Safety, Tolerability and Pharmacokinetics of L-Ornithine Phenylacetate in Patients with Acute Liver Injury/Failure

R. Todd Stravitz[1], Valerie L. Durkalski[2], Robert J. Fontana[3], A. James Hanje[4], David Koch[2], Bilal Hameed[5], Daniel R. Ganger[6], Ram Subramanian[7], Michelle Gottfried[2], Edward Doo[8], Averell H. Sherker[8], William M. Lee[9], for the ALF Study Group.

[1]Virginia Commonwealth University, Richmond, VA; [2]Medical University of South Carolina, Charleston, SC; [3]University of Michigan, Ann Arbor, MI; [4]Ohio State University, Columbus, OH; [5]University of California, San Francisco, CA; [6]Northwestern University, Chicago, IL; [7]Emory University, Atlanta, GA; [8]NIH/NIDDK, Bethesda, MD; [9] University of Texas, Southwestern Medical Center, Dallas, TX.

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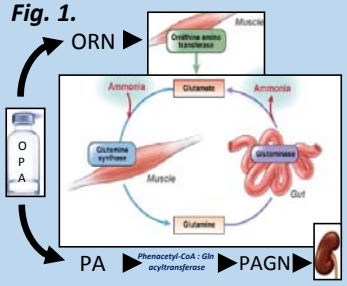
Background. Cerebral edema (CE) remains a significant cause of morbidity and mortality in patients with acute liver failure (ALF). Ornithine (ORN) phenylacetate (PA); [OPA] generates glutamate, binds ammonia, and promotes its renal excretion as phenylacetylglutamine (PAGN), and may lower ammonia and decrease the risk of CE (Figure 1, below).

Fig. 1.



Objective. To evaluate the safety, tolerability, and pharmacokinetics of OPA in patients with ALF and acute liver injury, including those with renal failure.

Patients.

-ALF defined according to standard criteria; ALI, no encephalopathy
-Ages 18-65
-Serum ammonia ≥60μM within 8h of OPA infusion
-MAP >65mmHg
-Excluded:
  Etiologies: Wilson's, ischemia, malignancy, pregnancy
  Uncontrollable ICP or herniation
  QTc >500msec on baseline ECG
  Lactulose or rifaximin

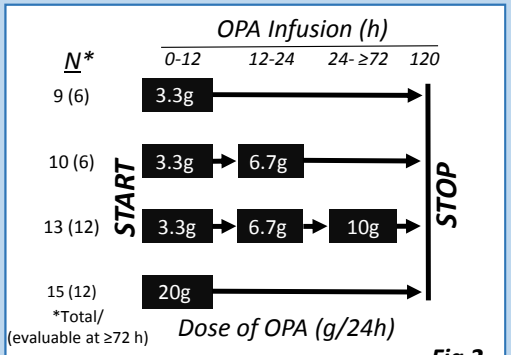


Fig 2.

Methods.

-Safety: Patients with "normal" renal function (Cr ≤1.5mg/dl) received 3.3g OPA/d as a constant infusion. Safety reviewed by committee before approving incremental doses up to 10g/d.
-Tolerability: Adverse events and PK reviewed by committee before approving use in patients with impaired renal function (Cr >1.5mg/dl) in doses up to 20g/d for the entire infusion period.
-Patients received up to 120h infusion, and were defined *a priori* as "evaluable" after receiving ≥72h.

Characteristic	Normal Renal Function (Cr ≤1.5mg/dl)	Impaired Renal Function (Cr >1.5gm/dl)
OPA ≥72h (evaluable)/ OPA <72h (non-evaluable) (N)	23/7	13/4
Age (y ± SD)	37 ± 13	42 ± 15
Female Gender	80%	41%
APAP/non-APAP (N)	25/5	7/10
ALT (IU/L ± SD)	5836 ± 4479	3501 ± 3657
INR (mean ± SD)	2.9 ± 0.6	3.3 ± 1.7
Ammonia (μM ± SD)	119.3 ± 45.3	155.4 ± 158.5
Creatinine (mg/dl ± SD)	0.7 ± 0.3	3.2 ± 2.0
Renal Replacement Therapy	3%	63%

Table 1. Baseline clinical characteristics of study population.

Event	N	Description of Event
Expected Events	47 Events	Events anticipated in the course of ALF
Adverse Events	103 Events (35 Subjects)	Pyrexia (5), progressive liver failure (4), headache (4), pneumonia (4), UTI (4), ↑K (4); *most common*
Serious Adverse Events	19 Events* (14 Subjects)	*11 resulting in death (none related to study drug)
Relatedness to study drug	Probably: 3 Events** Possibly: 8 Events Unlikely: 29 Events Not Related: 63 Events	**Nausea, vomiting, headache

Table 2. Adverse events (AEs) in all enrolled patients.

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Fig. 3. Serum PA concentrations at steady-state according to OPA infusion.

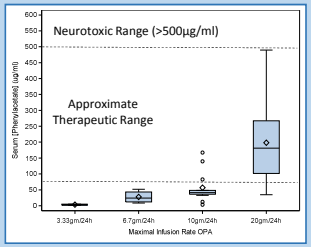


Fig. 4. Serum ammonia concentrations according to study day.

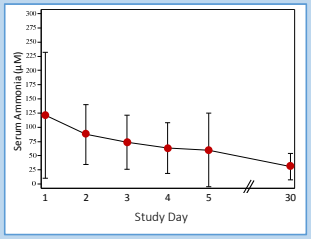


Fig. 5. Serum PA concentrations at steady-state according to baseline Cr.

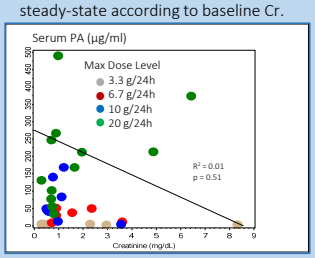


Fig. 6. Serum PAGN concentrations at steady-state according to baseline Cr.

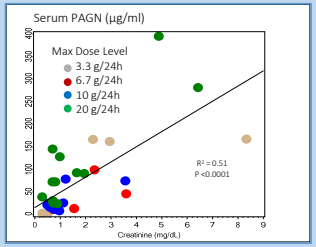
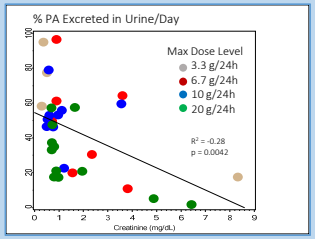


Fig. 7. Baseline Cr *vs.* percent PA excreted in urine as PAGN.



Summary/Conclusions.

- OPA was safe and well-tolerated
- PA exposure was below therapeutic threshold in all dosing groups except 20g/d
- PAGN, but not PA, accumulated in serum in proportion to renal dysfunction
- PAGN was recovered in urine in inverse proportion to renal dysfunction
- Further studies are required to assess efficacy in patients with ALF.