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The acceptability and visual impact of 0.01% atropine in a Caucasian population

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ABSTRACT

Background Myopia is a condition of enormous public health concern, affecting up to 2.5 billion people worldwide. The most effective treatment to prevent myopia progression is atropine but at the cost of accommodative paresis and mydriasis, necessitating the use of bifocal glasses. Low-dose atropine (0.01%) has been found to be almost as effective with significantly reduced side effects. Since there are well-recognised differences in the effect of atropine between heavily pigmented Asian eyes and Caucasian eyes, this study aimed to determine the acceptability and tolerability of 0.01% atropine (by measuring visual performance and quality of life) as a treatment for myopia control in a Caucasian population exhibiting light irides.

Methods 14 university students aged 18–27 were recruited to the study. Participants received one drop of 0.01% atropine daily into each eye over 5 days. A range of physiological, functional and quality of life measures were assessed at baseline, day 3 and day 5.

Results The effect of atropine was statistically significant for pupil size ($p=0.04$) and responsiveness ($p<0.01$). While amplitude of accommodation reduced, the change was not statistically significant. Visual acuity (distance and near) and reading speed were not adversely affected. While there was a slight increase in symptoms such as glare, overall there was no quality of life impact associated with the use of low-dose atropine.

Conclusions Overall, 0.01% of atropine was generally well tolerated bilaterally and no serious adverse effects were observed. Therefore this dose appears to provide a viable therapeutic option for myopia control among Caucasian eyes.

INTRODUCTION

Myopia has now reached pandemic proportions and is expected to affect a staggering 2.5 billion people by 2020.[1] Yet standard clinical care today treats only the optical and medical consequences of this condition, rather than addressing its underlying biological basis. In developed countries in East and Southeast Asia, the prevalence of myopia has doubled in the past 30 years to over 90% of young adults in some countries.[2] Similar extraordinary increases in prevalence are affecting Western society, with myopia prevalence doubling to almost 50% among school-leavers in the USA[3] and over 50% in parts of Europe,[4] including the UK.[5] The existing and future public health implications of myopic progression and of increasing myopia prevalence are considerable.

The primary risks associated with myopia progression relate to its associations with ophthalmic disease and blindness. Epidemiological studies indicate that myopia is second only to age as a risk factor for many of the major eye diseases, including glaucoma, cataract and retinal detachment,[6] and is the primary risk factor in myopic maculopathy.[7] Even outside Asia, myopic maculopathy is one of the leading causes of blindness among working-age people, including in the UK,[8] Ireland,[9] Israel[10] and across other parts of Europe.[11–13] Atrophic myopic maculopathy is unique, however, in having no forms of available treatment, no current treatment trials and a proven aetiological basis.

The incidence of retinal detachment has been observed to increase over 45% in Scotland over a 20-year period, a phenomenon that, although unproven, may well be linked to the evolving profile of myopia.[14] In terms of overall risk, mild levels of myopia appear to be as dangerous to ocular health as smoking and hypertension are to cardiovascular health.[6] Although myopia is not currently considered by clinicians to be a modifiable risk factor for blindness, the evidence is compelling that the introduction of a safe and effective method of reducing myopic progression would have a significant public health benefit.

A recent Cochrane review of the interventions for myopia control reported that there is no conclusive evidence that optical control modalities such as undercorrection, multifocal spectacles or contact lenses yield benefits in terms of reductions in the rate of progression, and may, in some instances, exacerbate the rate of myopia progression.[15] Recent evidence suggests, however, that contact lenses which correct for peripheral hyperopia may have a clinically significant benefit for myopia control.[16 17] The Cochrane review concluded that topical antimuscarinic medication is the most likely effective treatment to slow myopia progression.[15]

Atropine was originally used for myopia control at its standard 1% dose, and while this proved highly effective in reducing the rate of axial elongation and myopia progression, it was, unsurprisingly, associated with the expected side effects, including pupillary dilatation, photophobia, cycloplegia and allergy.[18] The most recent evidence (ATOM2 study), however, in relation to the relative efficacy of various concentrations of atropine, suggests that, over a 5-year follow-up period, a low-dose 0.01% concentration actually exhibits the highest efficacy in slowing myopia progression with less visual side effects compared with higher doses of atropine.[19] Such a low dose may, therefore, prove more tolerable and acceptable to patients as a means of effective myopia control. The ATOM2 study of low-dose atropine was conducted in Singapore on a population with heavily pigmented irides. Since race and iris colour are known factors

that influence cycloplegia, one valid concern about applying such treatment in lightly pigmented Caucasian eyes is that the side effect profile may be more severe.[20]

This study has been designed, therefore, to assess the feasibility of low-dose atropine (0.01%) for use as a potential myopia control agent in a Caucasian population exhibiting lightly pigmented irides. Specifically, the effect of low-dose atropine on (1) functional vision measures including visual acuity (VA) and reading speed; (2) physiological measures including amplitude of accommodation (AA), pupil size and convergence; and (3) vision-related quality of life were the primary objectives of the study.

MATERIALS AND METHODS

University students were invited to participate in this study, which was approved by the Research Ethics Committee at Dublin Institute of Technology. Written informed consent was obtained from all subjects, and the study adhered to the tenets of the Declaration of Helsinki. Inclusion criteria were age 18+ years, VA better than logMAR 0.3, light irides, refractive error ranging from emmetropia to 6 D of myopia, Caucasian race, AA >6 D and normal systemic and ocular health. Volunteers were to be excluded on the basis of any evidence of a narrow anterior chamber drainage angle, known allergy to atropine or any systemic condition contraindicating the use of atropine.

Demographic information, including age and gender, were recorded for each participant. Iris colour was assessed under ambient room illumination, and eligibility confirmed under slit lamp biomicroscope illumination (absence of any conspicuous brown iris melanin pigmentation).

Non-cycloplegic autorefraction (and focimetry of existing spectacle prescription where relevant) was performed to provide an estimate of refractive error (Topcon TRK-2P Auto Kerato-Refractor). Distance VA was measured using the early treatment of diabetic retinopathy study (ETDRS) logMAR chart at 6 m. Test letters were randomised on each visit. Near VA was measured with a reduced logMAR reading chart held at 40 cm. AA was measured monocularly and binocularly and the near point of convergence (NPC) was measured binocularly with a Royal Air Force rule as the average of three measurements. Reading speed was assessed using the Wilkins Rate of Reading Test, which was recorded as the number of correctly identified words per second (WPS). Four separate passages of text were used to avoid any bias due to familiarity with the text. All of the above measurements were taken with distance spectacle correction worn where appropriate.

Pupil size was measured using the Neuroptics VIP-200 Pupillometer. The direct pupillary response was checked using an light emitting diode (LED) pen torch, and recorded on a scale ranging from 0 (non-responsive) to 3 (brisk).

Atropine 0.01% was prepared by dilution of unpreserved atropine 1% minims (Bausch & Lomb) into a well-tolerated ocular vehicle (Tears Naturale, Alcon Laboratories).

On completion of all baseline tests, one drop of 0.01% atropine was instilled in both eyes of eligible participants. Participants returned to the clinic at the same time each day for repeat instillation of the eyedrops on four subsequent days. Each of the baseline tests were repeated on two subsequent days, yielding a total of three sets of measurements for each participant (baseline (day 1), day 3, final (day 5)).

Participants also completed the visual function-14 quality of life questionnaire at baseline and on the final visit to explore the presence of any difficulties affecting routine vision-related activities. Subjects were required to assign their level of difficulty

with each of the 14 vision-related tasks into one of the following grades: none, a little, moderate, great deal and unable to do. At the final visit, participants were also asked the generic question, 'Was the use of atropine eyedrops (a) acceptable/tolerable to you as a therapy for myopia control (yes or no?) and (b) compatible with the continuation of normal vision-related activities such as reading and studying (yes or no?)'.

Statistical analysis

All statistical analysis was performed using the statistical software package SPSS (V.22.0; IBM, New York, New York, USA). The Shapiro–Wilk's test was used to determine normality of the data distributions. A one-way repeated measures analysis of variance (RM-ANOVA), including Greenhouse–Geisser correction for violations of sphericity and post-hoc tests where appropriate, was used to explore the effect of the atropine preparation on measures of visual function across the duration of the study. A statistical significance level of 5% was adopted throughout the analysis.

RESULTS

A total of 14 participants were enrolled in the study, with equal gender representation and comprising 11 myopes (refractive error range −0.75 to −3.25 D spherical equivalent) and three emmetropes. The mean (SD) age of participants was 22 (3).

Ocular physiology

On average, photopic pupil size increased by 1.31 mm (OD, right eye) and 1.08 mm (OS, left eye). The degree of change in pupil size was largest initially, with a 13.1%–18.9% increase between the baseline and day 3 measures, which then moderated to a 4.1%–4.9% further increase between day 3 and day 5. RM-ANOVA revealed that the change in pupil size was statistically significant in each eye ($p=0.04$). Post-hoc analysis using a paired t test revealed that the pupil size at the final visit was statistically significantly different from baseline ($p=0.04$), but not from the day 3 measure ($p=0.79$). Pupillary response also became statistically significantly more sluggish by the final visit ($p<0.01$). The NPC receded slightly at the final visit relative to baseline, but the difference was not statistically significant ($p=0.25$). Binocular AA exhibited an 11% reduction over the study duration (figure 1), but the change was not statistically significant ($p=0.08$).
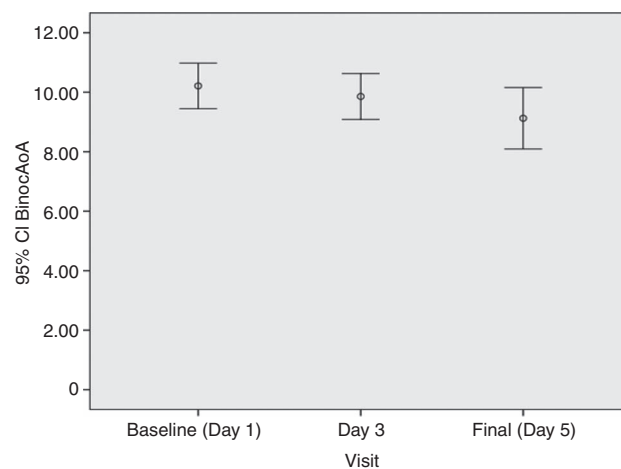
Figure 1 Change in amplitude of accommodation during the course of the study.
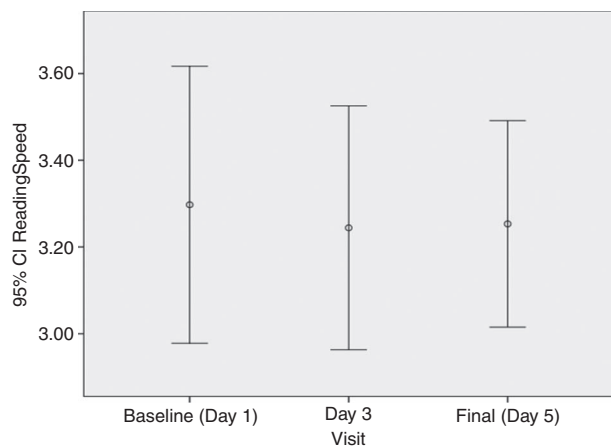
Figure 2 Change in reading speed during the course of the study.

Visual function

Reading speed remained essentially unchanged throughout the study (figure 2), ranging from 3.29 WPS at baseline to 3.25 WPS at completion (p=0.45). Furthermore, distance VA exhibited only a one-letter change that was not statistically significant, while near VA remained unchanged throughout.

The mean (SD) of all clinical measurements at baseline, and across all three subsequent study visits, along with the RM-ANOVA are presented in table 1.

Quality of life

At baseline, all 14 participants reported no difficulty with any of the 14 vision-related activities contained in the visual function-14 questionnaire. At the final visit four subjects remained entirely asymptomatic. Eight subjects reported a one-grade increase in their level of difficulty (from 'none' to 'a little') with one of the 14 vision-related tasks, while two subjects reported an identical one-grade increase in their level of difficulty in two of the 14 vision-related tasks. Glare was the most commonly reported symptom by six subjects.

In response to the additional quality of life questions, all 14 reported that (1) atropine was acceptable/tolerable to them as a form of therapy for myopia control and (2) atropine was compatible with the continuation of normal vision-related activities.

DISCUSSION

As well as being effective, any intervention that requires treatment over an extended period of time must also be well tolerated. The results of this study show that low-dose atropine has minimal impact on accommodation, reading speed and visually dependent daily activities. The age profile of this study was higher than in the ATOM2 study (age group: 6–12 years), but the age-related reduction in AA means that older subjects are more sensitive to the cycloplegic side effects of low-dose atropine. The inclusion of university students, at a time of year when course exams were ongoing, meant that the visual demands of study participants were particularly exacting, more so than would be typical of younger children. In addition, the higher rate of adult-onset myopia in Europe relative to Asia requires that treatments (if available) be applied to older subjects than were recruited to the ATOM2 study.

Atropine is a competitive and non-selective antagonist of the muscarinic acetylcholine receptors. In ophthalmic use, topical atropine is used as a cycloplegic, to temporarily paralyse the accommodation reflex, and as a mydriatic, to dilate the pupils. Atropine at standard doses reaches peak cycloplegia within 1 h and degrades slowly, wearing off in 7–14 days, and so it is generally used as a therapeutic agent rather than as a diagnostic drug, for example, in the treatment of anterior uveitis or amblyopia in children. Despite established merits for myopia control, the adverse effects associated with the standard 1% dose of atropine (eg, blurred near vision which is exploited as a monocular penalisation technique in amblyopia treatment) have inhibited its emergence as a viable control therapy.[15]

A serendipitous discovery in a trial conducted in Singapore has provided a solution to the side effects observed at the 1% dose, by demonstrating that low-dose atropine (0.01%) remains effective at reducing myopic progression, while having minimal impact on pupil size and range of accommodation.[19 21 22] The efficacy of the 0.5% and 0.1% dose was effectively equal to the 1% standard dose. Myopia progression after 2 years in the 1.0%, 0.5% and 0.1% groups was minimal at −0.29 D, −0.30 D and −0.38 D, respectively, while the progression in the 0.01% group was not statistically significantly different at 0.49 D. That 0.01% remains effective relates to the very high level of affinity atropine has to muscarinic receptors. At normal clinical doses atropine blocks all receptor subtypes (M1–M5), but the 0.01% dose has minimal impact on pupil size and

Table 1 Impact of low-dose (0.01%) atropine on measures of ocular physiology and visual function

Variable	Baseline (day 1)	Day 3	Final (day 5)	RM-ANOVA p Value
Distance VA OD	−0.10 (0.10)	−0.08 (0.07)	−0.08 (0.05)	0.547
Distance VA OS	−0.10 (0.07)	−0.08 (0.06)	−0.08 (0.05)	0.644
Near VA OD	N5	N5	N5	−
Near VA OS	N5	N5	N5	−
AA OD	9.5 D (1.78)	9.3 D (1.44)	9.1 D (2.83)	0.18
AA OS	9.3 D (2.14)	9.8 D (1.94)	8.6 D (1.90)	0.11
AA OU	10.2 D (1.42)	10 D (1.39)	9.1 D (2.12)	0.08
Pupil size (mm) OD	5.51 (1.74)	6.55 (1.12)	6.82 (0.61)	**0.04**
Pupil size (mm) OS	5.81 (1.73)	6.57 (1.32)	6.89 (0.92)	**0.04**
Reading speed (WPS)	3.36 (0.55)	3.16 (0.54)	3.25 (0.45)	0.12
Pupillary responses	3.0 (0.00)	2.8 (0.45)	1.1 (0.90)	**0.00**
NPC (cm)	6.8 (2.43)	7.0 (2.19)	8. (3.24)	0.25

Statistically significant findings are highlighted in bold text.
AA, amplitude of accommodation; NPC, near point of convergence; OD, right eye; OS, left eye; OU, both eyes; RM-ANOVA, repeated measures analysis of variance; VA, visual acuity; WPS, words per second.

accommodation (M3 receptors),[23] while retaining most of its beneficial effects on myopic progression (M1 and M4).[24] An additional advantage of the low-dose atropine is that a rebound acceleration of myopia progression observed on cessation of 1% atropine treatment is not observed at this 0.01% concentration.[22] The benefit is such that after 5 years of follow-up, the progression of myopia is actually least in the 0.01% group relative to all higher concentrations.[19] A recent retrospective case–control study has also reported that atropine 0.01% eyedrops significantly reduced the rate of myopic progression over 1 year with minimal side effects (progression −0.1 D compared with −0.6 D for controls). This study suggests that the low dose appears most effective in children with low initial myopia but may not control rapid myopic progression in some patients.[25]

Topical antimuscarinic drugs are unusual in that there is a well-described racial variation in sensitivity to such drugs that relates to the amount of pigmentation (specifically melanin) within the iris.[20 26] Iris melanin content is important in the context of atropine use as melanin is known to sequester anticholinergic compounds.[27] An eye with dark brown irides has two to four times more ocular melanin than one with blue irides.[28] The effect is such that the same concentration of drug has less cycloplegic and mydriatic effect on darker relative to lighter irides. Melanin-bound atropine is slowly released such that recovery from the effect on accommodation and pupil size is longer seen in darker irides. The ability of melanin to bind and alter the pharmacokinetics of a drug such as atropine may have an impact on the tolerability or efficacy of the therapy, and therefore limits the extrapolation of results from a trial conducted in Asia to Europe. While one might expect increased efficacy of atropine in Caucasian eyes, there is also the concern that the possible side effects might be worse. Such racial differences may, therefore, reduce the acceptability of the therapy in populations with a higher proportion of Caucasians.

The physiological, functional and quality of life impact of low-dose atropine in a Caucasian population are critical in terms of the future acceptability of atropine as a viable therapeutic intervention. Importantly, this study included only those with light irides of most concern from a safety and tolerability perspective.

As expected, the use of atropine was associated with physiological changes such as pupillary dilatation, decreased pupillary response and accommodative amplitude. The magnitude of such changes appears small and was not associated with any detectable loss of functional vision. Reading speed and VA, both distance and near, remained essentially unchanged throughout the study.

There was, however, some quality of life impact associated with the physiological response to the low-dose atropine. Only four participants remained entirely asymptomatic, and it is unsurprising to note that glare, presumably associated with the reduced pupillary responsiveness and increase in pupil size, was the most frequently cited quality of life impact. The impact again was minimal, and perhaps the most important finding of this pilot investigation is that all 14 participants found the use of low-dose atropine tolerable, and it did not adversely impact the continuation of their exacting visual activities. These results are compatible with those obtained among Asian participants with darker irides. In particular, the 0.01% dose employed in the ATOM2 trial was not associated with the side effects typical of the standard clinical dose.[19 21] Even the reduced 0.5% and 0.1% doses employed in ATOM2 were associated with a negative impact on participant quality of life, with 70% and 61% of participants on these respective doses requesting the prescription of progressive addition lenses to assist their reading during

the study, compared with only 6% in the 0.01% group. More recently, a 0.02% concentration has been established as the maximum atropine dose that can be administered in Asian eyes without a clinical impact on vision.[29]

The results of this study indicate, therefore, that 0.01% of atropine instilled bilaterally over a period of 5 days was generally well tolerated without serious adverse effects. While these findings are limited in terms of sample size and duration, we would suggest that, as a pilot investigation, they are sufficient to confirm the acceptability and minimal side effect profile of low-dose atropine for myopia control in a Caucasian population likely to exhibit lighter irides than is typical in Asia.

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