Population Pharmacokinetics of Sertraline: A Model-based Meta-Analysis

Ali Alhadab1, Richard Brundage1

1University of Minnesota, Minneapolis, MN

Objective: To develop a population pharmacokinetics of sertraline in healthy subjects using mean-level data from the literature and model-based meta-analysis (MBMA), and to use estimated clearance and absorption later as inputs for a PBPK model to predict sertraline concentrations at various target tissues.

Methods: PubMed literature search was performed to identify pharmacokinetics studies of sertraline that include at least one arm of healthy subjects who are 18-year or older and have the mean concentration-time profile data tabulated or plotted. Data were extracted using the software “WebPlotDigitizer” then modeled with NONMEM 7.30. Three-level nested random effects were included exponentially for study (ISV) and study arm (IAV), and proportionally for residual error (RUV). IAV and RUV were weighed by the inverse square root of total number of subjects in an arm. Time-dependent absorption was used with a fixed KA50 of 3 hr informed by sensitivity analysis. After visual screening, steady-state status (Y/N) and dose were added and found significant on inter-compartmental clearance (Q) and oral bioavailability (F), respectively. Final model was selected based on OFV, diagnostic plots, plausibility of parameter estimates, and relative standard of errors and assessed by visual predictive check. Bootstrap was not performed due to the long computation times.

Results: A total of 712 observed concentrations of 57 mean concentration-time profiles from 26 studies with doses ranging from 5 to 400 mg daily were included in the MBMA. Data were best fitted by 2-compartment model with dose-dependent bioavailability, time-dependent absorption, and 1st-order elimination. Estimated maximum F was 62% and 15 mg daily was the dose at which F was half maximum (D50). Maximum absorption rate constant (KAMAX) was 0.52/hr with a shape factor of 1.47 (GAM). Body clearance was similar for single and multiple dosing at 55 L/h while Q for steady state was 60% lower than that of a single dose.

Conclusion: This meta-analysis suggests that nonlinear changes in exposure are due to changes in bioavailability with dose, rather than being mediated through an effect on clearance.