

Retardation of myopic progression and axial length growth by atropine in children

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Abstract

Aim: To determine the effect of atropine on axial length elongation by prospectively examining axial lengths and measures of refraction in atropine-treated and untreated eyes of myopic children.

Patients and methods: 492 children with myopia participated in this randomized prospective clinical trial. Initial examination for both the treated and control groups included cycloplegic refraction (initial refraction between -0.50 and -3.50 D), tonometry, keratometry, and axial length measurement by A-scan ultrasonography. Atropine-treated eyes received 1 drop of atropine sulfate 1% daily in both eyes at night. Measurements were repeated every 6 months for 2 years.

Results: The control eyes showed steady myopic progression, with mean refractive error changes of -0.25 D after 6 months, -0.56 D after 1 year, and -0.93 D after 2 years. The atropine-treated eyes demonstrated statistically significant mean refractive error changes of +0.30 D after 6 months, +0.09 D after 1 year, and -0.50 D after 2 years. The control eyes demonstrated steadily increasing axial lengths (+0.13 mm in 6 months, +0.35 mm in 1 year, and +0.45 mm in 2 years). The atropine-treated eyes showed virtually no axial length elongation after 6 months, significantly reduced axial length elongation (0.18 mm vs 0.35 mm) after 1 year, and no significant difference compared with control eyes after 2 years.

Conclusions: Daily atropine for children with myopia retards myopic progression and axial length elongation. A non-selective antimuscarinic blocker, atropine seems to retard myopic progression by a combination of deep cycloplegia and reduction of fibroblast proliferation in the sclera.

Key words: Atropine, Myopia, Refraction, ocular

Introduction

The development and progression of myopia in children has been demonstrated to be due to axial elongation of the eye in the majority of cases.^{1,2} While many studies of atropine treatment in schoolchildren report partial inhibition of myopic progression,³⁻⁷ it was not until 1986 that research into the effects of atropine on axial length in humans was performed. Previous animal studies of form-deprivation myopia showed that atropine inhibited axial elongation in treated eyes.^{8,9}

Accommodation has been postulated to be one of the factors involved in myopic progression, whereby extended periods of accommodative effort render the individual unable to fully relax accommodation, and hence becomes increasingly myopic. Numerous studies have associated environmental factors that require increased accommodative work with a higher incidence of myopia.¹⁰⁻¹² Wiesel and Raviola observed axial length enlargement of the eyes of lid-sutured

newborn monkeys,¹³ and this has since been observed in newborn animals of other species such as chicks¹⁴ and rabbits.¹⁵ Wiesel and Raviola postulated that degradation of the retinal image causes elongation of the globe via neuronal influence on trophic forces in the growing eye tissue.¹³ These researchers further observed that application of atropine ointment in lid-sutured *Macaca arctoides* monkeys prevented such elongation of the globes, and concluded that the elimination of accommodation by atropine may prevent elongation of newborn monkey eyes.¹⁶ However, several recent studies suggest that atropine inhibits myopic progression by mechanisms other than by inhibition of accommodation.^{8,9,17-19} Previous studies of animals certainly have limitations, as the phenomena observed have variations by species, and the form deprivation and neuronal control theories still lack support. This study was performed to ascertain whether the effects of atropine seen in other animals occur in human children.

The purpose of the study was therefore to determine the effect of atropine on axial length in children by prospectively examining atropine-treated and untreated children. Axial length and other measures of refraction were serially assessed and were compared between the 2 groups. This study re-examines the postulated role of atropine or muscarinic inhibitors in myopic eyes.

Patients and methods

In this randomized prospective clinical trial, 492 consecutive children with myopia who presented to a private ophthalmology office in New York, USA, and who met the inclusion criteria for the study were asked to participate in a clinical trial of atropine treatment for myopia. The inclusion criteria were as follows:

- refractive error at the initial visit between -0.50 D and -3.50 D in spherical equivalent errors, as measured by cycloplegic refraction 40 minutes after instillation of 1% cyclopentolate
- total astigmatism less than 1 D
- age at the initial visit between 5 and 16 years
- initial axial length between 22.0 mm and 26.0 mm, as measured by A-scan ultrasonography
- absence of tropia, amblyopia, media opacity, or other ocular structural abnormalities.

Spherical equivalent refractive errors, keratometric measurements, and intraocular pressure (IOP) were compared between the control eyes and the atropine-treated eyes. The ethnic background of the children was mostly Asian — the majority were Japanese, and some Chinese and Korean children were included.

Before entering the study, patients and their parents were advised that the role of atropine in the treatment of myopia was still under investigation. As the study was conducted in a private office in New York before 1986, there was no requirement of approval by an ethics committee of any institutions, but the patients and their parents were informed

of the investigational nature of the trial and they consented to the trial. The children were randomly assigned to the treatment or control groups. Children in both groups were instructed to instill 1 drop of solution into each eye once a day from a bottle with the label covered with a special label with identification numbers. The bottles of atropine contained 1% atropine sulfate with buffered preservatives. The control bottles contained artificial tears with preservatives. The children, their parents, and the personnel who distributed the bottles to the children were unaware of the contents of the bottles.

After visual acuity tests using Snellen charts projected on the screen in darkened examination rooms and refractometry by an RK-2 autorefractor (Cannon, Tokyo, Japan), each child was given 1 drop of 1% cyclopentolate in each eye. After 40 minutes, refractometry and manifest refraction were repeated, and the axial length was measured using A-scan ultrasonography (DBR-300; Sonometrics, New York, USA) with a waterbath probe.

Initial and subsequent examinations for both the treated and control groups included the following: Snellen visual acuity testing, retinoscopic and manifest refractions 40 minutes after instillation of 1% cyclopentolate, Goldmann applanation tonometry, keratometry by Haag-Streit ophthalmometry, and axial length measurement by A-scan ultrasonography. Measurements were made with the children seated upright and comfortably positioned in a chin and forehead rest. The A-scan probe tip was aligned with the visual axis of the tested eye as the fellow eye was given full refractive correction and fixated on a target at 6 m. A set of 10 acceptable measurements were made per visit, with an acceptable measurement defined as having minimal probe compression, maximal peaks on the ultrasonogram, and a standard deviation of less than 0.1 mm for the set of measurements. The axial length was calculated assuming an average sonic velocity of 1550 m/s. The examiners were given a daily refraction worksheet per child, with an identification number but no other information about the patients. All refractions were performed 40 minutes after cyclopentolate application. The patients were given distance correction and bifocal add of +2.50 D to +3.00 D was prescribed, and the children were instructed to use them as needed. Cycloplegic refraction after 1% cyclopentolate and axial length measurements were repeated every 6 months.

Results

A total of 300 eyes were treated with atropine and 192 eyes served as controls. The control and treated groups were consecutively randomized, but only those who returned to the first follow-up examination after the initial assignment were included in the study so there was a difference in the number of patients in each group. The mean age at entry into the study was 10.1 years for the control eyes and 10.2 years for the atropine-treated eyes. The sex distribution was even in both groups. The mean initial refractive power for all age groups was -1.47 D for atropine-treated eyes, and -0.92 D

for control eyes. The mean initial axial length for all age groups was 24.12 mm for the atropine-treated eyes, and 23.66 mm for the control eyes (**Table 1**). To evaluate the possibility that age differences may influence results, the children were subdivided into 3 groups based on their age at entry into the study, as follows: group 1, younger than 9 years; group 2, age 9 years to younger than 12 years; and group 3, age 12 years and older. The mean initial refractive power and the mean initial axial length in those groups are shown in **Table 2**. A-scan axial length measurement was not successful for every patient at every visit. Only successful measurements were included in this report. The numbers shown in the Tables represent the number of examinations performed, and there were fewer axial length measurements than refractive power measurements. Although the atropine-treated eyes had slightly higher mean initial myopic power and slightly larger axial length than the control eyes, these differences were not statistically significant. The error ranges for the data are presented as standard deviations.

All control eyes for all age groups showed a steady myopic progression of -0.25 D at 6 months, -0.56 D at 1 year, and -0.93 D at 2 years (**Table 3**). In contrast, atropine-treated eyes lost myopia by +0.30 D at 6 months and +0.09 D at 1 year. After 2 years of atropine treatment, a statistically significant mean change of -0.50 D was noted — this amounted to approximately 50% of the amount of myopic progression observed in control eyes after the second year.

The number of the observed examinations in this report decreased during the 2 years because of untimely visits in subsequent examinations — only data from patients attending within 1 month of the scheduled visits were included. Furthermore, some families relocated and hence dropped out from the investigation.

Serial mean axial length measurements for all ages demonstrated a steady and continuous increase in the control eyes (**Table 3**). The control eyes demonstrated steadily increasing axial lengths (by 0.13 mm in 6 months, 0.35 mm in 1 year, and 0.45 mm in 2 years). In the atropine-treated eyes, there was virtually no elongation at 6 months — axial length decreased in some eyes, including one-third of the eyes in group 1 ($p < 0.01$), and axial length increased by 0.18 mm in some eyes. This was 50% of that observed in the control eyes (0.35 mm) at 1 year ($p < 0.01$). After 2 years, no significant difference in axial length between the 2 groups was noted.

After 6 months, the atropine-treated eyes in group 1 showed a significant reduction in myopic power by +0.25 D compared with -0.29 D myopic progression in the control eyes (**Table 4**). The atropine-treated eyes shortened by an average of 0.08 mm, although one-third of the eyes showed significant shortening of up to 0.3 mm, one-third remained unchanged, and the remaining one-third showed an elongation compared with a mean elongation in the control eyes of 0.21 mm (**Table 4**).

Table 1. Patients' characteristics.

	Control patients (n = 192)	Atropine-treated patients (n = 300)
Mean age $\pm$ standard deviation (range) [years]	10.1 $\pm$ 1.5 (6 - 14)	10.2 $\pm$ 1.5 (6 - 14)
Refractive error $\pm$ standard deviation (D)	-0.92 $\pm$ 0.69	-1.47 $\pm$ 0.69
Axial length $\pm$ standard deviation (mm)	23.66 $\pm$ 0.58	24.12 $\pm$ 0.48
Sex		
Male (%)	51.0	47.2
Female (%)	49.0	52.8

Table 2. Mean ($\pm$ standard deviation) initial axial length and refractive error.

Age group	Initial axial length (mm)			Initial refractive error (D)		
	Control eyes	Atropine-treated eyes	p Value	Control eyes	Atropine-treated eyes	p Value
All groups (years)	23.66 $\pm$ 0.58 (n = 68)	24.12 $\pm$ 0.48 (n = 146)	>0.1	-0.92 $\pm$ 0.69 (n = 192)	-1.47 $\pm$ 0.69 (n = 300)	>0.1
Group 1: <9 years	23.44 $\pm$ 0.54 (n = 20)	23.83 $\pm$ 0.46 (n = 44)	>0.1	-0.87 $\pm$ 0.36 (n = 52)	-1.33 $\pm$ 0.47 (n = 90)	>0.1
Group 2: 9 to <12 years	23.66 $\pm$ 0.48 (n = 36)	24.13 $\pm$ 0.43 (n = 74)	>0.1	-0.99 $\pm$ 0.46 (n = 84)	-1.40 $\pm$ 0.51 (n = 162)	>0.1
Group 3: $\geq$ 12 years	23.99 $\pm$ 0.73 (n = 12)	24.53 $\pm$ 0.48 (n = 28)	>0.1	-0.96 $\pm$ 0.60 (n = 56)	-1.60 $\pm$ 0.69 (n = 48)	>0.1

Table 3. Mean ($\pm$ standard deviation) change in axial length and refractive power.

	Change in axial length (mm)			Change in refractive power (D)		
	Duration of treatment			Duration of treatment		
	0.5 Year	1 Year	2 Years	0.5 Year	1 Year	2 Years
Control eyes	+0.13 $\pm$ 0.16 (n = 68)	+0.35 $\pm$ 0.35 (n = 48)	+0.45 $\pm$ 0.29 (n = 24)	-0.25 $\pm$ 0.50 (n = 158)	-0.56 $\pm$ 0.68 (n = 186)	-0.93 $\pm$ 0.80 (n = 78)
Atropine-treated eyes	+0.01 $\pm$ 0.23 (n = 128)	+0.18 $\pm$ 0.24 (n = 142)	+0.41 $\pm$ 0.37 (n = 84)	+0.30 $\pm$ 0.52 (n = 300)	+0.09 $\pm$ 0.65 (n = 264)	-0.50 $\pm$ 0.70 (n = 136)
p Value	<0.01	<0.01	>0.1	<0.01	<0.01	<0.01

Table 4. Mean ($\pm$ standard deviation) change in axial length and refractive power in group 1 (age, <9 years).

	Change in axial length (mm)			Change in refractive power (D)		
	Duration of treatment			Duration of treatment		
	0.5 Year	1 Year	2 Years	0.5 Year	1 Year	2 Years
Control eyes	+0.21 $\pm$ 0.22 (n = 20)	+0.51 $\pm$ 0.34 (n = 14)	+0.50 $\pm$ 0.32 (n = 6)	-0.29 $\pm$ 0.58 (n = 52)	-0.59 $\pm$ 0.57 (n = 40)	-0.82 $\pm$ 0.89 (n = 18)
Atropine-treated eyes	-0.08 $\pm$ 0.16 (n = 28)	+0.17 $\pm$ 0.27 (n = 44)	+0.44 $\pm$ 0.40 (n = 20)	+0.25 $\pm$ 0.47 (n = 90)	0.00 $\pm$ 0.46 (n = 86)	-0.70 $\pm$ 0.78 (n = 36)
p Value	<0.01	<0.01	>0.1	<0.01	<0.01	>0.1

Table 5. Mean ($\pm$ standard deviation) change in axial length and refractive power for group 2 (age, 9 to <12 years).

	Change in axial length (mm)			Change in refractive power (D)		
	Duration of treatment			Duration of treatment		
	0.5 Year	1 Year	2 Years	0.5 Year	1 Year	2 Years
Control eyes	+0.07 $\pm$ 0.12 (n = 36)	+0.29 $\pm$ 0.33 (n = 22)	+0.47 $\pm$ 0.25 (n = 10)	-0.28 $\pm$ 0.39 (n = 76)	-0.63 $\pm$ 0.64 (n = 84)	-1.21 $\pm$ 0.84 (n = 36)
Atropine-treated eyes	+0.05 $\pm$ 0.17 (n = 72)	+0.21 $\pm$ 0.26 (n = 74)	+0.42 $\pm$ 0.36 (n = 52)	+0.32 $\pm$ 0.51 (n = 162)	-0.19 $\pm$ 0.70 (n = 138)	-0.49 $\pm$ 0.71 (n = 78)
p Value	>0.1	>0.1	>0.1	<0.01	<0.01	<0.01

Table 6. Mean ($\pm$ standard deviation) change in axial length and refractive power for group 3 (age, $\geq$ 12 years).

	Change in axial length (mm)			Change in refractive power (D)		
	Duration of treatment			Duration of treatment		
	0.5 Year	1 Year	2 Years	0.5 Year	1 Year	2 Years
Control eyes	+0.16 $\pm$ 0.28 (n = 12)	+0.36 $\pm$ 0.44 (n = 10)	+0.25 $\pm$ 0.32 (n = 6)	-0.09 $\pm$ 0.33 (n = 30)	-0.47 $\pm$ 0.60 (n = 56)	-0.67 $\pm$ 0.52 (n = 22)
Atropine-treated eyes	+0.01 $\pm$ 0.21 (n = 28)	+0.10 $\pm$ 0.20 (n = 26)	+0.28 $\pm$ 0.24 (n = 12)	+0.34 $\pm$ 0.48 (n = 48)	-0.01 $\pm$ 0.51 (n = 40)	-0.35 $\pm$ 0.63 (n = 20)
p Value	>0.1	< 0.01	>0.1	<0.01	<0.01	>0.1

After 1 year, the atropine-treated eyes showed no change in refraction from baseline, as opposed to a -0.59 D myopic increase in the control eyes. Atropine-treated eyes elongated by 0.17 mm, whereas the control eyes elongated by 0.51 mm.

After 2 years, the protective effect of atropine in inhibiting both myopic progression and axial length elongation decreased. In the atropine-treated eyes, myopic progression was -0.70 D, and axial length elongation was 0.44 mm, while the myopic progression was -0.82 D and axial elongation was 0.50 mm in the control eyes. These differences were not statistically significant.

Similar changes were observed for axial length and refractive errors in all age groups. **Table 5** shows the results for group 2 and **Table 6** shows the results for group 3.

Discussion

Several authors have shown that the empirical use of atropine may prevent or inhibit the progression of juvenile onset physiologic myopia.³⁻⁷ This study concurs with previously published reports, which show an average myopic progression rate of approximately 0.3 to 1.0 D per year in patients with untreated myopia.^{3,6,20,21}

Axial length increase is commonly accepted as the basic event in juvenile onset myopia. This study revealed variable degrees of arrest or deceleration of axial length elongation in atropine-treated eyes, especially in the eyes of children younger than 9 years (group 1). The initial reduction in axial length, which occurred in one-third of the atropine-treated eyes in group 1 was an unexpected observation. This phenomenon was observed after 6 months of atropine treatment, followed by slow and gradual axial elongation, which continued until the axial length eventually caught up with control eyes after 2 years. The lack of statistical significance may be due to the decrease in the number of patients, causing inadequate power to detect the difference. There are many animal studies reporting retardation of axial growth with atropine. This study concurs with the observations for chicks and newborn monkeys.¹⁶

The measurement accuracy and instrument sensitivity are also concerns. The range of measurement error for the Sonometrics' DBR-300 ultrasonography unit is less than 0.02 mm per measurement. Larger errors may be caused by variations in surface contact or patient fixation, which potentially account for additional errors. The difference between axial length changes between atropine-treated and control eyes exceeds the range of these measurement errors.

By averaging multiple measurements and by increasing the sample size, the effect of measurement error is considered to be insignificant.

To review the pharmacology of atropine and the muscarinic receptor, atropine is a non-selective competitive inhibitor of muscarinic receptors that acts by preventing acetylcholine (ACh) from reaching its receptors. Prolonged use of atropine may decrease the sensitivity of muscarinic receptors and may also downregulate the number of muscarinic receptors, in either case reducing the long-term pharmacological efficacy of atropine. This is consistent with the data from this study, which demonstrate the initial efficacy of atropine in inhibiting accommodation and axial length elongation in the first year, followed by diminishing efficacy after the first year of treatment. The M1 subunit of muscarinic receptor is not present in the ciliary body, but is found in the retina and sclera.²²⁻²⁴ M1 activation has been observed to promote the growth of scleral fibroblasts, whereas M2 muscarinic receptor activation has been observed to inhibit the growth of scleral fibroblasts.^{17,18} ACh has been theorized to act directly on the scleral fibroblast M1 receptors to promote scleral growth.¹⁷ Pirenzepine, a relative M1 antagonist has a weak effect on accommodation and dilation of pupils (M2 effect).³ Pirenzepine has been noted to inhibit fibroblast cell cycle progression in addition to inhibiting scleral extracellular matrix and collagen formation, changes that are normally seen in form deprivation myopia. M2 and M3 antagonists were found to be ineffective in blocking the development of form deprivation myopia in chicks.⁸

Muscarinic antagonists may also mediate their action indirectly, by way of growth factors, which then modulate scleral fibroblast activity. Two such growth factors are epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1). It has been shown that EGF acts by tripling the scleral fibroblast proliferation rate in culture²⁵; IGF-1 has been shown to participate in the pathogenesis of myopia.^{25,26} Neonatal human scleral fibroblasts have been shown to have a high density of EGF receptors.¹⁸ M1 activation increases EGF-receptor density and M2 activation decreases EGF-receptor density.^{17,18} Receptor densities for both IGF-1 and EGF diminish with age.^{17,26} This may partially account for the reduced incidence of myopia, as well as the slowed or halted progression of myopia observed with increasing age.

Recent animal studies have suggested a pharmacologic role for muscarinic inhibitors as direct modulators of scleral growth, thus possibly elucidating the mechanism by which atropine inhibits myopic progression.^{8,9,17-19} Several points can be made that support this hypothesis. Myopia often develops or progresses despite cycloplegia, implying a mechanism other than accommodation for myopia progression. Ciliary muscles lack the M1 subunit,^{22,24} the operative subtype whose inhibition prevents scleral fibroblast growth. Atropine instillation in humans yields pupillary dilatation because atropine inhibits muscarinic receptor

subunits other than M1 in the human ciliary body to cause pupillary dilatation. It seems that cycloplegia is not the only mechanism by which atropine inhibits myopic progression, as it is the inhibition of the scleral M1 receptors that is protective in preventing myopic progression. In addition, chicks lack muscarinic receptor or smooth muscle tissue in their ciliary muscles and receive primarily nicotinic innervation, as evidenced by the chicks' lack of mydriasis with atropine treatment.^{8,17}

Nevertheless, atropine treatment was noted to reduce both deprivation myopia⁸ and spectacle lens compensation in chicks.^{27,28} This implies that an effect of atropine other than that of muscarinic blockade of accommodation (cycloplegia) is operative in reducing the deprivation myopia and spectacle lens compensation. This is most likely via inhibition of scleral M1 receptors. The eastern gray squirrel is a mammal that lacks the ability to accommodate, yet it also develops form-deprivation myopia.²⁹ A recent study supports the theory that atropine promotes scleral remodeling, whereby effective doses of muscarinic antagonists have been shown to reduce the synthesis of scleral extracellular matrix.¹⁹ These animal models for myopia suggest active scleral growth as the primary event in axial elongation of the globe. One could potentially test the theory of scleral remodeling by noting whether atropine inhibits scleral growth in normal eyes.

Several retinal neurotransmitters have been studied for their effects either directly on the sclera or relating to the release of growth factors from the retina or retinal pigment epithelium, with secondary effects on the sclera. Recent studies in chicks have suggested a role of the retina in directing ocular growth. Experimental myopia has been shown to be regional in location in certain cases,³⁰ and several local retinal factors have been implicated in causing or potentiating myopia. Decreased dopamine levels were noted in myopic chick eyes³¹ and the dopaminergic agonist apomorphine was found to partially prevent deprivation myopia in chicks and monkeys.³² This implies that dopamine plays a protective role in the pathogenesis of myopia. Increased levels of vasoactive intestinal polypeptide (VIP) were found in the retinas of myopic monkeys^{33,34} and increased VIP messenger RNA expression was noted in the retinal amacrine cells of myopic monkeys.³⁵ ACh, when released into a synaptic junction and then bound to a muscarinic receptor, yields a classical cholinergic response. Chew et al theorized that ACh acts on the sclera either by direct action on the sclera or by triggering release of a growth factor from the retina or retinal pigment epithelium, which leads to scleral growth.¹⁷ ACh may interact with retinal dopaminergic neurotransmission, synergistically inducing cyclic adenosine monophosphate (cAMP) formation,³⁶ suggesting a role for dopamine agonists in preventing experimental form deprivation myopia.

Arguments may be made against retinal ACh as the controller of scleral growth. Although it is conceivable that muscarinic antagonists act at the retina to block ACh-mediated control of scleral growth, acetylcholinesterases are abundant

in both the retinal and the choroidal circulation, and would likely cleave ACh before it reached the sclera from the retina. Topical or subconjunctival delivery of muscarinic antagonist would thereby be greatly diluted before reaching the retina. An adequate systemic level of muscarinic antagonist would therefore be required in order to elicit the desired local scleral effect. This may indeed be the case, as a study showed that a single drop of 1% atropine sulfate solution administered to humans produced a mean plasma level of 0.86 mg/mL within 8 minutes.³⁷ Systemic absorption after unioocular topical atropine administration may therefore be potentially significant, and fellow-eye controls of eyes treated with atropine would thereby be inadvertently exposed to significant concentrations of muscarinic inhibitor, thus obviating the validity of the fellow eye controls. This potential confounding factor was eliminated in this study, as different individuals were used as controls. There have been no studies that have demonstrated that atropine primarily targets the retina after topical application. Rather, most experiments in the literature that show the efficacy of muscarinic antagonist in modulating scleral growth have utilized the subconjunctival route of delivery, which theoretically maximizes scleral exposure to the drug. No report has measured retinal ACh levels in animal myopia models, which is a potential topic for future study.

The effects of atropine other than on muscarinic receptor inhibition should also be considered. Doses of both atropine and pirenzepine needed to prevent myopic progression have been shown to be much higher than those needed to block the muscarinic receptor.³⁸ This implies possible non-specific effects of these drugs, including retinal toxicity, as suggested by changes in the electroretinogram. Prolonged application of atropine in children is a safety concern and these authors do not advocate atropine as a treatment modality for myopia at this time.

The recent report by the Pirenzepine Study Group is an interesting development.³⁹ In this 1-year multicenter double-masked placebo-controlled parallel study performed at 13 centers in the USA, 2% pirenzepine ophthalmic gel was given to children with myopia aged 8 to 12 years (117 children were given pirenzepine and 57 were given placebo). The number of patients enrolled in the pirenzepine study was smaller than that of the atropine study, and the therapeutic

efficacy in preventing myopic growth was also less than that seen in the atropine study. Pirenzepine has been known for decades, but it has difficulty penetrating the globe and the M1 muscarinic receptor inhibition is partial, while atropine is a non-selective and strong inhibitor of all muscarinic receptors. Probably owing to the smaller sample size, the Pirenzepine Study Group did not report a significant effect on axial length changes in treated eyes.

The study reported here has limitations. A prospective controlled long-term study is difficult to arrange owing to frequent mobility of families for employment purposes and to maintaining scheduled clinic visits. Although a relatively large number of children initially enrolled in the study, many data from the follow-up visits were invalid due to untimely visits, and there was loss of follow-up due to relocation of families. Although changes in keratometric power significantly alter refractive errors, changes in keratometric power or IOP were not analyzed in detail, as the primary intention was to investigate changes in refractive state and axial length. A future prospective study with pirenzepine analogues should include measurements of keratometric power, IOP, anterior chamber depth, and axial length by non-contact IOL Master (Zeiss, Jena, Switzerland) to further investigate the changes in ocular characteristics with such medications.

This prospective controlled study shows that atropine used on a daily basis by children has a retarding effect on myopic progression and retardation of axial elongation similar to that observed in experimental animals.^{8,9,13-19} Several plausible hypotheses are presented as to the mechanism by which atropine may be effective. It was not possible to conclude whether there is a neurochemical trophic effect on the retina as proposed by Raviola and Weisel.¹⁶ There is increasing evidence that prohibition of growth factor or fibroblast by M1 receptor blockage may be a possible mechanism. The authors do not advocate use of atropine for treatment of juvenile myopia at this time, but the experience with atropine was a necessary stepping stone for a trial of pirenzepine and future development of similar pharmaceuticals. Pirenzepine and other drugs that block M1 muscarinic receptors are of interest for clinicians in investigating the mechanism of axial elongation and ultimately in preventing myopic progression in children.

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