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Ophthalmic applications of cyclopentolate

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ABSTRACT

Cyclopentolate is a drug that causes paralysis of accommodation and induces mydriasis. It is widely used around the world. In view of its relatively short duration of action and effective induction of cycloplegia, cyclopentolate is particularly useful in screening children for refractive errors. In addition to diagnostic applications, it is also used for therapeutic purposes, e.g. in uveitis. In October 2021, cyclopentolate, which had not been approved in Poland for years, was authorized for marketing.

The authors of the paper reviewed the literature on cyclopentolate. The properties of the drug were analyzed, and its action was compared with other available cycloplegic agents. In addition, the potential uses of cyclopentolate and its special role in facilitating the ophthalmological examination of children were discussed.

KEY WORDS: cyclopentolate, tropicamide, atropine, cycloplegia, refraction assessment after accommodation paralysis, uveitis.

INTRODUCTION

Cyclopentolate is a drug that has been used in ophthalmology in the form of 0.5%, 1% and 2% drops since 1951. In view of its cycloplegic action, cyclopentolate is the world's most common agent used for refractive error assessment, next to atropine and tropicamide, especially in children. Cyclopentolate is also used for therapeutic purposes, mostly in the treatment of uveitis. The drug is included in the WHO Model Lists of Essential Medicines 2021.

For many years, cyclopentolate was not authorized for marketing in Poland, and was available solely under the direct imports procedure. In October 2021, the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products granted a marketing authorization in Poland for the drug called Cykloftyal (Ofta) in the form of cyclopentolate hydrochloride eye drops 10 mg/ml (1%).

Like atropine and tropicamide, cyclopentolate is an anticholinergic drug. Being an acetylcholine antagonist, it blocks the activation of cholinergic receptors, specifically muscarinic receptors. Consequently, cyclopentolate induces the paralysis of the pupillary sphincter muscle, which causes mydriasis (dilation of the pupil), and of the ciliary muscle, which leads to the paralysis of accommodation (cycloplegia). In addition, like other anticholinergics, it increases intraocular pressure by decreasing the outflow of aqueous humor because of the narrowing of the filtration angle.

Cyclopentolate drops are administered into the conjunctival sac. The drug has a shorter duration of action than atropine, and longer than tropicamide. Maximum pupillary dilatation and paralysis of accommodation are reached 30 to 60 minutes and 25 to 70 minutes after drug instillation, respectively. Mydriasis usually resolves within 24 hours of the application of drops, while the cycloplegic effect persists for up to 12-24 hours. A comparison of the duration of action of atropine, tropicamide and cyclopentolate is shown in Table I.

INDICATIONS FOR THE USE OF CYCLOPENTOLATE

Cyclopentolate is approved in Poland both for diagnostic and therapeutic applications. In diagnostics, the drug can be used for fundus examinations after pupil dilation and for inducing accommodation paralysis and determining the actual refractive error. Cyclopentolate is suitable for patients of any age, but its diagnostic value is particularly strong in children, adolescents, and young adults, as complete paralysis of accommodation is crucial in these age groups for matching the correction to the refractive error of the patient.

The drug is approved for use in adults for the treatment of inflammations of the uvea (iritis, iridocyclitis, and choroiditis). The drug's action contributes to preventing the formation of iridolenticular adhesions by dilat-

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Tabela I. Comparison of the duration of action of cycloplegics most commonly used in ophthalmology

Maximum	Cycloplegic effect		Mydriatic effect	
	(minutes)	Duration of action (hours)	Maximum (minutes)	Duration of action (hours)
Atropine [1]	60-180	168-240 (7-10 days)	30-40	168-240 (7-10 days)
Cyclopentolate*	25-70	6-24	30-60	24
Tropicamide*	25-55	3	20-120	3-5

** Data extracted from the SmPC*

ing the pupil and reducing contact between the iris and the lens, while cycloplegia reduces pain resulting from ciliary muscle contraction and hypersensitivity of the ciliary body.

DOSAGE

To achieve accommodation paralysis before an ocular examination in adults under 65 years of age, one drop of 1% cyclopentolate should be instilled into the eyes twice, five minutes apart. The examination should be performed approximately 30-40 minutes after the last administration of the drug. In patients with uveitis, one drop should be applied 3 to 4 times a day. The duration of treatment depends on the patient's clinical condition.

In children and adolescents, for the purpose of achieving accommodation paralysis and performing an ophthalmic assessment, one drop of 1% cyclopentolate should be instilled into the eye 40 minutes before the examination. If necessary, the dose may be repeated after 15 minutes.

CONTRAINDICATIONS

Based on the drug's approval indications, 1% cyclopentolate is contraindicated in children under 3 months of age and in adults over 65 years of age because of the risk of systemic toxicity.

Cyclopentolate should not be used in patients with hypersensitivity to the active substance and with narrow-angle glaucoma, as it may lead to acute closure of the iridocorneal angle. In addition, cyclopentolate is contraindicated in children with organic brain dysfunctions (including congenital or developmental defects or disorders of the nervous system, especially those predisposing to epileptic seizures).

ADVERSE EFFECTS

In general, adverse effects associated with cyclopentolate are rare and mild. They may present as transient local effects, such as a burning sensation in the eyes or photosensitivity, or as a systemic reaction usually manifested as drowsiness [2, 3].

A large Japanese multicenter study (2018) [2] found that in children below 15 years of age the rate of adverse effects for atropine (8.8%) was seven times higher than for cyclopentolate (1.2%). Facial flushing and fever accounted for 86.2% of all atropine-induced adverse effects. The side effects triggered by cyclopentolate included drowsiness (37.0%), red eyes (14.8%), fever (11.1%) and facial flushing (11.1%). Among 2,238 children who received cyclopentolate, all the symptoms were transient and no serious adverse effects were observed, even though the study group included patients with genetic disorders (e.g. Down's syndrome) and chronic systemic diseases.

Another large study from 2020 looked at the incidence and risk factors of adverse effects after using 1% cyclopentolate twice in a group of 646 children aged 0-15 years. Despite the drops being administered twice, all the reported adverse effects were mild and transient [3]. Even though concerns are occasionally raised about the use of cyclopentolate in children with organic brain lesions, no significant correlation has been found between patients' disorders of the central nervous system and increased incidence rates of cyclopentolate side effects [3].

PREGNANCY AND LACTATION

According to the US Food and Drug Administration (FDA) classification, cyclopentolate is assigned pregnancy category C, which means that it should be used only if the expected benefits of treatment outweigh the potential risks. No information is available on the use of cyclopentolate during breastfeeding.

OTHER POTENTIAL USES OF CYCLOPENTOLATE

Similarly to other cycloplegic agents, cyclopentolate is used to relieve pain and treat inflammation in patients with multiple diseases and injuries of the anterior segment of the eye.

Cyclopentolate is indicated for the treatment of all types of keratitis (bacterial, including syphilitic interstitial, fungal, and viral) associated with iritis, for reducing pain and preventing the formation of posterior adhesions [1, 4, 5].

Postoperatively, cycloplegics can be used, if necessary, after penetrating keratoplasty [5]. Cyclopentolate has also been reported to be an effective and well-tolerated drug for the management of eye pain after pterygium excision surgery [6].

Similarly, cycloplegic agents are used as adjunctive therapy for the purpose of pain relief in patients with acute conditions such as acute keratoconus [5].

Cycloplegics are recommended for the management of chemical burns in patients experiencing discomfort or sig-

nificant inflammatory response in the anterior chamber, and in patients with thermal burns [5].

Cycloplegic agents are also commonly used in the management of anterior segment injuries. It is believed that the drugs in this group may improve the comfort of patients with corneal erosions [4]. In post-traumatic cyclodialysis, cycloplegics help to relax the ciliary muscle, which moves the detached ciliary body closer to its attachment to the scleral spur, facilitating healing [5]. In post-traumatic hyphema, it may be beneficial to administer long-acting topical cycloplegic agents initially to control inflammation and improve patient comfort, and to facilitate posterior segment evaluation and eliminate iris movement [5].

The beneficial effects of cycloplegics have also been reported in such rare events as bee and wasp stings in the cornea and/or conjunctiva or corneal/conjunctival damage by plant material [5] causing acute conjunctival hyperemia and chemosis, corneal edema and infiltration, and hard-to-control pain.

The effect of cycloplegics in relieving pain associated with anterior segment diseases is still debated in the literature. A large systematic review and meta-analysis published in 2021 [7] showed a significant pain reduction after two days of treatment with homatropine and cyclopentolate. However, the authors point to the need for randomized multicenter studies with long follow-ups to fully understand the role that cycloplegics play in relieving pain in inflammatory conditions of the anterior segment.

Cyclopentolate also has applications in refractive surgery. In addition to diagnostic uses in refraction testing, according to the recommendations of the Polish Society of Ophthalmology (PTO) cyclopentolate can be used after the implantation of multifocal artificial intraocular lenses during refractive lens replacement (RLE) procedures when near vision is affected as a result of small pupil width [8].

CYCLOPENTOLATE USE IN CHILDREN

The approval of cyclopentolate in Poland was welcomed by pediatric ophthalmologists because a full ophthalmological examination in children must include a cycloplegic refraction test, and out of all the available cycloplegics, cyclopentolate exhibits optimum properties.

In order to accurately determine the correct refractive power of the optical system in children, accommodation must be completely paralyzed; otherwise the results may be falsified. Miscorrection of refractive error can lead to amblyopia and impair the development of the child who, in addition to poor vision, also feels unwell, gets tired quickly, and may suffer from headaches that hinder daily functioning. Consequently, the ophthalmological examination of children requires eye drops to paralyze the ciliary muscle.

The most common refractive error in pre-school and early school-age children is hyperopia. However, because of their wide range of accommodation, children have the ability to compensate for this defect. Consequently, full visual acuity is found in many cases. A constant state of accommodative tension produces so-called asthenopic symptoms, which usually manifest as headaches and problems with concentration, especially when reading. Moreover, accommodative convergence, which is closely associated with strong accommodation, may result in decompensated esotropia [6]. In turn, school-age children are frequently affected by accommodative spasm due to excessive near activities. Accommodative spasm is known to falsify the refractive results before cycloplegic drops are administered, thus overestimating myopia.

Refraction assessment after the administration of drops inducing accommodation paralysis allows accurate assessment of hyperopia in patients with accommodative esotropia and prevents overcorrection in patients with myopia [10]. It is also essential for prescribing correction to amblyopic patients with impaired accommodation [10].

One percent cyclopentolate hydrochloride has long been the preferred cycloplegic agent in many European countries and the US for routine use in children [11]. Even though Cycloftyal 1% is approved for use in children from 3 months of age, Kanski's Clinical Ophthalmology recommends a lower concentration (0.5%) in children between 3 and 6 months of age.

A definite advantage of cyclopentolate is its rapid onset of action and relatively short duration of mydriasis and cycloplegia. In most patients, a single instillation of drops is sufficient, which reduces the level of stress associated with drug administration. In young children (up to the age of 6 years), patients with dark skin and/or dark irises, the drops may need to be re-administered. Research indicates that in patients with accommodative esotropia, who are a group in which determining the full refractive error is of particular significance, cyclopentolate has a similar effect to atropine and is sufficient to achieve good cycloplegia [12]. In the PTO's guidelines, cyclopentolate is included among the recommended cycloplegic agents and indicated for use at a concentration of 1% in patients from the age of 1 year, for the assessment of refractive error in children with strabismus and with suspected amblyopia [13, 14].

In contrast, tropicamide (0.5% or 1%) is not an effective cycloplegic drug in children. Even after multiple administrations complete accommodation paralysis may not be achieved. The authors of studies comparing the effectiveness of cycloplegia achieved by the instillation of tropicamide and cyclopentolate highlight that refraction tests performed after the application of tropicamide may give inaccurate results in children or adult patients with hyperopia [15]. Another problem is the short duration of action. Tropicamide reaches its maximum cycloplegic effect after 20 minutes, but almost immediately after this time point cycloplegia begins to wear off. This is especially important in younger children who, on account of difficulties with following the examining practitioner's instructions, need to be allocated more time for the examination. Unlike tropicamide, cyclopentolate causes accommodation paralysis that persists for several dozen minutes (Figure 1). Consequently, ophthalmologist do not need to worry about a rapid return of accommoda-

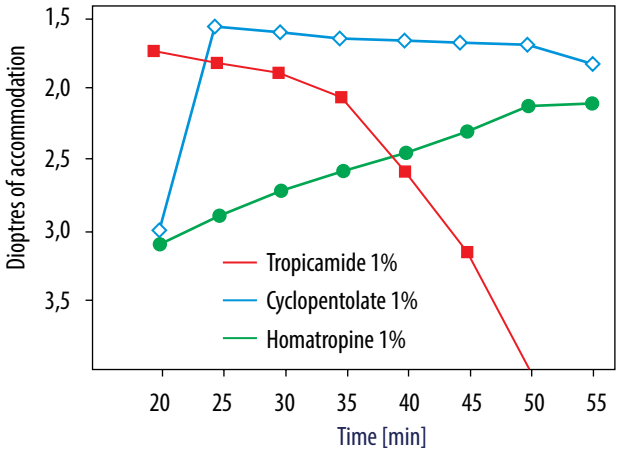

Figure 1. Mean residual accommodation (subjective measurement) after the application of 1% tropicamide, 1% cyclopentolate, and 4% homatropine [acc. 16]

tion after the application of cyclopentolate, so the examination can be more stress-free, and proceed with the patient's needs in mind.

Atropine induces complete cycloplegia, but compared to other cycloplegics, its use is associated with the most adverse effects. In addition, its prolonged duration of action adversely affects children's functioning for many days, as pupillary dilation causes photophobia and impairs visual acuity.

Cyclopentolate 1% is a safe drug, as confirmed by the latest reports, and any side effects associated with its use are local and transient, even in young children [2, 3].

CONCLUSIONS

On the Polish pharmaceutical market, there was no drug with intermediate properties between the very short-acting and relatively weak tropicamide and the long-acting atropine. Cyclopentolate has filled this gap. As an effective cycloplegic agent, cyclopentolate is especially suitable for refraction testing in children. The approval of cyclopentolate in Poland also opens up possibilities for using the drug in other indications as an alternative to atropine and tropicamide.

DISCLOSURE

The authors declare no conflict of interest.

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