Pediatric use of mydriatic eye drops for pupil dilation: preterm infants, newborns, children.

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Context

Pharmacovigilance studies have highlighted the existence of serious, sometimes fatal, cases in children who received mydriatic eye drops.

These data have led the ANSM to take the following actions:

- contraindicate the use of proprietary medicines containing phenylephrine 10% used as eye drops in children under 12 years;
- only use atropine 1% in adults and adolescents over 12 years;
- strengthen safety measures for eye drop administration to avoid systemic route.

The objective of this development is to provide a protocol for the use of mydriatic eye drops for pupil dilation in preterm infants, newborns and children.

Mydriatic eye drops for pediatric use marketed in France

Mydriatic: data from the MA

Therapeutic class	INN	Presentation	Contraindications and warnings	Pharmacokinetic data
Anticholinergic and antimuscarinic agents	Atropine Eye drops 0.3%, 0.5% and 1%	10-mL vial 0.03, 0.05 or 0.1 g of atropine per vial	Maximum dose from 30 months to 15 years = 3 instillations of 2 drops of atropine 0.3% / 24 hours	Long elimination half-life (13-38 hours) Disappearance of mydriasis within 7-10 days.
	Cyclopentolate	Skiacol 0.5% Single-dose vial 2.5 mg of cyclopentolate/single dose	CI in infants <1 year old 1-3-years old children 1 single drop in each eye Children >3 years old 1 drop in each eye and then a second drop 10 min later if needed	Faster elimination than that of atropine. Mydriasis for 6-24 hours.
	Tropicamide	Mydriaticum 0.5% 10-mL vial (or 50 mg of tropicamide) or single dose vial (or 2 mg of tropicamide) Tropicamide Faure 0.5%	1 or 2 drops 15 min before examination or surgery	Mydriasis for 3-6 hours. Faster elimination than that of atropine.
	Homatropine	Isopto-Homatropine 1%	1 drop 2-3 times a day	Mydriasis after 10 min, maximum for 3-4 h, return to normal after 12-24 h.
Alpha 1 +	Phenylephrine	Neosynephrine 5% and 10%	Eye drops 5% and 10% are not recommended in children because of the risk of systemic effects	Mean half-life of 2.5 hours

Risks related to the use of mydriatic eye drops

- Atropine

Mydriatic eye drops may have a stronger action than oral treatment because they are not metabolized by the digestive tract.

The most commonly found and more serious systemic effects of atropine are neuropsychiatric effects:
- convulsions,
- delirium,
- agitation,
- thermoregulatory disorders.

Children and elderly subjects are particularly sensitive.

The most common effects in newborns and preterm infants are gastrointestinal effects, mainly affecting the ileus, including occlusion.

Cases of ulcerative necrotizing enterocolitis (UNEC) have been observed in newborns monitored as part of the retinopathy of prematurity (ROP) screening. These cases have been observed in infants who received a combination of mydriatic eye drops (most often phenylephrine and cyclopentolate).
Pharmacovigilance observations indicate the existence of repeated instillations in cases of UNEC.

It should be noted that 10 mg of atropine, i.e. the content of an eye drop vial, may be fatal in children.

- Phenylephrine

Although administered locally, phenylephrine may cause potentially serious systemic effects.

Phenylephrine is a potent vasoconstrictor; its systemic effects are primarily cardiovascular effects:
- high blood pressure,
- rhythm disorders,
- intense vasoconstriction.

In children, malaises with breathing pause and profound bradycardia, desaturation, may occur with phenylephrine eye drops. That is why in preterm infants the use protocols no longer refer to eye drops at the concentrations of 5% and 10%.

Practical data

The standard volume of a single drop is estimated at 50 µl. It is extremely difficult to know how much of the active ingredient reaches the eye. However, a small proportion of the volume of one drop reaches the anterior chamber of the eye for local action. The remaining is rapidly drained by the nasolacrimal duct.

Reducing the drop size does not decrease its efficacy, but leads to a lower risk of high blood pressure.
Similarly in preterm infants, decreasing the size of the administered drop results in sufficient pupil dilation while limiting the risk of adverse events (Wheatcroft, 1993).

Therapeutic schemes: data from the literature

Author	Study	Effect on pupil dilation
		Preterm infants
Isenberg (1984)	Open-label N=30 Preterm infants	1- Weight: 1198+220 g: Cyclopentolate 0.5% 2- Weight: 1027+220 g: Cyclopentolate 0.5% + tropicamide 0.5% 3- Weight: 1273+251 g: Cyclopentolate 0.2% + phenylephrine 1% Tolerance: 1=2=3
Bolt (1992)	Double-blind N=39 Preterm infants	Phenylephrine 2.5% + tropicamide 0.5% > Cyclopentolate 0.5% + tropicamide 0.5%
Chew (2005)	Double-blind Cross-over N=39 Preterm infants Dark iris	1- Cyclopentolate 0.2% + phenylephrine 1% 2- Cyclopentolate 1% + phenylephrine 2.5% 3- Tropicamide 1% + phenylephrine 2.5% Adequate dilation in the 3 groups but in terms of tolerance: 1>2=3
		Newborns
Ogüt (1996)	Open-label N=80 newborns	A- Cyclopentolate 1% B- Tropicamide 1% C- Phenylephrine 2.5% D- : A + B E- : C + B F- Cyclopentolate 0.5% + Tropicamide 0.5% + Phenylephrine 2.5% G- : A + C H- 0.9% NaCl Most severe adverse events: C Less severe adverse events: B The largest mydriasis: F
Elibol (1997)	Retrospective N=61 newborns	<u>Dilation</u>: Standard drops = microdrops for cyclopentolate and phenylephrine Standard drops > microdrops for tropicamide
		Children
Fan (2004)	Open-label N=25 [age: 5.7 years]	1- Tropicamide 0.5% + phenylephrine 0.5% 2- Cyclopentolate 1% + tropicamide 1% 3- Atropine 1% ointment Adequate dilation in the 3 groups but statistically: 3>2>1
Hug (2007)	Blinded N=50 [1-7 years]	1- Right eye = control group: Cyclopentolate 1% (group A) 2- Left eye: - tetracaine 0.5% + cyclopentolate 1% (group B) - tetracaine 0.5% + cyclopentolate 1% + phenylephrine 2.5% (group C) If inadequate dilation after 30 min: 2nd dose Dilation: A = B = C

Published recommendations

- UK (2007)

For pupil dilation in preterm infants, the British guidelines recommend:
- phenylephrine 2.5% + cyclopentolate 0.5%,
- one drop in each eye.
- 2-3 times, every 5 minutes,
- one hour before examination.

Recommendations

When mydriatic eye drops are administered in pediatric patients, it is recommended to:

- Press the inner angle of the eye during eye drop application
- Close the eyelid
- Wipe on the child cheek the flowing portion of administered eye drops

Protocol for **pupil dilation** in preterm infants, infants and children:

- In infants and children, tropicamide 2-3 times within the 30 minutes before examination. If the dilation is insufficient (especially in melanoderm children), possibility to add one drop of atropine (0.3% until 2 years old, 0.5% thereafter).
- In preterm infants, tropicamide + neosynephrine **2.5 % (hospital preparation)**: 1 drop 30 minutes then a second drop 15 minutes before examination.

Protocol for **cycloplegia** in infants and children:

- 1 drop of cyclopentolate (Skiacol®) and another drop after 10 minutes, measurement 45-60 minutes after the first instillation. Contraindicated under 1 year of age and in patients with history of convulsions.
- For more exhaustive cycloplegia or if cyclopentolate is insufficient (especially in melanoderm children) or contraindicated, 1 drop of atropine twice a day for 5-7 days before measurement (0.3% until 2 years, 0.5% thereafter).

References

Bolt B j Pediatr Ophtalmol Strabismus 1992 May
Chew C j Pediatr Ophtalmol Strabismus 2005 May
Wheatcroft S Br J Ophtalmol 1993
UK retinopathy of prematurity guideline 2007