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Three-day trial of n-carbamylglutamate improves nitrogen metabolism and decreases ammonia in inherited hyperammonemias and healthy adults

Background: Inherited hyperammonemia (HA) from dysfunction of the urea cycle can lead to lethargy, encephalopathy, coma and even death. Current therapy includes ammonia scavenger medications and dietary protein restriction, but these treatments are suboptimal and affected patients still present with recurrent hyperammonemic crises. New therapies are therefore sorely needed. N-acetylglutamate (NAG) is the essential allosteric activator of carbamyl phosphate synthetase I (CPS1), which catalyzes the first step of the urea cycle in the liver. NAG is produced by NAG synthase (NAGS). Absence of or insufficient NAG results in blocked or decreased flux through the urea cycle, with ensuing hyperammonemia. We therefore studied the efficacy of N-carbamylglutamate (NCG), a synthetic analog of NAG, in the treatment of patients with various forms of inherited HA. In order to better understand the effect of NCG in affected patients, we also studied healthy adult volunteers.

Methods: We enrolled 34 subjects with inherited hyperammonemias (NAGS deficiency, CPS1 deficiency, ornithine transcarbamylase deficiency, methylmalonic acidemia, and propionic acidemia) and 10 healthy adult subjects. Identical studies were performed immediately before and at the end of a 3-day trial of oral NCG (Carbaglu, Orphan Europe). Following an oral bolus of [13C] sodium acetate, blood samples were collected at pre-determined intervals to measure the levels of [13C] urea, ammonia, urea, and amino acids.

Results: NCG reduced blood ammonia levels, reduced glutamine, and increased urea levels in several inherited hyperammonemias. Surprisingly, these same changes, albeit to a smaller degree, were also observed in healthy adult volunteers.

Conclusion: NCG improves or restores ureagenesis and decreases or normalizes ammonia in patients with several forms of inherited hyperammonemia. A similar, but smaller magnitude response in healthy adult volunteers, suggests that NCG may even be effective in patients with acquired forms of hyperammonemia, such as liver failure.

Biography

Leslie Atley is a Clinical Research Coordinator II at Children's National Medical Center, in Washington, DC. In this position she oversees the regulatory requirements, recruitment and administration of several genetic research studies with a focus in Urea Cycle Disorders. Leslie has a Bachelor of Science Degree in Biology and Chemistry from North Carolina Central University. She is currently enrolled in George Washington University's Masters of Public Health Program in Washington, DC. She serves on The Children's National Rare Disease Institute's Research Committee. She is the president and founder of 2Live International a non-profit organization specializing in health and wellness for women and children. Leslie is committed to and passionate about making a difference in the sphere of rare disease and health disparities.

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