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REVIEW

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),[1,2] mainly mAChR M3, in the ciliary muscle and iris.[3,4]

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 $G_{q/11}$ group, while the two remaining subtypes (M2 and M4) are part of the $G_{i/o}$ group of G proteins.[5]

Five ocular mydriatics and cycloplegics are currently available: atropine sulfate, homatropine hydrobromide, scopolamine hydrobromide, tropicamide and cyclopentolate hydrochloride.[1,6]

Cyclopentolate [2-(dimethylamino)ethyl 2-(1-hydroxycyclopentyl)-2-phenylacetate],[7] a competitive non-selective mAChR antagonist,[8–10] was synthesized by Teves and Testa in 1951.[11] It was used for the first time in the early 1950s,[12,13] and initially approved in 1953 by Schieffelin.[14,15]

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),[16] Canada (Cyclogyl,

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Alcon, 1972),[17] the United States (Cyclogyl, Alcon, 1974),[18] and the United Kingdom (Minims, Bausch & Lomb, 1987).[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).[20–23] Once absorbed, it is rapidly distributed to the bloodstream, exhibiting its maximum systemic concentration after between 10 and 60 minutes,[24,25] with a half-life of around 100 minutes.[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%.[25]

Mechanism of Action

The pharmacological effect of cyclopentolate is due to the competitive antagonism of mAChR (mainly through the stereoisomer [-] of cyclopentolate),[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).[28]

Its maximum effect ranges from 20 to 60 minutes after installation in hyperpigmented irises and 10 to 30 minutes in hypopigmented ones.[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.[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.[32,35,36] The timely diagnosis and treatment of hyperopic amblyopia prevents its progression of accommodative esotropia and the resultant strabismic amblyopia.[35,36] Also, studies have been published assessing the need to further extend the use of cycloplegia into adolescence and adulthood.[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;[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.[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

Drug	Posology	Residual Accommodation	Mydriasis Maximal	Cycloplegic Maximal	Mydriasis Recovery	Cycloplegic Recovery
Atropine[1,45,56,60]	2–3 drops of 1% for 3–4 days[§]	0.5–1.1 D	30–40 min	60–180 min	7–10 days	6–12 days
Scopolamine¥,[1,45,61]	1 or 2 drops of 0.25%	0.99–1.6 D	20–130 min	30–60 min	3–7 days	3–7 days
Homatropine‡,[1,45]	1 or 2 drops of 2 or 5%	1.6–2.5 D	40–60 min	30–60 min	1–3 days	1–3 days
Cyclopentolate[1,45,56,61,62]	1 or 2 drops*	0.5–1.75 D	20–60 min	25–75 min	1 day	6–24 hours
Tropicamide[1,45,63]	1 or 2 drops[†]	1.3–6.5 D	20–30 min	30 min	6 hours	0.5–6 hours

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, Diopter; Min, Minutes.

Tropicamide

The treatment choice for cycloplegic and mydriatic procedures, especially in children, is either tropicamide or cyclopentolate,[55] 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)[55,65–67] (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, synechiae and blurred vision.[68–70]

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),[1,65,68,71–79] visual or tactile hallucinations (mentioned 11 times),[1,65,71,72,74–76,78–82] ataxia (mentioned 10 times),[1,65,68,71–74,76,77,80] seizures (mentioned 7 times),[1,72,83–87] restlessness (mentioned 6 times),[1,71,74,75,79,80] inability to recognize people (mentioned 5 times),[1,71,74,75,79] space-time disorientation (mentioned 5 times),[1,68,74,75,81] confusion (mentioned 4 times),[71,77,79,80] drowsiness (mentioned 4 times),[1,70–72] amnesia (mentioned 4 times),[74,75,79,81] disorientation (mentioned 4 times),[79–81,88] behavioral disturbance (mentioned 4 times),[21,78,81,88] acute psychotic reaction (mentioned 3 times),[68,71,75] tachycardia (mentioned 3 times),[1,71,80] facial flush (mentioned 3 times),[70,71,78] dizziness (mentioned 2 times),[74,80] nausea (mentioned 2 times),[70,80] mucosal dryness (mentioned 2 times),[1,71] urinary retention (mentioned 2 times),[1,78] vasodilation (mentioned 2 times),[1,80] waning of the intensity of the voice (mentioned 1 time),[75] Inappropriate behavior or language (mentioned 1 time),[78] Impairment of cognitive functions (mentioned 1 time),[89] Emotional distress (mentioned 1 time),[72] hyperactivity (mentioned 1 time),[1] hyperpyrexia (mentioned 1 time),[1] wandering (mentioned 1 time),[75] decreased gastrointestinal motility (mentioned 1 time),[1] spinal cord paralysis (mentioned 1 time),[1] skin rash (mentioned 1 time),[1] anaphylactic reaction (mentioned 1 time),[90] pathological laughing (mentioned 1 time),[80] decreased sweet gland secretion (mentioned 1 time),[1] sadness (mentioned 1 time),[80] coma (mentioned 1 time);[1] but unlike ocular adverse events, systemic ADRs are infrequent and mainly occur in patients with risk factors.[83,84,91–94]

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.[95]

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.[1,65,68,71–79]

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.[74,96]

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.[68,97]

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.[72]

Case 2. 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.[72]

Case 3. 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.[98]

Case 4. 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.[99]

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.[100]

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.[101]

Precautions

Special care must be taken during cyclopentolate use in patients with certain conditions due to the possibility of severe ADRs,[74,78,93,94] ie children (tachycardia, language problems, feeding intolerance, seizures, toxicity in CNS, delirium, ataxia, decreased motility, necrotizing enterocolitis, paralytic ileus),[21,68,78,83–86,90,94] geriatrics (toxicity in CNS, delirium, dementia).[68,74,86] Patients with brain damage (psychotic reactions, seizures, memory loss, ataxia, disorientation, language problems),[74,78,83–85,102] patient with low blood level of pseudocholinesterase (seizures),[83,92,103] narrow anterior chamber or glaucoma patients (increased of intraocular pressure, angle-closure glaucoma),[1,68,78,104,105] and users of substances with CNS effects (amantadine: confusion, hallucinations; belladonna: excessive sedation, dry mouth, constipation, reduced urination; fluvoxamine: acute psychotic reactions).[68,80] 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.[71,75,77–79,86,89,93,106] Likewise, the occlusion of the nasolacrimal duct after instillation limits the drug's absorption, reducing the risk of systemic adverse events.[71,76,86,93]

When present, early recognition of signs and symptoms of systemic toxicity is essential.[83] 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.[21,78,83,87,91,94]

Table 2 Special Populations and/or Conditions of Special Care with the Use of Cyclopentolate

Condition	Effect
Children Neonates Premature[21,68,76,82,84,92]	Cardiovascular, nervous, digestive, metabolic and excretory system immaturity
	Lower blood volume
	Increase brain–blood permeability
Geriatrics[68,92]	Impaired nervous system
Epilepsy Brain damage Down's syndrome[68,76,83,84,86,94,102]	Disjointed stimulation of the nervous system
Mutant pseudocholinesterase Low activity or serum level of pseudocholinesterase[71,76,103]	Decreased metabolism of cyclopentolate
Glaucoma Narrow anterior chamber[1,68,84,104,105]	May interfere with anti-glaucoma action of carbachol or pilocarpine
	Significant changes in anterior chamber structure and anterior segment angle
Use of substances with a central nervous system effect[68,85]	Interference with the cholinergic system

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.[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.[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.[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 physostigmine the treatment of choice. Other treatments, such as benzodiazepines, can also be used.

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References

1. Frazier M, Jaanus SD. Chapter 9 - cycloplegics. In: Bartlett JD, Jaanus SD, Fiscella RG, Holdeman NR editors. *Prokopich CLBT-COP*. Butterworth-Heinemann; 2008:125–138. doi:10.1016/B978-0-7506-7576-5.50014-8
2. Sastry BV. Cholinergic systems and multiple cholinergic receptors in ocular tissues. *J Ocul Pharmacol*. 1985;1(2):201–226. doi:10.1089/jop.1985.1.201
3. Matsumoto S, Yorio T, DeSantis L, Pang IH. Muscarinic effects on cellular functions in cultured human ciliary muscle cells. *Investig Ophthalmol Vis Sci*. 1994;35(10):3732–3738.
4. Gil DW, Krauss HA, Bogardus AM, WoldeMussie E. Muscarinic receptor subtypes in human iris-ciliary body measured by immunoprecipitation. *Investig Ophthalmol Vis Sci*. 1997;38(7):1434–1442.
5. Kruse AC, Kobilka BK, Gautam D, Sexton PM, Christopoulos A, Wess J. Muscarinic acetylcholine receptors: novel opportunities for drug development. *Nat Rev Drug Discov*. 2014;13(7):549–560. doi:10.1038/nrd4295
6. Hammer RH, Wu W, Sastry JS, Bodor N. Short acting soft mydriatics. *Curr Eye Res*. 1991;10(6):565–570. doi:10.3109/02713689109001765
7. PubChem. Cyclopentolate. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Cyclopentolate. Accessed February 12, 2022.
8. Cuprian-Beltechi AM, Solanki P, Teramoto N, Cunnane TC. High spatial resolution studies of muscarinic neuroeffector junctions in mouse isolated vas deferens. *Neuroscience*. 2009;162(4):1366–1376. doi:10.1016/j.neuroscience.2009.05.064
9. Fang F, Huang F, Xie R, et al. Effects of muscarinic receptor modulators on ocular biometry of Guinea pigs. *Ophthalmic Physiol Opt*. 2015;35(1):60–69. doi:10.1111/opo.12166
10. Mitchell A, Hall RW, Erickson SW, Yates C, Hendrickson H. Systemic absorption of cyclopentolate and adverse events after retinopathy of prematurity exams. *Curr Eye Res*. 2016;41(12):1601–1607. doi:10.3109/02713683.2015.1136419
11. Treves GR, Testa FC. Basic esters and quaternary derivatives of β-hydroxy acids as antispasmodics 1. *J Am Chem Soc*. 1952;74(1):46–48. doi:10.1021/ja01121a012
12. Nyhan WL, Shirkey HC, Bauer CR, Trepanier Trottier MC, Stern L. Systemic cyclopentolate (Cyclogyl) toxicity in the newborn infant. *J Pediatr*. 1973;82(3):501–505. doi:10.1016/S0022-3476(73)80134-9
13. Hancox J, Murdoch I, Parmar D. Changes in intraocular pressure following diagnostic mydriasis with cyclopentolate 1%. *Eye*. 2002;16(5):562–566. doi:10.1038/sj.eye.6700146
14. William Andrew Publishing. C. *Pharmaceutical Manufacturing Encyclopedia*. 3rd ed. William Andrew Publishing; 2007:783–1186. doi:10.1016/B978-0-8155-1526-5.50007-6
15. National Center for Advancing Translational Sciences. Cyclopentolate. Available from: https://drugs.ncats.io/drug/I76F4SHP7J. Accessed February 4, 2022.
16. Spanish Agency of Medicines and Medical Devices. Colircusi cicloplejico [Cycloplegic colircusis]. Available from: http://cima.aemps.es/cima/publico/lista.html. Accessed February 22, 2022. Spanish.
17. Health Canada. Cyclogyl. Available from: https://health-products.canada.ca/dpd-bdpp/dispatch-repartition.do;jsessionid=6AB1BFE14A8EC3BABE83E22227AE772E. Accessed February 7, 2022.
18. Food and Drug Administration. Cyclogyl. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=084108. Accessed February 15, 2022.
19. Medicines and healthcare products regulatory agency. minims. Available from: https://products.mhra.gov.uk/search/?search=cyclopentolate&page=1. Accessed March 3, 2022.
20. Gray RH, Bates AK, Twomey JM, Claridge K. Textbook of ocular pharmacology edited by Thom J. Zimmerman, Karanjit S. Kooner, Mordechai Sharir and Robert D. Fechtner. *J Pharm Pharmacol*. 1998;50(7):827. doi:10.1111/j.2042-7158.1998.tb07147.x
21. Pooniya V, Pandey N. Systemic toxicity of topical cyclopentolate eyedrops in a child. *Eye*. 2012;26(10):1391–1392. doi:10.1038/eye.2012.149
22. Salminen L. Review: systemic absorption of topically applied ocular drugs in humans. *J Ocul Pharmacol*. 1990;6(3):243–249. doi:10.1089/jop.1990.6.243
23. Lahdes KK, Huupponen RK, Kaila TJ. Ocular effects and systemic absorption of cyclopentolate eyedrops after canthal and conventional application. *Acta Ophthalmol*. 1994;72(6):698–702. doi:10.1111/j.1755-3768.1994.tb04683.x
24. Kaila T, Huupponen R, Salminen L, Iisalo E. Systemic absorption of ophthalmic cyclopentolate. *Am J Ophthalmol*. 1989;107(5):562–564. doi:10.1016/0002-9394(89)90515-1
25. Haaga M, Kaila T, Salminen L, Ylitalo P. Systemic and ocular absorption and antagonist activity of topically applied cyclopentolate in man. *Pharmacol Toxicol*. 1998;82(1):19–22. doi:10.1111/j.1600-0773.1998.tb01392.x
26. Lahdes K, Huupponen R, Kaila T, Monti D, Saettone MF, Salminen L. Plasma concentrations and ocular effects of cyclopentolate after ocular application of three formulations. *Br J Clin Pharmacol*. 1993;35(5):479–483. doi:10.1111/j.1365-2125.1993.tb04173.x
27. Smith SA. Factors determining the potency of mydriatic drugs in man. *Br J Clin Pharmacol*. 1976;3(3):503–507. doi:10.1111/j.1365-2125.1976.tb00628.x
28. Waller DG, Sampson AP. 50 - the eye. In: Waller DG editor. *Sampson APBT-MP and T*. Elsevier; 2018:569–578. doi:10.1016/B978-0-7020-7167-6.00050-6
29. Manny RE, Fern KD, Zervas HJ, et al. 1% Cyclopentolate hydrochloride: another look at the time course of cycloplegia using an objective measure of the accommodative response. *Optom Vis Sci off Publ Am Acad Optom*. 1993;70(8):651–665. doi:10.1097/00006324-199308000-00013

30. Portello JK. Chapter 8 - mydriatics and mydriolytics. In: Bartlett JD, Jaanus SD, Fiscella RG, Holdeman NR editors. *Prokopich CLBT-COP*. Butterworth-Heinemann; 2008:113–123. doi:10.1016/B978-0-7506-7576-5.50013-6
31. Laojaroenwanit S, Layanun V, Praneeprachachon P, Pukrushpan P. Time of maximum cycloplegia after instillation of cyclopentolate 1% in children with brown irises. *Clin Ophthalmol*. 2016;10:897–902. doi:10.2147/OPTH.S102611
32. Hashemi H, Khabazkhoob M, Asharlous A, et al. Cycloplegic autorefraction versus subjective refraction: the Tehran eye study. *Br J Ophthalmol*. 2016;100(8):1122–1127. doi:10.1136/bjophthalmol-2015-307871
33. Saunders KJ. Early refractive development in humans. *Surv Ophthalmol*. 1995;40(3):207–216. doi:10.1016/S0039-6257(95)80027-1
34. Asharlous A, Hashemi H, Jafarzadehpur E, et al. Does astigmatism alter with cycloplegia? *J Curr Ophthalmol*. 2016;28(3):131–136. doi:10.1016/j.joco.2016.05.003
35. Morgan IG, Iribarren R, Fotouhi A, Grzybowski A. Cycloplegic refraction is the gold standard for epidemiological studies. *Acta Ophthalmol*. 2015;93(6):581–585. doi:10.1111/aos.12642
36. Arici C, Türk A, Keskin S, Ceylan OM, Mutlu FM, Altinsoy HI. Effect of cycloplegia on refractive errors measured with three different refractometers in school-age children. *Turkish J Med Sci*. 2012;42(4):657–665. doi:10.3906/sag-1104-44
37. Jorge J, Almeida JB, Parafita MA. Refractive, biometric and topographic changes among Portuguese university science students: a 3-year longitudinal study. *Ophthalmic Physiol Opt J Br Coll Ophthalmic Opt*. 2007;27(3):287–294. doi:10.1111/j.1475-1313.2007.00475.x
38. Krantz EM, Cruickshanks KJ, Klein BEK, Klein R, Huang G-H, Nieto FJ. Measuring refraction in adults in epidemiological studies. *Arch Ophthalmol*. 2010;128(1):88–92. doi:10.1001/archophthalmol.2009.349
39. Wallace DK, Morse CL, Melia M, et al. Pediatric eye evaluations preferred practice pattern®: i. vision screening in the primary care and community setting; II. comprehensive ophthalmic examination. *Ophthalmology*. 2018;125(1):P184–P227. doi:10.1016/j.ophtha.2017.09.032
40. Chuck RS, Jacobs DS, Lee JK, et al. Refractive errors & refractive surgery preferred practice pattern®. *Ophthalmology*. 2018;125(1):P1–P104. doi:10.1016/j.ophtha.2017.10.003
41. Celebi S, Aykan U. The comparison of cyclopentolate and atropine in patients with refractive accommodative esotropia by means of retinoscopy, autorefractometry and biometric lens thickness. *Acta Ophthalmol Scand*. 1999;77(4):426–429. doi:10.1034/j.1600-0420.1999.770414.x
42. Babu K, Mahendradas P. Medical management of uveitis - current trends. *Indian J Ophthalmol*. 2013;61(6):277–283. doi:10.4103/0301-4738.114099
43. Dacey M. Ankylosing spondylitis BT - Uveitis: a practical guide to the diagnosis and treatment of intraocular inflammation. In: Papaliodis GN editor. *Uveitis*. Springer International Publishing; 2017:135–141. doi:10.1007/978-3-319-09126-6_19
44. Barb SM. Post-traumatic Uveitis and post-operative inflammation BT - Uveitis: a practical guide to the diagnosis and treatment of intraocular inflammation. In: Papaliodis GN editor. *Uveitis*. Springer International Publishing; 2017:275–284. doi:10.1007/978-3-319-09126-6_40
45. Henderer JD, Rapuano CJ. Farmacología ocular [Ocular pharmacology]. In: Brunton LL, Chabner BA, Knollmann BC, editors. *Goodman & Gilman: The Pharmacological Basis of Therapeutics, 13e*. McGraw-Hill Education; 2019. Spanish.
46. Bayer G. Martindale: the complete drug reference. *Aust Prescr*. 2015;38(2):59. doi:10.18773/austprescr.2015.023
47. Ye L, Li S, Shi Y, et al. Comparisons of atropine versus cyclopentolate cycloplegia in myopic children. *Clin Exp Optom*. 2021;104(2):143–150. doi:10.1111/cxo.13128
48. Yen MY, Liu JH, Kao SC, Shiao CH. Comparison of the effect of atropine and cyclopentolate on myopia. *Ann Ophthalmol*. 1989;21(5):180–182.
49. Rathi M, Chhabra S, Sachdeva S, Rustagi IM, Soni D, Dhania S. Correlation of parental and childhood myopia in children aged 5–16 years in North India. *Indian J Ophthalmol*. 2022;70(9):3366–3368. doi:10.4103/ijo.IJO_653_22
50. Pérez-Flores I, Macías-Murelaga B, Barrio-Barrio J. A multicenter Spanish study of atropine 0.01% in childhood myopia progression. *Sci Rep*. 2021;11(1):21748. doi:10.1038/s41598-021-00923-1
51. Hieda O, Hiraoka T, Fujikado T, et al. Efficacy and safety of 0.01% atropine for prevention of childhood myopia in a 2-year randomized placebo-controlled study. *Jpn J Ophthalmol*. 2021;65(3):315–325. doi:10.1007/s10384-021-00822-y
52. Ahmed S, Mann P, Gaskell A, Roxburgh S. Effect of postoperative mydriatics on the iris. *J Cataract Refract Surg*. 1996;22(5):597–600. doi:10.1016/S0886-3350(96)80016-2
53. Goktas S, Sakarya Y, Ozcimen M, et al. Effect of topical cyclopentolate on post-operative pain after pterygium surgery. *Clin Exp Optom*. 2017;100(6):595–597. doi:10.1111/cxo.12513
54. Tsuyoshi O, Gimbel HV, DeBroff BM. Effects of cycloplegia and iris pigmentation on postoperative intraocular inflammation. *Ophthalmic Surg Lasers Imaging Retina*. 1993;24(11):746–752. doi:10.3928/1542-8877-19931101-08
55. Yoo SG, Cho MJ, Kim US, Baek SH. Cycloplegic refraction in hyperopic children: effectiveness of a 0.5% tropicamide and 0.5% phenylephrine addition to 1% cyclopentolate regimen. *Korean J Ophthalmol*. 2017;31(3):249–256. doi:10.3341/kjo.2016.0007
56. Ebri A, Kuper H, Wedner S. Cost-effectiveness of cycloplegic agents: results of a randomized controlled trial in Nigerian children. *Invest Ophthalmol Vis Sci*. 2007;48(3):1025–1031. doi:10.1167/iovs.06-0604
57. Micromedex. Atropine. Available from: https://www.micromedexsolutions.com/micromedex2/librarian/CS/036929/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/D2E6A2/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.DoIntegr. Accessed April 6, 2022.
58. Rosenbaum AL, Bateman JB, Bremer DL, Liu PY. Cycloplegic refraction in esotropic children. Cyclopentolate versus atropine. *Ophthalmology*. 1981;88(10):1031–1034. doi:10.1016/S0161-6420(81)80032-2
59. Auffarth G, Hunold W. Cycloplegic refraction in children: single-dose-atropinization versus three-day-atropinization. *Doc Ophthalmol*. 1992;80(4):353–362. doi:10.1007/BF00154384
60. Salvesen S, Køhler M. Automated refraction. A comparative study of automated refraction with the Nidek AR-1000 autorefractor and retinoscopy. *Acta Ophthalmol*. 1991;69(3):342–346. doi:10.1111/j.1755-3768.1991.tb04825.x
61. Khurana AK, Ahluwalia BK, Rajan C. Status of cyclopentolate as a cycloplegic in children: a comparison with atropine and homatropine. *Acta Ophthalmol*. 1988;66(6):721–724. doi:10.1111/j.1755-3768.1988.tb04069.x

62. Micromedex. Homatropine. Available from: https://www.micromedexsolutions.com/micromedex2/librarian/CS/961F91/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/298C6F/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.DoIntegr. Accessed April 6, 2022.
63. Micromedex. Scopolamine. Available from: https://www.micromedexsolutions.com/micromedex2/librarian/CS/1CF636/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/77A1CC/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.DoIntegr. Accessed April 8, 2022.
64. Choi O, Choo CH, Cho SC. The studies on the residual accommodation of Koreans. II. The residual accommodation under 0.5 percent scopolamine and 1 percent cyclogyl cycloplegia. *Yonsei Med J*. 1964;5:62–64. doi:10.3349/ymj.1964.5.1.62
65. Yazdani N, Sadeghi R, Momeni-Moghaddam H, Zarifmahmoudi L, Ehsaei A. Comparison of cyclopentolate versus tropicamide cycloplegia: a systematic review and meta-analysis. *J Optom*. 2018;11(3):135–143. doi:10.1016/j.optom.2017.09.001
66. Moghadas Sharif N, Shoeibi N, Heydari M, Yazdani N, Ghasemi-Moghaddam S, Ehsaei A. Effect of cyclopentolate versus tropicamide on anterior segment angle parameters in three refractive groups. *Clin Exp Optom*. 2021;104(2):151–155. doi:10.1111/cxo.13103
67. Manny RE, Hussein M, Scheiman M, Kurtz D, Niemann K, Zinzer K. Tropicamide (1%): an effective cycloplegic agent for myopic children. *Invest Ophthalmol Vis Sci*. 2001;42(8):1728–1735.
68. Micromedex. Cyclopentolate. Available from: https://www.micromedexsolutions.com/micromedex2/librarian/CS/C2B299/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/8E39D9/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.DoIntegr. Accessed May 5, 2022.
69. Bartlett JD. *Ophthalmic Drug Facts*. 25th ed. Facts & Comparisons; 2013.
70. Imai T, Hasebe S, Furuse T, et al. Adverse reactions to 1% cyclopentolate eye drops in children: an analysis using logistic regression models. *Ophthalmic Physiol Opt J Br Coll Ophthalmic Opt*. 2021;41(2):424–430. doi:10.1111/opo.12773
71. Adcock EW. Cyclopentolate (Cyclogyl) toxicity in pediatric patients. *J Pediatr*. 1971;79(1):127–129. doi:10.1016/s0022-3476(71)80074-4
72. Sato EH, de Freitas D, Foster CS. Abuse of cyclopentolate hydrochloride (Cyclogyl) drops. *N Engl J Med*. 1992;326(20):1363–1364.
73. Simcoe CW. Cyclopentolate (Cyclogyl) toxicity. Report of a case. *Arch Ophthalmol*. 1962;67:406–408. doi:10.1001/archopht.1962.00960020408005
74. Mark HH. Psychotogenic properties of cyclopentolate. *JAMA*. 1963;186:430–431. doi:10.1001/jama.1963.63710040009018c
75. Binkhors RD, Weinstein GW, Baretz RM, Clahane AC. Psychotic reaction induced by cyclopentolate (Cyclogyl). Results of pilot study and a double-blind study. *Am J Ophthalmol*. 1963;55:1243–1245.
76. Praeger DL, Miller SN. Toxic effects of cyclopentolate (Cyclogel). Report of a case. *Am J Ophthalmol*. 1964;58:1060–1061. doi:10.1016/0002-9394(64)90021-2
77. Schmidt I. Two patients with unusual reaction to drugs used in optometric practice. *Am J Optom Arch Am Acad Optom*. 1970;47(4):312–315. doi:10.1097/00006324-197004000-00010
78. Bhatia SS, Vidyashankar C, Sharma RK, Dubey AK. Systemic toxicity with cyclopentolate eye drops. *Indian Pediatr*. 2000;37(3):329–331.
79. Khurana AK, Ahluwalia BK, Rajan C, Vohra AK. Acute psychosis associated with topical cyclopentolate hydrochloride. *Am J Ophthalmol*. 1988;105(1):91. doi:10.1016/0002-9394(88)90128-6
80. Mirshahi A, Kohnen T. Acute psychotic reaction caused by topical cyclopentolate use for cycloplegic refraction before refractive surgery: case report and review of the literature. *J Cataract Refract Surg*. 2003;29(5):1026–1030. doi:10.1016/S0886-3350(02)01651-6
81. Shihab ZM. Psychotic reaction in an adult after topical cyclopentolate. *Ophthalmol J Int D'ophtalmologie Int J Ophthalmol Zeitschrift Fur Augenheilkd*. 1980;181(3–4):228–230. doi:10.1159/000309057
82. Rosembaum AL, Bateman JB, Bremer L, Liu PY. Cycloplegic refraction in esotropic children. *Amer J Ophthalmol*. 1981;88(10):1031–1034.
83. Büyükcam A, Celik HT, Korkmaz A, Yurdakök M. Myoclonic seizure due to cyclopentolate eye drop in a preterm infant. *Turk J Pediatr*. 2012;54(4):419–420.
84. Kennerdell JS, Wucher FP. Cyclopentolate associated with two cases of grand mal seizure. *Arch Ophthalmol*. 1972;87(6):634–635. doi:10.1001/archopht.1972.01000020636004
85. Mwanza JC. Cyclopentolate and grand mal seizure. *Bull Soc Belge Ophtalmol*. 1999;273:17–18.
86. Fitzgerald DA, Hanson RM, West C, Martin F, Brown J, Kilham HA. Seizures associated with 1% cyclopentolate eyedrops. *J Paediatr Child Health*. 1990;26(2):106–107. doi:10.1111/j.1440-1754.1990.tb02399.x
87. Wygnanski-Jaffe T, Nucci P, Goldchmit M, Mezer E. Epileptic seizures induced by cycloplegic eye drops. *Cutan Ocul Toxicol*. 2014;33(2):103–108. doi:10.3109/15569527.2013.808654
88. Mohan K, Sharma A. Optimal dosage of cyclopentolate 1% for cycloplegic refraction in hypermetropes with brown irides. *Indian J Ophthalmol*. 2011;59(6):514–516. doi:10.4103/0301-4738.86329
89. Carpenter WTJ. Precipitous mental deterioration following cycloplegia with 0.2 percent cyclopentolate HCl. *Arch Ophthalmol*. 1967;78(4):445–447. doi:10.1001/archopht.1967.00980030447006
90. Tayman C, Mete E, Catal F, Akca H. Anaphylactic reaction due to cyclopentolate in a 4-year-old child. *J Investig Allergol Clin Immunol*. 2010;20(4):347–348.
91. Rajeev A, Gupta G, Adhikari KM, Yadav AK, Sathyamoorthy M. Neurotoxic effects of topical cyclopentolate. *Med Journal*. 2010;66(3):288–289. doi:10.1016/S0377-1237(10)80069-3
92. Demayo AP, Reidenberg MM. Grand mal seizure in a child 30 minutes after Cyclogyl (cyclopentolate hydrochloride) and 10% Neo-Synephrine (phenylephrine hydrochloride) eye drops were instilled. *Pediatrics*. 2004;113(5):e499–e500. doi:10.1542/peds.113.5.e499
93. Ashok A, Bhat YM. Systemic toxicity in a child after topical cyclopentolate eye drops application. *Karnataka Pediatr J*. 2021;36:138–139. doi:10.25259/KPJ_23_2021
94. Turan C, Keskin G, Gunes S, Yurtseven A, Saz EU. Infantil delirium induced by cycloplegic eye drops. *Hong Kong J Emerg Med*. 2017;25(4):226–228. doi:10.1177/1024907917748726
95. Aarsland D, Larsen JP, Reinvang I, Aasland AM. Effects of cholinergic blockade on language in healthy young women: implications for the cholinergic hypothesis in dementia of the Alzheimer type. *Brain*. 1994;117(6):1377–1384. doi:10.1093/brain/117.6.1377
96. Perry EK, Perry RH. Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. *Brain Cogn*. 1995;28(3):240–258. doi:10.1006/brcg.1995.1255

97. Zhang C, Zhou P, Yuan T. The cholinergic system in the cerebellum: from structure to function. *Rev Neurosci*. 2016;27(8):769–776. doi:10.1515/revneuro-2016-0008
98. Ostler HB. Cycloplegics and mydriatics. Tolerance, habituation, and addiction to topical administration. *Arch Ophthalmol*. 1975;93(6):423. doi:10.1001/archopht.1975.01010020446011
99. Darcin AE, Dilbaz N, Yilmaz S, Cetin MK. Cyclopentolate hydrochloride eye drops addiction: a case report. *J Addict Med*. 2011;5(1):84–85. doi:10.1097/ADM.0b013e3181dd4f90
100. Akkaya C, Zorlu Kocagoz S, Sarandol A, Eker SS, Kirli S. Addiction to topically used cyclopentolate hydrochloride: a case report. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(7):1752–1753. doi:10.1016/j.pnpbp.2008.07.003
101. Al-Khalaileh W, Wazaify M, Van Hout MC. The misuse and abuse of ophthalmic preparations: a scoping review of clinical case presentations and extant literature. *Int J Ment Health Addict*. 2018;16(4):1055–1084. doi:10.1007/s11469-017-9868-2
102. Sinton JW, Cooper DS, Wiley S. Down syndrome and the autonomic nervous system, an educational review for the anesthesiologist. *Paediatr Anaesth*. 2022;32(5):609–616. doi:10.1111/pan.14416
103. Hu L, Dow K. Focal seizures after instillation of cyclomydril to a neonate with congenital CMV infection. *J Neonatal Perinatal Med*. 2014;7(2):147–149. doi:10.3233/NPM-1476413
104. Alghamdi WM, Alrasheed SH, Nair V, Alluwimi MS. Effects of cyclopentolate hydrochloride dosage on anterior segment parameters in young adults (measured with pentacam). *Clin Ophthalmol*. 2021;15:891–898. doi:10.2147/OPTH.S291991
105. Hashemi H, Asharlous A, Khabazkhoob M, et al. The effect of cyclopentolate on ocular biometric components. *Optom Vis Sci off Publ Am Acad Optom*. 2020;97(6):440–447. doi:10.1097/OPX.0000000000001524
106. Patel AJ, Simon JW, Hodgetts DJ. Cycloplegic and mydriatic agents for routine ophthalmologic examination: a survey of pediatric ophthalmologists. *J AAPOS off Publ Am Assoc Pediatr Ophthalmol Strabismus*. 2004;8(3):274–277. doi:10.1016/j.jaapos.2004.01.004