Aim: To develop a model describing the pharmacokinetics of S-mephenytoin, a probe for CYP2B6 and CYP2C19 activity, and its metabolites S-nirvanol and S-4-hydroxyphenytoin in healthy volunteers.

Background: S-mephenytoin 4-hydroxylation is catalyzed by CYP2C19 which displays a genetic polymorphism with 3 phenotypes, extensive metabolizers (EMs), intermediate metabolizers (IMs) and poor metabolizers (PMs). The N-demethylation of S-mephenytoin is catalyzed by CYP2B6 and CYP2C9.

Methods: The population pharmacokinetic of S-mephenytoin and its metabolites were described using nonlinear mixed effects modeling and the first-order method (FO) and first-order conditional estimation method (FOCE) in NONMEM. Data were pooled from two studies (Table 1).

Results: The data were analyzed sequentially by first fitting S-mephenytoin data, followed by development of 4-hydroxyphenytoin submodel based on fixed mephenytoin pharmacokinetic parameters. Finally all three substances were simultaneously fitted using fixed mephenytoin and 4-hydroxyphenytoin pharmacokinetic parameters.

First-pass formation of S-4-hydroxymephenytoin was modeled by a hypothetical absorption compartment. Individual estimates of bioavailability from the first-pass absorption compartment were restricted by those of mephenytoin bioavailability so that the total bioavailability does not exceed one. Two transit compartments were used to describe S-nirvanol concentration-time data in PMs to account for probable enterohepatic recirculation (Figure 1).

The SMIXTURE subroutine and FO were used to estimate 3 subpopulations based on the formation clearance of S-4-hydroxymephenytoin (CL25), S-nirvanol peripheral volume (V9) and a third S-mephenytoin clearance pathway (CL20). The percentage of subjects estimated to be EMs, IMs and PMs were about 60, 23 and 17%, respectively. The extent of S-4-hydroxymephenytoin first-pass formation (F6) was estimated only for EMs. Bioavailability of mephenytoin (F1) was fixed to 1 for PMs and was estimated relative to PMs in the rest of the population. The formation rate constant of S-nirvanol was estimated separately for PM (k210) versus the rest of the population (k28). S-nirvanol elimination clearance (CL80) was estimated while its central volume (V8) was fixed to different values in PM versus the rest of the population (Table 2). The final model parameters were then estimated using FOCE with the individual subpopulations, estimated from FO, used a covariate to distinguish the parameters that are different among the different subpopulations.

The residual variability of 4-hydroxyphenytoin was best described by a proportional error of 0.28 (SD) with relative standard error (RSE) of 0.15. To account for potential covariation between the measurements of the substances, a common epsilon between 4-hydroxyphenytoin and mephenytoin (0.45, RSE; 0.17) and a common epsilon between 4-hydroxyphenytoin and nirvanol (0.39, RSE; 0.13) were estimated.

Table 2: Final parameter estimates of S-mephenytoin and its metabolites S-nirvanol and S-4-hydroxyphenytoin. The estimates for EMs, IMs and PMs were estimated from pooled data. F1 and F6 were fixed to 1 for EMs and IMs, respectively. The estimation of the same parameter was done in three subpopulations: 1 and 2 for mephenytoin (F1) and F6 of EMs and IMs and PMs, respectively, and 1 and 2 for 4-hydroxyphenytoin (F6) of EMs and IMs and PMs, respectively.