JIMD Short Report #024 (2006) Online
DOI 10.1007/s10545-006-0229-8

SHORT REPORT

Dramatic reduction in self-injury in Lesch–Nyhan disease following *S*-adenosylmethionine administration

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Received: 8 September 2005 / Submitted in revised form: 30 June 2006 / Accepted: 3 July 2006

Summary A man with Lesch–Nyhan disease (LND; OMIM 300322) experienced significantly reduced self-injury and improved comfort while receiving *S*-adenosylmethionine.

Abbreviations

AdoMet	*S*-adenosylmethionine
HPRT	hypoxanthine-guanine phosphoribosyltransferase
LND	Lesch–Nyhan disease

A 43-year-old man had developmental delay, self-mutilation (lip avulsion and hand-biting starting at age 3 years), severe screaming (onset age 4 years), dystonic paralysis, seizures, suspected but ill-defined pain, and renal stones. The diagnosis of LND was based on clinical presentation and absent hypoxanthine-guanine phosphoribosyltransferase (HPRT) activity in cultured fibroblasts (Felix and DeMars 1971).

At age 38 years, fentanyl 25 μg (by skin patch, every three days) partially reduced suspected musculoskeletal pain. One month later, however, the serum ALT was 95 U/L and AST 115 U/L. In order to reduce transaminases and continue fentanyl, *S*-adenosylmethionine (AdoMet; Nature Made, Mission Hills, CA, USA) 400 mg twice daily (on an empty stomach) by gastrostomy was added for liver detoxification (Bottiglieri 2002). Transaminases promptly fell and, within a month his affect unexpectedly improved. After increasing AdoMet to 800 mg twice daily, attempts to self-injure and actual self-injury decreased from 31.7 per month and essentially disappeared within 1 1/2 years. Irritability decreased, as measured by a Percent Positive Mood Rating (percentage of waking hours during which positive mood was observed, documented hourly), with the Mood Rating improving from 36% initially to 58% at one year, 82% at two years, and 96% at three years. He had more interest in attempting verbal and computer-assisted communication training. Fluoxetine, given for suspected depression, was stopped without consequence. Methadone, substituted for fentanyl, was tapered and stopped.

These improvements have persisted for 4 1/2 years. His direct-care staff and his parents observe that he enjoys life more than at any time in the past 30 years.

Current medications and the rationale for their use are presented. They include: AdoMet 800 mg twice daily, which, in the presence of liver disease, restores hepatic glutathione content (Bottiglieri 2002); allopurinol 200 mg twice daily to reduce uric acid production; multivitamins with minerals one tablet/day; tizanidine 10 mg/day in divided doses, for spasticity; carbamazepine 200 mg twice daily for seizures; and lanzoprazole 30 mg/day for gastro-oesophageal reflux. Six years before AdoMet, carbidopa/levodopa 12.5 mg/125 mg three times daily and dantrolene 50 mg three times daily were started in order to increase dopamine availability and reduce unexplained febrile episodes that he had experienced and which are known to occur in people with LND (Jinnah and Friedmann 2001). Three years before AdoMet, potassium citrate 10 mEq twice daily was started to reduce stone formation following low 24-hour urine citrate (45 mg; reference range 300–320). Two to three years later, serum creatinine fell from 70 to 35 μmol/L, the passage of urinary stones (calcium phosphate by analysis) ceased, and stones disappeared from urinary tract ultrasonic studies. Two years before AdoMet, glucose 15 g three times daily was started for its

Communicating editor: Garry Brown

Competing interests: None declared

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protein-sparing effect in order to reduce protein catabolism. Ten months after AdoMet, ursodiol 300 mg/day was started for suspected biliary sludge; one year after AdoMet, folic acid 1 mg/day, pyridoxine 25 mg three times daily, and cyanocobalamin 1000 μg/day, were started for macrocytosis.

The childhood-onset self-injury started before any routine medications were given. The prominent temporal association between the elimination of self-injury and the introduction of AdoMet was not observed after the introduction or withdrawal of other medications. Similarly, the introduction of none of the above agents was followed by increased self-injury.

Random morning urine oxypurines (University of California-San Diego, Biochemical Genetics Laboratory, San Diego, CA, USA) were serendipitously obtained for evaluation of chronic macrocytosis (MCV 128–130 fl) 5 months before AdoMet and were repeated 3 years later(see Table 1). On the basis of absolute concentrations, uric acid, hypoxanthine and oxypurinol fell significantly. However, on the basis of the urine creatinine concentration, hypoxanthine fell marginally.

The urine data must be interpreted cautiously even though this individual had a diurnally consistent feeding-tube schedule. First, these were not 24-hour samples, the most reliable standard. Second, during the 3-year sampling interval, unmeasured changes in body composition, such as decreased muscle mass due to decreased agitation, could explain the decline in urine creatinine. Third, when muscle mass is decreased, urine creatinine has been shown to be a less reliable common denominator for measurement of urine solutes (Richmond et al 2005). Fourth, synthesis of creatine, an AdoMet-dependent process (Stead et al 2006), and its subsequent transformation to creatinine, may have been affected by the additional methyl groups. The net effect upon creatinine synthesis cannot be assumed since this occurred in the context of a suspected decline in muscle mass. Fifth, the concentration of oxypurinol, an allopurinol metabolite and also an inhibitor of xanthine oxidase, apparently changed and, as a consequence, may have modified the purine excretion pattern.

Serum homocysteine fell from 12.9 to10.6 μmol/L after AdoMet was started, but there was no change in macrocytosis. (An earlier trial of betaine did not affect the macrocytosis.) After starting folic acid, pyridoxine and cyanocobalamin, serum homocysteine fell to 9.9, but the macrocytosis did not improve.

The neuropathogenesis of LND has not been established, and the addition of methyl and adenosyl moieties (1600 mg AdoMet contains 1070 mg adenosine) may have had complex effects. Although the evidence in this case is inconclusive, it is consistent with the adenosine-depletion hypothesis. Adenosine monophosphate (AMP), normally formed from adenosine via the action of adenosine kinase, is known to inhibit amidophosphoribosyltransferase (AMPRT) (Jinnah and Friedmann 2001). Exogenous AdoMet-derived adenosine could, theoretically, reduce *de novo* purine oversynthesis. Likewise, the additional methyl groups may have had widespread consequences, considering that AdoMet is present in all living cells and is the proximate methyl group donor in more than 100 methyltransferase-catalysed reactions (Bottiglieri 2002). Clinically, AdoMet has been shown to have a role in depression and osteoarthritis, as well as in liver disease (Bottiglieri 2002). AdoMet is not known to affect the activity of other drugs.

Further studies were not pursued because discontinuation of successful AdoMet treatment was felt to be unethical and because of strong parental (guardian) objection.

In subsequent cases, preliminary clues to pathogenesis and management may be provided by additional studies. Serial pre- and post- serum AdoMet and adenosine concentrations, as well as pre- and post- 24-hour urine oxypurines after a shorter period of AdoMet administration, may indirectly clarify whether AdoMet is truly reducing purine oversynthesis and whether the AdoMet dosage is optimal. As a precaution,

Table 1 Laboratory parameters

Parameter	25 July 2000	28 May 2003
Absolute urine concentrations		
Uric acid (μmol/L)	1699.5	1119.1
Hypoxanthine (μmol/L)	2356.3	908.8
Xanthine (μmol/L)	1685.9	1715.1
Oxypurinol (μmol/L)	1077.1	687.9
AICAR (μmol/L)	0	0
Creatinine (mmol/L)	3.8	1.68
Urine concentrations relative to urine creatinine concentrations		
Uric acid (mmol/mmol creatinine)	0.444	0.666
Hypoxanthine (mmol/mmol creatinine)	0.620	0.541
Xanthine (mmol/mmol creatinine)	0.523	1.021
Oxypurinol (mmol/mmol creatinine)	0.283	0.409
Serum creatinine (μmol/L)	35.4	35.4
Body weight (kg)	52.4	55.6

if allopurinol is not given, urine 8,10-dioxyadenine excretion should be assessed. Although the conversion of adenosine to adenine is normally limited, allopurinol further inhibits the conversion of adenine to this nephrotoxic metabolite (Bührdel et al 1985).

Acknowledgement The helpful comments of Milton Fischer, PhD and William Adkins, MD are greatly appreciated.

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