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Rapid Communication

Sodium acetate improves the ocular/systemic absorption ratio of timolol applied ocularly in monoisopropyl PVM-MA matrices

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Summary

The safety of ocularly applied timolol can be increased by administering the drug in polymer matrices instead of eye drops. This study shows that addition of sodium acetate to the monoisopropyl PVM-MA matrices improves the aqueous humor/plasma concentration ratio of timolol about 20-fold as compared to the matrices buffered with disodium phosphate. Thus, sodium acetate seems to decrease specifically the systemic but not the ocular absorption of timolol.

Timolol eye drops are the most frequently used treatment in open angle glaucoma at the moment. Timolol lowers increased ocular pressure by decreasing the rate of aqueous humor formation (Zimmerman et al., 1977; Schenker et al., 1981; Miichi and Nagataki, 1983). The major disadvantage of topical ocularly applied timolol is its absorption to the systemic circulation (Chang and Lee, 1987). Systemic absorption may cause severe respiratory and cardiovascular side-effects that can be fatal in patients with predisposing diseases (Nelson et al., 1986). Accordingly, reduction of the systemic absorption of ocularly applied timolol is desired. Previously, we showed that systemic absorption of ocularly applied timolol can be reduced by administering the drug in a poly(vinyl methyl ether-maleic anhydride) (PVM-MA) matrix instead of eye drops (Finne et al., 1990).

Dissociation and dissolution of monoesters of PVM-MA are highly dependent on the surrounding pH (Heller et al., 1979). We have shown previously that drug release both in vitro (Finne et al., 1989) and in vivo in the tear fluid (Finne et al., 1990) can be modified by adding basic salts to matrices of monoesters of PVM-MA. Disodium phosphate added to the monoisopropyl PVM-MA matrices accelerated the dissolution of the polymer matrix and the rate of timolol release from the insert several fold in tear fluid of rabbits (Finne et al., 1990). Interestingly, timolol release in vitro from the monoisopropyl PVM-MA matrices buffered with sodium acetate was 55% faster than from those buffered with disodium phosphate when a slow stirring rate (35 rpm) was used

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(Finne et al., 1991). In contrast to the phosphate buffered matrices, timolol is released at a constant rate from the acetate buffered matrices probably by erosion of the polymer matrix whereas timolol release from the phosphate buffered matrices deviated from constant release probably due to diffusional leaching (Finne et al., 1991). The aim of this study was to determine whether the matrices buffered with sodium acetate will prove to be better than disodium phosphate buffered matrices also in vivo in rabbit eyes.

Matrices of monoisopropyl ester of PVM-MA containing 50 mg (0.12 mmol) of timolol maleate (INTER$_x$ Research Corp., MSDRL, Lawrence, KS, U.S.A.) and 2.11 mmol of sodium acetate (E. Merck, Darmstadt, Germany) were prepared by solvent casting using a 50% isopropanol solution of the polymer (Gantrez^R ES-335, GAF Europe, Esher, U.K.) as described earlier (Finne et al., 1989). Circular matrices (diameter 5 mm, weight 6.0–6.9 mg, thickness 0.59 ± 0.02 mm) were cut from the film with a cork bore.

Monoisopropyl PVM-MA matrices were carefully applied in the lower conjunctival sac of pigmented rabbits (both sexes; 1.9–2.8 kg). Tear fluid and plasma samples were collected at different intervals during a period of 8 h. Timolol concentration in tear fluid and plasma was measured with a radioreceptor assay as described previously (Finne et al., 1990). The assay measures displacement of a β-antagonist, (−)-[^{3}H]CGP-12177 (spec. act. 48.8 Ci/mmol, radiochemical purity 99.1%; Amersham International, Bucks, U.K.) from β_2-receptors of rat reticulocyte membranes by timolol.

For aqueous humor measurement, tritiated matrices were prepared using [^{3}H]timolol (34.5 nCi/μg timolol base) (spec. act. 2.1 Ci/mmol, radiochemical purity 98.2–99.0%; Merck, Sharp & Dohme, Inc., Rahway, NJ, U.S.A.). Rabbits were killed by injection of T-61 euthanasia (Hoechst Corp., Sommerville, NJ, U.S.A.) solution (i.v.) at 0.5, 2.5, 4.0 or 8.0 h after application of the labeled matrices in the lower conjunctival sac of rabbits. Timolol concentration in aqueous humor was measured with liquid scintillation counting as described earlier (Finne et al., 1990).

Areas under the curves ($AUC_{0-8\,h}$) of timolol activity in tear fluid, plasma and aqueous humor were calculated using the trapezoidal method (Gibaldi and Perrier, 1982). Peak β-blocking activity (C_{max}) in tear fluid, plasma and aqueous humor was determined from the data points. Statistical significance of the differences was assessed by Mann-Whitney U-test.

Monoisopropyl PVM-MA matrices buffered

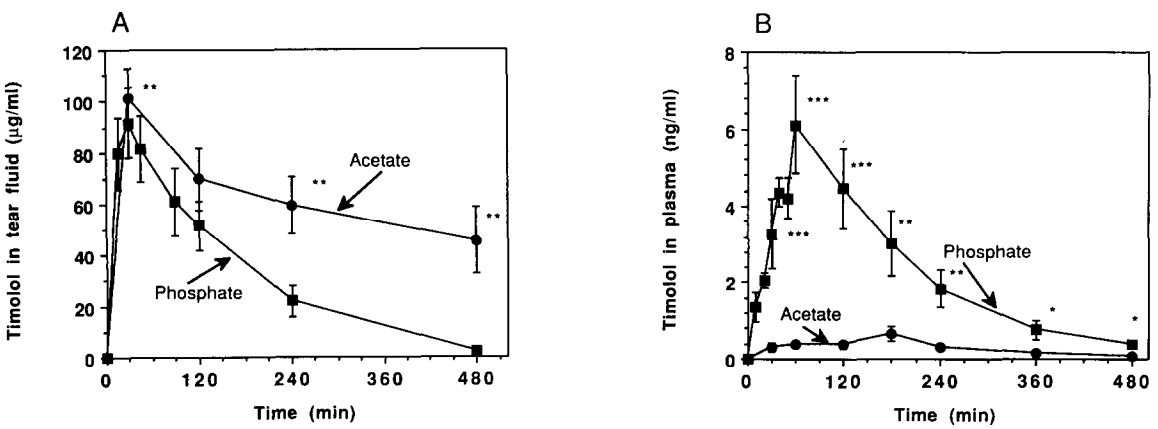

Fig. 1. Timolol concentration in tear fluid (μg/ml) (n = 6–18) (A) and in plasma (ng/ml) (n = 6–12) (B) after application of 125 μg timolol maleate in monoisopropyl PVM-MA matrices in both eyes of pigmented rabbit. Means ± SE are shown. *, **, *** Phosphate buffered vs acetate buffered, $p < 0.05$, < 0.01, < 0.001.

either with sodium acetate or with disodium phosphate softened within a few minutes after application in the eye (Finne et al., 1990). The inserts were not observed to cause any irritation in rabbit eyes. In contrast to the phosphate buffered matrices those buffered with acetate retained their shape until they were completely dissolved.

In tear fluid the matrices containing sodium acetate yielded a peak in timolol concentration (101 ± 12 μg/ml) at 30 min after application similarly to the phosphate buffered (104 ± 8 μg/ml) matrices (Fig. 1A). Accordingly, timolol was released at about the same rate from both types of matrices. Compared with the phosphate buffered matrices, administration of timolol in the acetate buffered matrices resulted in an $AUC_{0-8\ h}$ value (492 ± 42 h μg ml^{-1}) almost twice as large as after the phosphate buffered matrices (255 ± 32 h μg ml^{-1}) in the tear fluid. This is due to the much slower disappearance of timolol from the tear fluid after acetate than phosphate buffered matrices.

In contrast to the matrices with disodium phosphate (7.3 ± 1.1 ng/ml) (Finne et al., 1990), the acetate buffered matrices resulted in a very low plateau concentration (0.3 ± 0.1 ng/ml) of timolol in plasma (Fig. 1B). Accordingly, the $AUC_{0-8\ h}$ in plasma after the acetate buffered matrices (2.3 ± 0.5 h ng ml^{-1}) was only about 1/10 of that of the phosphate buffered ones (21.9 ± 3.9 h ng ml^{-1}) (Finne et al., 1990). Acetate might have an effect on the conjunctival and nasal epithelia to change the permeability of timolol, which could reduce the absorption of timolol to the systemic circulation.

Timolol was absorbed into the eye more efficiently from the acetate than phosphate buffered matrices, which can be seen in the higher drug levels in aqueous humor after the matrices containing sodium acetate (Fig. 2). The concentration profiles of timolol in aqueous humor reflected those in tear fluid (Figs 1A and 2). Timolol concentration in aqueous humor was significantly higher at 2.5 and 8.0 h after application of the acetate buffered matrices as compared to the phosphate buffered matrices, thus, it is presumable that with these matrices the effect of timolol

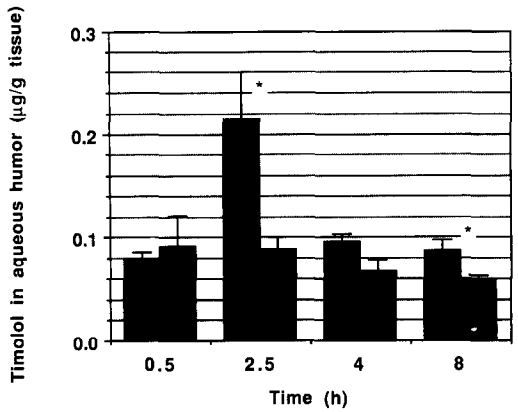

Fig. 2. Timolol concentration in aqueous humor (μg/g tissue) ($n = 5$) after application of 125 μg timolol maleate in monoisopropyl PVM-MA matrices in both eyes of pigmented rabbit. Means $\pm$ SE are shown. * Phosphate buffered vs acetate buffered, $p < 0.05$.

will last longer. When the $AUC_{0-8\ h}$ values of timolol activity in aqueous humor are compared the acetate buffered matrices (0.91 h μg g^{-1}) result in a 60% higher $AUC_{0-8\ h}$ value than the phosphate buffered ones (0.57 h μg g^{-1}). Addition of sodium acetate instead of disodium phosphate to the monoisopropyl PVM-MA matrices increased the aqueous humor/plasma $AUC_{0-8\ h}$ ratio 14-fold from 26 to 396.

The aqueous humor/plasma concentration ratio of a drug describes the safety of a drug in terms of its systemic side-effects (Chang and Lee, 1987). In the case of timolol it was increased almost 20-fold by applying the drug in acetate as compared to phosphate buffered matrices.

These results show that addition of sodium acetate instead of disodium phosphate to the monoisopropyl PVM-MA matrices improves the safety of ocularly applied timolol remarkably. The mechanism of this effect will be examined in the future.

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