

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

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Summary The pH, osmotic pressure (cryoscopy), viscosity, squeeze force, spray angle, and spraying frequency of nasal spray containing ketotifen fumarate (1 brand-name product and 8 generic products) were measured. Based on the results of pH measurement, all products were weakly acidic (4.0 to 5.1). For all products, the osmotic pressure ratio to physiological saline was approximately 1. The viscosity of various products ranged from approximately 1.0 to 1.5 mPa·s. The spray angle of drug solution differed among the products: minimum, 46 degrees (Sawai and Fusachol); and maximum, 68.7 degrees (Sekiton). In particular, TOA, Sawai, Fusachol, and TYK showed significantly smaller angles compared to Zaditen (brand-name product). Container properties varied among the products: minimum squeeze force, 19.0 N (Sekiton); and maximum squeeze force, 43.1 N (Sawai). Based on these results, although all the above products are identical in dosage form and active ingredient, the differences in pharmaceutical properties, such as container operations and drug-solution spraying/attachment, may markedly influence patients' subjective opinions.

Keywords: Brand-name product, generic products, pharmaceutical properties, ketotifen fumarate, nasal spray

1. Introduction

In Japan, health expenditures have rapidly increased with the aging of society. Since the establishment of the Medical System for the Elderly in 2006, the budget deficits of health insurance societies have exceeded 300 billion yen (6 consecutive years) (1). As a strategy to efficiently improve the public finance of pharmaceutical insurance, the widespread use of generic products has been emphasized, and official name-based prescriptions have been promoted under the government's policy so that pharmacists may recommend and deliver generic products (2). In this prescription system, the selection of generic products depends on pharmacists' evaluation. Therefore, pharmacists must select safe, equivalent

generic products from a pharmaceutical point of view, and explain them to patients.

In March 2015, the National Federation of Health Insurance Societies published the results of a survey regarding health insurance societies' health expenditure in 2013, in which the contents of the total health expenditure of 609 societies (1,456.4 billion yen) were investigated (3). According to this report, health expenditure for respiratory diseases accounted for 15.43%, and was the highest percentage among 19 disease categories. In particular, health expenditure for allergic rhinitis accounted for 2.93%, the second highest percentage, following that for asthma (3.07%). Furthermore, the number of patients with a type of seasonal allergic rhinitis, hay fever, is still increasing.

In the "Practical Guideline for the Management of Allergic Rhinitis in Japan" (4), a second-generation antihistaminic drug, ketotifen fumarate, is recommended as a first-choice drug for mild, rhinorrhea-type moderate, or severe allergic rhinitis. It exhibits antihistaminic actions (5) by suppressing

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Table 1. Various products used in this experiment

Product name	Abbreviated name	Class	Company	Price (¥)/bottle	Serial number
Zaditen [®] nasal solution 0.05%	Zaditen	brand-name	Novartis Pharma K. K.	781.1	375
Electer [®] nasal solution 0.05%	Electer	generic	Mylan Seiyaku Ltd.	442.6	M001AU3
Ketotifen nasal solution 0.05% "TOA"	TOA	generic	Toa Pharmaceutical Co., LTD.	442.6	S01SF
Sekiton [®] nasal solution 0.05%	Sekiton	generic	Kyorin Rimedio Co., Ltd.	341.1	18KA
Ketotifen nasal solution 0.05% "CH"	CH	generic	Choseido Pharmaceutical Co., Ltd.	341.1	WK031
Supdel [®] nasal solution 0.05%	Supdel	generic	Towa Pharmaceutical Co., Ltd.	341.1	A015
Ketotifen nasal solution 0.05% "Sawai"	Sawai	generic	Sawai Pharmaceutical Co., Ltd.	341.1	12108
Fusachol [®] nasal solution 0.05%	Fusachol	generic	Nitto Medic Co., Ltd.	341.1	11601
Ketotifen nasal solution 0.05% "TYK"	TYK	generic	Taisho Pharm. Ind., Ltd	341.1	WJ01

the release of chemical mediators (6), reducing the hypersensitivity of the nasal mucosa (antiallergic actions) (7).

In Japan, capsules, syrup, nasal drops, and eye drops have been approved as the dosage forms of ketotifen fumarate. In the package inserts of a brand-name product, Zaditen, it is described that patients with allergic rhinitis who responded to capsules and nasal drops accounted for 59.0% (138/234) and 60.1% (184/306), respectively; the percentages were similar. However, the incidences of an adverse reaction of the central nervous system, sleepiness, were 4.4 and 1.0%, respectively. Nasal drops have the merit of reducing adverse reactions. On the other hand, such drops are characterized by differences in availability, such as the availability of spraying containers or intranasal sensation on drug-solution attachment, among products from different manufacturers, differing from oral formulations, such as capsules. This leads to switching of a generic product to the brand-name product in some cases. In others, switching of the brand-name product to a generic product improves availability, increasing the degree of satisfaction (8). The patient-based selection of formulations may facilitate the use/promotion of generic products, improving the comfortableness, degree of satisfaction, and adherence, and leading to favorable treatment responses.

We previously reported the physical properties of various formulations with respect to brand-name and generic products (9-12). However, few studies have compared the pharmaceutical properties of various formulations, including brand-name and generic products. In this study, the pharmaceutical properties of brand-name and generic products of nasal sprays containing ketotifen fumarate were investigated to provide information to patients and health-care professionals.

2. Materials and Methods

2.1. Materials

Ethical pharmaceuticals of nasal sprays containing ketotifen fumarate (1 brand-name and 8 generic products) were used in this study. The names, manufacturers, sales

agencies, prices, and lot numbers of these products are presented in Table 1.

2.2. Measurement of pH

The fluid content pH of each nasal-spray preparation was measured using a Benchtop pH meter F-74 (HORIBA, Ltd., Kyoto, Japan). Measurement was performed 3 times at $25 \pm 5^\circ\text{C}$, and the mean \pm standard deviation (S.D.) was calculated.

2.3. Measurement of osmotic pressure

The fluid content osmotic pressure of each nasal-spray preparation was measured using cryoscopy with an OSMOMAT device (030-D, Gonotec GmbH, Berlin, Germany). The osmotic pressure ratio to physiological saline was calculated. Measurement was performed 3 times, and the mean \pm S.D. was calculated.

2.4. Measurement of viscosity

The viscosity of the fluid content of each nasal-spray preparation was measured using a cone-plate-type rotary viscometer (TPE-100, Toki Sangyo Co., Ltd., Tokyo, Japan) at 100 rpm at 3 different temperatures (20, 25, and 35°C). Measurement was performed 3 times, and the mean \pm S.D. was calculated.

2.5. Measurement of power on the finger required for a mist

Using a ZTS-50N digital force gauge (Imada Co., Ltd., Aichi, Japan), each nasal-spray preparation was covered with a test tube, set in a stand, and pressed from the upper side for measurement. Measurement was performed 10 times, and the mean \pm S.D. was calculated.

2.6. Measurement of the mist angle

Video filming of the mist angle of each nasal-spray preparation was performed from the side, and the angle was measured using a protractor. Measurement was performed 3 times, and the mean \pm S.D. was calculated.

2.7. Measurement of the number of mists

The number of mists from each preparation was measured at room temperature. The values (%) represent the number of effective mists as a percentage of the total number of mists. The total number of mists was defined as that until the residual drug solution volume became zero. Based on the results of measurement, the number of effective mists was defined as the number of mists until the slope of a graph for the standard deviation increased. Measurement was performed 3 times, and the results are expressed as the mean \pm S.D.

2.8. Investigation of ingredient composition

We investigated the composition of ingredients using the package inserts and interview form for each sample.

3. Results and Discussion

3.1. Measurement of pH

The nasal mucosal pH is reportedly approximately 5.5 to 6.5 in healthy adults and approximately 7.2 to 8.3 in those with rhinitis (13). On the other hand, a study reported that when buffer solution was sprayed into the nasal cavity, the nasal mucosal pH changed through the effects of the buffer solution (14). We measured the pH of each preparation. The results are shown in Figure 1.

As shown in Figure 1, all preparations were weakly acidic: pH range, 4.0 (TYK) to 5.1 (Electer). This was possibly because the pH was established, considering the stability of each preparation, based on the finding that the water solubility of ketotifen fumarate is higher at a lower pH (15). According to a study, pollen rupture, which is the process of allergen release from pollen, may occur in an alkaline state (16). Low-pH preparations may adjust the nasal cavity, which tends to become weakly alkaline, to a weakly acid state.

In the package inserts, it is described that the standard pH values of preparations other than Electer range from 3.8 to 4.6, whereas that of Electer ranges from 4.9 to 5.5. It was reported that the partition coefficient of ketotifen was greater at a higher solution pH (17). The absorption of high-pH preparations through the nasal mucosa may be promoted with a higher molecule-type percentage of ketotifen in comparison with low-pH preparations.

3.2. Measurement of osmotic pressure

With respect to the osmotic pressure of nasal spray, a study using rabbits indicated that the hypotonic adjustment of preparations improved drug permeability (18). On the other hand, according to a survey using guinea pigs, the infusion of low-osmotic-pressure liquid, such as tap water, led to marked enlargement of the intercellular space of the nasal mucosa (19).

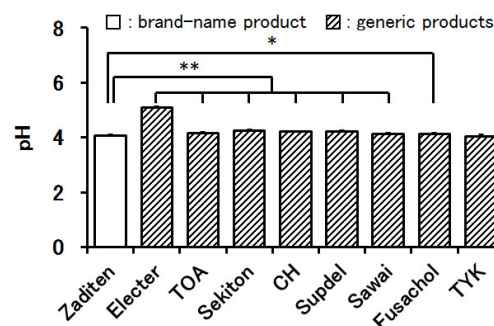


Figure 1. pH comparison of various products ($n = 3$). $*p < 0.05$, $p < 0.01$ (brand-name vs. generics, *Dunnnett's test*).**



Figure 2. Osmolarity comparison of the various products ($n = 3$). The ratio of osmotic pressure to isotonic saline containing 0.9% NaCl. $p < 0.01$ (brand-name vs. generics, *Dunnnett's test*).**

Furthermore, a study regarding the influence of the osmotic pressure of nebulizer solution on the human nasal mucosa reported that the administration of hypertonic salt solution significantly increased the volume of nasal discharge (20).

To examine the influence of the osmotic pressure of preparations on the nasal mucosa, nasal discharge, and drug permeability, the osmotic pressure was measured. The osmotic pressure ratio of each sample is shown in Figure 2.

As presented in Figure 2, all preparations showed an osmotic pressure ratio of approximately 1. It was possibly established to reduce the influence of stimuli on the mucosa. Furthermore, these preparations may have been designed to avoid hypertonic solution-related nasal discharge.

3.3. Measurement of viscosity

The viscosity of drug solution may influence its retention at the affected site or dripping. We measured the viscosity of each preparation. The results are shown in Figure 3. Concerning temperatures of measurement, 20 and 25°C were established as room temperature, and 35°C as intranasal temperature.

As presented in Figure 3, the viscosity of each preparation ranged from approximately 1.0 to 1.5 mPa·s. After spraying, more viscous preparations may

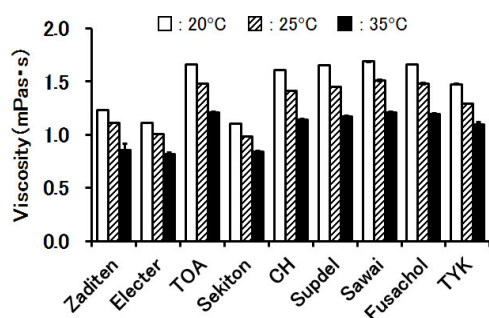


Figure 3. Viscosity comparison of the various products ($n = 3$).

be retained at the affected site without dripping in comparison with less viscous preparations.

3.4. Measurement of the spray angle of drug solution

The spray angle of drug solution may contribute to the retention of drug solution at the affected site and dripping. We measured the spray angle of drug solution for each preparation. The results are shown in Figure 4.

The spray angle of drug solution differed among the preparations: 46 (Sawai and Fusachol) to 68.7 degrees (Sekiton). In particular, the spray angles of TOA, Sawai, Fusachol, and TYK were significantly smaller than that of the brand-name product (Zaditen), suggesting that sprayed drug solution reaches the deep area of the nasal cavity, reducing the volume of drug solution directly attached to the lateral side of the nasal cavity. This also reflects that there is no dripping after spraying, whereas the effects on symptoms of the lateral side, onto which drug solution is not readily attached, are reduced.

3.5. Measurement of the force required for spraying

Container-operating properties on spraying contribute to availability for patients. They may influence adherence. We measured the finger force required for spraying, that is, the squeeze force for each sample container. The results are shown in Figure 5.

The container properties varied among the preparations: 19.0 (Sekiton) to 43.1 N (Sawai). Preparations that can be sprayed using a relatively light force may be appropriate for children, females, elderly persons, and hand-disabled persons, whose finger forces are weak. When switching from the brand-name product to a generic product, patients may feel difficulty in spraying, if the force required for spraying is greater than that for the brand-name product; caution is needed.

These results showed that there were differences in the pharmaceutical properties among the products. Although the efficacy of each product may be similar, the differences in pharmaceutical properties, such as container-operating properties and drug-solution spraying/attachment, may markedly influence

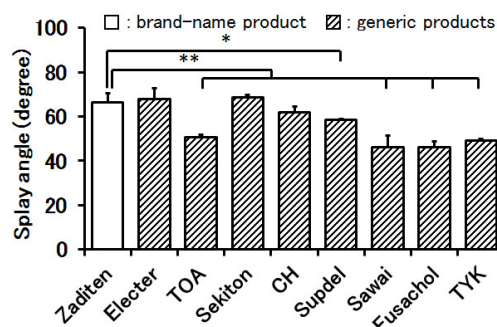


Figure 4. Comparison of spray angle of the various products ($n = 3$). $*p < 0.05$, $**p < 0.01$ (brand-name vs. generics, Dunnett's test).

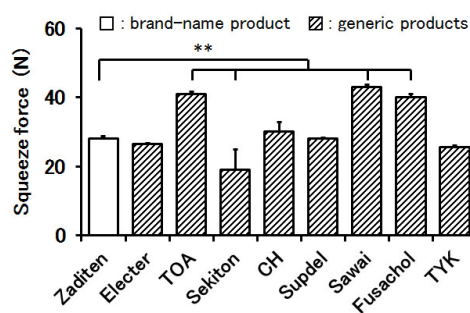


Figure 5. Comparison of squeeze force requirement of the various products ($n = 3$). $**p < 0.01$ (brand-name vs. generics, Dunnett's test).

availability for patients. As TYK contains peppermint oil, its scent-related freshness may be obtained on spraying, but some persons may dislike it. Pharmacists may play an important role in the selection of nasal spray, as an external preparation, for which usability may contribute to adherence, in accordance with individual patients' needs.

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References

- 2014 Coercive union budget early aggregate result summary, National Federation of Health Insurance Societies, April 18, 2014. <http://nakyblog.cocolog-nifty.com/blog/2014/04/26-514e.html> (accessed April 9, 2016). (in Japanese)
- 2012 Ministry of health, labour and welfare notification No. 76. Partial revision of the calculation method of medical treatment fees (Notification). http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryuu/iryuhoken/iryuhoken15/index.html (accessed April 9, 2016). (in Japanese)
- National Federation of Health Insurance Societies IT Promotion Department data analysis Promotion Group, Research and analysis report on trends in the 2013 fiscal health insurance medical expenses, p23 (2015) http://www.kenporen.com/study/toukei_data/pdf/chosa_h27_3.

- pdf* (accessed April 9, 2016). (in Japanese)
4. Okubo K. Practical guideline for the management of allergic rhinitis in Japan. *Jpn Soc Allergol.* 2013; 62:1458-1463. (in Japanese)
 5. Ney UM, Bretz U, Martin U, Mazzoni L. Pharmacology of ketotifen. *Res Clin Forums.* 1982; 4:9-16.
 6. Martin U, Römer D. The pharmacological properties of a new, orally active anti-anaphylactic compound: Ketotifen, a benzocycloheptathiophene. *Arzneim Forsch.* 1978; 28:770-782.
 7. Usui N, Iwata A, Uchiyama M, Tsukasa M. Study of inhibitory effect of Ketotifen (HC 20-511) for the nasal provocation test by house dust antigen. *JIBI INKOKA TEMBO.* 1984; 27(Suppl 1):107-114. (in Japanese)
 8. Kakuyama A, Tamaki T, Iizuka T, Ariumi H, Miyazaki T, Kido M, Kumai M, Noda T, Ohodo S, Yoshiyama Y. Database of value added generic drugs. *JIBI INKOKA TEMBO.* 2010; 53(Suppl 2):85-89. (in Japanese)
 9. 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 Community Pharm Pharm Sci.* 2014; 6:97-105. (in Japanese)
 10. Nozawa M, Wada Y, Yamazaki N, Shimokawa K, Ishii F. Generic selection criteria for safety and patient benefit [II] Physicochemical characteristics of original versus generic drugs for different difluprednate-containing products (ointment, cream, and lotion). *Jpn Soc Community Pharm Pharm.* 2014; 2:37-48. (in Japanese)
 11. 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. *Jpn Soc Pharm Health Care Sci.* 2015; 41:394-403. (in Japanese)
 12. 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 types. *Drug Discov Ther.* 2015; 9:229-233.
 13. England RJ, Homer JJ, Knight LC, Ell SR. Nasal pH measurement: A reliable and repeatable parameter. *Clin Otolaryngol Allied Sci.* 1999; 24:67-68.
 14. Washington N, Steele RJC, Jackson SJ, Bush D, Mason J, Gill DA, Pitt K, Rawlins DA. Determination of baseline human nasal pH and the effect of intranasally administered buffers. *Int J Pharm.* 2000; 198:139-146.
 15. Abd El-Bary AA, Salem HF, Kharshoum RM. 2-Hydroxypropyl- β -cyclodextrin complex with ketotifen fumarate for eye drops preparations. *Int J Drug Delivery.* 2011; 3:228-240.
 16. Nohara O. The effect of nasal fluid on the release of major allergens from Japanese cedar (*Cryptomeria japonica*) pollens. *JIBI INKOKA TEMBO.* 1996; 39:483-495. (in Japanese)
 17. Kimura C, Tojo K. Development of a stick-type transdermal eyelid delivery system of ketotifen fumarate for ophthalmic diseases. *Chem Pharm Bull.* 2007; 55:1002-1005.
 18. Nishibe Y, Nagano A, Uejima Y. Nasal suspensions with low osmolality and drug permeability. *JIBI INKOKA TEMBO.* 2002; 45(Supplement 1):46-49. (in Japanese)
 19. Odaira H, Koike S, Takasaka T, Sawai T. Influence of various solutions injected into the nasal cavity on nasal epithelium. *Nippon Jibiinkoka Gakkai Kaiho* 1987; 90:1951-1962. (in Japanese)
 20. Komori M, Miwa M, Mamiya T, Kondo Y, Miyagishima T, Takasu A, Iwata S. Effects of osmolality changes in nebulizer solutions on nasal mucosa. *JIBI INKOKA TEMBO.* 1999; 42(Supplement 2):181-185. (in Japanese)
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