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Comparative bioavailability of adrenaline-containing ophthalmic solutions: use of an in vitro method of evaluation

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Summary

A previously developed in vitro method of evaluation of ophthalmic bioavailability was used to compare the ocular uptake of adrenaline from 3 commercially available preparations. From the results obtained it was apparent that the bioavailability of adrenaline is affected quite dramatically by vehicle composition and the type of salt used. Of the products tested Isopto Epinal 1% gave the highest ocular levels of adrenaline, possibly as a result of optimum pH, viscosity and the epinephryl–borate complex in the formulation. This study demonstrates again the value of in vitro determinations in assessment of ophthalmic bioavailability of drugs.

Introduction

Adrenaline stimulates both α- and β-adrenergic receptors, its action on the α receptors of the dilator pupillae producing mydriasis (O'Connor-Davies, 1981) which is advantageous in elderly patients with central lens opacities who would be visually handicapped by the pupillary constriction of miotics (Reynolds, 1982). β receptor stimulation by adrenaline reduces intra-ocular pressure by decreasing aqueous humour production and is therefore of use in chronic simple glaucoma (Reynolds, 1982; Weekers et al., 1955).

The availability of drugs instilled into the eye can be modified by a number of factors – drug kinetics in the conjunctival cul-de-sac, corneal permeability, rate of drug elimination from the eye and the concentration of drug in the vehicle (Mishima, 1981). Corneal permeability and rate of drug elimination are usually constant for a particular drug and are not affected to a large extent by formulation differences. Drug kinetics in the conjunctival cul-de-sac, however, can vary substantially as a result of changes in vehicle composition. In general the higher the vehicle viscosity the slower the drainage rate from the cul-de-sac although increase in viscosity is not directly proportional to increase in ocular bioavailability. The viscosity regarded as optimal is between 15 and 25 centipoises, the range found in Isopto vehicles (Akers, 1983) which should theoretically provide the best bioavailability. Drug concentration in the vehicle can also influence bioavailability and, as with differences in vehicle viscosity, absorption is not always proportional to drug concentration in the ophthalmic solution. The aims of this study were to compare bioavailability of several com-

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mercially available ophthalmic adrenaline preparations, and in so doing further validate an in vitro technique developed and used successfully in two previous studies (Flint and Morton, 1984; Ismail and Morton, 1987).

Materials and Methods

Materials

DL-[7-^{14}C]Adrenaline DL-bitartrate (1.85 gBq/mmol) was obtained from Amersham PLC (Bucks, U.K.). Isopto Epinal 1% was supplied by Alcon Laboratories (U.K.) Ltd.; Eppy 1% and Simplene 0.5% by Smith and Nephew Pharmaceuticals (U.K.) Ltd. Millipore filters (0.8 μm) were obtained from Millipore (Bedford, MA), Instagel scintillation cocktail from Packard (Downers Grove, IL) and Scintran tissue solubiliser from BDH (Poole, U.K.).

Ovine eyes were obtained within 15 min of slaughter from the National Sheep and Goat Producers Co-operative (Mount Hampden, Harare). All eyes selected for use had firm, rounded intact corneas free from visible damage.

Preparation of test preparations

Sufficient [^{14}C]adrenaline was added to commercial bottles of the ophthalmic solutions to give a final radioactive concentration of 0.9 MBq/mmol in Eppy and Isopto Epinal and 0.45 MBq/mmol in Simplene.

Preparation of eyes

A previously developed method was used (Flint and Morton, 1984) with modifications (Ismail and Morton, 1987). Eyes were transported in Krebs solution on ice and used within 30 min of collection. Eyes were placed in beakers in the cornea superior position and surrounded with Krebs solution to a depth of 0.5 cm below the cornea; Millipore filter discs cut radially at intervals of 0.5 cm were placed onto each cornea, moistened with Krebs solution and test preparations pipetted directly onto the filter discs (50 μl). Eyes were removed at set time intervals, a 0.25 ml sample of aqueous humour collected and placed in 10 ml Instagel. The cornea was dissected free from surrounding tissue, rinsed to remove residual test preparation and soaked in 250 μl Scintran for 5 days prior to addition of 10 ml Instagel. Radioactivity present was determined by scintillation spectrometry. A 0.25 ml sample of aqueous humour was used as the mean corneal volume was found to be 0.25 ml and therefore direct comparison of the results could be made.

Data analysis

Each value shown represents the mean of 10 separate determinations with the S.E.M. given in μg adrenaline absorbed per unit time. Probabilities were determined using the Student's *t*-distribution.

Results and Discussion

Adrenaline, being a weak base, exists predominantly in the unionised form at physiological pH and as its lipid solubility is relatively high adequate corneal uptake would be expected (Akers, 1983). The large differences in corneal uptake from the various preparations shown in this study (Table 1; Figs. 1 and 2) imply that physiological pH is not necessarily optimum for uptake of adrenaline as both Simplene 0.5% (pH 6.0) and Isopto Epinal 1% (pH 6.4) showed higher corneal levels than Eppy 1% (pH 7.4) when consideration is taken of the differences in concentration between Simplene 0.5% and the other two preparations.

That Isopto Epinal 1% had an overall bioavailability more than 3 times as great as Eppy 1%

TABLE 1

Total uptake of adrenaline over 10 h into cornea and aqueous humour of ovine eyes following application of the test preparations

Test preparation	Mean adrenaline concentration	
	Cornea (μg)	Aqueous humour ($\pm$S.E.) (μg)
Simplene 0.5%	61.8 $\pm$ 7.9	44.7 $\pm$ 6.6
Eppy 1%	100.6 $\pm$ 16.8	112.3 $\pm$ 21.3
Isopto Epinal 1%	359.1 $\pm$ 44.9	226.1 $\pm$ 36.1

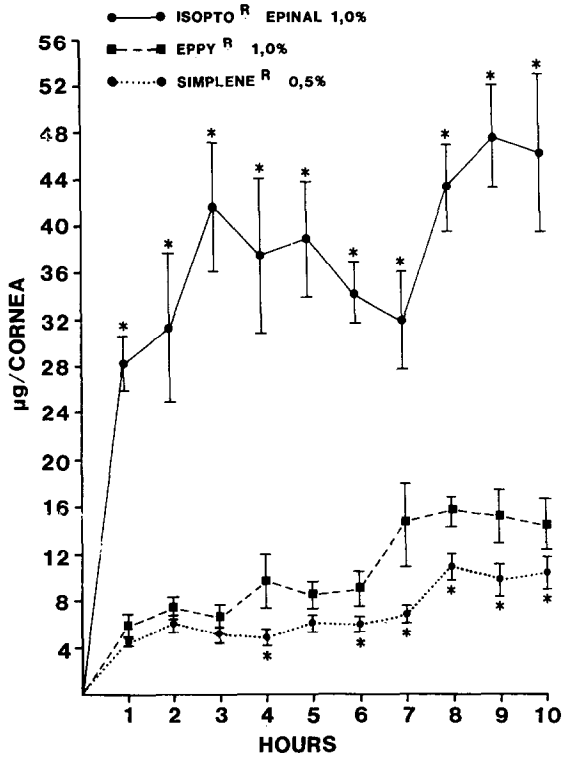

Fig. 1. Corneal adrenaline concentration with time resulting from application of Simplene 0.5%, Eppy 1% and Isopto Epinal 1% to ovine eyes. *, $P < 0.05$. Each point shows the mean (±S.E.) of 10 determinations.

(Table 1) cannot be explained merely on the basis of the pH of the solution as Simplene 0.5% did not show the same difference and some other factor must be involved. Isopto Epinal 1% contains an adrenryl–borate complex in a structured vehicle and it is possible that a combination of the salt form and the increased viscosity of the preparation were responsible for the dramatic observed difference in bioavailability.

The differences observed between corneal and aqueous humour uptake (Table 1; Figs. 1 and 2) were interesting in that Eppy 1% application resulted in higher aqueous humour levels relative to the corneal concentration of adrenaline while the other two preparations showed corneal drug levels higher than the respective aqueous humour values. In the case of Simplene 0.5% and Isopto Epinal 1% application, it appears that the cornea is acting as a rate-limiting barrier for drug release into the aqueous humour whereas with Eppy 1% any barrier effect was less pronounced. The less pronounced barrier effect following Eppy 1% application could be due, in part at least, to a more gradual rate of corneal uptake of the drug which was then redistributed to the aqueous humour at a rate that exceeded corneal accumulation. With the other preparations, on the other hand, corneal uptake exceeded the rate of redistribution to the aqueous humour resulting in the relatively higher corneal levels of adrenaline.

On the basis of the results presented it is apparent that Isopto Epinal 1% was the most bioavailable preparation, possibly due to a combination of ideal pH, viscosity and salt form of adrenaline. Considering a report of systemic toxicity following use of ophthalmic adrenaline (Obstbaum et al., 1974) the ideal preparation should be capable of attaining and maintaining adequate ocular concentrations of the drug without causing

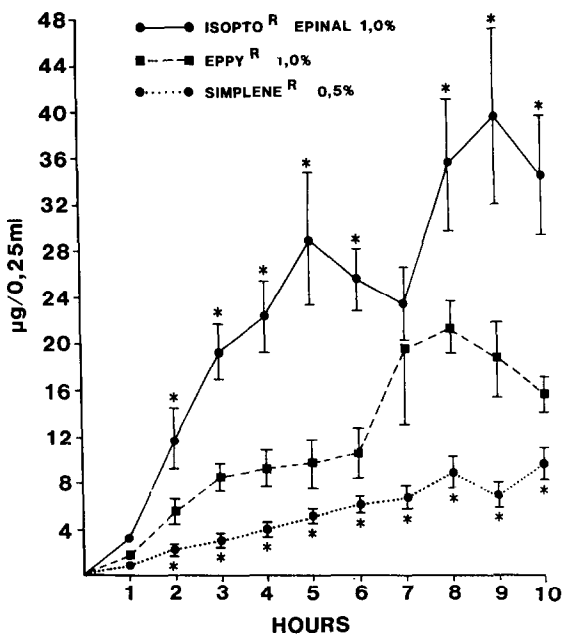

Fig. 2. Aqueous humour adrenaline concentration with time resulting from application of Simplene 0.5%, Eppy 1% and Isopto Epinal 1% to ovine eyes. *, $P < 0.05$. Each point shows the mean (±S.E.) of 10 determinations.

undue systemic side-effects. That the adrenryl–borate complex has been shown to be stable at neutral pH and dissociates in lacrimal fluid to yield free adrenaline (Wilson and Doerge, 1977) and that Isopto vehicles have the optimum viscosity for ophthalmic preparations (Akers, 1983) would suggest that Isopto Epinal 1% would be the best of the test preparations. These theoretical observations were found to hold true in practice as Isopto Epinal 1% used in this study best satisfied the optimum criteria listed above and further validates the described in vitro method of evaluation of bioavailability using isolated ovine eyes.

Acknowledgements

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