Single-Dose Kinetics of Primidone in Human Subjects: Effect of Phenytoin on Formation and Elimination of Active Metabolites of Primidone, Phenobarbital and Phenylethylmalonamide

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Effect of repetitive administration of phenytoin (PHT) on the single-dose pharmacokinetics of primidone (PRM) was investigated in 3 healthy male subjects. The peak concentration of unchanged PRM was achieved at 12 and 8 h after the administration of PRM in the absence and the presence of PHT, respectively. The elimination half-life of PRM was decreased from 19.4 ± 2.2 (mean ± S.E.) to 10.2 ± 5.1 h (p < 0.05) and the total body clearance was increased from 24.6 ± 3.1 to 45.1 ± 5.1 ml/h/kg (p < 0.01) in the presence of PHT. No significant change was observed for the apparent volume of distribution between the two treatments. In the absence of PHT, the measurable amount (≥0.1 μmol/l) of phenobarbital (PB) and phenylethylmalonamide (PEMA) did not appear in the serum until 5.3 and 1.3 h after the PRM administration, and the peak concentrations of PB and PEMA were achieved at 52 and 36 h, but the concentrations of both metabolites were very low (PB 1.3 μmol/l; PEMA 1.7 μmol/l). In the presence of PHT, within 0.8 and 0.5 h after the administration of PRM, the derived PB and PEMA appeared in the serum. About a 6-fold increase in the peak concentrations of both the metabolites were observed (PB 8.2 μmol/l; PEMA 11.0 μmol/l). No significant changes were observed for the elimination half-lives of both PB and PEMA in the absence and presence of PHT. These results indicate that the induction of the enzyme system responsible for the oxidation of PRM to PB and PEMA mainly contribute to the alteration in the PRM disposition by PHT in the single-dose condition.

Keywords — primidone; pharmacokinetics; active metabolite; phenobarbital; phenylethylmalonamide; interaction; phenytoin; human serum

Introduction

Primidone (PRM) is an antiepileptic drug used to treat partial complex and generalized tonic-clonic seizures. Previous investigations have demonstrated that PRM is partly metabolized in man to two active metabolites, phenobarbital (PB) and phenylethylmalonamide (PEMA).1—9 Effective clinical use of PRM, therefore, requires detailed information on its pharmacokinetics including the kinetics of the formation and the elimination of both the active metabolites. The serum level profile and pharmacokinetics of PRM after single-dose administration to healthy subjects and epileptic patients were previously examined in some detail.8—10 However, little information is available on the kinetics of the formation and the elimination of the active metabolites derived.

The PRM kinetics can be changed by other antiepileptic drugs, particularly phenytoin (PHT).3,6,9—13 The interaction between PRM and PHT is clinically important, because these drugs are often combined in the treatment of intractable seizures.3,6,9—13 Modification of the kinetics of PRM and its active metabolites may play a significant role in determining therapeutic and toxic effects during treatment with PRM.2,4

The present study was designed to investigate the single-dose kinetics of PRM based on the serum concentration–time data of PRM and its active metabolites in healthy subjects. The effect of repetitive administration of PHT on the single-dose kinetics of PRM was also investigated.

Materials and Methods

Subjects and Study Design — Three healthy
male volunteers (aged 22—51 years and weighing 55—68 kg) participated in the study after giving informed consent of written form. They were judged to be in good health on the basis of history, physical examination and routine clinical laboratory test (hemogram, urinalysis, total serum protein and serum albumin, total serum bilirubin, serum transaminases and alkaline phosphatase, serum creatinine, and electrolytes). None received any drugs for at least a month before the study. The study consists of 2 treatments, PRM alone and PRM with PHT. In one treatment, the subjects received a single oral dose of 600 mg PRM (Mysoline® granules, Dainippon Pharmaceutical Co.); in the other treatment they received PHT (Aleviatin® Tab., Dainippon Pharmaceutical Co.) orally twice daily (8:00 to 9:00 AM and 8:00 to 9:00 PM) for 28 to 30 d before a single oral dose of 600 mg PRM and thereafter for 10 d. PHT dose was adjusted to maintain serum PHT levels between 5 to 15 μg/ml. Each dose of PRM was given in the morning after an overnight fast and food was not allowed until 8 h after administration of PRM. Two of the subjects (No. 1 and 2) were treated at first with PRM alone, whereas the other (No. 3) was treated at first with PRM in the presence of PHT. A 4 to 5 weeks washout period separated the treatment periods.

Venous blood samples were drawn from the antecubital vein at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 120, 168, and 240 h after PRM. The separated serum samples were stored at −20 °C until analysis.

**Assay** — Concentrations of PRM and its active metabolites, PB and PEMA, in serum were determined by a sensitive HPLC method reported previously. The within-assay coefficients of variation over a 50 ng/ml to 20 μg/ml concentration range were less than 7.6% for PRM and the metabolites. The detection limit of the method was 10 ng/ml using 200 μl serum. PHT concentrations in serum were determined by a previous HPLC method. The within-assay coefficients of variation over a 0.5 to 20 μg/ml concentration range were less than 3.5%.

**Kinetic Analysis** — Peak serum concentration \( C_{\text{max}} \) and time to \( C_{\text{max}} \) \( t_{\text{max}} \) for PRM, PB and PEMA were directly read from the observed data. The elimination rate constant \( \lambda_2 \) was determined by linear regression of log-concentration versus time plots, using data obtained from the terminal monoexponential part of the curve. The half-life \( t_{1/2} \) was calculated by using the following equation, \( t_{1/2} = \ln 2 / \lambda_2 \).

The area under the serum concentration–time curve from time 0 to infinity \( (AUC) \) was calculated as the sum of the cumulative area obtained by the trapezoidal rule from time 0 to time of last sample \( t \), and \( C(t) / \lambda_2 \), where \( C(t) \) is the concentration at time \( t \). The total body clearance \( (CL) \) and the apparent volume of distribution \( (V_c) \) of PRM were estimated as Dose/AUC and Dose/(\( \lambda_2 \cdot AUC \)), assuming complete absorption of PRM.

**Statistical Analysis** — Statistical significance was calculated by Student’s \( t \)-test for paired data. \( p<0.05 \) was considered statistically significant.

**Results**

The serum concentrations of unchanged PRM and the active metabolites, PB and PEMA, after the single oral administration of PRM to healthy subjects in the absence (control) and presence of PHT are shown in Fig. 1. The pharmacokinetic parameters were listed in Table 1. The peak concentration of unchanged PRM was achieved at 12 and 8 h after a relatively slow absorption phase in the absence and presence of PHT, respectively. Then, the serum concentration of PRM declined more rapidly in the presence of PHT. The elimination half-life of PRM was shortened (19.4 ± 2.2 to 10.2 ± 0.4 h) and the total body clearance was increased (24.6 ± 3.1 to 45.1 ± 5.1 ml/h/kg) in the presence of PHT, significantly. No significant change was observed for the apparent volume of distribution between the two treatments.

The measurable amount (≥0.1 μmol/l) of PB and PEMA did not appear in the serum until 5.3 and 1.3 h after the administration of PRM in the absence of PHT. The peak concentrations of PB and PEMA were achieved at about 52 and 36 h, but the concentrations of both metabolites were extremely low (PB 1.3 μmol/l; PEMA 1.7 μmol/l). In the presence of PHT, on the other hand, within 0.8 and 0.5 h after the administra-
Fig. 1. Serum Concentrations of Unchanged Primidone (PRM) and Derived Metabolites, Phenobarbital (PB) and Phenylethylmalonamide (PEMA) after Oral Administration of a Single-Dose of 600 mg PRM to 3 Healthy Male Subjects in the Absence (Open Symbols) and Presence (Closed Symbols) of Phenytin (PHT).

(A) PRM; (B) PB; (C) PEMA; 1 μmol/l PRM = 0.218 μg/ml, 1 μmol/l PB = 0.252 μg/ml, 1 μmol/l PEMA = 0.206 μg/ml.
### Table 1. Pharmacokinetic Parameters of Unchanged Primidone (PRM) and Derived Metabolites, Phenobarbital (PB) and Phenytoethylmalonamide (PEMA), after a Single-Dose Administration of 600 mg PRM Orally to Healthy Subjects in the Absence (Control: CON) and Presence of Phenytoin (PHT)

<table>
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<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Weight (kg)</th>
<th></th>
<th>$t_{\text{max}}$ (h)</th>
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<tr>
<td></td>
<td></td>
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<td>CON</td>
<td>PHT</td>
<td>CON</td>
<td>PHT</td>
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<td>CON</td>
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<td>37.0</td>
<td>18.8</td>
<td>10.0</td>
<td>1709</td>
<td>967</td>
<td>29.3</td>
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</tr>
<tr>
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<td>12</td>
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<tr>
<td>3</td>
<td>M</td>
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<td>12</td>
<td>8</td>
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<td>51.3</td>
<td>23.5</td>
<td>10.9</td>
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<tr>
<td>Mean</td>
<td></td>
<td>36</td>
<td>61</td>
<td>12</td>
<td>8</td>
<td>41.2</td>
<td>40.6</td>
<td>19.4</td>
<td>10.2</td>
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<td>24.6</td>
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<td>5.4</td>
<td>2.2</td>
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<td>134</td>
<td>3.1</td>
<td>5.1</td>
<td>0.06</td>
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| Subject No. | $t_{\text{sp}}$ (h) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|             | CON | PHT | CON | PHT | CON | PHT | CON | PHT | CON | PHT | CON | PHT | CON | PHT | CON | PHT | CON | PHT |
| 1           | 8 | 1 | 36 | 48 | 1.2 | 6.9 | 106 | 101 | 242 | 1296 | 1 | 0.5 | 36 | 24 | 1.6 | 9.8 | 27.0 | 24.6 | 124 | 680 |
| 2           | 4 | 1 | 72 | 48 | 1.6 | 10.9 | 103 | 97 | 341 | 2058 | 1 | 0.5 | 36 | 36 | 2.3 | 14.1 | 27.8 | 25.2 | 212 | 1053 |
| Mean        | 5.3 | 0.8 | 52 | 44 | 1.3 | 8.2 | 125 | 101 | 288 | 1554 | 1 | 0.5 | 36 | 28 | 1.7 | 11.0 | 26.5 | 20.7 | 143 | 724 |
| S.E.        | 1.3 | 0.2 | 11 | 4 | 0.2 | 1.4 | 20 | 3 | 29 | 252 | 0.3 | 0 | 4 | 0.3 | 1.6 | 1.0 | 2.3 | 36 | 179 |

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$a)$ $t_{\text{sp}}$, time when the measurable amount (0.1 µmol/l) of the metabolites appeared in the serum. $b$—$e$) Significantly different from control value (paired $t$-test): $p<0.05$, $c)$ $p<0.02$, $d)$ $p<0.01$, $e)$ $p<0.001$. 

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tion of PRM, the measurable amount of PB and PEMA appeared in the serum, and the peak concentrations were achieved somewhat quickly as compared with those observed in the absence of PHT. Moreover, about a 6-fold increase in the peak concentrations of both the metabolites were observed (PB 8.2 µmol/l; PEMA 11.0 µmol/l). No significant differences were observed for the elimination half-lives of both PB and PEMA between the two treatments.

Discussion

Following single-dose administration of PRM to man, the pharmacokinetic information on the formation and the elimination of the active metabolites, PB and PEMA, is rather scarce. Only Pisani et al.8) have previously shown the plasma peak levels of PEMA derived after single-dose administration of PRM to normal subjects.

The present study clearly showed not only the serum concentration–time profiles of PRM and its active metabolites PB and PEMA following the single oral dose administration of PRM to healthy human subjects, but also the pharmacokinetic information on the formation and the elimination of both the metabolites. The elimination half-lives of parent PRM and the metabolites, PB and PEMA, estimated in the present control were nearly matched by those reported by previous investigators,8,16–20 in which each compound was administered independently to normal subjects.

In the presence of PHT, the elimination half-life of PRM was shortened and the total body clearance was increased. The measurable amount of the derived metabolites appeared in the serum more rapidly. In addition, the 5 to 6 fold increases in the peak concentrations and the AUCs of both metabolites were observed, although the difference in the AUC of PEMA was not statistically significant (0.05 < p < 0.1). Previous investigators have demonstrated that the plasma concentrations of PB and PEMA in patients taking PRM with PHT on a chronic basis were higher than those in patients taking PRM alone.3,6,9–13) Concerning the mechanisms involved in the PHT effect on the PRM disposition in man, the induction of the enzyme system responsible for the oxidation of PRM to PB and PEMA, and/or the inhibition of the hydroxylation or renal excretion of PB were considered.3,6,9–13) In this regard, the present results, as no significant changes were observed for the elimination half-lives of PB and PEMA, strongly suggest that the induction of PRM metabolism mainly contribute to the alteration in PRM disposition by PHT at least in the single-dose condition. For full understanding of the contribution of other possible mechanisms such as the inhibition of metabolism or impaired renal excretion of PB or PEMA, however, further studies on the kinetics of the renal excretion of PRM and the metabolites will be needed. Binding of PRM to plasma proteins may not play an important role in this interaction because of its low plasma protein binding.21

The PHT effect on the peak concentrations and the AUCs of PB and PEMA in the single-dose condition was extensively large (5 — 6 fold) as compared with that on the steady state concentrations of PB and PEMA observed in patients taking PRM on a chronic basis,3,6,9–13) in which the increases in the steady state concentrations of the metabolites by PHT were less than twice. It is inferred that the biotransformation of PRM to PB and PEMA would be increased by autoinduction during continued use of PRM. However, further detailed investigations are necessary to definitively determine whether induction of PRM metabolism is a main cause of the increase in the plasma concentration of PB and PEMA in patients taking PRM with PHT on a chronic basis.

References

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