Symptomatic Hyperammonemia Secondary to Recombinant Erwinia Asparaginase

Catherine E. Martin[1], Mira Kohorst[1], Asmaa Ferdjallah[1], Jessica L. Kalmes[1], Heather M. Johnson[1], Paul Galardy[1], Shakila Khan[1], and Alexis Kuhn[1]

[1]Mayo Clinic Minnesota

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Catherine E. Martin, Pharm.D., Department of Pharmacy – Ambulatory Service, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Mira A. Kohorst, M.D., Department of Pediatric and Adolescent Medicine, Division of Pediatric Hematology/Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Asmaa Ferdjallah, M.D., M.P.H, Department of Pediatric and Adolescent Medicine, Division of Pediatric Hematology/Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Jessica L. Kalmes, APRN, C.N.P., M.S.N, Department of Pediatric and Adolescent Medicine, Division of Pediatric Hematology/Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Heather M. Johnson, APRN, C.N.P., M.S.N, Department of Pediatric and Adolescent Medicine, Division of Pediatric Hematology/Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Paul J. Galardy, M.D., Department of Pediatric and Adolescent Medicine, Division of Pediatric Hematology/Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Shakila P. Khan, M.D., Department of Pediatric and Adolescent Medicine, Division of Pediatric Hematology/Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Alexis K. Kuhn, Pharm.D., Department of Pharmacy – Ambulatory Service, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Corresponding author: Catherine E. Martin; address: 200 First Street SW, Rochester, MN 55905; phone: 507-284-2695; fax: 507-266-4912; email: martin.catherine3@mayo.edu

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Abbreviations

Abbreviation	Full term
ALL	Acute lymphoblastic leukemia
IM	Intramuscular

Abbreviation	Full term
NSAA	Nadir serum asparaginase activity
ULN	Upper limit of normal

Asparaginase is well recognized as a crucial element in the treatment of pediatric acute lymphoblastic leukemias (ALL).[1] It is an enzyme that exerts its anti-leukemic effects by catalyzing the breakdown of asparagine to aspartic acid and ammonia.[1]The *E. coli* -derived asparaginase formulations, L-asparaginase and pegaspargase, have high rates of antibody development that can ultimately lead to inadequate asparaginase activity.[2]To combat this, *Erwinia chrysanthemi* -derived asparaginase was developed, of which several products exist: conventional Erwinia asparaginase (Erwinaze), and, the newest formulation, recombinant Erwinia asparaginase (Rylaze).[2,3]

As ammonia is a byproduct of asparaginase's mechanism, acute, transient hyperammonemia is expected.[4,5] Symptomatic hyperammonemia may present as headache, nausea, vomiting, lethargy, or in severe cases, encephalopathy, coma, or death.[6–8]There are several case reports describing symptomatic hyperammonemia in patients receiving pegaspargase and conventional Erwinia asparaginase, but herein we describe two patients who developed symptomatic hyperammonemia secondary to recombinant Erwinia asparaginase.[6,9,10]

Patient 1:

Patient 1 is an 18-year-old male with very high-risk B-cell ALL. During his third dose of pegaspargase, he experienced a grade 3 hypersensitivity reaction. Though he clinically tolerated a desensitization protocol, resultant asparaginase activity levels were undetectable; therefore, his therapy was modified to substitute recombinant Erwinia asparaginase for all future doses of pegaspargase.

His next scheduled dose of pegaspargase was substituted with 6 doses of recombinant Erwinia asparaginase 50 mg (25 mg/m2) intramuscularly (IM) every 48 hours.[11] Within minutes of his fourth dose, he reported feeling nauseous and light-headed. He was treated with a fluid bolus and promethazine. A post-dose ammonia level resulted at 275 μmol/L (upper limit of normal (ULN) 60 μmol/L). Given the symptomatic hyperammonemia with the previous dose, an ammonia level and a nadir serum asparaginase activity (NSAA) were measured prior to the next dose (dose #5 of 6). His pre-dose ammonia level remained elevated at 248 μmol/L, and his NSAA was 0.54 IU/mL (goal NSAA [?]0.1 IU/mL).[12] His ammonia level immediately following dose 5 was 321 μmol/L. He reported feeling fatigued and nauseous for about 24 hours after each recombinant Erwinia asparaginase dose.

With the sixth recombinant Erwinia asparaginase dose, the patient received lactulose 20 grams by mouth three times daily (titrated to three soft stools per day) with symptomatic improvement noted within a few days of initiation. Four days after starting lactulose, and with no further asparaginase, ammonia normalized. Due to the high NSAA during the previous course, and to prevent further accumulation of ammonia, the recombinant Erwinia asparaginase dose was decreased by 20% and the frequency was changed to every 72 hours for the next course. Repeat NSAA after the first dose of this new dosing schedule was undetectable, and the dose was increased to 50 mg every 72 hours with a resultant NSAA of 0.34 IU/mL. With the dose adjustment, he has been able to discontinue the lactulose without recurrence of symptomatic hyperammonemia. At the time of publication, the plan for patient 1 is to continue an every 72-hour dosing schedule with NSAA monitoring.

Patient 2:

Patient 2 is a 17-year-old male with T-cell ALL. During his third dose of pegaspargase, he had a grade 3 hypersensitivity reaction. An asparaginase activity panel was drawn 7 days after the dose, and he had undetectable asparaginase activity with anti-asparaginase antibodies present. He clinically tolerated a pegaspargase desensitization, but like patient 1, was unable to regain sufficient asparaginase activity. For every dose of pegaspargase, 6 doses of recombinant Erwinia asparaginase 40 mg (25 mg/m2) IM every 48 hours was substituted.[11]

Due to complaints of nausea during and after receiving his recombinant Erwinia asparaginase injections, an ammonia level was obtained prior to the second dose of the fifth and final course and was found to be 325 μmol/L (ULN 30 μmol/L). He was also initiated on lactulose 20 grams by mouth 4 times daily titrated to three soft stools per day. He reported improvement of symptoms after initiation of lactulose, and subsequent ammonia decreased to 136 μmol/L. An NSAA was measured before dose five and was markedly elevated at 0.84 IU/mL, however this level was not resulted in time to modify his final remaining dose.

Discussion:

We present two patients receiving recombinant Erwinia asparaginase who developed symptomatic hyperammonemia concurrent with robust asparaginase activity levels. Fortunately our patients had relatively minor symptoms, but hyperammonemia can be severe.[7,8] These are the first reported cases of hyperammonemia with recombinant Erwinia asparaginase and will hopefully bring awareness to this potentially serious complication. Minimal literature is available regarding appropriate treatment for asparaginase-induced hyperammonemia, and sodium benzoate and arginine have been trialed without success.[13] Our experience, coupled with the case series published by Nussbaum and colleagues, support the use of lactulose.[9] Interestingly, both of our patients and the patients presented by Nussbaum were all adolescents/young adults.[9]

Our report has several limitations. First, the latency with which our asparaginase activity levels resulted, in the context of every 48-72 hour dosing, presented a challenge in clinical practice. Second, due to its retrospective nature, we cannot assure ourselves that the ammonia levels were handled appropriately (e.g. placed on ice immediately)—which could falsely elevate the levels.[14] However, our institutional laboratory catalog does instruct immediately placing the sample on ice, and the symptoms that our patients reported were consistent with hyperammonemia.

Recombinant Erwinia asparaginase is relatively new, and its use is reserved for patients with hypersensitivity to *E. coli*asparaginase products. This limited use may explain a lack of data outlining symptomatic hyperammonemia. Secondly, while there are no head-to-head trials, published literature supports that there may be a lower incidence of symptomatic hyperammonemia with Erwinia asparaginase products compared to pegaspargase.[6,10] Further research is needed to provide guidance on which patients receiving recombinant Erwinia asparaginase warrant ammonia and asparaginase activity level monitoring and recommended management.

Dr. Kuhn discloses recent participation on an advisory board for Rylaze for Jazz Pharmaceuticals. No other authors have any conflicts of interest.

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