Influence of aging on serum phenytoin concentrations:
a pharmacokinetic analysis based on therapeutic
drug monitoring data

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Abstract

The influence of aging on the pharmacokinetics of phenytoin at steady-state was evaluated retrospectively by comparing apparent oral clearance values (CL/F) in 75 patients aged 65–90 years (mean, 71.7 $\pm$ 5.3 years) receiving phenytoin alone ($n = 58$) or in combination with phenobarbital ($n = 17$) and in an equal number of control patients aged 20–50 years (mean, 36.7 $\pm$ 8.5 years) matched for gender, body weight, and comedication. All data were derived from the database of the therapeutic drug monitoring service (TDMS) of an academic neurological hospital. On average, elderly patients were found to exhibit slightly higher CL/F values compared with controls (14.6 $\pm$ 4.7 ml h$^{-1}$ kg$^{-1}$ versus 13.1 $\pm$ 4.2 ml h$^{-1}$ kg$^{-1}$, $P < 0.05$), the difference being probably related to the dose-dependent nature of phenytoin metabolism and the fact that elderly patients received lower dosages (4.4 $\pm$ 1.1 mg kg$^{-1}$ day$^{-1}$ versus 5.3 $\pm$ 1.1 mg kg$^{-1}$ day$^{-1}$, $P < 0.001$) and had lower serum phenytoin concentrations (14.1 $\pm$ 5.7 mg ml$^{-1}$ versus 18.6 $\pm$ 6.8 mg ml$^{-1}$, $P < 0.0001$). Gender and phenobarbital comedication were not found to exert any statistically significant influence on phenytoin CL/F. By contrast, in the elderly group, CL/F values were negatively correlated with age. On average, CL/F values decreased by about one-third between 65 and 85 years of age, but interindividual variability was considerable and age explained only 7.8% of the variation in CL/F in the elderly group. Overall, these findings indicate that aging is associated with a progressive decline in phenytoin clearance, presumably as a result of decreased drug metabolizing capacity. Because assessment was based on total serum phenytoin concentrations and the unbound fraction of phenytoin is known to decrease in old age, the influence of aging as quantified in this study may underestimate the magnitude of changes in the clearance of unbound, pharmacologically active drug.

Based on these data, it is prudent to utilize initially smaller phenytoin dosages in old patients, and to make subsequent dose adjustments based on clinical response and serum drug level measurements. Interpretation of the latter, however, should take into account the possibility of an increase in the fraction of unbound drug.

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1. Introduction

Epileptic seizures are common in the elderly, as indicated by an annual incidence which has been found...
to increase from 76 per 100,000 in sexagenarians to 179 per 100,000 in septuagenarians, and an overall prevalence of 13 per 1000 above 80 years of age (Tallis et al., 1991). Cerebrovascular disease is the most common cause of epileptic seizures with onset in old age. In particular, the incidence of epilepsy after stroke has been estimated to range between 3.4 and 15%, with higher rates being recorded after hemorrhagic than after ischemic stroke (Giroud et al., 1994; Lancman et al., 1993).

In the light of the above observations, it is not surprising that antiepileptic drugs (AEDs) are among the most commonly prescribed therapeutic agents in elderly people (Garrard et al., 2000). In a study of 996 residents of nursing homes in Minnesota, the prevalence of AED use was as high as 7.7% (Cloyd et al., 1994). In another survey of five pharmacy provider organizations in the US, 892 (8.8%) out of 10,168 nursing home residents were found to receive AEDs for the treatment of epilepsy, and an additional 2.2% were prescribed AEDs for other conditions, including psychiatric disorders and neuropathic pain (Schachter et al., 1998). While AED use may be lower in community dwelling residents (Nitz et al., 2000; Pugh et al., 2004), a recent survey of 10,318 residents, 65 years and older, admitted to 510 nursing homes in the US, revealed that 7.7% were already receiving AEDs at admission, three-fifths for a seizure indication (Garrard et al., 2003). Post-admission initiation of AEDs was 2.7% in one-fifth for a seizure indication.

Although there is increasing interest in the use of new AEDs for the management of seizure disorders in the elderly (King-Stephens, 1999; Willmore, 2000), the majority of these patients are still treated with traditional anticonvulsants. Despite the fact that current guidelines do not recommend using phenytoin as a first line drug in the elderly (Scottish Intercollegiate Guidelines Network, 2001; Karceski and Morrell, 2001), phenytoin is still widely used in this patient group, accounting overall for more than 50% of AED prescriptions both in nursing homes (Schachter et al., 1998) and in outpatient facilities (Pugh et al., 2004) in the US. There are many reasons for this: (i) phenytoin is effective against partial and generalized tonic-clonic seizures, which are the most prevalent seizure types in the elderly; (ii) it is a relatively non-sedating drug; (iii) it can be given once or twice daily; (iv) it is available in formulations suitable for oral and parenteral use; and (v) it is less likely to produce hyponatremia and cardiac rhythm disturbances compared with carbamazepine (Battino et al., 2000; Wilder and Bruni, 2002).

Because of phenytoin’s narrow therapeutic index, Michaelis-Menten kinetics, and close relationship between serum concentration and clinical effects, rational prescribing requires an understanding of the factors affecting its pharmacokinetics (Perucca et al., 2001). This is especially important in the elderly, in whom age-related changes in distribution, metabolizing capacity, and renal function coupled with the confounding influence of drug interactions may result in profoundly altered dose requirements of many drugs (Parker et al., 1995). Despite the fact that phenytoin has been used for over half a century, however, information on the influence of aging on its pharmacokinetics remains fragmentary and inconclusive (Bachmann and Belloto, 1999). Because of this, we considered it of interest to perform a comprehensive evaluation of the influence of age, dosage, and comedication on the apparent oral clearance of phenytoin in a large population of elderly patients attending a therapeutic drug monitoring service (TDMS) at our hospital. An appropriately selected population of younger adults matched for gender, body weight, and comedication was investigated for comparison purposes.

2. Material and methods

2.1. Patients

The study material was derived retrospectively from the electronic database of the therapeutic drug monitoring service of the National Neurological Institute Carlo Besta in Milan. In- and outpatients receiving AEDs at this institution are regularly monitored for serum drug concentrations; and at each assessment, the TDMS personnel collects carefully information on the patient’s demographics, clinical status, and details on medication(s) taken, including dose per kilogram (dose kg
\(^{-1}\)), time of administration, and duration of therapy. All patients who had one or more serum phenytoin concentrations measured during the period January 1990 to April 2002 were individually assessed to determine their eligibility for the inclusion in the present survey.
According to the study protocol, two cohorts of patients were identified and evaluated. The first cohort (test population) consisted of elderly subjects selected on the basis of the following inclusion criteria: (i) age ≥ 65 years; (ii) treatment with phenytoin at a stable dosage for at least 3 weeks, without concomitant changes in the type of associated comedication (if applicable); (iii) absence of associated drugs, other than anticonvulsants, known to interfere with cytochrome P450 (CYP) enzyme activity; (iv) absence of associated liver or renal disease; (v) no evidence of poor compliance, as defined by variable (>25% difference) concentration values on repeated measurements on the same dosage and comedication. For patients who had more than one concentration value, the last concentration determined was used in the comparison. The second cohort (control population) consisted of patients selected according to the same eligibility criteria outlined above, except that their age had to fall within the 20–50 years range. One non-elderly control was selected for each elderly patient and in addition to fulfilling eligibility criteria, each control was matched for gender, body weight (within 10%), and type of anticonvulsant comedication. No matching for phenytoin dose or serum phenytoin concentration was done because this could have introduced selection bias (see Section 4).

To ensure the highest possible accuracy of the information used, all TDMS request forms originally compiled by the treating physicians were reviewed separately by two investigators, and all patients whose data were incomplete or inconsistent (for example, when comparing data recorded in multiple request forms) or whose TDMS forms were compiled by physicians outside the hospital were excluded. In practice, virtually all patients included in the final analysis were referred by a team of 10 physicians from the hospital epilepsy clinic.

2.2. Drug assays

Serum samples were taken between 08:00 and 10:00 a.m., before the administration of the morning dose. Serum phenytoin concentrations were determined by using a commercial fluorescence polarization immunoassay (TDx, Abbott Diagnostics, Rome, Italy). The laboratory proficiency was monitored through internal quality control procedures and participation in two external quality control scheme at national (Regione Lombardia, Milan, Italy) and international (Healthcontrol, Cardiff, UK) level. Day-to-day precision at clinically relevant concentrations during the study period ranged from 3.4 to 4.8%.

2.3. Pharmacokinetic and statistical analysis

For each subject, apparent oral clearance values (CL/F) were calculated by using the following equation:

\[
\text{CL}_F \left( \text{ml h}^{-1} \text{ kg}^{-1} \right) = \frac{\text{daily phenytoin dose (mg kg}^{-1})}{C_{\text{ss (mg ml}^{-1})} \times 24h}
\]

where CL is the total body clearance of the drug, F is the oral bioavailability, and C_{ss} is the serum phenytoin concentration at steady-state.

For each data set (age, body weight, drug dosages, serum drug concentrations, and CL/F values), deviations from a Gaussian distribution and equality of group variances were assessed by means of the Kolmogorov–Smirnov test and the Bartlett's test. When data were consistent with a normal distribution and equal variances, mean and S.D. were calculated and compared by using the Student’s t-test, 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 (which was the case for age and body weight), comparisons were made by using the Mann–Whitney's U-test or the Kruskal–Wallis test in the case of multiple comparisons. Differences were considered statistically significant at \( P \leq 0.05 \). To assess correlations between patients’ age, body weight, phenytoin dosages, and phenytoin CL/F values, a variety of linear and non-linear models were tested by means of a best fitting curve program. A linear regression model was selected as it was found to provide the best fit, and the validity of this model was confirmed by using the runs test. Analysis of covariance (ANCOVA) was used to compare slopes and intercepts of the regression lines generated for subgroups homogenous for presence/absence of comedication and/or for elderly patients and controls. Again, the level of significance was set at \( P \leq 0.05 \). The relative contribution of each covariate to the variability in phenytoin CL/F values
(ml h$^{-1}$ kg$^{-1}$) was further assessed by using a linear regression model which included the following variables: age (years), body weight (kg), phenytoin dose (mg kg$^{-1}$ day$^{-1}$), gender, and comedication. 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 level of significance ($P = 0.05$) were ultimately excluded from the model.

All statistical tests were performed using the GraphPad Instat and the GraphPad Prism Version 4.0a for Macintosh, GraphPad Software, San Diego California, USA.

3. Results
3.1. Characteristics of the study populations

Out of 10,043 patients included in the TDMS database, 546 were treated with phenytoin and of these, 111 aged 65 years and above fulfilled the eligibility criteria for inclusion in the study. Of these, 58 (52%) were on phenytoin monotherapy, 17 (15%) received phenytoin in combination with phenobarbital, and 36 (32%) received phenytoin in combination with a variety of other AEDs. Since the number of patients comedicated with any specific AED other than phenobarbital was too small for meaningful analysis, the final evaluation was restricted to the monotherapy group and the group receiving combination therapy with phenobarbital.

Demographic characteristics and therapeutic details of the patients included in the analysis are listed in Table 1. Overall, the two study populations consisted of 75 patients aged 65–90 years (mean, 71.7 ± 5.3 years) and 75 controls aged 20–50 years (mean, 36.7 ± 8.5 years). As a result of the matching procedure, the two groups had an equal gender distribution (43 men, 32 women) and virtually identical mean body weight (test, 68.5 ± 12.3 kg; controls, 68.2 ± 12.5 kg; $P > 0.05$). Mean phenytoin dosage and mean serum phenytoin concentrations were moderately lower in the elderly than in controls (4.4 ± 1.1 mg kg$^{-1}$ day$^{-1}$ versus 5.3 ± 1.1 mg kg$^{-1}$ day$^{-1}$, $P < 0.001$; 14.1 ± 5.7 μg ml$^{-1}$ versus 18.6 ± 6.8 μg ml$^{-1}$, $P < 0.0001$). Within each age group, phenytoin dosage, and serum phenytoin concentrations in patients receiving monotherapy were very similar to those observed in patients receiving phenobarbital comedication (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Elderly</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.7 ± 5.3</td>
<td>36.7 ± 8.5</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>66.5 ± 12.3</td>
<td>68.2 ± 12.5</td>
</tr>
<tr>
<td>Gender distribution (males/females)</td>
<td>43/32</td>
<td>43/32</td>
</tr>
<tr>
<td>Patient on phenytoin monotherapy (n)</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Patient on phenobarbital comedication (n)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Phenytoin dosage (mg kg$^{-1}$ day$^{-1}$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>4.4 ± 1.1*</td>
<td>5.3 ± 1.1</td>
</tr>
<tr>
<td>Patients on monotherapy</td>
<td>4.5 ± 1.1*</td>
<td>5.3 ± 1.0</td>
</tr>
<tr>
<td>Patients comedicated with phenobarbital</td>
<td>4.2 ± 0.8</td>
<td>5.1 ± 1.4</td>
</tr>
<tr>
<td>Serum phenytoin concentration (μg ml$^{-1}$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>14.1 ± 5.7**</td>
<td>18.6 ± 6.8</td>
</tr>
<tr>
<td>Patients on monotherapy</td>
<td>13.7 ± 5.4*</td>
<td>18.3 ± 6.6</td>
</tr>
<tr>
<td>Patients comedicated with phenobarbital</td>
<td>14.7 ± 6.4</td>
<td>19.6 ± 7.7</td>
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<tr>
<td>Phenytoin dosage (mg kg$^{-1}$ day$^{-1}$)</td>
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<td></td>
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<tr>
<td>Serum phenobarbital concentration (μg ml$^{-1}$)</td>
<td>25 ± 13.4</td>
<td>19.3 ± 8.1</td>
</tr>
</tbody>
</table>

Unless indicated otherwise, data represent mean ± S.D.

* $P < 0.001$ (vs. corresponding controls).

** $P < 0.0001$ (vs. corresponding controls).
3.2. Comparison of phenytoin CL/F values across age groups

Phenytoin CL/F values in elderly patients were about 10% higher than those found in controls (14.6 ± 4.7 ml h⁻¹ kg⁻¹ versus 13.1 ± 4.2 ml h⁻¹ kg⁻¹, \( P < 0.05 \)), the magnitude of the difference being virtually identical for the subgroups receiving phenytoin monotherapy (14.8 ± 4.7 ml h⁻¹ kg⁻¹ versus 13.3 ± 4.1 ml h⁻¹ kg⁻¹, \( P > 0.05 \)) and for those receiving phenobarbital comedication (13.7 ± 4.7 ml h⁻¹ kg⁻¹ versus 12.1 ± 4.3 ml h⁻¹ kg⁻¹, \( P > 0.05 \)).

Within each of the two age groups, there were no statistically significant differences in phenytoin CL/F between patients receiving monotherapy and patients receiving combination therapy with phenobarbital.

3.3. Relationship between phenytoin CL/F values and age

The relationship between phenytoin CL/F values and age in the two age groups is illustrated in Fig. 1. While no significant correlation was identified among controls, a significant inverse relationship between CL/F and age was observed for the elderly group (\( r = -0.28 \), \( P < 0.05 \)). This negative correlation could also be confirmed separately for the subgroup of elderly patients receiving monotherapy (\( r = -0.29 \), \( P < 0.05 \)), whereas the number of patients in the comedication subgroup was too small for statistical significance to be meaningfully assessed.

3.4. Comparison of phenytoin CL/F between genders

Gender-related differences in phenytoin pharmacokinetics were assessed by comparing CL/F values in men and women within each age group. CL/F values were slightly lower in men than in women both in the elderly group (13.9 ± 4.6 ml h⁻¹ kg⁻¹ versus 15.5 ± 4.8 ml h⁻¹ kg⁻¹) and in controls (12.5 ± 4.0 ml h⁻¹ kg⁻¹ versus 13.8 ± 4.4 ml h⁻¹ kg⁻¹) but the differences were not statistically significant.

3.5. Relationship between phenytoin CL/F values and dosage

Within each of the two age groups, no significant relationship was identified between phenytoin CL/F and dosage (Fig. 2). Lack of a significant correlation was confirmed when subgroups receiving monotherapy or phenobarbital comedication were analysed separately.

3.6. Multiple regression analysis

To further assess the potential relative contribution of age, gender, dosage, and comedication to the observed variability in CL/F values, each of these factors was evaluated by multiple regression analysis. In the elderly population, age was the only variable that was found to exert a significant influence on phenytoin CL/F, as indicated by the following equation:

\[
\text{CL/F} = 32.3 - 0.25 \times \text{age}
\]

The standard error of the intercept was 7.2 (95% confidence interval, 18.0–46.6), the standard error of the slope was –0.10 (95% confidence interval, –0.45 to –0.05) and \( r \) was –0.28 indicating that age accounted for 7.8% of the variance in CL/F explained by the model (\( P = 0.015 \)).

For controls, CL/F was not statistically correlated with any of the variables assessed.

4. Discussion

Available information on the pharmacokinetics of phenytoin in old age has been reviewed in detail by Bachmann and Belloto (1999). Some studies have shown an increase in serum drug concentration (or a decrease in CL/F values) attributable to age (Bach et al., 1981; Bauer and Blouin, 1982; Crowley et al., 1988; Houghton et al., 1975), while others have failed to identify significant pharmacokinetic differences between elderly and younger subjects (Estruch et al., 1992; Grasela et al., 1993; Ismail et al., 1994; Quintana et al., 1995). At least to some extent, these discrepancies may have been accounted for differences in methodological approaches, with some studies only providing serum concentration (or CL/F) data and others assessing Michaelis-Menten parameters by a variety of models. Bachmann and Belloto (1999) concluded that “there are few carefully controlled studies that have evaluated the effect of age on phenytoin steady-state kinetics” and that interpretation of data
Fig. 1. Relationship between phenytoin CL/F values and age in elderly patients (upper panel) and in controls (lower panel): (○) patients on phenytoin monotherapy and (●) patients comedicated with phenobarbital. The equations of the lines were $\text{CL/F} = 32.3 - 0.25 \times \text{age}$ ($r = -0.28$, $P < 0.05$) for elderly patients and $\text{CL/F} = 13.9 - 0.02 \times \text{age}$ ($r = -0.05$, NS) for controls. For results of analysis on comedication subgroups, see Section 3.3.

is made difficult by “the small number of individuals in these studies and the confounding influence of polypharmacy in others, coupled with a limited knowledge basis about aging and drug oxidations in general, and the structural bias in the parameter estimates depending on which linear transformation of the Michaelis–Menten equation is used to secure those estimates”. In spite of those limitations, the data were considered to suggest that phenytoin oxidation rates in patients receiving monotherapy are modestly reduced in old age, and that treatment in these patients should be initiated at lower dosages than it would be customary in younger adults. On the other hand, because limited data suggest that any significant age-dependent decline in phenytoin clearance may be offset by the inducing effects of associated anticonvulsants, it was also concluded that in patients on enzyme inducing comedication there is no pharmacokinetic
Fig. 2. Relationship between phenytoin CL/F values and dose in elderly patients (upper panel) and in controls (lower panel): (○) patients on phenytoin monotherapy and (●) patients comedicated with phenobarbital. The equations of the lines were CL/F = 15.0 − 0.09 × dose ($r = −0.02$, NS) for elderly patients and CL/F = 12.2 + 0.16 × dose ($r = −0.04$, NS) for controls.

A distinctive feature of our investigation lies in the fact that it was possible to evaluate a population of elderly patients much larger than assessed in previous studies. A second innovative approach consisted in the selection of non-elderly adult controls matched for gender, body weight, and type of comedication, thereby, minimizing the potential confounding influence of these variables. Matching for dose
or serum drug concentrations was avoided because in populations where dose allocation is not random-
ized this could have led to serious selection bias. For example, utilization of therapeutic drug monitoring
could have led physicians to select dosages yielding comparable serum concentrations in all patients, and
under these circumstances matching for dose would have led to missing potentially important differences
in CL/F between groups. Likewise, if physicians had adopted differential dosing policies in the elderly com-
pared with the young (e.g., using lower dosages for fear of side effects), matching for serum phenytoin
concentrations could have led to identifying falsely lower CL/F values in the elderly group. In view of the
model-dependent structural bias involved with the esti-

mation of V_{max} and K_{m} values from population data
(Bachmann and Belloto, 1999) and the fact that the
relationship between serum concentration and dosage
was distorted by non-randomized dose allocation (see above), we also elected not to attempt calculation of
Michaelis–Menten parameters, but to base our anal-

ysis on comparison of CL/F values, which represent
more clinically meaningful indicators of dose require-
ments.

Because, due to saturation of the drug metaboliz-
ing enzymes, phenytoin CL/F values within patients
decrease with increasing dosage and serum concentra-
tion (Richens, 1975), the observation that CL/F val-
ues in our elderly group were slightly higher than
those found in younger matched controls may be ex-
plained by the fact that on average older patients were
prescribed lower dosages, which yielded lower serum
drug concentrations. According to Michaelis–Menten
theory, CL equals V_{max}/(K_{m} + C_{ss}), where V_{max} is
the maximum velocity of the enzyme system, K_{m} is
the Michaelis constant of the system (concentra-
tion at which half V_{max} is attained), and C_{ss} is the
serum drug concentration at steady-state (Bachmann
and Belloto, 1999). Therefore, changes in CL can re-
sult from a change in V_{max}, K_{m}, or C_{ss}. By applying
standard published values for V_{max} (6.2 μg ml^{-1}) and
K_{m} (0.45 μg ml^{-1} h^{-1}) in adults (Browne and Leduc,
2002) to the equation above, one can predict that at the
C_{ss} values observed in our study CL/F values should
be 22% higher in elderly subjects than in controls as a
consequence of differences in phenytoin concentration
alone. In other words, the observed difference in CL/F
could be entirely ascribed to differences in phenytoin
concentration between the two groups.

In the presence of Michaelis–Menten kinetics, CL/F
values would be expected to be inversely related the
dose, but this pattern was not evident in our patients
(Fig. 2), most probably due to non-randomized dose
allocation, with patients showing the highest CL/F
being more likely to have their dosage increased to
achieve therapeutic serum drug levels. Thus, in the
population studied, the influence of Michaelis–Menten
kinetics (which would cause an inverse relationship
between CL/F and dosage) was overshadowed by the
opposing influence of bias in dose allocation (which
would result in dosage being positively correlated with
CL/F). While these confounding influences complicate
assessment of any direct influence of the aging
process, a significant role of the latter was strongly
suggested in our study by: (i) the inverse relationship
between phenytoin CL/F value and age, which was
detectable only in the above 65-year-old group; (ii)
the results of multiple regression analysis, which iden-
tified age as the only clinical variable that affected
phenytoin CL/F within the elderly group. Overall, these
findings are in agreement with the results of other
studies suggesting a modest decline in total phenytoin
pharmacokinetics among elderly individu-
als. Whether intraindividual variability contributed to
this variation cannot be ascertained from the present
data, but it is of interest that in a recent study con-
ducted in 56 elderly nursing home residents in the US,
total phenytoin concentrations measured on different
occasions in patients stabilized on a constant dosage
varied as much as two- to three-fold (Birnbaum et al.,
2003). The phenomenon was speculatively ascribed to

Based on the regression equation shown in Fig. 1,
phenytoin CL/F values in our population decreased by about one-third between 65 and 85 years of age,
but the wide scatter around the regression line and the
results of multiple regression analysis indicate that
age alone explained less than 10% of the variation in
phenytoin pharmacokinetics among elderly individu-
als. Whether intraindividual variability contributed to
this variation cannot be ascertained from the present
data, but it is of interest that in a recent study con-
ducted in 56 elderly nursing home residents in the US,
total phenytoin concentrations measured on different
occasions in patients stabilized on a constant dosage
varied as much as two- to three-fold (Birnbaum et al.,
2003). The phenomenon was speculatively ascribed to
erratic changes in absorption efficiency, and the suggestion was made that a single total phenytoin measurement should not be used to guide treatment in an elderly patient.

None of the other variables that were assessed in our study as possible predictors of phenytoin CL/F were identified at multiple regression analysis as having a significant influence. Phenobarbital comedication, in particular, did not appear to affect significantly phenytoin CL/F, and indeed, serum phenytoin levels (and phenytoin dosages) in patients comcomicated with phenobarbital were very similar to those observed in patients on monotherapy. This is in keeping with evidence that phenobarbital may induce and inhibit phenytoin metabolism at the same time, and therefore, no consistent changes in serum phenytoin levels are observed in patients commedicated with this drug (Booker et al., 1971; Patsalos and Perucca, 2003). While it has been suggested that the decline in phenytoin clearance with aging may be offset by enzyme inducing comedication (Bachmann and Belloto, 1999), the number of patients receiving phenobarbital in our study was too small to confirm or refute this possibility.

One important limitation of our study (and of most other studies conducted to date) is that CL/F estimates were derived from total serum drug concentrations. Because the serum unbound fraction of phenytoin increases in old age proportionally with the decline in serum albumin concentration (and with accumulation of endogenous displacing agents, in the case of severely impaired renal function) (Anderson et al., 1997; Bach et al., 1981; Baird-Lambert et al., 1987; Dasgupta and Abu-Alfa, 1992; Hayes et al., 1975; Monaghan et al., 2001; Patterson et al., 1982; Perucca, 1980; Peterson et al., 1982; Verbeek et al., 1984), the reduction in CL/F of unbound, pharmacologically active drug is likely to be considerably greater than the reduction in CL/F values calculated from total drug concentrations. This phenomenon should always be kept in mind when interpreting serum phenytoin concentrations in clinical practice. Tomson (1988), for example, reported the case of a 81-year-old woman with hypoalbuminemia in whom adjustment of phenytoin dosage based on total serum drug concentration led to development of severe toxicity. Subsequent measurement of the unbound serum phenytoin concentration revealed a drug level into the toxic range, despite the fact that the total drug concentration was within the range commonly regarded as therapeutic.

In conclusion, the present investigation provides evidence in support of previous smaller-scale studies indicating that phenytoin clearance declines with aging, even though age explains only a minor part of the variability in CL/F. In the light of these considerations, and the evidence for an increased sensitivity of the elderly to the effects of many AEDs (Brodie et al., 1999; Ramsay et al., 1994), it is prudent to utilize initially smaller phenytoin dosages in these patients, and to make subsequent dose adjustments based on clinical response and serum drug level measurements. When interpreting drug concentrations, however, it should be remembered that the unbound fraction of phenytoin may be increased in the elderly, and that therefore, therapeutic and toxic effects may appear at lower concentrations than those producing equivalent responses in younger patients.

References


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