Role of 7-methylxanthine in myopia prevention and control: a mini-review

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Abstract

● Myopia is becoming increasingly common. By 2050 around 10% of the world’s population is expected to be highly myopic (<-5 diopters) and therefore particularly at risk of suffering from sight-threatening complications. Currently used myopia control treatments, such as multifocal soft contact lenses or spectacle lenses, orthokeratology, and atropine eyedrops, either do not completely arrest myopia progression or are associated with significant ocular and possibly systemic side effects. A new candidate for pharmaceutical control of myopia progression and excessive eye elongation, the non-selective adenosine antagonist 7-methylxanthine (7-MX), appears to be non-toxic and effective in reducing myopia progression and axial eye growth in experimental and clinical studies. The latest findings regarding 7-MX for myopia control and evaluate its potential as a supplement to existing treatment options were reviewed.

● KEYWORDS: 7-methylxanthine; myopia; pharmaceutical; therapy

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INTRODUCTION

Myopia is usually caused by excessive axial elongation of the eye during childhood[1]. The prevalence of myopia is increasing world-wide, especially in East Asia[2-3]. Myopia can be corrected optically, but due to stretching of the retina, retinal pigment epithelium (RPE), and choroid, myopic individuals are at increased risk of developing sight-threatening complications. According to a recent estimate, each additional diopter (D) of myopia is associated with a 58%, 20%, and 30% increase in the incidence of myopic maculopathy, open-angle glaucoma, and retinal detachment, respectively[4]. This has prompted research in methods to curb the progression of myopia.

Currently, myopia control methods consist of optical devices (multifocal contact or spectacle lenses and orthokeratology) and atropine eye drops[5]. However, optical devices usually do not completely stop the myopia progression and their effect seems to decrease with duration of use. For example, in one study, orthokeratology lenses reduced axial growth by a total of 0.42 mm over a period of five years, but the effect was limited to the first three years, with no significant additional reduction during the last two years[6]. The largest reduction of axial growth achieved by an optical device was 0.44 mm over a seven-year period in children using orthokeratology[7]. However, a 0.44 mm reduction of axial growth corresponds to less than 1.25 D of myopia progression, a fraction of the 4.86 D accumulated myopia progression found in one sample of European children with myopia onset before the age of 10y[8]. Because optical devices alone cannot protect all children from developing high myopia, combinations of optical devices and pharmaceutical treatment are now being tried. The only currently available pharmaceutical myopia control treatment option is atropine eyedrops. However, to achieve a robust effect, the atropine concentration must be at least 0.05%, and at this concentration adverse effects, such as photophobia, blurred near vision, or local allergic reactions limit its use[9-11]. Even in combination with an optical device, low-concentration atropine eyedrops do not effectively stabilize fast-progressing myopia[12-14]. Thus, alternative pharmaceutical myopia control options are needed.

Since myopia control needs to be continued for many years, the ideal molecule must have very low toxicity, high efficacy, and be relatively low-cost.
A new candidate for pharmaceutical myopia control, 7-methylxanthine (7-MX) has attracted interest as the first myopia control pharmaceutical for oral use. 7-MX has been shown to reduce experimental myopia and clinical data suggest that 7-MX slows down myopia progression in children and adolescents.\[^{15}\]

We here review the latest findings regarding 7-MX for myopia control and evaluate its potential as a supplement to existing treatment options.

**PRECLINICAL STUDIES**

The initial interest in 7-MX was generated by the discovery that 7-MX modulates biochemistry and ultrastructure of rabbit sclera.\[^{16}\] 7-MX was found to increase posterior sclera collagen concentration and collagen fibril diameter. The animals were given 30 mg/kg body weight per day for ten weeks. The treatment produced no apparent adverse effects and the authors concluded that 7-MX potentially could be used to treat or prevent conditions with poor quality of scleral collagen, such as axial myopia. Subsequently, a series of animal experiments demonstrated the effectiveness of 7-MX in slowing down myopia progression. In guinea pigs subjected to form-deprivation, 7-MX reduced myopia and axial eye growth. 7-MX also prevented thinning of the sclera and thinning of scleral collagen fibrils, changes typically accompanying experimental myopia. The animals were given 300 mg/kg body weight once per day for three weeks with no adverse effects observed.\[^{17}\] Similar results were found in pigmented rabbits subjected to form-deprivation and treated with 7-MX at a dose of 30 mg/kg body weight per day for four weeks.\[^{18}\]

The effect of 7-MX was also studied in rhesus monkeys. In animals wearing a -3 D myopic lens, 7-MX reduced the amount of induced axial myopia, and in animals wearing a +3 D hyperopic lens it augmented hyperopic shifts. The animals were given 100 mg/kg body weight orally twice per day for five months. No apparent adverse effects occurred. The authors concluded that 7-MX may have therapeutic potential for slowing the progression of myopia in humans.\[^{19}\]

In contrast to the results found in guinea pigs and rabbits, no effect of 7-MX (100 mg/kg body weight twice per day) on refractive development, axial growth, or scleral fibrous layer thickness was found in chickens subjected to form deprivation.\[^{20}\] Only a minor effect on choroidal thickness and retinal dopamine content was found. The negative result of this experiment may be due to it being short-term (13d) or to anatomical differences between birds and mammals. Nevertheless, a previous experiment using chickens showed that, although 7-MX had no effect on form-deprivation myopia, it had some effect on lens-induced myopia.\[^{21}\]

Likewise, in a short-term (12d) experiment in three shrews, 7-MX had no effect on form-deprivation myopia, but it was weakly effective in preventing lens-induced myopia.\[^{22}\]

**CLINICAL STUDIES**

In a clinical trial in Denmark, 77 myopic children aged 8-13y with a minimum baseline myopia of -0.75 D were randomized to either 400 mg 7-MX once per day or placebo for 12mo. In the following 12mo period, all 68 remaining participants received 7-MX, and in the last 12mo of the 36-month study all 61 remaining children received no treatment. During the first year, axial elongation in children randomized to 7-MX was reduced by 0.04 mm compared with placebo-treated children. Axial growth was significantly reduced in children treated with 7-MX continuously for 24mo compared with children treated with placebo for the first 12mo and with 7-MX for the following 12mo. For axial growth in children with a base-line axial growth rate of 0.075–0.190 mm per 6mo, the difference between the 7-MX group and placebo/7-MX group was -0.098 mm [95% confidence interval (CI) -0.211 and 0.013 mm, \(P=0.048\)]. And the corresponding axial growth difference was -0.037 mm (95% CI -0.195 and 0.120 mm, \(P=0.667\)) in children with a high base-line axial growth (0.200–0.390 mm per 6mo). In the period 12–24mo, the difference in myopia progression in children with a base-line axial growth rate of 0.075–0.190 mm per 6mo was -0.217 D (95%CI -0.478 and 0.044 D, \(P=0.141\)), and 0.121 D (95%CI -0.267 and 0.508 D, \(P=0.541\)) in children with a base-line axial growth rate of 0.200–0.390 mm per 6mo. During treatment cycle, axial growth rate was significantly lower than in the precedent period (\(P<0.00001/P=0.001\), first year and \(P=0.006/P=0.001\), second year), but in the third year, after discontinuation of treatment, axial growth rate was not different from the precedent year (\(P=0.533/P=0.179\)). The axial eye growth rate slowed down as long as 7-MX treatment was continued and increased once treatment was stopped, but without signs of a rebound effect, i.e. accelerated myopia progression after stopping treatment.

There were no differences between the 7-MX group and the placebo group as regards safety measures such as blood pressure, heart rate, weight, or height during the trial, and no subjective side-effects were reported. The treatment appeared safe and without side effects and could therefore be continued long-term until the myopia had stabilized. It should be noted that dosing once per day was not optimal in view of the short half-life of 7-MX (estimated 200min) and this initial trial may therefore have failed to show the full potential of 7-MX.

Following the trial, the Danish Medicines Agency (DMA) allowed the use of 7-MX for myopia control in children and adolescents. Initially, the children were prescribed 400 mg once per day (in the morning), but from 2011 dosing was increased to twice per day (one tablet in the morning and one...
in the evening), and from 2017 to three times per day (one tablet approximately every 8h). At each visit, the number of tablets provided by the pharmacy was obtained from a central registry, and parents were asked how many tablets were left, thus making it possible to calculate the average daily dose taken by each child since start of treatment.

Recently, longitudinal cycloplegic refraction and axial length data from 711 myopic Danish children treated in the period 2000-2021 with different doses of oral 7-MX (0-1200 mg/d) were analyzed using linear mixed models[15]. The children had a baseline age ranging from 7 to 15y, a baseline myopia ranging from -0.5 to -9.875 D, and an observation period ranging from 0.9 to 9.1y. Myopia progression and axial growth were found to be associated with 7-MX dose. For children with a baseline age of 7, 9, or 11y, the model uniformly predicted a three-year cumulative reduction of myopia progression of 0.68 D and a six-year reduction of 0.84 D for a child taking an average dose of 1000 mg/d (one tablet of 400 mg taken on average 2.5 times per day) compared with a non-treated child. In terms of axial growth, the cumulative reduction for the same child was 0.07 mm over the first year, 0.16 mm over 3y, and 0.18 mm over 6y. For example, an 11-year-old child with an average refraction of -2.49 D at baseline would develop -2.27 D more myopia and 1.01 mm more axial length over the next 6y if left untreated, but with an average 7-MX dose of 1000 mg/d, this child's myopia would only have increased -1.43 D and the axial length 0.84 mm. It should be noted that this analysis was based on data from children with up to -10 D of myopia at baseline. A preventive treatment should of course ideally be initiated before the myopia has progressed to such high levels and 7-MX seems to be somewhat more effective in children with a more moderate level of myopia at baseline. For example, according to the model analysis, a child with less than -2 D of myopia at baseline and taking an average dose of 1000 mg/d would have around 0.93 D less myopia progression over 6y compared to an untreated child. Axial growth was not modeled for these subsets of children.

Comparison with other myopia control methods is difficult, as no long-term studies using similar methodology are available. Furthermore, due to possible confounders, the efficacy of 7-MX can only be reliably determined through a randomized placebo-controlled trial. However, based on this observational study the one-year efficacy in terms of axial growth (-0.07 mm) of taking 1000 mg/d seems comparable to that of 0.01% atropine eyedrops or multifocal soft contact lenses of various designs (-0.06 to -0.11 mm)[29]. There are very few truly placebo-controlled myopia control studies lasting more than two years, but MiSight multifocal soft contact lenses reduced myopia progression by 0.73 D over three years in a trial including children with an average baseline age of 10.1y and -4 D or less myopia, corresponding to a relative effect of 59%[25]. According to the model analysis for 7-MX, a child with less than -4 D at baseline taking an average of 1000 mg/d for three years would have 0.70 D less myopia progression than an untreated child. For children aged 7, 9, and 11y at baseline, this myopia progression corresponds to a relative reduction to the control group of 31%, 39%, and 48%, respectively. Axial growth was not modeled for these subsets of children[15].

Thus, the three-year efficacy in terms of myopia progression achieved by taking an average of 2.5 tablets of 400 mg 7-MX per day does not seem much different from that of MiSight, and for all age groups it exceeds the minimum clinical effect of 30% (myopia progression less than controls) set by the U.S.A. FDA[26]. The efficacy of 7-MX appears to be proportional to dosing frequency. According to the model analysis the absolute effect, both in terms of myopia progression and axial growth, of taking an average of 2.5 tablets per day is roughly double that of taking an average of 1.25 tablets per day. In view of the rapid elimination of 7-MX from the bloodstream, it is therefore possible that the efficacy could be further improved if dosing was increased beyond three times per day. However, a more practical solution would be to administer 7-MX as a sustained release formulation capable of maintaining a stable serum concentration with only once or twice a day dosing. It is noteworthy that the absolute effect size achieved by 7-MX appears to be independent of age. This contrasts with atropine eyedrops (0.01%-0.05%), which seems to work less well in younger children[27]. Orthokeratology, on the other hand, seems to work better in younger children than in older[28]. It remains to be seen if the effect of 7-MX is additive to that of an optical device or atropine eyedrops. In rhesus monkeys fitted with plus lenses, 7-MX treatment was found to enhance hyperopia[19]. This finding suggests that 7-MX potentially could boost the efficacy of optical devices designed to reduce myopia progression, as such devices typically incorporate areas with plus addition in the periphery of a minus lens. As an oral treatment, 7-MX is easily administered and can conveniently be combined with both spectacles and contact lenses. In contrast, the combination of atropine eyedrops and contact lenses is not ideal because atropine or the preservatives contained in the eyedrops may cause allergy, dry eyes, or local irritation. Atropine appears to be toxic to human corneal epithelium and endothelium cells at concentrations as low as 0.03%[29-30].

It should be noted that 7-MX for myopia control treatment only has been tested clinically in Denmark. It is therefore possible that the findings do not apply to populations outside of Denmark.

**SAFETY**

Since the use of 7-MX tablets for myopia control was
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approved by the DMA in 2009 a total of 1171 children and adolescents have been treated and no side effects have been reported (personal communication July 2022, DMA). This includes children who have taken 7-MX continuously for 10y. 7-MX is produced in the human body after ingestion of caffeine- or theobromine-containing dietary products such as coffee, tea, and cocoa. Caffeine is metabolized to paraxanthine (1,7-dimethylxanthine), theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine). The cytochrome P450 enzyme CYP1A2 is important for clearance of both caffeine and several of its metabolites[33]. Caffeine is hydrophobic and reabsorbed in the kidneys, and the elimination of caffeine from the body therefore depends on its conversion into more hydrophilic metabolites like paraxanthine, 1-methylxanthine and 7-MX. Paraxanthine is degraded to 1-methylxanthine, 1-methyluric acid, 5-acetyl-amino-6-formylamino-3-methyluracil (combined 67% of paraxanthine clearance), and 7-MX (6% of paraxanthine clearance), 1,7-dimethyluric acid, 1-methyluric acid, 5-acetyl-amino-6-formylamino-3-methyluric acid, which is partly excreted directly by way of glomerular filtration in the kidneys, and partly degraded to 7-methyluric acid, which is also excreted by the kidneys[39].

The pharmacological effects of methylxanthines vary with such factors as their affinity to receptors, specificity for subgroups of receptors, ability to penetrate the blood-brain barrier, and pharmacokinetics. Caffeine metabolites such as 7-MX penetrate only slightly to the central nervous system (CNS)[34]. Theobromine in doses of up to 3000 mg per day was earlier used as a treatment for asthma in children but was abandoned in favour of more potent bronchodilator drugs such as theophylline, which is still used in children in doses of up to 600 mg per day.

Repeated dose testing of 7-MX has demonstrated its non-genotoxicity and non-mutagenicity and it inhibits urethane-induced tumours, malformations, and somatic mutations in mice[35-36]. 7-MX also inhibits formation of xanthine crystals in vitro and has therefore been suggested as a treatment to prevent renal calculi in patients with xanthinuria[37].

Like caffeine, 7-MX extends the lifespan of the nematode Caenorhabditis elegans, a model organism used to study aging[38]. The ability of caffeine to increase longevity may be related to its ability to block adenosine receptors (ADORs)[39].

Acute and repeated dose 28-day oral (subacute) toxicity studies have shown 7-MX to be widely non-toxic[40]. In an acute toxicity study, 7-MX, caffeine, and theobromine were administered to two rodent species (rats and mice) at 300 and 2000 mg/kg body weight. 7-MX was found to be non-toxic, whereas an increased mortality rate was observed for caffeine and theobromine treated mice (66.6%) and rats (33.3%).

subacute toxicity was tested in rats at doses of 250, 500, and 1000 mg/kg body weight per day for 28d in repeated doses. Mortality, body weight, food consumption, and neurological functions were found to be unaffected by 7-MX, and there were no signs of ophthalmic, clinicopathological, or gross pathological changes. In another study, sub-chronic (90-day repeated dose) and chronic toxicity (180-day repeated dose) were assessed. Animals treated with 7-MX in doses up to 1000 mg/kg body weight per day for 180d did not display any organ changes or increased mortality[41]. This dose corresponds to around 30 000 mg/d for a 7-year-old child or around 25 times more than the highest daily dose currently used for myopia control.

Thus, 7-MX appears to be considerably safer than its precursor caffeine, which has been classified by the U.S.A. FDA as G.R.A.S. (Generally Regarded as Safe) and therefore can be added to dietary products without limitations. Since most people in the western world ingest dietary product containing caffeine or theobromine daily, most of the population is constantly exposed to minor concentrations of 7-MX. For example, one cup of cocoa, which contains around 200 mg of theobromine, produces a steady state serum concentration of 7-MX formed from metabolized theobromine of around 10% of that of theobromine, equivalent to the serum concentration resulting from ingesting 20 mg 7-MX[33].

For comparison, atropine is highly toxic and its therapeutic window narrow[42]. The justification for year-long daily use of atropine eyedrops in concentrations higher than 0.1% in minor children should be carefully evaluated in consideration of the potential risk of CNS side-effects due to systemically absorbed atropine. The systemically absorbed dose resulting from administration of one drop of 0.1% atropine in each eye can be up to 0.1 mg and atropine in doses of 0.4-2 mg has been shown to produce CNS effects in adult humans[43-46].

MECHANISM OF ACTION

The effects of 7-MX in pharmacological doses are related to its ability to block ADORs, but it is uncertain which specific subtype is involved and whether the target tissue is the sclera, the choroid, the RPE, or the retina. Since 7-MX has limited ability to penetrate the blood-brain barrier and presumably little ability to penetrate the blood-retina barrier, other structures than the retina, such as the sclera, the choroid, or the RPE are more likely targets for 7-MX[34].

Compared to 7-MX, topical caffeine, another non-selective ADOR antagonist, readily penetrates the globe[47]. Caffeine eye drops have been reported to reduce cataract formation[48]. The effects of topical caffeine on refractive development, which were qualitatively similar to those produced by oral administration of 7-MX, that both ADOR antagonists prevented myopic compensation to imposed hyperopic
defocus, and both ADOR antagonists appeared to facilitate the compensating hyperopic shifts produced by imposed myopic defocus. However, the amount of caffeine was more difficult to control precisely than 7-MX, and it’s easily blinked out of the palpebral fissure. Therefore, the actual concentration of caffeine in animals tends to deviate from expectations. While much is to be learned about the protective effects of caffeine eye drops and 7-MX, further investigations of the potential benefits of ADOR antagonists in the management of myopia were justified.

ADORs are activated by adenosine, a metabolite of ATP, the primary energy unit of living systems. Four ADOR isoforms have been identified, namely ADORA1, ADORA2a, ADORA2b, and ADOR3, all of which are expressed in the retina, choroid, and sclera in rat, guinea pigs and rhesus monkeys, and in human scleral fibroblasts and RPE cells. Experimental evidence suggests that ADORs play a role in the development of myopia. Compared to wild-type mice, ADORA2a knockout mice display relative myopia and a reduced density of reduced diameter scleral collagen fibrils, and reduced ADORA1 and increased ADORA2b protein expression were found in the retina of guinea pigs with form deprivation myopia. Furthermore, single nucleotide polymorphisms detected in the ADORA2a exon seems to be associated with high myopia in the Chinese population. The excessive eye elongation during myopia development in mammals is associated with remodeling of the sclera, in particular collagen depletion due to increased activity of matrix metalloproteinases (MMPs). This renders the sclera less resistant to irreversible stretching by the forces of the intraocular pressure. The posterior sclera of myopic eyes is thinner than normal, and the thickness of its collagen fibrils is reduced. In normal rabbits and guinea pigs, treatment with 7-MX causes thickening of the posterior sclera and thickening of the collagen fibrils and prevents loss of scleral collagen in response to form deprivation. 7-MX stimulates the synthesis of collagen I and fibronectin in scleral fibroblasts but inhibits their synthesis in choroidal fibroblasts. Retinal inflammation and scleral hypoxia have separately been suggested to be involved in the pathogenesis of myopia.

Both conditions are associated with increased extracellular levels of adenosine and up-regulation of ADORA2b, and the effect of 7-MX on myopia development could therefore be related to its ability to block downstream effects of hypoxia and inflammation. Human studies and experimental work indicate that eye growth is controlled by visual stimuli, and that the scleral changes taking place during development of myopia may be secondary to a cascade of signals originating in the retina and transmitted by way of the RPE and the choroid.

RPE cells play an important role in regulating retinal function and balancing the extracellular environment, and adenosine released from the retina activate ADORs in the RPE. In human RPE cells cultured in vitro and treated with 7-MX, the proportion of cells in the G1 phase increased slightly at 24h but decreased at 48h and returned to normal at 72h. The expression of ADORA1, ADORA2a, and ADORA2b protein was suppressed at 48h but rebounded at 72h. Thus, 7-MX had little effect on the proliferation or apoptosis of human RPE cells but disrupted the proportion of cells in the G1 phase and inhibited the expression of ADORA1, ADORA2a, and ADORA2b during short-term treatment.

ADOR2a and dopamine D2 receptors (DRD2) form functional heterodimers in human RPE cells. Thus, knockdown of ADORA2b by siRNA increased DRD2 protein expression in human RPE cells, and the same effect could be produced by treating RPE cells with 7-MX. Correspondingly, protein expression of DRD2 knocked down by siRNA could be restored to control levels by incubation with 7-MX for 48h. Therefore, through the ADORA2a-DRD2 heterodimer, ADORA2a inhibits the DRD2 receptor, and blocking of ADORA2a by 7-MX consequently increases protein expression of DRD2, a receptor known to inhibit experimental myopia.

Progression of myopia and axial growth in myopic children seems to increase in periods with few hours of daylight. In the dark-adapted state, the energy consumption of the retina increases, and this leads to an accumulation of adenosine, the waste product of ATP degradation. 7-MX may therefore protect the eye from the myopia-promoting effects of low levels of ambient light by blocking adenosine receptors.

A common feature of other myopia control methods such as atropine eyedrops, orthokeratology, and multifocal spectacle lenses is their ability to cause a reversible thickening of the choroid, a phenomenon believed to function as a stop-signal for axial eye growth. While choroidal thickening was initially reported in normal monkeys receiving oral 7-MX, a more recent article by the same research group reported that the choroidal thickening previously observed may have been an artefact due to limited amount of control data. The effect of 7-MX on choroidal thickness in humans has not been studied, but short-term experiments indicate that the acute effect of caffeine, which blocks the same receptors, is thinning, and not thickening, of the choroid. This suggests that 7-MX relies on a different mechanism of action than other myopia control methods, thus theoretically increasing the likelihood that the effects of 7-MX are additive to that of other myopia control methods.

DISCUSSION

7-MX has been shown to reduce experimental myopia in...
mammals and retrospective analysis of real-life clinical data collected over a period of 21y has shown increasing doses of 7-MX to be associated with decreasing myopia progression and axial growth. Modeling suggests that the efficacy of 7-MX dosed three times per day is comparable to that of existing myopia control methods such as low-concentration atropine eye drops or optical devices. However, randomized placebo-controlled trials are needed to confirm causality and determine the effect size. Given the short half-life of 7-MX it is likely that the efficacy of a sustained release formulation of 7-MX will be better than that of the current formulation. In conclusion, 7-MX shows promise as a non-toxic, side-effect free, oral myopia control pharmaceutical, suitable as a supplement when myopia progression cannot be completely arrested by monotherapy with low-dose atropine or an optical device.

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