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Mini Review

Reincarnation in Ophthalmic Pharmacotherapy

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Abstract

Background: Atropine is the most commonly used pharmacologic agent as a cycloplegic and mydriatic. Taken into account current economical burden worldwide, the well-known drugs are "reincarnated' and repurposed. In this light of view atropine is highlighting new properties and new target in modern ophthalmology.

Objective: The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that atropine may be useful in slowing the progression of myopia opening new avenue of intervention in myopia.

Keywords: *Atropine; Accommodation; Retinal Biochemical Changes; Myopia*

Introduction

In the past few years there has been an increased interest in drug reprofiling due to sustained high failure rates and the rising costs involved in attempts to bring new drugs to the market [1].

Currently "reincarnation" of approved drugs is widely accepted by the industry and encouraged by worldwide regulatory agencies. The general use of an approved medication for a new indication recognized by the medical community but not specifically indicated by a regulatory agency (FDA) is referred to as off-label use. Once the FDA approves a drug, ophthalmologists may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient. Specifically, the exploration of Atropine use in myopia was a result due to a lack of treatment in effect. As researchers and practioners considered the properties of atropune, it became reasonable to trial them in patients with myopia.

The goal of this review is to discuss "reincarnation" in ophthalmic pharmacotherapy, specifically to highlight new properties of Atropine and their clinical implications in modern ophthalmology as an off-label use.

Atropine

Atropine was extracted from Atropa belladonna- a perennial herb with dark purple flowers and shining purplish-black berries. Belladonna translated from Italian means beautiful lady. Atropine is a anticholinergic agent -nonselective antagonist of the muscarinic acetylcholine receptor types M1, M2, M3, M4, and M5; and is the most commonly used pharmacologic agent. Atropine is a hydrophilic drug that can easily penetrate the sclera and reach the choroid.

Topical atropine is used as a cycloplegic, to temporarily paralyze the accommodation reflex, and as a mydriatic, to dilate the pupils. It works by blocking the chemical acetylcholine, which relaxes the ciliary muscle of the eye and causes the pupil to dilate. Atropine degrades slowly, typically wearing off in 7 to 14 days, so it is generally used as a therapeutic mydriatic, whereas tropicamide (a shorter-acting cholinergic antagonist) or phenylephrine (an α-adrenergic agonist) is preferred as an aid to ophthalmic examination. Cycloplegic properties

of Atropine drops are widely used in the treatment of corneal disorders and uveitis therapy. In refractive and accommodative amblyopia, when occlusion is not appropriate sometimes atropine is given to induce blur in the good eye is equally as occlusion in improving visual acuity.

Currently, the new indication of atropine based on new properties was discovered.

Predictably rational current use of Atropine in Myopia

Atropine now is considered as a most potent drug to control the progression of myopia in children, with strong supporting evidence from well-conducted clinical trials [2-4]. However, the exact site and mechanism of action of atropine in slowing myopia progression is still insufficiently understood [5,6]. One of the proposed mechanism is an impact of Atropine on choroidal thickness. The study of Karapetyan., *et al.* [7] reproduced previously found relations between thinner choroids and longer axial lengths, and increasing myopic refraction.

In a longitudinal study, Read and associates [8] reported that a significant increase in subfoveal choroidal thickness of myopic and nonmyopic children was observed over 18-month follow-up, and children showing faster axial eye growth exhibited significantly less choroidal thickening over time compared with children showing slower axial eye growth. The results suggested that there may be a potential role for the thicker choroid in the mechanisms inhibiting eye growth in childhood. In this respect, if the choroid of children is thickened by atropine, which might be a part of mechanism to slow the progression of myopia. Similar to the iris, which is also a part of the uvea, the choroid may also likely display certain changes following the use of a mydriatic agent. The latest study conducted by Zhang., *et al.* [9] found that the use of topical 1% atropine gel administration for a week significantly increased the choroidal thickness under the fovea and at all parafoveal locations.

Another various mechanisms have been proposed for Atropine in myopia: increased dopamine release by atropine binding to muscarinic receptors of amacrine cells; reduction of γ-aminobutyric acid (GABA) levels; atropine binding to muscarinic receptors on scleral fibroblasts and interfering with scleral remodeling. Moreover, it is possible that atropine may indirectly affect the retina, by causing the release of dopamine or other neurotransmitters [10], and it has been reported that dopamine can cause increase in choroidal thickness [11].

Atropine eye drops have been quite extensively used in clinical practice in Asian countries.

The landmark Atropine in the Treatment of Myopia (ATOM) study [2] performed their large randomized clinical trial in 400 children of Asian ethnicity and found a beneficial effect for 1% atropine.

This 2-year study found 75% reduction of myopic progression with atropine 1%, and did not report serious side effects. Cochrane review on atropine studies reported that myopia progression can be reduced by 0.80–1.0D after a year of treatment of atropine 0.5 and 1%, respectively [12].

The ATOM2 study [3] relied only on historical controls. It was conducted in a Singaporean population between six-12 years of age, which both racially and in terms of pattern of myopic progression is very different to Europe. Chia., *et al.* [3] randomly assigned myopic children to 0.5%, 0.1%, and 0.01% atropine eye drops. Over 2 years, myopia progressed −0.30 ± 0.60 D for the 0.5% group, −0.38 ± 0.60 D for the 0.1% group, and −0.49 ± 0.63 D for the 0.01% groups. All were significantly slower than the historical placebo control group.

There are also questions regarding the effect on axial length from the study data, although a recent network meta-analysis indicates that low-dose atropine had significant effect on axial length [5,13]. One year after discontinuation of the various concentrations of atropine eye drops, the most effective myopia control was provided by 0.01% atropine [14]. There is potential for myopia control with fewer side effects using lower concentrations, because as speculated by authors, the accommodative tonus returned to normal, negating the stronger myopia control effect due primarily to changes in tonic accommodation.

The general consensus is that a low concentration of atropine, which has less severe side-effects, is also effective.

Atropine is the preferred practice pattern for progressive myopia in Taiwan [15]. As early as the year 2000, the Ophthalmological Society of Taiwan advised to use atropine to slow down myopia progression. This treatment is prescribed to nearly 50% of Taiwanese children with progressive myopia. Although topical use of atropine is known to cause photophobia and accommodation lag, these adverse events do not appear to hamper its implementation in Taiwanese children. By contrast, the lighter iris color in Europeans is generally considered as a barrier for its use in the Western world [16]. Moreover, some studies have suggested that atropine is less effective in persons of non-Asian descent [17].

Several recent studies [13,18-21] have shown that lower concentrations of atropine slow the progression of myopia control with fewer side effects than 1% atropine.

Lee., *et al.* [19] investigated topical use of low concentration atropine (0.125% and 0.25%) and concluded that in one year its effectively retards myopic progression and does not induce ocular hypertension, but further large scale studies are necessary to validate the long term safety and efficacy. Five-year results of atropine use by Chia., *et al.* [20] evidenced that low- dose atropine 0.01% may provide clinically meaningful myopia control while minimizing side effects.

Huang., *et al*. [21] based on meta-analysis concluded that low dose atropine - 0.01% is still one of the most effective interventions and has been found to induce minimal clinical symptoms for myopia control in children. These findings were reconfirmed by Morgan and He [6], Grzybowski., *et al* [13].

The general consensus is that a low concentration of atropine 0.01% showed great promise for myopia control. Taken into account that there are well-recognised differences in the effect of atropine between heavily pigmented Asian eyes and Caucasian eyes, Loughman and Flitcroft [22] initiated the 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. The authors evidenced that overall, 0.01% of atropine was generally well tolerated bilaterally and no serious adverse effects were observed, concluding that this dose appears to provide a viable therapeutic option for myopia control among Caucasian eyes. Similar effectiveness study was performed by Clark and Clark [23] and Pollling., *et al.* [24]. The purpose of retrospective case-control study [25] was to assess also the effectiveness of 0.01% atropine in 60 children aged 6 to 15 years mostly Caucasian origin with myopia up to -8.0D during 12 months. At the end of study 82% of children from subgroup with low myopia up to -1.0D had emmetropic or hyperopic shift in contrast to 100% of controls showing progression of myopia. The authors highlighted that 0.01% atropine drops significantly reduced rates of myopic progression in case group compared with the controls despite 1-year period duration of study. Polling., *et al.* [24] investigated effect of higher concentration of topical atropine (0.5%) daily during 1 year in progressive myopia up to -6.6D. Obtained findings could have potential clinical significance as they suggest that progression rate of spherical equivalent decreased, despite the association of adverse events, such as photophobia and difficulties with reading is high.

The latest review by Tan., *et al.* [25] assessing the most recent findings and literature on the effect of atropine in the prevention of myopia progression in childhood reaffirms its potential as a pharmacotherapy, however underscores the importance of addressing such questions as treatment schedules in detail – initiation, duration, repeatability, when formulating myopia progression strategies. The need still exists to further assess the long-term effects of atropine, in bridging gaps in scientific knowledge –exact mechanism of it's action in slow down or myopia control.

Summarising, a large body of evidence suggests that lower concentrations of atropine may provide clinically meaningful myopia control while minimizing side effects.

In conclusion, based on currently available findings atropine can be effective for progressive myopia in daily clinical practice and should be considered as a viable treatment option for myopia control anywhere in the world. Following the statement "Everything new is well forgotten old", Atropine was rediscovered enriching by new properties and new avenue of intervention in myopia being explored.

Bibliography

1. Tobinick EL. "The value of drug repositioning in the current pharmaceutical market". *Drug News Perspectives* 22.2 (2009): 119-125.

2. Chua WH., *et al*. "Atropine for the treatment of childhood myopia". *Ophthalmology* 113.12 (2006): 2285-2291.

3. Chia A., *et al*. "Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2)". *Ophthalmology* 119.2 (2012): 347-354.

4. Chia A., *et al*. "Five-year clinical trial on atropine for the treatment of myopia 2". Ophthalmology 123.2 (2016): 391-399.

5. Shih KC., *et al*. "Use of atropine for prevention of childhood myopia progression in clinical practice". *Eye Contact Lens* 42.1 (2016): 16-23.

6. Morgan IG and He M. "An important step forward in myopia prevention: low-dose atropine". *Ophthalmology* 123.2 (2016): 232-233.

7. Karapetyan A., *et al*. "Choroidal thickness in relation to ethnicity measured using enhanced depth imaging optical coherence tomography". *Retina* 36.1 (2016): 82-90.

8. Read SA., *et al*. "Longitudinal changes in choroidal thickness and eye growth in childhood". *Investigative Ophthalmology and Visual Science* 56.5 (2015): 3103-3112.

9. Zhang Z., *et al*. "The effect of topical atropine on the choroidal thickness of healthy children". *Scientific Reports* 6 (2016): 34936.

10. Schwahn HN., *et al*. "Effects of atropine on refractive development, dopamine release, and slow retinal potentials in the chick". *Visual Neuroscience* 17.2 (2000): 165-176.

11. Dhillon B., *et al*. "The ocular growth inhibition effected by dopamine agonists and atropine is associated with transient increases in choroidal thickness in chicks". *Investigative Ophthalmology and Visual Science* 49 (2008): 1732-1732.

12. Walline JJ., *et al*. "Interventions to slow progression of myopia in children". *Cochrane Database of Systematic Reviews* 12 (2011): CD004916.

13. Grzybowski A., *et al*. "The Role of Atropine Eye Drops in Myopia Control". *Current Pharmaceutical Design* 21.32 (2015): 4718-4730.

14. Chia A., *et al*. "Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%". *American Journal of Ophthalmology* 157.2 (2014): 451-457.e1.

15. Fang YT., *et al*. "Prescription of atropine eye drops among children diagnosed with myopia in Taiwan from 2000 to 2007: a nationwide study". *Eye (London)* 27.3 (2013): 418-424.

16. Shih YF., *et al*. "An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression". *Acta Ophthalmologica Scandinavica* 79.3 (2001): 233-236.

17. Li SM., *et al*. "Atropine slows myopia progression more in Asian than white children by meta-analysis". *Optometry and Vision Science* 91.3 (2014): 342-350.

18. Smith MJ and Walline JJ. "Controlling myopia progression in children and adolescents". *Adolescent Health, Medicine and Therapeutics* 6 (2015): 133-140.

19. Lee CY., *et al*. "Effects of topical atropine on intraocular pressure and myopia progression: a prospective comparative study". *BMC Ophthalmology* 16 (2016): 114.

20. Chia A., *et al*. "Five-year clinical trial on atropine for the treatment of myopia 2: myopia control with atropine 0.01% eyedrops". *Ophthalmology* 123.2 (2016): 391-399.

21. Huang J., *et al*. "Efficacy Comparison of 16 Interventions for Myopia Control in Children: A Network Meta-analysis". *Ophthalmology* 123.4: 697-708.

22. Loughman J and Flitcroft DI. "The acceptability and visual impact of 0.01% atropine in a Caucasian population". *British Journal of Ophthalmology* (2016).

23. Clark TY and Clark RA. "Atropine 0.01% eyedrops significantly reduce the progression of childhood myopia". *Journal of Ocular Pharmacology and Therapeutics* 31.9 (2015): 541-545.

24. Polling JR., *et al*. "Effectiveness study of atropine for progressive myopia in Europeans". *Eye (London)* 30.7 (2016): 998-1004.

25. Tan D., *et al*. "Topical Atropine in the Control of Myopia". Asia-Pacific Journal of Ophthalmology (Philadelphia) 5.6 (2016): 424-428.

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