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 Fraunfelder *et al* acknowledged that "the unpublished cases were not fully investigated."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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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

We prefer short letters that relate to a recently published article and we are unlikely to publish letters longer than 400 words and containing over five references. Letters may be shortened. Your letters should be typed with double spacing and include a word count. All authors need to sign the letter and provide one current appointment and address. We encourage you to declare any conflict of interest. Please enclose a stamped addressed envelope if you require an acknowledgment.

blood dyscrasias, including 12 of aplastic anaemia, possibly related to topical administration of chloramphenicol have been registered at the National Registry of Drug-Induced Ocular Side Effects in the United States.² The duration of treatment ranged from 18 to 1460 days (median 120 days).

Doona and Walsh affirm that framycetin and fusidic acid are equally effective. These agents do not cover the wide range of bacterial pathogens implicated in eye infections, and when used alone they promote rapid emergence of resistance. Fusidic acid is an antistaphylococcal agent, and framycetin lacks activity against anaerobes and streptococci. The treatment whose antibacterial spectrum approaches that of chloramphenicol, but with reduced anaerobic activity, is a combination of neomycin, polymyxin B, and gramicidin. This costs £5.36 for 5 ml, compared with 50p for 10 ml of chloramphenicol eye drops.

Although there is potential for topical chloramphenicol to produce aplastic anaemia, more hard data on the absolute risk are needed before such a hard judgment is passed on a product that is effective, cheap, and well tolerated. To minimise toxicity even further, treatment with chloramphenicol should be short and avoided in patients with a personal or family history of bone marrow abnormality.

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General practitioners would expect to see aplasia roughly once each century

EDITOR,—Although chloramphenicol eye drops may induce bone marrow aplasia, it might be helpful to put the risk in perspective.¹ In our practice of 4600 patients we use chloramphenicol eye drops as our first line treatment for conjunctivitis and after removal of foreign bodies. We also frequently prescribe chloramphenicol drops on the advice of local ophthalmologists. In total, we issue 360 prescriptions for chloramphenicol drops or ointment a year. Assuming that the risk of aplastic anaemia after topical administration is the same as that after oral administration, we would expect to see one case every 83-138 years in the practice as a whole, or one case every 240-400 years per general practitioner.

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Prospective study of aplastic anaemia should give definitive answer

EDITOR,—We disagree with Marie Doona and J Bernard Walsh's conclusions and recommendations relating to chloramphenicol eye drops and aplastic anaemia.¹ Many drugs have been implicated as causing aplastic anaemia, but for most the evidence is weak, and no in vitro tests are available to prove causation. Furthermore, an apparent association may not mean causality: the exposure may have been a response to the early features of aplastic anaemia itself.

An association between use of chloramphenicol and the development of aplastic anaemia was predicted because of the drug's structure, and many reports appeared in the literature during the 1950s and '60s. The risk of developing aplastic anaemia after exposure to oral or intravenous chloramphenicol has been estimated at somewhere between 1 in 25 000 and 1 in 800 000 exposures, with a figure of about 1 in 60 000 being the most acceptable.² This compares with the overall incidence of aplastic anaemia of two or three cases per million per year. Most patients have received prolonged courses of chloramphenicol, though one report recorded aplastic anaemia after a single day's exposure.

Since the introduction of chloramphenicol 45 years ago about 20 cases of aplastic anaemia possibly associated with the use of chloramphenicol eye drops have been reported in the world literature.³ Doona and Walsh give no indication of the number of patients exposed to chloramphenicol eye drops, but it must be high. In a study in the Netherlands, where 3% of the population was exposed to ophthalmic chloramphenicol, no association was found with blood dyscrasias.⁴ Many of the reported cases of aplastic anaemia after exposure to eye drops have a weak association between the use of the drops and the development of the anaemia, and the incidence after the use of eye drops seems extremely unlikely to be higher than the background incidence. A hypothetical risk of a low incidence of aplastic anaemia after use of the eye drops has to be weighed against the clinical usefulness and lack of other side effects of this particular preparation.

Case-control studies have failed to show any association between chloramphenicol eye drops and aplastic anaemia. The United Kingdom aplastic anaemia study, funded by the Health and Safety Executive and the Leukaemia Research Fund, is a national perspective case-control epidemiological study of aplastic anaemia that is registering all new cases of aplastic anaemia occurring in the United Kingdom over the next four years. All patients will be administered a detailed questionnaire concerning possible domestic medicinal exposure, including eye drops. This will be the largest prospective study of the epidemiology of aplastic anaemia, and we hope that it will clarify some of the controversies relating to drug exposure in aplastic anaemia. In the meantime it seems a pity to exaggerate the risk of aplastic anaemia associated with the widely used preparation of chloramphenicol eye drops.

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Authors' reply

EDITOR,—We take issue with several of the points raised in the letters in response to our editorial. R J Mulla and colleagues accept that after systemic use of chloramphenicol the risk of aplastic anaemia is 13 times higher than that in the general population. Yet we know that topical ophthalmic chloram-

phenicol is absorbed systemically¹ and that the development of aplastic anaemia is an idiosyncratic response; therefore any exposure is a risk factor regardless of dose or route of administration.

R J Buckley and colleagues state that patients with a proved personal or family history of blood dyscrasias should probably not receive chloramphenicol. In many instances a patient will not be aware of familial blood dyscrasias, and how often are patients asked about blood dyscrasias before they start treatment with ocular chloramphenicol preparations?

We accept that chloramphenicol provides broad spectrum cover, as alluded to by A V Hall and colleagues, but we believe that it should be reserved for resistant eye infections rather than be used as a first line agent.

Jim Cox and Eleri M Roderick believe that the risk is low. While we accept this, the mortality associated with aplastic anaemia induced by chloramphenicol is so high that the risk is unacceptable when the initial condition requiring treatment with chloramphenicol is benign.

We welcome the United Kingdom aplastic anaemia study mentioned by E C Gordon-Smith and colleagues and hope that it will improve knowledge and understanding of aplastic anaemias induced by drugs. We cannot, however, ignore the well documented relation between chloramphenicol and aplastic anaemia regardless of the route of administration.^{2,5}

In contrast to the *British National Formulary*, the *Physician Desk Reference* used in the United States emphasises, in boxed warnings repeated throughout the text, that ocular chloramphenicol should not be used unless there is no alternative. We support the American view—that chloramphenicol does not have a role as routine eye treatment.

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Should herbal medicines be licensed?

EDITOR,—The editorial by Dr Peter A G M De Smet highlighted the need for regulation of herbal medicine-like products.¹ We are particularly concerned about imported herbal medicines that contain heavy metals; this has been well documented in medicines from the Indian subcontinent.² We recently investigated the potential hazards of some Chinese patent medicines with high concentrations of mercurial ingredients that are used for the treatment of AIDS.

The labels and instructions were available only in Chinese, making identification of the product and ingredients difficult. The medicines were Angong Niu Huang Wan and Zhusha Aushen Wan pills, both of which are listed in the *Pharmacopoeia of the People's Republic of China*.³ The ingredients were primarily herbal and mineral and included cinnabar and arsenic. On analysis Angong