children.

Design Prospective observational cohort study.

Setting Ophthalmology outpatient clinic Dutch metropolitan hospital; February, March and April 2009.

Participants 3 to14 year old children receiving two drops of cyclopentolate 1% (C+C) or one drop of cyclopentolate 1% and one drop of tropicamide 1% (C+T). Patients were categorised by age (3 to 6, 7 to 10 and 11 to 14 years), sex, ethnicity and BM (low, normal or high).

Outcome measures Rate and nature of adverse reactions reported at 45 minutes following treatment. Crude and adjusted odds ratios (OR) for reporting an adverse reaction using stepwise regression analysis with BMI, age, ethnicity and sex.

Results 912 of 915 eligible patients participated (99.7%). Adverse reactions were reported for C+C in 10.3% and in C+T in 4.8% (42/408 and 24/504, p=0.002). Central effects were present in 95% (C+C) respectively 92% (C+T). Compared to C+T an increased risk was present in C+C (crude OR 2.3 [1.4 to 3.9], p=0.002). Forward adjustment showed BMI to be an influencing factor in treatment (OR 3.1 [1.7 to 5.6], p<0.001). In a multivariate model, dose of cyclopentolate remained associated with adverse reactions. Analysis per BMI- respectively age category and regime, indicated associations with low BMI (OR C+C 21.4 [6.7 to 67.96], p<0.001 respectively C+T 5.2 [2.1 to 12.8], p<0.001) and young age (OR C+C 8.1 [2.7 to 24.8], p<0.001).

Conclusions Adverse reactions were common and almost exclusively involved the central nervous system. Both presence and severity were associated with repeated installation of cyclopentolate 1%, low BMI and young age. In specific paediatric populations a single dose of cyclopentolate must be considered. Vital function monitoring facilities are advisable. Adjustment of guidelines is recommended.

Strengths and limitations of this study

- This study investigated presence and nature of adverse reactions in commonly used cycloplegic regimes and determined risk factors.
- Evidence for a dose response mechanism is provided.
- Observer bias could not be ruled out completely.
- Some sub-groups comprised a limited number of subjects.
- This study warrants a critical approach to the use of cyclopentolate 1% in specific paediatric populations and adjustment of guidelines and product documentation.

INTRODUCTION

In children, refractive errors can cause decreased visual acuity and problems in binocularity such as strabismus. Due to strong accommodative reflexes and the inability to respond reliably to subjective refraction, objective refraction in children is required to assess their refractive state. Objective refraction can only be obtained with cycloplegia through anticholinergic eye drops. Cyclopentolate 1% and tropicamide 1% are both commonly used anticholinergic eye drops for objective refraction in the paediatric population. Depending on ocular alignment, the (expected) refractive error and iris colour, cyclopentolate will be applied once, twice or three times[1]. In subjects with darker irises a combination with tropicamide is often required.[1] The use of anticholinergic eye drops in children is generally considered to be safe.[1,2] Severe adverse reactions following administration are very rare.[2] With regards to tropicamide, the literature agrees that it provokes rarely adverse reactions.[1,3-5] Adverse reactions following the application of cyclopentolate are more common and could be dose related.[6] Young children are most at risk.[1] The adverse reactions occur between 15 to 60 minutes following on administration, often impact the central nervous system (CNS), but subside within 2-6 hours with no permanent sequelae.[7-9] Anticholinergic CNS adverse reactions include; psychotic reactions and behavioural disturbances, ataxia, incoherent speech, restlessness, hallucinations, hyperactivity or drowsiness, seizures, disorientations as to time and place and failure to recognize people.[1] Peripheral anticholinergic adverse reactions include; urinary retention, diminished gastrointestinal motility, tachycardia, hyperpyrexia, vasodilation, skin rash, decreased secretion in salivary and sweat glands, pharynx, bronchi and nasal passages.[1]

For reports on rates and nature of the milder adverse reactions one can only refer to the rates encountered during surveys or efficacy studies. For rates on adverse reactions we searched in larger sample sized studies since the rates of small sample sized studies cannot be extrapolated to the general population.[10] With regards to tropicamide, several very large surveys report an absence of adverse reactions.[3-5] A study of Bagheri and colleagues[6] involving 96 six to twenty year old subjects, reports an adverse reaction rate of 5%, 11% and 24% after one dose, a double dose and a triple dose of cyclopentolate 1%. In contrast, a smaller study of Mohan and Sharma[11] observed the absence of ocular or systemic side effects in a similar population receiving the same treatment regimes. Although Bagheri and colleagues[6] report adverse reaction rates, they do not specify the nature of these adverse reactions. A study of Egashira and colleagues[12] involving 20 six to twelve year old subjects, reports one subject with drowsiness and two subjects with hyperactivity, of whom one also suffered from visual hallucinations, following one dose of cyclopentolate 1%.

In young children, about 5 to 9% need objective refraction because of failure in vision screenings programs due to either strabismus or decreased visual acuity.[13,14] With older children and children in puberty visual acuity complaints increases up to 14%.[15-19] A relatively large part of this group requires objective refraction to assess their refraction.

Depending on the health care arrangements of individual countries the objective measurement of refraction is performed in hospitals or health care centers, as well as in local optometric practices. The latter usually do not have facilities to monitor vital functions. In our Dutch metropolitan hospital ophthalmology outpatient clinic with an ethnically diverse population we use routinely either a double dose of cyclopentolate 1% (C+C) or one dose of cyclopentolate 1% followed by one dose of tropicamide 1% (C+T). Adverse reactions following both regimes are seen, but a larger number of adverse reactions were encountered using C+C. Besides an apparent association with regime, our observations also suggested a possible correlation with younger age and/or lower body mass index (BMI). The available literature does not provide sufficient evidence to show the presence and nature of adverse reactions and relating factors. This survey does not address the reason for the choice of, or the effectiveness of, the departmental routinely used regimes. However both regimes are commonly used worldwide.[1] The purpose of this study was to gain more insight into the presence and nature of adverse reactions following administration of C+C and C+T for objective refraction assessment in children. A secondary aim was to investigate whether the frequency of adverse reactions was associated with age and/or BMI.

METHODS

This study was designed as a prospective, single-centre, cross-sectional and observational cohort study. The study group investigators were research assistants and 4 orthoptists. The study population were all patients between 3 and 14 years who required an objective refraction at our ophthalmology department during February, March and April 2009. The study period of three months was chosen because of the high return rate of our subjects after this three month period. The lower limit of 3 year was chosen because of cooperation problems associated with length and weight measurements below this 3 year age limit. Furthermore possible adverse reactions might not be distinguishable from common sleepiness or behavioural problems due to normal wake/sleep patterns seen in children below this age. The upper limit of 14 years was chosen because there are a limited number of patients requiring an objective refraction beyond this age. Treatment was given in accordance with standard departmental protocol. The orthoptists were not restricted in their choice of medication and used their normal individual regime to assess objective refraction with either C+C or C+T.

Ethical considerations

The study was conducted according to the principles of the Declaration of Helsinki (version 59th WMA General Assembly, Seoul, Republic of Korea, October 2008) the Dutch Agreement on Medical Treatment Act (WBGO) and the Dutch Personal Data Protection Act. The Medical Research Involving Human Subjects Act (WMO) did not apply to this study according to the Dutch Central Committee on Research Involving Human Subjects (CCMO, The Hague) and therefore a written waiver of the CCMO was provided. All parents and children were asked if they would participate in an observational survey where length and weight measurements would be recorded to establish if

there was the need to develop new departmental guidelines for the eye examination of children. Subsequently oral consent to participate in this observational survey was asked of both parents and children. The parents and children were free to refuse to participate in the survey. Both oral explanation as well as length and weight measurements were conducted upon arrival at our department.

Procedures

The participating subjects were numbered consecutively. Length and weight were determined. BMI was calculated according to the formula: BMI= Weight/height. Subjects were divided between three categories: low BMI, normal BMI or high BMI, according to the international cut off values for under- and overweight by sex between 2 and 18 years.[20,21] For South Asian subjects cut-off values according to the guidelines of Wilde et al[22] were used. Subjects were allocated to the following ethnic main groups: Dutch, Turkish, Moroccan, Indian-subcontinental (including Indian, Pakistani and Surinam-Hindoestani) or Black West-African (including Black African of the African Gold Coast, Black subjects from both the Dutch Antilles and Surinam). Remaining subjects were assigned to category "Other". Subjects were also subdivided into three age categories; 3 to 6, 7 to10 or 11 to14 years. A case record form with the designated number of each subject was added to the outpatient chart. The examining orthoptist noted either no drops, C+C or C+T on this form. For children receiving eye drops the examining orthoptist made enquiries approximately 45 minutes following the first eye drop. The parents and children were asked "did you notice anything different following the eye drops". Any responses relating to blurred vision and/or photophobia were excluded. All other responses were noted. Adverse reactions were classified as, severe to moderate drowsiness, mild drowsiness or apathy, excitation & hyperactivity and/or behavioral problems, dizziness, red face and/or cheeks and/or nose bleeding. A further classification was recorded as being either a "central (CNS)" or "peripheral" adverse reaction in accordance with the list provided in the first paragraph of the introduction of this manuscript. Parents were instructed to contact us if adverse reactions did not disappear within 4 hours.

Bias

To avoid treatment bias the examining orthoptist was kept unware of the BMI status of the subjects. To avoid response bias from parents and/or children two procedures were followed. Firstly, the length and weight measurements were introduced as being part of a departmental paediatric population survey and this was done to establish if there was a requirement for the development of new departmental guidelines for the eye examination of children. Secondly the inquiries about the adverse reactions were made with an open question technique

Data analysis

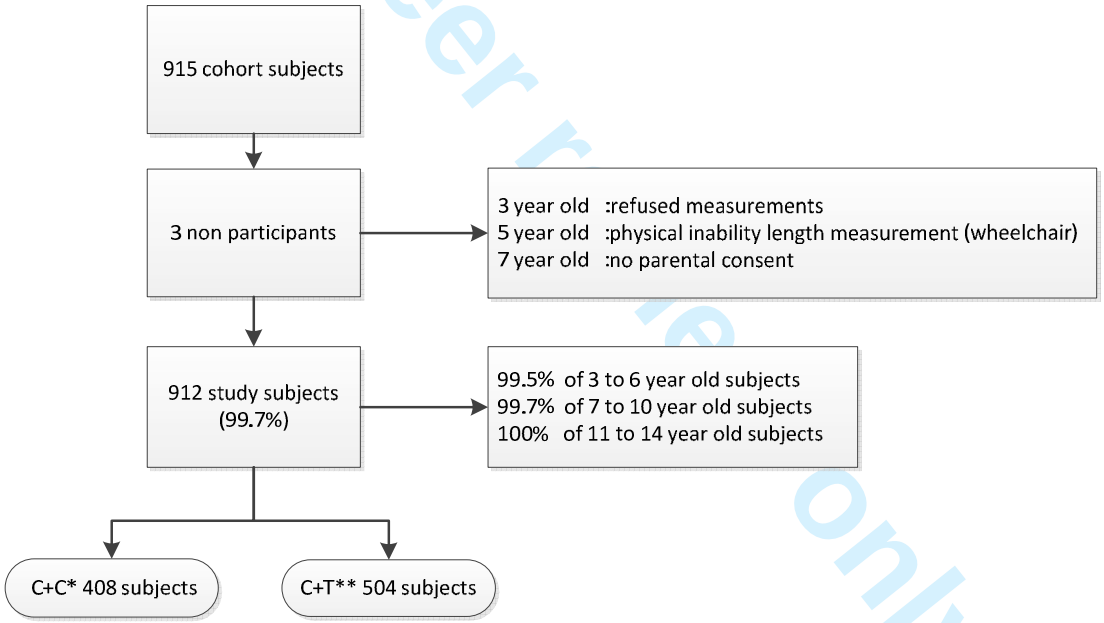
Data were analyzed in SPSS 22 for Windows. Differences were considered statistically significant if $p<0.05$; two-sided. A difference of >2% in reported adverse reactions was considered clinically significant. Variables were

compared between the treatment C+C and C+T using the independent samples T-test or the X^2- test, as appropriate. Univariate stratified and multivariate logistic regression analyses were performed to assess the impact of variables on the likelihood that a subject would report an adverse reaction. Odds ratios for treatment were calculated without and with adjustment for BMI, age, ethnicity and sex in a forward model. Odds ratios for BMI; for treatment, with normal BMI subjects receiving C+C as reference group, and age; for treatment, with 6 to 10 year old subjects receiving C+C as reference group, unadjusted and adjusted for age, sex and ethnicity respectively sex, ethnicity and BMI were computed in a multivariate backwards model.

RESULTS

912 of 915 eligible patients participated (99.7%; figure 1). 408 received C+C and 504 received C+T (figure 1).

Figure 1 Flow chart diagram showing number of subjects in the cohort and number of subjects participating in the study.



**C+C: Two drops of cyclopentolate 1%*

***C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

Table 1 reflects the baseline group characteristics stratified by regimes C+C and C+T.

Table 1 Baseline characteristics of children who underwent objective refraction assessment stratified by cycloplegic eye drop treatment.

	C+C[a]		C+T[b]		p-value
	n (%)	mean	n (%)	mean	
Total	408 (44.7)		504		
Age in years	408	7.6 ± 3.1	504	7.6 ± 3.1	p=0.997[c]
Sex	408		504		p=0.85[d]
Male	207 (50.7)		260 (51.6)		
Female	201 (49.3)		244 (48.4)		
BMI	408		504		p=0.50[e]
Low BMI	18 (4.4)		29 (5.8)		
Normal BMI	292 (71.6)		366 (72.6)		
High BMI	98 (24)		109 (21.6)		
Ethnicity	408		504		p=0.95[e]
Moroccan	81 (19.9)		107 (21.2)		
Turkish	71 (17.4)		86 (17.1)		
Indian Sub-continent	68 (16.7)		73 (14.5)		
Dutch	110 (27.0)		137 (27.2)		
Chinese	9 (2.0)		12 (2.4)		
Black West-African	29 (7.1)		34 (6.7)		
Other	41 (10.0)		55 (10.9)		
Age category	408		504		p=0.92[e]
3 to 6 years	163 (40.0)		200 (39.7)		
7 to10 years	158 (38.7)		191 (37.9)		
11 to14 years	87 (21.3)		113 (22.4)		

[a] *C+C: Two drops of cyclopentolate 1%*

[b] *C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[c] *Independent Samples T-test*

[d] *X^2-test with Yates Continuity Correction*

[e] *X^2-test*

Adverse reactions; presence and nature.

Adverse reactions were reported in 10.3% (42/408) of children following C+C administration and in 4.8% (24/504) of subjects following C+T administration (p=0.002). Central effects were present in 95.2% (C+C; 40/42) and 91.7% (C+T; 22/24, table 2). Severe to moderate drowsiness was the most frequently reported adverse reaction (5.4%) following C+C administration. It was most often present in children aged 3 to 6 years and predominantly present in children with low BMI (table 2). Reports of severe to moderate drowsiness and excitation, hyperactivity and/or behavioral problems were significantly less often present following C+T administration. Excitation, hyperactivity and/or behavioral disorder was the only adverse reaction expressed in high BMI and only reported in the youngest age category following either treatment (table 2). None of the parents contacted us after leaving the outpatient clinic.

Table 2 Number and calculated percentages of clustered adverse reactions stratified by cycloplegic eye drop treatment and their distribution across age- and BMI categories.

		C+C							
				3 to 6 years		7 to10 years		11 to14 years	
Complaint		n	AR[a] n(%)	n	AR[a] n(%)	n	AR[a] n(%)	n	AR[a] n(%)
Severe or moderate drowsiness[b]		408	22 (5.4)	163	18 (11.0)	158	2 (1.3)	87	2 (2.3)
Mild drowsiness or apathy[b]		408	10 (2.5)	163	9 (5.5)	158	1 (0.6)	87	0
Excitation, hyperactivity and/or behavioral problems[b]		408	6 (1.5)	163	6 (3.7)	158	0	87	0
Dizzyness[b]		408	2 (0.5)	163	0	158	0	87	2 (2.3)
Red cheeks or face (feverish, flushing)[c]		408	2 (0.5)	163	1 (0.6)	158	1 (0.6)	87	0
Nose bleeding[c]		408	0	163	0	158	0	87	0
	BMI								
Severe or moderate drowsiness	Low BMI	18	13 (72.2)	13	11 (84.6)	3	1 (33.3)	2	1 (50.0)
	Normal BMI	292	9 (3.1)	125	7 (5.6)	104	1 (1.0)	63	1 (1.6)
	High BMI	98	0	25	0	51	0	22	0
Mild drowsiness or apathy	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	10 (3.4)	125	9 (7.2)	104	1 (1.0)	63	0
	High BMI	98	0	25	0	51	0	22	0
Excitation, hyperactivity and/or behavioral problems	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	5 (1.7)	125	5 (4.0)	104	0	63	0
	High BMI	98	1 (1.0)	25	1 (4.0)	51	0	22	0
Dizzyness	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	2 (2.0)	125	0	104	0	63	2 (3.2)
	High BMI	98	0	25	0	51	0	22	0
Red cheeks or face (feverish, flushing)	Low BMI	18	0	13	0	3	1 (33.3)	2	0
	Normal BMI	292	2 (2.0)	125	1 (0.8)	104	0	63	0
	High BMI	98	0	25	0	51	0	22	0
Nose bleeding	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	0	125	0	104	0	63	0
	High BMI	98	0	25	0	51	0	22	0
		C+T							
				3 to 6 years		7 to10 years		11 to14 years	
Complaint		n	AR[c] n(%)	n	AR[c] n(%)	n	AR[c] n(%)	n	AR[c] n(%)
Severe or moderate drowsiness[d]		504	8 (1.6)	200	6 (3.0)	191	1 (0.5)	113	1 (0.9)
Mild drowsiness or apathy[d]		504	11 (2.2)	200	4 (2.0)	191	5 (2.6)	113	2 (1.8)
Excitation, hyperactivity and/or behavioral problems[d]		504	3 (0.6)	200	3 (1.5)	191	0	113	0
Dizzyness[d]		504	0	200	0	191	0	113	0
Red cheeks or face (feverish, flushing)[e]		504	1 (0.2)	200	1 (0.5)	191	0	113	0
Nose bleeding[e]		504	1 (0.2)	200	1 (0.5)	191	0	113	0
	BMI								
Severe or moderate drowsiness	Low BMI	29	5 (17.2)	14	3 (21.4)	9	1 (11.1)	6	1 (16.7)
	Normal BMI	366	3 (8.2)	157	3 (1.9)	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Mild drowsiness or apathy	Low BMI	29	5 (17.2)	14	1 (7.1)	9	2 (22.2)	6	2 (33.3)

	Normal BMI	366	6 (1.6)	157	3 (1.9)	129	3 (2.3)	80	0
	High BMI	109	0	29	0	53	0	27	0
Excitation, hyperactivity and/or	Low BMI	29	0	14	0	9	0	6	0
behavioral problems	Normal BMI	366	2 (0.6)	157	2 (1.3)	129	0	80	0
	High BMI	109	1 (0.9)	29	1 (3.0)	53	0	27	0
Dizzyness	Low BMI	29	0	14	0	9	0	6	0
	Normal BMI	366	0	157	0	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Red cheeks or face (feverish, flushing)	Low BMI	29	0	14	0	9	0	6	0
	Normal BMI	366	1 (0.3)	157	1 (0.6)	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Nose bleeding	L-BMI	29	0	14	0	9	0	6	0
	N-BMI	366	1 (0.3)	157	1 (0.6)	129	0	80	0
	H-BMI	109	0	29	0	53	0	27	0

[a] *C+C: Two drops of cyclopentolate 1%*

[b] *C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[c] *AR: Adverse reactions*

[d] *CNS adverse reactions*

[e] *Peripheral adverse reactions*

Relation of adverse reactions with sex, BMI, ethnicity and age.

Neither sex nor ethnicity was related with adverse reactions (table 3). In both interventions low BMI subjects had a statistically highly significantly increased risk for adverse reactions, however the odds ratio for adverse reactions was significantly higher in C+C compared to C+T (table 3). In both treatment groups the frequency of adverse reactions was highest in the youngest age group. Only in C+C younger age was associated with a statistically highly significantly increased risk for adverse reactions (table 3). A borderline significance; p=0.06 instead of p<0.05, however was present in C+T. Furthermore, in both interventions for all age categories, adverse reactions were more frequently reported in children with low BMI compared to those with normal BMI (table 3).

Table 3 Frequencies, percentages and crude odds ratios of adverse reactions with respect to sex, BMI, ethnicity and age category stratified by cycloplegic eye drop treatment.

	C+C[a]				C+T[b]			
	n	n (%) AR[c]	Crude OR[d] 95% CI[e]	P value	n	n (%) AR[c]	Crude OR[d] 95% CI[e]	P value
	408	42 (10.3)			504	24 (4.8)		
Sex	408	42			504	24		
Male	207	25 (12.1)	1[f]		260	12 (4.6)	1[f]	
Female	201	17 (8.5)	0.7 (0.4 to1.3)	0.23	244	12 (4.9)	0.9 (0.4 to 2.1)	0.87
BMI category	408	42			504	24		
Low BMI	18	13 (72.2)	24.5 (8.1 to 73.8)	<0.001	29	10 (34.5)	14.3 (5.6 to 36.8)	<0.001
Normal BMI	292	28 (9.6)	1[f]		366	13 (3.6)	1[f]	
High BMI	98	1 (1.0)	0.1 (0.01 to 0.7)	0.02	109	1 (0.9)	0.3 (0.03 to 1.9)	0.19
Ethnic main group	359	39 (10.9)			437	21 (4.9)		
Dutch	110	13 (11.8)	1[f]		137	6 (4.4)	1[f]	
Moroccan	81	10 (12.3)	1.1 (0.4 to 2.5)	0.91	107	5 (4.7)	1.1 (0.3 to 3.6)	0.91
Turkey	71	5 (7.0)	0.6 (0.2 to 1.7)	0.30	86	4 (4.7)	1.1 (0.3 to 3.9)	0.92
Indian-subcontintent	68	10 (14.7)	1.3 (0.5 to 3.1)	0.58	73	5 (6.8)	1.6 (0.5 to 5.5)	0.45
Negro	29	1 (3.4)	0.3 (0.03 to 2.1)	0.21	34	1 (2.9)	0.7 (0.08 to 5.7)	0.71
Other	49	3 (6.1)	0.5 (0.1 to 1.8)	0.28	67	3 (4.5)	1.0 (0.3 to 4.2)	0.97
Age category	408	42			504	24		
3 to 6 year	163	34 (20.9)	10.2 (3.5 to 29.4)	<0.001	200	15 (7.5)	2.5 (0.95 to 6.6)	0.06
7 to10 year	158	4 (2.5)	1[f]		191	6 (3.1)	1[f]	
11 to14 year	87	4 (4.6)	1.9 (0.5 to 7.6)	0.39	113	3 (2.7)	0.8 (0.2 to 3.4)	0.81
Age category 3 to 6	163	34			200	15		
Low BMI	13	11 (84.6)			14	4 (28.6)		
Normal BMI	125	22 (17.6)			157	10 (6.4)		
High BMI	25	1 (4.0)			29	1 (3.4)		
Age category 7 to10	158	4			191	6		
Low BMI	3	1 (33.3)			9	3 (33.3)		
Normal BMI	104	3 (2.9)			129	3 (2.3)		
High BMI	51	0			53	0		
Age category 11 to14	87	4			113	3		
Low BMI	2	1 (50.0)			6	3 (50.0)		
Normal BMI	63	3 (4.8)			80	0		
High BMI	22	0			27	0		

[a] *C+C: Two drops of cyclopentolate 1%*

[b] *C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[C] *AR: Adverse reactions*

[d] *OR: Odds ratio*

[e] *CI: Confidence Interval*

[f] *1: Reference group*

Relation of adverse reactions with dose of cyclopentolate, BMI and age.

For children receiving C+C there was a significantly increased overall risk for adverse reactions compared to those receiving C+T (OR 2.3 [1.4-3.9]; table 4). In a forward model we explored the influence of the variables BMI, age, ethnicity and sex on the odds ratio for treatment. Only BMI was found to have a significant influence (table 4).

Table 4 Odds ratio for reporting adverse reactions for treatment, and stepwise adjustment of this odds ratio with BMI, age, ethnicity and sex.

Step	Factors	OR[a] + 95% CI[b]	P value
1	Treatment	2.3 (1.4 to 3.9)	0.002
2	Treatment + BMI [cat]	3.1 (1.7 to 5.6)	<0.001
3	Treatment + BMI [cat] + Age [cat]	3.0 (1.6 to 5.5)	<0.001
4	Treatment + BMI [cat] + Age [cat] + Ethnicity [cat]	3.0 (1.6 to 5.5)	<0.001
5	Treatment + BMI [cat] + Age [cat] + Ethnicity [cat] + Sex [cat]	3.0 (1.5 to 5.4)	<0.001

[a]*OR: Odds ratio*

[b]*CI: Confidence Interval*

Our analysis indicated that the dosage of cyclopentolate saw the most adverse reactions when administered to young children with low BMI. These relations were explored in more detail. Table 5 shows the unadjusted, crude, odds ratios for reporting adverse reactions per BMI category and regime, with normal BMI subjects receiving C+C as reference group in a multivariate model. Following adjustment for gender, ethnicity and age, dose of cyclopentolate remained highly significantly associated with adverse reactions. We also explored age category and regime (table 5). Following adjustment for gender, ethnicity and BMI, dose of cyclopentolate was associated with adverse reactions in the youngest subjects.

Table 5 Odds ratios for reporting adverse re actions per BMI category respectively age category and regime, with normal BMI respectively 7 to 10 year old children receiving C+C[a] as reference group; backwards analysis.

Regime	BMI	Crude OR[c] (95% CI)[d]	P value	Adjusted[e] OR[c] (95% CI)[d]	P value
C+C[a]	High	0.1 (0.01 to 0.7)	0.02	0.1 (0.02 to 0.9)	0.04
	Normal	1[e]		1[e]	
	Low	24.6 (8.2 to74.1)	<0.001	21.4 (6.7 to 67.96)	<0.001
C+T[b]	High	0.09 (0.01 to 0.7)	0.02	0.1 (0.01 to 0.8)	0.03
	Normal	0.35 (0.2 to 0.7)	0.02	0.34 (0.2 to 0.7)	0.02
	Low	4.98 (2.1 to 11.8)	<0.001	5.2 (2.1 to 12.8)	<0.001

Regime	Age	Crude OR[c] (95% CI)[d]	P value	Adjusted[f] OR[c] (95% CI)[d]	P value
C+C[a]	11 to 14	1.8 (0.4 to 7.4)	0.41	0.17 (0.4 to 7.4)	0.48
	7 to 10	1[e]		1[e]	
	3 to 6	10.2 (3.5 to 29.5)	<0.001	8.1 (2.7 to 24.8)	<0.001
C+T[b]	11 to 14	1.1 (0.2 to 4.9)	0.92	0.7 (0.1 to 3.5)	0.66
	7 to 10	1.3 (0.4 to 4.6)	0.72	0.9 (0.2 to 3.5)	0.88
	3 to 6	3.1 (1.0 to 9.7)	0.046	1.97 (0.6 to 6.5)	0.26

[a]*C+C: Two drops of cyclopentolate 1%*

[b]*C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[c]*OR: Odds ratio*

[d]*CI: Confidence Interval*

[e]*1: Reference group*

[f]*Adjusted for sex (cat), age (cat) and ethnicity (cat)*

[g]*Adjusted fot sex (cat), BMI (cat) and ethnicity (cat)*

DISCUSSION

This study showed that adverse reactions following cycloplegic eye drops are common in children. Adverse reactions were highest following the administration of a double dose of cyclopentolate to young children with a low BMI. Adverse reactions were virtually absent in subjects with high BMI. Our data suggest a dose response mechanism.

Interpretation of findings.

One objective of this study was to gain more insight in the nature of the adverse reactions. All adverse reactions reported were expected adverse reactions; they were observed and documented previously. Drowsiness was the most frequently reported adverse reaction. According to the international guidelines of the Council of International Organizations of Medical Sciences the rate of both severe and mild drowsiness can be classified as "commonly present" (≥1% and <10%).[23] For a double dose of cyclopentolate 1%, the severe to moderate drowsiness rate as reported in the youngest age category, can even be classified as "very commonly" present (≥10%).[23] Furthermore, regardless the amount of cyclopentolate, severe to moderate drowsiness was very commonly present in low BMI subjects of all age categories. Worldwide only a limited number of companies produce cyclopentolate 1% and tropicamide 1%. In general manufacturers provide a summary of product characteristics for the individual countries.[24-37] The summaries of product characteristics give a wide variety of possible central effects. CNS involvement in children is mentioned as being uncommon[24,25] or rare[24]; e.g. present in >0.1% but <1%.[23] Drowsiness is mentioned in few, but without any further reference to the frequency.[27,28] An increased risk for adverse reactions is identified for infants and young children, but no statements are made about the risks for low weight subjects in the documents we studied.

In addition to classification by frequency, adverse reactions can also be classified by severity. The Common Terminology Criteria for Adverse Events grades adverse reactions according to a System Organ Class.[38] This system has 5 levels of grading; where grade 1 represents mild symptoms, grade 2 represents moderate symptoms up to grade 5, representing death related to the adverse reaction. The adverse reactions reported in our survey mainly belong to the "nervous system disorders". Dizziness, hyperactivity and/or behavioral problems, and mild drowsiness or apathy are classified as grade 1 adverse reactions. Severe or moderate drowsiness are classified as grade 2 adverse reactions. The peripheral adverse reactions reported are all grade 1 adverse reactions. A significant difference between the interventions was present. A double dose of cyclopentolate had 52.4% grade 2 adverse reactions while one dose of cyclopentolate had 33.3%.

The present study showed that adverse reactions were present in 4.8% and 10.3% of children receiving one dose versus two doses of cyclopentolate 1%. Both rates and the 2.2 fold difference in rate is in concordance with Bagheri and colleagues.[6] Our findings support their statement that the incidence of adverse reactions increases with

repeated installation of cyclopentolate. The reported adverse reactions in our study almost exclusively involved the CNS. This is not in line with a report of Pi and colleagues.[39] Although not reporting actual rates, they mention eye irritation and conjunctival hyperemia as the most common adverse reactions in a large cohort of six to fifteen year old subjects receiving 3 drops of cyclopentolate 1%. In our study we focused on all unwanted reactions without influencing patients and/or parents beforehand by providing a specified list. This might have given an underestimation of minor unwanted effects. The complaints reported by Pi and colleagues[39] were expected effects immediately following eye drop application. They generally subside quite quickly and might have been forgotten at the time of our inquiry.

Worldwide tropicamide and cyclopentolate have been used for decades. The lack of adverse reactions following tropicamide is acknowledged and well described. Although an effect of tropicamide on adverse reactions cannot be ruled out, we believe that the adverse reactions can only be attributed to cyclopentolate. The frequent involvement of the CNS following instillation of cyclopentolate is in line with the literature.[7-9] Drowsiness was the most frequently reported adverse reaction, followed by excitation and hyperactivity and/or behavioral changes. The factor 3.4 higher rate of severe to moderate drowsiness and the factor 2.5 higher rate of excitation and hyperactivity and/or behavioral problems in a double dose of cyclopentolate compared to a single dose of cyclopentolate are more evidence for the impact of cyclopentolate.

Our study shows that adverse reactions occurred most frequently in young- and low BMI subjects. In general one can state that young children have an increased risk for drug related adverse events. The dose relative to blood volume and body weight is greater compared to adults.[8, 40-42] Children have a higher cutaneous blood flow and tissues are less dense; thus absorption may be more profound and rapid.[41,42] Children have a limited serum protein binding capacity.[41,42] The smaller the protein binding capacity, the greater the availability of the drug in the blood plasma. Metabolic systems and organs are immature and clearing is slower, resulting in a prolonged half-life.[41,42] In subjects with low BMI the dose relative to blood volume and body weight is higher compared to subjects with normal and high BMI.

Children have a large brain mass in relation to body volume and a higher blood brain barrier permeability than adults, thereby facilitating CNS adverse reactions.[42,43] The thalamus plays an important role in regulating states of sleep, wakefulness, attention and alertness. The hippocampus is involved in memory, spatial navigation and inhibition. Hippocampal dysfunction is associated with poor impulse control, hyperactivity, behavioral changes and disorientation.[44] It seems likely that these areas play a role in the central effects of cyclopentolate. The high incidence of reported adverse reactions especially in the youngest children of our study supports the hypothesis that immaturity of the CNS plays a key role in cyclopentolate's potency for adverse reactions.

In this study adverse reactions were mostly present in the youngest children. However in the children in puberty a considerable amount of adverse reactions were still reported. Although no longer immature, the hormonal changes, rapid restructuration of the brain and the increased physical growth might explain the relatively high susceptibility for cyclopentolate in puberty.[39-41]

Oral consent was obtained from all children and parents. The procedure of consent was carefully considered. The Dutch Agreement on the Medical Treatment Act justified oral consent since the additional length and weight measurements can be considered to cause insignificant burden and no risk. Also the Dutch Central Committee on Research Involving Human Subjects agreed that no written consent was required. Furthermore, a written informed consent procedure would have interfered with the observational character of the study and would have biased the results regarding adverse reactions following the standard cycloplegic treatment.

Study limitations.

Our observational study has several potential limitations.1) We realize that an actual dose response relationship could only be determined with plasma concentrations using intravenous measurements of the dose. But this is not feasible in an observational design and more importantly to invasive for children. If a regime with one dose and three doses of cyclopentolate were added to this observational study we might have established a dose response relationship in the more true sense. These regimes however are infrequently used by our staff. Despite the limitations, we feel we have found enough evidence to state there is an indication of "a dose response mechanism". 2) Despite the apparent lack of adverse reactions with regards to tropicamide in the literature, a tropicamide effect could only have been ruled out if a regime using one drop of tropicamide 1% was admitted in this survey. Again, such a regime in infrequently used. 3) The design of this study did not allow determination of the exact time of onset of the adverse reaction, but an onset of approximately 15 to 30 minutes after leaving the examining room was reported in both regimes. We did not gather information on the duration of the reported adverse reactions. However all effects were still present at departure of the subject from our department, indicating that the adverse reactions lasted at least 45 to 60 minutes after onset. None of the parents contacted us after leaving the outpatient clinic. This could be considered an indication that all adverse reactions had disappeared after this time period. 4) Although the examiner was unaware of the BMI status of the subjects, clinical observations might unconsciously have influenced their inquiries, which might have resulted in an observer bias. However the open question technique should have eliminated such an effect. 5) Besides age and BMI there are more variables influencing the amount of active compound a subject might receive; such as firmly squeezing the eyelids or crying of the subject, thereby reducing the amount of active compound one receives. We did not take these variables into account. 6) Treatment with either a single or double dose of cyclopentolate was not randomized. However the individual orthoptists of this study had their fixed preference for one of the two regimes, and subjects were planned for examination several weeks prior by

administration staff who were unaware of the treatment regimes administered. As such, this can be considered as pseudo-randomisation.[45] 7) Finally, some sub-groups comprised a limited amount of subjects. This could have influenced outcomes; both in rates and subsequent analyses.[10] The questioning technique used ensured prevention of provoked adverse reactions reports. Furthermore, the results of the 95% CI limits enable generalisation to the population.

Conclusions and implications for healthcare professional and policymakers.

Although cyclopentolate 1% generally can be considered to be a safe cycloplegic, the high incidence of adverse events following cyclopentolate in young, low BMI children poses the question whether it is acceptable to use cyclopentolate in a setting without facilities to monitor vital functions. This study provides evidence for a dose response mechanism with the occurrence of adverse reactions. Both presence and severity of adverse reactions are increased in low BMI, young age and in repeated installation of cyclopentolate 1%. The results of this survey can be generalized to the population. As a result of this survey we changed our departmental guidelines for use of cyclopentolate 1%. In young, low BMI subjects the increased risk for drowsiness should be taken into account. In this category of children assessment should be performed with use of a single dose of cyclopentolate, and if necessary combined with tropicamide 1%. Adverse reactions, especially severe drowsiness, were far less common following this regime. With increasing age and increasing BMI, a double dose of cyclopentolate can be administered safely. When a double dose of cyclopentolate 1% is necessary in young and/or low BMI subjects, e.g. children up to at least 6 years of age and low BMI subjects of all ages, the objective refraction should be performed in a hospital setting, or at least in a location where vital functions can be monitored. We propose to make adjustments in the (inter)national guidelines for objective refraction in children. This advice would be especially applicable for settings without facilities to monitor vital functions. This survey shows once again that cyclopentolate is a potent drug that can cause moderate adverse reactions to the CNS in children. For young children and children with a low BMI, the risk of a seriously adverse reaction is rare; however the possibility of an occurrence should always be taken into consideration. Finally, we recommend general adjustment of product documentation.

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writing. DG was involved with data abstraction, data analysis and especially in data interpretation and writing. NESD was involved with data interpretation and editing the manuscript for important intellectual content. She is the guarantor. All authors had full access to the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis prepared the initial manuscript drafts, which were subsequently edited by all authors. All authors agreed to submission.

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Data sharing: No additional data available.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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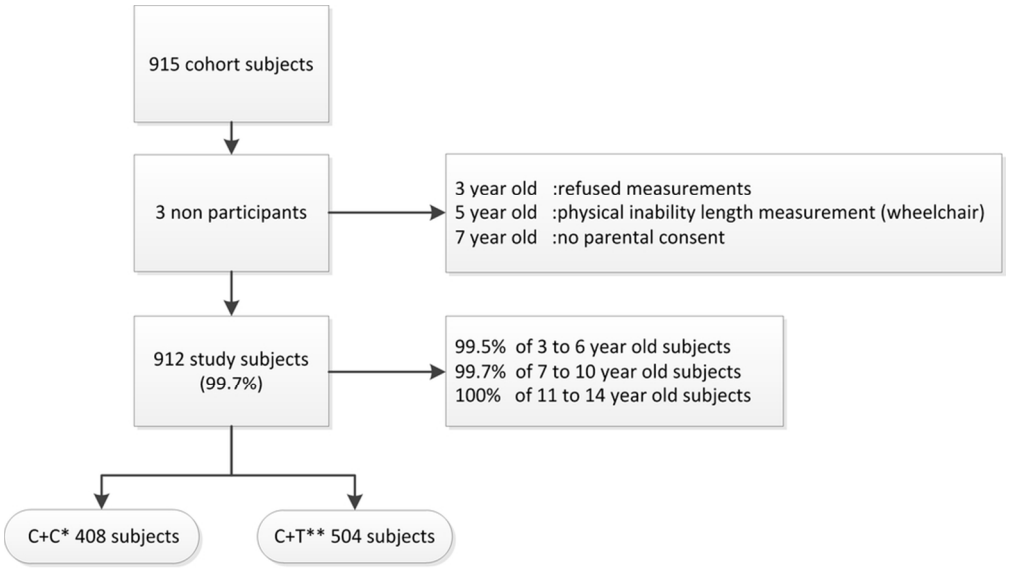

*C+C: Two drops of cyclopentolate 1%
**C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%

87x49mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Manuscript	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	X	Title; page 1 Abstract; page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	X	Page 2
Introduction				
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	X	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses		Page 4
Methods				
Study design	4	Present key elements of study design early in the paper	X	Page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X	Page 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	X	Page 4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X	Page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X	Page 5
Bias	9	Describe any efforts to address potential sources of bias	X	Page 5
Study size	10	Explain how the study size was arrived at	X	Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X	Page 5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	X	Page 5 and 6
		(*b*) Describe any methods used to examine subgroups and interactions	X	Page 6
		(*c*) Explain how missing data were addressed	n.a.	
		(*d*) If applicable, explain how loss to follow-up was addressed	n.a.	
		(*e*) Describe any sensitivity analyses	n.a.	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X	Page 6 and 7

		(b) Give reasons for non-participation at each stage	X	Page 6
		(c) Consider use of a flow diagram	X	Page 6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	X	Page 7
		(b) Indicate number of participants with missing data for each variable of interest	n.a.	
		(c) Summarise follow-up time (eg, average and total amount)	n.a.	
Outcome data	15*	Report numbers of outcome events or summary measures over time	X	Page 7-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X	Page 7-11
		(*b*) Report category boundaries when continuous variables were categorized	X	Page 7-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	X	Page 7-12
Discussion				
Key results	18	Summarise key results with reference to study objectives	X	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X	Page 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X	Page 13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	X	Page 16
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X	Page 17

*Give information separately for exposed and unexposed groups.

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Adverse reactions following routine anticholinergic eye drops in a paediatric population: an observational cohort study.

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Adverse reactions following routine anticholinergic eye drops in a paediatric population: an observational cohort study.

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ABSTRACT

Objectives To investigate the presence, nature and relationship to age, sex, ethnicity and body mass index (BMI) of adverse reactions following routine cycloplegic eye drops in children.

Design Prospective observational cohort study.

Setting Ophthalmology outpatient clinic Dutch metropolitan hospital; February, March and April 2009.

Participants 3 to14 year old children receiving two drops of cyclopentolate 1% (C+C) or one drop of cyclopentolate 1% and one drop of tropicamide 1% (C+T). Patients were categorised by age (3 to 6, 7 to 10 and 11 to 14 years), sex, ethnicity and BM (low, normal or high).

Outcome measures Rate and nature of adverse reactions reported at 45 minutes following treatment. Crude and adjusted odds ratios (OR) for reporting an adverse reaction using stepwise regression analysis with BMI, age, ethnicity and sex.

Results 912 of 915 eligible patients participated (99.7%). Adverse reactions were reported for C+C in 10.3% and in C+T in 4.8% (42/408 and 24/504, p=0.002). Central effects were present in 95% (C+C) respectively 92% (C+T). Compared to C+T an increased risk was present in C+C (crude OR 2.3 [1.4 to 3.9], p=0.002). Forward adjustment showed BMI to be an influencing factor in treatment (OR 3.1 [1.7 to 5.6], p<0.001). In a multivariate model, dose of cyclopentolate remained associated with adverse reactions. Analysis per BMI- respectively age category and regime, indicated associations with low BMI (OR C+C 21.4 [6.7 to 67.96], p<0.001 respectively C+T 5.2 [2.1 to 12.8], p<0.001) and young age (OR C+C 8.1 [2.7 to 24.8], p<0.001).

Conclusions Adverse reactions were common and almost exclusively involved the central nervous system. Both presence and severity were associated with repeated installation of cyclopentolate 1%, low BMI and young age. In specific paediatric populations a single dose of cyclopentolate must be considered. Vital function monitoring facilities are advisable. Adjustment of guidelines is recommended.

Strengths and limitations of this study

- This study investigated presence and nature of adverse reactions in commonly used cycloplegic regimes and determined risk factors.
- Evidence for a dose response mechanism is provided.
- Observer bias could not be ruled out completely.
- Some sub-groups comprised a limited number of subjects.
- This study warrants a critical approach to the use of cyclopentolate 1% in specific paediatric populations and adjustment of guidelines and product documentation.

INTRODUCTION

In children, refractive errors can cause decreased visual acuity and problems in binocularity such as strabismus. Due to strong accommodative reflexes and the inability to respond reliably to subjective refraction, objective refraction in children is required to assess their refractive state. Objective refraction can only be obtained with cycloplegia through anticholinergic eye drops. Cyclopentolate 1% and tropicamide 1% are both commonly used anticholinergic eye drops for objective refraction in the paediatric population. Depending on ocular alignment, the (expected) refractive error and iris colour, cyclopentolate will be applied once, twice or three times[1]. In subjects with darker irises a combination with tropicamide is often required.[1] The use of anticholinergic eye drops in children is generally considered to be safe.[1,2] Severe adverse reactions following administration are very rare.[2] With regards to tropicamide, the literature agrees that it provokes rarely adverse reactions.[1,3-5] Adverse reactions following the application of cyclopentolate are more common and could be dose related.[6] Young children are most at risk.[1] The adverse reactions occur between 15 to 60 minutes following on administration, often impact the central nervous system (CNS), but subside within 2-6 hours with no permanent sequelae.[7-9] Anticholinergic CNS adverse reactions include; psychotic reactions and behavioural disturbances, ataxia, incoherent speech, restlessness, hallucinations, hyperactivity or drowsiness, seizures, disorientations as to time and place and failure to recognize people.[1] Peripheral anticholinergic adverse reactions include; urinary retention, diminished gastrointestinal motility, tachycardia, hyperpyrexia, vasodilation, skin rash, decreased secretion in salivary and sweat glands, pharynx, bronchi and nasal passages.[1]

For reports on rates and nature of the milder adverse reactions one can only refer to the rates encountered during surveys or efficacy studies. For rates on adverse reactions we searched in larger sample sized studies since the rates of small sample sized studies cannot be extrapolated to the general population.[10] With regards to tropicamide, several very large surveys report an absence of adverse reactions.[3-5] A study of Bagheri and colleagues[6] involving 96 six to twenty year old subjects, reports an adverse reaction rate of 5%, 11% and 24% after one dose, a double dose and a triple dose of cyclopentolate 1%. In contrast, a smaller study of Mohan and Sharma[11] observed the absence of ocular or systemic side effects in a similar population receiving the same treatment regimes. Although Bagheri and colleagues[6] report adverse reaction rates, they do not specify the nature of these adverse reactions. A study of Egashira and colleagues[12] involving 20 six to twelve year old subjects, reports one subject with drowsiness and two subjects with hyperactivity, of whom one also suffered from visual hallucinations, following one dose of cyclopentolate 1%.

In young children, about 5 to 9% need objective refraction because of failure in vision screenings programs due to either strabismus or decreased visual acuity.[13,14] With older children and children in puberty visual acuity complaints increases up to 14%.[15-19] A relatively large part of this group requires objective refraction to assess their refraction.

Depending on the health care arrangements of individual countries the objective measurement of refraction is performed in hospitals or health care centers, as well as in local optometric practices. The latter usually do not have facilities to monitor vital functions. In our Dutch metropolitan hospital ophthalmology outpatient clinic with an ethnically diverse population we use routinely either a double dose of cyclopentolate 1% (C+C) or one dose of cyclopentolate 1% followed by one dose of tropicamide 1% (C+T). Adverse reactions following both regimes are seen, but a larger number of adverse reactions were encountered using C+C. Besides an apparent association with regime, our observations also suggested a possible correlation with younger age and/or lower body mass index (BMI). The available literature does not provide sufficient evidence to show the presence and nature of adverse reactions and relating factors. This survey does not address the reason for the choice of, or the effectiveness of, the departmental routinely used regimes. However both regimes are commonly used worldwide.[1] The purpose of this study was to gain more insight into the presence and nature of adverse reactions following administration of C+C and C+T for objective refraction assessment in children. A secondary aim was to investigate whether the frequency of adverse reactions was associated with age and/or BMI.

METHODS

This study was designed as a prospective, single-centre, cross-sectional and observational cohort study. The study group investigators were research assistants and 4 orthoptists. The study population were all patients between 3 and 14 years who required an objective refraction at our ophthalmology department during February, March and April 2009. The study period of three months was chosen because of the high return rate of our subjects after this three month period. The lower limit of 3 year was chosen because of cooperation problems associated with length and weight measurements below this 3 year age limit. Furthermore possible adverse reactions might not be distinguishable from common sleepiness or behavioural problems due to normal wake/sleep patterns seen in children below this age. The upper limit of 14 years was chosen because there are a limited number of patients requiring an objective refraction beyond this age. Treatment was given in accordance with standard departmental protocol. The orthoptists were not restricted in their choice of medication and used their normal individual regime to assess objective refraction with either C+C or C+T.

Ethical considerations

The study was conducted according to the principles of the Declaration of Helsinki (version 59th WMA General Assembly, Seoul, Republic of Korea, October 2008) the Dutch Agreement on Medical Treatment Act (WBGO) and the Dutch Personal Data Protection Act. The Medical Research Involving Human Subjects Act (WMO) did not apply to this study according to the Dutch Central Committee on Research Involving Human Subjects (CCMO, The Hague) and therefore a written waiver of the CCMO was provided. All parents and children were asked if they would participate in an observational survey where length and weight measurements would be recorded to establish if

there was the need to develop new departmental guidelines for the eye examination of children. Information on the aims of the survey e.g. investigation of presence and nature of adverse reactions and related factors, was given. Subsequently oral consent to participate in this observational survey was asked of both parents and children. The parents and children were free to refuse to participate in the survey. Both oral explanation as well as length and weight measurements were conducted upon arrival at our department.

Procedures

The participating subjects were numbered consecutively. Length and weight were determined. BMI was calculated according to the formula: BMI= Weight/height. Subjects were divided between three categories: low BMI, normal BMI or high BMI, according to the international cut off values for under- and overweight by sex between 2 and 18 years.[20,21] For South Asian subjects cut-off values according to the guidelines of Wilde et al[22] were used. Subjects were allocated to the following ethnic main groups: Dutch, Turkish, Moroccan, Indian-subcontinental (including Indian, Pakistani and Surinam-Hindoestani) or Black West-African (including Black African of the African Gold Coast, Black subjects from both the Dutch Antilles and Surinam). Remaining subjects were assigned to category "Other". Subjects were also subdivided into three age categories; 3 to 6, 7 to10 or 11 to14 years. A case record form with the designated number of each subject was added to the outpatient chart. The examining orthoptist noted either no drops, C+C or C+T on this form. For children receiving eye drops the examining orthoptist made enquiries approximately 45 minutes following the first eye drop. The parents and children were asked "did you notice anything different following the eye drops". Any responses relating to blurred vision and/or photophobia were excluded. All other responses were noted. Adverse reactions were classified as, severe to moderate drowsiness, mild drowsiness or apathy, excitation & hyperactivity and/or behavioral problems, dizziness, red face and/or cheeks and/or nose bleeding. A further classification was recorded as being either a "central (CNS)" or "peripheral" adverse reaction in accordance with the list provided in the first paragraph of the introduction of this manuscript. Parents were instructed to contact us if adverse reactions did not disappear within 4 hours.

Bias

To avoid treatment bias the examining orthoptist was kept unware of the BMI status of the subjects. To avoid response bias from parents and/or children two procedures were followed. Firstly, the length and weight measurements were introduced as being part of a departmental paediatric population survey and this was done to establish if there was a requirement for the development of new departmental guidelines for the eye examination of children. Secondly the inquiries about the adverse reactions were made with an open question technique

Data analysis

Data were analyzed in SPSS 22 for Windows. Differences were considered statistically significant if $p<0.05$; two-sided. A difference of >2% in reported adverse reactions was considered clinically significant. Variables were compared between the treatment C+C and C+T using the independent samples T-test or the X^2- test, as appropriate. Univariate stratified and multivariate logistic regression analyses were performed to assess the impact of variables on the likelihood that a subject would report an adverse reaction. Odds ratios for treatment were calculated without and with adjustment for BMI, age, ethnicity and sex in a forward model. Odds ratios for BMI; for treatment, with normal BMI subjects receiving C+C as reference group, and age; for treatment, with 6 to 10 year old subjects receiving C+C as reference group, unadjusted and adjusted for age, sex and ethnicity respectively sex, ethnicity and BMI were computed in a multivariate backwards model.

RESULTS

912 of 915 eligible patients participated (99.7%; figure 1). 408 received C+C and 504 received C+T (figure 1).

Figure 1 Flow chart diagram showing number of subjects in the cohort and number of subjects participating in the study.

**C+C: Two drops of cyclopentolate 1%*

***C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

Table 1 reflects the baseline group characteristics stratified by regimes C+C and C+T.

Table 1 Baseline characteristics of children who underwent objective refraction assessment stratified by cycloplegic eye drop treatment.

	C+C[a]		C+T[b]		p-value
	n (%)	mean	n (%)	mean	
Total	408 (44.7)		504		
Age in years	408	7.6 ± 3.1	504	7.6 ± 3.1	p=0.997[c]
Sex	408		504		p=0.85[d]
Male	207 (50.7)		260 (51.6)		
Female	201 (49.3)		244 (48.4)		
BMI	408		504		p=0.50[e]
Low BMI	18 (4.4)		29 (5.8)		
Normal BMI	292 (71.6)		366 (72.6)		
High BMI	98 (24)		109 (21.6)		
Ethnicity	408		504		p=0.95[e]
Moroccan	81 (19.9)		107 (21.2)		
Turkish	71 (17.4)		86 (17.1)		
Indian Sub-continent	68 (16.7)		73 (14.5)		
Dutch	110 (27.0)		137 (27.2)		
Chinese	9 (2.0)		12 (2.4)		
Black West-African	29 (7.1)		34 (6.7)		
Other	41 (10.0)		55 (10.9)		
Age category	408		504		p=0.92[e]
3 to 6 years	163 (40.0)		200 (39.7)		
7 to10 years	158 (38.7)		191 (37.9)		
11 to14 years	87 (21.3)		113 (22.4)		

[a] *C+C: Two drops of cyclopentolate 1%*

[b] *C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[c] *Independent Samples T-test*

[d] *X^2-test with Yates Continuity Correction*

[e] *X^2-test*

Adverse reactions; presence and nature.

Adverse reactions were reported in 10.3% (42/408) of children following C+C administration and in 4.8% (24/504) of subjects following C+T administration (p=0.002). Central effects were present in 95.2% (C+C; 40/42) and 91.7% (C+T; 22/24, table 2). Severe to moderate drowsiness was the most frequently reported adverse reaction (5.4%) following C+C administration. It was most often present in children aged 3 to 6 years and predominantly present in children with low BMI (table 2). Reports of severe to moderate drowsiness and excitation, hyperactivity and/or behavioral problems were significantly less often present following C+T administration. Excitation, hyperactivity and/or behavioral disorder was the only adverse reaction expressed in high BMI and only reported in the youngest age category following either treatment (table 2). None of the parents contacted us after leaving the outpatient clinic.

Table 2 Number and calculated percentages of clustered adverse reactions stratified by cycloplegic eye drop treatment and their distribution across age- and BMI categories.

		C+C							
				3 to 6 years		7 to10 years		11 to14 years	
Complaint		n	AR[a] n(%)	n	AR[a] n(%)	n	AR[a] n(%)	n	AR[a] n(%)
Severe or moderate drowsiness[b]		408	22 (5.4)	163	18 (11.0)	158	2 (1.3)	87	2 (2.3)
Mild drowsiness or apathy[b]		408	10 (2.5)	163	9 (5.5)	158	1 (0.6)	87	0
Excitation, hyperactivity and/or behavioral problems[b]		408	6 (1.5)	163	6 (3.7)	158	0	87	0
Dizzyness[b]		408	2 (0.5)	163	0	158	0	87	2 (2.3)
Red cheeks or face (feverish, flushing)[c]		408	2 (0.5)	163	1 (0.6)	158	1 (0.6)	87	0
Nose bleeding[c]		408	0	163	0	158	0	87	0
	BMI								
Severe or moderate drowsiness	Low BMI	18	13 (72.2)	13	11 (84.6)	3	1 (33.3)	2	1 (50.0)
	Normal BMI	292	9 (3.1)	125	7 (5.6)	104	1 (1.0)	63	1 (1.6)
	High BMI	98	0	25	0	51	0	22	0
Mild drowsiness or apathy	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	10 (3.4)	125	9 (7.2)	104	1 (1.0)	63	0
	High BMI	98	0	25	0	51	0	22	0
Excitation, hyperactivity and/or behavioral problems	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	5 (1.7)	125	5 (4.0)	104	0	63	0
	High BMI	98	1 (1.0)	25	1 (4.0)	51	0	22	0
Dizzyness	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	2 (2.0)	125	0	104	0	63	2 (3.2)
	High BMI	98	0	25	0	51	0	22	0
Red cheeks or face (feverish, flushing)	Low BMI	18	0	13	0	3	1 (33.3)	2	0
	Normal BMI	292	2 (2.0)	125	1 (0.8)	104	0	63	0
	High BMI	98	0	25	0	51	0	22	0
Nose bleeding	Low BMI	18	0	13	0	3	0	2	0
	Normal BMI	292	0	125	0	104	0	63	0
	High BMI	98	0	25	0	51	0	22	0
		C+T							
				3 to 6 years		7 to10 years		11 to14 years	
Complaint		n	AR[c] n(%)	n	AR[c] n(%)	n	AR[c] n(%)	n	AR[c] n(%)
Severe or moderate drowsiness[d]		504	8 (1.6)	200	6 (3.0)	191	1 (0.5)	113	1 (0.9)
Mild drowsiness or apathy[d]		504	11 (2.2)	200	4 (2.0)	191	5 (2.6)	113	2 (1.8)
Excitation, hyperactivity and/or behavioral problems[d]		504	3 (0.6)	200	3 (1.5)	191	0	113	0
Dizzyness[d]		504	0	200	0	191	0	113	0
Red cheeks or face (feverish, flushing)[e]		504	1 (0.2)	200	1 (0.5)	191	0	113	0
Nose bleeding[e]		504	1 (0.2)	200	1 (0.5)	191	0	113	0
	BMI								
Severe or moderate drowsiness	Low BMI	29	5 (17.2)	14	3 (21.4)	9	1 (11.1)	6	1 (16.7)
	Normal BMI	366	3 (8.2)	157	3 (1.9)	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Mild drowsiness or apathy	Low BMI	29	5 (17.2)	14	1 (7.1)	9	2 (22.2)	6	2 (33.3)

	Normal BMI	366	6 (1.6)	157	3 (1.9)	129	3 (2.3)	80	0
	High BMI	109	0	29	0	53	0	27	0
Excitation, hyperactivity and/or	Low BMI	29	0	14	0	9	0	6	0
behavioral problems	Normal BMI	366	2 (0.6)	157	2 (1.3)	129	0	80	0
	High BMI	109	1 (0.9)	29	1 (3.0)	53	0	27	0
Dizzyness	Low BMI	29	0	14	0	9	0	6	0
	Normal BMI	366	0	157	0	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Red cheeks or face (feverish, flushing)	Low BMI	29	0	14	0	9	0	6	0
	Normal BMI	366	1 (0.3)	157	1 (0.6)	129	0	80	0
	High BMI	109	0	29	0	53	0	27	0
Nose bleeding	L-BMI	29	0	14	0	9	0	6	0
	N-BMI	366	1 (0.3)	157	1 (0.6)	129	0	80	0
	H-BMI	109	0	29	0	53	0	27	0

[a] *C+C: Two drops of cyclopentolate 1%*

[b] *C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[c] *AR: Adverse reactions*

[d] *CNS adverse reactions*

[e] *Peripheral adverse reactions*

Relation of adverse reactions with sex, BMI, ethnicity and age.

Neither sex nor ethnicity was related with adverse reactions (table 3). In both interventions low BMI subjects had a statistically highly significantly increased risk for adverse reactions, however the odds ratio for adverse reactions was significantly higher in C+C compared to C+T (table 3). In both treatment groups the frequency of adverse reactions was highest in the youngest age group. Only in C+C younger age was associated with a statistically highly significantly increased risk for adverse reactions (table 3). A borderline significance; p=0.06 instead of p<0.05, however was present in C+T. Furthermore, in both interventions for all age categories, adverse reactions were more frequently reported in children with low BMI compared to those with normal BMI (table 3).

Table 3 Frequencies, percentages and crude odds ratios of adverse reactions with respect to sex, BMI, ethnicity and age category stratified by cycloplegic eye drop treatment.

	C+C[a]				C+T[b]			
	n	n (%) AR[c]	Crude OR[d] 95% CI[e]	P value	n	n (%) AR[c]	Crude OR[d] 95% CI[e]	P value
	408	42 (10.3)			504	24 (4.8)		
Sex	408	42			504	24		
Male	207	25 (12.1)	1[f]		260	12 (4.6)	1[f]	
Female	201	17 (8.5)	0.7 (0.4 to1.3)	0.23	244	12 (4.9)	0.9 (0.4 to 2.1)	0.87
BMI category	408	42			504	24		
Low BMI	18	13 (72.2)	24.5 (8.1 to 73.8)	<0.001	29	10 (34.5)	14.3 (5.6 to 36.8)	<0.001
Normal BMI	292	28 (9.6)	1[f]		366	13 (3.6)	1[f]	
High BMI	98	1 (1.0)	0.1 (0.01 to 0.7)	0.02	109	1 (0.9)	0.3 (0.03 to 1.9)	0.19
Ethnic main group	359	39 (10.9)			437	21 (4.9)		
Dutch	110	13 (11.8)	1[f]		137	6 (4.4)	1[f]	
Moroccan	81	10 (12.3)	1.1 (0.4 to 2.5)	0.91	107	5 (4.7)	1.1 (0.3 to 3.6)	0.91
Turkey	71	5 (7.0)	0.6 (0.2 to 1.7)	0.30	86	4 (4.7)	1.1 (0.3 to 3.9)	0.92
Indian-subcontintent	68	10 (14.7)	1.3 (0.5 to 3.1)	0.58	73	5 (6.8)	1.6 (0.5 to 5.5)	0.45
Negro	29	1 (3.4)	0.3 (0.03 to 2.1)	0.21	34	1 (2.9)	0.7 (0.08 to 5.7)	0.71
Other	49	3 (6.1)	0.5 (0.1 to 1.8)	0.28	67	3 (4.5)	1.0 (0.3 to 4.2)	0.97
Age category	408	42			504	24		
3 to 6 year	163	34 (20.9)	10.2 (3.5 to 29.4)	<0.001	200	15 (7.5)	2.5 (0.95 to 6.6)	0.06
7 to10 year	158	4 (2.5)	1[f]		191	6 (3.1)	1[f]	
11 to14 year	87	4 (4.6)	1.9 (0.5 to 7.6)	0.39	113	3 (2.7)	0.8 (0.2 to 3.4)	0.81
Age category 3 to 6	163	34			200	15		
Low BMI	13	11 (84.6)			14	4 (28.6)		
Normal BMI	125	22 (17.6)			157	10 (6.4)		
High BMI	25	1 (4.0)			29	1 (3.4)		
Age category 7 to10	158	4			191	6		
Low BMI	3	1 (33.3)			9	3 (33.3)		
Normal BMI	104	3 (2.9)			129	3 (2.3)		
High BMI	51	0			53	0		
Age category 11 to14	87	4			113	3		
Low BMI	2	1 (50.0)			6	3 (50.0)		
Normal BMI	63	3 (4.8)			80	0		
High BMI	22	0			27	0		

[a] *C+C: Two drops of cyclopentolate 1%*

[b] *C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[C] *AR: Adverse reactions*

[d] *OR: Odds ratio*

[e] *CI: Confidence Interval*

[f] *1: Reference group*

Relation of adverse reactions with dose of cyclopentolate, BMI and age.

For children receiving C+C there was a significantly increased overall risk for adverse reactions compared to those receiving C+T (OR 2.3 [1.4-3.9]; table 4). In a forward model we explored the influence of the variables BMI, age, ethnicity and sex on the odds ratio for treatment. Only BMI was found to have a significant influence (table 4).

Table 4 Odds ratio for reporting adverse reactions for treatment, and stepwise adjustment of this odds ratio with BMI, age, ethnicity and sex.

Step	Factors	OR[a] + 95% CI[b]	P value
1	Treatment	2.3 (1.4 to 3.9)	0.002
2	Treatment + BMI [cat]	3.1 (1.7 to 5.6)	<0.001
3	Treatment + BMI [cat] + Age [cat]	3.0 (1.6 to 5.5)	<0.001
4	Treatment + BMI [cat] + Age [cat] + Ethnicity [cat]	3.0 (1.6 to 5.5)	<0.001
5	Treatment + BMI [cat] + Age [cat] + Ethnicity [cat] + Sex [cat]	3.0 (1.5 to 5.4)	<0.001

[a]*OR: Odds ratio*

[b]*CI: Confidence Interval*

Our analysis indicated that the dosage of cyclopentolate saw the most adverse reactions when administered to young children with low BMI. These relations were explored in more detail. Table 5 shows the unadjusted, crude, odds ratios for reporting adverse reactions per BMI category and regime, with normal BMI subjects receiving C+C as reference group in a multivariate model. Following adjustment for gender, ethnicity and age, dose of cyclopentolate remained highly significantly associated with adverse reactions. We also explored age category and regime (table 5). Following adjustment for gender, ethnicity and BMI, dose of cyclopentolate was associated with adverse reactions in the youngest subjects.

Table 5 Odds ratios for reporting adverse re actions per BMI category respectively age category and regime, with normal BMI respectively 7 to 10 year old children receiving C+C[a] as reference group; backwards analysis.

Regime	BMI	Crude OR[c] (95% CI)[d]	P value	Adjusted[e] OR[c] (95% CI)[d]	P value
C+C[a]	High	0.1 (0.01 to 0.7)	0.02	0.1 (0.02 to 0.9)	0.04
	Normal	1[e]		1[e]	
	Low	24.6 (8.2 to74.1)	<0.001	21.4 (6.7 to 67.96)	<0.001
C+T[b]	High	0.09 (0.01 to 0.7)	0.02	0.1 (0.01 to 0.8)	0.03
	Normal	0.35 (0.2 to 0.7)	0.02	0.34 (0.2 to 0.7)	0.02
	Low	4.98 (2.1 to 11.8)	<0.001	5.2 (2.1 to 12.8)	<0.001

Regime	Age	Crude OR[c] (95% CI)[d]	P value	Adjusted[f] OR[c] (95% CI)[d]	P value
C+C[a]	11 to 14	1.8 (0.4 to 7.4)	0.41	0.17 (0.4 to 7.4)	0.48
	7 to 10	1[e]		1[e]	
	3 to 6	10.2 (3.5 to 29.5)	<0.001	8.1 (2.7 to 24.8)	<0.001
C+T[b]	11 to 14	1.1 (0.2 to 4.9)	0.92	0.7 (0.1 to 3.5)	0.66
	7 to 10	1.3 (0.4 to 4.6)	0.72	0.9 (0.2 to 3.5)	0.88
	3 to 6	3.1 (1.0 to 9.7)	0.046	1.97 (0.6 to 6.5)	0.26

[a]*C+C: Two drops of cyclopentolate 1%*

[b]*C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%*

[c]*OR: Odds ratio*

[d]*CI: Confidence Interval*

[e]*1: Reference group*

[f]*Adjusted for sex (cat), age (cat) and ethnicity (cat)*

[g]*Adjusted fot sex (cat), BMI (cat) and ethnicity (cat)*

DISCUSSION

This study showed that adverse reactions following cycloplegic eye drops are common in children. Adverse reactions were highest following the administration of a double dose of cyclopentolate to young children with a low BMI. Adverse reactions were virtually absent in subjects with high BMI. Our data suggest a dose response mechanism.

Interpretation of findings.

One objective of this study was to gain more insight in the nature of the adverse reactions. All adverse reactions reported were expected adverse reactions; they were observed and documented previously. Drowsiness was the most frequently reported adverse reaction. According to the international guidelines of the Council of International Organizations of Medical Sciences the rate of both severe and mild drowsiness can be classified as "commonly present" (≥1% and <10%).[23] For a double dose of cyclopentolate 1%, the severe to moderate drowsiness rate as reported in the youngest age category, can even be classified as "very commonly" present (≥10%).[23] Furthermore, regardless the amount of cyclopentolate, severe to moderate drowsiness was very commonly present in low BMI subjects of all age categories. Worldwide only a limited number of companies produce cyclopentolate 1% and tropicamide 1%. In general manufacturers provide a summary of product characteristics for the individual countries.[24-37] The summaries of product characteristics give a wide variety of possible central effects. CNS involvement in children is mentioned as being uncommon[24,25] or rare[24]; e.g. present in >0.1% but <1%.[23] Drowsiness is mentioned in few, but without any further reference to the frequency.[27,28] An increased risk for adverse reactions is identified for infants and young children, but no statements are made about the risks for low weight subjects in the documents we studied.

In addition to classification by frequency, adverse reactions can also be classified by severity. The Common Terminology Criteria for Adverse Events grades adverse reactions according to a System Organ Class.[38] This system has 5 levels of grading; where grade 1 represents mild symptoms, grade 2 represents moderate symptoms up to grade 5, representing death related to the adverse reaction. The adverse reactions reported in our survey mainly belong to the "nervous system disorders". Dizziness, hyperactivity and/or behavioral problems, and mild drowsiness or apathy are classified as grade 1 adverse reactions. Severe or moderate drowsiness are classified as grade 2 adverse reactions. The peripheral adverse reactions reported are all grade 1 adverse reactions. A significant difference between the interventions was present. A double dose of cyclopentolate had 52.4% grade 2 adverse reactions while one dose of cyclopentolate had 33.3%.

The present study showed that adverse reactions were present in 4.8% and 10.3% of children receiving one dose versus two doses of cyclopentolate 1%. Both rates and the 2.2 fold difference in rate is in concordance with Bagheri and colleagues.[6] Our findings support their statement that the incidence of adverse reactions increases with

repeated installation of cyclopentolate. The reported adverse reactions in our study almost exclusively involved the CNS. This is not in line with a report of Pi and colleagues.[39] Although not reporting actual rates, they mention eye irritation and conjunctival hyperemia as the most common adverse reactions in a large cohort of six to fifteen year old subjects receiving 3 drops of cyclopentolate 1%. In our study we focused on all unwanted reactions without influencing patients and/or parents beforehand by providing a specified list. This might have given an underestimation of minor unwanted effects. The complaints reported by Pi and colleagues[39] were expected effects immediately following eye drop application. They generally subside quite quickly and might have been forgotten at the time of our inquiry.

Worldwide tropicamide and cyclopentolate have been used for decades. The lack of adverse reactions following tropicamide is acknowledged and well described. Although an effect of tropicamide on adverse reactions cannot be ruled out, we believe that the adverse reactions can only be attributed to cyclopentolate. The frequent involvement of the CNS following instillation of cyclopentolate is in line with the literature.[7-9] Drowsiness was the most frequently reported adverse reaction, followed by excitation and hyperactivity and/or behavioral changes. The factor 3.4 higher rate of severe to moderate drowsiness and the factor 2.5 higher rate of excitation and hyperactivity and/or behavioral problems in a double dose of cyclopentolate compared to a single dose of cyclopentolate are more evidence for the impact of cyclopentolate.

Our study shows that adverse reactions occurred most frequently in young- and low BMI subjects. In general one can state that young children have an increased risk for drug related adverse events. The dose relative to blood volume and body weight is greater compared to adults.[8, 40-42] Children have a higher cutaneous blood flow and tissues are less dense; thus absorption may be more profound and rapid.[41,42] Children have a limited serum protein binding capacity.[41,42] The smaller the protein binding capacity, the greater the availability of the drug in the blood plasma. Metabolic systems and organs are immature and clearing is slower, resulting in a prolonged half-life.[41,42] In subjects with low BMI the dose relative to blood volume and body weight is higher compared to subjects with normal and high BMI.

Children have a large brain mass in relation to body volume and a higher blood brain barrier permeability than adults, thereby facilitating CNS adverse reactions.[42,43] The thalamus plays an important role in regulating states of sleep, wakefulness, attention and alertness. The hippocampus is involved in memory, spatial navigation and inhibition. Hippocampal dysfunction is associated with poor impulse control, hyperactivity, behavioral changes and disorientation.[44] It seems likely that these areas play a role in the central effects of cyclopentolate. The high incidence of reported adverse reactions especially in the youngest children of our study supports the hypothesis that immaturity of the CNS plays a key role in cyclopentolate's potency for adverse reactions.

In this study adverse reactions were mostly present in the youngest children. However in the children in puberty a considerable amount of adverse reactions were still reported. Although no longer immature, the hormonal changes, rapid restructuration of the brain and the increased physical growth might explain the relatively high susceptibility for cyclopentolate in puberty.[39-41]

Oral consent was obtained from all children and parents. The procedure of consent was carefully considered. The Dutch Agreement on the Medical Treatment Act justified oral consent since the additional length and weight measurements can be considered to cause insignificant burden and no risk. Also the Dutch Central Committee on Research Involving Human Subjects agreed that no written consent was required. Furthermore, a written informed consent procedure would have interfered with the observational character of the study and would have biased the results regarding adverse reactions following the standard cycloplegic treatment.

Study limitations.

Our observational study has several potential limitations.1) We realize that an actual dose response relationship could only be determined with plasma concentrations using intravenous measurements of the dose. But this is not feasible in an observational design and more importantly to invasive for children. If a regime with one dose and three doses of cyclopentolate were added to this observational study we might have established a dose response relationship in the more true sense. These regimes however are infrequently used by our staff. Despite the limitations, we feel we have found enough evidence to state there is an indication of "a dose response mechanism". 2) Despite the apparent lack of adverse reactions with regards to tropicamide in the literature, a tropicamide effect could only have been ruled out if a regime using one drop of tropicamide 1% was admitted in this survey. Again, such a regime is infrequently used. 3) The design of this study did not allow determination of the exact time of onset of the adverse reaction, but an onset of approximately 15 to 30 minutes after leaving the examining room was reported in both regimes. We did not gather information on the duration of the reported adverse reactions. However all effects were still present at departure of the subject from our department, indicating that the adverse reactions lasted at least 45 to 60 minutes after onset. None of the parents contacted us after leaving the outpatient clinic. This could be considered an indication that all adverse reactions had disappeared after this time period. 4) Although the examiner was unaware of the BMI status of the subjects, clinical observations might unconsciously have influenced their inquiries, which might have resulted in an observer bias. However the open question technique should have eliminated such an effect. 5) Besides age and BMI there are more variables influencing the amount of active compound a subject might receive; such as firmly squeezing the eyelids or crying of the subject, thereby reducing the amount of active compound one receives. We did not take these variables into account. 6) Treatment with either a single or double dose of cyclopentolate was not randomized. However the individual orthoptists of this study had their fixed preference for one of the two regimes, and subjects were planned for examination several weeks prior by

administration staff who were unaware of the treatment regimes administered. As such, this can be considered as pseudo-randomisation.[45] 7) Finally, some sub-groups comprised a limited amount of subjects. This could have influenced outcomes; both in rates and subsequent analyses.[10] The questioning technique used ensured prevention of provoked adverse reactions reports. Furthermore, the results of the 95% CI limits enable generalisation to the population.

Conclusions and implications for healthcare professional and policymakers.

Although cyclopentolate 1% generally can be considered to be a safe cycloplegic, the high incidence of adverse events following cyclopentolate in young, low BMI children poses the question whether it is acceptable to use cyclopentolate in a setting without facilities to monitor vital functions. This study provides evidence for a dose response mechanism with the occurrence of adverse reactions. Both presence and severity of adverse reactions are increased in low BMI, young age and in repeated installation of cyclopentolate 1%. The results of this survey can be generalized to the population. As a result of this survey we changed our departmental guidelines for use of cyclopentolate 1%. In young, low BMI subjects the increased risk for drowsiness should be taken into account. In this category of children assessment should be performed with use of a single dose of cyclopentolate, and if necessary combined with tropicamide 1%. Adverse reactions, especially severe drowsiness, were far less common following this regime. With increasing age and increasing BMI, a double dose of cyclopentolate can be administered safely. When a double dose of cyclopentolate 1% is necessary in young and/or low BMI subjects, e.g. children up to at least 6 years of age and low BMI subjects of all ages, the objective refraction should be performed in a hospital setting, or at least in a location where vital functions can be monitored. We propose to make adjustments in the (inter)national guidelines for objective refraction in children. This advice would be especially applicable for settings without facilities to monitor vital functions. This survey shows once again that cyclopentolate is a potent drug that can cause moderate adverse reactions to the CNS in children. For young children and children with a low BMI, the risk of a seriously adverse reaction is rare; however the possibility of an occurrence should always be taken into consideration. Finally, we recommend general adjustment of product documentation.

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writing. DG was involved with data abstraction, data analysis and especially in data interpretation and writing. NESD was involved with data interpretation and editing the manuscript for important intellectual content. She is the guarantor. All authors had full access to the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis prepared the initial manuscript drafts, which were subsequently edited by all authors. All authors agreed to submission.

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Data sharing: No additional data available.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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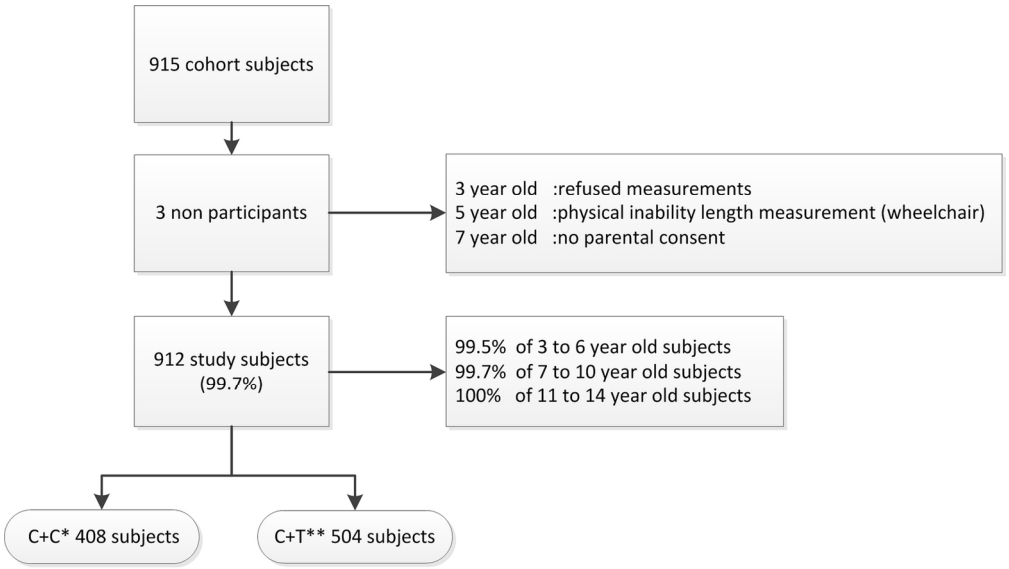

*C+C: Two drops of cyclopentolate 1%
**C+T: One drop of cyclopentolate 1% followed by one drop of tropicamide 1%

142x80mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Manuscript	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	X	Title; page 1 Abstract; page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	X	Page 2
Introduction				
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	X	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses		Page 4
Methods				
Study design	4	Present key elements of study design early in the paper	X	Page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X	Page 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	X	Page 4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X	Page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X	Page 5
Bias	9	Describe any efforts to address potential sources of bias	X	Page 5
Study size	10	Explain how the study size was arrived at	X	Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X	Page 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	X	Page 6
		(*b*) Describe any methods used to examine subgroups and interactions	X	Page 6
		(*c*) Explain how missing data were addressed	n.a.	
		(*d*) If applicable, explain how loss to follow-up was addressed	n.a.	
		(*e*) Describe any sensitivity analyses	n.a.	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X	Page 6 and 7

		(b) Give reasons for non-participation at each stage	X	Page 6
		(c) Consider use of a flow diagram	X	Page 6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	X	Page 7
		(b) Indicate number of participants with missing data for each variable of interest	n.a.	
		(c) Summarise follow-up time (eg, average and total amount)	n.a.	
Outcome data	15*	Report numbers of outcome events or summary measures over time	X	Page 7-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X	Page 7-11
		(*b*) Report category boundaries when continuous variables were categorized	X	Page 7-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	X	Page 7-12
Discussion				
Key results	18	Summarise key results with reference to study objectives	X	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X	Page 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X	Page 13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	X	Page 16
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X	Page 17

*Give information separately for exposed and unexposed groups.