Prediction of Percutaneous Absorption in Human of Nicotine from Marketed TTS using Three-dimensional Human Cultured Epidermis

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ABSTRACT SUMMARY

The objective of this study is to establish an alternative method with reconstructed human epidermis (RHE) to decrease sacrifice of experimental animals and predict the skin penetration and plasma concentration profile in human. Skin penetration experiments across RHE and animal skin were performed with transdermal therapeutic systems (TTS) in vitro.

INTRODUCTION

Animal skin has been widely used for research and development (R&D) of TTS in vitro. However, it is important to establish an alternative method with RHE instead of animal skin. Moreover, the OECD regulations accepted the results obtained from RHE.¹

Our studies aim to establish an alternative method with RHE for R&D of TTS in human. We previously reported a relationship of skin penetration parameters, diffusion coefficient D, partition coefficient K, and skin surface concentration Cm, between RHE and hairless mouse (HLM) skin and predicted the profiles of the skin penetration and plasma concentration in human.² The influence of chemical enhancers and iontophoresis on the penetration flux across RHE was also investigated.³

We further carried out the skin penetration experiment with TTS in this study. We then calculated the penetration parameters based on the bi-layer skin model and simulated the plasma concentration of drug in human using the simulation software SKIN-CAD®.

EXPERIMENTAL METHODS

Materials

LabCyte EPI-MODEL (LabCyte) as RHE was obtained from Japan Tissue Engineering Co. Ltd. (Gamagori, Aichi, Japan). Animal model, HLM (Hr/Kud, female, 7 weeks old), was purchased from Kyudo Co. (Tosu, Saga, Japan).

Transdermal nicotine delivery system Ciganon® CQ2 (NicoDerm® CQ® Step3) was evaluated as TTS in this study. The effective area, thickness, and the dose of nicotine are 7 cm², 228 μm, and 36 mg, respectively.

In vitro skin penetration experiments

LabCyte is cultured from human epidermis and consists of stratum corneum (SC) and viable epidermis (VE). One week cultivation did not form the SC (1W model = VE) and the barrier function of SC matured after 2 weeks cultivation (2W model = SC+VE). The thickness of 1W and 2W model was estimated at 50.6 and 60.6 μm, respectively.² stripped skin removed SC by tape-stripping technique (viable skin VS = VE+dermis) and intact skin (IS = SC+VS) were prepared from abdominal skin of HLM. TTS, skin sample, and teflon adaptor (internal diameter; 9 mm, thickness; 1 mm) was mounted on side-by-side in vitro diffusion cell (Figure 1). The nicotine concentration in receptor solution was assayed by HPLC. All animal studies conformed to the “Principles of Laboratory Animal Care,” NIH publication #85-23, revised 1996.

Figure 1. In vitro skin penetration diffusion cell.

RESULTS AND DISCUSSION

Figure 2 shows the penetration profiles across LabCyte and HLM skin, respectively. The SC barrier function was insufficient for the skin absorption of nicotine because the lag-times, x-axis of steady-state penetration flux, for LabCyte and HLM skin were less than 0.2 h.
The penetration parameters calculated from the flux and lag-time for LabCyte and HLM skin were summarized in Table 1. The value of $D_{SC}$ in LabCyte was the same with that in HLM skin. On the other hand, the value of $K_{SC}/K_{VE}$ in LabCyte was 0.09 times lower than that in HLM skin.

Table 1. Penetration parameters in LabCyte and HLM skin.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LabCyte</th>
<th>HLM</th>
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<tbody>
<tr>
<td>$D_{SC}$ [cm$^2$/sec]*</td>
<td>1.16x10^{-9}</td>
<td>1.09x10^{-9}</td>
</tr>
<tr>
<td>$D_{VE}$ [cm$^2$/sec]*</td>
<td>2.96x10^{-8}</td>
<td>1.63x10^{-6}</td>
</tr>
<tr>
<td>$K_{SC}/K_{VE}$ [-]*</td>
<td>9.95</td>
<td>1.11x10^{2}</td>
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*subscript SC and VE represented stratum corneum and viable epidermis (viable skin)

The plasma concentration in human was simulated by skin bi-layer / two compartment model using the SKIN-CAD® (Figure 3). The clinical data (closed circle) and pharmacokinetic parameters (volume of central and peripheral compartment; 63.8 and 149 L, transfer rate constants $k_{12}$ and $k_{21}$; 4.78x10^{-2} and 1.45x10^{-2} min$^{-1}$, elimination rate constant $k_e$; 2.23x10^{-2} min$^{-1}$) in human were referred. The solid and dashed lines were expressed the simulated profiles with the penetration parameters in LabCyte and HLM skin, respectively. By the SKIN-CAD® approach, the simulated profiles predicted from HLM skin well agreed with the clinical data. The simulated profile predicted from LabCyte approximately agreed with the clinical data with respect to the peak time and the profile after removed TTS. However, the peak concentration from LabCyte was almost 2 times lower than that from the clinical data and HLM skin. This is mainly caused by low solubility of nicotine in SC of LabCyte.

CONCLUSIONS
The penetration parameters determined from in vitro experiments of HLM well predicted the clinical profile of plasma concentration of nicotine. Both skin specimens can predict the clinical time-profile of nicotine after transdermal delivery.

REFERENCES