MedicalXpress

An 'elegant' idea proves its worth 25 years later

May 31 2007

The simple notion of copying the body's own natural "waste disposal" chemistry to mop up potentially toxic nitrogen has saved an estimated 80 percent of patients with urea cycle disorders --- most of them children – according to a report in this week's New England Journal of Medicine summarizing a quarter century of experience with the treatment.

The effectiveness of sodium phenylacetate and sodium benzoate, two chemicals the body already makes to carry nitrogen for disposal in urine "just knocked my socks off from the moment we first tried them," recalls Saul Brusilow, M.D., professor emeritus of pediatrics at Hopkins who first had the notion to use the drugs. "In all my years I never came across another disease where patients come in near-comatose and you stick a needle in them and lo and behold, they wake up—just like that. It was just astonishing," he says.

"His elegant idea was to give patients chemicals they already make in small amounts in large doses to make up for the missing urea cycle enzyme they inherited," says Ada Hamosh, M.D., M.P.H, clinical director of the McKusick-Nathans Institute of Genetic Medicine. "Sodium phenylacetate and sodium benzoate already know how to eliminate nitrogen in urine, so having more in the body carries more nitrogen out and reduces the toxic effects of excess nitrogen accumulation."

Excess nitrogen yields ammonia, which is poisonous and in the case of urea cycle disorders, causes brain damage, retardation, coma and even

death.

Despite the immediate clinical success of the treatment, the drug combination was finally approved by the U.S. Food and Drug Administration only in 2005.

Brusilow, Hamosh, and colleagues at Stanford University, University of Minnesota, Thomas Jefferson University and the Medical College of Wisconsin looked back at 299 urea cycle disorder patients with a total of 1,181 hyperammonemia "episodes" from 118 hospitals around the United States from August 1980 until March 2005.

The regimen consisted of high-dose intravenous sodium phenylacetate and sodium benzoate for two hours followed by "maintenance infusions" until blood ammonia levels were normal. The patients' overall survival rate was 84 percent, and 96 percent survived episodes of severe ammonia poisoning.

An estimated one in 40,000 live births is a child with a urea cycle disorder, according to Hamosh, who says early and accurate detection can now assure prompt treatment.

"We're teaching all medical students at Hopkins to consider hyperammonemia and immediately do blood tests when they see a combative, lethargic or comatose newborn or child," she says. "The longer the hyperammonemia lasts, the higher the risk for brain damage."

"This is a happy story," says Brusilow. "It isn't too often in genetic medicine that we can intuitively develop a treatment with already available chemicals and save lives."

Source: Johns Hopkins Medical Institutions