Generic selection criteria for safety and patient benefit [VIII]: Comparing the physicochemical and pharmaceutical properties of brand-name and generic diclofenac sodium tapes

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Summary
With respect to diclofenac sodium-containing tape preparations of nonsteroidal antiphlogistic drug, we compared the pharmaceutical properties (pH, elongatedness, water-vapor permeability, adhesive force, and peeling-force) of 11 medicinal drugs (2 brand-name and 9 generic drugs) to obtain evidence for product selection in line with the needs of the patient. The elongatedness of the generic drugs Teikoku (1.39), Yutoku (1.40), and Nippon-zoki (1.43) were significantly higher than the brand-name drug Voltaren® (1.22). The adhesive force was measured using the probe tack test and the inclined ball tack test. The probe tack test results of Naboal® (6.8 N/cm²), Teikoku (6.1 N/cm²), Yutoku (5.9 N/cm²), Nippon-zoki (6.2 N/cm²), and Rakool (6.2 N/cm²) were higher than that of Voltaren (2.0 N/cm²). The inclined ball tack test results of Naboal (18.0), Teikoku (24.0), Yutoku (21.5), and Nippon-zoki (22.7) were also higher than that of Voltaren (7.2). Concerning peeling-force measurement, the 90° peeling-forces of Naboal (0.95 N), Teikoku (0.96 N), Yutoku (0.94 N), and Nippon-zoki (1.01 N) were higher than that of Voltaren (0.68 N). These results show that there were marked differences in the feeling of use of each product between the brand-name and generic drugs. The pharmacist indicates the basis for selection of a preparation according to the feeling of use desired by each patient. It has become possible to recommend products suitable for each patient, which will allow pharmacists to provide products according to the needs of each patient when a brand-name drug is changed to a generic one.

Keywords: Transdermal therapeutic drug, brand-name drug, generic drug, diclofenac sodium tape

1. Introduction

It is estimated that the medical care expense for citizens in Japan will be 52.3 trillion yen in 2025 from 34.8 trillion yen in 2008, among which the medical expenses of the late-stage medical care system for the elderly will increase from 11.4 trillion yen to 24.1 trillion yen (1). As a solution to this problem, the use of generic drugs containing the same principal ingredients as brand-name drugs is recommended. However, the brand-name and generic drugs differ in the manufacturing processes and additives (2), and their use has not progressed as a result of external appearance, feeling of use, and safety being not the same as brand-name drugs. Especially, the patient finds it easy to feel a difference in the feeling of use of a patch, and many cases have been reported cases in which patients complain of differences in the feeling of use when a brand-name drug is changed to a generic drug (3).

Diclofenac sodium tape is a nonsteroidal anti-inflammatory drugs (NSAIDs) discovered in 1965, and it is widely known that it shows strong anti-inflammatory and analgesic effects. It has gained a high reputation for many years. In Japan, "Voltaren" tape (4)
and “Naboal® tape” as patches were launched in 2004 as brand-name drugs.

In this study, we conducted a comparative evaluation of the brand-name and generic drugs of diclofenac sodium tape, and conducted research aimed at providing information that could be the basis for drug selection at the pharmacy. In addition, among the two types of the brand-name drugs, “Voltaren® tape” with many clinical research reports was compared with other patches (5).

2. Materials and Methods

2.1. Materials

As diclofenac sodium tape (7 cm × 10 cm), brand-name drugs, Voltaren® tape 15 mg (Dojin Iyaku-kako Co., Ltd., Tokyo, Japan) and Naboal® tape 15 mg (Hisamitsu Pharmaceutical Co., Inc., Tokyo, Japan), and generic drugs, diclofenac sodium tape 15 mg “Teikoku” (Teikoku Seiyaku Co., Ltd., Kagawa, Japan), diclofenac sodium tape 15 mg “Yutoku” (Yutoku Pharmaceutical Ind. Co., Ltd., Saga, Japan), diclofenac sodium tape 15 mg "Sanwa" (Sanwa Kagaku Kenkyusho Co., Ltd., Aichi, Japan), diclofenac sodium tape 15 mg "NP" (Nipro Pharma Co., Ltd., Osaka, Japan), diclofenac sodium tape 15 mg "JG" (Nihon Generic Co., Inc., Tokyo, Japan), diclofenac sodium tape 15 mg "Nippon-zoki" (Nippon Zoki Pharmaceutical Co., Ltd., Osaka, Japan), diclofenac sodium tape 15 mg "Nichi-Iko" (Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan), diclofenac sodium tape 15 mg "Towa" (Towa Pharmaceutical Co., Ltd., Osaka, Japan), and diclofenac sodium tape 15 mg "Rakool", (Mitomo Yakuhin Co., Ltd., Tokyo, Japan), were purchased and used in this experiment (Table 1). All the other reagents were of analytical grade.

Table 1 shows the product name, abbreviated name, classification, company name, and lot number of the diclofenac sodium tape used in this study. Lot numbers A and B were set according to the time when the test was carried out.

2.2. Measurement of pH

We measured pH values, as described by Wada et al. (6,7). Briefly, each preparation was cut into sections measuring 20 × 30 mm, placed in sample bottles containing 20 mL of purified water, and agitated for 185 rpm × 24 h. Subsequently, the pH of the solution was measured using a Benchtop pH meter F-74 and ISFET pH electrode 0040-10 D (HORIBA, Ltd., Kyoto, Japan). For each product, measurement was conducted 6 times at 24 ± 2°C, and the mean was adopted as its pH value.

2.3. Measurement of the elongatedness

An elongatedness test was performed, as described by Wada et al. (7). The end (70 mm) of a section of each product measuring 70 × 100 mm was fixed on an experimental table with the adhesive surface. A weight (300 g) was suspended on the other short side, and the length (mm) of the preparation after 10 seconds was measured. The elongatedness was calculated from the values before and after. For each product, a measurement was conducted 6 times, and the mean was regarded as the elongatedness. The elongatedness of change in elongation was calculated by the following formula: elongatedness \( E = L/L_0 \) [\( L_0 \): Length (mm) after 10 seconds, \( L \): Length before test (mm)]

2.4. Measurement of water-vapor permeability

The water-vapor permeability test was performed, as described by Sugino et al. (8). Briefly, 10 mL of purified water was placed in an Erlenmeyer flask, and its opening was covered with a round section of each product measuring 20 mm in diameter. After the weight was measured, each sample was allowed to stand for 24 hours in an environment chamber KCL-2000W (Tokyo Rikakikai Co., Ltd., Tokyo, Japan) under the following conditions: temperature, 25°C; relative humidity, 55%. Additionally, the weight was measured. As a control, the weight of the Erlenmeyer flask containing purified water

Table 1. Tape products used in this experiment

<table>
<thead>
<tr>
<th>Product name</th>
<th>Abbreviated name</th>
<th>Class</th>
<th>Company name</th>
<th>Lot number A</th>
<th>Lot number B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltaren® Tape 15 mg</td>
<td>Voltaren</td>
<td>BN</td>
<td>Dojin Iyaku-kako Co., Ltd.</td>
<td>40420</td>
<td>170190</td>
</tr>
<tr>
<td>Naboal® Tape 15 mg</td>
<td>Naboal</td>
<td>BN</td>
<td>Hisamitsu Pharmaceutical Co., Inc.</td>
<td>50103</td>
<td>U201U</td>
</tr>
<tr>
<td>Diclofenac sodium tape 15 mg</td>
<td>&quot;Teikoku&quot;</td>
<td>GE</td>
<td>Teikoku Seiyaku Co., Ltd.</td>
<td>4J150</td>
<td>7H010</td>
</tr>
<tr>
<td>Diclofenac sodium tape 15 mg</td>
<td>&quot;Yutoku&quot;</td>
<td>GE</td>
<td>Yutoku Pharmaceutical Ind. Co., Ltd.</td>
<td>LM068</td>
<td>17R201</td>
</tr>
<tr>
<td>Diclofenac sodium tape 15 mg</td>
<td>&quot;Sanwa&quot;</td>
<td>GE</td>
<td>Sanwa Kagaku Kenkyusho Co., Ltd.</td>
<td>AH00601</td>
<td>AL00101</td>
</tr>
<tr>
<td>Diclofenac sodium tape 15 mg</td>
<td>&quot;NP&quot;</td>
<td>GE</td>
<td>Nipro Pharma Co., Ltd.</td>
<td>4J130</td>
<td>7H040</td>
</tr>
<tr>
<td>Diclofenac sodium tape 15 mg</td>
<td>&quot;JG&quot;</td>
<td>GE</td>
<td>Nihon Generic Co., Ltd.</td>
<td>407060</td>
<td>710170</td>
</tr>
<tr>
<td>Diclofenac sodium tape 15 mg</td>
<td>&quot;Nippon-zoki&quot;</td>
<td>GE</td>
<td>Nippon-zoki Pharmaceutical Co., Ltd.</td>
<td>IP0801</td>
<td>KD2101</td>
</tr>
<tr>
<td>Diclofenac sodium tape 15 mg</td>
<td>&quot;Nichi-Iko&quot;</td>
<td>GE</td>
<td>Nichi-Iko Pharm. Co., Ltd.</td>
<td>5C050</td>
<td>88040</td>
</tr>
<tr>
<td>Diclofenac sodium tape 15 mg</td>
<td>&quot;Towa&quot;</td>
<td>GE</td>
<td>Towa Pharmaceutical Co., Ltd.</td>
<td>AL00101</td>
<td>A0122</td>
</tr>
<tr>
<td>Diclofenac sodium tape 15 mg</td>
<td>&quot;Rakool&quot;</td>
<td>GE</td>
<td>Mitomo Yakuhin Co., Ltd.</td>
<td>A02XW</td>
<td>A02XW</td>
</tr>
</tbody>
</table>

BN: brand-name drug, GE: generic drug.
constant rate (5 mm/sec) so that the adhesive surface was peeled off to be 90° or 180° to a digital force gauge, ZP-20N (Imada Co., Ltd., Aichi, Japan), until the tape had been completely exfoliated from the stainless plate. With respect to each product, measurement was conducted 6 times, and the mean was regarded as the peeling-force.

2.6.2. 90° peel test using EVA (Ethylene-vinyl acetate) membrane

The peeling-force was measured according to the Japanese Pharmacopoeia 17th Edition (9). According to the method of 2.6.1, after attaching the EVA membrane to the stainless plate, each product was further stuck thereon, and was performed 6 times for each patch. Incidentally, the peel test was measured 6 times for each patch 24 hours after attaching (24 h) and 24 hours after attachment in tepid water (40°C) for 30 minutes (24 h + tepid water).

2.7. Statistical analysis

For each experimental result, the values were compared using Dunnett’s test, Tukey-Kramer-test and Bonferroni/Dunn-test of the multiple comparison test or Pearson’s correlation coefficient test (10). A \( p \)-value of 0.05 (marked with *) or 0.01 (marked with **) was regarded as significant in the figure.

3. Results

3.1. Measurement of pH

The pH is an important factor reflecting the stability of the active component in each preparation or skin irritability. The results of pH measurements for each product are shown in Figure 1. There were marked differences in pH among the brand-name and generic products. The pH values of a brand-name drug Naboal (pH 5.2), generic drugs Sanwa (pH 5.2), NP (pH 5.1),

![Figure 1. pH measurement of various preparations (Lot #A) (n = 6). **p < 0.01 (vs. Voltaren, Dunnett-test).](image-url)
JG (pH 5.0), Nichi-Iko (pH 5.3) and Towa (pH 5.2) were similar to that of a brand-name drug Voltaren (pH 5.2). On the other hand, the pH values of the generic drugs Teikoku (pH 6.3), Yutoku (pH 6.1), Nippon-zoki (pH 6.0) and Rakool (pH 6.0) were significantly higher than the brand-name drug Voltaren (pH 5.2). Significance tests of these drugs were conducted. There were significant differences between Teikoku, Yutoku, Nippon-zoki, and Rakool ($p < 0.01$) (Figure 1).

3.2. Measurement of elongatedness

In many products, a stretchy material is used for the support layer to prevent turning-up or peeling after attachment to articular regions such as the knees and elbows. The results of elongatedness measurement are shown in Figure 2. The elongatedness of the generic drugs Teikoku (1.39), Yutoku (1.40), and Nippon-zoki (1.43) were significantly higher than the brand-name drug Voltaren (1.2). On the other hand, the elongatedness of a brand-name drug Naboal (1.22), generic drugs Sanwa (1.20), NP (1.20), JG (1.23), Nichi-Iko (1.19), Towa (1.24) and Rakool (1.26) were similar to that of a brand-name drug Voltaren (1.22). In addition, there were significant differences between Teikoku, Yutoku, Nippon-zoki, and Rakool ($p < 0.01$) (Figure 2).

3.3. Measurement of water-vapor permeability

The water-vapor permeability of each preparation may induce maceration stimuli when the skin water permeability is low on attachment. We measured the water-vapor permeability of each product. The results are shown in Figure 3. There were marked differences in the water-vapor permeability among the products; the water-vapor permeabilities of a brand-name drug Naboal (1.63%), generic drugs Sanwa (1.74%), NP (1.61%), JG (1.65%), Nichi-Iko (2.45%) and Towa (1.82%) were higher than the brand-name drug Voltaren (0.92%). On the other hand, Yutoku (0.42%), Nippon-zoki (0.67%) and Rakool (0.39%) were lower than that of Voltaren (0.92%).

3.4. Measurement of adhesive force

3.4.1. Probe tack testing

Preparations with a strong adhesive force may not peel off when attached to the skin, whereas those with a weak adhesive force tend to peel off. We measured the adhesive force of each product. The results (bar graph) of the probe tack testing of each product are shown in Figure 4. There were marked differences in the adhesive force among the products; the adhesive forces of the brand-name drug Naboal (6.8 N/cm$^2$) and the generic drugs Teikoku (6.1 N/cm$^2$), Yutoku (5.9 N/cm$^2$), Nippon-zoki (6.2 N/cm$^2$), and Rakool (6.2 N/cm$^2$) were higher than that of Voltaren (2.0 N/cm$^2$). In addition, the results showed significant differences between all products and Voltaren ($p < 0.01$) (Figure 4).

3.4.2. Inclined ball tack testing

The results (line graph) of the inclined ball tack testing...
of each product are shown in Figure 4. There were marked differences in the adhesive force among the products; the adhesive forces of the brand-name drug Naboal (18.0) and the generic drugs Teikoku (24.0), Yutoku (21.5), and Nippon-zoki (22.7) were higher than that of Voltaren (7.2). The numbers in parentheses for each of the above products indicate average ball number value. In addition, the results showed significant differences between all products \( p < 0.01 \) (Figure 4).

### 3.5. Measurement of peel force

#### 3.5.1. Measurement of 90° and 180° peel force

The peeling-force refers to a force required to peel off the preparation after attachment. We measured the 90° and 180° peeling-force of each product. The results are shown in Figure 5. The 90° peeling-forces of Naboal (0.95 N), Teikoku (0.96 N), Yutoku (0.94 N), and Nippon-zoki (1.01 N) were higher than that of Voltaren (0.68 N), whereas those of Rakool (0.58 N) was lower than that of Voltaren. Similarly, the 180° peeling-forces of Naboal (0.72 N), Teikoku (1.11 N), Yutoku (1.16 N), and Nippon-zoki (1.07 N) were higher than that of Voltaren (0.33 N). In addition, significance tests of various preparations were conducted. The brand-name drug Naboal and generic drugs Teikoku, Yutoku, and Nippon-zoki showed significant differences in comparison with Voltaren \( p < 0.01 \) (Figure 5, 90° peel force). All products showed significant differences in comparison with Voltaren \( p < 0.01 \) (Figure 5, 180° peel force).

#### 3.5.2. Measurement of 90° peel force using EVA membrane

The results of the 90° peel force using the EVA membrane of each product are shown in Figure 6. The peeling-forces of Teikoku (4.41 N), Yutoku (4.29 N), and Nippon-zoki (4.18 N) were higher than that of Voltaren (1.15 N). Teikoku, Yutoku, and Nippon-zoki showed significant differences in comparison with Voltaren \( p < 0.01 \). Similarly, the peeling-forces after 30 minutes in tepid water (40°C) of Yutoku (5.76 N) and Nippon-zoki (2.24 N) were higher than that of Voltaren (1.40 N). Yutoku and Nippon-zoki showed significant differences in comparison with Voltaren \( p < 0.01 \) (Figure 6).

In addition, in the case of 24 hours and 24 hours + tepid water (40°C), when compared with the values of Teikoku, Yutoku, and Nippon-zoki, the values of Yutoku increased to 1.47 N, but Teikoku and Nippon-zoki decreased to 2.68 N and 1.94 N, respectively. There were significant differences between Teikoku, Yutoku, and Nippon-zoki \( p < 0.01 \) (Figure 6).

### 4. Discussion

NSAIDs are widely used for the treatment of various disorders in expectation of analgesic/anti-inflammatory actions, but the incidence of adverse reactions has been reported to be higher in tape preparations compared with other dosage forms \( (11) \). Contact dermatitis is the most frequent adverse reaction, accounting for 80% of all adverse reactions. In elderly patients, who have thinner epidermis and are more sensitive to stimuli than younger patients, the incidence of adverse reactions is particularly high, and special attention to adverse reactions is required in using tape preparations.

Usually, the corneum is mildly acidic at a pH of 4.5 - 6.5 \( (12) \), and the use of a preparation with a pH that markedly deviates from this range may well induce skin irritation or skin trouble. As shown in Figure 1, the pH of all products was 5.0 - 6.3, and irritation of skin due to the pH is considered to be mild.

Elongatedness is considered to affect the feeling of use of adhesive skin patches when they are applied to flexible parts such as the knee and arm. As shown in Figure 2, Teikoku (1.39), Yutoku (1.40), and Nippon-zoki showed significant differences in comparison with Voltaren \( p < 0.01 \).
zoki (1.43), which showed significantly higher elongation rates than the brand-name drug Voltaren (1.22), were 14.0-17.2% more stretchable and are considered to be suited for application at movable areas, such as the joints, and to cause wide differences in the feeling of use in flexible areas.

Next, products with low water-vapor permeability have been reported to increase the wetness of the skin at the site of application, reduce the strength of attachment of corneocytes, and promote cuticle exfoliation (13). As shown in Figure 3, the water-vapor permeability (%) calculated from the amount of water-vapor permeation during 24 hours after application of each product was significantly higher in Nichi-Iko (2.45%) than in the brand-name drug Voltaren (0.92%), and Nichi-Iko is considered to be more permeable to moisture on the skin and less likely to cause skin wetting. Products with low water-vapor permeability are considered to allow less water to permeate and to be more likely to cause skin wetting, and Yutoku (0.42%) and Rakool (0.39%) were shown to be more likely to wet the application site than the brand-name drug Voltaren.

Next, tape preparations, which are attached to the skin, must have appropriate adhesive force. Therefore, we performed probe tack testing to compare the adhesive force of various products in peeling off. As shown in Figure 4, the adhesive force was significantly higher in Naboal (6.8 N/cm²), Teikoku (6.1 N/cm²), Yutoku (5.9 N/cm²), Nichi-Iko (5.2 N/cm²), and Rakool (6.2 N/cm²) compared with Voltaren (2.0 N/cm²), and these products are considered to be more adhesive. Similarly, from the results of the inclined ball tack testing, the adhesive force is considered to be stronger in the products with a higher ball number than the brand-name drug Voltaren (mean ball number: 7.2). Also, since the initial adhesiveness, which is derived from the adhesive components of the tape preparation (e.g., styrene-isoprene-styrene block copolymer), can be evaluated by the inclined ball tack testing (8), we consider that Naboal (18.0), Teikoku (24.0), Yutoku (21.5), NP (18.0), JG (17.5), and Nichi-Iko (22.7), which showed mean ball numbers higher than that of Voltaren, have a stronger initial adhesive force than Voltaren. We further examined the correlation between probe tack testing and inclined ball tack testing using Pearson’s correlation coefficient and found a significant difference (p = 0.0498) positive correlation (r = 0.52) between the two tests. Thus, following the initial adhesion of the tape product, the adhesiveness of products to the skin is considered to depend on adhesion between the skin and the product and cohesive force of the product itself that resists peeling off (14), and these two factors are considered to determine the total adhesive force, but the positive correlation demonstrated between the probe tack and inclined ball tack testing results is considered to suggest that the initial adhesive force is nearly proportionate to the cohesive force of the product itself that resists peeling off.

Next, unlike oral or injection preparations, tape products must be removed from the skin after a period of application. Since the force required to peel off the product greatly affects the compliance, the peeling force is an important criterion in its evaluation. The peeling force of a product is considered to depend on the adhesive force and cohesive force of the adhesive agent used on the adhesive surface of the product. Figure 5 compares the peeling forces in removing various tape products at 90° and 180°. First, at 90°, the peeling force was significantly higher in Naboal (0.95 N), Teikoku (0.96 N), and Nichi-Iko (1.01 N) than in the brand-name drug Voltaren (0.68 N). At 180°, the peeling force was significantly higher in Naboal (0.72 N), Teikoku (1.11 N), Yutoku (1.16 N), and Nichi-Iko (1.07 N) than in the brand-name drug Voltaren (0.33 N). In addition, when the correlation between the results of the peeling force testing were compared between 90° and 180° using Pearson’s correlation coefficient, a high positive correlation (r = 0.88) with statistical significance (p = 0.0002) was observed between 90° and 180°. Moreover, when the peeling force was compared between 90° and 180°, it was 0.68 N and 0.33 N, respectively, in Voltaren, indicating that it can be removed with about half the force at 180°. Similar results were obtained with Naboal, Sanwa, NP, JG, Nichi-Iko, Towa, and Rakool, but Teikoku, Yutaka, and Nichi-Iko could be removed with a weaker force at 90° than at 180°. From these results, the angle is a very important factor in peeling off tape products. Although we measured the peeling force only at 90° and 180° in this study, the stimulus to the skin is considered to be mitigated by appropriately adjusting the angle of removal in each product.

Next, regarding the dose and administration method, since the package inserts of the products used in this study say, "apply to the affected area once a day"; we attached each product to an EVA membrane (15), which is used as an artificial permeable membrane, with a fixed load and compared the peeling force in removing it from the EVA membrane after 24 hours. As shown in Figure 6, the peeling force was significantly higher in Yutoku (4.41 N), Nichi-Iko (4.29 N), and Rakool (4.18 N) than in Voltaren (1.15 N). Therefore, if Voltaren (1.15 N) or Naboal (0.89 N) has been changed to one of the above generic drugs because of the insufficient adherence of the brand-name drug, it is more likely to remain attached, but the patient may feel pain in the skin in removing it because of the large force, 3.63-3.83 times greater, required to peel it off. Therefore, assuming that the patient takes a bath 24 hours after application of a product without removing it, we performed the peeling off test after immersing the product in tepid water at 40°C for 30 minutes. As
a result, while Yutoku showed a significant increase of 1.47 N ($p = 0.00074$), Teikoku and Nippon-zoki showed significant decreases of 2.68 N ($p = 2.7E-0.5$) and 1.94 N ($p = 2.3E-0.7$), respectively. Since the peeling force increased in some products but decreased in others after immersion in tepid water at 40°C for 30 minutes, attention to the temperature at application is also considered necessary depending on the characteristics of the adhesive base used in each product. However, information concerning the constituent contents of each product obtained from the interview form was insufficient for thorough discussion. A large peeling force is a factor that contributes to detachment of the cuticle, other factors including "wetness" have also been reported to exert large effects (13). Therefore, in compliance guidance for patients, informing them that the tape can be removed more readily after a bath would be useful if a brand-name drug is changed to a generic drug such as Teikoku and Nippon-zoki.

From these results, in changing a brand-name product to a generic product, the feeling of use may be affected by selecting a product shown to have significantly different physicochemical properties compared with the one that has been used. Since, as indicated by the results of this study, pharmaceutical and physicochemical properties differ widely among the brand-name and generic products, the feeling of their use is expected to vary, and it becomes possible to select products according to the feeling of use preferred by each patient. Thus, in changing brand-name tape products to generic products, anticipating changes in the feeling of use and providing information based on the characteristics of each product are considered to contribute to the establishment of a relationship of trust between patients and medical staff.

References


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