

PAGN PRODUCTION AS AN ALTERNATE NITROGEN SCAVENGING PATHWAY USING OCR-002 (ORNITHINE PHENYLACETATE) IN CIRRHOTIC PATIENTS; POTENTIAL FOR ADDITIONAL RENAL METABOLISM



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Background

OCR-002 (ornithine phenylacetate) is a novel compound in development for the treatment of hyperammonemia and resultant hepatic encephalopathy in patients with acute liver failure and cirrhosis. This Phase 2a, randomized, double-blind, placebo-controlled ascending dose study was designed to evaluate the pharmacokinetics and safety of OCR-002 in a stable cirrhotic population.

OCR-002, an injectable systemic ammonia scavenger, directly reduces circulating ammonia levels by upregulating muscle glutamine synthetase and secreting glutamine as the conjugate phenylacetylglutamine (PAGN) in urine. Each mole of PAGN excreted results in two mole equivalents of nitrogen excreted acting as a surrogate marker of ammonia excretion.

Preclinical data has demonstrated that OCR-002 reduces ammonia and intracranial pressure in ALF and can normalize ammonia and neurologic function in HE^{1,2,3}. OCR-002 also reduces NFκB expression, restores eNOS activity and lowers portal pressure⁴.

OCR-002 is free of sodium content and can be administered in low fluid volumes.

Design

A double-blind, placebo-controlled study, in which cohorts of 6 stable Child's class A or B cirrhotics (n=43) were randomized to active or placebo (5:1) and received single ascending doses of study drug (1,3, 10, 20, 40g over 4h or 10, 20, 40g over 24h).

Inclusion criteria: Male or female, BMI 18-30 Kg/m², 18-55 yrs of age. MELD < 15, West Haven Score < 2 with no history of decompensation (GI bleed, OHE, refractory ascites).

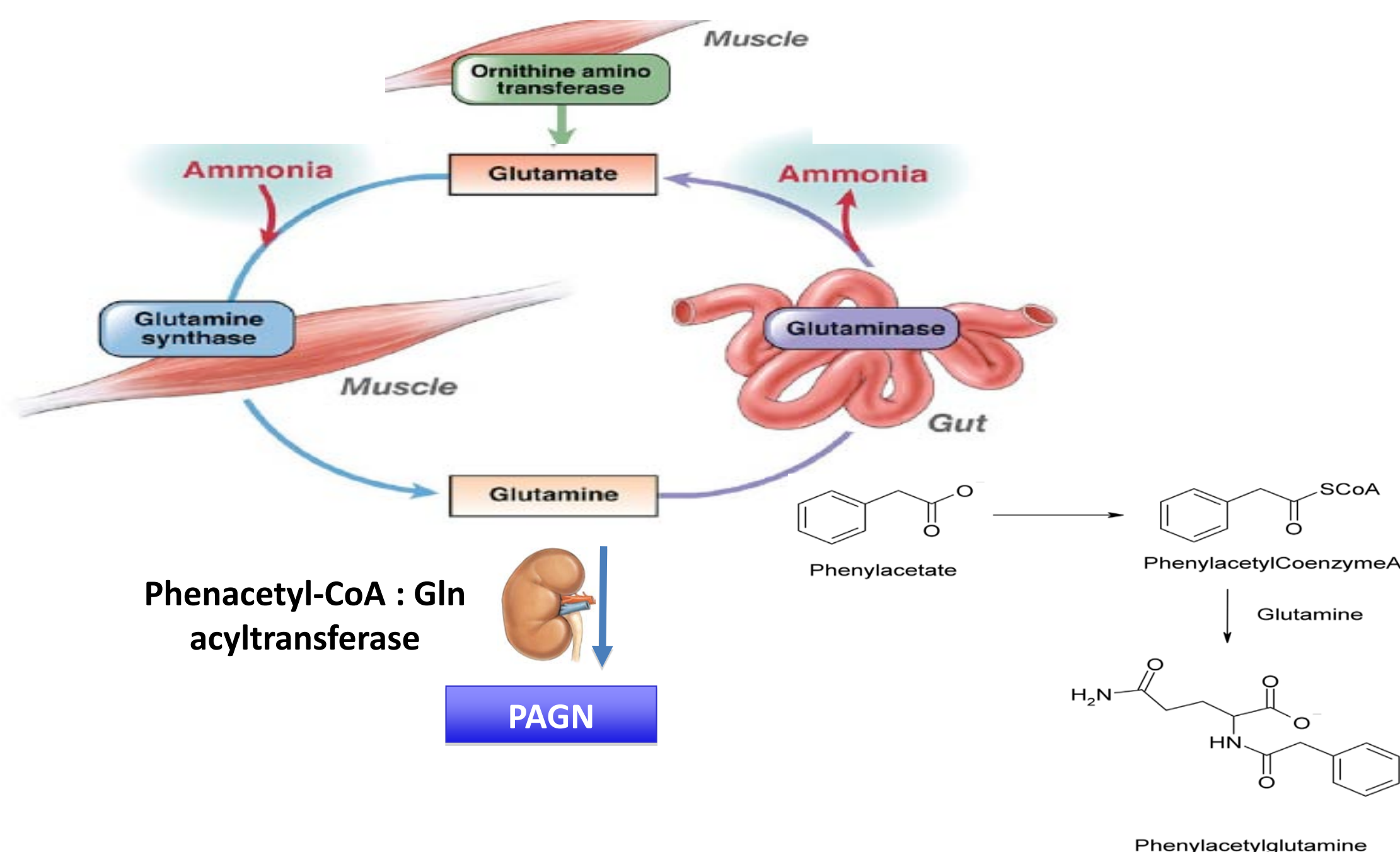
Patient population: 62.8% male, 74.3% Child Pugh A, mean age 52.7 yrs.

Primary PK analytes: phenylacetate (PAA), ornithine (ORN), phenylacetylglutamine (PAGN) in plasma and urine.

Safety evaluations included AE reporting, vital signs, pulse rate, body temperature, ECG, and standard clinical lab.

All patients were monitored up to 48h post dose with a 1 week follow up visit.

Mechanism



PK/PD : Phenylacetylglutamine formation and elimination

Figure 1. Plasma PAGN

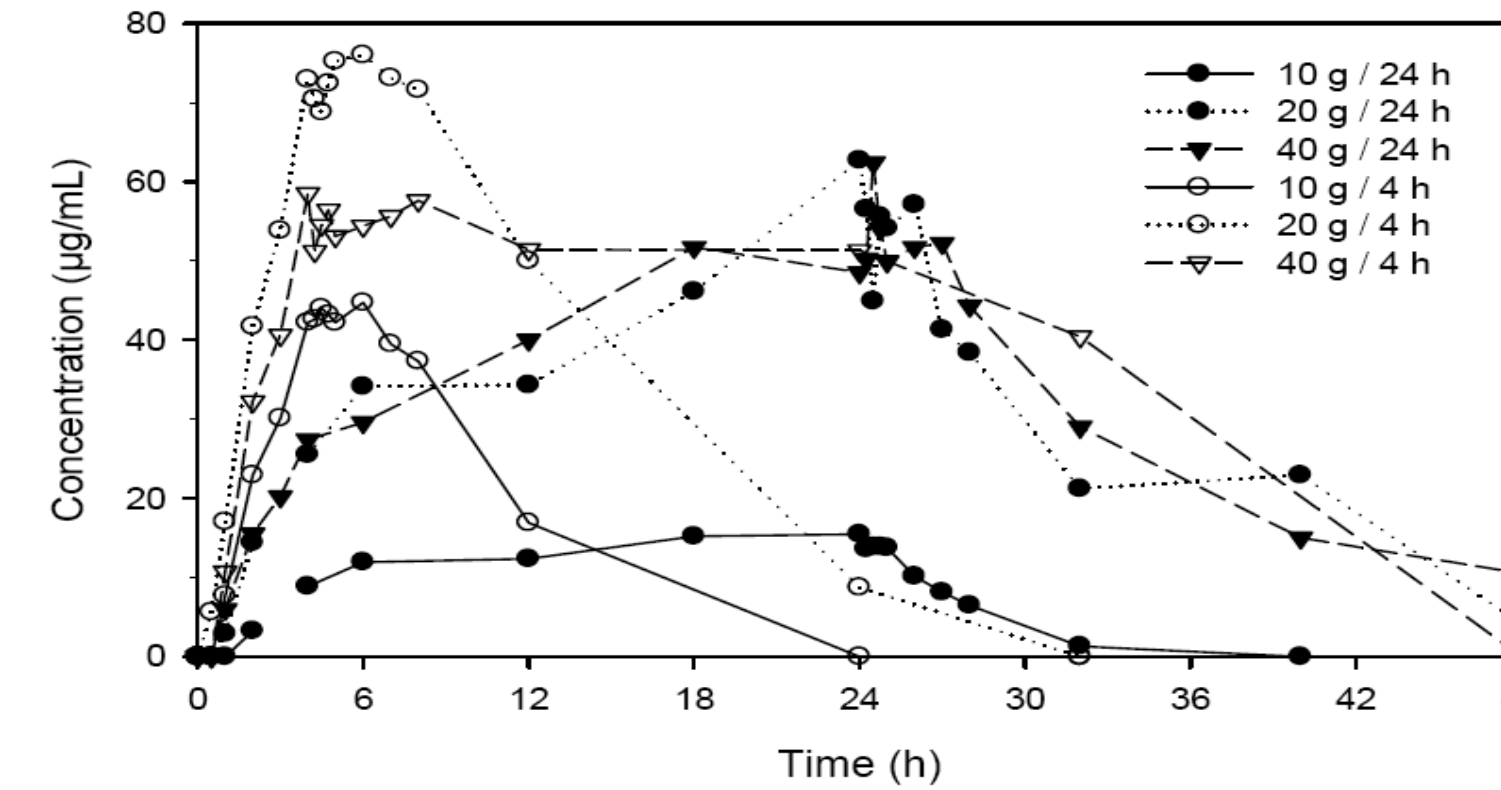


Figure 2. Cumulative PAGN urinary output

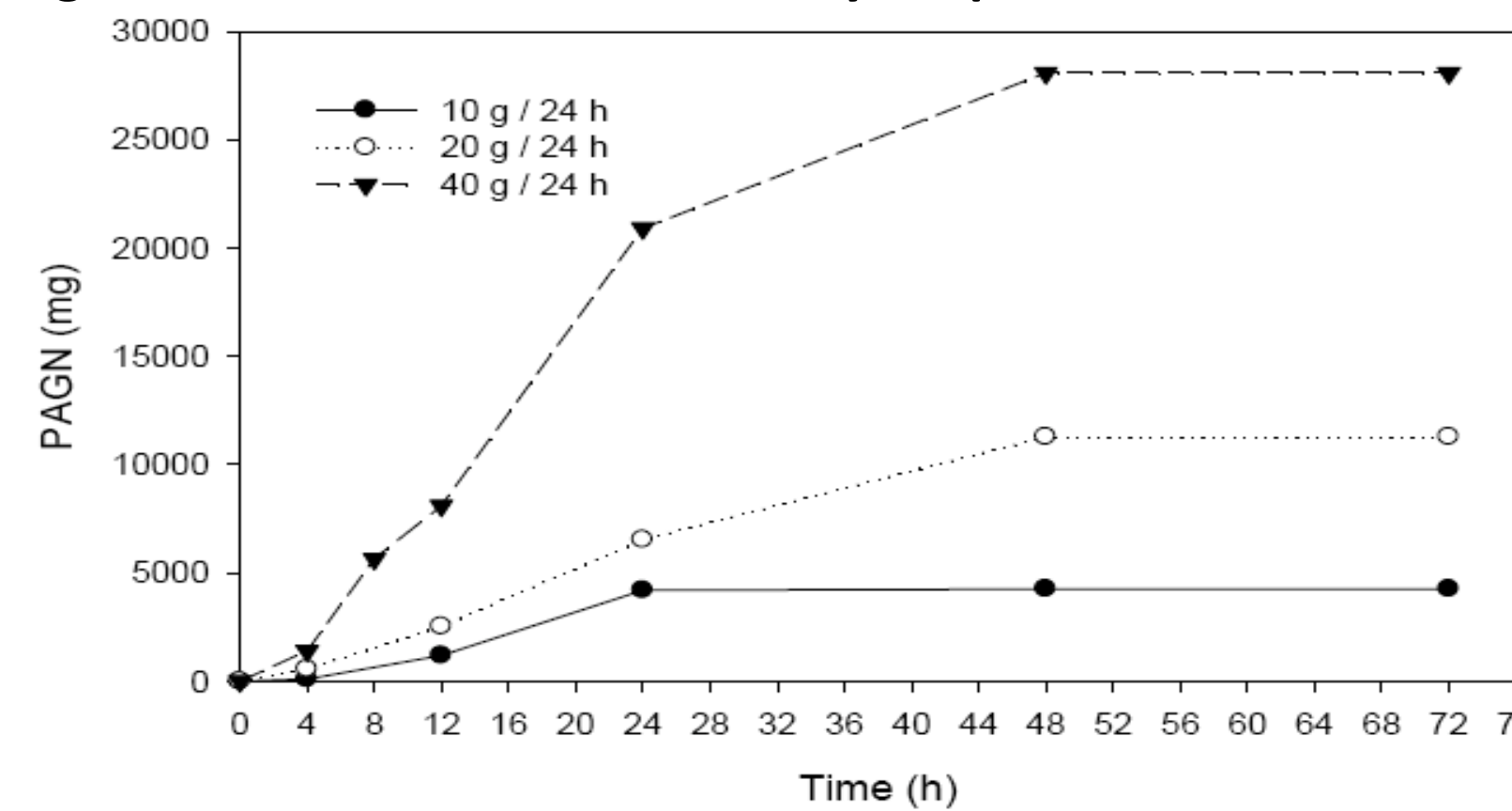


Figure 3. Plasma : Urine PAGN correlation

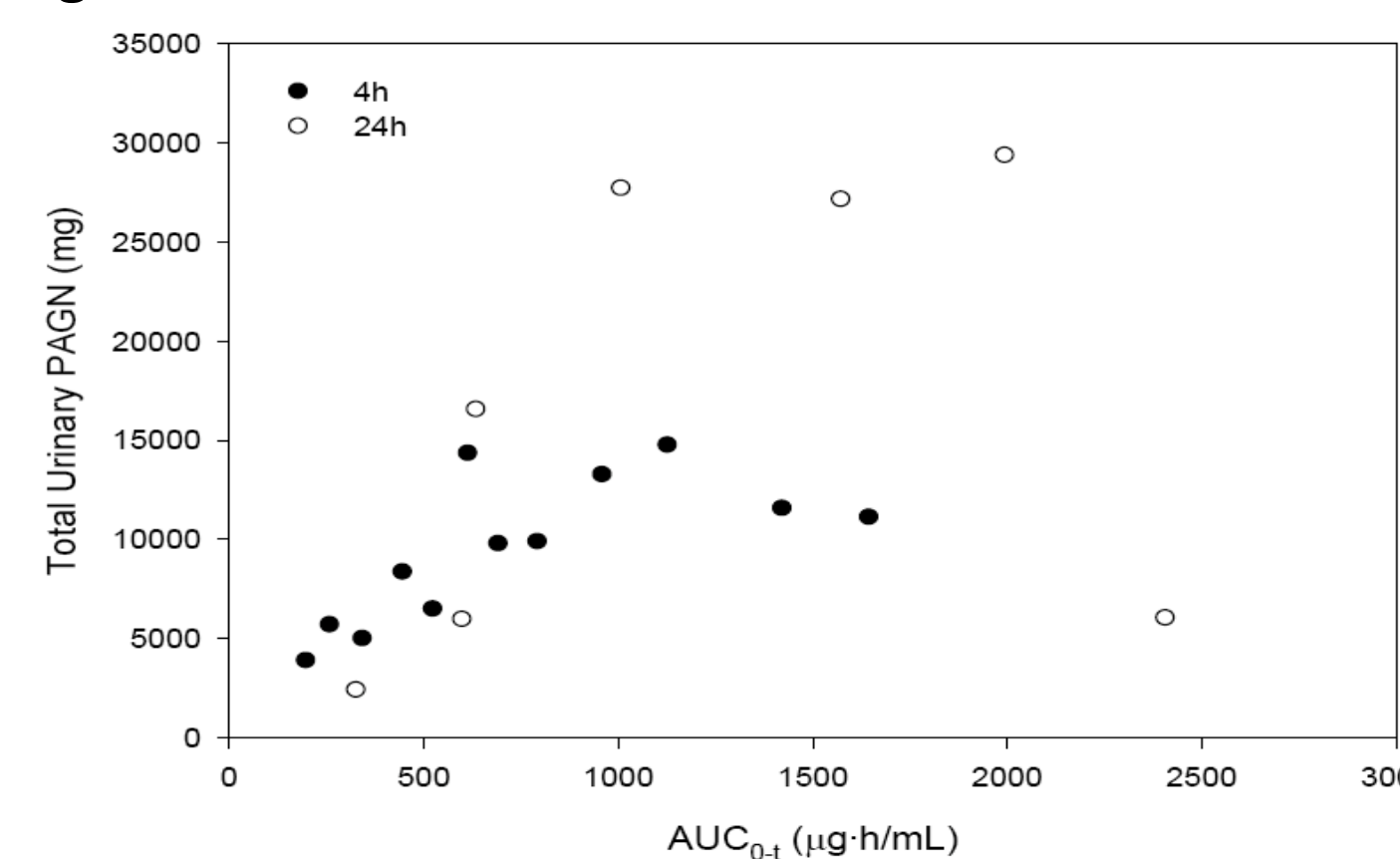


Table 1. PAGN Pharmacokinetics (24h infusion)

OCR-002 Dose (g)	Urinary Excretion (g)	AUC (µg·h/mL)
20 (0.83 g/h)	11.3 ± 7.4	1410 907
40 (1.67 g/h)	28.1 ± 1.2	1468 303

Table 2. PAGN production as a function of dose

OCR-002 Dose (g)	Relative PAA Dose (g)	PAGN Excreted in urine (mg)	Systemic Conversion ¹ (%)	PAGN renal excretion ² (%)
4h infusion				
10	5	5864	24	60
20	10	12388	16	63
40	20	11318	7	29
24h infusion				
10	5	4260	29	43
20	10	11278	32	57
40	20	28063	10	71

¹Systemic Conversion: (PAGN AUC₀₋₄/264.28g/mol)*(136.15g/mol/PAA AUC₀₋₁)*100

²PAGN renal excretion: (PAGN Urine (mg)/264.28 g/mol)/(PAA Dose/136.15g/mol*1000 mg/g)*100

Observations

- A doubling of the dose resulted in a >2-fold increase in urinary PAGN that was not reflective of plasma concentrations
- The systemic conversion of PAA to PAGN in plasma decreases at higher doses
- The systemic conversion of PAA to PAGN in plasma decreases at faster infusion rates
- The plasma PAGN exposure poorly correlates to urinary PAGN output

Conclusions

- Based on plasma PAGN profiles, the liver formation of PAGN is a saturable process
- The study suggests the kidney plays a major role in PAGN formation, further supported by literature⁵
- Plasma monitoring of PAGN is not representative of whole body nitrogen output
- Urinary PAGN output is a predictor of ammonia excretion and may be used as a surrogate marker in patients with liver disease

References

- [1] Ytrebø L et al, Hepatology 2009, [2] Davies et al, Hepatology 2009, [3] Oria et al, J Hepatol 2010, [4] Balasubramaniyan et al, Am J Physiol Gastrointest Liver Physiol 2011, [5] Moldave & Meister, J Biol Chem 1957

