# Valproate-induced hyperammonemia in asymptomatic children[1]

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**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 μg/dl compared to 28% of the control group ($p < 0.0001$). In 88% of the patients receiving VPA, the serum VPA level was <110 μg/ml (therapeutic range, 50–100 μg/ml), and all VPA levels were ≤168 μg/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

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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]

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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 μg/dl) compared to 28% of the control group ($p < 0.0001$). The mean serum ammonia level was 54.1 μg/dl for patients receiving VPA alone and 62.8 μg/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 μg/dl ($p < .002$ and 0.0001, respectively).

**Table.** Serum ammonia levels with administration of VPA

| Group | No. of patients with serum ammonia above 45 μg/dl | Mean serum ammonia concentration (μg/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) $p < 0.005$.

In 49 (88%) patients receiving VPA, the serum VPA level was 100 μg/ml or less (therapeutic range 50–100 μg/dl). The values ranged from 21 to 168 μg/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

and to follow developmental progress or functioning in school.

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