

EYE DROPS (Comment)

Use during screening for retinopathy of prematurity

Mydriasis: Effective ophthalmic screening is only possible if the pupil has been properly dilated (mydriasis). Most strategies involve the use of two drugs. One drug, usually tropicamide or cyclopentolate, is used to block the parasympathetic nerve supply to the pupillary sphincter muscle, while a second drug (usually phenylephrine) is used simultaneously to stimulate the pupillary dilator muscle. A range of strategies have been described. Most seem to work reasonably well, and several small studies have been undertaken to try and establish which strategy works best.

The most widely studied regimen involves a combination of cyclopentolate and phenylephrine, but both the preparations currently available in the UK contain significantly higher doses of these drugs [0.5% cyclopentolate and 2.5% phenylephrine] than the doses that were considered optimal in the comparative studies published to date (Khoo *et al.*, 2000; Bonthala *et al.*, 2000). Even the more dilute dose regimen studied [one drop of 0.2% cyclopentolate and one drop of 1% phenylephrine] repeated once after five minutes (or twice if necessary at 5 minute intervals if the irises are dark) can sometimes cause abdominal distension and slow gastric emptying for 2–3 hours (Bonthala *et al.*, 2000).

There have, as a result, been calls for a less concentrated commercial preparation, or for a dispenser capable of delivering a smaller size drop (Wheatcroft *et al.*, 1993), to be made available. However, although one study did show that a drop just one sixth the size of a normal (~35µl) drop was enough to produce comparable pupil dilation (Elibol *et al.*, 1997), no such delivery device has yet been made commercially available. In fact it is generally thought that most side effects can also be avoided by putting gentle pressure on the nasolacrimal duct for 1–2 minutes after the drops are instilled (see below). The pupils start to dilate within 5 minutes, cycloplegia (muscle paralysis) occurs after 30–60 minutes, and recovery takes 6–24 hours. While the manufacturers have not recommended the use of cyclopentolate in children less than 3 months old in the UK, clinicians have been using the drug widely for many years. A concentrated solution stings unless a corneal anaesthetic, such as proxymetacaine, is given first (Shah *et al.*, 1997).

However, the strategy recommended by the *Neonatal Formulary* has, for the last eleven years, been to use one drop of 0.5% **tropicamide** and one drop of 2.5% phenylephrine. There have been several published reports of the use of such an approach in that time, and several small trials comparing this strategy with a strategy involving cyclopentolate. Dilatation starts to occur within 5 minutes, cycloplegia (muscle paralysis) occurs after 20–30 minutes, and recovery occurs after about 6 hours. One drop of 0.5% tropicamide seems to dilate the pupil just as effectively as one drop of 2.5% cyclopentolate, does so rather more quickly, has been widely used for 25 years, and seems to trigger very few systemic side effects.

Pain Relief: Proxymetacaine hydrochloride eye drops are now increasingly used to minimise the undoubted pain caused by the use of a probe to indent the sclera and, more particularly, the use of an eyelid speculum during retinal examination, and this *Formulary* has been recommending the use of proxymetacaine to anaesthetise the cornea both of the term and the preterm baby for more than seven years. Nobody has ever suggested that simple sedation is enough to make the use of a local anaesthetic unnecessary in an older child, and there can be no excuse for doing less to reduce pain in the preterm baby.

A single drop of a 0.5% solution induces anaesthesia within 30 seconds, and this loss of sensation typically lasts for at least 15 minutes. Several publications now attest to the safety and efficacy of such a strategy. Further doses are often given every 5 to 10 minutes in older patients during cataract surgery. While proxymetacaine hydrochloride is the recommended (modified) international non-proprietary name (rINN), the drug is called proparacaine hydrochloride in America.

The paediatric formulary *Medicines for Children* published in 1999 by the Royal College of Paediatrics and Child Health did say that any use of this drug was ill-advised in the preterm baby “because of the immaturity of the enzyme system which metabolises the ester type local anaesthetics in premature babies”, and this assertion is still being replicated in *BNF for Children*. The original statement clearly reflected a theoretical concern, but it has to be said that there is no published evidence that use of proxymetacaine has actually proved hazardous. The recent report on the management of retinopathy issued by the Royal College of Paediatrics jointly with the Royal College of Ophthalmology and the British Association of Perinatal suggested in their report in 2008 that oxybuprocaine might be a possible alternative because this was not, at the time, listed as contraindicated in the preterm baby by the *BNFc*. Oxybuprocaine (like tetracaine) is, however, an ester of para-aminobenzoic acid in the same way as proxymetacaine is an ester of meta-aminobenzoic acid, and the *BNFc* have now listed this drug as also contraindicated in the preterm baby, leaving this authoritative text unwilling to endorse *any* topical anaesthetic as safe in the preterm baby. Given that it would be unthinkable not to offer every baby some pain relief, and given that there is no published work on the neonatal use of oxybuprocaine, most clinicians will not find it difficult to justify the continued use of proxymetacaine.

There have been many studies designed to see whether other strategies, such as swaddling, nesting, or the use of a pacifier, can reduce the extent to which the baby shows visual evidence of discomfort during retinal examination. While there are no grounds for discouraging the use of any of these approaches, there is very little evidence that sucrose (q.v.) does much to reduce the amount of pain suffered (Grabska, *et al.*, 2005; Gal, *et al.*, 2005; Boyle *et al.*, 2006). Distraction strategies can certainly render pain more bearable, but a boiled sweet would not be considered a reasonable substitute for local anaesthesia in an older child. Babies needing retinal surgery certainly deserve a general anaesthetic. A combination of IV propofol and IV remifentanyl (q.v.) is one strategy sometimes used.

Administration: Most texts now recommend that gentle pressure should be placed on the tear duct in the inner corner of the eye for 1–2 minutes after any of any of these drugs is given. It seems fairly clear that, if this is not done, up to three quarters of the drug will often pass through nasolacrimal duct, be absorbed through the nasal mucosa, and end up in the blood stream. Just how effective pressure is at reducing later systemic uptake is, as yet, less clear. However systemic side effects are particularly common when full strength 0.5% cyclopentolate and 2.5% phenylephrine are used if some of the drug does get into the nose and enter the blood stream.

Supply: Minims (designed for use by a single patient) are used almost exclusively in the UK, but multiple-dose dropper bottle preparations are normally used in America. Such products should never be refrigerated, or used if the solution has become discoloured or contains a precipitate. One strategy still widely adopted in America (Young and Magnum, 2007) involves the 'in house' preparation of an eye drop that contains 0.5% cyclopentolate, 0.5% tropicamide and 2.5% phenylephrine (Caputo *et al.*, 1982). While no recent studies seem to have been undertaken comparing this combination of drugs with any of the other strategies already mentioned, it seems clear that comparable pupil dilation can almost certainly be achieved without using both cyclopentolate and tropicamide. If such a mixed solution is prepared it should never be kept for more than 24 hours because it contains no preservative.

Click [here](#) for a copy of the UK guideline on the management of retinopathy of prematurity issued jointly by the Royal College of Paediatrics and Child Health, the Royal College of Ophthalmologists, the British Association of Perinatal Medicine, and BLISS (the UK Special Care Baby Charity), in 2008.

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