Original Article

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Generic selection criteria for safety and patient benefit [VII]: Comparing the physicochemical and pharmaceutical properties of brand-name and generic terbinafine hydrochloride cream

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Summary **We measured and compared the physicochemical properties (pH, yield value, and squeeze force) of a drug for dermatomycosis, terbinafine hydrochloride-containing cream (brand-name product), and 12 generic products to clarify the characteristics of each product. On pH measurement, the pH value of the brand-name product, Lamisil, was 4.8, and those of the generic products ranged from 4.3 to 5.5, showing no marked difference. Furthermore, the yield value of Lamisil, as an index of cream ductility, was 122.2 dyn/cm^2, and those of the generic products ranged from 42.1 to 1,621.5 dyn/cm^2. In particular, the value of a generic product, Taiyo (42.1 dyn/cm^2), was significantly lower, whereas that of another one, Viras (1,621.0 dyn/cm^2), was significantly higher. In addition, the squeeze force was measured by attaching a HapLog® to the thumb and second finger. The value of Lamisil was 12.9 N, and those of the generic products ranged from 8.0 to 15.4 N. The values of generic products, Mylan (8.6 N), Tebinaceil (9.0 N), and Kelger (8.0 N), were significantly lower, whereas that of another one, Viras (15.4 N), was significantly higher. These results showed that there were marked differences in the pharmaceutical properties between the generic and brand-name products. The above pharmaceutical characteristics of drugs facilitated the presentation of reasons for differences in the sense of use, which characterizes external preparations, suggesting that products appropriate for individual patients can be recommended.**

Keywords: Cream, terbinafine hydrochloride, brand-name drug, generic drug, HapLog®

1. Introduction

In Japan, national health expenditure has annually increased, raising a serious social issue (*1*). To overcome this, a strategy to reduce health expenditure by promoting generic products was proposed (*2*). Concerning the promotion of generic drug usage, the quantity share of generic products is 56.2% as of September 2015. There was a cabinet decision in June 2015, and new target quantity shares in 2017 and in the early phase between 2018 and 2020 were established as ≥ 70 and ≥ 80%, respectively. At each pharmacy, generic product-promoting strategies have been positively attempted to achieve the above targets (*2*).

It is important for pharmacists to understand the equivalence of a generic product to a brand-name product or physicochemical properties and recommend a generic product based on an adequate triage from the viewpoint of national health maintenance and health expenditure reduction. However, there are no criteria for selecting generic products; therefore, it is not easy to select drugs appropriate for individual patients.

We previously reported that various patient needs could be met by clarifying the physicochemical and

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pharmaceutical properties of various dosage forms, primarily consisting of external preparations, which markedly differ in the sense of use: ointments, creams, lotions (*3,4*), ophthalmic liquids/solutions (*5*), nasal spray (*6*), and tapes (*7,8*). The appearance-based stability of a brand-name drug, Rinderon®-VG (principal components: betamethasone valerate, gentamicin sulfate), and 10 generic products (5 ointments, 3 creams, and 2 lotions) was evaluated, and their pH, viscosity, and contents were measured. There were marked differences in the rheology among the ointments, creams, and lotions (*3*). These results may have been related to differences in pharmaceutical techniques or additives in the process of manufacturing among various pharmaceutical companies. The sense of use or effects of each product may differ among patients. We concluded that caution was particularly needed when switching a brand-name drug to a generic product.

In this study, we summarized information for pharmacists to adequately select preparations in accordance with patient needs by comparing/evaluating the pharmaceutical properties of a drug for dermatomycosis, terbinafine hydrochloride-containing cream, and generic products.

2. Materials and Methods

2.1. *Materials*

Ethical pharmaceuticals of cream containing terbinafine hydrochloride (1 brand-name "Lamisil® cream 1%" and 12 generic products) were used in this study. Product name, abbreviated name, class, company name and lot number of these products are presented in Table 1.

2.2. *Measurement of pH*

Each cream preparation (1.0 g) was heated and dissolved by adding 10 mL of purified water. After cooling, it was measured using a Benchtop pH meter F-74 and ISFET pH electrode 0040-10D (HORIBA, Ltd., Kyoto, Japan). Measurement was performed 3 times at 25 ± 2°C, and the mean ± standard deviation (S.D.) was calculated.

2.3. *Measurement of ductility*

The spread diameter of each cream preparation was measured using a spread meter 419 (Rigo Co., Ltd., Tokyo). Measurement was conducted 3 times at room temperature (25 ± 2°C), and the mean value was calculated. The spread diameter was determined at 34 points between 5 and 1,800 seconds after the start of measurement. The spread diameter (cm) of each cream preparation was plotted on a longitudinal axis, and the time (seconds) was plotted on a transverse axis to prepare a semilog graph. The spread and viscosity of each cream preparation were calculated from the slope and y-intercept (*9,10*). Furthermore, the yield value was calculated using the following formula (*11*):

$$S_0 = \frac{48PVG}{\pi^2 D^5}$$

S_0: yield value (dyn/cm^2), P: weight of glass plate (g), V: amount of sample (cm^3)

G: gravitational acceleration (980 cm/sec^2), D: maximum spreading diameter (cm)

π: the ratio of the circumference of a circle to its diameter

2.4. *Measurement of squeeze force*

To assess the squeeze force to push out various preparations from a container, a wearable tactile sensor (Haptic Skill Logger (HapLog®), Kato Tech Co., Ltd., Kyoto, Japan) was used as a tool for evaluating the sense of touch (*12,13*). For measurement, the tactile sensors were attached to the right thumb and second finger, respectively, and the total force (thumb + second finger) required to squeeze 1 fingertip unit (FTU: volume of cream squeezed between the first joint and tip of the second finger) of cream while putting the center of the container between the thumb and second finger

Table 1. Cream products used in this experiment

Product name	Abbreviated name	Class	Company name	Lot numbers
Lamisil® Cream 1%	Lamisil	brand-name	Novartis Pharma K. K.	P0942
Viras® Cream	Viras	generic	Towa Pharm. Co., Ltd.	A199
Terbinafine Hydrochloride Cream 1% "Mylan"	Mylan	generic	Mylan Seiyaku Ltd.	013AKM
Terbinafine Hydrochloride Cream 1% "F"	F	generic	Fuji Pharma Co., Ltd.	2E01
Terbinafine Hydrochloride Cream 1% "Sandoz"	Sandoz	generic	Sandoz	212370
Tebinaceil® Cream 1%	Tebinaceil	generic	TOA Pharm. Co., Ltd.	T07TW
Terbinabine® Cream 1%	Terbinabine	generic	Nichi-Iko Pharm. Co., Ltd.	H1060
Ramitect® Cream*	Ramitect	generic	Sawai Pharm. Co., Ltd.	12X03
Tebeana® Cream 1%	Tebeana	generic	Iwaki Seiyaku Co., Ltd.	2E013
Terbinafine Hydrochloride Cream 1% "MEEK"	MEEK	generic	Kobayashi Kako Co., Ltd.	02SP21
Kelger® Cream	Kelger	generic	Maeda Pharm. Industry Co., Ltd.	2JC
Terbinafine Hydrochloride Cream 1% "Taiyo"	Taiyo	generic	Teva Takeda Pharma Ltd.	B11491
Terbinafine Hydrochloride Cream 1% "JG"	JG	generic	Nihon Generic Co., Ltd.	204100

*Currently, Ramitect® cream has its name changed to terbinafine hydrochloride cream 1% "Sawai".

was regarded as the squeeze force (N). These sensors facilitate the simultaneous assessment of the sensor-wearing person's finger contact force and sense of touch through the free sense of touch at the fingertip, whereas there are errors in the contact force related to individual differences in the attachment method or finger size. For this reason, the values were corrected in each person. Measurement was conducted 7 times per bottle of cream with the same lot number. In addition, concerning a product with different lot numbers, measurement was conducted for a total of 3 bottles. Subsequently, the mean of respective means was calculated, and adopted as the value of the product.

2.5. *Statistical analysis*

The values were compared using *Dunnett's* test. A *p*-value of 0.01 was regarded as significant.

3. Results

3.1. *Measurement of pH*

The influence of pH on the stability of drugs has been indicated. We measured the pH value of each preparation used in this experiment. The results are shown in Figure 1. The pH value of the brand-name drug, Lamisil, was 4.8, and the values of the generic products ranged from 4.3 to 5.5, showing no marked difference.

3.2. *Measurement of ductility*

When applying a cream preparation to the skin, the sense of use depends on its ductility and viscosity. We measured the spread diameter and time of each cream preparation using a spread meter. In addition, we prepared a semilog graph (longitudinal axis: spread diameter, transverse axis: time) to calculate the slope and y-intercept of each preparation. The results are shown in Figures 2 and 3. The slope of Lamisil was 0.24, whereas those of the generic products ranged from 0.02 to 0.36 (Figure 2). In particular, the value of a generic product, Viras (0.02), was significantly lower than that of Lamisil, and the value of another generic product, Taiyo (0.36), was significantly higher than that of Lamisil.

On the other hand, the y-intercept of Lamisil was 3.05, whereas the values of the generic products ranged from 2.55 to 3.33, as shown in Figure 3. In particular, the value of a generic product, Viras (2.55), was significantly

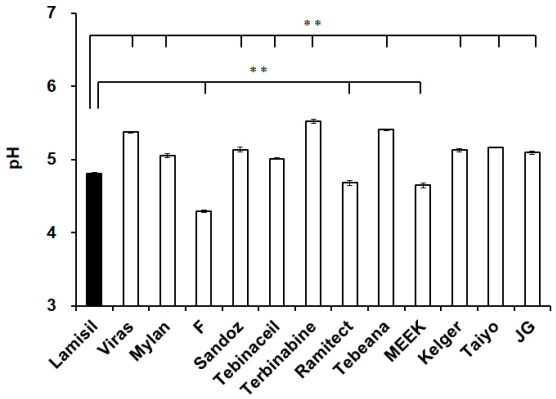

Figure 1. pH measurement of various preparations (*n* = 3). $^{**}p < 0.01$ (*vs*. Lamisil, *Dunnett*-test). ■: brand-name, □: generic.

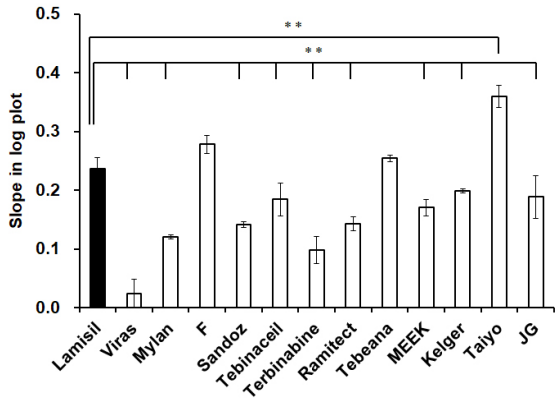

Figure 2. Slope measurement of various cream preparations (*n* = 3). $^{**}p < 0.01$ (*vs*. Lamisil, *Dunnett*-test). ■: brand-name, □: generic.

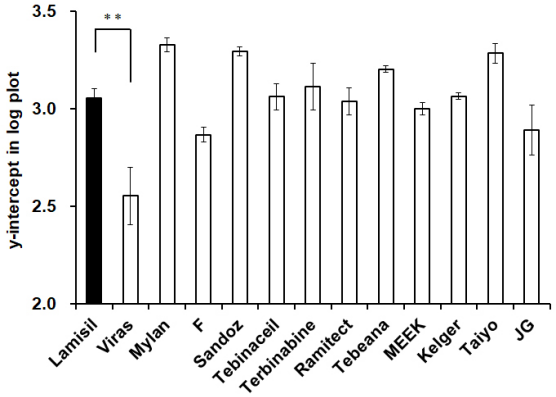

Figure 3. Y-intercept measurement of various cream preparations (*n* = 3). $^{**}p < 0.01$ (*vs*. Lamisil, *Dunnett*-test). ■: brand-name, □: generic.

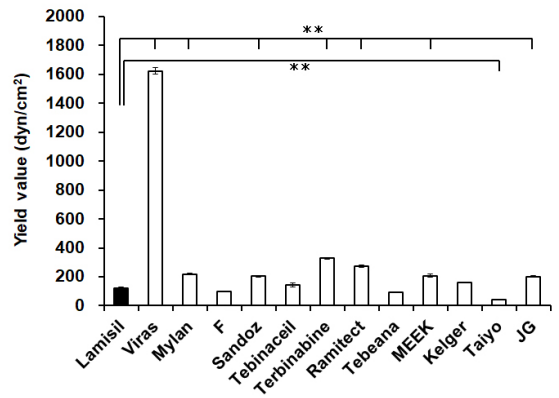

Figure 4. Yield value measurement of various cream preparation (*n* = 3). $^{**}p < 0.01$ (*vs*. Lamisil, *Dunnett*-test). ■: brand-name, □: generic.

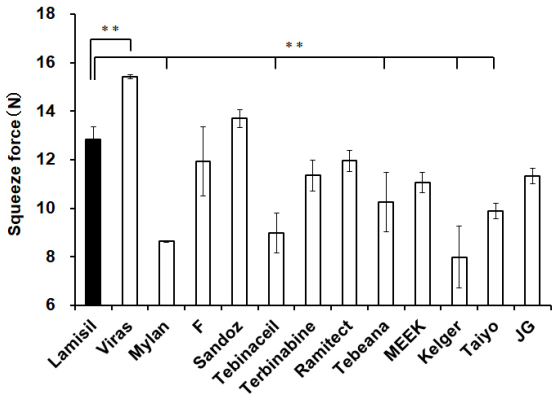

Figure 5. Squeeze force measurement of various cream preparations (n = 3). $^{**}p < 0.01$ (*vs*. Lamisil, *Dunnett*-test). ■: brand-name, □: generic.

lower than that of Lamisil, and the values of Mylan (3.33), Sandoz (3.29), and Taiyo (3.28) were higher than that of Lamisil.

The yield value is known as an index of cream ductility. As shown in Figure 4, the yield value of Lamisil was 122.2 dyn/cm^2, whereas the values of the generic products ranged from 42.1 to 1,621.0 dyn/cm^2. In particular, the value of a generic product, Taiyo (42.1 dyn/cm^2), was significantly lower, and that of Viras (1,621.0 dyn/cm^2) was significantly higher.

3.3. *Measurement of the squeeze force*

The squeeze force is expressed as a force required to push out a dose of each preparation. We measured the squeeze force by attaching a HapLog® to the right thumb and second finger, as shown in Figure 5. The squeeze force of Lamisil was 12.9 N, whereas the values of the generic products ranged from 8.0 to 15.4 N. In particular, the values of Mylan (8.6 N), Tebinaceil (9.0 N), and Kelger (8.0 N) were significantly lower, and that of Viras (15.4 N) was significantly higher.

4. Discussion

External preparations need to have adequate physiological/sensory properties, such as the sense of touch, ductility, color, and smell, in addition to pharmaceutical or pharmacological properties (*14*). As patients apply ointment or cream preparations to an affected site with their hands, low-ductility viscous preparations may be difficult to apply. A study suggested the necessity of improving a base, considering patients' availability or comfortableness (*15*).

For the use of an external preparation, a preparation with a pH similar to that of the skin surface should be selected. Non-stimulant preparations are recommended for affected sites. The pH of the epidermis is neutral, but that of the corneal layer is weakly acid. The pH of the skin surface ranges from 4.5 to 6.0 (*16*). Therefore, a pH of 4.5 to 6.0 may be optimal for external preparations, being similar to that of the skin surface. In particular, the use of an external preparation may deteriorate symptoms in sensitive-skin patients; a preparation with a pH similar to that of the skin surface should be selected to reduce the risk.

Based on the results of this experiment, the pH values of the generic products ranged from 4.3 to 5.5. Product F showed a slightly lower value (4.3), but the values of the other products were within the pH range of healthy skin (4.5 to 6.0). Therefore, there may have been no influence on the skin (Figure 1).

With respect to the ductility of various cream preparations, a semilog graph was prepared using a spread meter by plotting the spread diameter (cm) of each preparation on a longitudinal axis and the time (seconds) on a transverse axis. The linear expression of a logarithmic trendline for the plot was induced. The slope of this linear expression for Lamisil was 0.24, and the y-intercept was 3.05. Regarding these values as criteria, preparations with a greater slope can be evaluated as more ductile, and those with a higher y-intercept as less viscous (Figures 2 and 3). Initially, the ductility of a generic product (Taiyo) with a slope of 0.36, which was a maximum, was considered to be favorable, whereas that of Viras, with a slope of 0.02, which was a minimum, was considered to be unfavorable (Figure 2). On the other hand, generic products of which the y-intercept values were relatively high, Mylan (3.33), Sandoz (3.29), and Taiyo (3.28), were considered to be less viscous. These products may be spread with a weak force. Furthermore, the y-intercept value of Viras (2.55) was significantly lower; this preparation may be very viscous, requiring a strong force for spreading (Figure 3).

The yield value refers to a stress limiting the deformation/floating of semisolid substances, such as cream and ointment preparations; therefore, it is used as an index of easiness to apply. Preparations with a lower yield value may be more easily applied. A generic product of which the yield value was high (1,621.0 dyn/cm^2), Viras, was considered to be difficult to apply. The yield value of Taiyo (42.1 dyn/cm^2) was approximately 1/39 of that of Viras; therefore, Taiyo may be spread with a weak force (Figure 4). These results suggest that the sense of use markedly differs among the preparations.

The squeeze force of each cream preparation was measured using a HapLog®. A dose of most products, excluding Viras (15.4 N) and Sandoz (13.7 N), could be squeezed with a force similar to or weaker than that required for squeezing Lamisil (12.9 N). This may have been related to the rigidity of the container (Figure 5). Using a HapLog®, we detected the intensity of forces on fingers in contact with the container, and successfully assessed the sensor-wearing person's finger contact force while maintaining the free sense of touch at the fingertip (*13*).

Based on the results of this study, it may be important

for pharmacists to understand the pharmaceutical properties of many generic products in comparison with a brand-name drug in order to meet various patient needs. Considering the physicochemical properties of each preparation, an adequate drug must be selected in accordance with individual patients' skin conditions.

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References

1. 2012 national health care costs overview. Ministry of Health, Labor and Welfare, *http://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/12/dl/data.pdf* (accessed December 25, 2017). (in Japanese)
2. Promotion of use of generic drugs (generic drugs). Ministry of Health, Labor and Welfare, *http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryou/kouhatu-iyaku/* (accessed December 25, 2017). (in Japanese)
3. Wada Y, Nozawa M, Goto M, Shimokawa K, Ishii F. Generic selection criteria for safety and patient benefit [I] Comparing the original drugs and generic ones in pharmaceutical properties. J Comm Pharm Sci. 2014; 6:97-105. (in Japanese)
4. Nozawa M, Wada Y, Yamazaki N, Shimokawa K, Ishii F. Generic selection criteria for safety and patient benefit [II] Physicochemical characteristics of original and generic drugs for three different difluprednate-containing preparations (ointment, cream, and lotion). J Jpn Soc Comm Pharm. 2014; 2:37-48. (in Japanese)
5. Wada Y, Nozawa M, Goto M, Shimokawa K, Ishii F. Generic selection criteria for safety and patient benefit [III] Comparing the pharmaceutical properties and patient usability of original and generic ophthalmic solutions containing timolol maleate. J Jpn Soc Pharm Health Sci. 2015; 41:394-403. (in Japanese)
6. Wada Y, Ami S, Nozawa M, Goto M, Shimokawa K, Ishii F. Generic selection criteria for safety and patient benefit [V]: Comparing the pharmaceutical properties and patient usability of original and generic nasal spray containing ketotifen fumarate. Drug Discov Ther. 2016; 10:88-92.
7. Wada Y, Kihara M, Nozawa M, Shimokawa K, Ishii F. Generic selection criteria for safety and patient benefit [IV] Physicochemical and pharmaceutical properties of brand-name and generic ketoprofen tapes. Drug Discov Ther. 2015; 9:229-233.
8. Wada Y, Takaoka Y, Nozawa M, Goto M, Shimokawa K, Ishii F. Generic selection criteria for safety and patient benefit [VI]: Comparing the physicochemical and pharmaceutical properties of brand-name, generic, and OTC felbinac tapes. Drug Discov Ther. 2016; 10:300-306.
9. Watanabe K, Nakamura S, Shimamoto T, Uramatsu S, Kishi K, Uemura T, Shinike H. Preparation and evaluation of new metronidazole gel using hydroxypropyl methylcellulose. Jpn J Pharm Palliat Care Sci. 2009; 2:39-43. (in Japanese)
10. Yoshida M. Extensibility of beesoften oil cream at various temperatures of 0.3%. Jpn J Med Pharm Sci. 2014; 71:449-454. (in Japanese)
11. Komoda M, Akakuma S, Obara S, Koto A, Aono H, Kurahashi Y, Sugiyama N, Ishi N, Noda Y. Basic examination of bicarbonate sugar ointment neutralized reaction of leakage from gastrostomy fistula. Jpn Soc Par Ent Nutr. 2013; 28:819-825. (in Japanese)
12. Haptic Skill Logger, Kato Tech Co., Ltd. *http://english.keskato.co.jp/* (accessed December 25, 2017).
13. Nakatani M, Kawasoe T. Haptic Skill Logger (HapLog): The wearable sensor for evaluating haptic behaviors. J Robot Soc Jpn. 2012; 30:499-501. (in Japanese)
14. Shibata Y, Ikeda H, Kondou Y, Kihara K. Comparison of pharmaceutical properties of topical non-steroidal anti-inflammatory drug preparations on quality of life. Yakugaku Zasshi. 2005; 125:397-404. (in Japanese)
15. Nishizawa S, Yamaoka K, Yamaoka H, Yoshimura K, Hirabayashi S. Basic pharmaceutical research on formulation of kojic acid ointment for hospitals: *in vitro* releace test and evaluation of permeability. Jpn J Pharm Health Care Sci. 2004; 30:20-26. (in Japanese)
16. Mizoguchi M, Ohara K, Aiba Y, Takado T, Hino H, Matsunaga K, Watanabe S. The pH of the skin. In: Encyclopedia of skin. Asakura Bookstore, Tokyo, 2008; pp. 24. (in Japanese)

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