Pharmacological interventions in myopia management

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Daily low-dose atropine has been shown to result in a reduction of close to 60% in myopia progression over 5 years – with little to no rebound effect.

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Myopia can get worse very quickly. Drugs such as low-dose atropine can help. CAMBODIA

The myopia epidemic has been described across several articles in this issue of the *Community Eye Health Journal*. The long-term burden on the health care system, the global economy and individual quality of life requires that we do what we can to avoid or delay myopia onset and, when myopia is present, that we provide optical correction and do our best to slow its progression. Behaviour modifications such as increased time outdoors and reduced near work appear useful in avoiding or at least delaying onset of myopia, but have not been shown to slow progression once myopia is present. There is evidence that optical interventions (p. 19) and the pharmacological options presented here can reduce myopia progression in children. This may reduce the risk of vision impairment later in life from complications such as retinal detachment and myopic macular degeneration.

Daily low-concentration atropine

Daily low-dose atropine has been shown to result in a 59% reduction in myopia progression over 5 years, and it is virtually asymptomatic.

High quality (large cohort, randomised, masked and controlled) trials of 0.01%, 0.025% and 0.05% atropine eye drops have demonstrated significant myopia control effects over 1 year of daily use.[1,2] The ATOM2 study showed a 59% reduction in myopia progression over 5 years (which included periods of use and periods of non-use).[1]

This myopia control effect was measured by changes in spherical equivalent refraction; it is less clear whether low-concentration atropine controls myopia progression measured by axial elongation. This is an important distinction because we suspect that axial length is a stronger determinant than spherical equivalent of lifelong risk of complications such as retinal detachment and myopic macular degeneration. However, further studies are required to confirm this.

Daily 0.01% atropine shows little to no rebound effect when treatment is stopped, but the potential rebound effect of the other low concentrations is unknown.[1,2] Depending on uveal pigmentation and individual sensitivity, these dosages have subclinical effects on pupil size and accommodation, and are therefore very well tolerated.[1,2]

Low-concentration atropine: unresolved questions

Unsettlingly, we do not know exactly how atropine reduces myopia progression. Atropine has a dose-related effect on accommodation, pupil size, dopamine levels in the retina, and scleral fibroblast activity. Any or all of these mechanisms potentially explain atropine's myopia progression effect, as this effect also appears to be atropine dose-related, as does post-treatment rebound. However, retinal dopamine levels and/or scleral fibroblast activity appear the most likely candidates.

Low-concentration atropine: the challenges

Low-concentration atropine needs to be compounded in most countries, making it too expensive for many people who would benefit from it. It is also commonly an 'off-label' use – meaning reduction in myopia progression was not the reason atropine was approved for use in most countries, which can cause insurance and payment issues. Absence of a local compounding pharmacy can be overcome – compounding pharmacists commonly post or courier drops to patients, even between countries, depending on drug importation rules. The biggest problem remains cost. Pharmaceutical companies have not shown an interest in commercially manufacturing low-concentration

atropine because of regulatory hurdles in countries they are most likely to make profits in. This may change if preferred dosage and axial length effectivity questions are resolved.

We have not observed any significant complications from daily low concentrations of atropine, and none have been reported. However, given the potential complications of atropine generally, caution is warranted. Practitioners should note contra-indications (e.g., Down's Syndrome or spastic paralysis), provide patient information (including critical information about complications), advise sun protection if prescribing concentrations above 0.02%, and advise to return immediately or attend a hospital emergency department if signs of adverse reactions are observed.

Recommendation

Given the current evidence, our recommended regimen is **0.01% atropine, one drop in each eye once a day** (preferably at night, just before bed). We recommend reviewing patients one week after the initiation of atropine use to assess visual function (including distance visual acuity, refraction, accommodation accuracy, and pupil reactions) and to check for any adverse reactions.

After that, it is sensible to regularly review a child with progressive myopia as usual, e.g., every 6–12 months. The practitioner should have clear criteria for ceasing atropine management (e.g., a wash-out period after each 2 years of use, as used in the ATOM studies).[2] Various groups are actively investigating the effects of a range of low-concentration atropine regimens on myopia progression. Recommendations may change as future studies are published.

Avoid daily regular-concentration atropine

We *do not* recommend the use of daily regular-concentration atropine. Although 1% atropine is widely available, and high-quality randomised controlled trials of 0.1%, 0.5% and 1% atropine eye drops have demonstrated strongly significant myopia control effects over 2 years of daily use,[1,3] there is a significant rebound effect. One year after ceasing 2 years of daily 1% atropine, study participants showed almost as much cumulative myopia progression as if atropine had never been used.[1] Several options for reducing the rebound effect have been proposed (e.g. tapering atropine in either concentration or frequency of use), but none has been shown safe in prospective randomised controlled trials.

Other candidates

Pirenzepine

The use of pirenzepine 2% twice a day has been shown to have a significant myopia control effect over 2 years[4] There have been no studies about progression once treatment has stopped, so there is no information about a potential rebound effect. We are unaware of any jurisdictions in which pirenzepine is commercially available.

7-methylxanthine

7-methylxanthine (7-mx) appears to exhibit a safe, significant myopia control effect in both animals and humans.[5] As is the case with pirenzepine, there have been no studies about progression once treatment has stopped, so there is no information about a potential rebound effect. Denmark is the only jurisdiction we are aware of in which 7-mx is available and permitted for use.

Conclusion

Daily, low-concentration atropine appears safe and beneficial, leading to a 59% reduction in myopia progression over 5 years as measured by spherical equivalent refraction. This has the potential to reduce the frequency of high myopia by over 73%[6] and reducing the risk of visual impairment associated with higher myopia.

Even so, questions remain about the mechanism of action, efficacy (e.g., does it moderate progression of axial elongation?), the optimal dosage for myopia control, the effect of place and/or ethnicity on optimal dosage, and how atropine interacts with other myopia control interventions (e.g., does combining atropine with dual focus contact lenses or bifocal spectacles result in additive myopia control, does it multiply the effect, or do they interfere with each other?).

We advocate the evidence-based role of daily low-concentration atropine in moderating myopia progression so long as a clear administrative framework, patient safety protocols and drug cessation guidelines are employed.

In our opinion, this currently means considering prescription of 0.01% atropine for use in both eyes, once per day, at night, in appropriate patients.

References

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