A Mechanistic and Physiologically-Relevant PK/PD Model for the Drug of Abuse, γ-Hydroxybutyric Acid (GHB) in rats

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Objectives: Overdose of gamma-hydroxybutyric acid (GHB) leads to coma, seizures, and death due to its direct binding to GABAB receptors in brain [1]. Atypical pharmacokinetics of GHB includes its saturable absorption, hepatic metabolism, and active renal reabsorption [1]. Monocarboxylate transporters (MCTs) [2], namely, MCT1, predominantly mediates active renal reabsorption [1] and uptake into the brain of GHB [3]. The pharmacodynamic endpoint of GHB intoxication is dose-dependent respiratory depression [4]. This study developed a mechanistic and physiologically-relevant PK/PD model for GHB in rats.

Methods: The model was developed using data for GHB plasma concentrations and cumulative amount excreted unchanged into urine as well as respiration frequency for IV bolus doses of 200, 600, and 1500 mg/kg in ADAPT 5. We extended our previously established PK model for GHB [5] to include GHB PD. The proposed PK/PD model for GHB consists of non-linear metabolism, MCT1-mediated renal reabsorption with physiologically-relevant concurrent fluid-reabsorption and uptake into the brain, and direct effects of binding of GHB to GABAB receptors on respiration frequency. The Michaelis-Menten affinity constant (K_M) for metabolism, active renal reabsorption and uptake into brain were fixed to the observed in vitro/ in vivo values. EC50 value of GHB binding to GABAB receptors was also fixed to the reported value of 82.8 µg/mL. The model was further validated using an independent data set for 600 mg/kg dose of GHB.

Results: The model reassembly captured the PK/PD of GHB and had a strong quantitative power. The estimated values (mean, %CV), 633 µg/min (4.2%), 2870 µg/min (9.7%), and 11.6 µg/min (7.3%) of Michaelis-Menten capacity parameters (V_MAX) for metabolism, active renal reabsorption and uptake into brain, respectively, were, in agreement with the previously reported values. Model validation indicated the model was successfully validated.

Conclusion: We successfully developed and validated a mechanistic and physiologically-relevant PK/PD model for GHB in rats, which will be used to evaluate potential treatment strategies in GHB overdose in future.

References:
4. Morse, B.L., N. Vijay, and M.E. Morris. AAPS J, 2014. 16(4)