A Pharmacokinetic Model for Percutaneous Absorption of Valproic Acid and Prediction of Drug Disposition

Taro OGISO, Yoshimasa ITO, Masahiro IWAKI, Hidehiko ATAGO and Yuko YAMAMOTO

Faculty of Pharmaceutical Sciences, Kinki University, 4-1, Kowakae 3-chome, Higashi-Osaka, 577, Japan

(Received January 14, 1988)

To predict the plasma concentrations after percutaneous application of valproic acid (VPA), we presented a new pharmacokinetic model which includes simultaneous two absorption processes through the skin. The simulation contains four first-order rate constants for the following: a) absorption via the lipid and water routes in skin and b) uptake from the skin into systemic circulation and subsequent elimination. The fitness of the model presented for experimental data was compared with simple one-compartment models.

As a result, the new model was successfully able to describe the time course of the plasma VPA concentrations following percutaneous application of the ointments. VPA was found to be rapidly absorbed across the water routes ($k_{s1} = 2.60 \text{ h}^{-1}$), which accounted for about 70% of the total, followed by a lasting absorption via the lipid routes ($k_{s2} = 0.108 \text{ h}^{-1}$). The pharmacokinetic model with parallel lipid and aqueous pore skin transport pathways in skin was more adequate for the interpretation of p.c. absorption data of VPA than the models with an absorption process.

**Keywords** — percutaneous absorption; pharmacokinetics; plasma concentration prediction; pharmacokinetic model; water route; lipid route; valproic acid; ointment

**Introduction**

At present, there are many extensive investigations being conducted concerning the percutaneous (p.c.) absorption of drugs. The p.c. preparations are effective in avoiding hepatic first-pass metabolism and gastro-intestinal irritation, and are able to sustain an effective plasma concentration over a prolonged period of time. A pharmacokinetic analysis of drug penetration across the skin has been reported by many investigators, but their approaches are different from each other. To design the best administration schedule for p.c. application to human, it is necessary to derive a simple pharmacokinetic model by which one can predict the plasma concentration after p.c. application of drugs, and clarify the kinetics of drugs in the skin and plasma.

The p.c. absorption of a drug is a complex multistep process. To describe this phenomenon, Higuchi et al.\(^{1-5}\) introduced the concept of diffusion movement through skin. Subsequently, many investigators have carried out the theoretical consideration of p.c. drug absorption according to this theory.\(^{6-12}\) On the other hand, Guy et al.\(^{13-17}\) described a physically based pharmacokinetic model with four first-order kinetic processes for the p.c. absorption. This model includes a retardation process which retains the penetrant in the stratum corneum, an inverse rate constant from the viable skin to the stratum corneum.

We have clarified that valproic acid (VPA) and its calcium salt (VPA-Ca) are easily absorbed from rabbit skin.\(^{18}\) In this study, we present a pharmacokinetic model for p.c. absorption of VPA and have applied the model to plasma concentration data after dosing with VPA and VPA-VPA-Ca ointments. The plasma levels were described by four first-order rate constants, including simultaneous two absorption processes through the skin, which are assumed to be the penetration via the lipid phase and via water channels. The fitness of the model for the experimental data was compared with the simple one-compartment model with an absorption process and with the one-compartment model with a release process from the ointment base and an absorption step.\(^{19}\) The significance of the novel model and the predictive capacity of the approach are discussed.
Materials and Methods

Materials — 1) Reagent: VPA and cyclohexanecarboxylic acid, an internal standard for gas-liquid chromatography, were purchased from Tokyo Chemical Industry Co., Ltd. Sodium salt of VPA (VPA-Na) was a generous gift of Kyowa Hakko Industry Co., Ltd. Hiviswako 104® (gel base of ointment) and Cellophane Tubing-Seamless (36/32 inch) were obtained from Wako Pure Chemical Industry Co., Ltd. VPA-Ca was prepared by the method reported in the previous paper. All other chemicals used were of reagent grade.

2) Animals: Male Japanese white rabbits, weighing 2.5 to 3.5 kg, were used. The animals had free access to RC4 diet (Oriental Yeast Co., Ltd.) and water before the experiment.

Preparation of Ointment — VPA was dissolved in dimethylsulfoxide (DMSO) and ethanol. A mixture of VPA and VPA-Ca was dissolved in diethylene glycol monoethyl ether (carbitol). These solutions were separately mixed with a gel base (Hiviswako 104®) containing water, propylene glycol, diisopropyl adipate and diisopropanolamine. Details of the ointment compositions are listed in Table I.

Intravenous (i.v.) Administration Data — The pharmacokinetic parameters after i.v. administration (60 mg/kg as VPA) were obtained from our previous study.

In Vitro Release Experiment — The ointment (2.0 g) packed into a cellophane tubing (the area for penetration, 25 cm²) was suspended in 0.9% NaCl-phosphate buffer (pH 7.4, 50.0 ml) at 37°C, with stirring at 150 rpm. Samples (0.1 ml) of the solution were collected periodically for 6 h.

Percutaneous Absorption Experiment — The data of p.c. absorption of drugs were taken from the previous paper (3.0 g, 5.0 × 5.0 cm area, 36 h).183

Determination of VPA — VPA in samples was determined by the method described previously.

Analysis of Data — The area under the plasma concentration–time curve (AUC) after i.v. and p.c. administrations were determined by the trapezoidal rule up to 36 h. The plasma concentrations after i.v. administration were analyzed according to the one-compartment open model, and the elimination rate constant, \( k_e \), was calculated from the linear part of the logarithmic plasma concentration–time plots. The volume of distribution was calculated from \( V_d = D/C_0 \), where \( D \) is the dose and \( C_0 \) is the initial plasma drug level.

In the in vitro release experiment, we assumed that the release process was according to the first-order rate. The release rate constant was calculated by the following equation:

\[
C' = C_1 \times (1 - e^{-kt})
\]

where \( C' \) and \( C_1 \) are drug concentrations in the buffer at time \( t \) and at infinite time, respectively, and \( k_r \) is the release rate constant.

Plasma drug concentration after p.c. administration was analyzed by applying models I—III shown in Fig. 1. Model I is a well known one-compartment model with a first-order absorption process. Model II, described by Naito et al., is a one-compartment model with both a drug release process from ointment and a first-order absorption process. In this study, we present model III, which is a one-compartment model with simultaneous two first-order absorption processes. The theoretical plasma concentra-

<table>
<thead>
<tr>
<th>Rp.</th>
<th>Drug (w/w%) a)</th>
<th>Solvent (w/w%)</th>
<th>Base e) (w/w%)</th>
<th>DIA f) (w/w%)</th>
<th>DA g) (w/w%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VPA</td>
<td>VPA-Ca</td>
<td>PG b)</td>
<td>DMSO c)</td>
<td>Ethanol</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>—</td>
<td>12</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

a) Content as VPA. b) Propylene glycol. c) Dimethylsulfoxide. d) Diethylene glycol monoethyl ether (carbitol). e) Hiviswako 104. f) Diisopropanolamine. g) Diisopropyl adipate. The remainder was water.
Fig. 1. Compartment Models for Percutaneous Absorption of VPA

Model I is one-compartment model with absorption process. Model II is the model with drug release and absorption processes. Model III is the model including drug release process and simultaneous two absorption processes.

Where $k_a$, absorption rate constant; $k_e$, elimination rate constant; $k_r$, release rate constant; $k_{a1}$, absorption rate constant via water routes; $k_{a2}$, absorption rate constant via lipid routes.

The solutions according to these models are expressed by the following equations:

**model I**

$$C_t = \frac{D \cdot F}{V_d} \cdot \frac{k_a}{k_a - k_e} \left( e^{-k_a t} - e^{-k_a t} \right)$$

**model II**

$$C_t = \frac{D \cdot F}{V_d} \cdot \frac{k_r \cdot k_a}{k_r - k_a} \left\{ \frac{1}{k_a - k_e} \left( e^{-k_e t} - e^{-k_e t} \right) \right\}$$

**model III**

$$C_t = \frac{k_r \cdot D \cdot F}{V_d} \left\{ \frac{k_{a1} (k_{a2} - k_r) r + k_{a2} (k_{a1} - k_r) (1 - r)}{(k_{a1} - k_e) (k_{a2} - k_e) (k_a - k_e)} e^{-k_a t} \right. + \frac{k_{a1} (k_{a2} - k_{a1}) r}{(k_{a1} - k_a) (k_{a2} - k_{a1}) (k_a - k_e)} e^{-k_{a1} t} \right. \left. + \frac{k_{a2} (k_{a1} - k_{a2}) (1 - r)}{(k_{a1} - k_k) (k_{a1} - k_{a2}) (k_a - k_{a2})} e^{-k_{a2} t} \right. \left. + \frac{k_{a1} (k_{a2} - k_{a1}) r + k_{a2} (k_{a1} - k_{a2}) (1 - r)}{(k_r - k_a) (k_{a1} - k_e) (k_{a2} - k_e)} e^{-k_e t} \right\}$$

where $C_t$ is the plasma drug concentration at time $t$, $F$ is the fraction of drug absorbed, $k_{a1}$ and $k_{a2}$ are drug absorption rate constants via water and lipid routes, respectively, $r$ is the fraction of drug absorbed via water routes, $D$ is the amount of drug in ointment base, $F$ is the fraction of drug absorbed and is calculated from the

![Graph](image-url)

**Fig. 2. Release of VPA from Ointment**

Each point represents the mean ± S.D. of 4 experiments. The solid lines are calculated simulation curve.

- ●, 5% VPA ointment; ○, 10% VPA - VPA-Ca ointment.
AUC ratio. The release rate constant, $k_r$, is a parameter estimated from an in vitro release experiment. The $k_e$ and $V_d$ were estimated by kinetics following i.v. administration of the drug. The model was fitted to the data obtained from separate experiments using a MULTI program. Plasma concentration data obtained after administration and pharmacokinetic parameters were analyzed by an iterative least-squares regression procedure MULTI\textsuperscript{20} using a desk-top digital computer (PC9801VM, NEC Corp.).

Results

Pharmacokinetic Parameters after i.v. Administration

The $k_e$, $V_d$ and $AUC$ were $0.954 \pm 0.016$ (h\textsuperscript{-1}), $0.192 \pm 0.014$ (l/kg) and $353.1 \pm 38.3$ (µg·h/ml), respectively.

In Vitro Release

The in vitro release profiles of VPA from ointments through the cellophane tubing at 37°C are shown in Fig. 2. The release rate constants for 5% VPA and 10% VPA·VPA-Ca ointments, calculated from the release profiles, are $0.513 \pm 0.045$ and $0.461 \pm 0.080$ (h\textsuperscript{-1}), respectively. These values suggest that the release rate of VPA from the ointments is considerably rapid.

In Vivo p.c. Absorption

The plasma VPA concentrations after a single p.c. application of both ointments are shown in Fig. 3. After application of 5% VPA ointment, the rapid elevation of plasma VPA concentration was observed at the initial time stage and the peak plasma concentration ($C_{max}$) occurred 2 h after application of the ointment. On the other hand, after application of 10% VPA·VPA-Ca ointment, the absorption and
elimination of VPA were slower than those for 5% VPA ointment and the time to reach the peak plasma concentration ($T_{\text{max}}$) was about 4 h. Bioavailabilities after dosing of 5% VPA and 10% VPA-VAP-Ca ointments were 102.5 ± 4.3 and 97.3 ± 2.6 (%), respectively.

**Pharmacokinetic Analysis of Plasma Drug Concentration Data Using Models**

Figure 4 shows the plasma concentration-time profile after application of two types of ointments and the curve calculated based on model I. With the 5% VPA ointment, a relatively good simulation curve was obtained with this model for the first 12 h after dosing, however the curve at the later time stage did not satisfactorily fit the data. The simulation curve after application of 10% VPA-VAP-Ca ointment deviated from the data for both absorption and elimination phases.

To adequately describe the kinetics of p.c. absorption, it is necessary to take into considera-
tion the drug release rate from the base. Therefore, we applied the one-compartment model including both drug release and absorption processes, model II, to the plasma concentration data after dosing of 5% VPA and 10% VPA·VPA-Ca ointments. Figure 5 shows the mean plasma concentrations and the time course of plasma concentration simulated by this model. The results indicated that the absorption phases after applying both ointments were in relatively good agreement with the simulation curves using this model. However, the plasma concentration data for the elimination phase were far above the simulation curve. The fraction of the drug absorbed, calculated from the simulation curve by model II, was 0.903 ± 0.01 for 5% VPA ointment and 0.904 ± 0.05 for 10%

VPA·VPA-Ca ointment. These values were slightly lower than those (1.025 and 0.973) obtained by the noncompartmental method. These results indicate that this model did not fully describe the time course of plasma drug level after topical application of these ointments.

Model III includes a release rate of drug from the ointment and two absorption processes through two independent compartments; water routes through skin, especially via the stratum corneum, and lipid routes which are the transcellular routes.

The calculated plasma concentration-time curve based on model III is shown with the observed plasma concentrations in Fig. 6. The kinetic parameters obtained are listed in Table II. An excellent fit was obtained between the ob-

Table II. Model-dependent Pharmacokinetic Parameters after Administration of VPA and VPA-Ca Ointments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rp.</th>
<th>No. 1</th>
<th>No. 2</th>
<th>No. 3</th>
<th>No. 4</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F$</td>
<td>1</td>
<td>1.13</td>
<td>1.05</td>
<td>1.01</td>
<td>1.18</td>
<td>1.09</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.06</td>
<td>0.97</td>
<td>1.02</td>
<td>1.03</td>
<td>1.02</td>
<td>0.04</td>
</tr>
<tr>
<td>$r$</td>
<td>1</td>
<td>0.69</td>
<td>0.67</td>
<td>0.73</td>
<td>0.73</td>
<td>0.71</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.39</td>
<td>0.45</td>
<td>0.29</td>
<td>0.44</td>
<td>0.39</td>
<td>0.07</td>
</tr>
<tr>
<td>$k_{a1}$ (h$^{-1}$)</td>
<td>1</td>
<td>2.57</td>
<td>3.90</td>
<td>1.95</td>
<td>1.98</td>
<td>2.60</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.30</td>
<td>0.29</td>
<td>0.57</td>
<td>0.31</td>
<td>0.37</td>
<td>0.14</td>
</tr>
<tr>
<td>$k_{a2}$ (h$^{-1}$)</td>
<td>1</td>
<td>0.121</td>
<td>0.090</td>
<td>0.115</td>
<td>0.106</td>
<td>0.108</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.073</td>
<td>0.078</td>
<td>0.082</td>
<td>0.105</td>
<td>0.085</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Fig. 7. Contribution of Water and Lipid Routes to Total Plasma Concentrations after Percutaneous Administration of Ointments.

Each line was computed based on the fraction absorbed via individual route. Plasma concentration after 5% VPA ointment (a) and 10% VPA·VPA-Ca ointment (b) applications.

---, total plasma concentration; ----, plasma concentration via water routes; ------, plasma concentration via lipid routes.
served and the calculated curves for both absorption and elimination phases. The contribution of each individual route to the total plasma concentrations is shown in Fig. 7 by computation based on the fraction of drug absorbed. With 5% VPA ointment (Rp.1), the fraction of the drug absorbed via water routes was greater than that absorbed via lipid routes at the initial time stage, while the fraction from 10% VPA·VPA-Ca ointment (Rp.2) was not so large at the initial period. Upon application of 5% VPA ointment, the $r$ value was 0.71 and $k_{a1}$ was 2.6 h$^{-1}$, indicating that the fraction of drug absorbed via water routes was large and the absorption was rapid. On the other hand, after the application of 10% VPA·VPA-Ca ointment (Rp. 2), the $k_{a1}$ (0.37 h$^{-1}$) was also larger than $k_{a2}$ (0.085 h$^{-1}$), but the fraction of the drug absorbed via water routes was reduced. The fractions of the drug absorbed listed in Table II, were about 1 with both ointments, indicating the complete absorption of VPA and VPA-Ca.

Discussion

The stratum corneum acts as a barrier to p.c. drug absorption and controls drug penetration across the skin. The occlusion is a process which may result in the saturation of the stratum corneum with water and enhances the penetration of most drugs through the skin. This is based on the increase in “free water” in the skin and the pore size of the aqueous channel. The activity coefficient and permeability coefficient of the drug are also increased under occlusion. 34 Taka-
hashi et al. 21) suggest that water absorbed into human stratum corneum in relative humidity (RH) of 0 to 60% is “bound water”, but above 60% RH is “free water” which breaks hydrogen bonds in keratin. Therefore, the presence of free water may result in an increase in the flux of drugs. Scheuplein suggests that polar com-
pounds permeate from aqueous solution predomi-
nantly via shunt routes, 22) and Akhter and Barry also attributed the initial penetration of ibuprofen and flurbiprofen to shunt routes. 23) Naito and Tsai report that solution-type absorption ointment base yields the highest plasma concentration of indomethacin compared with other suspension-type ointment bases and explain the phenomenon by the penetration of the ionized form of the drug. 19) Based on these reports and our data, it would be reasonable to include the water (shunt) routes into the model. However, for hydrophobic or lipophilic drugs, the absorption via lipid routes is very important and cannot be ignored. Stoughton et al. report that p.c. absorption of drugs correlates with the oil-water partition coefficient and the skin is a lipophilic membrane. 24, 25) In model II, described by Naito et al., 19) the release process of the drug from the ointment is a rate-determining step. In this study, we used a hydrophilic gel base under occlusions and observed the rapid absorption. However, the model (model II) did not successfully describe the time course of the plasma drug levels at the elimination period (Fig. 5). It is thus necessary to include a route which can describe the slow elimination of the drug based on the sustained absorption.

In this paper, we analyzed p.c. absorption according to the one-compartment model which had rapid and slow penetration processes, the former is assumed to be the penetration via water (shunt) routes, and the latter is the penetration via lipid routes. There are many reports which conclude that the stratum corneum and viable tissues are different compartments and have separate rate constants for the transfer of drug. 13-17, 26) However, the stratum corneum is the rate determining barrier and the penetration rate of drug via viable tissues is controlled by the stratum corneum. Therefore, the rate via viable tissues was assumed to be equal to the rate via the stratum corneum. The fact that the bioavailability after application of the ointments was about 100% indicates that the metabolism of the drug in the skin was negligible. This demonstrates the ideal penetration of whole drug administered through the skin without metabolic conversion. By the best fit of the simulation curve given by model III to the plasma concentration–time profile after application of ointment (Fig. 6), the validity of this model was fully demonstrated.

The $k_t$ for 5% VPA ointment was larger than that of 10% VPA·VPA-Ca ointment. This may be explained by the slow release based on the hy-
doiophobic interaction of VPA with VPA-Ca. The fraction of the drug absorbed via water routes was 0.71 and 0.39 for 5% VPA and 10% VPA·VPA-Ca ointments, respectively. VPA being a small molecule dissolves in ethanol and propylene glycol and the solute, with the solvent, would rapidly penetrate via water routes (Fig. 7). The presence of DMSO, which decreases the permeability coefficient and activity coefficient of the skin and enhances the penetration of the drug across the skin,25,27–29 may partly contribute to the rapid penetration of VPA. On the other hand, since 10% VPA·VPA-Ca ointment contained carbaryl as a solvent and VPA-Ca is more lipophilic than VPA, the penetration rate might be slower than that of 5% VPA ointment, and the penetration via water routes would be probably less. This was reasonably demonstrated by the results computed in Fig. 7.

In conclusion, the new simple model presented in this paper adequately describes the time course of the plasma VPA concentration following p.c. application of the ointment. The pharmacokinetic model with parallel lipid and aqueous pore skin transport pathways in skin is more adequate for the interpretation of p.c. absorption data of VPA than the model including an absorption process.

References


23) S. A. Akhter and B. W. Barry: Absorption through


