Cyclopentolate
Newborn Use Only

2018

Alert	Watch for apnoeas and abdominal distension following administration. Lower concentration solutions and regimens minimising number of additional drops are recommended.
Indication	Mydriatic (dilates the pupil) and cycloplegic (prevents accommodation of the eye) for ophthalmic examinations and therapeutic procedures.
Action	Muscarinic acetylcholine receptor competitive antagonist. Prevents the accommodative muscle of the ciliary body and the sphincter muscle of the iris from responding to cholinergic stimulation.
Drug Type	Antimuscarinic.
Trade Name	Minims® Cyclopentolate hydrochloride.
Presentation	Cyclopentolate hydrochloride 0.5% single-use preservative free eye drop, 0.5 mL per minim.
Dosage/Interval	Cyclopentolate 0.5% is used in combination with phenylephrine 2.5% with or without tropicamide 0.5%. Suggested regimens are: **REGIMEN 1:** Phenylephrine 2.5% + cyclopentolate 0.5% + tropicamide 0.5% eye drops [1-4]. Instil one drop of each agent (5 minutes apart) into each eye 60 minutes prior to examination. Repeat if pupillary dilatation inadequate. Perform examination 60 to 120 minutes after instillation. **REGIMEN 2:** Phenylephrine 2.5% + cyclopentolate 0.5% eye drops [5]. Instil one drop of each agent (5 minutes apart) into each eye 60 minutes prior to examination. Repeat if pupillary dilatation inadequate. Perform examination 60 to 120 minutes after instillation. Dark irides may require additional drops.
Maximum daily dose	REGIMEN 1: 3 drops of each eye drop. REGIMEN 2: 4 drops of each eye drop.
Route	Topical instillation into the eyes from the minim or use a microdrop (5–7 microL) cannula.
Preparation/Dilution	Not applicable.
Administration	Apply pressure to the lacrimal sac during and for 60 seconds after instillation of eye drop to minimise systemic absorption. Wipe away excess medication. Consider withholding feeds for four hours from administration of the last drops to reduce incidence of feed intolerance.
Monitoring	Heart rate and oxygen saturation in infants with bronchopulmonary dysplasia. Signs of ileus.
Contraindications	Necrotising enterocolitis (NEC) at the time of eye examination.
Precautions	Bronchopulmonary dysplasia – may increase absorption and decrease clearance.[22,26] Severe neurological impairment – may increase risk of seizures. Feeding intolerance. Lower concentration solutions and regimens minimising number of additional drops are recommended to minimise toxicity.
Drug Interactions	
Adverse Reactions	Feeding intolerance, abdominal distension and increased gastric residuals. Apnoea, transient bradycardia (especially infants on respiratory support). Stinging or burning of eye. Tachycardia and increased blood pressure. Rarely, dry mouth, urinary retention, fever, vasodilatation, restlessness, agitation, seizures.

Compatibility	Phenylephrine, tropicamide, amethocaine
Incompatibility	No information.
Stability	Discard unused portion immediately after use.
Storage	Store in refrigerator at 2°C to 8°C. Do not freeze. Protect from light.
Special Comments	Check correct strength of Minims® Cyclopentolate Eye Drops. Do NOT use 1% in neonates.
Evidence summary	**Efficacy and safety** Cyclopentolate alone (muscarinic acetylcholine antagonist): Several controlled trials have compared cyclopentolate 0.5% to 1% versus other individual eye drops (phenylephrine [α1-adrenoceptor agonist] or tropicamide [muscarinic acetylcholine antagonist]) or combination eye drops. Caputo et al, in a controlled study of 40 preterm infants, reported phenylephrine 1.0% or 2.5% or cyclopentolate 1% or tropicamide 1% (3 drops) produced inadequate mydriasis for peripheral retinal examination. A combination of phenylephrine 2.5% + cyclopentolate 0.5% + tropicamide 0.5% 1 to 3 drops of each produced adequate mydriasis (average 7.0 mm). Cyclopentolate 1% increased heart rate and BP.[4] Isenberg et al, in a controlled study of 30 preterm infants, reported phenylephrine 1% + cyclopentolate 0.2% (2 drops) combination produced greater mydriasis than cyclopentolate 0.5% + tropicamide 0.5% (2 drops), or cyclopentolate 0.5% (2 drops) alone. There was no blood pressure increase with cyclopentolate 0.5% (2 drops).[6] Ogut et al, in a parallel RCT in 80 preterm infants, reported cyclopentolate 1% (2 drops) produced net pupillary dilatation 3.8 mm. Maximum mydriasis was achieved with cyclopentolate 0.5% + tropicamide 0.5% + 2.5% phenylephrine (1 drop). Adequate mydriasis without side effects was achieved with 1% cyclopentolate + 1% tropicamide (1 drop).[2] Conclusion: Cyclopentolate 0.5% alone does not achieve optimal mydriasis. Cyclopentolate 1% may be associated with physiological side effects. Combination eye drops produce greater mydriasis and/or fewer physiological side effects than cyclopentolate alone. [LOE II GOR B] Phenylephrine 2.5% + cyclopentolate combination may be more effective than tropicamide 0.5% + cyclopentolate combination. [LOE II GOR C] Cyclopentolate combination (excluding Cyclomydril [cyclopentolate 0.2% + phenylephrine 1%]): Several trials have assessed the efficacy and safety of cyclopentolate 0.5% to 1% in combination with phenylephrine [α1-adrenoceptor agonist] and/or tropicamide [muscarinic acetylcholine antagonist]. Chew et al, in a parallel RCT in 39 preterm infants, reported cyclopentolate 0.2% + phenylephrine 1% 3 drops provided adequate pupillary dilation with the least systemic side effects; combination cyclopentolate 1% + phenylephrine 2.5% and tropicamide 1% + phenylephrine 2.5% were associated with increased BP; and cyclopentolate 1% + phenylephrine 2.5% may be associated with feed intolerance.[7] Bolt et al, in a parallel RCT in 39 preterm infants, reported the mydriatic effect of the phenylephrine 2.5% + tropicamide 0.5% combination was significantly superior to that of the cyclopentolate 0.5% + tropicamide 0.5% combination. A significant increase inj BP and HR peak values was observed within 7 to 10 minutes after the cyclopentolate 0.5% + tropicamide 0.5% combination only.[8] Sindel et al, in a parallel RCT in 34 preterm infants, reported mydriasis with phenylephrine 1.0% + tropicamide 1.0% was significantly less than phenylephrine 2.5% + tropicamide 1.0% or phenylephrine 2.5% + tropicamide 0.5% + cyclopentolate 0.5%. Dilatation was sufficient to allow appropriate examination in all infants (pupillary diameter > 6.0 mm). BP and heart rate increased transiently in all groups receiving mydriatic but returned to baseline values in 25 minutes. This increase was significant with 2.5% phenylephrine.[3] Ogut et al, in a parallel RCT in 80 preterm infants, reported maximum mydriasis was achieved with cyclopentolate 0.5% + tropicamide 0.5% + 2.5% phenylephrine (1 drop each);

	and adequate mydriasis without side effects was achieved with 1% cyclopentolate + 1% tropicamide (1 drop each).[2] Merritt et al, in a crossover RCT in 30 preterm infants, compared phenylephrine 2.5% + tropicamide 0.5% + cyclopentolate 0.5% (1 drop each) to saline control and reported maximal mydriasis at 75–90 minutes with adequate fundoscopy at 120 minutes, and no significant effect on systolic BP.[1] Nefendorf et al, in a cohort of 1246 eyes screened during 623 examinations of 138 infants, reported phenylephrine 2.5% + cyclopentolate 0.5% eye drops (3 times 5 minutes apart) was efficacious with 98.8% successful dilatation and well-tolerated although 0.8% had significant clinical deterioration in the following 24 hours.[5] Wheatcroft et al, in a controlled study comparing effects in each eye in 26 preterm infants, reported no difference in mydriasis from 5 microL versus 26 microL drops of cyclopentolate 0.5% and phenylephrine 2.5% (mean pupil diameter 6.05 mm [range 4.5 to 7.1 mm]) in the eyes dilated with standard drops and 6.1 mm [range 5. 0 to 7.5 mm] in microdrop eyes).[9] Conclusion: Cyclopentolate 0.5% + phenylephrine 2.5% combination produces adequate mydriasis [5] but may have physiological side effects and was associated with clinical deterioration in the following 24 hours in 0.8% of infants examined.[5] (LOE II GOR C) Cyclopentolate 0.5% + tropicamide 0.5% may not produce adequate mydriasis.[8] [LOE II GOR C] Adequate mydriasis without side effects was achieved with 1% cyclopentolate + 1% tropicamide.[2] [LOE II GOR C] **Safety:** Cyclopentolate alone (muscarinic acetylcholine antagonist): Clinical studies have reported variable physiological effects from use of cyclopentolate. Caputo et al[4] reported cyclopentolate 1% increased heart rate and BP whereas Isenberg et al [6] reported no blood pressure increase with cyclopentolate 0.5% (2 drops). Nefendorf et al [5], in a cohort of 1246 eyes screened during 623 examinations of 138 infants, reported phenylephrine 2.5% + cyclopentolate 0.5% eye drops (3 times 5 minutes apart) was efficacious with 98.8% successful dilatation and well-tolerated. There were no systemic adverse reactions necessitating abandonment of the examination. However, 0.8% had significant clinical deterioration in the 24 hours after examination. Potential side effects reported in case series and case reports include: feeding intolerance (abdominal distension and increased gastric aspirates) within 24 hours of mydriatic administration including cyclopentolate [10, 11]; acute gastric dilatation with the use of cyclopentolate 0.5% and phenylephrine 2.5% [12]; necrotising enterocolitis following the use of cyclopentolate eye drops [13-15]; and seizures [16-18]. However, causation has not been proven. In an observational study, feeding intolerance was reported to be reduced after introducing a 4-hour fasting period after instillation of eye drops. [10] Conclusions: Cyclopentolate 1% produces greater physiological effects than cyclopentolate 0.5%. Three drop regimens of combination eye drops were associated with more acute physiological effects and feed intolerance. [7, 19] [LOE II GOR B] **Pharmacokinetics and pharmacodynamics** Merritt et al reported maximal mydriasis at 75–90 minutes with adequate fundoscopy at 120 minutes using phenylephrine 2.5% + tropicamide 0.5% + cyclopentolate 0.5% 1 drop each.[1] Approximately 80% of each drop may pass through the nasolacrimal system and be available for rapid systemic absorption by nasal mucosa without lacrimal sac occlusion.[20] Finger pressure on the lacrimal punctus at the medial canthus of the eye immediately after installation of eye drops for at least 60 seconds reduces systemic absorption.[20] Mitchell et al reported cyclopentolate and phenylephrine serum concentrations in 18 preterm infants one hour after instillation of cyclopentolate 0.2% and phenylephrine 1% one drop each eye every five minutes for a total of three doses. Cyclopentolate (range 6–53 ng/ml) was observed in 15 of 18 infants, while phenylephrine was not detected.

	Concentrations of cyclopentolate were significantly higher in infants who were on oxygen. There was a significant association between cyclopentolate concentrations and gastric residuals in tube-fed infants not receiving oxygen.[21]
References	1. Merritt JC, Kraybill EN. Effect of mydriatics on blood pressure in premature infants. Journal of Pediatric Ophthalmology and Strabismus. 1981;18:42-6. 2. Ogut MS, Bozkurt N, Ozek E, Birgen H, Kazokoglu H, Ogut M. Effects and side effects of mydriatic eyedrops in neonates. European Journal of Ophthalmology. 1996;6:192-6. 3. Sindel BD, Baker MD, Maisels MJ, Weinstein J. A comparison of the pupillary and cardiovascular effects of various mydriatic agents in preterm infants. Journal of Pediatric Ophthalmology and Strabismus. 1986;23:273-6. 4. Caputo AR, Schnitzer RE. Systemic response to mydriatic eyedrops in neonates: Mydriatics in neonates. Journal of Pediatric Ophthalmology and Strabismus. 1978;15:109-22. 5. Nefendorf JE, Michael Mota P, Xue K, Darius Hildebrand G. Efficacy and safety of phenylephrine 2.5% with cyclopentolate 0.5% for retinopathy of prematurity screening in 1246 eye examinations. European Journal of Ophthalmology. 2015;25:249-53. 6. Isenberg S, Everett S, Parelhoff E. A comparison of mydriatic eyedrops in low-weight infants. Ophthalmology. 1984;91:278-9. 7. Chew C, Rahman RA, Shafie SM, Mohamad Z. Comparison of mydriatic regimens used in screening for retinopathy of prematurity in preterm infants with dark irides. Journal of Pediatric Ophthalmology and Strabismus. 2005;42:166-73. 8. Bolt B, Benz B, Koerner F, Bossi E. A mydriatic eye-drop combination without systemic effects for premature infants: A prospective double-blind study. Journal of Pediatric Ophthalmology and Strabismus. 1992;29:157-62. 9. Wheatcroft S, Sharma A, McAllister J. Reduction in mydriatic drop size in premature infants. Br J Ophthalmol. 1993;77:364-5. 10. Hermansen MC, Hasan S. Abolition of feeding intolerance following ophthalmologic examination of neonates. J Pediatr Ophthalmol Strabismus. 1985;22:256-7. 11. Bonthala S, Sparks JW, Musgrove KH, Berseth CL. Mydriatics slow gastric emptying in preterm infants. Journal of Pediatrics. 2000;137:327-30. 12. Sarici SU, Yurdakok M, Unal S. Acute gastric dilatation complicating the use of mydriatics in a preterm newborn. Pediatric Radiology. 2001;31:581-3. 13. Nair AK, Pai MG, Da Costa DE, Al Khusaiby SM. Necrotising enterocolitis following ophthalmological examination in preterm neonates. Indian Pediatrics. 2000;37:417-21. 14. Ozgun U, Demet T, Ozge KA, Zafer D, Murat S, Mehmet Y, Nilgun K. Fatal necrotising enterocolitis due to mydriatic eye drops. Journal of the College of Physicians and Surgeons Pakistan. 2014;24:S147-S9. 15. Siu LY, Chan WH, Au SK, Kwong NS. Necrotising enterocolitis following the use of mydriatics: A case report of two triplets. Hong Kong Journal of Paediatrics. 2011;16:47-50. 16. Buyukcam A, Tolga Celik H, Korkmaz A, Yurdakok M. Myoclonic seizure due to cyclopentolate eye drop in a preterm infant. Turkish Journal of Pediatrics. 2012;54:419-20. 17. 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:e499-500. 18. Hu L, Dow K. Focal seizures after instillation of cyclomydril to a neonate with congenital CMV infection. Journal of Neonatal-Perinatal Medicine. 2014;7:147-9. 19. Khoo BK, Koh A, Cheong P, Ho NK. Combination cyclopentolate and phenylephrine for mydriasis in premature infants with heavily pigmented irides. Journal of Pediatric Ophthalmology and Strabismus. 2000;37:15-20. 20. Gray C. Systemic toxicity with topical ophthalmic medications in children. Paediatric and Perinatal Drug Therapy. 2006;7:23-9. 21. Mitchell A, Hall RW, Erickson SW, Yates C, Hendrickson H. Systemic Absorption of Cyclopentolate and Adverse Events After Retinopathy of Prematurity Exams. Current Eye Research. 2016;41:1601-7.

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