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Ophthalmic uptake of chloramphenicol from proprietary preparations using an in vitro method of evaluation

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Summary

An in vitro method using ovine eyes was used to evaluate bioavailability of chloramphenicol from ophthalmic ointment and solution preparations. The results obtained were consistent with the findings of other studies using rabbit and human subjects verifying the usefulness of this in vitro technique. It was apparent that the ointment tested gave better ophthalmic levels of chloramphenicol than the solution and the former is therefore preferable in the treatment of ocular infections.

Introduction

The low corneal toxicity of chloramphenicol makes it an ideal antibiotic for treatment or prophylaxis of corneal and intraocular infections [Flach, 1982] although fatality due to development of aplastic anaemia may result from ophthalmic administration [Fraunfelder et al., 1982]. It is, therefore, important that the preparation used be capable of achieving therapeutic levels within the eye without causing significant systemic distribution in order to minimise toxicity.

This study aimed to verify the usefulness of an in vitro method of evaluation of ophthalmic bioavailability and to compare chloramphenicol release from proprietary preparations.

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Materials and Methods

Materials

d-(−)-Threo-[dichloroacetyl-1-^{14}C]chloramphenicol (2.0 GBq/mmol) was obtained from Amersham plc, Bucks, UK; Chloromycetin redidrops and ophthalmic ointment from Parke-Davis (Pty) Ltd, South Africa; Millipore filters (1.2 μM) from Millipore, Bedford, MA, U.S.A.; Insta Gel scintillation cocktail from Packard, Downers Grove, IL, U.S.A. and Scintran tissue solubiliser from BDH, Poole, UK. All other chemicals and reagents were obtained from Merck, Darmstadt, F.R.G. and distilled deionised water was used throughout.

Determination of bioavailability

The method used was modified from a developed technique [Flint and Morton, 1984]. Ovine eyes collected directly after slaughter after ensuring that corneas were firm and rounded and free

from any visible damage were transported in oxygenated Krebs solution on ice after which they were transferred to beakers such that each eye was firmly supported in a cornea superior position. Krebs solution was added to the beakers to moisten the eyes to a level 0.5 cm below the cornea. Millipore filters (1.2 μM, 25 mm diameter) were moistened with Krebs solution and placed over each cornea. Radial incisions were made in the filter discs to ensure adequate contact between cornea and disc. For evaluation either a 50 μl sample of solution containing [^{14}C]chloramphenicol was pipetted onto the filter discs in place on the corneas or a 50 μl sample of ointment containing [^{14}C]chloramphenicol was spread evenly over the surface of a filter disc prior to being placed on the cornea. The beakers were gassed with 95% O_2/5%CO_2, sealed and incubated at 37°C. At set time intervals 0.25 ml of aqueous humour was removed from the eyes and the corneas were removed and liberally swabbed with distilled water to remove contaminants, and the samples were placed in individual scintillation vials with 5 ml Insta Gel. Corneal samples were soaked in Scintran for 5 days before addition of Insta Gel. Radioactivity was quantitated by scintillation spectrometry, counting efficiency exceeding 90% in all cases. Similar amounts of both ointment and solution were applied to the eyes for direct comparison of the quantity of chloramphenicol released into the eyes. As the mean corneal volume was found to be 0.25 ml, a similar volume of aqueous humour was used to allow for direct comparison of the results.

Analysis of data

Results are expressed as μg chloramphenicol absorbed per unit time and each point represents the mean of 15 determinations ($\pm$S.E.M.). Probabilities were calculated using the Student *t*-distribution.

Results and Discussion

The corneal levels of chloramphenicol from both preparations were substantially higher than those in the aqueous humour (Fig. 1 and 2) which can be expected due to the high lipophilicity of the drug which would lead to corneal retention. Partitioning from cornea into aqueous humour would, therefore, occur at a slower rate than the initial rate of uptake by the cornea due to the hydrophilic nature of the aqueous humour and consequently the cornea acts as a rate-limiting barrier for absorption of chloramphenicol by the aqueous humour.

Comparison of bioavailability of chloramphenicol from both preparations indicated that the Chloromycetin redidrops gave lower corneal and aqueous humour levels than the Chloromycetin ophthalmic ointment with greater significant differences occurring in the aqueous humour levels (Figs. 1 and 2). These results are consistent with previous reports using rabbit and human subjects [George and Hanna, 1977; Hanna et al., 1978] both of which showed ointment to give superior chloramphenicol levels when compared to solutions of the drug. In the experimental model used, both preparations were in constant contact with the eye whereas in the clinical situation normal tear turnover and washout would occur reducing the amount of solution available for absorption into the eye. The ointment on the other hand would resist washout and it is probable that when used clinically the differences in chloramphenicol levels achieved from the use of ointment and solution would be greater than expected from the results of this study. This supposition is supported by the findings that repeated use of chlo-

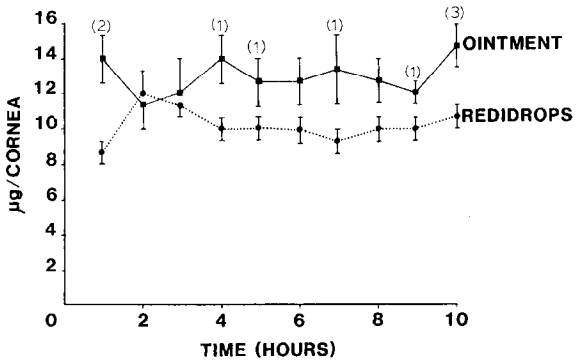

Fig. 1. Corneal concentration of chloramphenicol as a function of time resulting from application of ophthalmic solution and ointment. (1), $P = 0.05$; (2), $P = 0.01$; (3), $P = 0.005$.

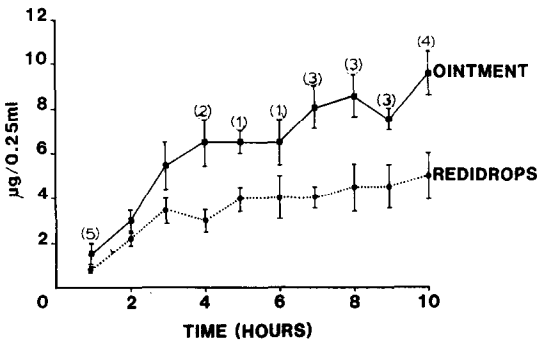

Fig. 2. Aqueous humour concentration of chloramphenicol as a function of time resulting from application of ophthalmic solution and ointment. (1), $P = 0.025$; (2), $P = 0.01$; (3), $P = 0.005$; (4), $P = 0.0025$; (5), $P = 0.001$.

ramphenicol solution was necessary to produce aqueous humour levels comparable to those achieved by a single application of ointment in rabbit eyes [George and Hanna, 1977].

Repeated use of chloramphenicol solutions, although capable of achieving therapeutic levels in the eye, would greatly enhance the risk of systemic toxicity due to loss through the nasolacrimal drainage system. The macromolecular structure of ointments on the other hand increases ocular contact time and the constituents are less readily removed via the lacrimal excretory apparatus [Hardberger et al., 1975] thus enhancing corneal uptake of chloramphenicol and reducing the risk of systemic toxicity.

In conclusion it is evident that the use of isolated ovine eyes to determine ophthalmic uptake of drugs produces results similar to those using rabbit and human eyes [George and Hanna, 1977; Hanna et al., 1978]. The major drawback is the fact that drug preparations are in constant contact with the eyes and therefore results do not take into account normal drainage and elimination of drugs that would occur in an intact animal. The technique, however, is useful for ascertaining the effect of vehicle and different drug salts on bioavailability being far more simple and cost effective than using a live animal model or human subjects.

From the results of this study it is evident that, in the clinical situation with normal lacrimation, the ointment would be superior in achieving therapeutic levels with a lower risk of toxicity whereas the solution, in order to achieve desirable ophthalmic concentrations, would also increase the risk of systemic toxicity. In the clinical situation it would be desirable to use chloramphenicol ophthalmic ointments and the solutions should be reserved for cases where the use of an ointment is impractical for some reason.

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References

Flach, A.J., Fatal aplastic anaemia following topical administration of ophthalmic chloramphenicol. *Am. J. Ophthalmol.*, 94 (1982) 420–421.

Flint, G.R. and Morton, D.J., Effect of derivatization on the bioavailability of ophthalmic steroids: development of an in vitro method of evaluation. *Arch Ophthalmol.*, 102 ((1984) 1808–1809.

Fraunfelder, F.T., Bagby, G.C. and Kelly, D.J., Fatal aplastic anemia following topical administration of ophthalmic chloramphenicol. *Am. J. Ophthalmol.*, 93 (1982) 356–360.

George, F.J. and Hanna, C., Ocular penetration of chloramphenicol. *Arch Ophthalmol.*, 95 (1977) 879–882.

Hanna, C., Massey, J.Y., Hendrickson, R.O., Williamson, J. Jones, E.M. and Wilson, P., Ocular penetration of topical chloramphenicol in humans. *Arch Ophthalmol.*, 96 (1978) 1258–1261.

Hardberger, R., Hanna, C. and Boyd, C.M., Effects of drug vehicles on ocular contact. *Arch Ophthalmol.*, 93 (1975) 42–45.