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.

A V HALL
Senior registrar

S S DAS
Consultant

S TABAQCHALI
Professor of medical microbiology

Department of Medical Microbiology,
St Bartholomew's Hospital,
London EC1A 7BE

- 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, Morgan RL, Yunis AA. Blood dyscrasias and topical ophthalmic chloramphenicol. *Am J Ophthalmol* 1993; 115:812-3.

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.

JIM COX
General practitioner

ELERI M RODERICK
General practitioner

Caldbeck Surgery,
Caldbeck,
Wigton,
Cumbria CA7 8DS

- 1 Doona M, Walsh JB. Use of chloramphenicol as topical eye medication: time to cry halt? *BMJ* 1995;310:1217-8. (13 May.)

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.

E C GORDON-SMITH
Professor of haematology

J C W MARSH
Honorary consultant haematologist

St George's Hospital Medical School,
London SW17 0RE

C G GEARY
Consultant haematologist

Manchester Royal Infirmary,
Manchester M13 9WL

- 1 Doona M, Walsh JB. Use of chloramphenicol as topical eye medication: time to cry halt? *BMJ* 1995;310:1217-8. (13 May.)
- 2 Smick KM, Condit PK, Proctor RL, Sutchter V. Fatal aplastic anemia: an epidemiological study of its relationship to the drug chloramphenicol. *J Chronic Dis* 1964;17:859-914.
- 3 Fraunfelder FT, Morgan RL, Yunis AA. Blood dyscrasias and topical ophthalmic chloramphenicol. *Am J Ophthalmol* 1993; 115:812-3.
- 4 Besamusca FW, Bastiaansen LA. Blood dyscrasias and topically applied chloramphenicol in ophthalmology. *Doc Ophthalmol* 1986;64:87-95.

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 systemically⁵ 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.

MARIE DOONA
Registrar

J BERNARD WALSH
Consultant physician

Department of Medicine for the Elderly,
St James's Hospital,
Dublin 8,
Republic of Ireland

- 1 Stevens JD, Mission GP. Ophthalmic use of chloramphenicol. *Lancet* 1987;iii:1456.
- 2 Abrams SM, Degnan TJ, Vinciguerra V. Marrow aplasia following topical application of chloramphenicol eye ointment. *Arch Intern Med* 1980;140:576-7.
- 3 Fraunfelder FT, Bagby GC, Kelly DJ, Abrams SM, Degnan TJ, Vinciguerra V. Fatal aplastic anaemia following topical administration of ophthalmic chloramphenicol. *Am J Ophthalmol* 1982;93:356-60.
- 4 Issaragrisil S, Pankajagum A. Aplastic anaemia following topical administration of ophthalmic chloramphenicol. *J Med Assoc Thai* 1985;68:305.
- 5 Sevilla TF, Alegre J, Vallespie T, Falco V, Varques J. Adult pure red cell aplasia following topical ocular chloramphenicol. *Br J Ophthalmol* 1990;74:640.

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