Population pharmacokinetics of phenytoin from routine clinical data in Saudi Epileptic Patients

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**Introduction**

Phenytoin (PHT) is an anticonvulsant widely used in the treatment of partial seizures, generalized tonic-clonic seizures and status epilepticus. The narrow therapeutic range and the nonlinear pharmacokinetic profile of the drug often constitute a difficulty for the optimization and individualization of its dosage regimen in patients of all ages. The pharmacokinetics of PHT are usually complicated by capacity-limited metabolism, interindividual variability, ethnic differences and drug interaction with concomitantly-administered medications. Because of the nonlinear kinetics manifested by PHT, small differences in the amount absorbed could result in larger changes in plasma concentrations in patients. Genetic differences and the effect of saturation kinetics are considered more important determinant of steady-state plasma concentration of PHT than any other variable (Houghton 1975).

Several studies have reported the pharmacokinetic parameters ($V_m$ and $K_m$) in various ethnic populations. Data relating to these parameters in Arab population are limited and controversial.

Recently, genetic polymorphism has been clarifying in cytochrome P450 enzymes in the liver, proving the formerly known concept of slow and fast metabolizers (Wilder 2001).
Aaron et al. (Aaron 2005) stated that the values for $V_m$ and $K_m$ in the epileptic population on the Arabian Peninsula (Saudi Arabia and Oman) seem to be the highest reported so far among all world population.

Saudi Arabia studied using graphical method.
Oman studied adults only ($\geq 18$ years) (used NONMEM)
Therefore, we should study both to validate the results of other investigators.

Oman found no correlation of $V_m$ with age or weight. We found correlation with weight but not with age.
Methods

Patients

The study was conducted at King Khalid University Hospital (KKUH) in Riyadh between June 2003 and October 2004. Blood samples from 101 epileptic patients were collected prospectively during the routine outpatient visits based on the recommendations of neurologist treating the patient. The number of samples collected during the study period was 251 blood samples with at least 2 samples per patient at 2 different daily dosing levels in two consecutive visits, at least one month apart. The patient was on the same dosing regimen for at least one month prior to sample collection to ensure steady state. PHT was prescribed for these patients as a capsule (Dilantin®) or a suspension. All samples were collected after 4 hours of the last dose. No patients took drugs known to exhibit interactions with PHT. The patients were 1-90 years old (mean±SD, 30.87±20.22 years), were 4-126 cm tall (mean±SD, 151.77±26.59 cm) and weighed 4-126 kg (mean±SD, 60.49±24.74 kg). None of the patients had significant cardiovascular, gastrointestinal, hematologic, hepatic, renal, psychiatric disease or alcohol or drug abuse. Table 1 shows the detailed demographic characteristics of the patient population studied. Seventy eight patients were on PHT alone and the rest of the patients were concomitantly on another drug with PHT, where 12 patients were on carbamazepine, 6 on Phenobarbital, 4 on valproate sodium and one on other drug. The dose averaged 4.81±2.65 mg/kg/day (range, 1.15-20.0 mg/kg/day) and the average PHT serum concentration was 12.9±7.9 mg/L (range, 0.5-49.9 mg/L). The study protocol was reviewed and approved by the Institutional Review Board at King Khalid University Hospital (KKUH), College of Medicine, Research Center, and the College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.
For each subject, the initial estimates of the maximum rate of metabolism \(V_{\text{max}}\) and Michaelis constant \(K_m\) were obtained by applying the following relationships (Ludden 1977):

\[
-K_m = \frac{R_1 - R_2}{R_1 C_1 - R_2 C_2}
\]

\[
V_{\text{max}} = \frac{R_1}{C_1} (K_m + C_1)
\]

where \(R_1\) and \(R_2\) are the dosing rates (mg/day) at the corresponding steady-state serum concentrations \(C_1\) and \(C_2\), respectively. The apparent oral clearance values \((CL/F)\) were also initially calculated at a particular steady-state serum concentration \((C_{ss})\) by using the following equation:

\[
\frac{CL}{F} \left( L \cdot h^{-1} \cdot kg^{-1} \right) = D \left( mg \cdot kg^{-1} \right) \frac{C_{ss} \left( mg \cdot L^{-1} \right)}{K_m + C_{ss}} \cdot \tau
\]

and

\[
\frac{CL}{F} = \frac{V_{\text{max}}}{K_m + C_{ss}}
\]

where \(CL\) is the total body clearance of the drug, \(F\) is the oral bioavailability, \(D\) is the daily PHT dose \((mg.kg^{-1})\), \(C_{ss}\) is the steady-state plasma concentration \((mg.L^{-1})\) and \(\tau\) is the dosing interval (usually one day). The final estimates of \(V_{\text{max}}\) and \(K_m\) were obtained using population approach by fitting the data to the Michaelis-Menten equation:

\[
R_{ij} = \frac{V_{m_j} \cdot C_{ss_j}}{K_{m_j} + C_{ss_j}} + \epsilon_{ij}
\]

where \(R_{ij}\) is the rate of PHT administration of the \(i\)th dose in the \(j\)th patient, \(C_{ss_j}\) is the PHT steady-state serum concentration resulting from the \(i\)th dose in the \(j\)th patient,
$K_{m_j}$ is the Michaelis constant (mg/L) in the jth patient and $\varepsilon_{ij}$ is the error terms which are assumed to be independent and normally distributed with expected value zero and variance of $\sigma^2_{\varepsilon}$.

The influence of weight on $V_{\text{max}}$, and the influence of age on $K_m$ were also examined using the following equation (Yukawa 1989):

$$V_{\text{max}j} = V_{\text{max}} \left( \frac{W_j}{60} \right)^{\theta_w}$$

where $V_{\text{max}j}$ is the predicted maximum rate of metabolism for the jth patient, $W_j$ is the weight of the jth patient and $\theta_w$ is the power of weight for size adjustment of $V_{\text{max}}$.

**Statistical Analysis**

The deviations of each continuous variable data set such as age, body weight, drug doses, plasma drug concentrations, and the total body clearance values from a Gaussian distribution were assessed by means of the Shapiro-Wilks test and Kolmogorov–Smirnov goodness-of-fit test. The homogeneity of group variances was evaluated by means of Bartlett’s test. If data were found to be normally distributed with equal variances, then the mean and the standard deviation were calculated and compared using an appropriate parametric statistical technique such as the independent Student’s t-test for the comparison between two groups, or one-way analysis of variance (ANOVA) in the case of multiple comparisons. When deviations from a normal distribution and/or different variances were found, comparisons were performed using the Wilcoxon rank sum test or the Mann–Whitney U test for pairwise comparison or the Kruskal–Wallis test in the case of multiple comparisons.
Differences were considered statistically significant at P ≤ 0.05. Linear and non-linear regression models were tested to explore potential relationships and correlations between the demographic characteristics and the total body clearance values CL/F were performed. The validity of these models was confirmed by using a plot of the standardized predicted residuals and the adjusted predicted residuals. To compare the slopes and the intercepts of the resulting regression lines for various groups, the analysis of covariance (ANCOVA) was utilized. The relative contribution of each covariate to the variability in PHT clearance values was further assessed by using a linear regression model which included the following variables: age (years), body weight (kg), PHT dose, gender, and co-administered drugs. Each of the variables was added and removed from the equation in a stepwise manner to optimize the multiple regression equation, and variables whose contribution to the equation was below the assigned level of significance were ultimately excluded from the model. The data were initially analyzed using the Statistical Package for Social Sciences (SPSS) version 13.0 for Windows (SPSS Inc., Chicago, Illinois). Population pharmacokinetics were analyzed using nonlinear mixed-effects modeling software WinNonMix® version 2.0.1 (Pharsight Corporation, CA, USA).

**Results**

One-hundred and one patients were enrolled in the study. Their
Discussion

Do not forget the possibility of interethnic differences. It is really clear between Arabs and other populations.
References


12.
Table 1. Demographic Characteristics of the 101 Saudi epileptic patients.

<table>
<thead>
<tr>
<th>Population</th>
<th>Males</th>
<th>Females</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients ≤15 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>15</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>7.87±4.99 (1-15)</td>
<td>7.88±4.67 (1-15)</td>
<td>0.9982</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>26.43±15.31 (4-58)</td>
<td>18.96±8.37 (10-34)</td>
<td>0.2442</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>114.73±42.47 (35-172)</td>
<td>121.21±22.42 (99.5-154)</td>
<td>0.7102</td>
</tr>
<tr>
<td>Daily Dose (mg/day)</td>
<td>172.33±106.52 (15-300)</td>
<td>133.75±89.91 (40-300)</td>
<td>0.3941</td>
</tr>
<tr>
<td>PHT C&lt;sub&gt;ss&lt;/sub&gt; (mg/L)</td>
<td>11.3±5.9 (0.5-20.7)</td>
<td>11.5±7.4 (1.6-24.6)</td>
<td>0.9639</td>
</tr>
<tr>
<td><strong>Patients &gt;15 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>43</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.40±19.42 (17-90)</td>
<td>37.97±16.08 (16-77)</td>
<td>0.5873</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.28±15.87 (45-126)</td>
<td>66.85±11.77 (37-87)</td>
<td>0.0237*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.13±4.15 (156-178)</td>
<td>157.70±5.64 (145-172)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Daily Dose (mg/day)</td>
<td>290.70±64.79 (100-500)</td>
<td>300.0±171.5 (100-1200)</td>
<td>0.4887</td>
</tr>
<tr>
<td>PHT C&lt;sub&gt;ss&lt;/sub&gt; (mg/L)</td>
<td>12.7±7.3 (0.5-30.5)</td>
<td>14.2±9.5 (1.4-49.9)</td>
<td>0.7900</td>
</tr>
</tbody>
</table>

* Significant (Wilcoxon rank sum test)