Lack of evidence for systemic toxicity following topical chloramphenicol use

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CLINICAL STUDY

Abstract

There has been considerable controversy regarding the safety of topical chloramphenicol in ophthalmic practice. The evidence for associated haematopoietic toxicity in idiosyncratic and dose-dependent forms was reviewed. The 7 cases of idiosyncratic haematopoietic reactions associated with topical chloramphenicol reported in the literature are refutable evidence for the existence of such a response. In Scotland, despite extensive prescription of topical chloramphenicol, the incidence of acquired aplastic anaemia was found to be low, as were associated reports of blood dyscrasias throughout the UK. The epidemiology of acquired aplastic anaemia failed to make an association with topical chloramphenicol use. High-performance liquid chromatography (minimum detection limit 1 mg/l) was used to investigate whether serum accumulation of chloramphenicol occurred after topical therapy in 40 patients. The mean dose of chloramphenicol eye drops used after 1 week of treatment was 8.0 mg, and after 2 weeks, 15.3 mg. As expected, chloramphenicol failed to accumulate to detectable levels. This supported the view that topical chloramphenicol was not a risk factor for inducing dose-related bone marrow toxicity. Calls for the abolition of treatment with topical chloramphenicol based on current data are not supported.

Key words Chloramphenicol, Blood dyscrasias, Drug-induced myelotoxicity, Aplastic anaemia

Chloramphenicol has been a widely used topical ophthalmic preparation, with a broad spectrum of activity,[1,2] good penetration of the cornea and anterior chamber,[3,4] low potential for sensitisation[5,6] and low cost. Although newer alternative ocular antibiotics are available for treating superficial infections, chloramphenicol has remained the gold standard with which others are compared.[7] There have, however, been recent recommendations that such routine therapy should be halted because of the risk of inducing fatal bone marrow aplasia.[8]

It has been universally recognised that bone marrow toxicity can follow systemic administration of chloramphenicol.[9–12] This adverse reaction has taken one of two forms.[13] The first was the rare, irreversible, idiosyncratic aplastic anaemia that occurred in predisposed patients independent of dose. This was thought to be mediated by a nitroreduction derivative of chloramphenicol which induced DNA damage in replicating haematopoietic stem cells, resulting in marrow hypocellularity and progressive pancytopenia. The second was the more common reaction of a generally reversible marrow suppression, which occurred in a dose-dependent manner with sustained serum levels greater than 25 mg/l. This has been associated with the inhibition of mitochondrial protein synthesis and characterised by mild marrow hypocellularity with a mild anaemia, thrombocytopenia and neutropenia. In a recent review of the pathophysiology of acquired aplastic anaemia, the authors argued that bone marrow failure resulted from immunologically mediated, tissue-specific organ destruction.[14] Whether chloramphenicol acted as an antigenic stimulus was not discussed.

A critical review of both the published literature and Committee on Safety of Medicines case reports was undertaken, these forming the circumstantial evidence for the existence of an idiosyncratic haematopoietic reaction following topical chloramphenicol. The existence of this disorder would be assessed by examination of Scottish epidemiological data. Current levels of topical chloramphenicol prescription were set against the actual incidence of aplastic anaemia, and compared with that expected from known risk rates associated with chloramphenicol use.

It has been suggested that systemic effects may be achieved following topical chloramphenicol administration.[8] Standard treatment with chloramphenicol 0.5% eye drops applied 4 times daily approximates to a dose of 1 mg. Systemic absorption follows drainage via

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the nasolacrimal duct. Expected serum concentrations of chloramphenicol after topical therapy should be low, but remain to be determined. This study used high-performance liquid chromatography to investigate whether accumulation to a detectable level occurred. Such data would quantify any risk of inducing dose-related haematopoietic reactions.

Methods

Following ethics committee approval, two groups of patients were recruited: group I consisted of 20 new patients attending a city centre eye casualty department; group II consisted of 20 routine ophthalmic post-operative cases in a teaching hospital. Both groups were commenced on guttae chloramphenicol 0.5% eye drops (Schering-Plough) 4 times daily to a single eye as treatment. Informed consent was obtained from each patient for the collection of a blood sample for chloramphenicol assay. This was taken within 4 h of the last drop administered, during the last day of treatment, for group I after 1 week, and for group II after 2 weeks. Blood was drawn into an additive-free tube, centrifuged and the serum stored at −20 °C. Serum assay for analyte was carried out by high-performance liquid chromatography (minimum detection limit 1 mg/l) using an RP-C18 column with a methanol and water eluant, and absorption at 280 nm.

An estimate of patient compliance was made by subtracting the weights of returned chloramphenicol bottles from the mean weight of a full bottle ($n = 10$) to obtain the weight of drops used. The doses of chloramphenicol assumed to be instilled into the conjunctival sac were calculated.

Results

Seven published case reports in the world literature of topical chloramphenicol being associated with aplastic anaemia were identified for review[15–21] (Table 1). Three of these patients were given other marrow toxic medication concurrently (C, D, G); 2 patients had liver disease (C, G); 3 patients received prolonged treatment (A, C, E); and the possibility of genetic predisposition was noted in 3 patients (A, D, G).

In the UK between 1966 and 1997 there were 11 reports to the Committee on Safety of Medicines detailing suspected ophthalmic chloramphenicol-related haematopoietic reactions which were reviewed (Table 2). The duration of treatment was not recorded in 5 patients (1, 2, 3, 5, 6), and was excessive in 2 patients (7, 8). Two patients had additional treatments that were possible causes of bone marrow suppression (8, 11).

In Scotland, during the financial year April to March 1995/6, there were 128 284 prescriptions for guttae 0.5% chloramphenicol (10 ml bottles) completed by general practitioners (personal communication, The Scottish Office), with a further 42 852 supplied by 45 Scottish hospitals (personal communications to hospital pharmacies, $n = 73$). Allowing for the 28 non-responding hospitals, a total of approximately 198 500 guttae chloramphenicol treatment episodes was estimated. Although the rate of repeat prescriptions was unknown, these figures would be consistent with 3–4% (1 in 25) of the Scottish population being exposed to chloramphenicol eye drops. Information regarding the prescription of chloramphenicol ointment was not directly sought; where it was detailed, however, it exceeded drop therapy usage for that particular hospital. The total annual number of prescriptions for topical chloramphenicol may therefore approach 400 000 (1 in 12 population exposure).

Table 1. *Published case reports of haematopoietic disorders associated with ophthalmic chloramphenicol*

Case no.	Age/ Sex	Suspect drugs	Duration	Reaction	Other drugs	Family history	Liver disease	Outcome	Author (year)
A	36/M	Chloramphenicol	23 months	Bone marrow hypoplasia	Antihistamine preparation	Aplastic anaemia with oral chloramphenicol	None	Reversible	Rosenthal (1965)[15]
B	37/M	Chloramphenicol	2 months	Aplastic anaemia	None	Unknown	None	Reversible	Carpenter (1975)[16]
C	33/M	Chloramphenicol Tetracycline	4 months 24 months	Aplastic anaemia	None	None	Yes	Fatal	Abrams (1980)[17]
D	73/F	Chloramphenicol Triamterene Hydrochlorothiazide Aspirin Phenacetin Caffeine	1 month Unknown Unknown Unknown Unknown Unknown	Aplastic anaemia	Guaifenesin and dextromethorphan carbachol	Pernicious anaemia	None	Fatal	Fraunfelder (1982)[18]
E	66/F	Chloramphenicol	5 years	Aplastic anaemia	Unknown	Unknown	None	Reversible	Issaragrissil (1985)[19]
F	85/M	Chloramphenicol	2 months	Red cell aplasia	None	Unknown	Unknown	Persistent anaemia	De Sevilla (1990)[20]
G	73/F	Chloramphenicol Flurbiprofen Acetazolamide	2 weeks Unknown 1 week	Aplastic anaemia	Ranitidine, sulindac, flurbiprofen, Predforte, vitamins B & C	Leukaemia	Yes	Fatal	McWhae (1992)[21]

Table 2. *Committee on Safety of Medicines reports of haematopoietic disorders associated with ophthalmic chloramphenicol*

Case no.	Age/ sex	Suspect drug	Duration	Reaction	Other drugs	Outcome	ADR no. year
1	12/F	Chloramphenicol	Unknown	Neutropenia, thrombocytopenia	Unknown	Reversible	014688 1968
2	8 months/M	Chloramphenicol	Unknown	Bone marrow depression	Trimeprazine	Unknown	015091 1968
3	63/F	Chloromycetin	Unkown	Hypoplastic anaemia	Unknown	Fatal	106937 1981
4	2/M	Chloromycetin	4 days	Bone marrow depression	Unknown	Reversible	139864 1984
5	58/F	Chloramphenicol	Unknown	Aplastic anaemia	Panadol, tenormin	Unknown	145190 1985
6	85/M	Chloramphenicol	Unknown	Pancytopenia	Nitrazepam, paracetamol, hexopal, co-danthrusate	Fatal	201003 1988
7	68/F	Chloramphenicol	3 years	Hypoplastic anaemia	Unknown	Unknown	250448 1990
8	56/M	Chloramphenicol Allopurinol	7 years Unknown	Pancytopenia	Sulphasalazine	Fatal	254094 1990
9	36/M	Chloramphenicol	1 week	Pancytopenia	Prednisolone, cyclopentolate, dexamethasone	Fatal	285461 1992
10	89/F	Chloramphenicol	1 week	Neutropenia	Paracetamol	Fatal	329771 1995
11	81/F	Chloramphenicol Carbimazole	10 weeks 10 days	Aplastic anaemia	Aspirin, anastrozole, omeprazole, metronidazole, ciprofloxacin	Fatal	B704496 1996

The doses of chloramphenicol used by 15 group I patients ranged from 2.9 mg to 18.1 mg, and the doses used by group II patients ranged from 3.6 mg to 32.1 mg (Table 3). Chloramphenicol eye drops were used by these 26 patients, and as such compliance proved satisfactory. Six of 15 patients in group I, and 4 of 11 patients in group II used less than the recommended daily dose of 1 mg, suggesting some missed applications. Compliance could not be assessed in 14 patients who failed to return their chloramphenicol bottles. The results from these questionably compliant patients were included as this reflected a typical clinical situation.

Chloramphenicol was not detected in the sera from any of the 40 patients.

Table 3. *Chloramphenicol usage by patient*

	Group I		Group II	
Patient no.	Weight (g) of drops used	Chloramphenicol dose (mg)	Weight (g) of drops used	Chloramphenicol dose (mg)
1	0.7001	3.5	0.8900	4.5
2	0.6177	3.1	1.1163	5.6
3	0.5823	2.9	1.0990	5.5
4	2.2704	11.4	3.1445	15.7
5	1.5396	7.7	6.4269	32.1
6	1.6981	8.5	5.9186	29.6
7	1.7334	8.7	3.0587	15.3
8	1.0140	5.1	2.8218	14.1
9	1.8147	9.1	0.7139	3.6
10	1.6311	8.2	4.7521	23.8
11	0.7260	3.6	3.6031	18.0
12	3.0714	15.4		NR
13	3.6252	18.1		NR
14	1.2581	6.3		NR
15	1.5469	7.7		NR
16		NR		NR
17		NR		NR
18		NR		NR
19		NR		NR
20		NR		NR

NR, chloramphenicol bottle not returned for weighing.

Discussion

In 1982, Fraunfelder *et al*.[18] published a case report and literature review which resulted in a decline in topical chloramphenicol use in the USA. The patient described (Table 1, case D) used topical chloramphenicol for 5 weeks, but received other drugs (triamterene, hydrochlorothiazide and phenacetin) for an unspecified length of time. Any one of these agents may have contributed to the development of aplastic anaemia.[22] In a subsequent letter, Fraunfelder *et al*.[23] outlined a further 23 cases of blood dyscrasias associated with topical chloramphenicol. These consisted of the 7 published case reports and 16 unpublished cases which were reported to the National Registry of Drug-induced Ocular Side Effects, but which the authors conceded were not fully investigated.

In their editorial, Doona and Walsh[8] reiterated the fears that topical chloramphenicol may precipitate fatal aplastic anaemia and called for its routine use to be discontinued. To support their case, they cited 'numerous' articles directly implicating chloramphenicol eye drops as having caused bone marrow aplasia. Their argument was based on the understanding that chloramphenicol-related, idiosyncratic aplastic anaemia occurred independent of dose, and on the assumption that topical administration of chloramphenicol 'achieves systemic effects'. They postulated that the risk may therefore be similar to that after oral therapy.

As we have seen, of the 7 case reports reviewed from the world literature, 3 patients received other marrow-toxic medication that may have been responsible for the development of aplastic anaemia. Direct causality has not been irrefutably proven in the remaining 4 cases, as coincidences may occur.[24]

Idiopathic aplastic anaemia has a global incidence of 3 per 1 000 000 population,[25] a rate recently confirmed in Scotland.[26] Aplastic anaemia developing after systemic chloramphenicol therapy has an associated risk estimated at 1 in 24 500 to 1 in 40 800 exposures.[27] Over the last three decades, topical chloramphenicol has been used extensively worldwide, without generating cases of associated bone marrow toxicity in numbers consistent with Doona and Walsh's postulate that the risk approaches that associated with systemic exposure.[7,28–32]

In Scotland, with a population of 5.1 million, around 15 new cases of idiopathic aplastic anaemia are expected annually. If topical chloramphenicol were responsible for cases of aplastic anaemia consistent with the risk figures quoted above, each year Scotland would expect 4 to 8 afflicted patients after drop therapy, with perhaps 8 to 16 cases if ointment therapy was included. On this basis, virtually all of the 15 so-called 'idiopathic' cases of aplastic anaemia would be directly attributable to topical chloramphenicol. This has not been observed in practice. The possibility of serious under-reporting of such frequently expected episodes would be unlikely.

The lack of an association between topical chloramphenicol and haematopoietic disorders was supported epidemiologically elsewhere. In a southern region of The Netherlands, with a population of 265 000, a 4 year study revealed that a total of 34 240 patients had used topical chloramphenicol. Of the 59 cases of idiopathic blood dyscrasias identified during this time, none could be unequivocally linked with previous topical chloramphenicol exposure.[29] The USA and France have similar incidence rates of aplastic anaemia, despite a 40-fold greater usage of topical chloramphenicol in Europe.[33] A 5 year prospective study of the epidemiology of acquired aplastic anaemia in Thailand identified 374 cases, none of which was associated with chloramphenicol use.[34]

On the basis of estimates that 75–80% of each topical eye drop passes into the nasolacrimal duct, for potential systemic absorption,[35,36] the mean doses of chloramphenicol available for systemic absorption in groups I and II of our study were therefore 6.0 mg and 11.5 mg, respectively. It is likely that these amounts would be completely absorbed by the body, given the lipophilic nature and high bioavailability of chloramphenicol. Following standard courses of treatment as followed by groups I and II, serum concentrations of chloramphenicol had not accumulated to detectable levels. The only other report on systemic absorption of chloramphenicol after topical treatment recorded similar results.[37] Urine samples from 5 children receiving 2 hourly chloramphenicol drops for 5–7 days (total dose 40–52 mg) were assayed by gas liquid chromatography without chloramphenicol detection.

Current data do not support an increased risk of bone marrow toxicity from the use of topical chloramphenicol. We await with interest the results of the UK aplastic anaemia prospective epidemiological study, anticipating further clarification of this issue.[38]

Conclusions

Epidemiological data do not support the occurrence of idiosyncratic blood dyscrasias after topical chloramphenicol. Case reports are extremely rare; some are refutable, others may be coincidental. An adverse reaction cannot be excluded, however, in patients with a genetic predisposition, after prolonged treatment periods, or when treatment is combined with other myelotoxic drugs.

The results of our study show that, after topical application of chloramphenicol for up to 2 weeks, serum concentrations do not accumulate to detectable levels (1 mg/l). Topical chloramphenicol therefore does not present a risk of inducing dose-related bone marrow toxicity.

Current evidence supports continued short-course use of topical chloramphenicol, but a personal or family history of blood dyscrasias must be excluded before prescribing.

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