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Topical chloramphenicol for eye infections

用於治療眼睛感染的局部氯黴素

Topical chloramphenicol has been widely used in the treatment and prevention of superficial eye infections due to its broad spectrum of activity and low cost. The use of this drug has decreased considerably in the United States since the first case of aplastic anaemia associated with topical chloramphenicol was reported in the 1960s. This medication, however, is still widely used in many other countries. This paper evaluates the evidence for and against the use of topical chloramphenicol in ocular diseases.

基於局部眼藥水或藥膏氯黴素的低成本和擁有廣泛的殺菌能力，它在多年前已被普遍地應用於治療和預防眼睛的表面感染。但自六十年代出現了第一個與局部氯黴素有關的發育不全的貧血病實例以來，美國已大大減少了這方面的使用。然而，局部氯黴素仍然被許多國家廣泛使用。本報告評價了在眼病中使用局部氯黴素的正反兩方面的證據。

Introduction

Since its introduction in the United States in 1948, topical chloramphenicol has been the preferred drug for the treatment and prevention of superficial eye infections in many countries around the world.[1] It is a relatively inexpensive, broad spectrum antibacterial agent, with a reported efficacy of 91% to 93% in ocular infections,[2] and is active against up to 94% of ocular pathogens.[3] In the early 1960s, the occurrence of aplastic anaemia following topical chloramphenicol use was reported.[1] By the 1980s, sales of topical chloramphenicol had substantially decreased in the United States, and the drug is now packaged with a warning that it should not be used unless there is no alternative treatment available.[1]

Spectrum of activity

Chloramphenicol has been proven to be effective against most Gram-positive and Gram-negative pathogens. It is also useful in treating anaerobes, mycoplasma, rickettsia, chlamydia, and spirochete species.[4] Of note, more than 95% of *Haemophilus influenzae*, *Neisseria meningitides*, *Neisseria gonorrhoeae*, *Salmonella typhi*, *Brucella* species, and *Bordetella pertussis* strains are susceptible to chloramphenicol. The intraocular penetration of chloramphenicol is excellent because of its high lipid solubility, and it is thus very effective in prophylaxis against ocular surgery infection.[5]

Adverse reactions

Although systemic chloramphenicol usually has relatively benign side-effects, such as gastrointestinal disturbances and rash, serious complications such as blood dyscrasias have also been reported. This complication occurs in between 1:24 500 to 1:40 800 exposures, and the incidence of chloramphenicol-induced aplastic anaemia (with systemic use) is reported to be 13 times that of the idiopathic form.[6]

In adults, idiosyncratic aplastic anaemia can occur in predisposed patients following the use of chloramphenicol, irrespective of the dosage.[7] This is thought to be due to production by the gut flora of a nitro reduction derivative of

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chloramphenicol. This derivative can induce DNA damage in replicating hematopoietic stem cells, resulting in marrow hypocellularity and progressive pancytopenia.[7] The more common presentation, however, is a reversible, dose-dependent bone marrow suppression, which usually occurs when serum chloramphenicol levels exceed 25 mg/L for prolonged periods of time.[8] This condition is associated with the inhibition of mitochondrial protein synthesis and is characterised by mild marrow hypocellularity, anaemia, neutropenia, and thrombocytopenia.[8]

'Grey baby' syndrome is another severe complication of chloramphenicol therapy.[9] It occurs primarily in neonates and is usually fatal. Clinical manifestations include abdominal distention, vomiting, progressive cyanosis, and circulatory collapse. The occurrence of this syndrome is also dose-related and is generally associated with infant serum concentrations of chloramphenicol greater than 5 mg/L.[9]

Topical chloramphenicol is generally very well tolerated, and adverse effects such as hypersensitivity, burning, and stinging sensations are uncommon.[10]

Discussion

A review of the literature revealed 23 cases of blood dyscrasias possibly related to the use of topical ocular chloramphenicol.[8] Only seven of these cases were published, while the rest were not fully investigated. The published cases are summarised in the Table.[8]

All but one patient had been exposed to relatively long periods of topical chloramphenicol therapy (mean, 13 months; range, 2 weeks-5 years). Three patients were given other marrow-toxic medications concurrently (patients 3, 4, and 7), and two of these patients also had liver disease (patients 3 and 7). A possible genetic predisposition (family history of aplastic anaemia, pernicious anaemia, or leukaemia) was present in three patients (patients 1, 4, and 7).[8]

As non-idiosyncratic aplastic anaemia and 'grey baby' syndrome are dose-dependent complications of chloramphenicol usage, sufficient absorption of chloramphenicol must occur via the nasolacrimal duct in order to increase serum chloramphenicol concentrations. Conventional treatment with 0.5% (0.5 mg/100 mL) chloramphenicol eye drops, four times daily, approximates to a total daily dose of 1 mg.[8] Walker et al[8] have estimated patient serum concentrations of chloramphenicol after topical therapy in one eye. Group 1 patients (n=20) received 0.5% eye drops four times daily for 1 week, while Group 2 patients (n=20) received 0.5% eye drops four times daily for 2 weeks. After allowing for non-compliance with the prescribed regimen, it was estimated that the cumulative exposure to topical chloramphenicol was between 2.9 mg and 18.1 mg in Group 1 and between 3.6 mg and 32.1 mg in Group 2. Serum chloramphenicol levels were assessed 4 hours after the last dose on the last day of treatment. Serum concentrations of chloramphenicol had not accumulated to measurable levels (1 mg/L) in either group. A further study measured urine chloramphenicol levels in five children receiving chloramphenicol eye drops every 2 hours for 5 to 7 days (total dose, 40-52 mg).[11] No evidence of systemic absorption of chloramphenicol was detected. Current evidence suggests that the minimum total topical dose associated with marrow toxicity is 30 mg, and the minimum associated duration of exposure 18 days.[12]

Although serum levels of chloramphenicol may not reach detectable levels after topical therapy, it is still possible that some systemic absorption occurs, since chloramphenicol is lipophilic and has high bioavailability. Such systemic absorption may be sufficient to precipitate idiosyncratic aplastic anaemia in predisposed individuals, since this is not a dose-dependent event. It is impossible to calculate this

Table. Published case reports of patients with blood dyscrasias associated with topical chloramphenicol[8]

Patient No.	Drug implicated	Duration of treatment	Reaction	Other drugs used	Liver disease	Family history	Outcome
1	Chloramphenicol	23 months	Bone marrow hypoplasia	Antihistamines	None	Aplastic anaemia with oral chloramphenicol	Reversible
2	Chloramphenicol	2 months	Aplastic anaemia	None	None	Unknown	Reversible
3	Chloramphenicol Tetracycline	4 months 24 months	Aplastic anaemia	None	Yes	None	Fatal
4	Chloramphenicol Triamterene Hydrochlorothiazide Aspirin Phenacetin Caffeine	1 month Unknown Unknown Unknown Unknown Unknown	Aplastic anaemia	Guaifenesin Dextromethorphan Carbachol	None	Pernicious anaemia	Fatal
5	Chloramphenicol	5 years	Aplastic anaemia	Unknown	None	Unknown	Reversible
6	Chloramphenicol	2 months	Red cell aplasia	None	Unknown	Unknown	Persistent anaemia
7	Chloramphenicol Flurbiprofen Acetazolamide	2 weeks Unknown 1 week	Aplastic anaemia	Ranitidine Sulindac Flurbiprofen Predforte	Yes	Leukaemia	Fatal

risk exactly given the current literature. However, since topical preparations bypass the gut flora, and thus the nitroderivatives of chloramphenicol implicated in idiosyncratic aplastic anaemia are not produced, it is uncertain how the absorbed drug would induce this reaction.[8] It is known that the risk of bone marrow toxicity is lower after parenteral compared with oral administration of the drug, however.[10]

If all 23 reported cases of aplastic anaemia following topical chloramphenicol use are considered to be adverse events associated with chloramphenicol, this would still amount to less than one case per year of this serious complication.[13] Fraunfelder et al[14] cautioned, however, that such cases may be under-reported because physicians do not ask patients diagnosed with blood dyscrasias about past exposure to topical chloramphenicol. Also, as there is a window period of up to 6 months between exposure and the development of marrow suppression, many patients may not remember past exposure to the drug.[14] Fraunfelder et al[14] have estimated that approximately 1.5 million observations would be necessary to establish a statistically significant association between chloramphenicol and aplastic anaemia.

Epidemiological evidence from Scotland, which has a population of 5.1 million, reports an incidence rate of 15 new cases of aplastic anaemia per year. Approximately 400 000 chloramphenicol eye drop and ointment products are sold annually in Scotland.[8] Since the incidence of chloramphenicol-induced aplastic anaemia is estimated at 1:30 000 to 1:50 000 cases, one would therefore expect an incidence of approximately eight to 13 cases of chloramphenicol-induced aplastic anaemia annually. On this basis, the 15 so-called 'idiopathic' cases of aplastic anaemia could be directly attributable to topical chloramphenicol, ignoring other possible causes of aplastic anaemia. Based on this data, the possibility of serious under-reporting of chloramphenicol-induced aplastic anaemia seems unlikely.

Chloramphenicol is prescribed 100 to 400 times more frequently in Hong Kong than in western countries, and the occurrence of aplastic anaemia is thought to be two to three times more common in the oriental as compared with the western population.[1] Despite this, the certified death rate from aplastic anaemia is only 0.4 per 1000 deaths in Hong Kong, compared with 1 per 1000 deaths in England and Wales.[1] A recent population-based study conducted in Thailand failed to show a significant association between chloramphenical use and aplastic anaemia.[15] Another population-based prospective case-controlled study in Spain indicated an association between topical chloramphenicol use and aplastic anaemia, but stated the risk as less than 1 per 1 000 000 treatment courses.[7] Thus, current epidemiologic data indicates that the risk of aplastic anaemia after topical chloramphenicol use is extremely low.

Lastly, although the risk of aplastic anaemia after topical use of chloramphenicol may be very low, the adverse reaction is often life-threatening. While this has been used as an argument against the use of chloramphenicol for relatively less severe ocular conditions, it must be remembered that a comparable incidence of severe anaphylactic reactions occurs after the use of drugs such as penicillin and sulpha.[10] Since these drugs are still used widely, it is difficult to justify demands for the cessation of topical chloramphenicol use on this basis.

Alternative agents

Doona and Walsh[16] suggested in 1995 that framycetin and fusidic acid are as effective as chloramphenicol in the treatment of superficial eye infections and should replace the latter drug. There have been no recent reports on the efficacy of framycetin, however. While framycetin is effective in treating *Staphylococcus aureus*, its ability to treat other pathogens is questionable. Framycetin has also been shown to cause blood dyscrasias when administered systemically.[17] Recent reports on the sensitivity of fusidic acid have shown that it is mainly effective against Gram-positive organisms.[18] Neither framycetin nor fusidic acid has as broad a spectrum of activity as chloramphenicol. Both framycetin and fusidic acid also promote rapid emergence of resistance if used alone.[17]

Quinolones, such as ciprofloxacin, appear to be a good alternative due to their enhanced ocular penetration, ophthalmic tolerance, and broad spectrum of antibacterial activity. Quinolones are effective against most Gram-positive and Gram-negative organisms, including *Pseudomonas* species, which are resistant to chloramphenicol as well as framycetin and fusidic acid.[19] Although topical quinolone preparations appear superior to chloramphenicol in many respects, they are currently the most potent antibiotics available for the treatment of common ocular infections, and their routine use would potentiate the emergence of resistant bacterial strains. They should thus ideally be used against organisms that are resistant to chloramphenicol.

Conclusion

Existing reports provide insufficient epidemiological and scientific data to implicate the use of topical chloramphenicol in the causation of aplastic anaemia. Four of the seven published cases to date had other predisposing conditions that could explain the subsequent development of aplastic anaemia. Dose-related aplastic anaemia and 'grey baby' syndrome are also unlikely to occur if patients adhere to the prescribed dose and duration of treatment. The theoretical risk of aplastic anaemia after the use of topical chloramphenicol is low and has to be balanced against the clinical utility of chloramphenicol. Chloramphenicol is one of the most cost-effective, topical ophthalmic antimicrobial preparations available today,[13] an important consideration, especially in third world countries where superficial eye infections are common. Current evidence supports the use of short courses of topical chloramphenicol in the treatment

of ocular infections. It would seem prudent, however, to avoid topical chloramphenicol use in patients with a genetic predisposition to haematological disorders or those needing prolonged treatment, and in conjunction with other bone marrow suppressive agents.

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