

Risk of Systemic Toxicity from Topical Ophthalmic Chloramphenicol

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Two recent papers report only a small effect of chloramphenicol eye drops in "acute infective conjunctivitis",^{1,2} probably because of adenovirus resistant to antibiotics was responsible.³ These findings add to the case against using this treatment based on the risk of systemic toxicity from local absorption.

It is already well-established general medical practice to avoid administering chloramphenicol systemically, with rare exceptions, because of the risk of blood dyscrasia.⁴ An idiosyncratic reaction can be expected from 1 in 19,000 of the population, attributed to mitochondrial inheritance;⁵ no predictive test is available. There is a more general risk from higher and more prolonged dosage.⁶

Systemic toxic effects from many eye drops are probably more common than is realised eg from atropine, beta-blockers etc. Chloramphenicol will be absorbed directly into the systemic circulation via the conjunctivae, the mucosae of the naso-lacrimal duct, nose and naso-pharynx. Seventy-five to eighty percent of eye drops are estimated to pass into the naso-lacrimal ducts.⁷ That amount of drug will by-pass the liver, the main site of breakdown,^{8,9} on the first pass, thereby gaining direct access to the bone marrow. But it will also continue its toxic activity on many subsequent passes. Less than 10% of the arterial blood volume will be channelled into the hepatic arteries^{10,11} and maybe only 50% of the drug in that 10% will be cleared. If 5% (50% of 10%) of the drug is cleared on each pass, 45 circuits, in around 45 minutes,¹⁰ will be required to reduce the concentration to less than 10% of the original content. Would it ever be eliminated completely?! Renal excretion would account for very little,^{9,12} and even less by other exit routes.¹³

Children are at particular risk because absorption is probably greater in relation to their body weight, and because of the grey baby syndrome.^{4,14} I would regard pregnancy and lactation as contra-indications, but the drug company's pamphlet gives discretion to the pharmacist.¹⁵

There is considerable evidence that cases of blood dyscrasia do occur from topical ophthalmic chloramphenicol^{16,17,18} and the complication is under-diagnosed,¹⁹ under-reported¹⁸ and underpublished.¹⁸ It is also under-referenced: a general review¹⁹ contains the only published reference I have found to a paper²⁰ wherein two "personal communications" concerning one case each are mentioned. Within two years of a report in 1982¹⁷ of a fatal case of aplastic anaemia, sales in the USA declined by 90%¹⁸ and "the Physicians Desk Reference used in the United States emphasises in boxed warnings repeated...that ocular chloramphenicol not be used unless there is no alternative".²¹ I would not agree with those who accept the treatment, although their figures do not completely exonerate chloramphenicol.^{22,23,24}

The reviewers in a well-argued editorial in the BMJ²⁵ concluded that they "no longer prescribe topical ocular chloramphenicol". Five letters to the editor disagreed,^{24,26,27,28,29} but the reviewers' response was robust.²¹

Accordingly, I was astonished when, in 2002, the Medicine and Healthcare Products Regulatory Agency, the UK drugs regulator, announced that topical ocular chloramphenicol is the first antibiotic to be made available without prescription.³⁰

In a very recent, short, and very unconvincing "Perspective",³¹ the two authors, one of whom had assembled many of the case reports,^{17,18} stated "...it was not our intention to eliminate the use in the United States" and "There is no proof of causality; however, we feel that the association is probable". They betray significant inconsistency in "Possibly the only indication for topical ocular chloramphenicol is if the organism is resistant to all other antibiotics". There was no mention of liver disease.

Chloramphenicol was not detected in the sera of 40 patients,³² but only one eye was treated in each, thereby reducing the usually absorbed dose by half; nor was it detected in the urine of five children treated for five to seven days.³³ I would think the bone marrow, especially if idiosyncratic, is more sensitive than liquid chromatography.

Personally, I have avoided topical ophthalmic chloramphenicol for many, many years, preferring the antiseptic brolene (propamidine isethionate), the active constituent of golden eye drops and eye ointment, but not to the exclusion of other antibiotics. Fuciden's efficacy equalled that of chloramphenicol in acute neonatal conjunctivitis.¹⁴

Absorption of the drug from an eye ointment (oculatum) is probably much less from eye drops, which probably explains the absence of systemic complications in the Netherlands,³⁴ but two case reports have been published,³⁵ one fatal.³⁶

Conclusion

Topical ophthalmic chloramphenicol, available without prescription, has little effect on acute infective conjunctivitis. Why take the risk from systemic absorption when other antibiotics can be prescribed (one cheaper) or, better, advise a traditional antiseptic (brolene) which can also be obtained over the counter.

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