

## Investigation of Patients' Satisfaction in Using Potent Topical Corticosteroid Preparations

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### ABSTRACT

The purpose of this study is to elucidate the physical properties of various commercially available topical corticosteroid preparations. We compared comfort after application and the physical properties affecting topical application among brands of commercially available topical corticosteroid ointments and creams to identify factors affecting quality of life after application. We investigated 12 commercially available brands of topical corticosteroid preparations (6 creams and 6 ointments), all classified as "potent" corticosteroid in Japan. Subjects were 122 healthy volunteers at 11 hospitals, all of whom had given their informed consent for this study. Physical properties were compared among test preparations as well as standard preparations. Ranked high in comfort, Nerisona<sup>®</sup> cream was easy to spread, odorless, and low in viscosity. Overall, it displayed better qualities than other creams tested. The spreadability of Rinderon<sup>®</sup>-DP ointment and Antebate<sup>®</sup> ointment ranked higher than other preparations, suggesting that these ointments may reduce mechanical irritation to lesions during topical application. The results of this study could be used by dermatologists and pharmacists to aid preparation choice and improve compliance with application recommendations.

**Key words:** *Topical corticosteroid, Physical property, Ointment, Cream*

Selection of a potent topical corticosteroid preparation for treatment of atopic dermatitis and other inflammatory skin diseases is determined mainly by the pharmacological efficacy of active ingredients and the nature of the condition to be treated. Since drying and depression of barrier functions usually occur in inflammatory skin disease, care must be taken to choose a treatment that does not irritate the diseased skin<sup>10</sup>. Even slight irritation can exacerbate inflammation. Unfavorable physical properties, such as poor spreadability, can cause such irritation. At present, ease of application and patient comfort often favor prescription of mixtures of two agents<sup>6</sup>. However, it cannot be ascertained from the physical properties of these mixed preparations whether or not they will cause irritation. Criteria for evaluating the vehicle of a topical preparation should give high consideration to patient convenience and comfort. Preparations with low spreadability and high viscosity are difficult to apply<sup>1,3,5,7,20</sup>. Although dermatologists and pharmacists are trained in the pharmacological properties of topical corticosteroid preparations, few reports have addressed the physical proper-

ties of various commercially available topical corticosteroid preparations<sup>4,16</sup>.

In this study we compared comfort after application and the physical properties affecting topical application among brands of commercially available topical corticosteroid creams and ointments to identify factors affecting quality of life after application.

### MATERIALS AND METHODS

#### **Test preparations**

We investigated 12 commercially available brands of topical corticosteroid preparation (6 creams and 6 ointments); all classified as "potent" topical corticosteroid preparations in Japan. Vehicles in the tested creams and ointments are listed on Table 1. An oil-in-water (O/W) emulsion was used in all cream preparations except for Topsy<sup>®</sup>, and white petrolatum was used as the vehicle in ointment preparations.

#### **Standard preparations**

A standard corticosteroid preparation of each

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**Table 1.** Characteristics of steroid preparations used in this study

	Trade name (abbrev.)	Active ingredient	Manufacturer	Vehicles
<b>Creams</b>	Myser <sup>®</sup> *	(MC) difluprednate	Mitsubishi Tanabe Pharma Corporation, Osaka Japan	oil in water
	Antebate <sup>®</sup>	(AC) betamethasone butyrate propionate	Torii Pharmaceutical Co., Ltd. Tokyo Japan	oil in water
	Topsym <sup>®</sup>	(TC) fluocinonide	Mitsubishi Tanabe Pharma Corporation, Osaka Japan	fatty alcohol propylene glycol
	Nerisona <sup>®</sup>	(NC) diflucortolone valerate	Intendis K.K. Osaka Japan	oil in water
	Fulmeta <sup>®</sup>	(FC) mometasone furoate	Shionogi & Co., Ltd. Osaka Japan	oil in water
	Rinderon <sup>®</sup> -DP	(RC) betametasone dipropionate	Shionogi & Co., Ltd. Osaka Japan	oil in water
<b>Ointments</b>	Myser <sup>®</sup> *	(MO) difluprednate	Mitsubishi Tanabe Pharma Corporation, Osaka Japan	white petrolatum
	Antebate <sup>®</sup>	(AO) betamethasone butyrate propionate	Torii Pharmaceutical Co., Ltd. Tokyo Japan	white petrolatum
	Topsym <sup>®</sup>	(TO) fluocinonide	Mitsubishi Tanabe Pharma Corporation, Osaka Japan	white petrolatum liquid petrolatum
	Nerisona <sup>®</sup>	(NO) diflucortolone valerate	Intendis K.K. Osaka Japan	white petrolatum
	Fulmeta <sup>®</sup>	(FO) mometasone furoate	Shionogi & Co., Ltd. Osaka Japan	white petrolatum
	Rinderon <sup>®</sup> -DP	(RO) betametasone dipropionate	Shionogi & Co., Ltd. Osaka Japan	white petrolatum

\*, standard drug

type was selected in accordance with Japanese guidelines for organoleptic tests (JIS Z 9080)<sup>8)</sup>, against which aspects of patient comfort after application of other preparations were evaluated. The standard preparation for each type was the one prescribed most often at the 11 hospitals participating in the study, all belonging to the Private Hospital Pharmacist Association in Aichi Prefecture. Accordingly, Myser<sup>®</sup> cream (MC: Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) and Myser<sup>®</sup> ointment (MO: Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) were taken as standard preparations for the two types.

### Volunteers

We studied 122 healthy volunteers at 11 hospitals after obtaining informed consent for this study. Subjects were 95 women and 27 men. Mean age ( $\pm$ SD) was  $32.1 \pm 10.2$  years (range, 20 to 60). Individuals previously treated with topical corticosteroid preparations were excluded to ensure that subjects could not distinguish brands of topical corticosteroid preparations as they were tested. If a participant had an adverse reaction to a test preparation, application of that item to that subject was stopped immediately.

### Application method

All creams and ointments for examination were transferred from the original container to stan-

dard containers identical in appearance to avoid brand-identification bias. Participants applied the standard preparation for each test group, then applied test preparations at random. The physical characteristics of test preparations were evaluated in comparison with standard preparations. One study supervisor distributed the test preparations to all participants. The amount of test preparation distributed was approximately 0.1 g<sup>9)</sup> for both types. Participants then had test preparations applied to a rectangular area of the inner forearm ( $5 \times 10$  cm area, 50 cm<sup>2</sup>). Test preparations were applied to different areas. The area was wiped with a tissue or washed with running water before application of the next test preparation. Twelve test preparations were applied in random order. Properties were evaluated within 15 min after application<sup>12)</sup>.

### Evaluation of physical properties and comfort

Spreadability, odor, viscosity, and comfort were evaluated by organoleptic tests of each test preparation<sup>11)</sup>. Participants were instructed before evaluation to use the following criteria. "Spreadability" denoted ease of application. "Viscosity" indicated stickiness. "Comfort" was overall patient satisfaction with the way the test preparations felt. These properties were compared among test and standard preparations.

**Table 2.** Criteria for evaluation relative to standard drug

Physical properties	Evaluation scores								
	1	2	3	4	5	6	7	8	9
Spreadability	low		←		standard preparation		→		high
Odor	strong		←		standard preparation		→		slight
Viscosity	high		←		standard preparation		→		low
Comfort	low		←		standard preparation		→		high

5: same as standard preparation

5±1: some difference between sample and standard preparation.

5±2: clear difference between sample and standard preparation.

5±3: some difference between sample and standard preparation evident even before application.

5±4: clear difference between sample and standard preparation evident even before application.

### Scoring methods

Scoring of properties was carried out in accordance with the Semantic Differential (SD) method<sup>19</sup>. Each property of each standard preparation was scored arbitrarily as 5, while participants scored each property of each test preparation with an integer score of 1 to 9 relative to the standard preparation, as shown in Table 2.

### Ambient conditions

The temperature of the room in which the preparations were applied was 21 to 25°C, with a relative humidity of 50 to 60%.

### Statistical methods

The six preparations in each group (cream or ointment) were ranked from 1 to 6 based on their evaluation scores by the SD method for each physical property. Preparations with the lowest score for spreadability, strong odor, high viscosity, and the lowest score in comfort were ranked as 1. When test preparations had the same score, they were given the same rank. Scores obtained from all participants were averaged. Each property of the test preparations was expressed by the averaged score and standard deviation. Statistical analysis was performed using multiple nonparametric comparative tests (Steel-Dwass method)<sup>15</sup>. Correlations between spreadability, odor, viscosity, and comfort were examined using Spearman's rank correlation coefficient.

## RESULTS

### Adverse reactions

No participants dropped out due to adverse reactions to the test preparations. There was no gender difference in these results.

### Creams (Fig. 1)

MC was selected as the standard preparation

in this group. Average ranking scores in spreadability from low to high were: FC (2.17±1.46), AC (2.80±1.63), RC (2.86±1.47), MC (2.88±1.18), TC (2.89±1.54), NC (5.10±1.42). Thus, NC was evaluated as significantly better than FC, AC, RC, MC, or TC in spreadability ( $p < 0.01$ ), while spreadability scores for AC, RC, MC, and TC were all significantly better than that of FC ( $p < 0.05$ ). Odor scores in organoleptic tests ranked slight to strong were: NC (3.86±1.72), AC (3.16±1.65), MC (3.06±1.25), RC (2.73±1.41), TC (2.11±1.50), and FC (2.07±1.45). Multiple comparisons showed that NC, AC, MC, and RC were significantly less odiferous than TC and FC ( $p < 0.01$ ). NC had less odor than RC ( $p < 0.01$ ). From low to high, viscosity rankings were NC (4.23±1.88), MC (3.06±1.25), RC (2.88±1.59), AC (2.82±1.69), FC (2.43±1.62), and TC (2.30±1.43). Multiple comparisons among brands showed that NC and MC were ranked significantly less viscous than FC and TC ( $p < 0.01$ ), while NC was significantly less viscous than RC or AC ( $p < 0.01$ ). Rankings for comfort in ascending order were: TC (2.39±1.42), FC (2.39±1.63), RC (2.82±1.57), AC (2.89±1.70), MC (2.93±1.24), and NC (4.14±1.89; Fig. 2). Multiple comparisons among brands found MC and NC significantly more comfortable than TC and FC ( $p < 0.05$ ), while NC was seen as significantly more comfortable than RC, AC, or MC ( $p < 0.01$ ).

### Ointments (Fig. 3)

MO was selected as the standard preparation in the ointment group. Spreadability ranks rose from NO (1.85±1.40) to TO (2.98±1.60), MO (3.03±1.25), FO (3.07±1.47), AO (3.40±1.63), and RO (4.00±1.72). Multiple comparisons among brands ranked TO, MO, FO, AO, and RO as significantly better than NO ( $p < 0.01$ ). The spreadability score of RO was significantly better than those of TO, MO, and FO ( $p < 0.01$ ). Odor was ranked in organoleptic tests from slight to strong: AO (3.45±1.82),

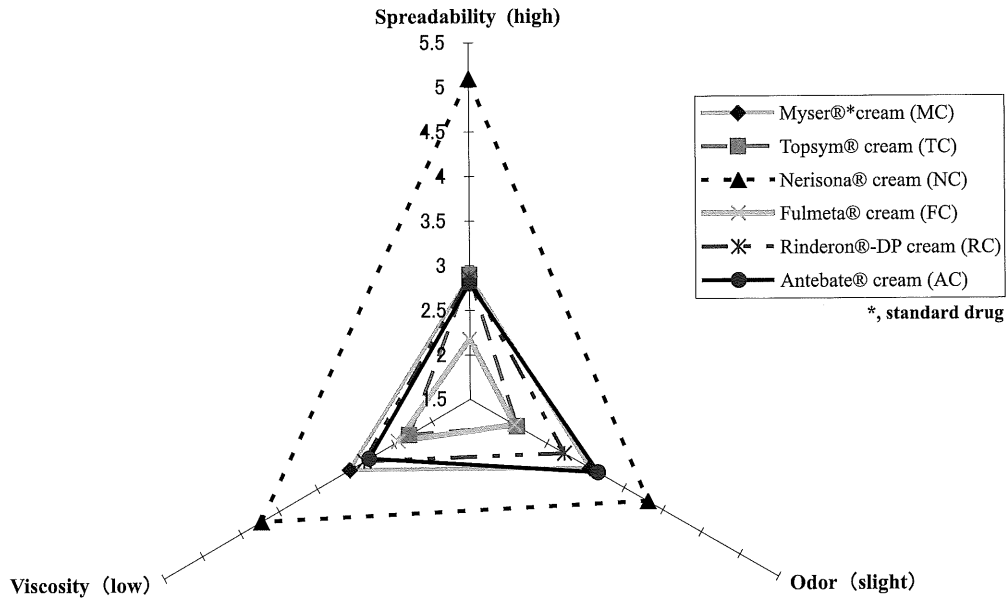


Fig. 1. Comparisons of spreadability, odor, and viscosity among 6 creams

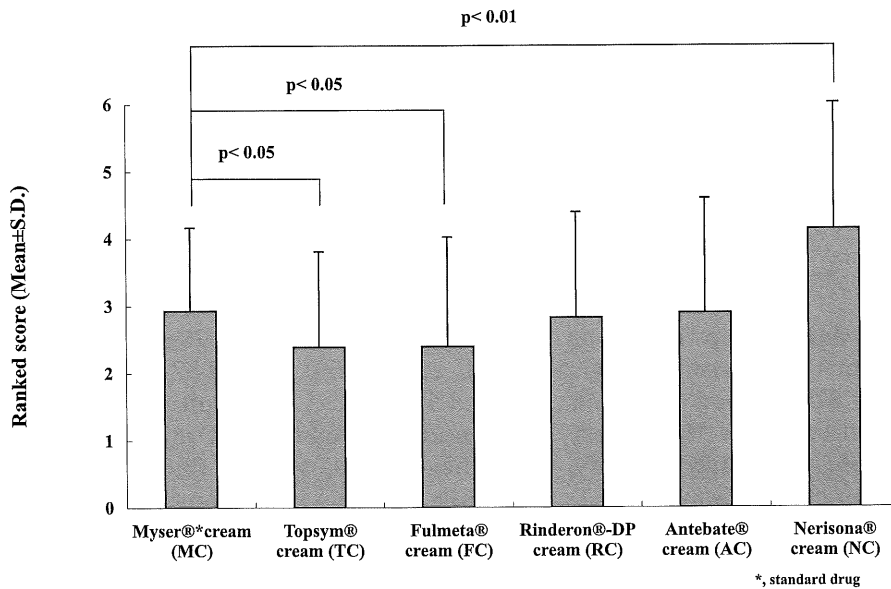
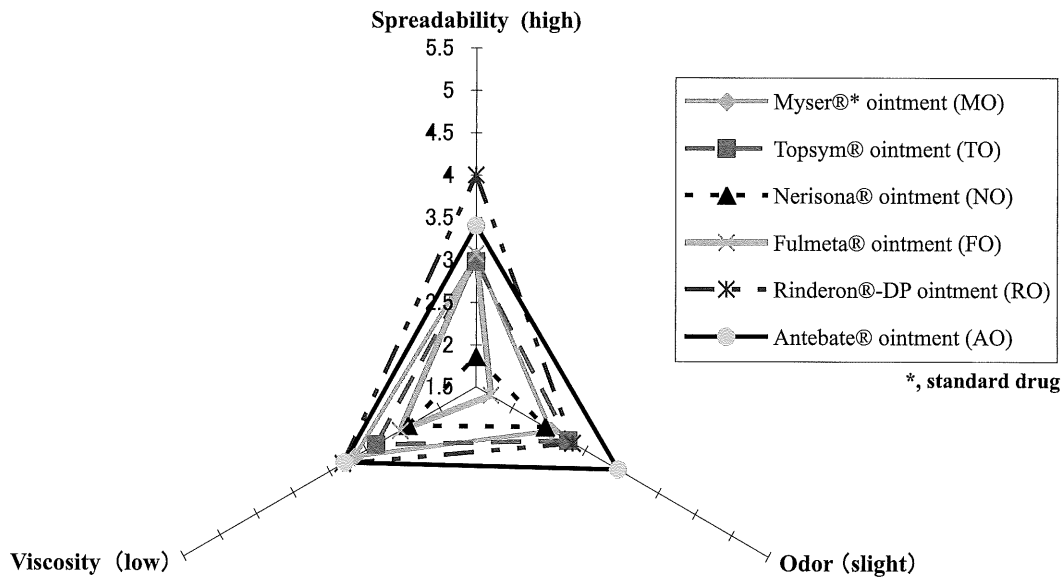


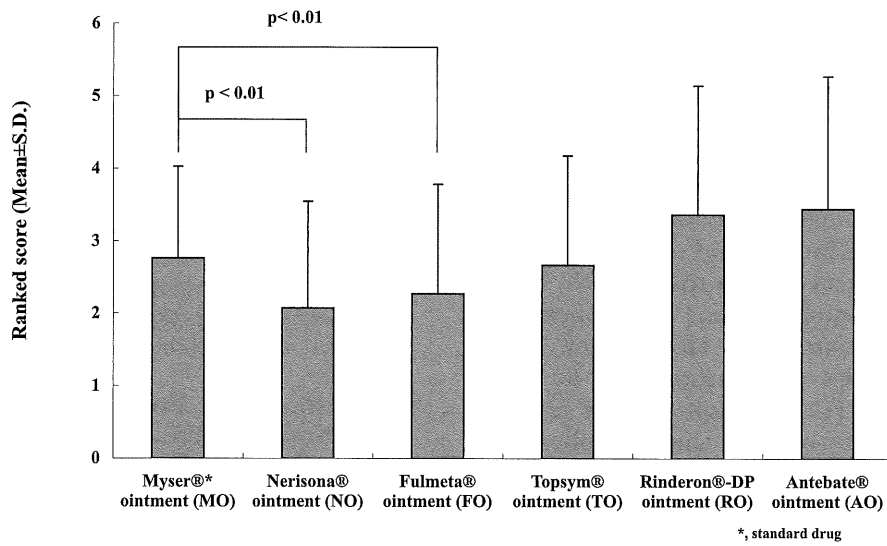
Fig. 2. Comparisons of comfort among 6 creams

RO (2.83±1.58), TO (2.76±1.43), MO (2.53±1.12), NO (2.45±1.57), and FO (1.70±1.10). In multiple comparisons among brands, the odors of AO, RO, TO, MO, and NO were found to be significantly weaker than that of FO (p<0.01). AO was significantly less odiferous than MO or NO (p<0.05). From low to high, viscosity rankings were RO (3.32±1.95), AO (3.30±1.83), MO (3.15±1.24), TO (2.87±1.63), FO (2.53±1.60), and NO (2.43±1.78). In multiple comparisons among brands, FO and NO were ranked significantly more viscous than RO, AO, or MO (p<0.05). In order of increasing comfort, the brands were ranked: NO (2.07±1.47),

FO (2.27±1.51), TO (2.66±1.51), MO (2.76±1.26), RO (3.36±1.78), and AO (3.44±1.83; Fig. 4). In multiple comparisons among brands, TO, MO, RO, and AO were ranked significant higher than NO (p<0.01). RO and AO were ranked significantly more comfortable than FO or TO (p<0.05), and MO was significantly more comfortable than FO (p<0.01). When comfort was examined for correlation with spreadability, odor, and viscosity (Table 3), correlations were significant between comfort and spreadability, odor, and viscosity among both creams and ointments (p<0.001).



**Fig. 3.** Comparisons of spreadability, odor, and viscosity among 6 ointments



**Fig. 4.** Comparisons of comfort among 6 ointments

**Table 3.** Correlation between comfort and spreadability, odor, and viscosity

Preparation	Rank correlation coefficient	Spreadability and comfort	Odor and comfort	Viscosity and comfort
Cream*	$r_s$	+0.449	-0.227	-0.599
	P (two-sided)	<0.001	<0.001	<0.001
Ointment*	$r_s$	+0.459	-0.310	-0.535
	P (two-sided)	<0.001	<0.001	<0.001

\*, n=732 (number of participants x test preparations).  $r_s$ , Spearman's rank correlation coefficient

## DISCUSSION

Topical corticosteroid drugs are frequently applied to areas which patients cannot reach, such as the back, and to extensive areas of skin, including the whole body<sup>17</sup>. Patient understanding and cooperation are not the only factors important for compliance with treatment; ease of application is important as well, especially for long-term treatment. Clinical research concerning topical drugs often focuses on indications for use rather than physical properties affecting topical application. We therefore studied these properties in healthy volunteers.

### Creams

Ranked high in comfort, spreadability, and odorlessness, and low in viscosity, NC displayed better qualities overall than the other creams tested. In clinical application, patients are required to rub the preparation into the lesion while taking care not to irritate the skin. At the same time, patients tend to over-apply topical drugs with O/W emulsion or gel vehicles because application is extremely easy and soothing<sup>13,14</sup>. Patients need to be warned against over-application of NC and other preparations ranked high in comfort. However, NC, which was rated well for spreadability, appeared suitable for a variety of sites, including sweaty or damp areas such as the axilla and extensive areas. It is appropriate even for older patients with compromised activities of daily living. Although this point was not examined here, the selection of topical preparations with high spreadability for extensive areas of application may limit skin irritation. Fatty-alcohol propylene glycol (FAPG) provides a gel suspension for the active ingredient in TC, the most viscous cream in this study. It was reported that the physical properties of FAPG positioned it between a cream and an ointment<sup>13</sup>. Participants sometimes complained that TC did not appear to behave as a cream. The results of this study supported a previous report that TC is more viscous than NC<sup>2</sup>.

### Ointments

RO and AO were ranked higher than other preparations for spreadability, suggesting that they might reduce mechanical irritation to lesions during topical application. Although not tested in this study, the viscosity of topical preparations may change with temperature. Since viscosity is particularly an issue in hot-weather<sup>18</sup>, low-viscosity preparations like RO, AO and MO would be recommended for patients who complain of discomfort after application in the heat. AO might be suitable for reducing the burden of long-term treatment, as it has only the slightest odor. High comfort with AO and RO appears to originate from high spreadability and low viscosity. The results

of the present investigation could be included in the drug information given to patients, such as "This medicine has a characteristic odor," or "This drug may feel sticky after application". Use of this information should aid preparation choice and improve compliance with treatment, making it useful for both dermatologists and pharmacists.

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