Bioequivalence of Marketed Transdermal Delivery Systems for Tulobuterol

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Tulobuterol permeation through skin from various transdermal delivery systems has been compared for the bioequivalence among devices marketed. Both the permeation profiles across the hairless mouse skin and the release profiles from the devices were measured under well-controlled in vitro conditions. The release rate of the drug from the devices was appreciably higher than the penetration rate across the intact skin, indicating the skin-controlled delivery systems. However the deviation between the release rate and the permeation rate differs depending upon the system design. The brand patch showed the least difference between the release and permeation profiles among the brand and three generic devices examined. From the in vitro permeation profiles for both intact and stripped skins, the diffusion coefficient and the partition coefficient were evaluated on the basis of bi-layer skin model. The effect of the stratum corneum thickness was then simulated by SKIN-CAD®. The simulated profile has suggested that the clinical performance for transdermal tulobuterol delivery is influenced not only by the thickness of the stratum corneum but by the device design as well. This is particularly the case for the stratum corneum, thinner than about 10 µm or damaged skin with the decreased barrier capacity. For the stratum corneum thicker than 20 µm, on the other hand, the clinical performance may not be significantly influenced by the device designs investigated in this study.

Key words tulobuterol; transdermal delivery; bioequivalence; penetration; release

Recently various once-a-day transdermal delivery systems for tulobuterol have been developed for treating asthma and chronic obstructive pulmonary disease. Since major resistance to drug transport through the intact skin resides usually in the diffusion process across the stratum corneum, the barrier capacity of the skin may significantly influence the clinical performance of the transdermal delivery systems. The bioequivalence of devices should, therefore, be confirmed by appropriate investigation. The bioequivalence of the transdermal nitroglycerin delivery systems was previously investigated by comparing the release profile with the penetration profile.

In the present paper, we examine various tulobuterol systems for the bioequivalence of the patches marketed. The original brand patch and three generic transdermal tulobuterol delivery systems are evaluated in terms of the release kinetics and the permeation profiles through either intact skin or stripped skin without stratum corneum.

The penetration profiles are then compared with the release profiles.

MATERIALS AND METHODS

Materials

Four types of transdermal tulobuterol delivery systems recently marketed (products A, B, C and D, A: Hokunarin (brand), B, C and D: generic devices) have been evaluated. The effective area and the dose of the drug are 5 cm² and 1 mg, respectively.

In Vitro Experiments

A hydrodynamically well-calibrated skin permeation system was used in this investigation. Abdominal skin of full thickness of hairless mouse (Hr/Kud strain, Kyudo Co., Ltd.) or after stripping the stratum corneum with cellophane tape, was freshly excised from 7—8 weeks old hairless mice and carefully mounted in each of the in vitro vertical cells (modified Franz diffusion cell, effective area and volume: 1.70 cm² and 10.8 ml, respectively. Fig. 1). The temperature of the solution was controlled at 37°C by a circulating water bath. After soaking the dermal side of the skin in the elution solution (phosphate buffer solution pH 7.4), one unit of the transdermal delivery system was applied to the stratum corneum side of the skin and the skin permeation profile of tulobuterol was then followed by sampling and assaying the tulobuterol in the receptor solution using an HPLC system (LC-10A, Shimadzu Co.) and Inertsil ODS-2 (64.6 mm×150 mm, GL Sciences Inc.) column. The UV detector was operated at 215 nm. A combination of 975 ml acetonitrile and 1810 ml distilled water contained 6 g 1-octanesulfonic acid sodium salt and 10 ml 1/150 phosphoric acid solution was used as the mobile phase. At 30°C, a flow rate of 1 ml/min was used. Immediately after sampling, the same volume of fresh elution medium was returned to maintain the same total volume.

All animal studies conformed to the “Principles of Laboratory Animal Care,” NIH publication #85-23, revised 1985.

The release kinetics of the drug from the transdermal delivery systems was also evaluated under the same conditions in the absence of skin.
The radial diffusion of drugs released from delivery devices was previously evaluated assuming two-dimensional diffusion. In spite of the existence of radial diffusion, the overall penetration was mainly controlled by the longitudinal diffusion across the stratum corneum; in the present in vitro diffusion cell, the effective area for release and penetration is about 35% of the effective area of the patch (5 cm²). The diffusion coefficient in the device is the order of $10^{-8}$ to $10^{-9}$ cm²/s. For the diffusion path length of 0.1 cm, the time lag for diffusion becomes approximately 46 to 460 h ($t_d = \frac{l^2}{6D}$, $t_d$: lag time, $l$: diffusion path length and $D$: diffusion coefficient). This analysis indicates that the surface or radial diffusion is not significant for either release or permeation experiments.

RESULTS AND DISCUSSION

Both release and permeation profiles are plotted in Figs. 2a to d. The release profile (circle symbol) is markedly influenced by the device design. System A (brand device) shows a sustained release profile, while systems C and D provided a typical bursting release initially. However the penetration profiles across intact skin was less affected by the system design. This finding clearly indicates that the major resistance to tulobuterol transdermal delivery resides in the stratum corneum penetration and therefore the clinical performance may depend on the system design as well as the site of device application. Among the four devices investigated, the brand patch (system A) can minimize some possible bursting release of the drug by accident or damage of the stratum corneum barrier capacity. The other three types of devices, B, C and D, show that the overall permeation is strongly controlled by the stratum corneum diffusion process instead of the system design. It is therefore necessary to properly determine the site of application where the stratum corneum is not too thin or too thick and intact with respect to the barrier capacity. The brand patch indicates that the bursting release during the initial one hour was approximately 20%, while the one for systems B, C and D were 40%, 70% and 80% respectively. The large fraction of initial bursting may cause an unexpected high dose of penetration for damaged skin. It is also important to see that the penetration rate across intact skin is relatively close to that for release profile for the brand patch. This suggests that the brand patch is partly a device-control transdermal delivery system. The other generic patches clearly indicate the skin-controlled systems. The fraction of penetration across the intact skin at 6 h for systems A, B, C and D are approximately 30, 40, 50 and 60%, respectively.

In order to investigate the relationship between the device design and the stratum corneum barrier function, the effect of the stratum corneum thickness on the rate of permeation was simulated on the basis of the present in vitro permeation experiment and the commercially available PC software for TTS design, SKIN-CAD® assuming the bi-layer skin model. The diffusion coefficient and the partition coefficient were evaluated from the penetration profiles for both the intact and stripped skin after analyzing the initial linear portion of the in vitro profiles (Fig. 2). The diffusion coefficient in the viable skin was determined from $D_v = \frac{h^2}{6t_d}$; where $h$ is the thickness of the viable skin (360 μm) and $t_d$ is the lag time. The values of the model parameters and the physicochemical properties are summarized in Table 1. The values of the diffusion coefficient and the partition coefficient determined from the hairless mouse skin can be used for human skin,

![Fig. 2. Release and Penetration Profiles for Tulobuterol (Mean Values ± S.D., n=4)](image)

Keys: ○ release (without skin), ■ penetration (stripped skin), ● penetration (intact skin). (a) System A (brand patch), (b) system B (generic), (c) system C (generic), (d) system D (generic).
while the thickness of the skin should be modified for the clinical conditions; the thickness of the human stratum corneum varies approximately from 5 to 40 $\mu$m and the effective thickness or the distance from the skin surface to the capillary front is approximately 200 $\mu$m. For the simulation, therefore, we assume 200 $\mu$m as the human skin thickness. We also assume that the concentration on the surface of the stratum corneum is constant for the initial several hours when the cumulative amount of the drug released is less than 20% of the initial loading dose in the device.

The simulated profiles for initial penetration profiles are shown in Figs. 3 to 6. The effect of the device design on the rate of permeation is not significant for the skin with the stratum corneum thicker than 20 $\mu$m for systems A, B and C. On the other hand, if the stratum corneum is thinner than 10 $\mu$m, the permeation rate is appreciably influenced not only by the thickness but by the device design. Since the penetration of tulobuterol is influenced by the stratum corneum barrier capacity, the site of application must be carefully determined. Because of the skin-controlled delivery for tulobuterol, the site of patch application should be recommended as the place with intact barrier capacity and constant thickness. Although the thickness of human stratum corneum is site-dependent, it is relatively constant among the back, shoulder, abdomen, arm and chest. This is particularly important when the brand patch is switched to the generic devices or vice versa. The other important consideration with respect to the bioequivalence of the transdermal tulobuterol patches is on the disease state of the stratum corneum. For instance, the transepidermal water loss (TEWL) in atopic dermatitis (AD) patients was found to be much higher than healthy skin condition. Because the rate of drug penetration is approximately proportional to the TEWL, this finding indicates that the skin penetration for AD patients is appreciably higher than that for healthy skin. Since the tulobuterol transdermal systems are skin-control systems, the reduced barrier capacity due to AD should be carefully examined.

CONCLUSION

The present comparative study on transdermal tulobuterol

Table 1. Physicochemical Properties of Transdermal Tulobuterol Delivery Determined by the Bi-layer Skin Model

<table>
<thead>
<tr>
<th>System</th>
<th>$D_{sc}$ $\times 10^{10}$ [cm$^2$/s]</th>
<th>$D_{vs}$ $\times 10^6$ [cm$^2$/s]</th>
<th>$K_{sc/vs}$ [–]</th>
<th>$C_s$ [mg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.86</td>
<td>0.59</td>
<td>161.85</td>
<td>107.07</td>
</tr>
<tr>
<td>B</td>
<td>1.01</td>
<td>0.85</td>
<td>105.88</td>
<td>81.95</td>
</tr>
<tr>
<td>C</td>
<td>0.86</td>
<td>1.74</td>
<td>123.72</td>
<td>97.56</td>
</tr>
<tr>
<td>D</td>
<td>1.27</td>
<td>1.20</td>
<td>39.94</td>
<td>85.56</td>
</tr>
</tbody>
</table>

$D_{sc}$: diffusion coefficient for the stratum corneum, $D_{vs}$: diffusion coefficient for the viable skin, $K_{sc/vs}$: partition coefficient between the stratum corneum and viable skin, $C_s$: skin surface concentration.
delivery clearly indicates that the skin permeation for tulobuterol is influenced by the barrier capacity of the stratum corneum, in spite of the relatively well controlled system design for the brand patch. The clinical performance of generic tulobuterol transdermal delivery systems investigated is mainly influenced by the stratum corneum thickness as well as the barrier capacity of the skin. It is therefore necessary to carefully select the site of application in order to achieve the bioequivalence characteristics of the different generic patches with respect not only to the therapeutic efficacy but the possible undesired side effects due to bursting release.

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REFERENCES