

Survey of Mixing Commercially Available Corticosteroid Ointments with Other Ointments and the Anti-inflammatory Activity of the Admixtures

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We surveyed the prescriptions from the Department of Dermatology in a city hospital to determine the status of the use of admixtures of corticosteroid ointments with other ointments. Thirty percent of the prescriptions of topical ointment therapy for outpatients of the Department were for admixture ointments. They were prescribed for patients aged 2 months to over 90 years. The mixing ratios of corticosteroid ointments with other ointments were 1 : 1 to 5 : 3. One-to-one dilution was most frequently used. Corticosteroid ointments classified into strongest, very strong, strong and medium groups were used for admixtures. We studied the effect of admixture ointments on carrageenan-induced edema in rat hind paws to assess the anti-inflammatory activity of these admixtures. Dermovate™, its 1 : 3-diluted preparation with white petrolatum and 1 : 1-diluted preparation of Lidomex™ with white petrolatum exerted significant anti-inflammatory activity ($p < 0.05$, compared with white petrolatum). These results suggest that the admixtures of different corticosteroid ointments have different anti-inflammatory activities. When admixture preparations are used, the properties of the corticosteroid and other ointments should be taken into account individually.

Key words—corticosteroid ointment; admixture; survey; anti-inflammatory activity; carrageenan

INTRODUCTION

Commercially available topical corticosteroid ointments and/or creams (corticosteroid ointments) are well recognized as the first line for treatment of various inflammatory conditions of the skin such as atopic dermatitis. Although corticosteroid ointments are effective when applied alone, the dilution or mixing of corticosteroid ointments is a common practice in our country because of the expected improvement of compliance and reduction of the adverse effects of the corticosteroid.¹⁾ However, the practical status of mixing of corticosteroid and other ointments still remains unclear.

The pharmaceutical stability of the corticosteroid in the admixtures, permeability of the corticosteroid through the skin, and vasoconstriction activity of admixtures of corticosteroid ointments have been studied.^{2–4)} However, there have been no reports on the anti-inflammatory activity of admixtures of corticoid ointments.

To determine the status of the use of mixtures of

these ointments, we surveyed the current state of mixing of commercially available corticosteroid ointments with other ointments based on dermatological prescriptions in a city hospital.

We also studied the effect of admixtures of corticoid ointments and other ointments on carrageenan-induced edema in rat hind paws to determine the *in vivo* anti-inflammatory effects of these admixtures.

MATERIALS AND METHODS

Survey of Mixing of Corticosteroid Ointments with Other Ointments with respect to Dermatological Prescriptions in a City Hospital

We surveyed the number of prescriptions for ointments containing mixtures of corticosteroid and other ointments for both in-patients and out-patients in the Department of Dermatology, St. Luke’s Hospital (Tokyo, Japan). The period of the survey was 6 months from May to October 2001. The surveyed items in the prescriptions were age of the patient, kind of corticosteroid ointment used for admixture preparation, kind of other ointment used for admixture preparation, frequency of the admixture use, and mixing ratio of corticosteroid and other ointments.

Anti-inflammatory Effects of the Admixtures of Corticosteroid and Other Ointments : Materials Male Wistar rats (5 weeks old) were supplied by Sankyo Labo Service Co. (Tokyo, Japan). The rats were kept under a 12 h/12 h light/dark cycle with free access to food and water.

Dermovate™ ointment (clobetasol propionate 0.5 mg/g, Lot No. DG4P1) was purchased from GlaxoSmithKline Co. Ltd. (Tokyo, Japan), Lidomex™ ointment (prednisolone valerate acetate 3 mg/g, Lot No. ST1H) was purchased from Kowa Co. Ltd. (Nagoya, Japan). White petrolatum (Lot No. 661620), which has no pharmacological activity, was purchased from Maruishi Co. Ltd. (Osaka, Japan).

λ -Carrageenan was purchased from Wako Pure Chemical Industries Inc. (Osaka, Japan).

Preparation of Admixture Ointments for Animal Experiments Dermovate™ and Lidomex™ corticosteroid ointments were selected for use based on the results of the survey of prescriptions. Corticosteroid and other ointments were mixed at ratios that were decided based on the results of the survey of the prescriptions (see "Results").

Anti-inflammatory Effect of the Admixtures of Corticosteroid Ointments on Carrageenan-induced Edema in Rat Hind Paws After initial measurement of the hind-paw volume using a water plethysmometer (TK101P, UNICOM Inc. Chiba, Japan), 0.1 g of ointment was applied to the right hind paw, and the paw was wrapped with cotton and a latex sac to avoid the removal of ointment by grooming. The left hind paw was wrapped only with cotton and a latex sac. After 4 hours, 0.1 mL of suspension containing 1% λ -carrageenan in saline was injected subcutaneously in both the left and right hind paws of rats. Since our preliminary experiments revealed that the edema in rat hind paws reached a peak 4 hours after the subcutaneous injection of carrageenan (data not shown), we measured the volume of the rat hind paw 4 hours after the carrageenan injection.

The rate of edema suppression was calculated from the volumes of rat hind paws 4 hours after carrageenan injection by using the following equations:

$$\text{edema rate} = \frac{\text{hind paw volume 4 hours after carrageenan injection}}{\text{initial hind paw volume}}$$

$$\text{edema suppression rate} = 1 - (\text{edema rate of the ointment-applied paw} / \text{edema rate of the control paw})$$

For statistical analysis test, Turkey's honesty significant difference test (SPSS 10.0 J) was used. A significant level lower than 5% was defined as significant.

RESULTS

Survey of Mixing of Corticosteroid Ointments with Other Ointments with respect to Prescriptions in the Department of Dermatology : Number of Prescriptions of Topical Ointments and Admixtures of Corticosteroid Ointment with Other Ointments During the period of the survey, the numbers of prescriptions for topical ointments were 1145 for outpatients and 1392 for inpatients. Among these prescriptions, 219 prescriptions for outpatients (39%) and 85 prescriptions for inpatients (6%) were for admixtures of corticosteroid ointments with other ointments. The age of the patients was distributed from 2 months to 96 years, with a median of 20 years.

Corticosteroid Ointments in Admixture Prescriptions As shown in Table 1, nine corticosteroid ointments were prescribed for admixture preparations. These corticosteroid ointments were classified into a strongest group, very strong group, strong group, and medium group according to our classification system for corticosteroid ointments.

Myster™ ointment and Rinderon VG™ ointment were used most frequently, and 60% of the ointments in the mixed preparations were in the very strong group.

Other Ointments in Admixture Prescriptions Nine ointments other than corticosteroid ones were prescribed for the mixing preparations (Table 2). Keratinamin™ ointment, which is a urea ointment, zinc oxide ointment, and Hirudoidosoft™ were frequently used. White petrolatum was used for admixture preparations as a basal material without pharmacological action.

Mixing ratio of Corticosteroid Ointment and Other Ointment The mixing ratio of corticosteroid ointments and other ointments ranged from 1 : 1 to 5 : 3 (weight/weight ratio). The ratio most frequently prescribed was 1 : 1 (94%), followed by 1 : 3 (Table 3).

Anti-inflammatory Effect of Admixture Ointments of Corticosteroid and Other Ointments Since corticosteroid ointments of the strongest group and the strong group were among those prescribed for the admixture preparations in the survey, Dermovate™

Table 1. Classification of Corticosteroid Ointments Used in Admixture Preparations

Classification of corticosteroid ointment	Corticosteroid ointments	Number of prescriptions (%)
Strongest	Dermovate™ Ointment (clobetasol propionate)	1 (0.3)
Very strong	Myser™ Ointment (difluprednate)	85 (28.0)
	Rinderon VG™ Ointment (betamethasone valerate/gentamicin sulfate)	71 (23.4)
	Pandel™ Ointment (hydrocortisone butyrate propionate)	13 (4.3)
	Nerisona™ Ointment (diflucortolone valerate)	13 (4.3)
Strong	Lidomex™ Ointment (prednisolone valerate acetate)	63 (20.7)
	Lidomex™ Cream (prednisolone valerate acetate)	12 (3.9)
Medium	Kindavate™ Ointment (clobetasone butyrate)	32 (10.5)
	Almeta™ Ointment (aclometasone dipropionate)	14 (4.6)
Total		304 (100)

Table 2. Non-corticosteroid Ointments Used for Admixture Preparations with Corticosteroid Ointments

Non-corticosteroid ointments	Number of prescriptions (%)
Keratinamin™ Ointment (urea)	100 (32.9)
Zinc Oxide Ointment	96 (31.6)
Hirudoidosoft™ (heparinoid)	35 (11.5)
Hirudoid™ (heparinoid)	29 (9.5)
Zahne™ Ointment (vitamin A)	21 (6.9)
White Petrolatum	17 (5.6)
Azunol™ Ointment (azulene)	2 (0.7)
Fucidin Leo™ Ointment (sodium fusidate)	2 (0.7)
10% Salicylic acid Petrolatum	2 (0.7)
Total	304 (100)

Table 3. Mixing Ratio and Number of Prescription for Admixture Preparations

Corticosteroid ointment : Non-corticosteroid ointment	Number of prescriptions (%)
1 : 1	285 (93.8)
1 : 2	5 (1.6)
1 : 3	8 (2.6)
1 : 4	1 (0.3)
2 : 3	1 (0.3)
2 : 5	1 (0.3)
3 : 5	2 (0.7)
5 : 3	1 (0.3)
Total	304 (100)

ointment (strongest group) and Lidomex™ ointment (strong group) were selected as corticosteroid ointments for experimental^M evaluation.

White petrolatum, which exerted no edema suppressive effects, was used for mixing with corticosteroid ointments. Since 1 : 1 dilutions were most frequently used in the clinical prescriptions, a mixing ratio of 1 : 1 was used. A 1 : 3-dilution was also used for the admixture preparations.

The admixture of Dermovate™ with white petrolatum (1 : 3) showed almost the same edema suppressive activity as Dermovate™ itself ($p < 0.05$), but the 1 : 1 admixture preparation of these ointments had only weak suppressive activity. The admixture of Lidomex™ and white petrolatum (1 : 1) significantly suppressed ($p < 0.05$). The edema whereas Lidomex™ itself and 1 : 3-diluted Lidomex™ with white petrolatum had weaker edema suppressive activity than 1 : 1-diluted preparation (Fig. 1).

DISCUSSION

Admixture preparations of corticosteroid ointments with other ointments are frequently prescribed by dermatologists in our country. Eto et al. reported that 85% of dermatologists prescribed admixture preparations of corticosteroid ointments to improve compliance of patients, to reduce adverse reactions and to obtain possible additive or synergistic effects.¹⁾

In the present survey, it was also shown that admixture preparations were widely prescribed for patients with a wide range of age, *i.e.*, infants to elderly patients older than 90. Nine corticosteroid ointments (ranging from a strongest group to a medium group) were prescribed for the admixture preparations (Table 1). Nine ointments other than corticosteroid ointments were used for preparing the admixtures with corticosteroid ointments (Table 2). Keratinamin™

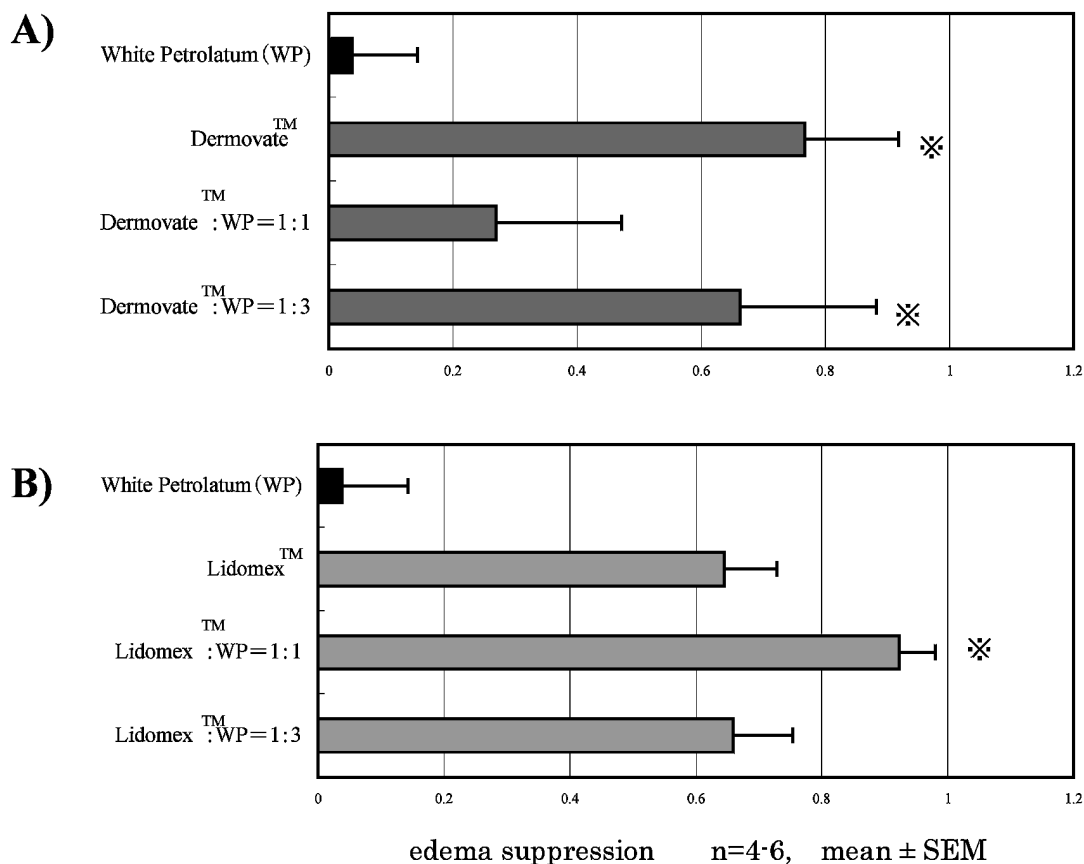


Fig. 1. Effect of Dermovate™ and Its Admixture Preparations (A), and Lidomex™ and Its Admixture Preparations (B) on Carrageenan-induced Edema in Rat Hind Paw

* $p < 0.05$, as compared with white petrolatum (Turkey's honesty significant difference test).

ointment and Hirudoidosoft™, both of which have a high moisturizing property, were used frequently for admixture preparations.

With regard to admixture preparations, there have been many reports showing changes in the appearance or stability of the active component. However, there have been few reports on the effect of mixing these ointments on the clinical effect and/or adverse effects.³⁻⁶ Guin et al. reported that the vasoconstrictive effect of a corticosteroid ointment containing fluocinolone acetonide did not decrease in dilutions with white petrolatum, and showed augmentation in some cases.³ For commercially available corticosteroid ointments, the base materials and concentrations of active components have been decided based on the properties of the active agents. In the development of these ointments, the effect of mixing and/or dilution with other ointments has not been studied in most cases. Thus, it is possible that the physicochemical properties of the base material might be affected by mixing ointments, and that this might

lead to the eventual acceleration of the release of the active component.^{3,7)}

In this study, our survey provided information about the dilutions of corticosteroid ointments with other ointments actually used clinically in the dermatological field. However, the precise purpose and mechanisms of these admixtures remain unclear. We studied the anti-inflammatory effect of admixtures of two corticosteroid ointments, i.e., Dermovate™ and Lidomex™, with white petrolatum. Dermovate™ itself and the 1 : 3-diluted ointment caused significant suppression of carrageenan-induced edema, which is an anti-inflammatory effect, but the 1 : 1-diluted ointment had weaker activity (Fig. 1). Furthermore, the 1 : 1-diluted Lidomex™ ointment had stronger anti-inflammatory activity than Lidomex™ itself or the 1 : 3-diluted ointment (Fig. 1).

These results suggest that the anti-inflammatory activities of admixtures of corticosteroid ointments differ from each other in a manner that appears to depend on the corticosteroid ointment.

In this study, we found that admixtures or dilutions of corticosteroid ointment with other ointments are frequently prescribed in the dermatological field. We suggest that some admixtures or diluted ointments might have good anti-inflammatory activity with weaker adverse effects. Dermatologists should know the characteristics of each corticosteroid ointment in order to decide whether to prescribe the ointment itself or a diluted admixture of ointments.

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