J. Pharm. Pharmacol. 1985, 37: 614–617
Received February 25, 1985

Influence of ophthalmic formulations on sodium cromoglycate disposition in the albino rabbit eye

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The effect of different ophthalmic vehicles on the disposition of sodium cromoglycate in tears and ocular tissues of the rabbit eye has been studied over 6 h. The vehicles contained sodium cromoglycate, 2% in an aqueous solution, 2 and 4% in an oleaginous formulation of polyethylene and mineral oil (Plastibase 5W), and 4% in an absorption ointment base of 10% hypoallergenic acetylated lanolin (Modulan) in paraffins. The last formulation was superior to all others studied over 6 h in prolonging the retention of sodium cromoglycate in the precorneal area and the conjunctiva. The concentration of sodium cromoglycate in the tears, conjunctiva and cornea 6 h after administration of the acetylated lanolin base equalled or exceeded the concentrations obtained with the aqueous solution 1 h post-instillation.

Sodium cromoglycate is effective in the treatment of conditions in which an allergic component may be involved (Pepys & Edwards 1979). Removal of most drugs in solution from the precorneal area is relatively fast, because the drainage process from the anterior chamber of the eye into the naso-pharyngeal duct is efficient. This has been observed with 2% sodium cromoglycate aqueous solutions (I) in the rabbit eye (Lee et al 1983a). The influence of vehicle composition on the ocular disposition from aqueous solution was demonstrated by Lee et al (1983b) who studied three additional vehicles containing 4% sodium cromoglycate over 4 h in the rabbit eye. These vehicles were an absorption base containing 10% hypoallergenic acetylated lanolin (Modulan) in paraffins (II), a semisolid oleaginous base containing polyethylene and mineral oil (Plastibase 30W) (III), and a water-soluble base of 15% polyvinyl alcohol (Polyviol) in water (IV). Formulations (II) and (III) were superior to (IV) in prolonging retention in the rabbit eye. The data indicated that the latter formulation could be expected to produce significantly higher concentrations of sodium cromoglycate in the tears 4 h post-instillation.

The present study extends the comparative evaluation of vehicle effects over 6 h. Two of the formulations selected were identical to those used previously, namely (I) and (II). The two other formulations were polyethylene and mineral oil (Plastibase 5W) containing 2% (V) or 4% (VI) sodium cromoglycate as oily suspensions. A preliminary communication dealing with certain aspects of this study has already been published (Swarbrick & Shrewsbury 1984).

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MATERIALS AND METHODS

Materials

Four formulations containing sodium cromoglycate and ^{14}C-labelled sodium cromoglycate (spec. act. 11·79 μCi mg^{-1} and of greater than 99% purity) were supplied by Fisons plc, Pharmaceutical Division (Loughborough, UK) and used as received. The formulations were: (I) 2% w/w sodium cromoglycate in water containing 0·01% w/w benzalkonium chloride plus 0·4% w/w phenylethyl alcohol (spec. act. 19·82 μCi g^{-1}); (II) 4% w/w sodium cromoglycate dispersed in an absorption ointment base containing 10% hypoallergenic acetylated lanolin (Modulan) in paraffins (spec. act. 19·30 μCi g^{-1}); (V) 2% w/w sodium cromoglycate in a polyethylene and mineral oil oleaginous base (Plastibase 5W), (spec. act. of 19·03 μCi g^{-1}); and (VI) 4% w/w sodium cromoglycate in the Plastibase 5W base (spec. act. 19·29 μCi g^{-1}). Male albino rabbits (Franklin Rabbitry, Greensboro, North Carolina), 2·2–2·5 kg, were used. They were fed a regular diet with no restriction as to food or water.

Administration of formulations

Administration of the formulations has been described previously (Lee et al 1983a, b). Liquid formulations were administered as drops directly onto the cornea. With (I), two different weights were used, averaging 18 mg (19 μl) and 23 mg (25 μl). The average weights of (V) and (VI) applied were 18 mg (20 μl) and 17 mg (19 μl), respectively. For the semisolid (II), individual amounts, of approximately 18 mg, were applied to the centre of the lower eyelid with a microspatula.

Collection of tears and ocular tissues

The general techniques used have been described by Lee et al (1983a, b). One-μl tear samples were obtained at 1, 2, 3, 4, 5, 7 and 10 min, every hour post-instillation, and immediately before the time the animal was killed. The dosing schedule was so designed that half of the ocular tissue samples collected came from eyes which were dissected first from any one rabbit.

Determination of sodium cromoglycate in tears and ocular tissues

The preparation of tears and ocular tissues for liquid scintillation counting has been described (Lee et al 1983a, b). Each sample was counted on three occasions using a Tri-Carb spectrometer, model 3320 (Packard Instrument Co., Downers Grove, Illinois). The average counts min^{-1} were corrected for background, counting efficiency and tissue, vial and cocktail quenching. Micromoles of sodium cromoglycate determined in each sample were converted to μmol g^{-1} of tissue using the following average tissue weights (n = 6): conjunctiva, 0·09353 g; cornea, 0·07165 g; iris-ciliary body, 0·03781 g; and aqueous humour, 0·22870 g. Tear samples were normalized to a volume of 1 ml assuming a tear density of 1·0.

RESULTS AND DISCUSSION

This study investigated the effect of vehicle formulation on the disposition of sodium cromoglycate in the rabbit eye. Table 1 shows the sodium cromoglycate concentrations in tears for the first 10 min following instillation of approximately equal weights of the four vehicles studied while Figs 1–5 show the concentrations in tears, conjunctiva, cornea, iris-ciliary body and aqueous humour over 6 h. Early times in Fig. 1, other than for 5 and 10 min, have been omitted for clarity.

The results from the various formulations fall logically into two parts: drug clearance in tears during the first 10 min and drug concentrations in the tissues from 0·5 to 6 h post-instillation. To rationalize and compare tear concentrations and disappearance rate constants during the first 10 min (Table 1), it is necessary to consider the different events that can be expected to occur between the liquid formulations (I, V, VI) and the semisolid formulation (II). These differences involve the miscibility of the vehicle with tears, the ability of the vehicle to resist clearance along with the tears, and the rate of drug release from the vehicle into tears. The magnitudes of these effects can be expected to differ with the vehicles used.

When 18 mg (19 μl) of (I) is added as a drop into the precorneal area, it is reasonable to assume that it mixes rapidly with the normal (resting) tear volume of approximately 8 μl in the rabbit (Chrai et al 1973). As this mixing takes place, the total volume of fluid in the precorneal area is being cleared from the eye by a first-order rate related to the extra volume of liquid introduced by the formulation. With (I), where the drug is already in solution, it can be calculated that for a total fluid volume of 27 μl (i.e. 19 + 8), the maximum sodium cromoglycate concentration will be approximately 13 mg ml^{-1}, assuming instantaneous mixing and no loss due to clearance.

Table 1. Tear concentrations of sodium cromoglycate, precorneal fluid volumes and pharmacokinetic parameters for formulations studied during first 10 min post-instillation.

Time, min post-instillation	Formulation administered I	II	V	VI
1	12·90 ± 1·61 (35)[a]	42·79 ± 5·69 (67)	4·63 ± 0·60 (69)	7·66 ± 0·86 (69)
2	9·40 ± 1·38 (35)	33·12 ± 6·06 (68)	3·30 ± 0·44 (69)	5·36 ± 0·56 (68)
3	7·27 ± 1·19 (35)	27·13 ± 8·40 (70)	2·86 ± 0·39 (67)	4·06 ± 0·55 (68)
4	4·96 ± 0·90 (35)	13·41 ± 2·09 (70)	1·70 ± 0·21 (67)	3·48 ± 0·38 (69)
5	3·66 ± 0·71 (35)	7·18 ± 1·14 (70)	1·61 ± 0·22 (69)	2·83 ± 0·34 (69)
7	1·80 ± 0·36 (33)	4·40 ± 0·51 (70)	0·85 ± 0·11 (69)	2·09 ± 0·27 (69)
10	1·13 ± 0·26 (34)	3·67 ± 0·51 (69)	0·56 ± 0·07 (69)	1·48 ± 0·23 (69)
k, min^{-1}	0·283	0·305	0·240	0·176
Estimated aqueous (tear) volume, μl[b]	27	8	8	8
Assumed clearable volume, μl[c]	27	8	28	27

[a] mg mol^{-1} ± s.e.m. (number of eyes).
[b] Resting tear volume of 8 μl (Chrai et al 1973) plus volume of aqueous vehicle added.
[c] Resting tear volume plus volume of mobile vehicle added.

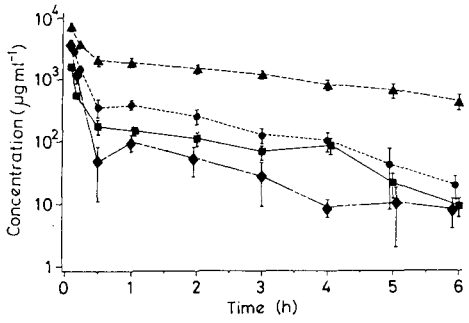

FIG. 1. Sodium cromoglycate concentration (μg ml^{-1}) in the tears following administration of formulations: I, ◆; II, ▲; V, ■; VI, ●. Error bars represent ± s.e.m.

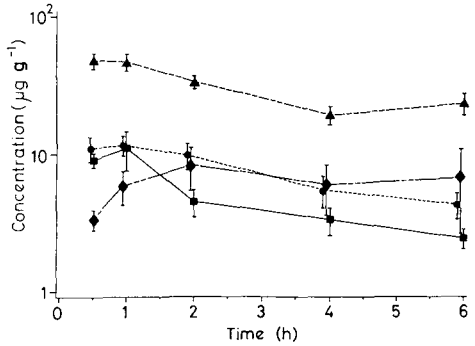

FIG. 3. Sodium cromoglycate concentration (μg g^{-1}) in the cornea following administration of formulations. Key: See Fig. 1.

This concentration compares well with the value 12·90 ± 1·61 mg ml^{-1} determined 1 min post-instillation (Table 1) and implies that rapid mixing occurs and that the experimental and analytical techniques employed are adequate.

After applying 18 mg of (II) to the eye, concentrations of sodium cromoglycate in the tears over the first 10 min were 3 to 4 times greater than (I). Formulation (II) is an ointment, not miscible with tears, and can be expected to remain in the precorneal area longer than the other formulations. While not miscible, some dispersion of (II) in tears apparently took place since virtually all tear samples taken contained small particles of the formulation. These particles, estimated to be no more than 5% of the total sample volume, occurred uniformly throughout the samples as judged by the s.e.m.s for this formulation, which are comparable to those for the presumed homogeneous tear samples of (I). Two possible explanations for the higher sodium cromoglycate levels produced by (II) are that the tear volume does not change unduly and/or that the presence of discrete particles of (II) contributes to a significant error. A simple calculation shows that in the latter case the extra contribution from approximately 0·05 mg of (II) in the sample capillary cannot exceed 2 mg of sodium cromoglycate per ml of tears. However, if the volume of the tear pool remains unchanged at approximately 8 μl when (II) is placed in the eye, the expected concentration, assuming instantaneous and total release into the tears, would be 90 mg ml^{-1}. This value is twice that actually found 1 min post-instillation. It thus appears that the major factors contributing to the initial high tear concentration are rapid release of 50% of the drug and little, if any, increase in tear volume. This increased tear concentration raises the initial concentration gradient in the ocular tissues, particularly the conjunctiva and the cornea.

Formulations (V) and (VI), although oleaginous, are reasonably mobile liquids and disperse as droplets when placed in the precorneal area as drops. While these dispersed droplets are not miscible with the tears, they will contribute to the volume of fluid in the precorneal area and are subject to clearance along with tears. Given immiscibility between the vehicle and tears and assuming that drug release is instantaneous and only tears are obtained on sampling, the predicted concentrations for (V) and (VI) are 45 and 85 mg ml^{-1}, respectively. The values

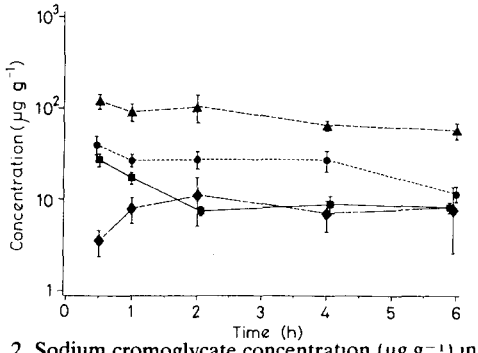

FIG. 2. Sodium cromoglycate concentration (μg g^{-1}) in the conjunctiva following adminstration of formulations. Key: See Fig. 1.

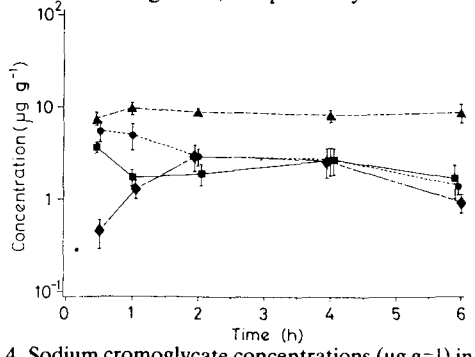

FIG. 4. Sodium cromoglycate concentrations (μg g^{-1}) in the iris-ciliary body following administration of formulations. Key: See Fig. 1.

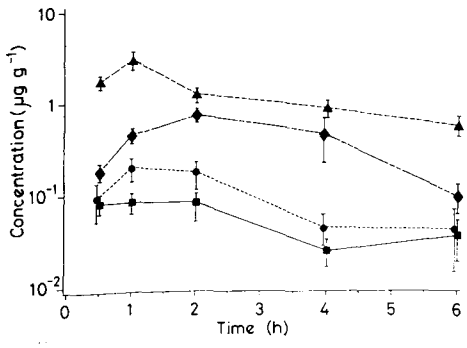

FIG. 5. Sodium cromoglycate concentrations (μg g^{-1}) in the aqueous humour following administration of formulations. Key: See Fig. 1.

observed 1 min post-instillation are much lower (Table 1), suggesting, in fact, that little of the sodium cromoglycate is released initially from these formulations into the tears.

Thus, relative to (I)—where all sodium cromoglycate is immediately available, the dispersion is homogeneous and the total volume clearable—(V) and (VI) appear to have low immediate availability, are not miscible with tears, yet the total volumes are clearable. Accordingly, sodium cromoglycate concentrations in tears following instillation of (V) and (VI) are low. On the other hand, (II) has good immediate availability, is not miscible with tears and is not readily cleared. These factors combine to produce a high drug concentration in the precorneal area following instillation of (II) compared to (I).

The disappearance rate constant for (I) dosed at a volume of 19 μl was 0·283 min^{-1}, a value consistent with data reported by Lee et al (1983a) for similar sodium cromoglycate solutions, namely 0·368 min^{-1} for 25 μl and 0·499 min^{-1} for 50 μl. The rate constants for the loss of sodium cromoglycate using (V) and (VI) are lower, suggesting that the clearance of aqueous liquid in the precorneal area is slowed by the presence of the more viscous dispersed Plastibase 5W vehicle as it undergoes clearance. The disappearance rate constant for (II) is not significantly different from that for (I), suggesting that the vehicle used in (II) has no direct influence on sodium cromoglycate disposition other than to act as a reservoir.

The levels of sodium cromoglycate found in tears and the four ocular tissues over the 6 h studied show clearly the superiority of (II) (Figs 1–5). The levels were significantly higher ($P < 0·05$, t-test) than those of all other formulations except the 30 min value in the iris-ciliary body for (VI). The next highest concentrations in tears and all other tissues except the aqueous humour were found with (VI). As seen from Table 2, these higher levels are reflected in significantly larger AUC's for (II) compared with the other formulations, particularly in conjunctiva, the tissue of primary interest in the therapeutic use of sodium cromoglycate. Based on the data in Table 2,

Table 2. Effect of formulation on sodium cromoglycate AUCs from 0·5 to 6 h.

Tissue	Formulation administered I	II	V	VI
Tears	286[a]	6689	489	999
Conjunctiva	46[b]	415	63	145
Cornea	37[b]	170	29	44
Iris-ciliary body	12[b]	49	13	18
Aqueous humour	2·4[b]	7	0·3	0·6

[a] μg h ml^{-1}.
[b] μg h g^{-1}.

(II) is 4·5 times more available to the conjunctiva than (I) and 2·9–3·3 times more available than (V) and (VI). The levels obtained in the conjunctiva are obviously a reflection of the concentration gradients set up between the formulations and the tears which bathe the conjunctiva.

In a previous communication (Swarbrick & Shrewsbury 1984) comparing 25 μl of (I) against 17·5 (normalized to 25) mg of (II), it was shown that the concentration of sodium cromoglycate produced in the tears, conjunctiva and cornea 6 h after administering (II) equalled or exceeded the values arising from (I) 1 h after instillation. The more extensive data presented in this paper for the four formulations dosed at approximately equal weights permit the same conclusion to be drawn. Thus, of those formulations studied, the one of choice for retaining sodium cromoglycate in the tears, conjunctiva and cornea for at least 6 h is (II), which consists of a dispersion of the drug in a hypoallergenic acetylated lanolin/paraffins base.

Acknowledgement

This work was supported by a grant from Fisons plc, Pharmaceutical Division, Loughborough, UK.

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