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Effect of different ointment bases on ocular disposition of ethylphenylephrine in rabbit eyes

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Summary

The influence of vehicle composition on the ocular disposition of ethylphenylephrine, a mydriatic drug used for the treatment of wide-angle glaucoma, has been studied. The vehicles investigated consisted of a hydrocarbon base, an absorption base (10% lanolin in a paraffin base) and a water-soluble base (polyvinyl alcohol, PVA, 15% in water). The albino rabbit was chosen as the animal model. The disposition of the drug in conjunctiva, cornea, iris-ciliary body and aqueous humor of the rabbit was monitored at 1, 2 and 4 h post-instillation using extraction technique. At the early time period (1 h post-adminsitration) both oleaginous and water-soluble bases were judged to perform adequately in that they provided approximately the same drug concentrations in various ocular tissues at the aqueous vehicle. However, after 4 h, the oleaginous base provided the highest concentrations of drug in the conjunctiva. The water-soluble PVA formulation gave significantly lower levels in the conjunctiva and the cornea. At this same point, the absorption base containing lanolin produced the highest drug concentration in the cornea, iris-ciliary body and aqueous humor. Collectively, these data suggest that of the 3 bases studied, the oleaginous base and the absorption base show most promise as vehicles to extend the residence time of ethylphenylephrine in the eye. Obviously the final choice of vehicle will also be influenced by factors such as the physical and chemical stability of the drug in the formulation chosen and patient acceptance.

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Introduction

Ethylphenylephrine hydrochloride has been used in the form of eye drops as a mydriatic drug for the treatment of open-angle glaucoma either alone or in combination with pilocarpine hydrochloride (Habib, 1978). Because of the efficient solution drainage process in the eye, the rate of removal of drug from the precorneal area is relatively fast. Lee et al., (1983a), incorporated sodium cromoglycate into a 5% polyvinyl alcohol solution. They found that the rate at which the drug was removed by the tears was reduced, thereby the concentration of the drug in the conjunctiva, the target tissue, was elevated by a factor of 2–4. A frequently used alternative or adjunct approach to ophthalmic therapy involves the use of eye ointments and viscous gels. It has been shown (Sieg and Robinson, 1975, 1977, 1979; Saettone et al., 1980) that, depending on the interplay in physicochemical properties between the drug and the base, such preparations can significantly prolong the presence of a drug in various ocular tissues. In the case of ethylphenylephrine, such an effect is highly desirable in the treatment of glaucoma, a chronic condition, particularly since the preparation could be used overnight.

The purpose of this study was to evaluate the ability of three bases to affect the release of ethylphenylephrine hydrochloride and its subsequent uptake and retention in the different ocular tissues. The vehicles chosen, which have a varying ability to mix with aqueous systems such as tears, were PVA, a water-soluble base; 10% lanolin in a paraffin base, an absorption base; a hydrocarbon base, an oleaginous base. Ethylphenylephrine concentrations in various ocular tissues of the rabbit were monitored at 1 and 2 h following application of the vehicle, with a view to evaluating the initial rate of drug release from the base, and at 4 h to assessing the duration of drug release. Experiments concerning some physicochemical properties of the drug were carried out.

Experimental

Materials

Three formulations containing 3% ethylphenylephrine hydrochloride were obtained from Boehringer Ingelheim (F.R.G.). The three bases were: (i) 15% polyvinyl alcohol in water from BDH (Poole, U.K.); (ii) lanolin, 10% in a paraffin base, from Merck, (Darmstadt, F.R.G.); (iii) beeswax, 40% in liquid paraffin (hydrocarbon base). Male albino rabbits weighing 1.8–2.0 kg were used throughout the study. They were fed a regular diet with no restriction on food or water consumed.

Solubility determination

The solubility of ethylphenylephrine hydrochloride was determined in water at 37°C. About 5 g of the drug was placed in 10 ml of water, in 50 ml screw-capped tubes. The tubes were placed horizontally on a shaker in a water-bath, and shaken at 60 rpm until the equilibrium was reached. This stage was determined by repetitive sampling. The concentration determination was made by the UV absorption measurement at 273 nm.

Solubility of ethylphenylephrine hydrochloride in liquid paraffin was determined because it was the major component of different types of ointment bases and the solubility of the drug in this vehicle could give an indication to its solubility in other similar semi-solid or solid components of the ointments used.

The solubility determination was made by incorporating known amounts of drug in increasing amounts in a known quantity of solvent. The solubility value of the drug in liquid paraffin was accepted as the highest concentration that could be completely solubilized in the referred solvent.

Partition coefficient determination

Ten ml of 1-octanol was added to 10 ml ethylphenylephrine hydrochloride solution (16 mg/10 ml), in 50 ml screw-capped tubes. The tubes were shaken on a horizontal shaker at 37°C until no difference was observed between the repetitive sampling. The water and octanol phases were separated and assayed for drug concentration. The results of these experiments are shown in Table 1.

Preparatin of ointments

Ointments were prepared in absorption and hydrocarbon bases as follows: the drug was dissolved in the least possible amount of water and incorporated with melted lanolin or wax and paraffin. The mixtures were mixed until cooling to achieve homogeneity. Water-soluble base was prepared by soaking PVA with water for some time and the specified amount of the drug was added. After thorough mixing a clear viscous ointment was formed.

Dissolution studies

The ointment (5 g) was accurately weighed and placed in a conical flask containing 50 ml distilled water, placed in a shaking water-bath (100 rpm) at 37°C. Samples each of 1 ml were withdrawn from the flask at 15, 30, 60, 90 and 120 min intervals. After appropriate dilution the samples were assayed for drug content at 273 nm.

Adminstration of ointment formulation

During the experiments, all rabbits were kept in restraining boxes in a normal upright posture. Two rabbits were used for the determination of the drug in the different tissues at each time interval. Three eyes were used for the determination of

TABLE 1

SOME PHYSICOCHEMICAL PROPERTIES OF ETHYLPHENYLEPHRINE HYDROCHLORIDE

	Solubility
In water (37°C)	0.4 mg/ml
In liquid paraffin (37°C)	0.022 mg/10 g
Partition coefficient (1-octanol/water)	0.035

ethylphenylephrine and the fourth one was used as a control. Individual doses of 100 mg of the formulation were weighed immediately before application to the centre of the lower yield of the rabbit with a microspatula. During dosing care was taken not to irritate the eye or touch the corneal surface with the spatula. The lower eyelid was gently moved upward to spread the dose over the corneal surface and then released. No other manipulative technique was used during the run to distribute the formulation in the precorneal area.

Extraction technique of the drug from ocular tissues

The in vivo availability of ointments were followed after 1, 2 and 4 h. At each time the conjunctiva, cornea and iris-ciliary body of a single eye were separated immidiately, weighed and ground with powdered glass in a mortar. The ground tissues were extracted with 10 ml of water followed by centrifugation for 30 min. The supernatent liquid was measured at 273 nm. A 0.5-ml volume of aqueous humor was aspirated from the anterior chamber and its contents of the drug was determined.

Results and Discussion

Drug release from ointment and gel bases can involve one or more of several processes, including partitioning, diffusion, dissolution and facilitated release. The latter process refers to the mechanical rupture of dispersed droplets in emulsion systems (Sieg and Robinson, 1979). With the bases used in this study, drug release from the water-soluble PVA base probably only involve diffusion since the hydrophilic character of PVA base would cause the absorption of water to such an extent that eventually the whole base would become a solution. In contrast, drug release from the absorption base and oleaginous base due to the effective drug concentration in the ointments will be higher than an aqueous solution of the same volume. In the case of absorption base, some emulsion formation may occur and lead to facilitated release. Each of these mechanisms can be expected to affect the rate and duration of drug release and, in turn the drug concentrations attained in ocular tissues. The dissolution of ethylphenylephrine hydrochloride from the three ointments was illustrated in Fig. 1. From the results obtained, it can be noticed that PVA, the water-soluble base, gave the highest dissolution of the drug, comparing to the other two ointment bases. This can be explained by the higher affinity of PVA to water, which leads to the whole ointment being dissolved, while the absorption of the hydrocarbon bases gave the lowest dissolution of the drug into the dissolution medium. These results coincide with the low partition coefficient of the drug as shown in Table 1.

Lee et al. (1983b) proved that the rate and extent of drug release from the vehicles to the tear pool will ultimately affect the drug concentration attained in the conjunctiva, cornea, iris-ciliary body and aqueous humor. As with solutions in water, the uptake of ethylphenylephrine from the tear with the three vehicles studied was greatest in conjunctiva, followed by the cornea, the iris-ciliary body and aqueous humor, in that order. During the first 1 h of drug administration, the concentration

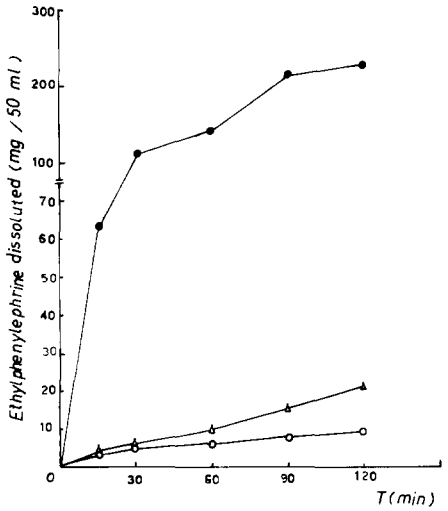

Fig. 1. Dissolution of ethylphenylephrine from different ointment bases. ●, water-soluble base; △, absorption base; and ○, hydrocarbon base.

of drug achieved in the conjunctiva and cornea, the tissues in direct contact with the tear pool, was not statistically different among the three bases (Fig. 2). In spite of the high drug dissolution obtained by PVA in the in vitro study at the first 1 h of the experiment, the in vivo study gave insignificant difference among the three bases concerning the disposition of the drug in both conjunctiva and cornea at the same period of time (1 h). In deeper tissues, iris-ciliary body and aqueous humor, absorption base appeared to be the most effective in providing the higher concentration. The absorption base not only produced this higher drug level in these two tissues, but also provided the highest concentration of the drug 2 h post-dosing in all tissues. Concerning the absorption base, one can explain the low concentration of the drug in conjunctiva and cornea during the first hour post-administration by the fact that the drug release from the absorption base into the tear pool is able to quickly penetrate through the cornea to the deeper tissues with the aid of blinking, as is the opinion of most workers (Patton, 1980), or laterally from the cornea into the iris-ciliary body (Lee et al., 1983a). Thus the concentration of the drug in the iris-ciliary body during all the experimental times exceeds those in the aqueous humor. This implies that the drug which appears in the aqueous humor has come from the iris-ciliary body and/or endothelial surface of the cornea. The in vitro dissolution of the drug using the three ointments, gave an indication that the PVA ointment would give a higher disposition of the drug in the in vivo study than with the other two ointments, but the reverse occurred. This is due to the large receptor medium volume (50 ml), while this result did not occur in vivo due to the limited volume (about 7 μl). This conclusion is in agreement with that of Sieg and Robinson (1975). They pointed out that the drugs in ophthalmic ointments, irrespective to their solubility or diffusion characteristics in the vehicle, will have to partition into the tear film or epithelium directly in order for corneal absorption to occur.

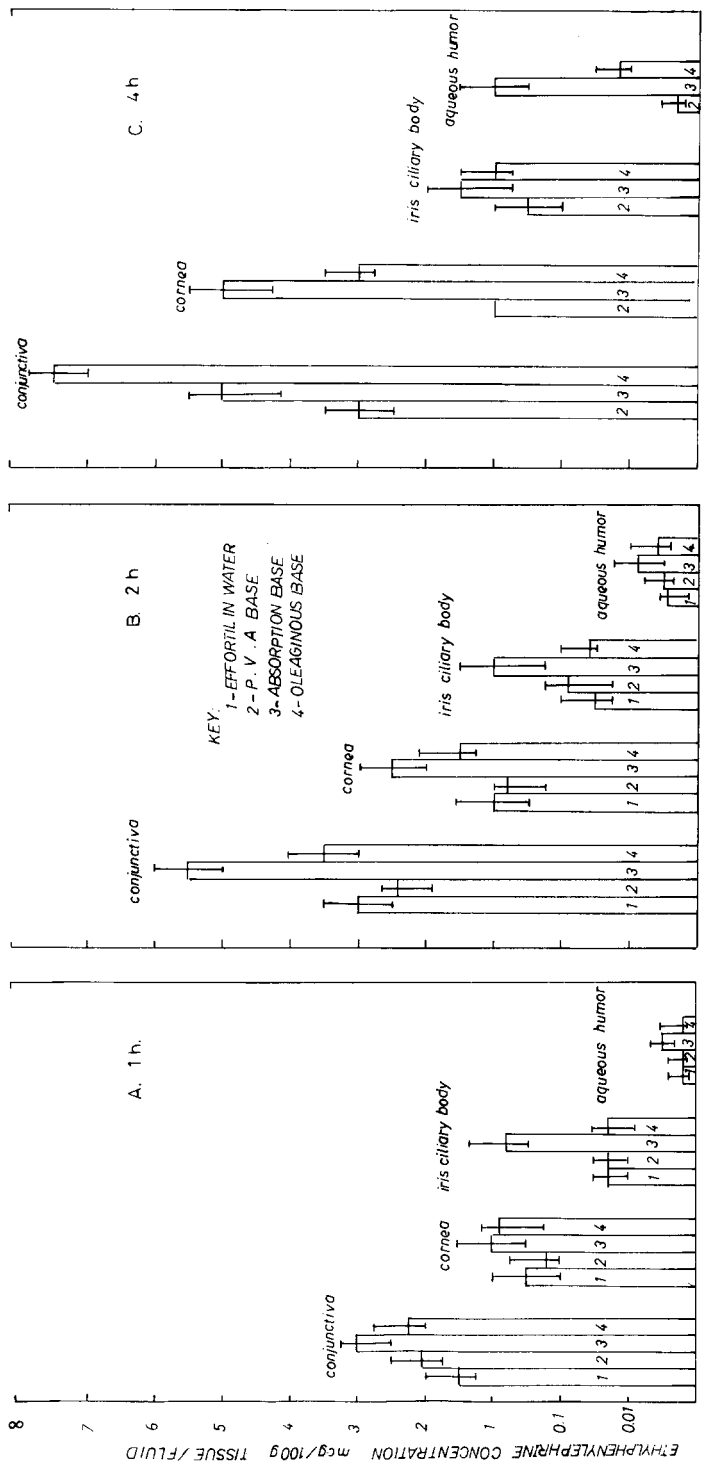

FIG.(2) ETHYLPHENYLEHRINE CONCENTRATION-IN VARIOUS OCULAR TISSUES AND AQUEOUS HUMOR AT 1, 2 AND 4 h. FOLLOWING TOPICAL ADMINISTRATION OF DRUG IN VARIOUS VEHICLES; error bars represent range of the mean.

Fig. 2. Effortil concentration in various ocular tissues and aqueous humor at 1, 2 and 4 h following topical administration of drug in various vehicles; error bars represent range of the mean.

In conclusion, the ocular disposition of ethylphenylephrine is influenced by the lipophilic characteristics of the base housing the drug. PVA behaved approximately in a manner similar to the aqueous solution of the drug, while lipophilic bases, absorption and hydrocarbon, by comparison, were much more capable of maintaining a high drug concentration in conjunctiva, cornea, iris-ciliary body and aqueous humor over a 4-h period, even though they produced somewhat lower concentrations at the earlier time. As early as 1 h post-dosing, alll three bases were capable of providing the drug to the conjunctiva at a concentration higher than that resulting from an aqueous solution. Of the three bases studied, the hydrocarbon base was the most effective in producing a higher drug concentration in conjunctiva 4 h post-dosing, while the absorption base was the most effective in producing a higher drug concentration in the cornea, iris-ciliary body and aqueous humor 4 h post-dosing. The results obtained by Lea et al. (1983b) agree to a great extent with the results obtained in this study. Accordingly, absorption and hydrocarbon bases should be viable candidates for further evaluation in developing an effective ointment for ethylphenylephrine in the treatment of glaucoma. Obviously, the choice of vehicle will also be influenced by other factors, such as patient acceptance, the potential for visual disturbances and the physical and chemical stability of the product.

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