

Valproate-induced hyperammonemia in asymptomatic children¹

Elaine Wyllie, M.D.
Robert Wyllie, M.D.
A. David Rothner, M.D.
Gerald Erenberg, M.D.
Robert P. Cruse, D.O.

Since its introduction in the United States in 1978 for treatment of seizure disorders, valproic acid (VPA) has been associated with hepatic dysfunction. Patients who received VPA have developed a spectrum of toxicity from fulminant hepatic failure to lethargy with elevated serum ammonia levels and normal transaminase. To determine the frequency of hyperammonemia, venous ammonia levels were obtained in three groups of asymptomatic patients: 16 receiving VPA only, 40 receiving VPA plus other anticonvulsants, and 32 control patients receiving a variety of other seizure medications. Seventy-three percent of patients receiving VPA had elevated serum ammonia levels greater than 45 $\mu\text{g}/\text{dl}$ compared to 28% of the control group ($p < 0.0001$). In 88% of the patients receiving VPA, the serum VPA level was $<110 \mu\text{g}/\text{ml}$ (therapeutic range, 50–100 $\mu\text{g}/\text{ml}$), and all VPA levels were $\leq 168 \mu\text{g}/\text{ml}$. There was no correlation between serum VPA levels and ammonia levels. Patients receiving VPA demonstrated hyperammonemia more frequently than did the control group, regardless of the concurrent use of additional anticonvulsants.

Index terms: Epilepsy • Hyperammonemia • Valproic acid

Cleve Clin Q 50:275–277, Fall 1983

¹ Departments of Neurology (E.W., A.D.R., G.E., R.P.C.), Gastroenterology (R.W.), and Pediatric and Adolescent Medicine (R.W., A.D.R., G.E., R.P.C.). Submitted for publication Feb 1983; accepted April 1983.

Since its introduction in the United States in 1978 for treatment of seizure disorders, valproic acid (VPA) has been associated with hepatic dysfunction. Patients receiving VPA have been reported to develop a spectrum of toxicity including elevated serum transaminases,¹ fulminant hepatic failure,^{2–8} and lethargy with elevated serum ammonia levels and normal transaminase values.^{9–13} Recently, asymptomatic hyperammonemia was reported in 10 children taking VPA.⁹

To determine the frequency of this complication, we measured serum ammonia levels in asymptomatic children on VPA, with or without other anticonvulsant drugs, comparing them with control children taking other seizure medications. We also compared serum valproate concentrations and serum glutamic oxalacetic transaminase (SGOT) levels in each group of patients.

Materials and methods

Fifty-six epileptic patients (mean age, 11.4 years; range, 7 months to 25 years) who were receiving VPA comprised the patient population. They were receiving either VPA alone ($n = 16$) or VPA plus other anticonvulsants ($n = 40$). The control group ($n = 32$) consisted of epileptic patients (mean age, 13 years; range, 3 1/2–24 years) receiving any of 10 other seizure medications used singly and in combination. None had developed lethargy or changes in neurologic or mental status during the course of therapy.

Venous blood for ammonia concentration was drawn, transported on ice, and analyzed immediately by the glutamate dehydrogenase method.¹⁴ Anticonvulsant serum concentrates were obtained by the enzyme-mediated immunoassay technique and SGOT values by the coupled GOT-malate dehydrogenase method.

Data were analyzed by the two sample Student's *t*-test and the test of equal proportions.

Results

The *Table* summarizes the incidence of hyperammonemia and the mean serum ammonia concentration in each group. Seventy-three percent of patients receiving VPA had elevated serum ammonia levels (above 45 $\mu\text{g}/\text{dl}$) compared to 28% of the control group ($p < 0.0001$). The mean serum ammonia level was 54.1 $\mu\text{g}/\text{dl}$ for patients receiving VPA alone and 62.8 $\mu\text{g}/\text{dl}$ for

patients receiving VPA plus other anticonvulsants. This difference was not statistically significant. There was a significant difference, however, between these two groups and the controls with a mean ammonia level of 41.8 $\mu\text{g}/\text{dl}$ ($p < .002$ and 0.0001 , respectively).

In 49 (88%) patients receiving VPA, the serum VPA level was 100 $\mu\text{g}/\text{ml}$ or less (therapeutic range 50–100 $\mu\text{g}/\text{dl}$). The values ranged from 21 to 168 $\mu\text{g}/\text{ml}$. There was no correlation between VPA concentration and ammonia levels. Age was not a factor in the development of hyperammonemia. Mild elevations of SGOT did not correlate with hyperammonemia and were seen in 8 of 41 patients with hyperammonemia as well as in 5 of 34 patients with normal serum ammonia levels.

Discussion

The mechanism of development of VPA-induced hyperammonemia remains unclear. VPA and its metabolites chemically resemble other hepatotoxic short-chain organic acids such as 4-pentanoic acid,^{4,15} which produces mitochondrial injury to rat hepatocytes,¹⁶ and octanoic acid, which causes hyperventilation and hyperammonemia in rabbits.¹⁷ Increased propionic acid levels have been reported in patients with VPA-induced hyperammonia,¹⁸ perhaps causing suppression of intramitochondrial carbamyl phosphate synthetase activity as is seen in propionic acidemia.^{19–21}

Hyperammonemia was demonstrated in the majority of children receiving VPA with no significant difference between the children taking VPA alone and those taking VPA with other anticonvulsants. There was a significant difference between the frequency of hyperammonemia and mean serum ammonia concentration between these two groups and controls who were on anticonvulsants other than valproic acid. Age, sex, and the serum concentration of valproic acid did not correlate with hyperammonemia. There was no statistically significant correlation between SGOT and ammonia level.

Subtle neurologic dysfunction has been demonstrated in adults with mild chronic hyperammonemia.²² The effect of ammonia on the developing central nervous system has not been examined, but higher intellectual function may be impaired before the onset of lethargy or gross neurologic changes (which become evident on physical examination). Until long-term studies are completed, it may be prudent to monitor serum ammonia levels of patients on valproic acid

Table. Serum ammonia levels with administration of VPA

Group	No. of patients with serum ammonia above 45 $\mu\text{g}/\text{dl}$	Mean serum ammonia concentration ($\mu\text{g}/\text{ml}$)
Patients receiving VPA	41 (73%)* ^a	60.3* ^a
Patients receiving VPA and other anticonvulsants	32 (80%)* ^a	62.8* ^a
Patients receiving VPA only	9 (56%)* ^b	54.1* ^c
Controls	9 (28%)	41.8

* Significant difference from control values: (a) $p < 0.0001$, (b) $p < 0.05$, (c) $p < 0.005$.

and to follow developmental progress or functioning in school.

References

1. Willmore LJ, Wilder BJ, Bruni J, Villarreal HJ. Effect of valproic acid on hepatic function. *Neurology* 1978; **28**:961-964.
2. Suchy FJ, Balistreri WF, Buchino JJ, Sondheimer JM, Bates SR, Kearns GL. Acute hepatic failure associated with the use of sodium valproate; report of two fatal cases. *N Engl J Med* 1979; **300**:962-966.
3. Donat JF, Bocchini JA Jr, Gonzalez E, Schwendimann RN. Valproic acid and fatal hepatitis. *Neurology* 1979; **29**:273-274.
4. Gerber N, Dickinson RG, Harland RC, Lynn RK, Houghton D, Antonias JI. Reye-like syndrome associated with valproic acid therapy. *J Pediatr* 1979; **95**:142-144.
5. Jacobi G, Thorbeck R, Ritz A, Janssen W, Schmidt HL. Fatal hepatotoxicity in child on phenobarbitone and sodium valproate. *Lancet* 1980; **1**:712-713.
6. Addison GM, Gordon NS. Sodium valproate and acute hepatic failure. *Develop Med Child Neurol* 1980; **22**:248-249.
7. Young RSK, Bergman I, Gang DL, Richardson EP Jr. Fatal Reye-like syndrome associated with valproic acid (letter). *Ann Neurol* 1980; **7**:389.
8. Rothner AD. Valproic acid; a review of 23 fatal cases (abst). *Ann Neurol* 1981; **10**:287.
9. Coulter DL, Allen RJ. Hyperammonemia with valproic acid therapy. *J Pediatr* 1981; **99**:317-319.
10. Zaret BS, Beckner RR, Marini AM, Wagle W, Passarelli C. Sodium valproate-induced hyperammonemia without clinical hepatic dysfunction. *Neurology* 1982; **32**:206-208.
11. Rawat S, Borkowski WJ, Swick HM. Valproic acid and secondary hyperammonemia. *Neurology* 1981; **31**:1173-1174.
12. Batshaw ML, Brusilow SW. Valproate-induced hyperammonemia. *Ann Neurol* 1982; **11**:319-321.
13. Sills JA, Trefor-Jones RH, Taylor WH. Valproate hyperammonemia and hyperglycinaemia. *Lancet* 1980; **2**:260-261.
14. Van Anken HC, Schiphorst ME. A kinetic determination of ammonia in plasma. *Clin Chim Acta* 1974; **56**:151-157.
15. Jakobs C, Löscher W. Identification of metabolites of valproic acid in serum of humans, dog, rat, and mouse. *Epilepsia* 1978; **19**:591-602.
16. Senior AE, Sherratt HSA. Biochemical effects of the hyperglycaemic compound pent-4-enoic acid and related non-hypoglycaemic fatty acids; oxidative phosphorylation and mitochondrial oxidation of pyruvate, 3-hydroxybutyrate and tricarboxylic acid cycle intermediates. *Biochem J* 1968; **110**:499-509.
17. Trauner DA, Huttenlocher PR. Short chain fatty acid-induced central hyperventilation in rabbits. *Neurology* 1978; **28**:940-944.
18. Coulter DL, Allen RJ. Secondary hyperammonemia; a possible mechanism for valproate encephalopathy. *Lancet* 1980; **1**:1310-1311.
19. Coude FX, Sweetman L, Nyhan WL. Inhibition of propionyl-coenzyme A of N-acetylglutamate synthetase in rat liver mitochondria. *J Clin Invest* 1979; **64**:1544-1551.
20. Gruskay JA, Rosenberg LE. Inhibition of hepatic mitochondrial carbamyl phosphate synthetase (CPSI) by acyl CoA esters; possible mechanism of hyperammonemia in the organic acidemias (abst). *Pediatr Res* 1979; **13**:475.
21. Stewart PM, Walser M. Failure of the normal ureagenic response to amino acids in organic acid-loaded rats. *J Clin Invest* 1980; **66**:464-492.
22. Rikkers L, Jenko P, Rudman D, Freides D. Subclinical hepatic encephalopathy; detection, prevalence, and relationship to nitrogen metabolism. *Gastroenterology* 1978; **75**:462-469.