

Title: Evaluation of Phenytoin Bioavailability in Subjects on Maintenance Therapy Using a Stable-labeled Isotope Approach.

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Objectives: Phenytoin (PHT) is widely used in the treatment of epilepsy, but due to the nonlinear elimination characteristics of PHT, good information on its oral bioavailability and the bioavailability of intramuscular fosphenytoin (FOS) at therapeutically relevant concentrations is limited. The purpose of this study was to investigate the oral and intramuscular bioavailability of PHT using stable-labeled (SL) isotopes of PHT or FOS administered intravenously or intramuscularly 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. On the study day, subjects were administered a single injection of a 100 mg dose of SL-PHT intravenously (IV) and/or SL-FOS intramuscularly (IM) followed by their usual morning PHT dose less 100 mg. Serial blood samples (pre-dose, 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, 168 and 192 h) were collected up to 192 hrs after the SL dose. Plasma concentrations of unlabeled PHT and SL-PHT were measured by a validated gas chromatographic-mass spectrometric assay. Three groups of observations were available from subjects in addition to the unlabeled PHT concentrations from the oral doses: 1) concentrations of both IM and IV SL-PHT following simultaneous administration of distinctly labeled IV SL-PHT and IM SL-FOS on the study day; 2) SL-PHT concentrations following IV administration on the study day; and 3) IM SL-PHT concentrations following SL-FOS on the study day. This study design enabled estimation of bioavailability of IM and PO administration of FOS and PHT, respectively. A fundamental assumption relevant to this design was made in the pharmacokinetic data analysis. As subjects (patients with epilepsy) were on their usual oral maintenance regimen, and a small dose of SL-PHT was administered, it was assumed that the fluctuation in the total concentration in plasma and at the enzyme site was minimal. This assumption imparts a constant clearance to PHT and it can then be modeled as having linear pharmacokinetics. A nonlinear mixed-effects analysis was used to model these data, and was conducted in two stages. In the first stage, log-transformed IV SL-PHT and IM SL-FOS concentrations were analyzed to obtain population estimates of clearance (CL), volume of distribution (V), the SL-FOS first-order absorption rate constant (K_{IM}), and of the SL-FOS bioavailability (F_{IM}). The structural model was a one-compartment model with linear elimination. NONMEM VI was implemented using ADVAN2/TRANS2 with FOCE. Between-subject variability on CL, V and K_{IM} was modeled as a log normal distribution. Residual unexplained variability was modeled as additive to the log-transformed predicted concentrations and the variability in the IV and IM concentrations was assumed to be the same. Individual estimates of CL and V were obtained. In the second stage, the unlabeled PHT concentrations (not log-transformed) were fit to a one-compartment model. Individual CL and V values were taken as known values from the first analysis. Oral absorption was assumed to follow a zero-order process, the duration of which was estimated. It was not assumed that subjects were at steady state; rather the amount in the central compartment at time=0 was calculated as the product of the observed pre-dose concentration and the volume of distribution (both available on the data records). In addition, a between-subject variability term was placed on this initial amount to allow an individual to deviate from the calculated value. The primary parameters of interest in the analysis of this stage were the typical value and between-subject variability of PHT oral bioavailability. Residual variability was modeled as additive to the predicted concentrations with a proportional inter-individual variability on the estimates of additive variance. This error structure was chosen to down-weight individuals with relatively higher fluctuations in their concentrations. The model was fit using the FOCE-I method of estimation.

Results: Sixty three subjects, 39 females and 24 males, age range of 21-93 years, taking oral PHT (100-700mg/day) were enrolled in the study. Visual plots, generalized additive modeling and log-likelihood ratio tests did not show significant effects of either age or sex on clearance and volume of distribution of phenytoin in the

analysis of the IV and IM data. Clearance was estimated to be 1.22 L/h with the volume of distribution of 0.89 L/Kg. FOS was rapidly absorbed with the population absorption rate constant (K_{IM}) of 1.56 1/h. The population bioavailability (F_{IM}) was not significantly different from 100%. Between-subject variability on CL, V and K_{IM} were 51%, 26% and 98%, respectively. The correlation between CL and V was estimated to be 0.36. Residual variability for the IV and IM data was estimated to be 21%. In the second phase of analysis, the population bioavailability (F_{PO}) of oral PHT was estimated to be 93.3%, and was significantly different from unity. The duration of zero order absorption phase was estimated to be 11.3 h. Inter-individual variability on F_{PO} was modeled additively with an estimated SD of 0.24. Inter-individual variability on pre-dose amount was estimated to have SD of 60.8 mg. Additive error variance for oral data was estimated to be 1.16 mg/mL, with inter-individual variability of 60%.

Conclusions: Age and sex were not found to significantly affect the absorption of phenytoin. Bioavailability of phenytoin after IM FOS administration is close to 100% and approximately 93% following standard oral doses. These values are consistent with commonly held clinical assumptions on PHT bioavailability. However, the typically observed PHT half-lives of 40 hours are considerably longer than the clinical belief of 24 hours. From a pharmacokinetic perspective, once-daily dosing of PHT is expected to be adequate for most patients. A study design using stable-labeled isotopes is able to identify characterize the bioavailability of a nonlinear drug while the subject is continued on their usual maintenance regimen.