Modeling the pharmacokinetics of phenylbutyrate in fed and fasted states

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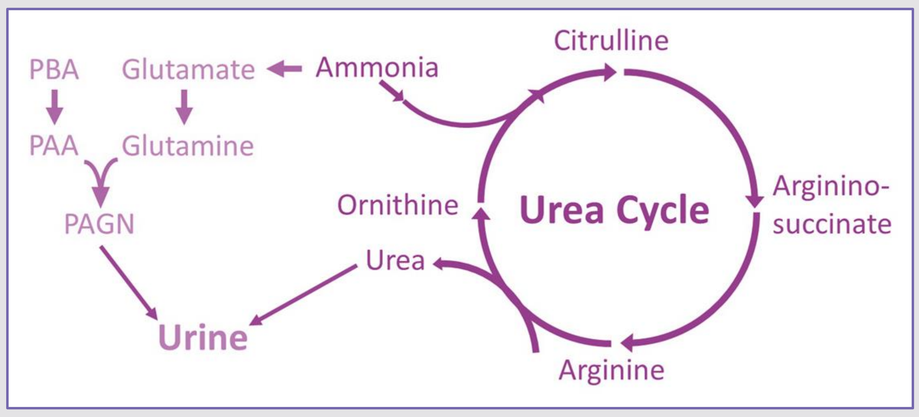
Background

- Pharmacokinetic (PK) modeling can be useful in drug development, particularly in rare diseases where clinical trial subject recruitment can be challenging
- Sodium phenylbutyrate (NaPBA) and glycerol phenylbutyrate (GPB) are nitrogen-scavenging agents indicated as adjunctive therapy in the chronic treatment of [some] urea cycle disorders (UCDs), a group of rare inherited metabolic disorders characterized by hyperammonemia[1]
- Phenylbutyrate (PBA) in NaPBA and GPB is metabolized to phenylacetic acid (PAA), which conjugates with glutamine to form phenylacetylglutamine (PAGN) that is excreted via the kidneys, thereby providing an alternate pathway for nitrogen excretion[2]
- All formulations of NaPBA and GPB available in the United States are to be administered with food[3-6]; however, previously conducted PK modeling and human studies in UCDs have evaluated the PK of NaPBA in fed vs. fasted states and found increased drug exposure and potential for increased efficacy in the fasted state[7,8]
- We employed PK modeling to further elucidate whether NaPBA could be safely and effectively administered while fasting



PBA: phenylbutyrate, PAA: phenylacetic acid, PAGN: phenylacetylglutamine.

Methods

- A previously-published mechanistic PK/PD model of NaPBA and GPB in UCDs was implemented in MATLAB SimBiology® and simulated results were confirmed to match the published outcomes[9]
- The model was extended to incorporate further NaPBA data from formulation bioequivalence studies[10]
- The model was used to compare the effects of different doses of NaPBA and GPB administered in the fed state to corresponding doses of NaPBA (ACER-001) administered fasting, covering the full dose ranges approved for PBA use, and using two Virtual Patients (VPs), an adult (>18 yrs) and a child (3-5 yrs). ACER-001 is polymer-coated pellets of NaPBA[11]
- Simulation outcomes included plasma PBA and urinary PAGN (UPAGN) for efficacy and plasma PAA for toxicity; these results were further compared to fed PK data collected from healthy adult volunteers administered two NaPBA formulations

Results

- In both VPs, simulated administration of NaPBA in the fasted state showed greater drug absorption and bioavailability (Figure 1) compared to fed administration of NaPBA and GPB. This coincided with a proportional increase in UPAGN by 43% (Figure 2), predicting an increase in efficacy
- Model calculations found a 30% reduction in fasted-administered NaPBA to achieve equivalent UPAGN excretion compared to fed-administered NaPBA and GPB
- High doses of NaPBA administered in the fasted state resulted in elevated PAA levels, potentially exceeding 500 mcg/mL in the child VPs (Figure 3); PAA plasma concentrations ≥ 500 µg/dL have been reported to be associated with reversible neurological adverse events[10]
- Simulated results closely matched previously-published outcomes measured in healthy adult volunteers[11]

Figure 1: Cmax PBA in Adult and Child VPs

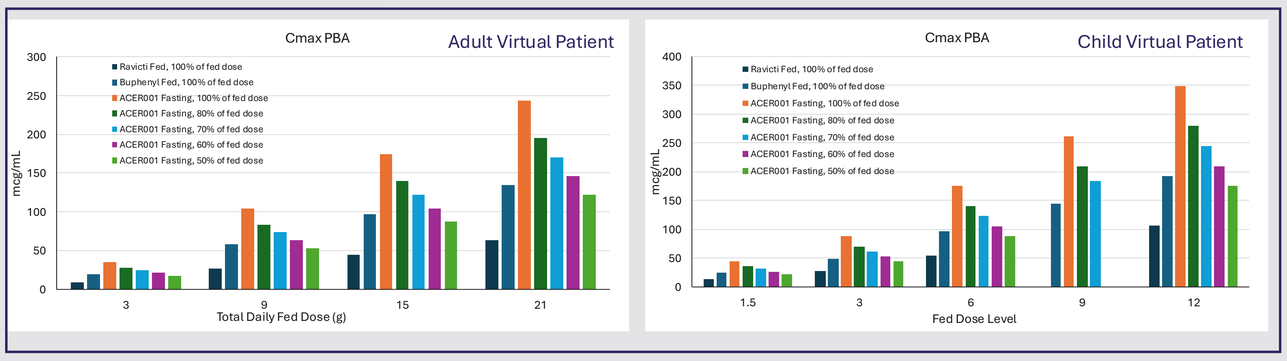
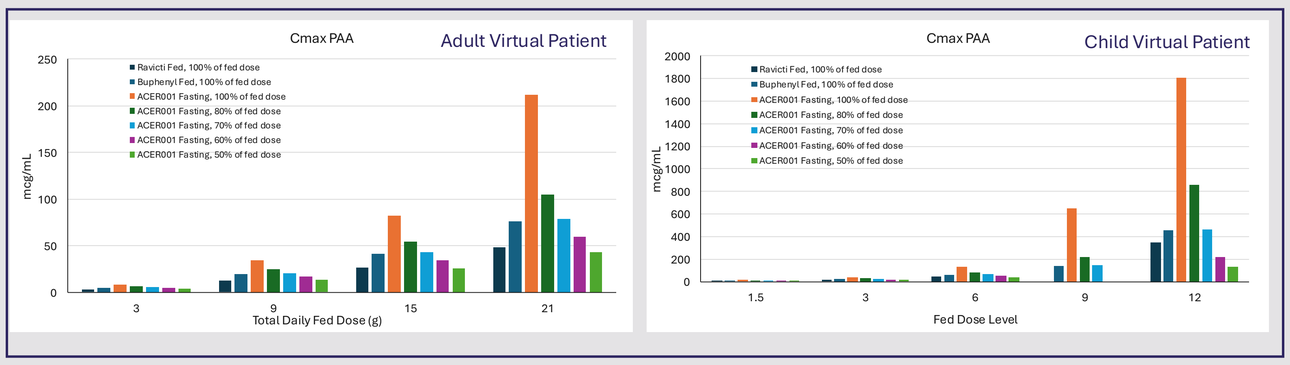


Figure 2: UPAGN in Adult and Child VPs

Figure 3: PAA levels in Adult and Child VPs



Conclusion

- Similar to previous reports, this PK modeling profile showed greater absorption and bioavailability with increased drug exposure in fasted administration of NaPBA compared to fed administration of NaPBA and GPB in both an adult and child VPs
- Fasting administration of NaBPA in VPs is predicted to increase efficacy in proportion to increased drug exposure, theoretically allowing for a 30% dose decrease compared to fed conditions; however, PAA toxicity risk with high doses in the fasted state should be taken into consideration, especially in children
- Further research into fed vs. fasted administration of PBA is warranted to better understand the PK, along with the potential clinical utility and impact on dosing practices, adherence, cost, and other real-world outcomes

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