Physiologically based pharmacokinetic (PBPK) simulations and modeling of botanical constituents

INTRODUCTION

Botanicals have broad use as traditional medicines, natural health products, and dietary supplements around the world. Due to the complexity and variability in chemical constituents, safety testing for botanicals is challenging. The Botanical Safety Consortium, created to address this challenge, is a partnership among industry, academia, and government experts to promote new approach methodologies, such as in silico modeling, to enhance the botanical safety toolkit. Here, high-throughput physiologically based pharmacokinetic (HTPK) simulations were used to predict pharmacokinetic (PK) properties of 211 constituents in 13 botanicals. Additionally, PBPK models were created to mimic in vivo PK profiles of constituents in Ashwagandha, Goldenseal, and Yohimbine.

METHODOLOGY

HTPK simulations were performed using ADMEt Predictor® (Simulations Plus) for a 100 mg dose of each constituent to a 70 kg human subject using an immediate release tablet dosage form. PBPK models were created using GastroPlus® (Simulations Plus). Input parameters, e.g., solubility, logP, permeability, and liver metabolism, were either predicted using artificial neural network models in ADMEt Predictor or obtained from in vitro studies. Parameters were adjusted to improve the match between predicted and observed in vivo profiles.

RESULTS

Below is a plot of the predicted percent absorbed (%Fa) versus oral bioavailability (%FdP) for the 211 constituents. Compounds in the lower left-hand corner will have low plasma concentrations because a small percent reaches systemic circulation. The compounds in the upper left-hand corner have low oral bioavailability due to high first pass metabolism.

Asian ginseng constituents have low predicted %Fa, for example (2OS)-protopanaxadiol and notoginsenoside R4 have predicted %Fa below 5%. (2OS)-protopanaxadiol has a low predicted aqueous solubility (S+Sw) that severely restricts its dissolution in the gastrointestinal (GI) tract. Notoginsenoside R4 contains five sugar rings that makes it very hydrophilic and capable of forming many hydrogen bonding pairs. This combination results in a low predicted human jejunal permeability. (S+Peff).

A PBPK model was created to mimic an oral dose of 0.48 mg/kg (0.01 mg) of withanolide A (WLD), a major phytochemical in Ashwagandha, to Swiss albino female mice. The plasma concentration versus time (Cp-time) curve contains a shoulder that could be modeled by optimizing the solubility and mean precipitation time. Liver intrinsic clearance (CLint) was also optimized. The red line in the graph below indicates that WLD initially precipitates in the GI tract and then dissolves slowly producing the shoulder.

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REFERENCES

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