Studies on Rabbit Corneal Permeability of the Amide-Type Local Anesthetics

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The relationship between the corneal permeability velocities of three agents (cocaine·HCl, procaine·HCl and tetracaine·HCl) and corneal hydration have been given in a previous report. (1). Tetracaine·HCl with the strongest topical anesthetic action showed the greatest corneal hydration and the smallest corneal permeability velocity constant among these local anesthetics. The corneal permeability decreased with increasing molecular length of these agents. The purpose of this communication is to describe the relationship between the corneal permeability velocities of amide-type local anesthetics (lidocaine·HCl, mepivacaine·HCl and prilocaine·HCl) and corneal hydration. These values of the amide-type were compared with those of the ester-type. In general, the values of the amide-type were slightly greater than the values of the ester-type. The experiments were performed on isolated cornea of albino rabbits weighing 3–4 kg. Preparations and experimental methods used in this study have been described in a previous paper (1). The isolated sclerocorneal specimen was placed in the center of a corneal permeability experimental chamber (2). A sample solution (3 ml) and artificial aqueous humor solution (3) were placed into the tear side and aqueous humor side of the chamber, respectively. The corneal permeability of the agents was facilitated by stirring during incubation. After incubation, the volumes of solutions on both sides of the chamber were measured. In addition, the amount of anesthetic on both sides was measured with a UV spectrophotometer (lidocaine·HCl: wave length 212 nm, mepivacaine·HCl: 212 nm and prilocaine·HCl

230 nm).

Then the wet and dry weights of only the corneal permeable area were measured for calculating corneal hydration. The formulas of the corneal permeability velocity constant (k), the corneal permeability constant (p) and corneal hydration were described in a previous paper (1). Blank experiments were performed, using the artificial tear solution without local anesthetics by a similar procedure (4, 5). Drugs used were lidocaine·HCl (Xylocaine®, Fujisawa Pharm. Co.), mepivacaine·HCl (Carbocaine®, Yoshitomi Pharm. Ind., Ltd.) and prilocaine·HCl (Citanest®, Fujisawa Pharm. Co.). The corneal hydration values at the 4 incubation periods ranged from 3.8 to 4.3 (Table 1).

As demonstrated by the blank experiments, no cornea turbidity was found with 60 min of incubation, and these values were approximately the same as those of Mishima (3.34–3.54) (6). In general, the corneal hydration values of the amide-type were slightly greater than the values of the ester-type, and the order of the corneal hydration values in these amide-type anesthetics was: lidocaine·HCl > prilocaine·HCl > mepivacaine·HCl. The inflow of water to the corneal stroma layer is controlled by the Na^+ - K^+ ATPase in the endothelial and epithelial layers, and it depends especially on the biological function of the endothelium layers (7).

The order of corneal hydration values permits the estimation of the degree of inhibition of Na^+ - K^+ ATPase activity; i.e., inhibition of the barrier effect in the corneal epithelial and endothelial layers. Lidocaine·HCl with the highest specific activity among

Table 1. Effect of local anesthetics concentration and incubation time on hydration of rabbit cornea in vitro

Local anesthetics concentration (%)	Corneal hydration			
	Incubation time (min)			
	10	15	30	60
0	3.2±0.1	3.4±0.2	3.5±0.2	3.5±0.3
Lidocaine·HCl				
0.25	3.8±0.1	3.8±0.1	3.9±0.1	4.0±0.3
0.50	3.8±0.1	4.1±0.2	4.1±0.1	4.1±0.1
1.00	4.1±0.2	4.2±0.2	4.3±0.2	4.3±0.3
Mepivacaine·HCl				
0.25	3.8±0.1	3.8±0.1	3.9±0.1	4.0±0.1
0.50	3.8±0.2	3.8±0.2	3.9±0.1	4.0±0.2
1.00	3.9±0.2	3.9±0.1	4.0±0.3	4.1±0.2
Prilocaine·HCl				
0.25	3.8±0.1	3.9±0.1	3.9±0.1	4.0±0.3
0.50	3.8±0.3	3.9±0.1	3.9±0.2	4.1±0.2
1.00	3.9±0.3	3.0±0.3	4.0±0.2	4.2±0.3

Values represent the mean±standard error for 5 experiments.

the amide-type materials tended to induce more remarkable swelling of the cornea than the two others, similarly to that of tetracaine·HCl (1). The corneal permeability velocity constant (k) of lidocaine·HCl was approximately $10.0\text{--}16.4 \times 10^{-6}$ cm/sec, mepivacaine·HCl $\div 6.1\text{--}12.0 \times 10^{-6}$ cm/sec and prilocaine·HCl $\div 7.9\text{--}13.2 \times 10^{-6}$ cm/sec. Comparison of the k values at incubation times of 15, 30 and 60 min with those at 10 min showed irrespective increase of approximately 1.1-, 1.4- and 1.5-fold for lidocaine·HCl; 1.2-, 1.7- and 1.8-fold for mepivacaine·HCl; and 1.1-, 1.5- and 1.6-fold for prilocaine·HCl (Fig. 1A). The k values of the amide-type ($6.1\text{--}16.4 \times 10^{-6}$ cm/sec) were remarkably greater than those of the ester-type ($0.5\text{--}6.0 \times 10^{-6}$ cm/sec) (1).

The mode for drug diffusion through the cornea seems to be intramembranous diffusion (multiple layer membrane) (8), so the degree of difficulty of permeability to local anesthetics was investigated by the membrane permeability constant (p). P values of lidocaine·HCl were $3.5\text{--}6.7 \times 10^{-7}$ cm²/sec, mepivacaine·HCl $\div 2.7\text{--}5.4 \times 10^{-7}$ cm²/sec and prilocaine·HCl $\div 2.8\text{--}5.8 \times 10^{-7}$ cm²/sec (Fig. 1B). The corneal permeability constant (p) is mostly defined by porosity of the membrane and the type of solute. Generally, permeability of the solute is examined using

a membrane found in a homogeneous structure.

The present investigation of permeability in the rabbit cornea showed that the amide-type anesthetics yield almost equal p values with an incubation time of both 10 and 15 min and 30 and 60 min. Compared to the values at 10 min, those at 60 min were approximately 1.5-fold for lidocaine·HCl, 1.8-fold for mepivacaine·HCl and 1.7-fold for prilocaine·HCl (Fig. 1B). The p values of the amide-type ($2.7\text{--}6.3 \times 10^{-7}$ cm²/sec) were remarkably greater than those of the ester-type ($0.4\text{--}0.5 \times 10^{-7}$ cm²/sec) (1).

When the local anesthetics are applied to the mucous membrane, it is evident that absorption velocity of drugs is necessarily slow, thus the interrelation between corneal permeability and permeability velocity(k) was examined. The k and p values of lidocaine·HCl were slightly greater than the values of two other amide-type anesthetics but there was no significant difference between the values of prilocaine·HCl and mepivacaine·HCl. The k and p values of the amide-type tended to increase with the incubation time; both the k and p values tended to be more dependent on the incubation time than concentration. This may be due to swelling of the corneal stroma layer with water and the consequent decrease in the barrier

Fig. 1. Permeability velocity constant (k) and permeability constant (p) of amide-type local anesthetics in rabbit cornea. Permeation time: 10 min (●), 15 min (○), 30 min (■) and 60 min (□). Values represent the mean $\pm$ standard error for 10 experiments.

effect of both corneal layers. The increased permeability by those local anesthetics as a result of swelling appears to be caused by expansion of the spaces in the corneal tissue. Local anesthetics action is in the order of lidocaine·HCl > prilocaine·HCl > mepivacaine·HCl. It seems that lidocaine·HCl with the highest corneal permeability velocity constant and permeability constant and the strongest local anesthetic action has the

greatest affinity for the sensory nerve of rabbit cornea among the three agents in this experiment.

Correlations were noted between rabbit corneal permeability and molecular length of the agents (prilocaine·HCl, 12.2 Å > lidocaine·HCl, 11.1 Å); however, mepivacaine·HCl (molecular length, 10.1 Å) with a heterocyclic ring of N-methyl-2-piperidino radical showed the lowest corneal hydration

and permeability. Lidocaine-HCl with the strongest local anesthetic activity showed the highest corneal hydration and the highest corneal permeability constant, possibly due to the higher degree of inhibition of Na^+ - K^+ ATPase (8).

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References

- 1 Igarashi, H., Sato, Y., Hamada, S. and Kawasaki, T.: Studies on rabbit corneal permeability of local anesthetics (I). Japan. J. Pharmacol. **34**, 429–434 (1984)
- 2 Iwata, S., Ohtani, Y., Osada, E. and Ogino, H.: Aspect on corneal permeability of bupranolol. Yakugaku Zasshi **100**, 402–406 (1980) (Abs. in English)
- 3 Mizukawa, T. and Kishida, K.: Preparation of artificial aqueous humor for ophthalmic surgery. Acta Soc. Ophthalmol. Japon. **74**, 687–691 (1970) (Abs. in English)
- 4 Takase, M.: Effects of topical isoproterenol and propranolol on flow-rate of aqueous humor in rhesus monkey. Acta Soc. Ophthalmol. Japon. **80**, 379–384 (1976) (Abs. in English)
- 5 Sasamoto, K. and Iwata, S.: Biophysicochemical properties of corneal swelling-analysis of swelling mechanism in electrolytic solution. Folia Ophthalmol. Japon. **30**, 218–224 (1979) (Abs. in English)
- 6 Mishima, S.: Maintenance of the corneal thickness. Folia Ophthalmol. Japon. **19**, 1241–1249 (1968) (Abs. in English)
- 7 Iwata, S.: Membranes and their function in visual organ. Surface chemical behavior of tear film and membrane function in cornea. Membrane **4**, 289–298 (1979) (in Japanese)
- 8 Mizukawa, T. and Iwata, S.: Effects of swelling on corneal transport. Acta Soc. Ophthalmol. Japon. **71**, 1069–1078 (1967) (Abs. in English)