Hyperammonemia and Coma Developed by a Woman Treated With Valproic Acid for Affective Disorder

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The authors report the case of a patient who developed hyperammonemia and coma during therapy with valproic acid for affective disorder. Onset of the coma was gradual and initially interpreted as a therapeutic reduction in the patient's anxiety. In a psychiatric setting, treatment of hyperammonemia may be delayed if a patient's increasing lethargy is interpreted as a therapeutic response. Staff may need to be educated about the potential for hyperammonemia, and patients whose tolerance for valproic acid is unknown may need to be monitored for liver function and blood levels of urea and ammonia. (*Psychiatric Services* 49:1358–1359, 1998)

The range of normal values for ammonia in the blood is 10 to 47 µmol/L. The presence of ammonia in the blood at only two times the upper limit of the normal range may cause central nervous system depression, resulting in lethargy, coma, and death. Most hyperammonemia cases occur among children, a manifestation of inborn errors of metabolism. Among adults, cases are often due to liver failure and toxic ingestion.

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The enzymes carbamoylphosphate synthetase and ornithine transcarbamoylase, found in mitochondria, are two of the five enzymes associated with the urea cycle. Deficiency of some isoenzymes that induct these two enzymes are believed to be associated with symptomatic hyperammonemia among adults (1–3). The isoenzyme deficiency that results in ornithine transcarbamoylase deficiency is genetically carried by women, and women are known to be prone to hyperammonemia (1). A laboratory test to identify ornithine transcarbamoylase enzyme deficiency using levels of glutamine is available. Patients receiving intensive chemotherapy for leukemia, in whom hyperammonemia occurs rarely, and patients receiving valproate therapy in which it occurs more mildly, may be heterozygotes for this enzyme deficiency (2,4).

The literature includes a description of a patient with valproic-acid-associated encephalopathy and coma (5) and a case report of a 46-year-old woman without hepatic dysfunction who developed hyperammonemia and coma after initiation of valproic acid therapy for seizures (1). The woman in the case report regained full consciousness after her blood ammonia concentration reached normal, three days after she was admitted to an intensive care unit. The case of this patient with seizure disorder parallels the case that we report below of a woman who developed hyperammonemia and coma while being treated with valproic acid for affective disorder.

Case report

The patient was a widowed 69-year-old woman living alone who had several previous psychiatric admissions for depression and anxiety. She had these illnesses most of her life. Previous treatment involved minor tranquilizers and antidepressants, most recently alprazolam and sertraline.

The patient was treated at another psychiatric unit and was released and referred to us by her physician for further treatment. She was hyperactive, nervous, and insomniac. She reported that she was afraid of being alone, afraid of passing out, and afraid she would "fall apart." The patient's goal was to get off alprazolam, on which she had become dependent over the years.

At a mental status examination the patient appeared her stated age and was clean and appropriately dressed, but was nervous, restless, and with labile affect. Her concentration was impaired, and she answered some questions inappropriately. Her memory was intact, and she was oriented to time, place, and person. However, she showed signs of loose associations and flight of ideas. She reported that she had not slept in 48 hours, nor eaten in the past 24 hours. She said she was grieving the loss of an aunt who was her roommate, who died three weeks before the patient's admission, and was still grieving the loss of her husband of 46 years, who had died three years before her admission.

The patient was preoccupied with obtaining and taking benzodiazapines. She was taking sertaline; alprazolam; trimipramine; meclizine hy-

drochloride, an antiemetic; and nabumentone, an anti-inflammatory. She had multiple somatic complaints of pain, vertigo, and weakness and was hypomanic. She was given the diagnoses of major affective disorder, bipolar II type, and benzodiazepine dependence, with impending withdrawal.

After several days during which the patient showed minimal improvement, valproic acid was started at a dosage of 250 mg three times a day, together with trazodone, 50 mg at bedtime, and clonidine, .1 mg twice a day. Trazadone and clonidine are not known to have adverse drug-drug interactions with valproic acid (6).

After four days, the patient's anxiety decreased, her sleep increased to four to eight hours a night, and her appetite returned. In addition, her somatic complaints subsided. Staff members noted that she was not hypomanic and that she appeared depressed. She was confused about the day of the week but was oriented to month, year, person, and place. Her vital signs were stable. The patient reported that she did not feel better and said that she felt slowed down, depressed, "no good," and off balance. She stated, "I can't understand why I'm like this." Staff members interpreted the lack of hypomanic symptoms as a therapeutic response to treatment.

The next day, the patient complained of feeling very tired, and she gradually became stuporous, proceeding to coma. Her blood level of valproic acid was slightly elevated at 107.2 µg/ml, and valproic acid was discontinued immediately. Results of tests of the patient's liver function were normal. The blood urea level was 18 mg/dL. Her blood ammonia level was 143 µmol/L, more than three times the upper limit of the normal range.

All psychotropic medications were discontinued, and naloxone hydrochloride, 2 mg in a 100 ml 5 percent dextrose saline solution, was given, slowly, in an attempt to reverse the depressant effect of valproate on the central nervous system. Supportive measures were started, including an intravenous line of dextrose with saline and measures to ensure adequate airways. A medical consultation was completed immediately. The patient was transferred to a medical unit.

The patient was given a lactulose enema, and 30 cc of lactulose every four hours by nasogastric tube. Oxygen was started, and albuterol aerosol treatment was administered every six hours. A computed tomography scan of the brain was normal. The patient was checked for neurological signs every two hours, and she was unresponsive. The Glasgow Coma Scale, which encompasses three subscales for rating the patient's level of eye opening, verbal response, and motor response, was used to assess the patient's coma. At this time the score was 3 on a scale from 1 to 15, on which lower scores indicate more severe coma.

The next day the intravenous drip of naloxone hydrochloride 2 mg was repeated. The patient's plasma ammonia level was 84 µmol/L, and dropping. The rating on the Glasgow Coma Scale was 6. She was unable to speak. She moved her legs when they were tested for a Babinski response, but she did not move her arms in response to stimuli or respond to pain. Because the valproic acid had been discontinued, the valproate level was not tested daily.

The next day the patient's coma scale score was 13, and her ammonia level was 74 µmol/L. She was more alert but sluggish and had positive bowel sounds. The next day her ammonia level was 13 µmol/L. The valproate level was less than 8 µg/ml. She was more alert, and her lungs were clear. She was talking, and her activity was increasing. She showed no signs of nausea or vomiting.

On the fifth day after the coma began, the patient's improvement continued. Her vital signs were stable, and she had no obvious neurological deficits. She was returned to the psychiatric unit.

Her recovery was total, and she had retrograde amnesia for the event. Drug-craving, drug-seeking, and demanding behavior did not return as the patient regained consciousness. The mental health unit staff noted that her level of anxiety was reduced and her mood was elevated, that she had a tendency to be hypervigilant, and that she showed some residual overactivity.

Discussion and conclusions

This case illustrates the danger of interpreting changes in mood and behavior that are due to hyperammonemia as a therapeutic response to valproic acid in treatment of a patient with hypomanic symptoms. Valproic acid is an effective treatment for affective disorders, and timely identification of this adverse reaction is crucial. Staff training in identification of the symptoms of hyperammonemia is essential. Further, it may be prudent to monitor liver function and blood urea and ammonia levels, in addition to blood levels of valproate, for patients on valproic acid therapy, if the patient's ability to tolerate this medication is unknown or questionable. Although these procedures may be costly, they may prevent the more costly treatment of serious side effects. ♦

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