Phenylephrine
Newborn use only

2022

Alert	Watch for apnoeas and abdominal distension following administration. Lower concentration solutions and regimens minimising number of additional drops are recommended.
Indication	Eye examination Retinopathy of prematurity (ROP) screening
Action	Selective alpha-1-adrenoceptor agonist. Contracts dilator muscle of pupil and constricts arterioles in conjunctiva.
Drug type	Sympathomimetic.
Trade name	Minims® Phenylephrine hydrochloride.
Presentation	Phenylephrine hydrochloride 2.5 % (25 mg/mL) single-use sterile eye drop, approximately 0.5 mL.
Dose	Use in conjunction with cyclopentolate 0.5% and/or tropicamide 0.5% eye drops. **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
Dose adjustment	Therapeutic hypothermia – No information. ECMO – No information. Renal impairment – No information. Hepatic impairment – No information.
Maximum dose	REGIMEN 1: 3 drops of each eye drop. REGIMEN 2: 4 drops of each eye drop.
Total cumulative dose	
Route	Topical instillation into the eyes from the container or use a microdrop (5–7 microL) cannula.
Preparation	
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	Blood pressure, heart rate and oxygen saturation in infants with bronchopulmonary dysplasia.
Contraindications	Necrotising enterocolitis (NEC) at the time of eye examination. Concurrent use with beta-adrenoceptor antagonists (beta-blockers).
Precautions	Infants with bronchopulmonary dysplasia. Lower concentration solutions and regimens minimising number of additional drops are recommended to minimise toxicity.
Drug interactions	Atropine, beta-adrenoceptor antagonists (beta-blockers).
Adverse reactions	Increased blood pressure, desaturations and tachycardia or bradycardia. [2, 4,5] Delayed gastric emptying, feed intolerance and necrotising enterocolitis. [11-17] Skin pallor around eyes. Decreased pulmonary compliance, tidal volume and peak air flow in babies with bronchopulmonary dysplasia. [18, 19]
Compatibility	Cyclopentolate, tropicamide, amethocaine
Incompatibility	
Stability	Discard immediately after use.
Storage	Store in refrigerator at 2oC to 8oC. Do not freeze. Protect from light.

Excipients	
Special comments	Cross check correct strength of Minims® Phenylephrine hydrochloride is used. Do NOT use 10 % in neonates.
Evidence	**Efficacy** Phenylephrine (α1-adrenoceptor agonist) alone: Ogut et al, in a RCT in 80 preterm infants screened for ROP, found two drops phenylephrine 2.5% resulted in a mean pupillary diameter 5.7 mm at 60 minutes and 4.7 mm with light. Maximum side effects (increased heart rate and BP) were seen with 2.5% phenylephrine.[2] Caputo et al, in a controlled study, reported three drops phenylephrine 10% or 2.5% produced inadequate mydriasis for peripheral retinal examination. Phenylephrine 10% caused skin blanching and elevation of heart rate and BP.[4] Conclusion: Phenylephrine alone is insufficient for adequate mydriasis. Phenylephrine 10% and 2.5% are associated with significant systemic physiological effects. [LOE II GOR A] Phenylephrine added to combination eye drops: Ogut et al, in a RCT in 80 preterm infants screened for ROP, found maximum mydriasis was achieved with cyclopentolate 0.5% + tropicamide 0.5% + 2.5% phenylephrine. Adequate mydriasis without side effects was achieved with 1% cyclopentolate + 1% tropicamide.[2] Several RCTs have reported increased mydriatic effect of added phenylephrine. Merritt et al reported phenylephrine 2.5% + tropicamide 0.5% + cyclopentolate 0.5% 1 drop each produced maximal mydriasis at 75–90 minutes with adequate fundoscopy at 120 minutes.[1] Fleck et al reported the mydriatic effect of phenylephrine 2.5% + tropicamide 0.5% 1 drop each was superior to tropicamide 0.5% alone (mean 6 mm versus 2.7 mm; $p < 0.001$), and adequate mydriasis in phenylephrine 2.5% + tropicamide 0.5% group only.[6] Lux et al reported phenylephrine 5% 1 drop + tropicamide 0.5% 2 drops produced pupil surface area 1.9 times greater than tropicamide 0.5% 3 drops alone. Visualisation of the retinal periphery was possible for 30 of 30 eyes dilated with the PTT regimen and for 16 of 30 eyes dilated with the TTT regimen.[9] Conclusion: Maximum mydriasis is achieved with addition of phenylephrine 2.5% in the combination (cyclopentolate 0.5% + tropicamide 0.5% + 2.5% phenylephrine). However, adequate mydriasis without side effects was achieved with 1% cyclopentolate + 1% tropicamide. [LOE II GOR B] Phenylephrine combinations: Several RCTs have assessed various phenylephrine combinations. Chew et al compared cyclopentolate 1% + phenylephrine 2.5% versus tropicamide 1% + phenylephrine 2.5% versus cyclopentolate 0.2% + phenylephrine 1% (all 3 drop regimens). 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% are associated with increased BP and cyclopentolate 1% + phenylephrine 2.5% may be associated with feed intolerance.[11] Khoo et al reported cyclopentolate 0.2% + phenylephrine 1% is as effective a mydriatic as tropicamide 0.5% + phenylephrine 2.5%. No significant differences in blood pressure over baseline values. Cyclopentolate 0.2% + phenylephrine 1% was as safe as tropicamide 0.5% + phenylephrine 2.5%.[7] Bolt et al reported the mydriatic effect of the phenylephrine 2.5% (1 drop) + tropicamide 0.5% (2 drops) combination was superior to that of cyclopentolate 0.5% + tropicamide 0.5% (2 drops) combination.[8] Sindel et al reported that, on exposure to bright light, the pupillary size with phenylephrine 1.0% + tropicamide 1.0% was significantly smaller than phenylephrine 2.5% + tropicamide 1.0% or phenylephrine 2.5% + tropicamide 0.5% + cyclopentolate 0.5%. Dialatation was sufficient to allow appropriate examination in all infants (pupillary diameter > 6.0 mm). Pulse and heart rate increased transiently in all groups receiving mydriatic but returned to baseline values in 25 minutes. This increase was significant in infants with 2.5% phenylephrine.[3] 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).[12]

	Conclusions: Phenylephrine 2.5% + cyclopentolate 0.5% (3 drops) produces adequate mydriasis in 98.8% of infants without side effects resulting in the need to discontinue examination. It is unclear if a reported 0.8% subsequent clinical deterioration in the next 24 hours is related to the use of mydriatics and examination.[5] [LOE IV GOR C] However, cyclopentolate 0.2% + phenylephrine 1% 3 drops provided adequate pupillary dilation with the least systemic side effects. [LOE II GOR B] **Safety** Caputo et al reported phenylephrine 10% causes skin blanching and elevation of heart rate and BP.[4] Ogut et al reported maximum side effects (increased heart rate and BP) were seen with 2.5% phenylephrine.[2] Chew et al reported 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.[10] 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 well-tolerated although 0.8% had significant clinical deterioration in the following 24 hours.[5] Feed intolerance [10], delayed gastric emptying [13], transient ileus [14], and necrotising enterocolitis [15-17] have been reported in infants after administration of mydriatics, including phenylephrine. [LOE IV] Low quality evidence reported the incidence of feed intolerance may be reduced by withholding feeds for four hours after eye examination.[18] [LOE IV GOR C] Phenylephrine 2.5% (every 15 minutes for three drops) caused decreased pulmonary compliance, tidal volume and peak airflow values in infants with bronchopulmonary dysplasia but not in infants without pulmonary disease.[19] Bronchoconstriction after phenylephrine 2.5% + tropicamide 1% instillation was reported in premature infants with BDP.[20] Conclusion: Combination eye drops containing phenylephrine 2.5% produce maximal mydriasis but produce acute physiological effects [2, 10]. [LOE II GOR B] Combination eye drops containing phenylephrine 1% produce adequate mydriasis with least physiological effect [7, 10]. [LOE II GOR B] Three drop regimens of combination eye drops were associated with more acute physiological effects and feed intolerance [7, 10, 11]. [LOE II GOR B] **Pharmacokinetics/pharmacodynamics** In preterm infants receiving phenylephrine 2.5%, mean phenylephrine concentration at 10 minutes was 0.9 ng/mL after 8 microlitre drops and 1.9 ng/mL after 30 microlitre drops.[21] In contrast, in preterm infants receiving phenylephrine 1%, phenylephrine blood concentrations were below the lower limit of detection.[22] Combined 0.75% tropicamide + 2.5% phenylephrine resulted in a mean time to pupillary diameter 7 mm of 46 minutes.[23] Cyclopentolate 0.2% and phenylephrine 1% produced a response by 45 minutes, maximal mydriasis at 90 minutes with effect sustained for at least 120 minutes.[24] 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. [25] In adults, duration of mydriasis is 3 to 8 hours. [26,27]
Practice points	
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. Fleck BW, Dhillon B, Mitchell A. Additive mydriatic effect of 2.5% phenylephrine and 0.5% tropicamide eyedrops in premature babies. Journal of Pediatric Ophthalmology and Strabismus. 1994;31:130.

7. 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.
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. Lux AL, Degoumois A, Barjol A, Mouriaux F, Denion E. Combination of 5% phenylephrine and 0.5% tropicamide eyedrops for pupil dilation in neonates is twice as effective as 0.5% tropicamide eyedrops alone. Acta Ophthalmologica. 2017;95:165-9.
10. 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.
11. Alpay A, Canturk Ugurbas S, Aydemir C. Efficiency and safety of phenylephrine and tropicamide used in premature retinopathy: a prospective observational study. BMC Pediatr. 2019 Nov 6; 19(1):415.
12. Wheatcroft S, Sharma A, McAllister J. Reduction in mydriatic drop size in premature infants. Br J Ophthalmol. 1993;77:364-5.
13. Bonthala S, Sparks JW, Musgrove KH, Berseth CL. Mydriatics slow gastric emptying in preterm infants. Journal of Pediatrics. 2000;137:327-30.
14. Degirmencioglu H, Oncel MY, Calisici E, Say B, Uras N, Dilmen U. Transient ileus associated with the use of mydriatics after screening for retinopathy of prematurity in a very low birth weight infant. Journal of pediatric ophthalmology and strabismus. 2014;51 Online:e44-e7.
15. 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.
16. 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.
17. Obata S, Imamura T, Kakinoki M, et al. Systemic adverse events after screening of retinopathy of prematurity with mydriatic. PLoS One. 2021 Sep 9; 16(9):e0256878.
18. Hermansen MC, Hasan S. Abolition of feeding intolerance following ophthalmologic examination of neonates. J Pediatr Ophthalmol Strabismus. 1985;22:256-7.
19. Mirmanesh SJ, Abbasi S, Bhutani VK. Alpha-adrenergic bronchoprovocation in neonates with bronchopulmonary dysplasia. Journal of Pediatrics. 1992;121:622-5.
20. Kim HJ, Choi JG, Kwak KH. Bronchoconstriction following instillation of phenylephrine eye drops in premature infants with bronchopulmonary dysplasia -two cases report. Korean Journal of Anesthesiology. 2015;68:613-6.
21. Lynch MG, Brown RH, Goode SM, Schoenwald RD, Chien DS. Reduction of phenylephrine drop size in infants achieves equal dilation with decreased systemic absorption. Arch Ophthalmol. 1987;105:1364-5.
22. 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.
23. Phamonvaechavan P, Chutasmit K, Damrongrak P, Koukiatkul S, Wongkiatkajorn T, Ngernchamm S. Comparison of the effectiveness of mydriasis by two instillation methods of combined 0.75% tropicamide and 2.5% phenylephrine eye drop in preterm infants. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2012;95 Suppl 4:S1-7.
24. Vicente GV, Bahri M, Palafoutas JJ, Wang H, Mehta N. A randomized controlled trial to determine the lowest effective dose for adequate mydriasis in premature infants. Journal of AAPOS. 2012;16:365-9.
25. Gray C. Systemic toxicity with topical ophthalmic medications in children. Paediatric and Perinatal Drug Therapy. 2006;7:23-9.
26. Phenylephrine (ophthalmic): Pediatric drug information. Lexicomp OnlineTM. Waltham, MA, 2017. Accessed via UpToDate https://www.uptodate.com (subscription required) 06/05/2017.
27. Phenylephrine (Ophthalmic) Drug Monograph. NeoFax® (electronic version). Truven Health Analytics. Greenwood Village, Colorado, 2017. Accessed via http://neofax.micromedexsolutions.com (subscription required) 12/05/17.

VERSION/NUMBER	DATE

Original	16/02/2018
Current 2.0	28/04/2022
REVIEW	28/04/2027

Authors Contribution

Original author/s	Michael Hewson, Cathy Langdon
Current author	Nilkant Phad
Evidence Review	David Osborn
Expert review	Mark Jacobs, Hughie Tsang, Kimberley Tan
Nursing Review	Eszter Jozsa, Priya Govindaswamy
Pharmacy Review	Jing Xiao, Mariella De Rosa, Cindy Chen
ANMF Group contributors	Srinivas Bolisetty, Bhavesh Mehta, John Sinn, Ian Callander, Cindy Chen, Mohammad Irfan Azeem, Thao Tran, Michelle Jenkins, Helen Huynh, Simarjit Kaur
Final editing and review of the original	Ian Whyte
Electronic version	Mariella De Rosa, Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty