Comparative Study of Skin Permeation Profiles between Brand and Generic Tulobuterol Patches

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Tulobuterol patches are long-acting bronchodilators for percutaneous absorption including the β₂-adrenoceptor agonist tulobuterol, as a main ingredient, used for long-term management of pediatric asthma. Since patients who have pediatric asthma often also have atopic dermatitis in which the skin barrier is impaired, we compared the skin penetration profiles of the brand and generic patches using a skin barrier-impaired rat model. Skin penetration was significantly (p<0.001) higher in the generic patches compared with the brand patch, suggesting that it is important to understand the pharmaceutical properties of available products by giving careful consideration not only to the patient’s asthma control but also to their skin condition before using tulobuterol patches.

Key words tulobuterol patch; generic product; skin permeation; asthma; atopic dermatitis

The brand tulobuterol patch (Hokunalin® Tape; Abbott Japan Co., Ltd.; Maruho Co., Ltd.), developed in Japan, is the world’s first bronchodilator for percutaneous absorption. It contains tulobuterol, a long-acting β₂-adrenoceptor agonist (LABA), as the main ingredient, and is used once-daily for long-term management of bronchial asthma. Since the maximum blood concentration of tulobuterol is reached 9–12 h after application of the patch, inhibitory effects on the “morning dip” can be expected if applied before going to bed. As the brand patch is designed to have a lower maximum blood concentration than oral products, few systemic adverse effects such as tremors or palpitations appear. In a double blind comparative study in children, it was reported that no adverse effects on airway hypersensitivity occurred when the brand patch was applied for 2 weeks.

Generic patches of tulobuterol have been marketed in recent years. The brand product Hokunalin® Tape contains both tulobuterol crystals and molecules in an adhesive layer. It is characterized by a drug release control system called the crystal reservoir system, in which crystals gradually dissolve and supply molecules as tulobuterol molecules disappear with skin penetration. However, the generic products use the matrix type without tulobuterol crystals because the crystal reservoir system is protected by a patent. Furthermore, the ingredients of adhesives and excipients differ by product.

We previously performed an in vitro study, using healthy skin excised from hairless mice, on skin permeation of 6 generic and the brand patches in consideration of the possibility that the drug release control system and properties of the adhesive might affect the skin penetration of the drug. We found significant differences in the skin permeation profiles of 5 generic patches from the brand patches.

In the pediatric clinical setting, there are patients who have both bronchial asthma and atopic dermatitis (AD). In patients with AD, there is a high level of transepidermal water loss (TEWL), so that the skin always becomes dry in not only the area of the lesions but also apparently healthy skin. Increase in TEWL may lead to functiona disorders of the skin water barrier, which makes it easy for allergens and stimulants to enter through the skin. It has been reported that skin penetration of drugs is increased under conditions of TEWL increase. When tulobuterol patches are used in children with skin barrier impairment such as in AD, skin penetration of tulobuterol might be higher than in those with healthy skin. Therefore, to estimate the effects on asthmatic children with skin barrier disorders, the skin penetration profiles of tulobuterol of the brand and generic patches were assayed in rats with healthy skin and those with skin barrier impairment. In this study, we measured TEWL of the stripped skin and showed a reduction in skin barrier function in the stripped skin. Thus, this study was designed to simulate conditions possibly encountered in clinical practice.

MATERIALS AND METHODS

Materials The brand and 2 generic patches were examined. According to the previous results of a skin permeation test in healthy skin of hairless mice, 2 generic patches were selected; one with no significant difference in permeation at any time (Generic A) and another with significant differences in permeation at all times (Generic B) from the brand patch. All 3 patches contained 1 mg of tulobuterol.

Methods After acclimation for 10 d, 6-week-old female Sprague-Dawley (SD) rats (CLEA Japan, Inc., Tokyo, Japan) were divided into a total of 6 groups including intact skin groups and stripped skin groups for each of the 3 products. On Day 1, hair trimming and shaving were performed, and on Day 2, the brand and generic tulobuterol patches (1 mg/animal) were applied to the back of the rats. Three rats were tested each time. In the stripped skin group, stratum corneum was removed by the tape stripping method of Robert and Raymond before application of test patches. At 2, 4, 8, 16, and 24 h after application, all of the patches were recovered and residual drug content was measured by HPLC. Each patch was placed in a glass test tube with a screw cap; 5 ml of hexane and 5 ml of 0.1 mol/l hydrochloric acid were added, and the test tube was shaken vigorously for 10 min. After separation by centrifugation at 3000 rpm for 2 min, exactly 1 ml of the lower layer (water layer) was placed in a glass test tube and 1 ml of 0.1 mol/l sodium hydroxide was added. Fifty microliters of the solution was placed in a tube.

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10 ml of water was added, and 0.5 ml subjected to HPLC after shaking. The HPLC conditions were as follows: Inertsil ODS-3 (GL Sciences Inc., Tokyo, Japan); column, 2.1×150 mm; column temperature, 40 °C; mobile phase, 50 mmol/l ammonium acetate/acetonitrile mixtures (mixtures at various ratios); detection method, MS.

The TEWL of the back skin immediately before application of the patches was measured in all animals at the same time using an evaporimeter (EP-1C, ServoMed, Stockholm, Sweden).

Skin penetration was defined as the initial amount (1 mg) minus the amount of the residual drug, and was expressed as a percentage.

**Statistical Analysis**  One-way analysis of variance was performed and multiple comparison tests were conducted using Tukey’s method. The level of significance was p<0.05.

**RESULTS**

**Transepidermal Water Loss (TEWL)**  The TEWL of the intact skin groups and stripped skin groups was not significantly different among Generic A, Generic B, and the brand patch groups. The skin conditions of rats in the three groups showed no differences.

The TEWL in the stripped skin groups was higher compared with the intact skin groups for all products (Table 1).

**Skin Penetration Test**  Figure 1 shows the skin penetration profiles over time. Although the brand patch caused higher skin penetration in the stripped skin groups than in the intact skin groups, the differences were small and not significantly different at any time point.

For both Generic A and Generic B, skin penetration was significantly (p<0.05) higher in the stripped skin groups than in the intact skin groups at all times after application. Furthermore, no differences were seen between the brand and generic patches for skin penetration in intact skin. Both generic patches showed a significantly higher skin permeation than the brand patch after 2, 4, 8, and 16 h in stripped skin. This suggests that there is a difference in the pharmaceutical properties of the brand and generic patches in impaired skin.

**DISCUSSION**

Tulobuterol patches were developed as once-daily LABA for long-term management of bronchial asthma. They are especially useful in children who cannot inhale drugs and it is possible to apply these patches with no age limits since the administration method is simple. In the Japanese Pediatric Guideline for the Treatment and Management of Asthma (JPGL2008), † tulobuterol patches are recommended for concomitant use with anti-inflammatory agents such as inhaled corticosteroids as adjuvant controller medication to treat moderate asthma and as standard controller medication for severe asthma in infants and growing children.

We previously investigated the add-on effects of the brand tulobuterol patch when concomitantly used with inhaled corticosteroids (ICS) compared with high-dose ICS in a randomized parallel-group study in 18 pediatric patients with severe bronchial asthma. The brand patch concomitant group showed significantly better improvement of both peak expiratory flow (PEF) and the number of symptom-free days than the high-dose ICS group, suggesting that the brand patch is useful for long-term management of pediatric asthma.10)

Generic tulobuterol patches were recently marketed. All generic patches have confirmed their bioequivalence for manufacturing approval. However, the skin penetration of the generic patches was highly increased immediately after application in the stripped skin group of rats. The rate-limiting step of skin penetration of tulobuterol is considered to be both the drug release and the penetration through the stratum corneum. Generic patches do not have a drug release control system like the brand patch, and penetration through the stratum corneum seems to be the rate-limiting step. Since skin penetration was increased in stripped skin after removal of the stratum corneum in our study, this could be the reason why generic patches enhanced skin penetration in stripped skin. This suggests that the generic patches show different skin permeation from the brand patch when the patches are applied to children with skin barrier impairment such as an increase of TEWL in AD. On the other hand, the brand patch showed the least difference in skin penetration between stripped skin and intact skin due to the presence of drug release control by its crystal reservoir system.

Although Generic B showed a different skin penetration from the brand patch in intact skin in the previous study,4) skin penetration in intact skin in the current study did not show any significant differences between the brand and Generic A and B patches. The reason for this is unclear, but it may be due to differences in experimental animal species and the method (in vitro and in vivo).

Tojo and Hikima13) investigated the in vitro penetration of
tulobuterol using hairless mice abdominal skin and found that generic patches tended to exhibit enhanced release versus the brand patch in stripped skin when compared with intact skin. They suggested that generic patches have different skin penetration from the brand patch as skin thickness decreases, correlating well with the present results in vivo. These results indicate that the skin penetration properties of tulobuterol differ by product.

Murata et al. investigated the drug disposition of tulobuterol patches and reported that tulobuterol shows excellent tissue penetration, and there is no accumulation in specific tissues. Thus, it is considered that the amount of penetrated drug correlates well with the amount of drug in blood. Generic patches might increase skin penetration in damaged skin, and therefore, clinicians have to be careful when prescribing generic patches to patients whose skin barrier function is reduced.

Asthmatic children exhibit a high frequency of allergic diseases as complications; the complication rate for asthma and AD has been estimated at 30.9%. Therefore, healthcare professionals should be aware that it is relatively common for asthmatic children to have possible skin barrier impairment.

When clinicians use tulobuterol patches as medication for long-term management of bronchial asthma in children, care should be taken to use such products with a clear understanding of their pharmaceutical properties as well as considering both the patient’s asthma and skin condition.

REFERENCES