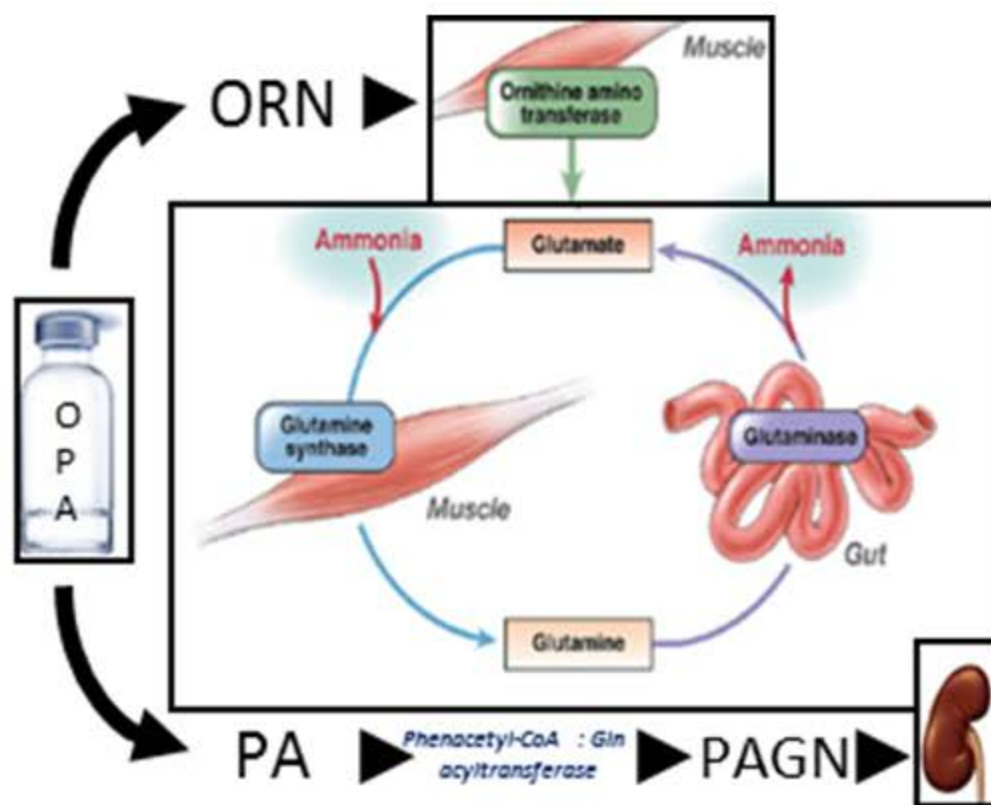


MedDRA Term	OPA Dose (g/24h)							
	3.3		6.7		10		20	
	N	%	N	%	N	%	N	%
Abdominal distension	1	2.6 %	0	0.0 %	0	0.0 %	0	0.0 %
Abdominal pain	0	0.0 %	0	0.0 %	0	0.0 %	2	6.8 %
Acute hepatic failure	1	2.6 %	1	6.2 %	2	8.3 %	0	0.0 %
Alcohol poisoning	0	0.0 %	0	0.0 %	1	4.1 %	0	0.0 %
Alcohol withdrawal syndrome	0	0.0 %	0	0.0 %	1	4.1 %	0	0.0 %
Anemia	1	2.6 %	0	0.0 %	0	0.0 %	0	0.0 %
Bradycardia	2	5.2 %	0	0.0 %	0	0.0 %	0	0.0 %
Brain edema	0	0.0 %	0	0.0 %	1	4.1 %	0	0.0 %
Cerebellar infarction	0	0.0 %	1	6.2 %	0	0.0 %	0	0.0 %
Circulatory collapse	1	2.6 %	0	0.0 %	0	0.0 %	0	0.0 %
Clostridial infection	0	0.0 %	1	6.2 %	0	0.0 %	0	0.0 %
Compartment syndrome	1	2.6 %	0	0.0 %	0	0.0 %	0	0.0 %
Confusional state	0	0.0 %	0	0.0 %	1	4.1 %	0	0.0 %
Constipation	0	0.0 %	0	0.0 %	3	12.5 %	0	0.0 %
Cough	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %
Deep vein thrombosis	2	5.2 %	0	0.0 %	0	0.0 %	0	0.0 %
Dyspnea	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %
Edema	0	0.0 %	2	12.5 %	0	0.0 %	0	0.0 %
Edema, peripheral	1	2.6 %	0	0.0 %	0	0.0 %	0	0.0 %
Electrocardiogram QT interval	0	0.0 %	0	0.0 %	1	4.1 %	0	0.0 %
Electrocardiogram QT prolonged	1	2.6 %	0	0.0 %	0	0.0 %	1	3.4 %
Electrocardiogram ST segment elevation	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %

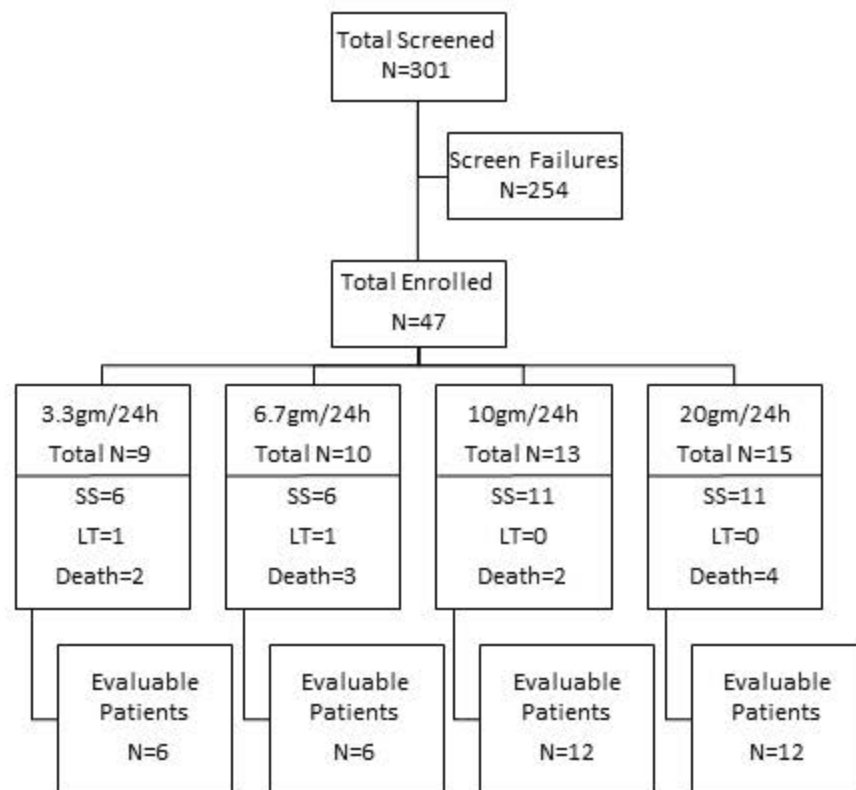
MedDRA Term	OPA Dose (g/24h)							
	3.3		6.7		10		20	
	N	%	N	%	N	%	N	%
Headache	1	2.6 %	3	18.7 %	0	0.0 %	0	0.0 %
Hepatic encephalopathy	1	2.6 %	0	0.0 %	0	0.0 %	0	0.0 %
Hypertension	0	0.0 %	1	6.2 %	0	0.0 %	1	3.4 %
Hypokalemia	0	0.0 %	1	6.2 %	1	4.1 %	2	6.8 %
Hypomagnesemia	1	2.6 %	0	0.0 %	0	0.0 %	1	3.4 %
Hypophosphatemia	0	0.0 %	0	0.0 %	1	4.1 %	2	6.8 %
Hypotension	0	0.0 %	0	0.0 %	0	0.0 %	3	10.3 %
Infusion site pain	0	0.0 %	1	6.2 %	0	0.0 %	0	0.0 %
Leukocytosis	1	2.6 %	0	0.0 %	0	0.0 %	0	0.0 %
Migraine	0	0.0 %	0	0.0 %	1	4.1 %	0	0.0 %
Multi-organ failure	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %
Nausea	1	2.6 %	1	6.2 %	1	4.1 %	1	3.4 %
Neurological decompensation	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %
Oliguria	7	18.4 %	0	0.0 %	0	0.0 %	0	0.0 %
Oropharyngeal pain	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %
Pelvic pain	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %
Peritonitis	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %
Pneumonia	2	5.2 %	1	6.2 %	1	4.1 %	1	3.4 %
Pyrexia	2	5.2 %	1	6.2 %	2	8.3 %	0	0.0 %
Red man syndrome	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %
Renal failure acute	1	2.6 %	0	0.0 %	1	4.1 %	0	0.0 %
Sepsis	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %
Septic shock	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %

MedDRA Term	OPA Dose (g/24h)							
	3.3		6.7		10		20	
	N	%	N	%	N	%	N	%
Sinus congestion	0	0.0 %	1	6.2 %	0	0.0 %	1	3.4 %
Subdural hematoma	0	0.0 %	1	6.2 %	0	0.0 %	0	0.0 %
Tachycardia	7	18.4 %	0	0.0 %	0	0.0 %	0	0.0 %
Tachypnea	1	2.6 %	0	0.0 %	0	0.0 %	0	0.0 %
Thrombocytopenia	0	0.0 %	0	0.0 %	1	4.1 %	0	0.0 %
Urinary tract infection	1	2.6 %	0	0.0 %	3	12.5 %	0	0.0 %
Vision blurred	1	2.6 %	0	0.0 %	0	0.0 %	0	0.0 %
Vomiting	0	0.0 %	0	0.0 %	1	4.1 %	2	6.8 %
Wheezing	0	0.0 %	0	0.0 %	0	0.0 %	1	3.4 %
Wound	0	0.0 %	0	0.0 %	1	4.1 %	0	0.0 %

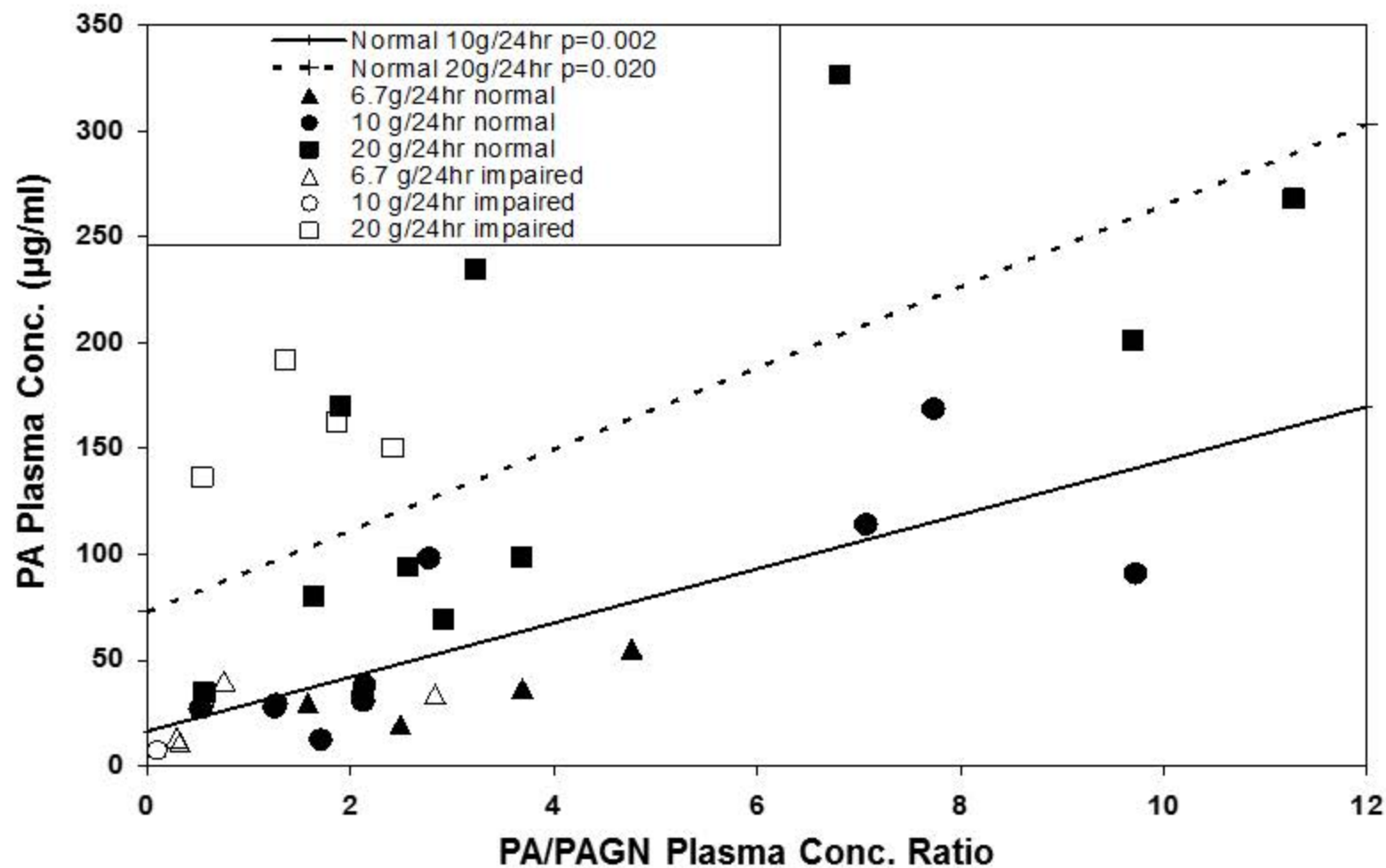
Supplemental Table 1. Complete reporting of adverse events by MedDRA Term according to infusion dose of OPA.



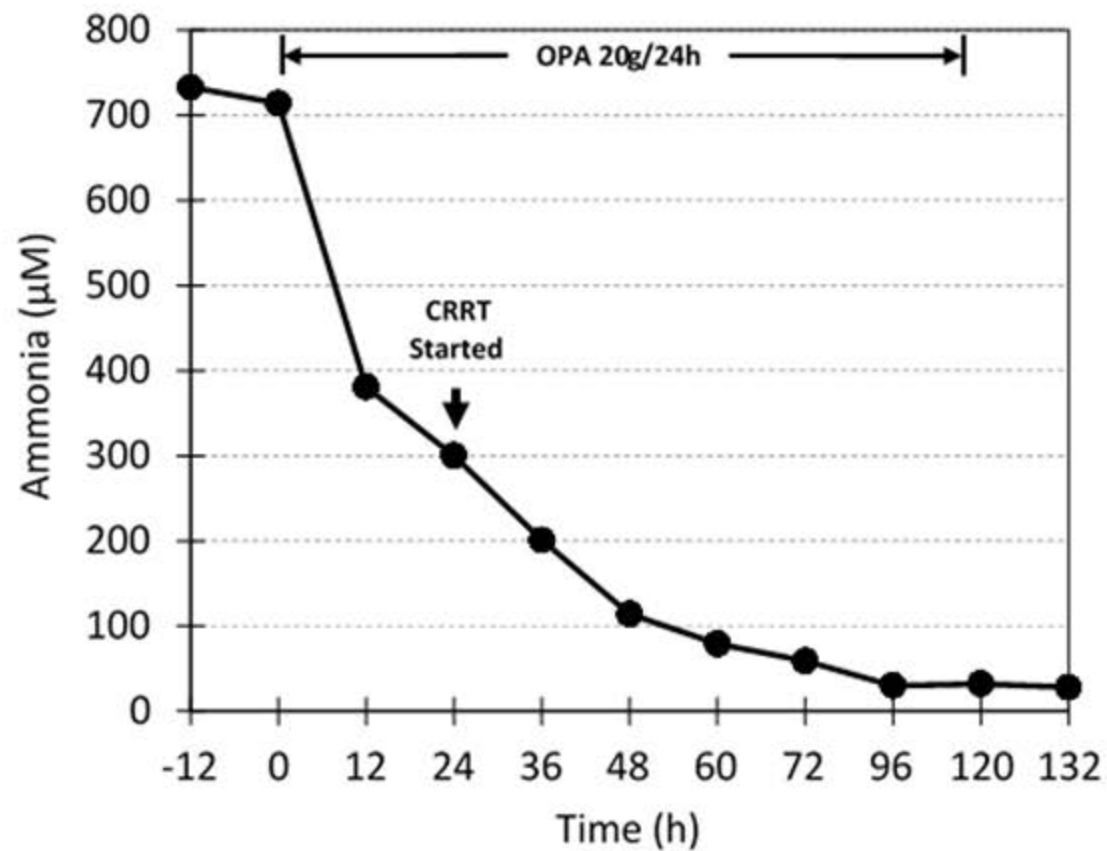
Supplemental Figure 1. **Proposed mechanism of ammonia elimination by ornithine phenylacetate.** The L-ornithine phenylacetate (OPA) salt dissociates in serum into ornithine (ORN) and phenylacetate (PA). Ornithine is biotransformed into glutamate by muscle ornithine aminotransferase, and ammonia is bound to glutamate by glutamine synthase in muscle to form glutamine. In order to prevent deamidation of glutamine by intestinal glutaminases and release of ammonia, PA is bound to glutamine by phenylacetyl-CoA:glutamine acyltransferase to form phenylacetylglutamine (PAGN), which is renally-excreted.



Supplemental Figure 2. **Consort diagram of study patients according to the maximal dose infusion of OPA.** “Evaluable Patients” are defined as those who received ≥ 72 h OPA infusion for purposes of evaluating lowering of serum ammonia. The outcomes at 21 days are depicted for each dose level (SS, spontaneous survival; LT, liver transplantation, and death).



Supplemental Figure 3. Plasma PA vs. plasma PA/PAGN ratio according to dose of OPA in normal and renally-impaired patients with ALI/ALF. Mokhtarani, *et al.* (8), have shown in patients with cirrhosis that plasma [PA], the moiety responsible for the neurotoxicity of sodium and glycerol phenylbutyrate (precursors of PA) increases as a function of the plasma PA/PAGN ratio, which in turn reflects the biotransformation of PA to PAGN primarily by the liver. As shown, none of the patients with ALI/ALF reached the neurotoxic plasma [PA] of 500µg/ml (17,18).



Supplemental Figure 4. Plasma ammonia concentration in a patient with adult Reye's Syndrome prior to, during, and after OPA infusion (20g/24h) and continuous renal replacement therapy (CRRT).