The use of pilocarpine in the treatment of presbyopia

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ABSTRACT
Presbyopia is a physiological process of progressive loss of accommodation, which leads to a deterioration in the ability to focus vision on objects at different distances. This is now thought to be a direct consequence of two causes: the design of the transparent lens and the way it has to change shape to allow focusing, and the instability of proteins over very long periods of time.

In recent years, various substances that temporarily narrow the pupil, causing a pinhole effect, have been intensively investigated to allow improved near vision acuity. The most commonly researched is 1.25\% pilocarpine solution. The substance itself has been known for more than 100 years, with a well-documented hypotensive effect and numerous side effects. However, the reduced concentration and less frequent dosing, as well as the addition of drugs with anti-inflammatory effects currently being studied, offer hope for efficacy in the treatment of presbyopia. The results of the studies so far are promising. Researchers point to improved near visual acuity and a low rate of mild side effects.

In the future, we will find out whether the optimistic observations mainly in short-term studies will also be effective and applicable in broad practice.

Keywords: pilocarpine, presbyopia, pupil, nonsteroidal anti-inflammatory drugs
INTRODUCTION
Presbyopia is the consequence of physiological processes that are very difficult to come to terms with, especially for ophthalmologists. The progressive deterioration of near visual acuity, which requires the use of optical aids and their regular replacement, the impossibility of stopping this process at least until the time when cataracts need to be removed, leads to the search for different ways to solve this problem.

WHAT IS PRESBYOPIA?
Presbyopia is a progressive loss of accommodation that results in a loss of visual ability to focus on objects at different distances. It is now thought to be a direct consequence of two causes; firstly the design of the transparent lens and the way it has to change shape to allow focusing, and second, protein instability over a very long period of time. Increasing changes in the lens lead to a loss of flexibility of the central area in middle age, with a consequent onset of presbyopia, and can probably also promote the later development of cataracts [1].

In humans, accommodation takes place through contraction of the ciliary muscle and iris sphincter, convergence and changes in the shape and position of the lens. The latter action is passive, meaning that changes in the lens depend on the contractions of the ciliary muscle and the iris. Furthermore, when the centre of accommodation is active, ciliary muscle contraction is stimulated, and pupil constriction and convergence occur in healthy binaural patients. The iris and ciliary muscle have muscarinic receptors that are stimulated by the parasympathetic nervous system through its cholinergic neurotransmitter acetylcholine. This stimulation causes the ciliary muscle to contract and change the size of the pupil by altering the shape and position of the lens, and consequently affects the accommodative abilities associated with parasympathetic activity [2].

To date, presbyopia has been standard corrected with glasses, contact lenses and surgery [2, 3].

PHARMACOLOGICAL TREATMENT OPTIONS FOR PRESBYOPIA
Two types of pharmacological effects on presbyopia are being investigated: pupil constricting agents and lens softening agents (e.g. 1.5% lipoic acid choline ester) [2, 4]. Pupil-constricting agents reduce presbyopia by creating a pinhole effect that can increase the depth of field at all distances. They have been studied for use in one eye for monovision or both eyes. Their effect is short-lived. Side effects such as headache and dim night vision may occur, but long-term safety and efficacy are unknown. Studies have been conducted on pupil constrictors in combination with other agents to produce an additive treatment effect or to reduce side effects, but these combined effects are not clear [4].

EFFECTS OF PILOCARPINE
Pilocarpine stimulates the parasympathetic nervous system, causing contraction of the ciliary muscles and thickening of the lens, resulting in increased focus depth. As a result, near-vision is improved, but far vision is reduced because the lens cannot change its thickness or position. Pilocarpine also causes contraction of the longitudinal bundles of the ciliary muscle, leading to stretching of the trabecular meshwork at the foveal angle. This leads to a reduction in the resistance to outflow of the aqueous fluid and facilitates outflow, resulting in a reduction in intraocular pressure. Pilocarpine was the first glaucoma drug used from 1875 to today [5]. During this time, both its advantages and disadvantages were very well understood. Today, in the treatment of glaucoma, it is a drug rarely and is usually used briefly in selected patients. This is due to the introduction of four groups of hypotensive drugs, characterised by similar efficacy as well as less frequent side effects and less frequent dosing of the drug and therefore better patient compliance.

Observations during the chronic use of pilocarpine eye drops in patients with glaucoma unfortunately showed unacceptable side effects. Chronic stimulation of the uvea membrane with pilocarpine resulted in inflammatory reactions, pigment dispersion, formation of posterior adhesions, and contraction of the ciliary muscle and iris, resulting in pupil immobilization and a shift towards myopia. This problem has been widely reported as a complication of long-term glaucoma treatment, when patients used a 4% pilocarpine solution 4 times a day for many years, at a time when pilocarpine was the only or main drug in the treatment of glaucoma [3].

By re-examining the potential use of pilocarpine in the treatment of presbyopia, a lower concentration (1.25% instead of 4%, used in the treatment of glaucoma) and less frequent use of the drug (once a day instead of 4 times a day in the treatment of glaucoma) were used. Furthermore, the addition of anti-inflammatory drugs to pilocarpine appears to have the effect of reducing side effects [1].

It has been noted that the combination of a parasympathomimetic drug with a nonsteroidal anti-inflammatory drug eliminates the local inflammation that always occurs secondary to chronic pilocarpine stimulation (fixed pupil, posterior adhesions, and pigment dispersion).

Non-steroidal anti-inflammatory drugs (NSAIDs), which are capable of inhibiting cyclooxygenase activity, act as an anti-inflammatory agents in the anterior uvea, reducing pupillary constriction and ciliary contraction, pigment dispersion, and posterior adhesions, as they reduce local...
inflammation caused by chronic infusion of parasympathetic drugs. The combination of pilocarpine and diclofenac has been extensively studied and patented by Benozzi (Benozzi method) for the treatment of presbyopia [3]. The effects of other drugs investigated to reduce side effects, such as conjunctival irritation or inflammation, caused by pilocarpine, such as the combination of carbachol with bromonidine, are also described [4]. There have also been attempts to use a parasympathetic agonist with a steroidal anti-inflammatory agent (dexamethasone) to prevent an inflammatory reaction. Pilocarpine has also been combined with oxmetazoline [6]. Several drugs have also been combined in one preparation, for example, pilocarpine, phenylephrine, polyethylene glycol, nepafenac, pheniramine and naphazoline [7].

Another example of drug combinations that are being investigated for the treatment of presbyopia is the combination of pilocarpine, brimonidine, oxymetazoline, and hyaluronic acid [7].

NEW DRUG, RESEARCH

Over the past decade or so, the results of a number of clinical trials have been published evaluating the efficacy of topical pupillary constrictor drugs applied to the conjunctival sac. This was predominantly 1.25% pilocarpine. The patients had their ocular sacs sprayed once or twice a day, and the duration of follow-up varied. Argentinian doctors followed up patients with emmetroopia from January 2011 to June 2018 with a binaural uncorrected visual acuity to distance (UDVA) of 25/20 or better and uncorrected visual acuity to near (UNVA). Patients were treated with eye drops containing pilocarpine and diclofenac (Benozzi method), and the main outcome measured was binocular UNVA in different follow-up periods. Other parameters such as UDVA and the presence of side effects were evaluated. A total of 910 patients were included, with a mean age of 49 years at the start of the study. The baseline UNVA was 4.74 ± 1.53 and decreased to 1.36 ± 0.48 (Jaeger scale) after 8 years of follow-up. All reported side effects (decreased light perception, headaches, dry eye symptoms and dizziness) resolved spontaneously in patients who continued treatment. The pharmacological treatment of presbyopia has been shown to be effective in improving UNVA without affecting UDVA. Side effects were well tolerated and resolved before 1 year of treatment [8].

In October 2021 the FDA (Food and Drug Administration) in the United States approved eye drops containing 1.25% pilocarpine hydrochloride for the treatment of presbyopia based on two short, 30-day studies (GEMINI 1 and GEMINI 2). In these studies, in total, 750 participants aged 40 to 55 years with presbyopia, the efficacy of placebo was compared to the 1.25% pilocarpine solution. In neither of the two clinical trials were serious adverse reactions observed in any of the patients. The most common adverse reactions that occur with a frequency of > 5% were headache and redness of the eyes. The indication for the drug is mild to moderate presbyopia.

In the results of the GEMINI 1 study, published in 2022, 323 subjects (163 subjects in the study group and 160 in the control group) with a mean age of 50 years were included. The baseline mean distance-corrected near visual acuity (DCNVA) was 29.2 letters. After 30 days, the percentage of participants with an improvement of 3 or more lines in DCNVA was 30.7% (50 of 163 patients) in the drug-taking group and 8.1% (13 of 160 patients) in the control group after 3 hours. After 6 h, these percentages were 18.4% (30 of 163 patients) and 8.8% (14 of 160 patients), respectively. At 8 h, the difference between the groups was not statistically significant. None of the participants with a DCNVA improvement of 3 or more lines at hour 3rd had a loss of more than 5 letters in high contrast visual acuity with binaural correction to distance. The onset of the visual improvement effect occurred after 15 min. and lasted 6 h. Patients were tested under mesopic conditions, i.e. insufficient light, also called twilight vision. Pilocarpine showed an acceptable safety and tolerability profile [9].

DANGERS OF THERAPY

In many published studies, the duration of 1.25% pilocarpine was short. On the other hand, it is intended more for long-term use, which, unfortunately, in the case of eye drops, can cause various problems. The first danger relates to the drug itself: will patients experience side effects previously observed in the treatment of glaucoma? There is certainly less risk, due to the lower concentration of the drug and less frequent dosing. However, potential side effects must be taken into account. It may also be possible in the future to introduce a restriction on drug use in patients with recurrent uveitis, for example. Another issue noted in patients who use eye drops is sensitisation or intolerance relating to the drug itself or other preservatives or solution stabilisers. Such complaints are a major problem in chronic users of eye drops, for example in the treatment of glaucoma. The longer the treatment, the less motivated patients are to use the medication. If they do not see an immediate benefit from the medication, it is difficult for them to maintain the discipline of taking more doses on a regular basis, which is perfectly evident in patients with glaucoma. However, in this case, this may not be much of a problem, as impaired near vision and its improvement after dropping the drug will motivate regular use.
CONCLUSION
Pilocarpine drops of 1.25% appear to be an interesting alternative for use in mild to moderate presbyopia. Certainly, many ophthalmologists will be interested in following the effects of long-term use of the drug, both in terms of treatment and possible side effects.

References
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