Ocular Cyclopentolate: A Mini Review Concerning Its Benefits and Risks

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Abstract: Cycloplegic and mydriatic agents are essential in ophthalmological clinical practice since they provide the means for diagnosing and treating certain eye conditions. In addition, cyclopentolate has proven to possess certain benefits compared to other available cycloplegics and mydriatics. Still, the incidence of some adverse drug reactions related to this drug, especially in susceptible patients, has created interest in reviewing the literature about the benefits and risks of using cyclopentolate. A literature search was conducted in Medline/PubMed and Google Scholar, focusing on identifying cyclopentolate’s benefits and risks; the most important benefit was its usefulness for evaluating refractive errors, especially for hyperopic children, pseudomyopia, anterior uveitis, treatment of childhood myopia, idiopathic vision loss, and during examinations before refractive surgery, with particular advantages compared to other cycloplegics. While the risks were divided into local adverse drug reactions such as burning sensation, photophobia, hyperemia, punctate keratitis, synechiae, and blurred vision, which are relatively frequent but mild and temporary; and systemic adverse drug reactions such as language problems, visual or tactile hallucinations and ataxia, but unlike ocular, systemic adverse drug reactions are rare and occur mainly in patients with risk factors. In addition, six cases of abuse were found. The treatment with cyclopentolate is effective and safe in most cases; nevertheless, special care must be taken due to the potential severe ADRs that may occur, especially in susceptible patients like children, geriatrics, patients with neurological disorders or Down’s syndrome, patients with a low blood level of pseudocholinesterase, users of substances with CNS effects, and patients with a history of drug addiction. The recommendations are avoiding the use of 2% cyclopentolate and instead employing solutions with lower concentrations, preferably with another mydriatic such as phenylephrine. Likewise, the occlusion of the nasolacrimal duct after instillation limits the drug’s absorption, reducing the risk of systemic adverse events.

Keywords: cycloplegic, cyclopentolate, benefits, risks, adverse drug reactions, abuse

Introduction

Cycloplegic and mydriatic agents are essential in the ophthalmological clinical practice since they provide the means to diagnosing and treating certain eye conditions. Cycloplegics and mydriatics inhibit parasympathetic stimuli through their competitive antagonistic effect on muscarinic acetylcholine receptors (mAChR), mainly mAChR M3, in the ciliary muscle and iris.

The mAChR include a family of five receptors coupled to the G protein (M1 to M5). Three of these (M1, M3 and M5) are coupled to G proteins of the Gq/11 group, while the two remaining subtypes (M2 and M4) are part of the Gi15 group of G proteins.

Five ocular mydriatics and cycloplegics are currently available: atropine sulfate, homatropine hydrobromide, scopoline hydrobromide, tropicamide and cyclopentolate hydrochloride.

Cyclopentolate [2-(dimethylamino)ethyl 2-(1-hydroxycyclopentyl)-2-phenylacetate], a competitive non-selective mAChR antagonist, was synthesized by Teves and Testa in 1951. It was used for the first time in the early 1950s, and initially approved in 1953 by Schieffelin.

Nowadays, there are several marketed cyclopentolate formulations (0.2%, 0.5%, 1% or 2%) in different countries such as México (Refractyl, Laboratorios Sophia, 1963), Spain (Colircusí ciclopléjico, Alcon, 1965), Canada (Cyclogyl, ...
Alcon, 1972),\textsuperscript{17} the United States (Cyclogyl, Alcon, 1974),\textsuperscript{18} and the United Kingdom (Minims, Bausch & Lomb, 1987).\textsuperscript{19}

Since its inclusion in clinical practice, cyclopentolate has proven to possess certain benefits compared to other available cycloplegics and mydriatics. Still, the incidence of some adverse drug reactions related to this drug, especially in susceptible patients, has created interest in reviewing the literature about the benefits and risks of using cyclopentolate.

This review’s objective is to elucidate the benefits and risk of the use of ophthalmic cyclopentolate and to provide information of this drug in susceptible patients.

**Methodology**
A literature search was conducted in Medline/PubMed, as well as Google Scholar, using relevant keywords (cyclopentolate, adverse drug reactions, adverse event, anticholinergics, cycloplegics drugs, cyclopentolate abuse).

**Pharmacokinetics**
For cyclopentolate to exert its pharmacological effect, it must infiltrate several ocular structures through to the aqueous humor, reaching its target tissues. However, its systemic absorption may lead to adverse effects. This absorption into the main bloodstream may take place through different mechanisms: corneal (through the vessels of the limbus), transconjunctival, dermal (occupational exposure), and nasolacrimal (exposing nasal, gastrointestinal, and respiratory mucous membranes).\textsuperscript{20–23} Once absorbed, it is rapidly distributed to the bloodstream, exhibiting its maximum systemic concentration after between 10 and 60 minutes,\textsuperscript{24,25} with a half-life of around 100 minutes.\textsuperscript{26} In order to minimize the risk for systemic adverse events through this mechanism, a post-instillation lacrimal obstruction may reduce systemic absorption by up to 60%.\textsuperscript{25}

**Mechanism of Action**
The pharmacological effect of cyclopentolate is due to the competitive antagonism of mAChR (mainly through the stereoisomer [-] of cyclopentolate),\textsuperscript{2,27} causing a mydriatic and cycloplegic effect. Clinically, it induces the relaxation of the circular muscle of the iris (mydriasis) and prevents the radial ciliary muscle’s contraction, relaxing the suspensory ligaments, and therefore the lens capsule (cycloplegia).\textsuperscript{28}

Its maximum effect ranges from 20 to 60 minutes after installation in hyperpigmented irises and 10 to 30 minutes in hypopigmented ones.\textsuperscript{23,25,29–31}

**Benefits**
**Cycloplegic Refraction**
Cycloplegic refraction is used mainly in refractive error evaluation, especially for hyperopic children, pseudomyopia, idiopathic vision loss, high degree of anisometropia, and during examinations prior to refractive surgery.\textsuperscript{32–34}

**Hyperopia**
As mentioned earlier, due to children’s high accommodation capacity, cycloplegia is an essential tool for the correct diagnosis of these patients’ refractive errors, avoiding their potential underestimation.\textsuperscript{32,35,36} The timely diagnosis and treatment of hyperopic amblyopia prevents its progression of accommodative esotropia and the resultant strabismic amblyopia.\textsuperscript{35,36} Also, studies have been published assessing the need to further extend the use of cycloplegia into adolescence and adulthood.\textsuperscript{35,37,38}

**Myopia**
The literature declares that in myopia, the focal point is in front of the retina and there is no accommodative effort to focus; consequently, cycloplegics would not be necessary;\textsuperscript{32,33,35} nevertheless, different studies have observed an overestimation of patients with myopia when a cycloplegic is not applied, predominantly shown in the early stages of life, where the accommodative power is still prominent.\textsuperscript{38–41}
Anterior Uveitis
Cyclopentolate can be used as adjunctive therapy in anterior uveitis to prevent posterior synechiae between the lens and the iris, as well as to relieve pain and discomfort caused by ciliary muscle spasms. 42–46

Treatment of Childhood Myopia
Several studies corroborate the use of cycloplegics in treating childhood myopia through the significant increase in choroidal thickness; however, treatment with cyclopentolate is not recommended due to other cycloplegics with a longer duration of effect. 47–51

Anterior Segment Analgesics
In the treatment of anterior segment analgesic, the literature shows contradictory results; while some articles showed a reduction in pain intensity in postoperative patients, others are inconclusive or without statistically significant differences; also, the publications do not show changes in the anterior segment cells. 52–54

Comparative Efficacy
Atropine
Atropine is considered the gold standard due to the greater amount of cycloplegia it produces, with fewer residual accommodation (0.5–1.1 D) compared to other cycloplegics like cyclopentolate (0.5–1.75 D). (Table 1) However, the long duration of its effect, its significant toxicity (tachycardia, tremor, lethargy, delirium, seizure, and respiratory depression) and the necessity of a further examination days after its administration mean that its use is usually avoided as a first option, especially in pediatric patients. 55–59 Nevertheless, some authors have shown that cyclopentolate’s cycloplegic effect is comparable to atropine with a shorter recovery time. 41,60

Homatropine
Homatropine hydrobromide is an inferior cycloplegic when compared to cyclopentolate (residual accommodation 1.6–2.5 D vs 0.5–1.75 D) (Table 1); also, it shows high cycloplegic variability among individuals and it is characterized by a moderate–high toxicity profile, mainly at the expense of CNS effects. 61,62

Scopolamine
Scopolamine, even in low doses, can affect the central nervous system (CNS) due to its incredible ease at crossing the blood–brain barrier; its main effect in the CNS is drowsiness and confusion. However, it can also provoke euphoria and amnesia; therefore, its use is not recommended for cycloplegia due to its frequent toxic secondary reactions. 1,28,63,64

Table 1 Comparison of the Main Characteristics of Mydriatic and Cycloplegic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Posology</th>
<th>Residual Accommodation</th>
<th>Mydriasis Maximal</th>
<th>Cycloplegic Maximal</th>
<th>Mydriasis Recovery</th>
<th>Cycloplegic Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>1,45,58,60</td>
<td>2–3 drops of 1% for 3–4 days†</td>
<td>0.5–1.1 D</td>
<td>30–40 min</td>
<td>60–180 min</td>
<td>7–10 days</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>1,45,61</td>
<td>1 or 2 drops of 0.25%</td>
<td>0.99–1.6 D</td>
<td>20–130 min</td>
<td>30–60 min</td>
<td>3–7 days</td>
</tr>
<tr>
<td>Homatropine</td>
<td>1,45</td>
<td>1 or 2 drops of 2 or 5%</td>
<td>1.6–2.5 D</td>
<td>40–60 min</td>
<td>30–60 min</td>
<td>1–3 days</td>
</tr>
<tr>
<td>Cyclopentolate</td>
<td>1,45,56,61,62</td>
<td>1 or 2 drops‖</td>
<td>0.5–1.75 D</td>
<td>20–60 min</td>
<td>25–75 min</td>
<td>1 day</td>
</tr>
<tr>
<td>Tropicamide</td>
<td>1,45,63</td>
<td>1 or 2 drops‡</td>
<td>1.3–6.5 D</td>
<td>20–30 min</td>
<td>30 min</td>
<td>6 hours</td>
</tr>
</tbody>
</table>

Notes: Residual accommodation: Amount of accommodation remaining after using a cycloplegic in its maximum cycloplegic capacity. †1% Adults, 0.5% pediatrics and children; ‖1% Adults, 0.5% pediatrics and children; †Safety and effectiveness not established in pediatric patients, ․in children less than 1 year, only one drop per day; †Only studied in subject from 15 to 37 years old.
Abbreviations: D, Diopeter; Min, Minutes.
Tropicamide

The treatment choice for cycloplegic and mydriatic procedures, especially in children, is either tropicamide or cyclopentolate, but they both have pros and cons. For example, tropicamide shows a quick and transient effect, with low systemic impact, while cyclopentolate shows a more significant cycloplegic effect and a minor variation of residual accommodation when compared to tropicamide (0.5–1.75 D vs 1.3–6.5 D) (Table 1).

Risk

Adverse Drugs Reactions

Ocular Adverse Events

These types of ADRs are relatively frequent but also mild and temporary. The ocular ADRs with the highest incidence are burning sensation, photophobia, hyperemia, increased intraocular pressure, punctate keratitis, synchiae and blurred vision. 

Systemic Adverse Drugs Reactions

The ADRs more frequently enounced were collected in the literature and mentioned below, considering the order of mentions: dysarthria or language problems (mentioned 12 times), visual or tactile hallucinations (mentioned 11 times), ataxia (mentioned 10 times), seizures (mentioned 7 times), restlessness (mentioned 6 times), inability to recognize people (mentioned 5 times), space-time disorientation (mentioned 5 times), confusion (mentioned 4 times), drowsiness (mentioned 4 times), amnesia (mentioned 4 times), disorientation (mentioned 4 times), behavioral disturbance (mentioned 4 times), acute psychotic reaction (mentioned 3 times), tachycardia (mentioned 3 times), facial flush (mentioned 3 times), dizziness (mentioned 2 times), nausea (mentioned 2 times), mucosal dryness (mentioned 2 times), urinary retention (mentioned 2 times), vasodilation (mentioned 2 times), waning of the intensity of the voice (mentioned 1 time), inappropriate behavior or language (mentioned 1 time), impairment of cognitive functions (mentioned 1 time), emotional distress (mentioned 1 time), hyperactivity (mentioned 1 time), hyperpyrexia (mentioned 1 time), wandering (mentioned 1 time), decreased gastrointestinal motility (mentioned 1 time), spinal cord paralysis (mentioned 1 time), skin rash (mentioned 1 time), anaphylactic reaction (mentioned 1 time), pathological laughing (mentioned 1 time), decreased sweet gland secretion (mentioned 1 time), sadness (mentioned 1 time), coma (mentioned 1 time), but unlike ocular adverse events, systemic ADRs are infrequent and mainly occur in patients with risk factors.

The three most frequent ADRs (language problems, visual or tactile hallucinations and ataxia) are described below.

Language Problems

Dysarthria and language problems are the most frequently cited systemic ADRs in the literature. The deterioration of verbal fluency after using anticholinergics is explained by mental deficiency caused by a decrease in acetylcholine in the central nervous system since the oral language fluency task requires high cognitive processing demands. This ADR is usually accompanied by other CNS problems such as visual or tactile hallucinations, ataxia, confusion, space-time disorientation, inability to recognize people, and memory deficits.

Visual or Tactile Hallucinations

This event is due to anticholinergic compounds like cyclopentolate can produce analogous psychotic symptoms like visual or tactile hallucinations in healthy subjects, due to cortical muscarinic receptors are responsible for improving the neuronal signal-to-noise ratio, and therefore, the absence of cortical acetylcholine may cause irrelevant sensory and intrinsic information (processed in parallel at the subconscious level) to invade the consciousness.

Ataxia

This event occurs because cholinergic conduction plays a significant role in the modulation of cerebellar function; consequently, an alteration in the cerebellum’s mACHr has been associated with motor problems and lack of coordination.
Abuse Cases

Another risk associated with cycloplegic drugs is the abuse cases; these issues have been reported with cyclopentolate, although this risk is uncommon. The cases of cyclopentolate abuse found in the literature are presented below.

**Case 1.** An 18-year-old female patient who administered 200 to 400 drops (approx. 20 mL at a 1% concentration) daily in both eyes came to the emergency room due to overdose. She showed photophobia, tearing, and eye irritation, diffuse corneal epithelial punctate keratitis, and dilated pupils without responding to light. A 30-year-old female patient with a history of chronic alcoholism with choroiditis and panuveitis treated with prednisolone (ophthalmic and systemic), azathioprine, and ophthalmic cyclopentolate administered 1035 mL over 7 months, approximately 5 mL (100 drops) daily.

**Case 2.** A 25-year-old male patient with bilateral epithelial keratitis was initially treated with topical antibiotics, steroids, tropicamide, and 1% cyclopentolate. Drug-induced toxicity was speculated to contribute to the keratitis, and the patient reported applying 100 to 200 drops of cyclopentolate and tropicamide many times daily. Weight loss and continued sleep were reported. On cessation, the keratitis resolved within 4 days but with withdrawal symptoms of excessive salivation, tremors, rigidity, nausea, vomiting, and anxiety.

**Case 3.** A 28-year-old male patient who abused cyclopentolate hydrochloride mentions that he liked the burning effect that the drug made him feel. Withdrawal symptoms on attempts to discontinue use included nausea and sweating.

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**Case 5.** A 39-year-old male patient with Behçet’s syndrome and a related vision disorder abused cyclopentolate eye drops and alcohol for 15 years and increased the dose to 100 drops per day. As a result, he reported blurred vision, impaired concentration, loss of interest, and increased anxiety when trying to lower or abstain from the dose. Dependence treatment was successful for alcohol, but not for eye drops, and the patient continued using 100 drops per day.

**Case 6.** A 28-year-old male patient with a history of bipolar illness, depression, and manic disorders since age 20 used intranasal administration with up to 100 drops each day. Cravings, manic episodes, and mood elevation were the driving forces for continued use.

**Precautions**

Special care must be taken during cyclopentolate use in patients with certain conditions due to the possibility of severe ADRs, such as children (tachycardia, language problems, feeding intolerance, seizures, toxicity in CNS, delirium, ataxia, decreased motility, necrotizing enterocolitis, paralytic ileus), geriatrics (toxicity in CNS, delirium, dementia), Patients with brain damage (psychotic reactions, seizures, memory loss, ataxia, disorientation, language problems), patient with low blood level of pseudocholinesterase (seizures), narrow anterior chamber or glaucoma patients (increased of intraocular pressure, angle-closure glaucoma), and users of substances with CNS effects (amantadine: confusion, hallucinations; belladonna: excessive sedation, dry mouth, constipation, reduced urination; fluvoxamine: acute psychotic reactions). Table 2, summarizes the main effects related to cyclopentolate in particular populations.

**Recommendations**

To prevent the systemic adverse effects of cyclopentolate, the literature recommends avoiding the use of 2% cyclopentolate and instead employing solutions with lower concentrations that still produce cycloplegia, such as 0.2%, 0.5%, or 1% concentrations, preferably with another mydriatic such as phenylephrine. Also, a limited dosage (instill one drop in the eye followed by a second drop after an interval of 5 to 15 minutes in the case of the unequivocal failure of cycloplegia and mydriasis) is recommended. Likewise, the occlusion of the nasolacrimal duct after instillation limits the drug’s absorption, reducing the risk of systemic adverse events.

When present, early recognition of signs and symptoms of systemic toxicity is essential. The treatment of cyclopentolate toxicity is essentially symptomatic. In case of severe adverse effects on the nervous system, the drug of choice is physostigmine, although it can be complicated to obtain in some countries since it is not always commercially available; in those cases, the options are benzodiazepines such as diazepam or midazolam.
Unfortunately, commonly used anticholinesterase agents such as neostigmine, pyridostigmine, and edrophonium, do not cross the blood–brain barrier, and hence are not helpful in treating these effects.\textsuperscript{21}

Several authors mention that the instillation of cyclopentolate should be used with caution in children, patients with neurological disorders, patients with Down’s syndrome and patients exposed to anticholinergics.\textsuperscript{77,80,86} On the other hand, although the abuse of cyclopentolate is infrequent, special care should be taken in patients with a history of drug abuse and those who request an excessive amount of cyclopentolate.\textsuperscript{72,101}

**Conclusion**

The main benefits of cyclopentolate are found in the diagnosis of refractive errors such as myopia and hyperopia (regarded as an effective option, second only to atropine, but with the advantage of a less toxic systemic profile), the treatment of anterior uveitis, the treatment of childhood myopia (there are more effective cycloplegics), and anterior segment analgesics (its effectiveness is contradictory). On the contrary, the identified risks are divided into ocular and systemic; the ocular risks are usually mild and transient, and the most frequent ADRs are burning sensation, photophobia, hyperemia, increased intraocular pressure, punctate keratitis, synechiae and blurred vision, on the other hand, systemic ADRs are infrequent and usually occur in susceptible patients, being the most important: dysarthria or language problems, visual or tactile hallucinations, ataxia, seizures and their potential dependence on populations with a history of abuse.

Special care must be taken in its use in susceptible patients such as children, geriatrics, brain damage, Down’s syndrome, patient with low activity or serum level of pseudocholinesterase and patients with a diagnosis of narrow anterior chamber, in turn in this type of patient, it is recommended avoid the use of 2% cyclopentolate and use other presentations such as 1%, 0.5% or 0.2% in conjunction with a mydriatic, in addition to the occlusion of the nasolacrimal duct since avoiding systemic adverse reactions because it decreases up to 60% its systemic absorption. In case of presenting systemic ARDs, treatment is usually symptomatic, being phystostigmine the treatment of choice. Other treatments, such as benzodiazepines, can also be used.

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