Evaluation of the Reference Scaled Average Bioequivalence Criteria on Phenytoin Using Population Pharmacokinetic Modeling and Simulation Approach

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Purpose

The unique non-linear pharmacokinetic properties of phenytoin have led to discussion about the use of a single-dose replicate design bioequivalence (BE) study in healthy subjects to establish bioequivalence of generic products in antiepileptic drugs or drugs with non-linear pharmacokinetics (PK) properties. The objective of this study was to quantitatively evaluate alternative BE designs and standards through a simulation study of phenytoin.

Methods

A nonlinear PK model was developed to describe the data of phenytoin reference listed drug (Dilantin®) from seven single-dose, two-treatment, four-period, fully replicated BE studies (n = 171). Due to the limited explored dose range, the maximal nonlinear clearance (V_{max}) was fixed to the literature value[1]. Within subject variability was incorporated onto the rate of absorption, k_a.

Two scenarios were assumed: *Scenario 1*, multiple-dose crossover design studies to mimic the clinical in use situation. Bioequivalence of test and reference drugs was evaluated with average bioequivalence (ABE) method; *Scenario 2*, single-dose fully replicate studies as suggested by current BE guidance. Bioequivalence was assessed with reference scaled ABE (RS-ABE) method along with variability comparison. In both scenarios, 1) two-hundred BE studies were simulated 2) each BE study consisted of twenty-four subjects 3) 300mg phenytoin capsule was administered 4) BE standards (i.e. C_{max} and AUC_{tlast}) were obtained from the non-compartmental analysis and 5) test drug was assumed to have a proportional dose of reference drug (-15% ~ +15%) to model the difference between test and reference drugs in terms of relative bioavailability. The sensitivity of the BE standards was assessed relative to changes in dose.

Results

Phenytoin PK model was developed as a one-compartment model with nonlinear elimination. Within subject variability was well characterized. A single-dose replicate design with RS-ABE method was more sensitive to detect changes in relative bioavailability than a multiple-dose crossover design with ABE method for the explored dose change (Figure 1).

Conclusion

A population PK model was updated and validated using data from 7 BE studies. The bioequivalence established based on the currently recommended single dose replicate design BE study with RS-ABE method is also valid following chronic dosing. Therefore, the modeling and simulation results provided additional support that the currently recommended RS-ABE along with variability comparison for phenytoin BE evaluation is adequate.

Reference: [1] Sheiner LB, Beal SL. J Pharmacokinet Biopharm. 1980 Dec;8(6):553-71.

Figure 1. Proportion of BE Studies that Pass the Bioequivalence Criteria in Response to the Dose Change