ICIEM 2021
14TH INTERNATIONAL CONGRESS OF INBORN ERRORS OF METABOLISM
21-23 NOVEMBER 2021, SYDNEY, AUSTRALIA

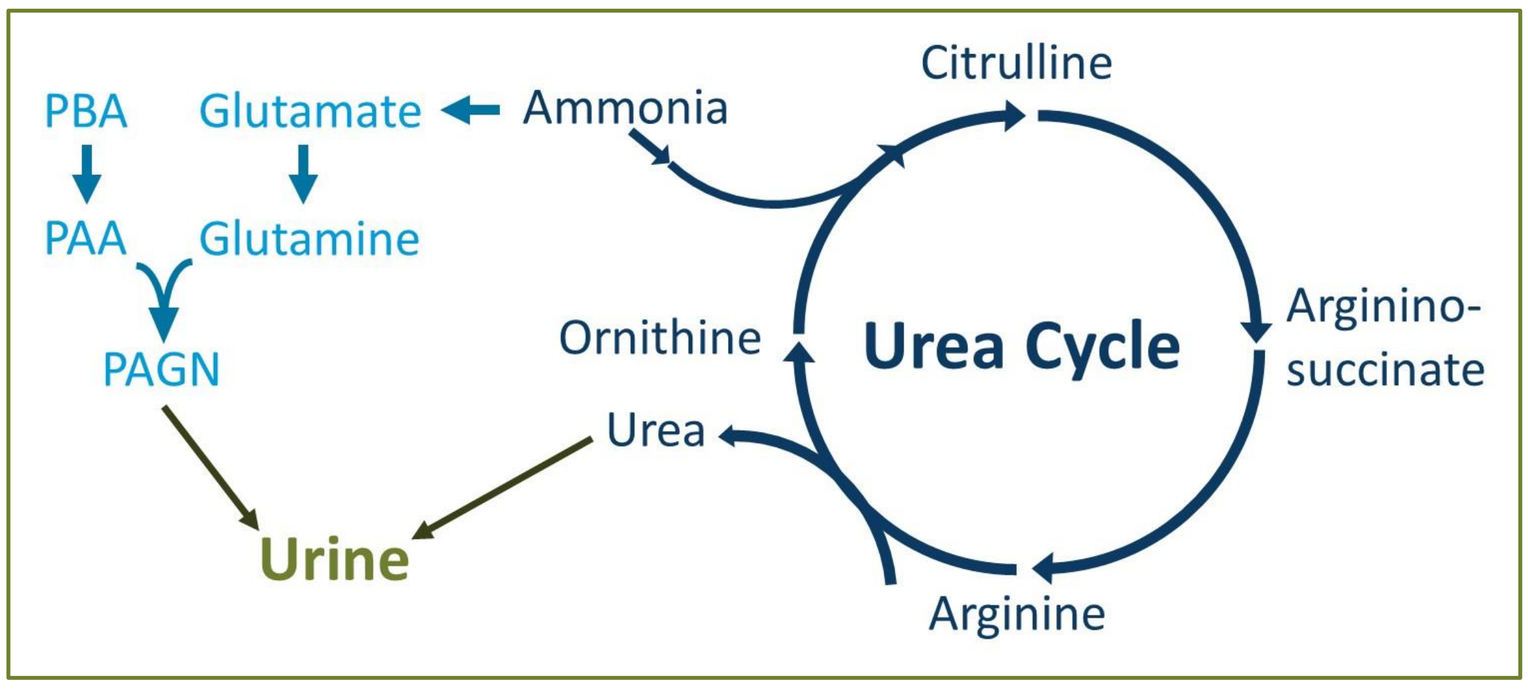
Using Modeling for Dose Recommendations of A Novel Drug for Urea Cycle Disorders

R. Baillie[1], C. Schelling[2], R. Ridgewell[2], T. Zhang[1], C. Friedrich[1], M. Reed[1]
[1]Rosa & Co. LLC, [2]Acer Therapeutics

Background

Drug development for rare disorders is complex. With few subjects available, designing trials and recruiting enough subjects to reach a meaningful outcome can be difficult. Modeling can help support drug development for rare disorders by optimizing trial design and dosing.

Urea cycle disorders (UCD) are rare genetic disorders associated with hyperammonemia[1]. In UCD, a mutation in a urea cycle enzyme results in lower activity and excretion of ammonia into the urine as urea is limited.



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

Sodium phenylbutyrate (Buphenyl, Ammonaps, NaPBA or PBA) is used to treat UCD. PBA provides an alternative pathway for the removal of ammonia from the body. It has a bitter taste and is labeled to be given with food[2].

ACER-001 is an investigational product, formulated as an immediate release, taste-masked formulation of NaPBA which has been shown to have a higher and more rapid exposure when administered in the fasting state.

A food effect study, which evaluated ACER-001 (administered in the fed and fasting states) compared to Buphenyl (administrated in the fed state), was conducted in support of a new drug application for use of ACER-001 in UCD patients.

Because the data are limited for UCD, modeling provided a method to evaluate the impact of potentially dosing without food on the efficacy and potential toxicity using data from a new investigational formulation of NaPBA.

Methods

A previously published population pharmacokinetic/pharmacodynamic (PKPD) model was modified for this work[3].

- Recreate the published model in SimBiology®
  - The published model includes a population PK and PD model for Buphenyl which was previously reviewed by the FDA as part of the RAVICTI NDA submission[3].
- Integrate fasting PK model for ACER-001
  - The ACER-001 PK model was based on proprietary data.
- Generate adult and pediatric VPs based on the publication
  - The published model includes data and parameters for different age groups. These data were used for the virtual patients (VPs).
- Test to ensure model quality
  - The model simulations were compared to the publication and to data from the original clinical trials.
- Perform model simulations to assess drug exposure
  - The simulations compared potential efficacy and toxicity measures for each drug across the VPs

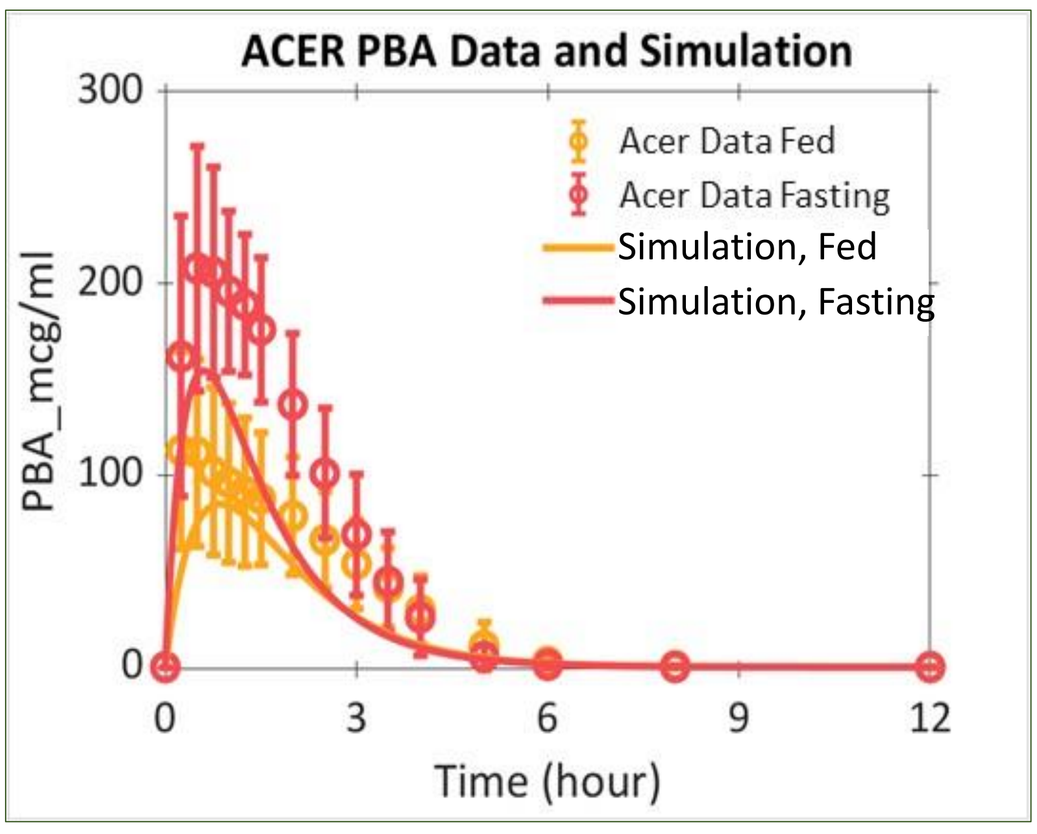
ICIEM 2021

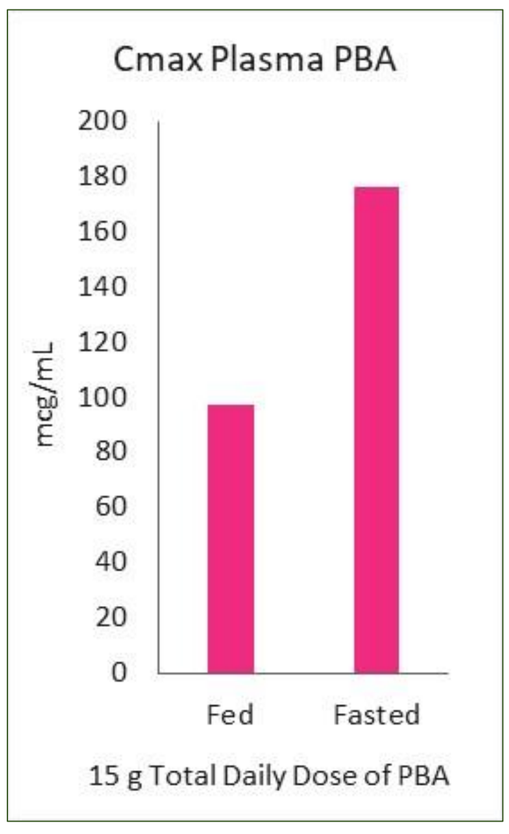
14TH INTERNATIONAL CONGRESS OF INBORN ERRORS OF METABOLISM

21-23 NOVEMBER 2021, SYDNEY, AUSTRALIA

Results

ACER-001 pharmacokinetics were incorporated in the model and compared to data.



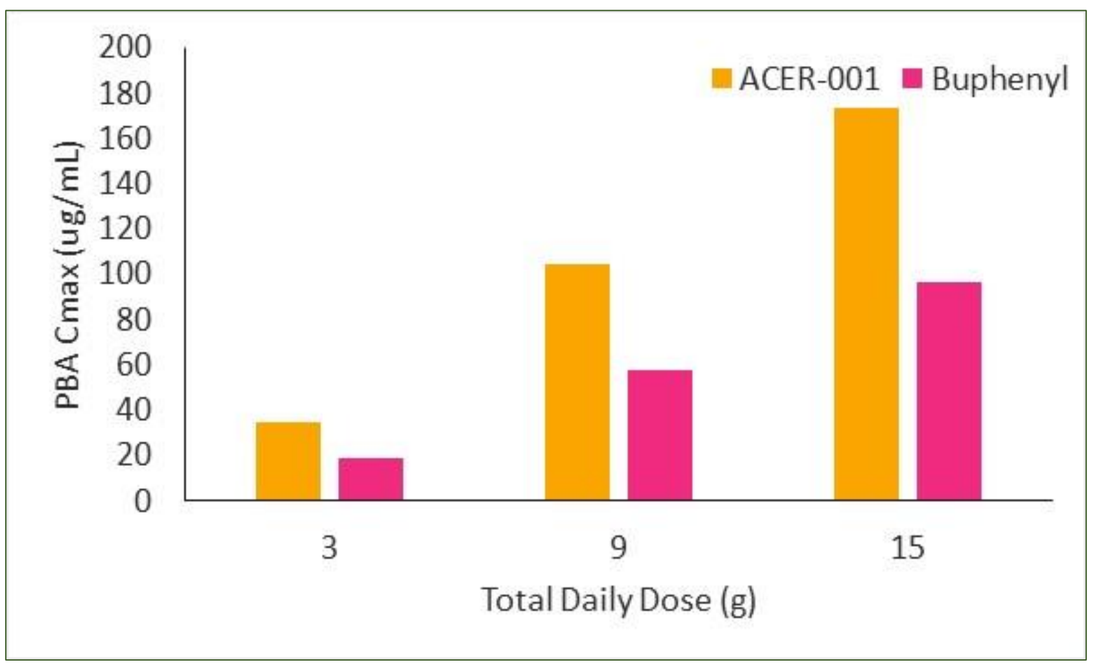


The previously published population PKPD model was developed using data from the drug administered in the fed state[3].

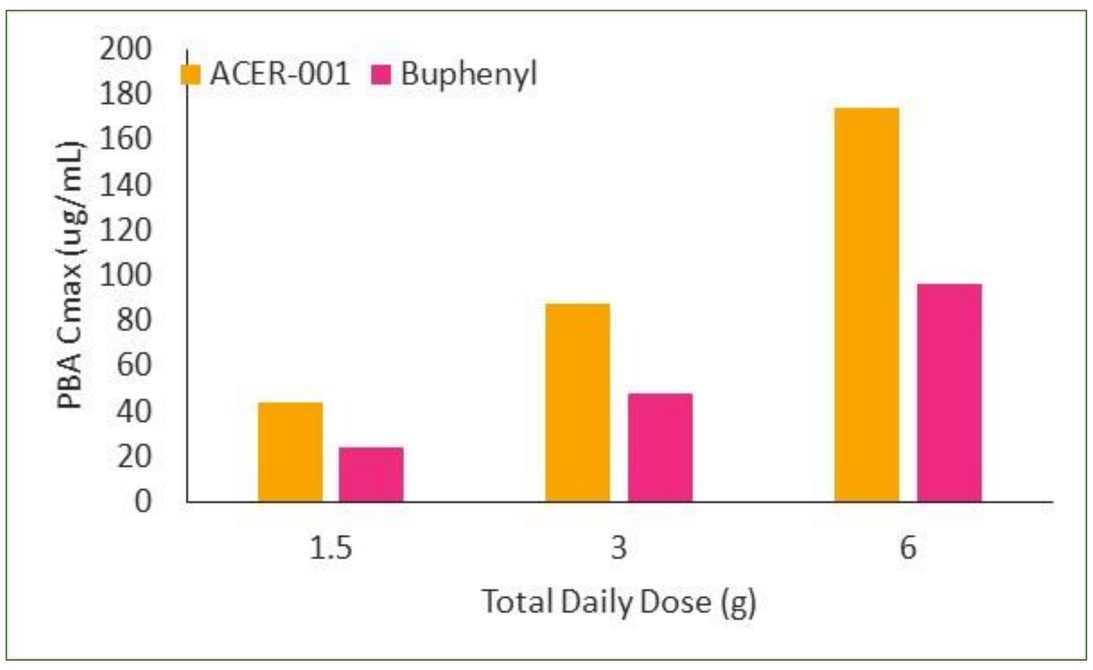
Proprietary data for NaPBA administered in the fasting state was used to create a fasting PK model. The fasting PK model was then incorporated into the SimBiology model.

To validate the model, simulation of fasting and fed administration of drug at a dose level of 5 g NaPBA was compared to proprietary data. Simulation results are shown as a line and data are shown as circles with standard deviation bars.

Adult Virtual Patient

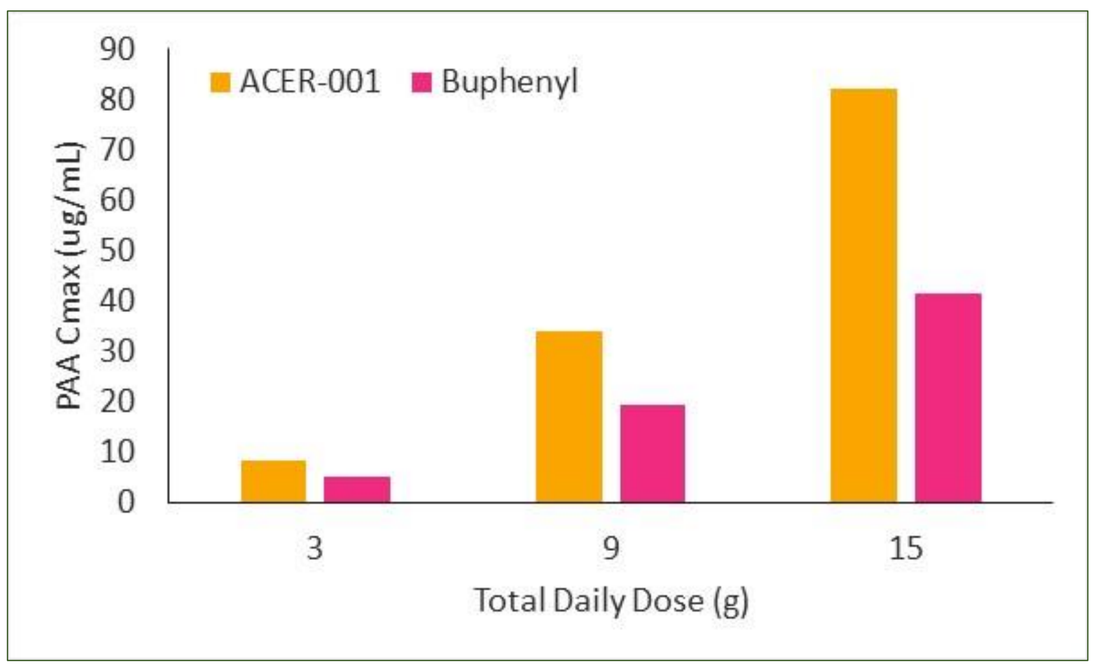


Child Virtual Patient

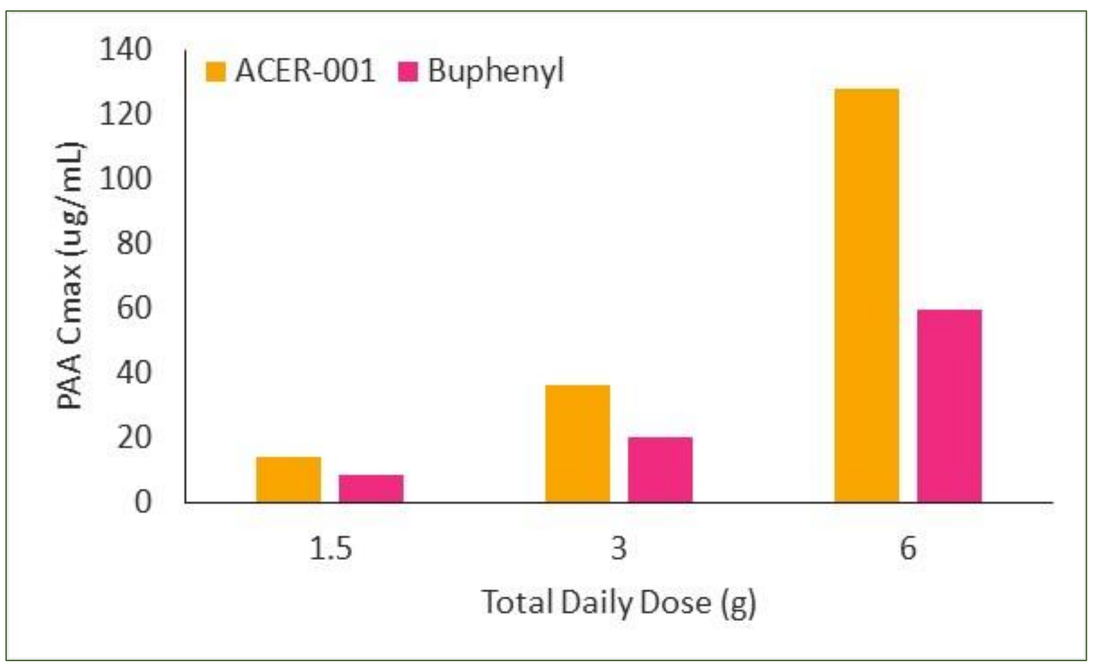


PK model simulations show that fasting administration of ACER-001 increases the peak PBA concentration (Cmax) in both Adult and Child Virtual Patients. ACER-001 (fasting) results are compared to fed administration of Buphenyl. The increase in drug concentration is dose proportional and is due to increased absorption of drug.

Adult Virtual Patient



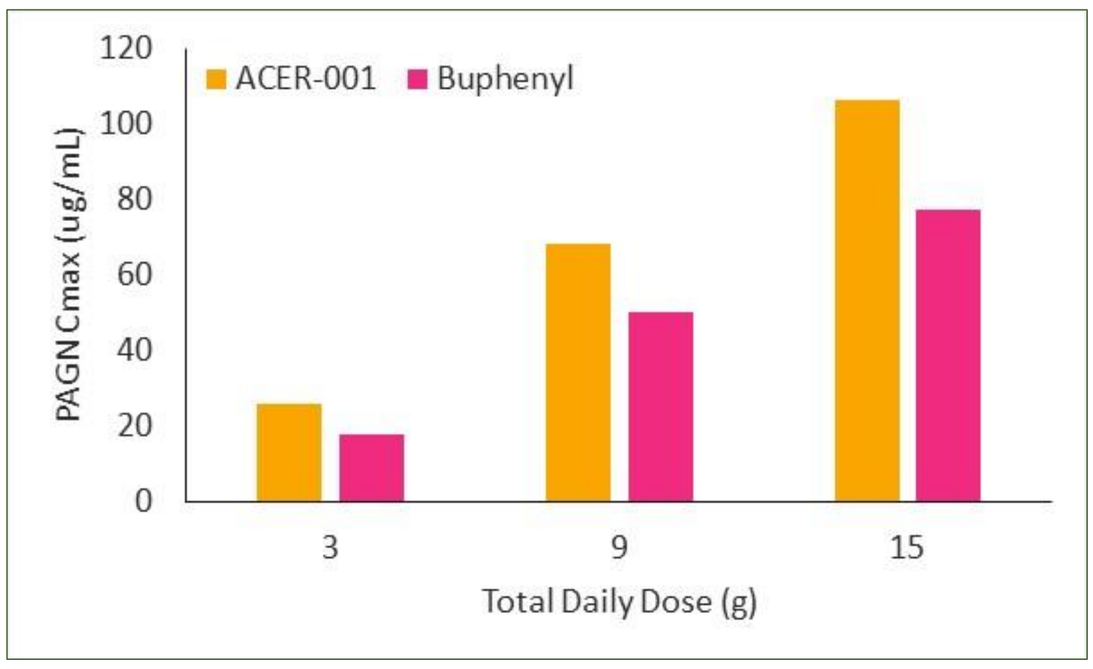
Child Virtual Patient



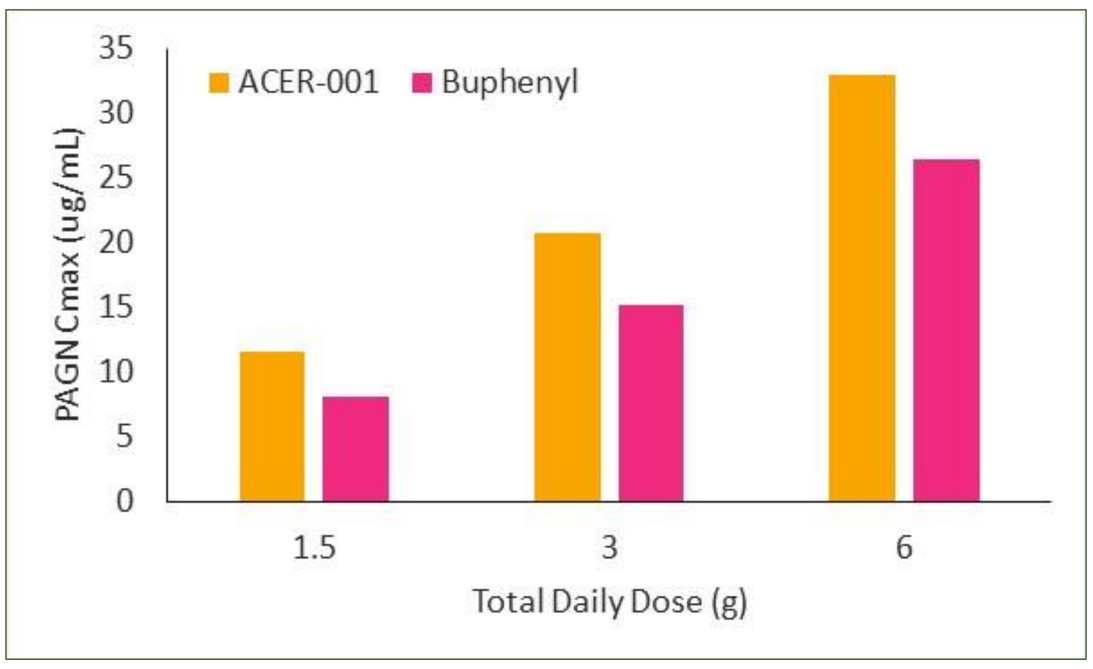
The maximum concentration of PAA is significantly increased in simulations when ACER-001 is given during fasting. Simulation results show the PAA Cmax may be increased in the Child Virtual Patient (right) which has limited enzyme capacity of glutamine N-acetyltransferase and thus limitations on metabolizing PAA to PAGN (note y-axis scales). PAA plasma concentrations ≥ 500 µg/dL have been reported to be associated with reversible neurological adverse events[4]. In the simulations shown, the maximum concentration of PAA does not exceed tolerable levels.

Results

Adult Virtual Patient

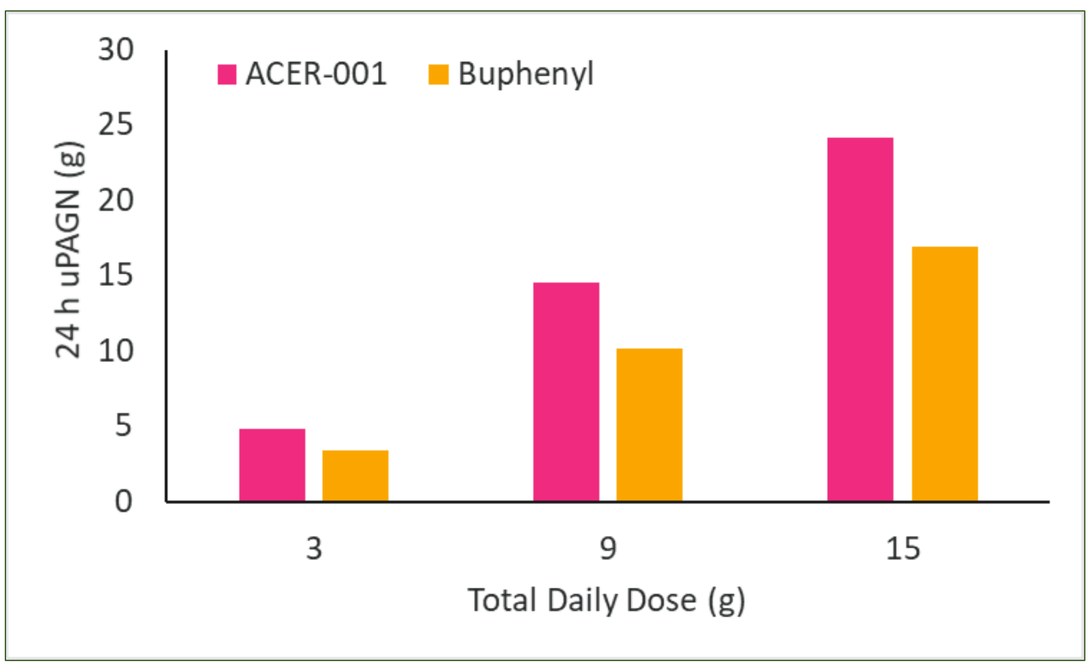


Child Virtual Patient

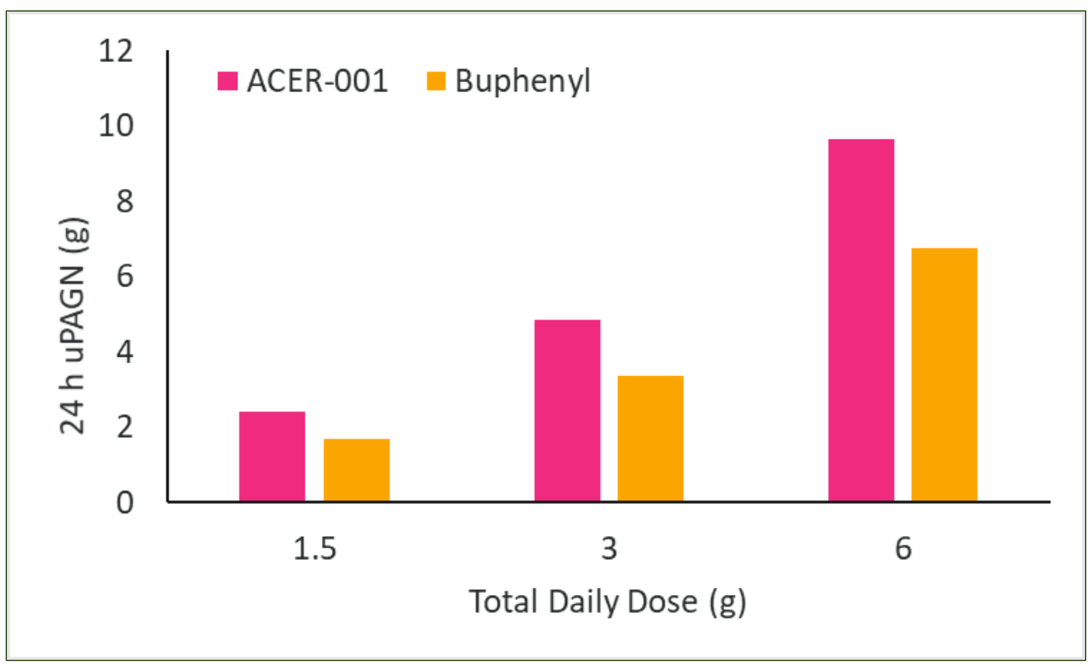


Dose response simulations of ACER-001 (fasting administration) vs. Buphenyl (fed administration) were conducted to evaluate the efficacy of the drugs. PAGN, which can be excreted in urine, is a marker of drug efficacy. Simulations show fasting administration of ACER-001 have a higher PAGN Cmax.

Adult Virtual Patient



Child Virtual Patient



Daily Urinary excretion of PAGN was evaluated in the Virtual Patients. Dose response simulations of ACER-001 (fasting administration) vs. Buphenyl (fed administration) have a higher excretion of PAGN in the Virtual Patients given ACER-001. Simulations show a 30% higher excretion of PAGN in the Virtual Patients treated with ACER-001 as compared to Buphenyl.

Conclusions

- Consistent with clinical observations, fasting administration of ACER-001 or Buphenyl (Ammonaps) resulted in increased drug exposure in the Virtual Patients.
- Based on the revised PK/PD model, fasting administration of ACER-001 or Buphenyl (Ammonaps) in the Virtual Patients is predicted to increase efficacy in proportion to the increased drug exposure, suggesting a 30% decrease in the administered dose under fasting conditions would still achieve the same level of exposure (efficacy and tolerability) as dosing under fed conditions.

References:

1. Brusilow, S.W. and N.E. Maestri, Adv Pediatr, 1996. 43: p. 127-70.
2. Shchelochkov, O.A., et al., Mol Genet Metab Rep, 2016. 8: p. 43-7.
3. Monteleone, J.P., et al., J Clin Pharmacol, 2013. 53(7): p. 699-710.
4. Mokhtarani, M., et al., Mol Genet Metab. 2013 Dec;110(4):446-53