Assessing the Role of Quantitative Systems Pharmacology Modeling in Early Stage Drug Development for Urea Cycle Disorders

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Introduction

- Urea cycle disorders (UCDs) are rare genetic diseases with a deficiency of one of the six enzymes in the urea cycle. UCDs can result in hyperammonemia causing irreversible brain damage and death.
- The onset and severity of UCDs is highly variable and depends on the amount of residual function of the urea cycle enzymes. Metabolic stressors may trigger events in patients with mild to moderate UCDs, potentially causing severe neurological symptoms.
- Development of therapies for UCD is complex due to the different role played by each urea cycle enzyme, gaps in the understanding of disease pathophysiology and high patient variability.
- Quantitative systems pharmacology (QSP) modeling can enable the development of therapies for UCD and other rare diseases by addressing these challenges and providing mechanistic insight to support decision making.

Objectives

The objectives of this research were to facilitate early-stage drug development for UCD by developing a QSP model that can be used to develop and test drug targets *in silico*, and to elucidate the effects of novel drug therapeutics on blood and urine metabolite levels.

Methods

A quantitative metabolic PhysioPD™ Research Platform was used as the basis for the UCD Platform development.

- A Urea Cycle Disorder PhysioPD™ Platform was developed to test potential drug treatments that affect the metabolism of amino acids (AA), ammonia, and urea. Rosa modified an existing PhysioPD™ Research Platform for this project. Urea and ammonia metabolism in the liver, kidney, and blood were incorporated into the original Research Platform that contained a quantitative mechanistic model of glucose, amino acid, and protein metabolism. The Platform included food intake with digestion and absorption of protein and amino acids.
- Pharmacokinetic representations for select AA transport inhibitor (SAATi) drugs were added to the Platform.
- Virtual Patients (VP) were created to simulate the physiology of an adult male with late onset ornithine transcarbamylase (OTC) deficiency, a representation of the UCD disease state. Changes in plasma ammonia and glutamine were evaluated after four weeks of simulated treatment with different hypothetical treatments, including restricted protein diets and a variety of SAATi.
- Based on the initial simulation results, an additional nine hypotheses were developed to explain the perceived discrepancies between simulations and preclinical data. Seven of these were evaluated further within the Platform. This hypothesis testing enabled the prioritization of experimental work to evaluate sensitive uncertainties
- The Platform was qualified in accordance with Rosa's Model Qualification Method[1] (MQM) (Figure 1).

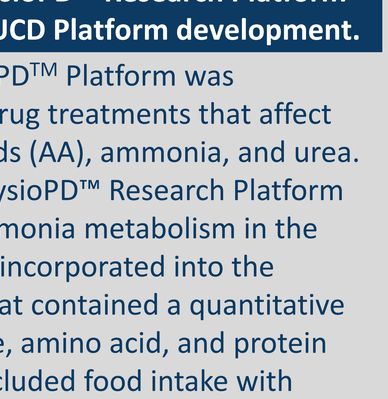
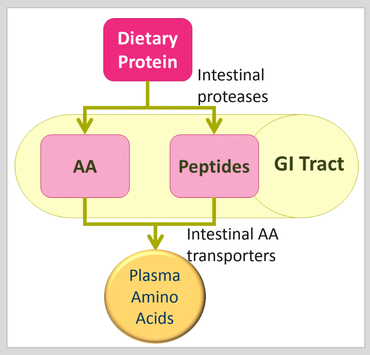


Figure 1. The Platform was qualified according to Rosa's Model Qualification Method[1] (MQM)

Results

A UCD PhysioPD Platform was developed and qualified.

- Platform qualification included comparison to preclinical and clinical data, including dietary and drug interventions. Diet interventions included response to fasting, oral glucose tests, and meal tests. Drug interventions included sodium phenylbutyrate (sodium PBA), arginine/citrulline, and a hypothetical ammonia (NH4+) binder.



Intestinal transporter	Gene	AA transported
rBAT	SLC3A1/SLC7A9	R,K,O, cystine
B0AT1	SLC6A19	AA°
PAT1	SLC36A1	P,G,A
SIT1	SLC6A20	P, HO-P
EAAT3	SLC1A1	E,D
PEPT1	SLC15A1	Di-, tri-peptides

Figure 2. The Platform includes dietary protein digestion and absorption. Clinically, AA absorption occurs through several transporters. Select AA and peptide transporters and inhibitors were incorporated within the Platform.

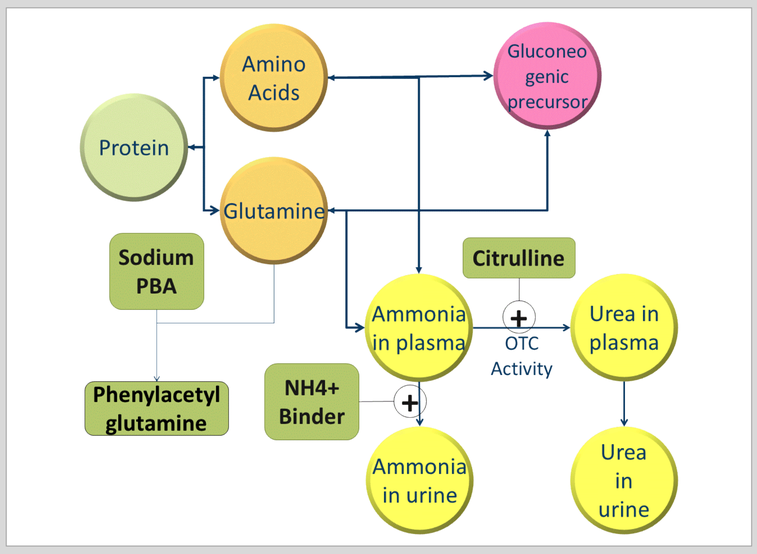


Figure 3. Graphic of the metabolism incorporated into the UCD Platform. Amino acid, ammonia, and urea metabolism were integrated with the existing protein, glucose, and lipid metabolism represented in the Platform.

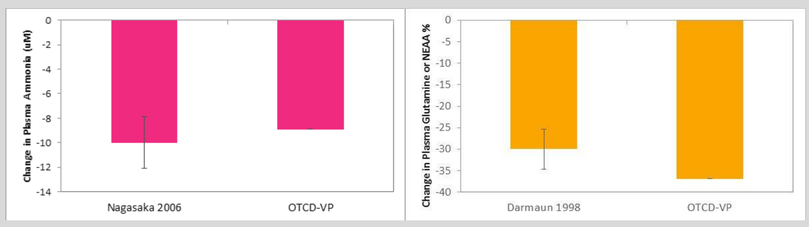


Figure 4. Treatment of the UCD-VP with UCD standard of care treatments results in similar changes in plasma ammonia or glutamine compared to literature values. Left graph shows results of treatment with sodium PBA on plasma ammonia concentrations. Right graph shows results of treatment with sodium PBA on change in plasma glutamate. Simulation measurement shown is nonessential amino acids (NEAA).

- The potential effects of muscle loss or adaptation with low protein diet were evaluated in the Platform.
- A standard diet with 15 or 7.5% protein was used. Protein kcals were replaced with both carbohydrates and fat. Protein is assumed to be very high quality with 40% essential AA.
- Release of AA from muscle has strong effects on increasing the amount of plasma AA or ammonia (Fig. 5).

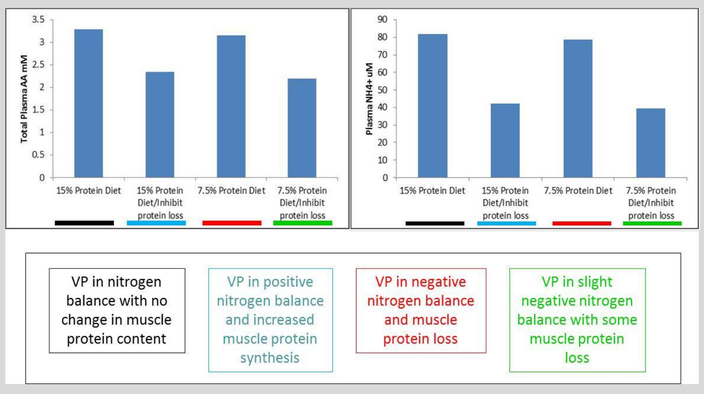


Figure 5. UCD VP was simulated with a standard or low protein diet and one of four hypotheses for protein metabolism: neutral, positive, negative, slight negative nitrogen balance.

Results

Inhibition of AA absorption lowers plasma levels of ammonia and excess glutamine.

- A severe UCD VP was simulated with either standard or restricted protein diets and/or SAATi treatment. A second experiment simulated a hypothetical ammonia binding drug. The amount of glutamine above a healthy concentration was counted as excess.
- The simulated treatments resulted in decreased ammonia production which may contribute to declines in plasma ammonia concentration.

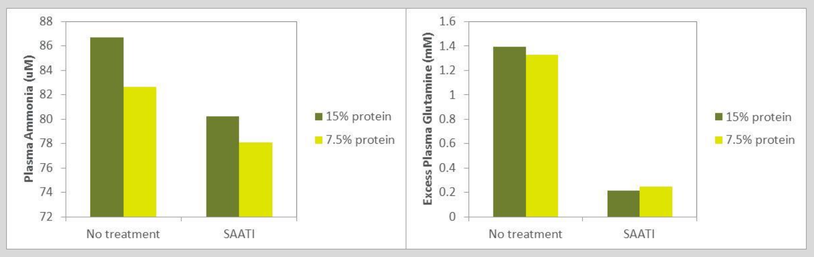


Figure 6. Changes in plasma ammonia and excess glutamine in severe UCD VP simulated with diet or select amino acid transport inhibitor. Left graph shows effects on plasma ammonia. Right graph shows effects on the levels of excess glutamine in the plasma.

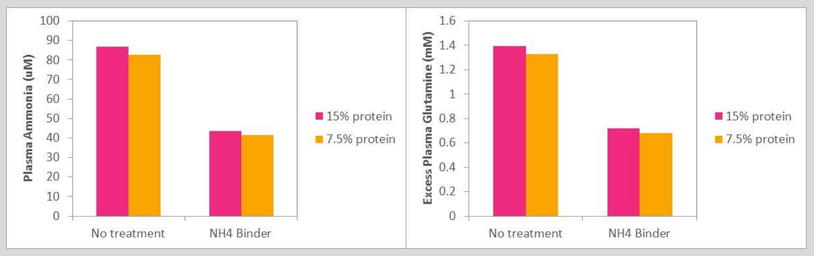


Figure 7. Simulated changes in plasma ammonia and excess glutamine in a UCD VP with diet or theoretical ammonia binder. Left graph shows effects on plasma ammonia. Right graph shows effects on the levels of total plasma glutamine.

Co-administration of an AA transport inhibitor with citrulline reduces plasma ammonia.

- A UCD VP was simulated with no treatment, SAATi, citrulline, or combination of SAATi and citrulline.
- Simulations suggest that adding citrulline allows the urea cycle to pull ammonia from the plasma ammonia pool, excrete it and lower ammonia concentrations.

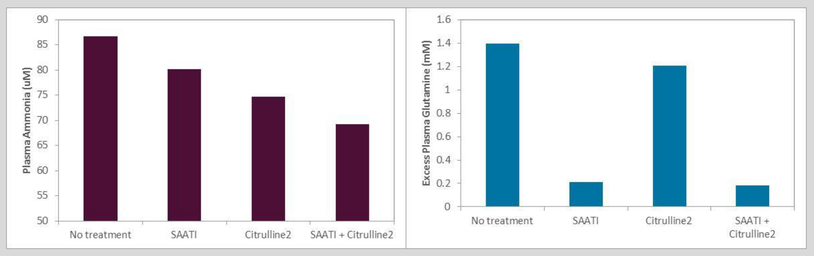


Figure 8. Simulations suggest that adding citrulline with SAATi reduces plasma ammonia and glutamine concentrations. Plasma ammonia is on the left and excess plasma glutamine is on the right.

- Platform research indicated that some SAATi would have improved efficacy if co-administered with citrulline or arginine.
- Additional hypotheses for SAATi mechanisms of action and combinations of hypotheses were identified for testing in the Platform.

Conclusions

- Research conducted in the UCD Platform provided guidance to support more definitive preclinical experimental design and compound evaluation.
- In addition, the research identified two therapeutic approaches that would combine well with a SAATi target.
- Quantitative modeling facilitated the development and testing of hypothetical drug targets in early-stage drug development.

References

1. Friedrich, CM. (2016) CPT: Pharmacometrics & Systems Pharmacology 5, 43-53 (MQM)
2. Frank TB, Ravishankar RV, Herbert MS. (2006) Current Proteomics 3, 181-97 (Jdesigner)

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