

PHARMACOKINETICS OF PHENYTOIN: REMINDERS AND DISCOVERIES

Phenytoin Half-Life and Clearance during Maintenance Therapy in Adults and Elderly Patients with Epilepsy.

Ahn JE, Cloyd JC, Brundage RC, Marino SE, Conway JM, Ramsay RE, White JR, Musib LC, Rarick JO, Birnbaum AK, Leppik IE. *Neurology* 2008;71(1):38–43. **BACKGROUND:** Phenytoin (PHT) is widely used to treat epilepsy in elderly patients, but information on its pharmacokinetics in this population is limited. **OBJECTIVE:** The purpose of this study was to investigate the effects of age and sex on PHT pharmacokinetics using stable-labeled (SL) isotopes of PHT or fosphenytoin (FOS) administered IV or IM while patients remained on their oral maintenance regimen. **METHODS:** Subjects were patients 18 years or older with epilepsy, but otherwise healthy, on a maintenance regimen of PHT who were not taking interacting medications. Subjects were given a single injection of a 100 mg dose of SL-PHT or SL-FOS followed by their usual morning PHT dose less 100 mg. Serial blood samples were collected up to 196 hours after the SL dose. Plasma PHT and SL-PHT concentrations were measured by a gas chromatographic-mass spectrometric assay. PHT pharmacokinetics were characterized using a population-based, nonlinear, mixed-effects model. **RESULTS:** Sixty-three subjects completed the study, 45 of whom were 65 years or older. There was no difference between adult and elderly or men and women in PHT clearance, distribution volume, and elimination half-life. The mean elimination half-life was 40 hours. **CONCLUSIONS:** Healthy elderly adults appear to have the same phenytoin (PHT) pharmacokinetics as younger adults. Reduced PHT dosage requirements may be due to age-related changes in patients' sensitivity to the therapeutic and toxic effects of the drug. The prolonged elimination half-life suggests that most patients can take PHT once daily and the time to reach steady-state may extend to 2–3 weeks.

COMMENTARY

The study by Ahn et al. demonstrates once again that facts *clinicians all know*, upon further reflection, simply may not be true, as demonstrated by carefully gathered scientific evidence. *Clinicians all know* that, in general, the half-life of phenytoin is about 22 hours and that the volume of distribution of phenytoin is about 0.75 L/kg (1,2). These assumptions

guide clinical decisions, such as the frequency of recommended daily dosing of phenytoin and calculations of dosing changes to achieve targeted serum levels.

Investigations of the pharmacokinetics of phenytoin in the older literature are largely represented by acute rather than steady-state studies, which often use low doses that more likely are associated with a shorter half-life. In addition, there are few studies of patients in the oldest age category (i.e., older than 84 years), when drug metabolism may change.

More recent studies of phenytoin have focused on differences in patient population and individual drug metabolism,

often during chronic drug use. Pharmacogenetic influences on drug metabolism are now widely appreciated, with polymorphisms in the gene for cytochrome P450 2C19 (CYP2C19) responsible for the most interindividual variability in the handling of phenytoin (3). Specific populations demonstrate significant variations in pharmacokinetics. For example, patients with severe, acute traumatic brain injury have shown clinically significant subacute alterations in metabolism of phenytoin, with differences in V_{max} (maximum rate of metabolism) of 400% occurring within the first 2 weeks of trauma (4). Significant, rapid posttraumatic increases in average free fractions of phenytoin, from 17% on day 1 to 24% on day 10, also have been documented (4). Alterations during pregnancy are well known (5).

The study of Ahn et al. draws from two groups of people on chronic phenytoin therapy: generally healthy people living in the community and relatively healthy elderly individuals from nursing homes. The study enrolled 18 younger people between 18 and 64 years of age and 63 older subjects: 45 between 65 and 75, 18 between 75 and 84, and 10 who were 85 years or older. On the day of the infusion, the study protocol allowed subjects to remain on their usual dosage of phenytoin but substituted 100 mg of their usual morning dose with radioactive-labeled phenytoin. The labeled drug was administered intravenously or intramuscularly, avoiding individual differences in gastrointestinal drug absorption. Free and unbound levels were measured over the next 192 hours. The total serum levels of all subjects remained stable, as levels of the single, labeled dose diminished over the succeeding 196 hours.

The significant findings of this study lie both in the refutation of some beliefs about using phenytoin in the elderly and in the conclusive confirmation of other data. For instance, the phenytoin clearance (and thus the half-life) did not appear to change significantly over the adult lifespan, although older studies had suggested that age-related pharmacokinetic changes required lower dosing in the elderly. In contrast, in the study by Ahn and colleagues, there was a dramatic reduction in phenytoin clearance in the subjects of all ages with higher initial serum concentrations of the drug. At a serum concentration of 5 g/dL, the average half-life was 23.3 hours, while at a concentration of 25 g/dL, the half-life climbed to 68.5 hours. This finding suggests that once daily dosing of phenytoin is reasonable and that the time period to achieve a new serum level after a dosing change may take 2 weeks or more. The study showed that the volume of distribution of phenytoin did not change over the lifespan, and that it is closer to 0.894 than to the 0.7 L/kg cited in standard texts. Likewise, the unbound fraction of the drug appeared to be stable with aging, contrary to popular wisdom, which predicts lower average serum albumen levels (and thus higher free fractions of phenytoin) in the elderly (6).

The design of this study, however, may limit the applicability of its findings in daily clinical practice, as the crucial issue of

bioavailability was sidestepped by the use of parenteral administration of the labeled drug. While the stability of phenytoin clearance and volume of distribution is convincingly demonstrated by the study, the question of possible changes in oral drug absorption with age is still unanswered. In addition, some subjects were drawn from a selected population of nursing home residents, and the relative proportion of these residents in each age group studied is not provided. The elderly subjects were screened to include only those deemed to be “relatively healthy,” an undefined term for a group that includes at least some individuals unable to care for themselves in the community. Study patients were not on drugs “known to interact with phenytoin.” As the authors admit, this restriction may limit the applicability of their findings to the typical elderly person with epilepsy, who may be on polypharmacy or suffer from age-related inefficiencies in renal or hepatic function.

How might the clinician respond to the new findings in this study? The pharmacokinetic data, at least from this relatively healthy population, strongly support the use of once daily dosing of phenytoin at any age, if desired. In addition, they suggest that checking the serum level of phenytoin sooner than 2 weeks after a dose change, in either older or younger adults, will underestimate the effect of the change. Finally, the results support the use of a higher volume of distribution when calculating the effects of dosing changes of phenytoin.

Perhaps, there is another lesson to be gleaned from the publication of this paper: *what clinicians all know* can be very difficult to alter. An earlier pharmacokinetic study of both young and elderly adults, using virtually the same study protocol, also found an unexpectedly long elimination half-life in adults of all ages (7). This finding was true not only for phenytoin (40–50 hours) but also for carbamazepine (21 hours, vs the usually cited 12–17 hours). Similar data are cited in an older, definitive text on antiepileptic drugs (i.e., a phenytoin half-life of over 69 hours at a serum concentration of 40 mcg/mL), yet most practitioners rely on *what everyone knows* (8). Perhaps the paper by Ahn et al. will serve as a corrective voice.

by Donna C. Bergen, MD

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