A Bayesian Population Compartmental Absorption and Transit Modeling Approach to Support Generic Drug Development and Regulation - Application to Bupropion

Nan-Hung Hsieh1, Frédéric Y. Bois2, Eletheria Tsakalozou3, Miyoung Yoon3, Brad Reisfeld4, Weihsueh A. Chiu1

1 Department of Veterinary Integrative Biosciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX, USA
2 Simcyp Division, Certara UK Limited, Sheffield, UK
3 Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), Silver Spring, MD, USA
4 Chemical and Biological Engineering and School of Biomedical Engineering, Colorado State University, Fort Collins, CO, USA

MOTIVATION

To support decision-making in drug development by:
1. Developing a compartmental absorption and transit model for bupropion hydrochloride in oral dosage forms including immediate release, sustained release and extended release formulations. The model integrates information on gut physiology, in vitro dissolution and systemic pharmacokinetics (PK).
2. Conducting a Bayesian calibration of the model, using in vitro dissolution data and clinical PK data.
3. Applying the calibrated model to define a dissolution "safe space" for bupropion hydrochloride.

WORKFLOW

1) We developed a physiologically-based absorption model based on the well-known compartmental absorption and transit (CAT) framework to describe absorption and disposition for oral dosage forms of bupropion hydrochloride including immediate release, sustained release and extended release formulations.
2) Informed parameter values from previous publications were used for the development of the CAT model.
3) Applied global sensitivity analysis to find the parameters that have a relatively high impact on plasma concentration, to focus parameter estimation and to improve computational efficiency (Hsieh et al., 2018).
4) Performed two-stage Bayesian model calibration (using in vitro and in vivo data from Connarn et al., 2017) to determine the posterior distribution of the model parameters (Smith et al., 2008).
5) Used clinical PK data (Connarn et al., 2017, secondary dataset for bupropion hydrochloride).
6) Conducted virtual bioequivalence (BE) trials with the calibrated model, varying the drug in vitro dissolution-related parameters.
7) We finally determined the "safe space" for in vitro dissolution profiles for bupropion hydrochloride; a space where BE is anticipated.

RESULTS

Bayesian-estimated in vitro dissolution profiles of bupropion hydrochloride formulations. (A) Box-plot of the posterior sample of Weibull function parameters describing in vitro dissolution profiles. (B) Posterior predicted in vitro dissolution profiles (mean, 5%/95% prediction intervals) plotted against observed in vitro dissolution data. (C) Central, 2.5% and 97.5% central prediction intervals across the observed dissolution profiles (Connarn et al., 2017).

Identification of influential parameters on bupropion plasma concentration

Heatmap of the time-dependent sensitivity coefficient of the influential parameters in the physiologically based absorption model.

Virtual BE assessment and safe space prediction

BE assessment of designed test formulations of bupropion hydrochloride with first-order and Weibull released patterns. The black triangle and bar represent the maximum a posterior and 90% credible interval of the immediate-release formulation. A successful trial was declared when both Cmax and AUC fell within the 80-125% BE limits.

6) Conducted virtual bioequivalence (BE) trials with the calibrated model, varying the drug in vitro dissolution-related parameters.
7) We finally determined the "safe space" for in vitro dissolution profiles for bupropion hydrochloride; a space where BE is anticipated.

Model building and calculations were performed with GNU MCSim (Bois, 2009).

SUMMARY

(A) Central (quantile-based) posterior interval estimates of drug-release related parameters (Weibull scale and slope) for each calibrated subjects (91-15, µ population mean) from Markov Chain Monte Carlo draws. The thick and thin lines represent 50% and 90% interval, respectively.
(B) Posterior predictive check across formulations and doses. The dotted and dashed lines represent the predicted-to-observed ratio over a factor of 2 and 5, respectively. The blue line is a linear regression fitted curve.
(C) Comparative analysis of predictive accuracy and precision.

References