GLUTAMINE THERAPY FOR HEMOLYSIS-ASSOCIATED PULMONARY HYPERTENSION

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Hypothesis:
The primary hypothesis of this study is that glutamine supplementation will improve the erythrocyte glutamine/glutamate ratio, a biomarker of oxidative stress, hemolysis and PH in SCD and Thal patients with PH. PH is defined as a tricuspid regurgitant jet velocity (TRV) on Doppler echocardiography > 2.5 m/s. We also predict that glutamine therapy will increase arginine bioavailability and subsequently alter sickle red cell endothelial interaction that can be identified using endo-PAT technology through NO generation, leading to changes in biological markers, and clinical outcome. Specifically our second hypothesis is that oral glutamine will decrease biomarkers of hemolysis and adhesion molecules, and improve the imbalanced arginine-to-ornithine ratio that occurs in hemolytic anemias, leading to improved arginine bioavailability and clinical endpoints of endothelial dysfunction and PH in patients with SCD and Thal.

Specific Aims:
1. To determine the efficacy of oral glutamine therapy on increasing erythrocyte glutamine bioavailability in patients with hemolysis-associated PH through an 8-week open-label trial.
2. To determine the pharmacokinetics and metabolic fate of glutamine supplementation within plasma and erythrocytes of patients with sickle cell disease and thalassemia.
3. To monitor for potential toxicities associated with repeated administration of L-glutamine.

Background Information and Significance:
Sickle cell disease (SCD) is an inherited hemolytic anemia that affects approximately 70,000 individuals in the US, primarily African-Americans. It represents a group of genetic disorders variably characterized by anemia, severe pain, and potentially life-threatening complications such as bacterial sepsis, splenic sequestration, acute chest syndrome, stroke and chronic organ damage. These and other manifestations result from chronic hemolysis and intermittent episodes of vascular occlusion that cause tissue injury and organ dysfunction. The thalassemia syndromes are a heterogeneous group of inherited hemoglobin disorders resulting from unbalanced production of the alpha and beta globin subunits of the hemoglobin tetramer. The clinical spectrum is a consequence of chronic hemolytic anemia and imbalanced globin chain accumulation. It is a growing global public health problem with an estimated 900,000 births of clinically significant Thal disorders expected to occur in the next 20 years, however it remains an orphan disease in the United States. Intravascular or intramedullary hemolysis, chronic anemia and a high frequency of PH represent common features of both SCD and Thal. Growing support for a new model of hemolysis-associated endothelial dysfunction and PH has accumulated that has important implications for these specific hemoglobinopathies. Hemolytic rate is also associated with a growing list of clinical complications of SCD, including multi-organ failure, priapism, leg ulcers, and stroke, in addition to PH and mortality and constitute what is now considered the hemolytic subphenotypes of SCD. Rapid consumption of NO by cell-free hemoglobin coupled with the simultaneous release of erythrocyte arginase during hemolysis evoke a global disruption of the arginine-nitric oxide pathway, and is a fundamental aspect of this model in PH.

The presence of PH carries a 10-fold increased risk of early mortality in SCD, making it a critical complication to target with novel therapeutic strategies. Although chronic hemolysis plays an important role in the pathogenesis of PH in these hemoglobinopathies, growing evidence suggests additional mechanisms involving a complex interaction of platelets, coagulation system, erythrocytes and endothelial cells along with inflammatory and vascular mediators. The sickle and Thal erythrocyte have increased concentrations of the reactive oxygen species compared with normal red blood cells. Recently we discovered that a depletion of erythrocyte glutamine concentration and aberrations in erythrocyte glutathione metabolism is linked to PH in SCD. Since alterations in the erythrocyte redox environment can contribute to both increased oxidative stress and hemolysis, it represents a mechanistic model bridging two critical pathways in the pathogenesis of PH in hemolytic disorders. Interventions that target both oxidative stress and hemolysis will likely improve PH in patients with SCD and Thal. Glutamine therapy is potentially one such intervention, and has already demonstrated promise in SCD, although its role in PH has not yet been investigated. Improving glutamine bioavailability through supplementation is a novel approach to hemolysis-associated PH that warrants further investigation.