Physiologically Based Pharmacokinetic Modeling of Buspirone and the Effect of Liver Cirrhosis on its Disposition

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PURPOSE

The aim of this work was to develop a physiologically based pharmacokinetic (PBPK) model of buspirone following oral administrations in healthy volunteers, and to extend this model to predict the effects of physiological changes associated with liver cirrhosis in compensated and decompensated hepatic impairment patients.

METHODS

- The GastroPlus™ 8.5 (Simulations Plus, Inc.) Advanced Compartmental Absorption and Transit™ (ACAT™) model and PBPKPlus™ module were used to build the buspirone model for absorption, distribution, and clearance mechanisms.
- Physicochemical and biochemical parameters that predict absorption and distribution were obtained from literature or were predicted from structure with ADMET Predictor™ 6.5 (Simulations Plus, Inc.).
- Human organ weights, volumes, and blood perfusion rates were generated by the Population Estimates for Age-Related (PEAR™) Physiology module.
- Individual tissues were represented as perfusion-limited (blood-flow-limited) models. Tissue/plasma partition coefficients (Kps) were calculated using the Lukacova method [1] from *in vitro* and *in silico* physicochemical properties.
- The metabolic clearances of buspirone and its 1-pyrimidinylpiperazine metabolite in gut and liver were estimated from *in vitro* enzyme kinetic constants for CYP3A4 [2] and CYP2D6 [3], respectively, along with GastroPlus' built-in expression levels for both enzymes in gut and liver.
- The model was validated by comparing simulated and observed plasma concentration-time profiles for the parent drug and its two major metabolites (1-pyrimidinylpiperazine and 6-hydroxybuspirone), obtained after multiple oral administrations of buspirone across several different dose levels (5, 7.5, 15, 20 and 30 mg) in healthy volunteers [4].
- Physiological changes including cardiac output, cytochrome P450 (CYP) enzyme expressions, liver size, hepatic blood flow, renal function, and levels of plasma proteins, all associated with different degrees of severity of liver cirrhosis [5], were incorporated into the PBPK model. Moreover, changes in small intestinal transit time [6] and stomach pH related to liver cirrhosis [7] were included in physiology.
- The final validated model was used to predict concentration-time profiles of buspirone and 1-pyrimidinylpiperazine metabolite in patients with both compensated and decompensated hepatic impairment [8].

RESULTS

- Simulated plasma concentration-time profiles for buspirone and two major metabolites were in close agreement with observed data across multiple dose levels from healthy subjects (**Figure 1**).
- The validated final model, which was extended to predict the effects of liver impairment by incorporating physiological changes associated with different degrees of severity of liver cirrhosis (**Figure 2**), agreed reasonably well with observed data from patients with compensated and decompensated hepatic impairment (**Figure 3**).

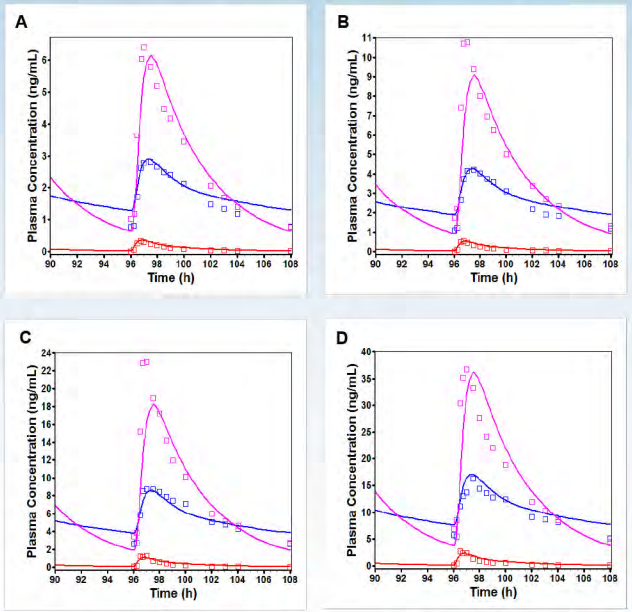

Figure 1. Predicted (lines) and observed (points) Cp-time profiles of buspirone (red), 1-pyrimidinylpiperazine metabolite (blue) and 6-hydroxybuspirone metabolite (pink) in healthy adult volunteers after 9 doses of (A) 5 mg (B) 7.5 mg (C) 15 mg (D) 30 mg buspirone hydrochloride administered once a day.

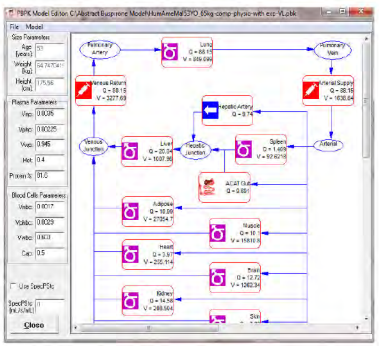

Figure 2. A default human physiology, created using the PEAR Physiology module, was modified by incorporating physiological changes associated with liver cirrhosis.

- Changes in perfusion to organs
  - ➢Increase cardiac output
  - ➢Increase hepatic arterial blood flow
  - ➢Decrease portal blood flow
  - ➢Increase blood flows in other organs
- Decrease in hematocrit
- Decrease in plasma proteins amount
- Decrease functional liver mass
- Decrease GFR
- Decrease hepatic enzymatic activity

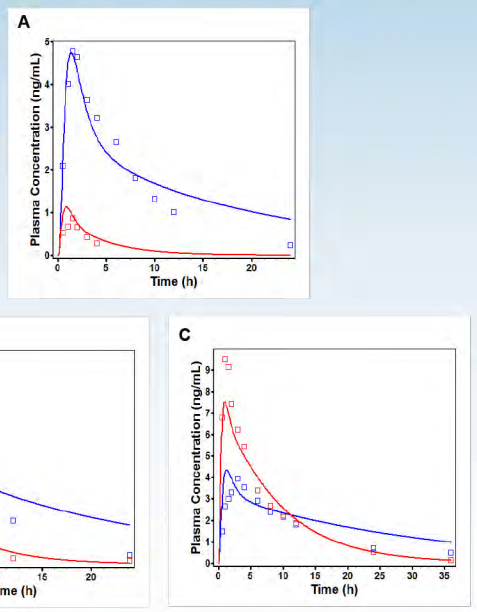

Figure 3. Predicted (lines) and observed (points) Cp-time profiles of buspirone (red) and 1-pyrimidinylpiperazine metabolite (blue) in (A) healthy volunteers (B) compensated (C) decompensated hepatic impairment patients after a single oral administration of 10 mg dose of buspirone hydrochloride.

CONCLUSIONS

- The absorption and pharmacokinetics of buspirone and its metabolites in healthy subjects were accurately simulated using *in silico* and *in vitro* data describing the drug's physicochemical and biopharmaceutical characteristics, along with *in vitro* enzyme kinetics.
- Accounting for physiological changes caused by the disease enabled successful prediction of systemic exposure in patients with different degrees of liver cirrhosis.
- The model indicated that buspirone pharmacokinetics was most sensitive to changes in CYP expression in patients with liver cirrhosis.

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