Is it time to stop using chloramphenicol on the eye?

Fears are based on only six cases

EDITOR,—Marie Doona and J Bernard Walsh highlight the association between topical ophthalmic use of chloramphenicol and bone marrow aplasia.¹ Although we accept that the risk of aplasia developing after systemic use of chloramphenicol is 13 times higher than that in the general population, we believe there is little evidence to implicate topical chloramphenicol as a cause of aplastic anaemia. We have reviewed the literature and were surprised that the "numerous" articles referred to by the authors amount to six published case reports.

Several important features of these cases come to light on close scrutiny. The most alarming feature is the period for which topical chloramphenicol was used, ranging from 40 days to five years.^{2,4} This to us suggests injudicious prescribing practice. At least two of the patients had other possible explanations for aplasia. One received topical chloramphenicol plus sulphonamide (sulfacetamide).² Another had abnormal results of liver function tests (hepatitis is a recognised cause of aplasia).² In the six patients reported on, aplasia was reversed by methyltestosterone in three patients. Two patients died, and one had been dependent on transfusions for red cell aplasia for two years at the time the case was reported.

The authors also refer to a report by Fraunfelder *et al*, in which figures from the national register in Oregon were cited,³ giving an additional 16 reported cases of blood dyscrasias in patients using topical chloramphenicol. Fraunfelder *et al* acknowledged that "the unpublished cases were not fully investigated."

When all the above cases are taken together less than one case a year was reported in the past 40 years, whereas the incidence of idiopathic bone marrow aplasia is said to be about three per million per year. It is therefore possible that these cases were chance events, unrelated to the use of topical chloramphenicol.

Topical chloramphenicol has been used extensively in Britain by general practitioners for conjunctivitis and by ophthalmologists for the treatment of and prophylaxis against infections after surgery. Chloramphenicol provides broad spectrum cover against the primary bacterial pathogens causing conjunctivitis—namely, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*. In addition, it is the cheapest topical ophthalmic preparation available.

We recognise that one should be alert to all potential causes of aplastic anaemia. We believe, however, that the evidence linking short term use of topical chloramphenicol with aplastic anaemia is insufficient to justify Doona and Walsh's cry to halt such treatment.

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- 1 Doona M, Walsh JB. Use of chloramphenicol as topical eye medication: time to cry halt? *BMJ* 1995;310:1217-8. (13 May.)
- 2 Fraunfelder FT, Bagby GC, Kelly DJ, Abrams SM, Degnan TJ, Vinciguerra V. Fatal aplastic anemia following topical administration of ophthalmic chloramphenicol. *Am J Ophthalmol* 1982;93:356-60.
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- 5 Fraunfelder FT, Morgan RL, Yunis AA. Blood dyscrasias and topical ophthalmic chloramphenicol. *Am J Ophthalmol* 1993;115:812-3.

Safe in patients with no history of blood dyscrasia

EDITOR,—Chloramphenicol, in drop or ointment form, is one of the most reliable ophthalmic preparations in existence. It has a broad spectrum of activity, is well absorbed by the ocular tissues, rarely provokes resistance in micro-organisms or damages the surface of the eye, and is both cheap and widely available. The evidence that, when delivered to the eye, it can cause aplastic anaemia remains unsubstantiated. We are therefore surprised that Marie Doona and J Bernard Walsh conclude, in the absence of new information, that the use of ophthalmic formulations of chloramphenicol should be restricted.¹ We base our reservations on the following points.

Firstly, the 1982 paper by Fraunfelder *et al*, which resulted in a drastic reduction in the use of ophthalmic formulations of chloramphenicol in the United States, cited a patient who died of aplastic anaemia after using such preparations for five weeks.² Yet the patient was receiving eight other drugs in addition, several of which (for example, triamterene, hydrochlorothiazide, and phenacetin) could have been implicated in her blood dyscrasia.

Secondly, between 1982 and 1994 the American National Registry of Drug-Induced Ocular Side Effects received 23 reports of blood dyscrasias associated with the topical administration of chloramphenicol.³ Only seven of these cases are available for study in the published literature. Given an incidence of idiopathic aplastic anaemia of three per million per year,⁴ and bearing in mind the size of the population of the United States, we would have expected more cases to be reported to this registry.

Thirdly, Doona and Walsh equate the risk of blood dyscrasia associated with the application of chloramphenicol to the eye with that associated with oral administration of the drug, but they advance no evidence in support of their hypothesis.

Finally, Doona and Walsh claim that "many safer and equally effective preparations" exist for "the treatment of most superficial eye infections"

but give only two examples, framycetin and fusidic acid. Framycetin is in a class of drugs (aminoglycosides) shown to cause blood dyscrasias when given systemically. The role of fusidic acid as an ophthalmic formulation has yet to be fully established. Neither drug has as broad a spectrum of antimicrobial activity as has chloramphenicol.

While we concede that patients with a proved personal or family history of blood dyscrasia should probably not receive chloramphenicol by any route, we continue to endorse the recommendation of the *British National Formulary* that chloramphenicol is a drug of choice for superficial eye infections.

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Risk is low in short courses

EDITOR,—We were concerned to read Marie Doona and J Bernard Walsh's editorial on the use of chloramphenicol as topical eye medication.¹ Despite the drug's widespread use, since 1966 the Committee on the Safety of Medicines has received only 11 reports of haematological reactions (all non-fatal) suspected to have been caused by ocular chloramphenicol (personal communication). In the past 10 years more than 200 million ocular topical chloramphenicol products were dispensed for community use in England alone (Department of Health, personal communication). In the Royal Hospitals NHS Trust (comprising St Bartholomew's, the Royal London, and the London Chest Hospitals), where almost 7000 ocular chloramphenicol products were dispensed in the past 12 months, no cases of bone marrow toxicity due to these products have been reported.

The authors state that the risk of aplastic anaemia associated with oral chloramphenicol is 1 in 30 000 to 1 in 50 000, and they postulate that the rate may be similar for topical use. There is little evidence to support the latter suggestion. Indeed, the above figures suggest that the risk is minimal, and the American practice of not recommending ocular chloramphenicol may be related to medicolegal concerns. Only 23 cases of

Advice to authors

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