BIOAVAILABILITY OF PHENYTOIN ON SINGLE AND MULTIPLE ORAL DOSES OF TWO DOSAGE FORMS IN NORMAL SUBJECTS

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The extent and rate of absorption of phenytoin (PHT) from tablet and powder were studied in four healthy adult volunteers.

It was demonstrated by urinary and fecal excretion that the almost all quantity of PHT in tablet was absorbed through the gastrointestinal tract, and the observed values of the estimated free concentration ($C_{est,f}$) estimated from mixed saliva concentration of PHT in the multiple dose were in fair agreement with the calculated values of that by using computer simulation in case of tablet. On the contrary, the variations were observed in $C_{est,f}$ using therapeutic dose of PHT powder.

The values of $C_{est,f}$ at steady-state in tablet administration were higher than those in powder administration. The absorption ratio of PHT powder was low and variable, and decreased upon increase of dose. The ratio calculated from the $C_{est,f}$ values of both dosage forms at steady-state were in good correspondence to the observed values of PHT excreted in feces.

Keywords—phenytoin; dosage form; tablet; powder; bioavailability; pharmacokinetics; Michaelis-Menten equation; urinary excretion; fecal excretion; computer simulation

INTRODUCTION

Significant variations in plasma levels of phenytoin (PHT) at steady-state after multiple oral doses of different dosage forms and commercial products of PHT have previously been reported. The cause was thought to be varying extent of PHT absorption from its dosage form in the gastrointestinal tract. In case of very high dose of PHT sodium, Jung et al. showed that the absorption of PHT decreased accompanying with increase of dose. In our previous report, the extent of PHT absorption from powder form was proved to be not only lower than tablet form, but also decreased upon increase of dose in therapeutic dose range of epileptic children.

In this study, the extent and rate of absorption of PHT from tablet and powder, which contained the free acid PHT, were studied in healthy adult subjects. The estimated free concentration ($C_{est,f}$) of PHT, i.e., plasma free concentration estimated from mixed saliva concentration by using salivary pH and the equation of Matin et al. was used instead of plasma total concentration. Furthermore, the extent of absorption was obtained from the amounts of PHT and its metabolites, $p$-hydroxyphenylphenylhydantoin and its glucuronide, excreted in urine and feces.

MATERIALS AND METHODS

Drugs and Subjects—PHT powder (Aleviatin®; Dainippon Pharmaceutical Co., Ltd., Osaka) was purchased from commercial sources.

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and of the Pharmacopoeia of Japan (JP) grade. Two brands of PHT tablet [Hydantol Tablet 25 mg (PHT 25 mg/tablet, Tablet-A, Fujinaga Pharmaceutical Co., Ltd., Tokyo) and Aleviatin® Tablet (PHT 100 mg/tablet, Tablet-B, Dainippon Pharmaceutical Co., Ltd.)] were purchased from commercial sources and of JP grade. All preparations contained the free acid PHT. All other reagents were commercially available and of analytical or reagent grade, except n-heptane which was of spectrophotometric grade.

Four adult subjects, one female and three males, were volunteers from the authors, and they were healthy as judged by ordinary clinical examination. Their age and weight were shown in Table I.

**Single Dose Study** — Each subject received single oral doses of 50, 100, and/or 150 mg for three PHT products as shown in Table I in a randomized sequence. Each single oral dose study was carried out three times every two weeks. At 10 a.m., 2 h after breakfast, each subject was administered with a PHT product wrapped in a medical wafer together with about 150 ml of water.

About 6 ml of mixed saliva were drawn by the aid of mouth and tongue movement alone into plastic tubes with stopper at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 h after oral administration of PHT. The saliva samples were collected for about 5 min, and the midpoint of a sample collection period was referred to as the sampling time. The salivary pH was determined as soon as possible by a pH meter, and the saliva samples were frozen at $-20^\circ\text{C}$ until analyzed.

Urine was collected at 24 h intervals for 144 h after administration of PHT, and its volume and pH were recorded. Feces were collected up to 144 h after administration of PHT. Each sample was added with about 1000 ml of 0.2 N NaOH and homogenized by a mixer for 5 min. Subsequently it was added 0.2 N NaOH up to 1500 or 2000 ml. A portion of the urine and homogenized feces were kept frozen at $-20^\circ\text{C}$ until analyzed.

**Multiple Dose Study** — Two male subjects (S.I. and Y.K.) and one female subject (K.N.) were administered with PHT products wrapped in medical wafer together with about 150 ml of water at every 10 a.m. and 10 p.m.

About 6 ml of mixed saliva were collected at 2, 4, 6, 8, 10, and 12 h after 10 a.m. dose, and at 2 and 12 h after 10 p.m. dose. When last dose was administered, sampling was continued at convenient times until salivary PHT concentrations became negligible. If necessary, blood was collected simultaneously to salivary sampling during PHT administration. The blood sample was drawn into heparinized plastic tube, plasma was immediately separated by centrifugation and kept frozen at $-20^\circ\text{C}$ until analyzed.

Urine and feces were collected during PHT administration and until PHT and its metabolites became undetectable in urine and feces after the last dose. Subsequently urine and feces were

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Dose (mg) Powder</th>
<th>Dose (mg) Tablet-A</th>
<th>Dose (mg) Tablet-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. I.</td>
<td>M</td>
<td>43</td>
<td>65</td>
<td>50</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>Y.K.</td>
<td>M</td>
<td>30</td>
<td>58</td>
<td>50</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>Y. S.</td>
<td>M</td>
<td>47</td>
<td>62</td>
<td>150</td>
<td>150</td>
<td>-</td>
</tr>
<tr>
<td>K.N.</td>
<td>F</td>
<td>34</td>
<td>51</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**TABLE I. Subject Characteristics and Dose Schedule of Phenytoin**
treated in the same manner as the single dose study. Administration of PHT was suspended at least three weeks between successive two runs of studies.

**Determination Procedures of PHT Concentration in Plasma, Plasma Water, and Mixed Saliva** — After defrosting and mixing, the mixed saliva sample was centrifuged at 3000 rpm by a centrifugal separator for 5 min. Two to four ml of the supernatant fluid were used for the determination of PHT concentration in saliva (C_s). After defrosting, 0.4 ml of plasma was used for the determination of total PHT concentration in plasma (C_p). About 0.2 ml of plasma water was obtained from 2 ml of plasma by using ultrafiltration method and was used for the determination of free PHT concentration in plasma (C_f). Ultraviolet spectrophotometric method was used for the determination of PHT concentration. The equation of Matin et al. was employed to calculate C_est from C_s, assuming that pH of plasma was 7.4, pK_a of PHT was 8.3, and fraction of PHT bound to protein was negligible in saliva.

**Determination Procedures of PHT and Its Metabolites in Urine** — p-Hydroxyphenylphenylhydantoin (HPPH) and its glucuronic acid conjugate, the main metabolites in humans, and PHT in urine were determined after hydrochloric acid hydrolysis by the ultraviolet spectrophotometry incorporated with thin layer chromatography.

**Determination Procedure of PHT and Its Metabolite in Feces** — After defrosting and stirring, homogenized feces was centrifuged at 3000 rpm for 5 min. One ml of supernatant fluid was added with 0.5 ml of 1 N HCl and 20 ml of diethylether, and shaken for 10 min. After centrifugation at 3000 rpm for 5 min, 18 ml of organic phase was transferred to the other test tube and was evaporated in vacuo. The residue was dissolved in methanol, PHT and HPPH were determined by a similar method to urine. PHT and HPPH were not adsorbed with solid bodies in feces, and PHT was not formed from HPPH in feces. These facts were confirmed by addition recovery tests carried out prior to this determination.

**Calculation of Pharmacokinetic Parameters and Simulation of C_est - Time Course** — Since the concentration of PHT in body fluid was sufficiently low in a single dose of PHT, the disposition of PHT was approximated by the one-compartment open model with apparent first-order absorption and elimination. The first-order rate constants for absorption (k_a) and elimination (k_e) were calculated by the method of residuals. The amount of absorption (D_f) of PHT was calculated by substitution for the amounts excreted in feces from dose of PHT, and by dividing D_f by the dose (D), the fraction of absorption (f) was obtained. The area under the C_est-time curve (AUC) was calculated by the trapezoidal rule and area to infinite time was added by integration (C_est/k_e), where C_est is the last value of C_est of PHT. The apparent volume of distribution (V_d) was calculated according to the following equation.

\[
V_d = D_f/(k_e\cdot AUC)
\]

In case of multiple dose studies on two subjects (Y.K. and K.N.), the simulation of C_est-time course was carried out by using the one-compartment open model with apparent first-order absorption and apparent Michaelis-Menten elimination. The simulation for subject S.I. was based on the first-order rate constants for absorption and elimination, because he could not carry out the multiple dose study in high dose of PHT to obtain the Michaelis-Menten parameters due to the side effects. The absorption rate constant was obtained from the single dose on each subject. The optimum numerical values of the Michaelis-Menten parameters for each subject were obtained by nonlinear least-squares iteration of the differential equation (1), and by the use of C_est-time data in the period later than 36 h after last dose on multiple dose study (subject Y.K.: 150 mg/12 h of Tablet-A, subject K.N.: 100 mg/12 h of Tablet-A).
\[
\frac{-dC_{\text{est,f}}}{dt} = \frac{V_{\text{max}} \cdot C_{\text{est,f}}}{K_m + C_{\text{est,f}}}
\]

where \(V_{\text{max}}\) (\(\mu\text{g/ml/h}\)) is the maximum rate of elimination, and \(K_m\) (\(\mu\text{g/ml}\)) is the \(C_{\text{est,f}}\) of PHT at which the rate of elimination is one-half the maximum rate.

The simulations of \(C_{\text{est,f}}\)-time course on multiple dose study were carried out by using the differential equation (2) and (3) for tablet.

\[
\frac{dDf}{dt} = -k_a \cdot Df
\]

\[
\frac{dC_{\text{est,f}}}{dt} = \frac{k_a \cdot Df}{Vd} - \frac{V_{\text{max}} \cdot C_{\text{est,f}}}{K_m + C_{\text{est,f}}}
\]

where \(Df\) is briefly the amount absorbed of PHT from PHT tablet per administration, \(i.e.,\) per 12 h (mg/kg), and \(k_a\) is the first-order rate constant for absorption (h\(^{-1}\)).

In preliminary experiments, the absorption phase was approximated by a monoexponential curve up to about 1.5 mg/kg of PHT powder or 3 mg/kg of that tablet in single dose, and the rate constant for absorption in each dosage form was approximately constant in the same subject. However, the absorption phase was approximated by a biexponential curve rather than a monoexponential that was more than about 1.5 mg/kg of PHT powder. Consequently, the simulations of \(C_{\text{est,f}}\)-time curves on multiple dose study were carried out by assuming the fairly rapid and slow phase for absorption, and by using the differential equation (4) and (5) for powder. The differential equations and prerequisite are as follows:

\[
\frac{dDf}{dt} = -k_a \cdot D_1 - k_{a2} \cdot D_2
\]

\[
\frac{dC_{\text{est,f}}}{dt} = \frac{k_a \cdot D_1 + k_{a2} \cdot D_2}{Vd} - \frac{V_{\text{max}} \cdot C_{\text{est,f}}}{K_m + C_{\text{est,f}}}
\]

\(Df = D_1 + D_2\). When \(Df \leq 1.5 \text{ mg/kg}\), \(Df = D_1\) and \(D_2 = 0\). When \(Df > 1.5 \text{ mg/kg}\), \(D_1 = 1.5 \text{ mg/kg}\) and \(D_2 = Df - 1.5 \text{ mg/kg}\).

Where \(D_1\) is the amount absorbed fairly rapidly (up to about 1.5 mg/kg parts of PHT) from each dose of powder, and \(D_2\) is that absorbed slowly (residual parts of PHT). And \(k_a\) and \(k_{a2}\) are the first-order rate constants for absorption corresponding to \(D_1\) and \(D_2\), respectively. These simultaneous differential equations were numerically integrated by the method combined Runge-Kutta-Gill method with Milne’s method.

These fitting and simulation were carried out using the HITAC 8800/8700 digital computer (Computer Centre University of Tokyo) and the ACOS 600 digital computer (Hospital Computer Center, University of Tokyo Hospital), respectively.

Relationship between Daily Dose and Mean \(C_{\text{est,f}}\) of PHT at Steady-State on Multiple Dose Study

—Relationship between the daily dose and the mean \(C_{\text{est,f}}\) of PHT at steady-state on multiple dose was described by the equation (6) as follows:

\[
D = \frac{D_{\text{max}} \cdot C_{\text{est,f}}}{K_m' + C_{\text{est,f}}}
\]

where \(D\) is the daily dose (mg/kg/d), \(C_{\text{est,f}}\) is the mean value of \(C_{\text{est,f}}\) in daytime obtained by dividing the AUC of 10 a.m. to 10 p.m. by 12 h at steady-state in the last 3 to 4 d on multiple dose study, \(D_{\text{max}}\) is the maximum velocity (maximum rate of administration, mg/kg/d) and \(K_m'\) is Michaelis constant (the \(C_{\text{est,f}}\) of PHT at which the rate of administration is one-half the maximum velocity, \(\mu\text{g/ml}\)). The optimum numerical values of Michaelis-Menten parameters \((D_{\text{max}}\) and \(K_m')\) were obtained by nonlinear leastsquares iteration using the ACOS 600 digital computer.

RESULTS

1. Relationship among \(C_P\), \(C_f\), \(C_P\), and \(C_{\text{est,f}}\)

Each mean value ± S.D. of the ratio of \(C_f/C_P\), \(C_s/C_f\), \(C_{\text{est,f}}/C_f\) and \(C_{\text{est,f}}/C_P\) for seven samples in the two subjects carried out multiple dose study was 0.099 ± 0.002, 0.909 ± 0.008, 0.988 ± 0.021 and 0.097 ± 0.004, respectively. There was good agreement between \(C_{\text{est,f}}\) and \(C_f\).
2. Single Dose Study

Urinary and Fecal Excretion of PHT and Its Metabolites — The extents were shown in Table II. The values of HPPH in urine and in feces were expressed as the sum of free HPPH and HPPH-glucuronide. However, HPPH conjugated with glucuronic acid was absent in feces. When HPPH-glucuronide was incubated with slurry feces diluted with normal saline at 37°C, that was immediately converted into HPPH. Accordingly, it is probable that HPPH-glucuronide excreted in bile is immediately hydrolyzed in intestinal tract.

Since PHT is thought to be neither excreted in bile, nor changed in gastrointestinal tract, about 1% excretion of PHT in feces in the Table II indicates that almost all quantity of PHT in Tablet-A was absorbed through gastrointestinal tract. Similar result was obtained with Tablet-B.

In contrast, the extent of PHT excretion in feces following PHT powder administration was larger than that after tablet administration as shown in Table II.

$C_{\text{est,f}}$-Time Course — The typical $C_{\text{est,f}}$-time courses obtained after the single oral administration were shown in Fig. 1, and the pharmacokinetic parameters obtained from the $C_{\text{est,f}}$-time data were shown in Table III.

The $k_e$ and $Vd$ values obtained in this study were in good agreement in every subject. The AUC values obtained with PHT tablet were proportional to the dose, while those obtained with PHT powder were not proportional to the dose but proportional to the amount of PHT absorbed. Thus the capacity-limited disposition was scarcely occurred in a single dose study.

The rate constant of absorption for Tablet-B was larger than for Tablet-A, but the AUCs for both tablets were equivalent in two subjects. Since Tablet-A (PHT 25 mg/tablet) was more convenient to adjust its dosage, it was used in the following multiple dose study.

3. Multiple Dose Study

Urinary and Fecal Excretion of PHT and Its Metabolites — The extents of excretion were shown in Table IV. In case of tablet administration, the extent of PHT excretion in feces were about 1% in every subject and dose level. In case of PHT powder administration, however, the extents ranged from 9 to 25%, and increased upon increase of dose in the subject Y.K.

### TABLE II. Percent of Dose of Phenytoin (PHT) and Its Metabolites as p-Hydroxyphenylphenylhydantoin (HPPH) excreted in Urine and Feces after Single Oral Dose of PHT in Four Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dosage form</th>
<th>Dose (mg)</th>
<th>Urine</th>
<th>Feces</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PHT</td>
<td>HPPH</td>
<td>PHT</td>
</tr>
<tr>
<td>S. I.</td>
<td>Tablet-A</td>
<td>50</td>
<td>0.3±0.1</td>
<td>97.1±1.1</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td></td>
<td>Powder</td>
<td>50</td>
<td>0.2±0.1</td>
<td>89.5±0.7</td>
<td>9.5±3.7</td>
</tr>
<tr>
<td>Y.K.</td>
<td>Tablet-A</td>
<td>50</td>
<td>0.4±0.2</td>
<td>98.8±0.4</td>
<td>0.9±0.3</td>
</tr>
<tr>
<td></td>
<td>Powder</td>
<td>50</td>
<td>0.2±0.2</td>
<td>85.2±15.2</td>
<td>150±13.9</td>
</tr>
<tr>
<td></td>
<td>Tablet-A</td>
<td>150</td>
<td>0.3±0.1</td>
<td>97.0±1.4</td>
<td>0.8±0.8</td>
</tr>
<tr>
<td></td>
<td>Powder</td>
<td>150</td>
<td>0.2±0.1</td>
<td>76.8±6.5</td>
<td>19.9±5.9</td>
</tr>
<tr>
<td>Y. S.</td>
<td>Tablet-A</td>
<td>100</td>
<td>0.6±0.2</td>
<td>98.2±2.4</td>
<td>0.6±0.4</td>
</tr>
<tr>
<td></td>
<td>Tablet-B</td>
<td>100</td>
<td>0.4±0.1</td>
<td>99.0±3.1</td>
<td>0.5±0.3</td>
</tr>
<tr>
<td></td>
<td>Powder</td>
<td>100</td>
<td>0.5±0.2</td>
<td>89.1±10.4</td>
<td>9.1±2.1</td>
</tr>
<tr>
<td>K.N.</td>
<td>Tablet-A</td>
<td>100</td>
<td>0.3±0.3</td>
<td>97.6±3.7</td>
<td>0.7±0.7</td>
</tr>
<tr>
<td></td>
<td>Tablet-B</td>
<td>100</td>
<td>0.7±0.2</td>
<td>96.9±4.6</td>
<td>0.5±0.2</td>
</tr>
<tr>
<td></td>
<td>Powder</td>
<td>100</td>
<td>0.6±0.2</td>
<td>85.4±13.1</td>
<td>10.3±4.3</td>
</tr>
</tbody>
</table>

Each observed value is expressed as the mean ± S.D. of three experiments.
**C_{est,f} - Time Course** — The values of $V_{\text{max}}$ and $K_m$, the parameters for elimination of PHT, were obtained from $C_{\text{est,f}}$-time data in the period later than 36 h after the last dose on multiple dose as 0.039 μg/ml/h and 0.512 μg/ml for subject Y.K., and 0.055 μg/ml/h and 0.788 μg/ml for subject K.N., respectively. For each subject, the $V_{\text{max}}/K_m$ value was in fair agreement with the first-order rate constant for elimination, $k_e$ in Table III, obtained from the single dose study.

**FIG. 1. Typical Time Course of Estimated Free Concentration (C_{est,f}) of Phenytoin (PHT) after Single Oral Dose of PHT in Four Subjects**

- ○: tablet-A 50 mg, △: tablet-A 100 mg, ▽: tablet-A 150 mg, □: tablet-B 100 mg, ●: powder 50 mg,
  ▲: powder 100 mg, ▼: powder 150 mg.
Fig. 2 and 3 showed the simulated and observed values obtained by the multiple dose studies, using PHT tablet and powder, respectively. The $C_{\text{est}}$-time courses, described in dotted lines, were simulated by the simultaneous differential equations (2)–(5), substituting the values observed from the single dose study to $k_a$, $k_{a2}$ and $Vd$, and those from multiple dose study to $V_{\text{max}}$, $K_m$ and $f$. In these figures, symbols showed the values of minimum $C_{\text{est}}$ obtained.

**TABLE III.** Pharmacokinetic Parameters of Phenytoin (PHT) after Single Oral Dose of PHT in Four Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dosage form</th>
<th>Dose (mg)</th>
<th>$Vd$ (l/kg)</th>
<th>$k_a$ (h$^{-1}$)</th>
<th>$k_e$ (h$^{-1}$)</th>
<th>AUC (µg·h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. I.</td>
<td>Tablet-A</td>
<td>50</td>
<td>7.94</td>
<td>0.87</td>
<td>0.044</td>
<td>2.18±0.19$^a)$</td>
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<td></td>
<td>Powder</td>
<td>50</td>
<td>8.18</td>
<td>0.47</td>
<td>0.045</td>
<td>1.49±0.19</td>
</tr>
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<td>Y.K.</td>
<td>Tablet-A</td>
<td>50</td>
<td>6.92</td>
<td>0.67</td>
<td>0.067</td>
<td>1.85±0.01</td>
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<tr>
<td></td>
<td></td>
<td>150</td>
<td>6.69</td>
<td>0.61</td>
<td>0.067</td>
<td>5.73±0.02</td>
</tr>
<tr>
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<td>Powder</td>
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<td>7.16</td>
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<td>0.066</td>
<td>1.56±0.30</td>
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<tr>
<td></td>
<td></td>
<td>150</td>
<td>7.51</td>
<td>0.28</td>
<td>0.064</td>
<td>4.32±0.48</td>
</tr>
<tr>
<td>Y. S.</td>
<td>Tablet-A</td>
<td>100</td>
<td>7.95</td>
<td>0.57</td>
<td>0.061</td>
<td>3.66±0.22</td>
</tr>
<tr>
<td></td>
<td>Tablet-B</td>
<td>100</td>
<td>7.90</td>
<td>0.82</td>
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<td>3.70±0.17</td>
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<td>Powder</td>
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<td>7.80</td>
<td>0.40</td>
<td>0.060</td>
<td>2.87±0.31</td>
</tr>
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<td>K.N.</td>
<td>Tablet-A</td>
<td>100</td>
<td>6.01</td>
<td>0.61</td>
<td>0.067</td>
<td>4.68±0.09</td>
</tr>
<tr>
<td></td>
<td>Tablet-B</td>
<td>100</td>
<td>6.10</td>
<td>0.78</td>
<td>0.067</td>
<td>4.65±0.12</td>
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<tr>
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<td>Powder</td>
<td>100</td>
<td>5.97</td>
<td>0.25</td>
<td>0.068</td>
<td>4.41±0.44</td>
</tr>
</tbody>
</table>

*Each observed value is expressed as the mean of three experiments.

*Vd*: apparent volume of distribution, $k_a$: first-order rate constant for absorption, $k_e$: first-order rate constant for elimination, AUC: total area under the $C_{\text{est}}$-time curve. $a$) mean ± S.D. $b$) $k_{a2}$ (see text).

**TABLE IV.** Percent of Dose of Phenytoin (PHT) and Its Metabolites as p-Hydroxyphenylphenylhydantoin (HPHPH) excreted in Urine and Feces during Multiple Dose of PHT in Three Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dosage form</th>
<th>Dose (mg)</th>
<th>Urine</th>
<th>Feces</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PHT</td>
<td>HPPH</td>
<td>PHT</td>
</tr>
<tr>
<td>S. I.</td>
<td>Tablet-A</td>
<td>50</td>
<td>1.0</td>
<td>96.2</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Powder</td>
<td>50</td>
<td>0.9</td>
<td>89.7</td>
<td>4.7</td>
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<tr>
<td>Y.K.</td>
<td>Tablet-A</td>
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<td>0.7</td>
<td>96.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Powder</td>
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<td>0.7</td>
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</table>
Bioavailability of Phenytoin

just before administration of PHT and those of $C_{ext,f}$ following the last dose.

The observed values of $C_{ext,f}$ were in fair agreement with the calculated values of that every subject and dose level in case of PHT tablet administration as shown in Fig. 2. On the contrary, the variation and discrepancy from calculated values were observed in $C_{ext,f}$ using higher dose of PHT powder as seen in Fig. 3.

However, in low dose level of 50 mg per 12 h (subject Y.K.), each $C_{ext,f}$ value calculated using the first-order or the Michaelis-Menten rate constant for elimination and the first-order rate constant for absorption was in agreement with the observed value for both forms on multiple dose.

The values of $C_{ext,f}$ at steady-state after tablet administration were clearly higher than those following powder administration to the subjects.

FIG. 2. Time Course of Minimum Estimated Free Concentration ($C_{ext,f}$) of Phenytoin (PHT) during Multiple Dose of PHT Tablet in Three Subjects

The dotted lines show the computer-simulated curves for $C_{ext,f}$: ○: Y.K. 150 mg/12 h, △: Y.K. 100 mg/12 h, □: Y.K. 50 mg/12 h, ◆: K.N. 100 mg/12 h, ▽: S.I. 50 mg/12 h.

FIG. 3. Time Course of Minimum Estimated Free Concentration ($C_{ext,f}$) of Phenytoin (PHT) during Multiple Dose of PHT Powder in Three Subjects

The dotted lines show the computer-simulated curves for $C_{ext,f}$: ●: Y.K. 150 mg/12 h, ▲: Y.K. 100 mg/12 h, ◇: Y.K. 50 mg/12 h, ○: K.N. 100 mg/12 h, ▼: S.I. 50 mg/12 h.

FIG. 4. Relationship between Daily Dose and Mean Estimated Free Concentration ($C_{ext,f}$) of Phenytoin (PHT) at Steady-State in Subject Y.K.

Each point and vertical bar indicate the mean value of $C_{ext,f}$ in daytime obtained dividing the AUC of 10 a.m. to 10 p.m. by 12 h at steady-state and the standard deviation in the last 3 to 4 d on multiple dose study, respectively.

The curves were drawn by optimum parameters calculated from computer using the Michaelis-Menten equation.

○: tablet-A, ●: powder.
at the same dose level except 50 mg.

4. Relationship between Daily Dose and Mean $C_{ext,f}$ of PHT at Steady-State on Multiple Dose Study

Fig. 4 showed the relationship between the daily dose and mean $C_{ext,f}$ of PHT in daytime at steady-state in subject Y.K. The optimum value $\pm$ S.E. of the Michaelis-Menten parameters were as follows: $D_{max} = 7.08 \pm 0.07$ mg/kg/d, $K_m' = 0.44 \pm 0.01 \mu g/ml$ in case of tablet; $D_{max} = 9.42 \pm 0.59$ mg/kg/d, $K_m' = 0.58 \pm 0.07 \mu g/ml$ in case of powder.

DISCUSSION

The extent of PHT absorption from PHT powder is low and decreases upon increase of dose. These phenomena demonstrated by fecal excretion of PHT in the present study coincided with those of our previous report 8) which were observed in the urinary excretion of PHT in epileptic children.

As stated in previous reports 3,8) the extent of PHT absorption from powder form was proved to be not only lower than tablet form, but also decreased upon increase of dose. As a result of that, $D_{max}$ in powder ($D_{max,p}$) becomes not only larger than that in tablet ($D_{max,t}$), but $K_m'$ in powder ($K_{m',p}$) also apparently becomes larger than that in tablet ($K_{m',t}$). Since it is confirmed that almost all quantity of PHT in tablet is absorbed through gastrointestinal tract, tablet/powder ratio of dose which provided the same level of PHT concentration is the absorption ratio from PHT powder. Consequently, the relationship between absorption ratio of PHT powder ($fr$) and daily dose of that ($D_p$) is logically formulated as a general equation which is

$$fr = D_{max,t} \cdot K_{m',t} / [(K_{m',t} \cdot D_{max,p} + D_p(K_{m',p} - K_{m',t}))].$$

The $fr$ values calculated from data in subject Y.K. at each level of 1.72, 3.45 or 5.17 mg/kg/d are 94, 89 or 84%, respectively, and are in fair correspondence to the excretion of PHT in feces in Table IV. Consequently, the validity of the above logical equation is confirmed.

In case of tablet, the scarcely wettable surfaces of PHT crystal are covered with hydrophilic binders such as starch paste, and thus higher dissolution rate and higher absorption rate of PHT will be resulted.

Even in therapeutic dose levels of 100 mg or 150 mg per 12 h, each $C_{ext,f}$ value calculated using the first-order rate constant for absorption in the single dose and the Michaelis-Menten rate constant for elimination in the multiple dose was in agreement with the observed value for tablet form (Fig. 2). Further, in subject Y.K., the $K_m'$ value is nearly equal with the $K_m$ value, and the $D_{max}$ value is in agreement with the value calculated by an equation as follows:

$$D_{max} (mg/kg/d) = 24 \cdot V_{max} (\mu g/ml/h) \cdot Vd (l/kg).$$

These results indicate that the $D_{max}$ and $K_m'$ values to the subject can be estimated from the $V_{max}$ and $K_m$ values, when PHT tablet is administered. If such parameters ($Vd$, $k_{as}$, $V_{max}$, $K_m$) are obtained with a patient, an ideal dosage regimen will be certainly estimated.

The observed $C_{ext,f}$ values of PHT obtained from 100 mg or 150 mg of PHT powder administration in Fig. 3 were much different from calculated ones assuming the extent of absorption was constant (see method). This is probably the reason for the variation in the extent of PHT absorption in every administration. The variation of PHT concentration in the administration of PHT powder in patients may result in unstable therapeutic effects, and not be reliable for the establishment of the dosage regimen for a patient under PHT powder administration.

From these viewpoints, it is undesirable to administer PHT powder to the patients, and development of powder form having the same property to tablet for the absorption 10) are urgently required not only for pediatric patients but for adult those.

REFERENCES

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