TOPICAL CHLORAMPHENICOL: USE OR ABUSE?

It is unusual for one journal to comment on the Editorial of another but a recent Editorial on the role of topical chloramphenicol in the *British Medical Journal*[1] raises issues peculiar to ophthalmology. Topical chloramphenicol in either drop or ointment form is one of the most reliable ophthalmic preparations in existence, and before its use is summarily abandoned the arguments on both sides should be carefully examined.

Doona and Walsh[1] base their case on the known potential for chloramphenicol to cause bone marrow suppression. There is a dose-related inhibition of erythropoiesis and marrow functions; this usually occurs at higher dosages (>50 mg/kg per day). There may also be inhibition of incorporation of iron into haemoglobin. In addition, idiosyncratic responses also occur more rarely – manifesting as granulocytopenia, agranulocytosis, aplastic or hypoplastic anaemia, or thrombocytopenia – in about 1 in 40 000 patients. There is, however, a high associated mortality, especially if the clinical onset is more than 2 months after the cessation of treatment. The precise nature of the toxic reaction is not fully understood but the mechanisms involved may be related to the mode of action of the drug on susceptible microbes. The drug binds to the 50S subunit, inhibits peptide chain elongation and movement of ribosomes along small mRNA, probably by inhibition of the peptidal transferase reaction.

Chloramphenicol is lipophilic, whch permits penetration through biological membranes. It does not readily inhibit protein synthesis in the larger ribosomes of eukaryotes. Mammalian mitochondria, however, have ribosomes similar in structure to those of bacteria. Chloramphenicol can inhibit mitochondrial protein synthesis and also reduce the ATP content of reticulocytes. The actions of chloramphenicol on the mitochondria underlie its toxicity on the bone marrow. The 'nitro' group may also contribute to toxicity since the related drug thianphenicol, which has a sulphomethyl group, does not exhibit the same toxic reactions. In cases of aplastic anaemia it remains uncertain as to the cause/effect relationship between drug and disorder. It is often difficult to disentangle the effects of chloramphenicol and other drugs being used by some patients. It is, however, simplistic to suggest that some doctors may not enquire into previous use of chloramphenicol. The low incidence of fatal aplastic anaemia with chloramphenicol suggests a special sensitivity in the few individuals who succumb. The case against chloramphenicol specifically when administered topically is even more difficult to disentangle. The report by Fraunfelder *et al.*[2] of a patient who died of aplastic anaemia following topical administration is not entirely clear. This patient was also receiving three other drugs with a similar potential, viz. triamterene, hydrochlorthiazide and phenacetin.[2] Subsequent collection of data has also been confusing. Buckley *et al.*[3] point out that the American National Registry of Drug-induced Ocular Side Effects received 33 reports of blood dyscrasias over a 12 year period, but only 7 cases are in published literature. With an incidence of 3 in 10^6 per annum we should have expected to see more cases reported if there was more than a chance association. Herein lies the difficulty: an extremely large number of cases would need to be audited to demonstrate a real effect. Doona and Walsh postulate without any evidence that the risk of topical chloramphenicol eye drops is the same as that from orally administered chloramphenicol. Absorption from the conjunctival sac is known to be good intraocularly,[4] but few, newer data exist as to the serum levels that may be reached following such topical administration. Without such information it is difficult to be sure whether bone marrow effects are feasible.

Accepting for the moment that there may be a problem, can we identify alternative antibiotic regimes to use? Chloramphenicol is used mainly: (1) to treat conjunctivitis in general practice and ophthalmology clinics, (2) to treat blepharitis and (3) for prophylaxis against infection at the time of ocular surgery. Part of its value, especially in (3), is due to its excellent penetration of ocular tissues and the low ocular surface toxicity combined with a broad spectrum of activity, low rates of development of resistance and its cheapness.

Conjunctivitis

There are alternative antibiotic preparations for treating bacterial conjunctivitis. Interestingly each new drug is tested for efficacy against chloramphenicol – an emphatic acknowledgement of its role as the gold standard for treating conjunctivitis. Few drugs have been identified as being superior, except in the treatment of *Chlamydia*, for which chloramphenicol is ineffective. Drugs such as Polytrim or fluoroquinalones may be as effective. Microbial keratitis is generally not treated with chloramphenicol.

Blepharitis

Blepharitis responds much less well to chloramphenicol than to other forms of treatment. There is evidence to suggest that topical fucithalmic or systemic tetracycline (particularly when blepharitis is associated with rosacea) offer effective means of dealing with this conditions.

Prophylaxis at and after surgery

Topical antibiotics themselves do not usually have time to eliminate bacteria when given pre-operatively and chloramphenicol is no different. Most reduce the bacterial flora, which may then be further significantly reduced by application of an aqueous 5% solution of povidone iodine. Chloramphenicol is useful because of the excellent ocular penetration it provides. Subconjunctival antibiotic injection at the end of the procedure may well provide an adequate immediate antibiotic prophylaxis but there may be a continuing need for topical antibiotics in the post-operative period until the eye has healed and steroids have been reduced or withdrawn. Chloramphenicol is superior to the alternatives, particularly neomycin (especially when combined with betamethasone), but Polytrim or fluoroquinalones might be adequate alternatives. As an overall antibiotic policy, however, the lack of emergence of drug resistance in the United Kingdom and other European countries may recommend chloramphenicol.

Endophthalmitis

Leopold[6] first suggested a role for chloramphenicol in the management of endophthalmitis but vitrectomy and intravitreal antibiotic injection have probably rendered this approach obsolete. Effective levels intravitreally may be reached by systemic administration of chloramphenicol and may occasionally be appropriate when vitrectomy is not feasible. It is one of the few drugs capable of penetration into the vitreous in effective concentrations after systemic administration.

Patients with a history or family history of blood dyscrasia should not receive chloramphenicol. Alternative drugs are available for almost any situation but we are not convinced that a case has been made for the total abandonment of topical chloramphenicol. Doona and Walsh[1] have resurrected the spectre of aplastic anaemia without new evidence implicating chloramphenicol. Guilt may be easy to demonstrate, innocence less so. For this reason in Scottish law we have a verdict of 'not proven'. The case against topical chloramphenicol appears to be not proven.

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References

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