Neurotoxicity Associated With Free Valproic Acid

TO THE EDITOR: Effective treatment of bipolar disorder with valproic acid is associated with serum levels of 45–125 μg/ml. Lower levels are associated with reduced clinical response, and higher levels with adverse events (1). Toxicity above 100 μg/ml is related to saturation of protein binding sites and nonlinear increases in free valproate (2). Although increased unbound valproic acid has been associated with toxicity in hypoalbuminemic patients (3), there are no reports, to our knowledge, of toxicity associated with free valproate in psychiatric patients. We report the case of a patient who experienced toxicity with increased unbound valproic acid and normal serum valproate and albumin.

Mr. A was a 49-year-old single Caucasian man who was admitted to a state hospital with a diagnosis of schizoaffective disorder, manic. His other disorders included type II diabetes mellitus and hyperlipidemia that were treated with metformin, 850 mg b.i.d., atorvastatin, 20 mg at bedtime, and regular insulin coverage. Vivid delusions and hallucinations were refractory to treatment with multiple antipsychotic agents. Agitation, irritability, and mood swings led to the addition of divalproex sodium. A regimen of 56 mg/day of perphenazine, 2000 mg/day of extended-release divalproex sodium, 6 mg/day of lorazepam, 50 mg/day of sertraline, and 2 mg/day of benztropine did not lead to symptom abatement or, initially, altered cognition or sensorium. After 2 months, the hospital staff noted an ataxic gait, confusion, and slurred speech. Reducing Mr. A's perphenazine dose yielded no benefit. Tapering his lorazepam and benztropine led to modest sensorium clearing; however, after 5–6 days, the staff noted increasing confusion, disorientation, and ataxia. His serum valproic acid level was 86.1 μg/ml (normal range=50–125), his albumin level was 3.8 g/dl (normal range=3.2–5.2), and his liver function tests, ammonia levels, and platelet count were within normal limits. His free valproic acid was found to be 15 μg/ml (normal range=5–10), so his dose of extended-release divalproex sodium was reduced to 1000 mg/day, and his sensorium returned to normal in approximately 3 days.

"Normal" serum valproic acid ranges anticipate typical protein binding; however, atypical saturation kinetics could result in increased free valproic acid disparate from that suggested by serum total concentrations (3, 4). No specific factors appeared to account for the patient's unexpectedly high free valproic acid level. His medical conditions and medications are not known to influence valproate binding. Our tapering of lorazepam (the levels of which may increase when valproate is added) did not resolve his cognitive impairments, which did respond to reduced valproate. Measurement of free valproate should be considered in patients with unexplained altered cognition, even when protein levels are apparently normal.

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Multiple Endocrine Neoplasia Type 1 Presenting as Psychosis

TO THE EDITOR: The syndrome of multiple endocrine neoplasia type 1 is an autosomal-dominant inherited disease affecting several endocrine organs (1). The affected organs include the pituitary gland, the parathyroid glands, and the endocrine pancreas. The multiple endocrine neoplasia type 1 gene is a tumor-suppressor gene located on chromosome 11q. The psychiatric symptoms associated with multiple endocrine neoplasia type 1 have not yet been reported. We report the first case to our knowledge of a patient with multiple endocrine neoplasia type 1 presenting as psychosis.

Ms. A was a 59-year-old Asian woman who had been hospitalized for approximately 3 years. Her first psychotic episode, characterized by auditory and visual hallucinations, delusions, and catatonia, occurred at age 44. She had been hospitalized at ages 47, 50, 53, and 54 for similar psychotic episodes, each persisting for about 3 months. At her most recent hospitalization, her psychiatric symptoms were not alleviated by any antipsychotics and mood stabilizers; only lithium was slightly effective. From a general examination to determine the cause of her severe constipation, a nonfunctioning islet cell carcinoma of the pancreas was unexpectedly discovered. Her serum levels of gastrin, insulin, and glucagon were normal. A subsequent partial pancreatectomy did not relieve her psychiatric symptoms. Three months after the operation, a high level of serum parathyroid hormone was found during an examination for osteoporosis. These two extraordinary endocrine findings led us to suspect multiple endocrine neoplasia type 1. Magnetic resonance imaging and ultrasonography revealed a microadenoma of the anterior pituitary gland and a swelling of the parathyroid gland. The diagnosis was confirmed by detection of a deficit of the heterozygous 357del4 multiple endocrine neoplasia type 1 gene on exon 2 chromosome 11q (2). The serum concentrations of prolactin, growth hormone, and adrenocorticotropic hormone were normal. The microadenoma of the anterior pituitary gland was nonfunctioning and did not need treatment in particular. The parathyroid swelling necessitated surgical treatment. A high level of serum parathyroid hormone recovered within normal limits after the partial parathyroidectomy; however, the psychiatric symptoms did not improve.

We investigated the profile of hereditary disposition of Ms. A's family. Two of her three descendants could be ex-

amined; however, we could not confirm the multiple endocrine neoplasia type 1 gene mutation and did not observe any endocrine disorders and psychiatric symptoms in these two descendants. On the contrary, her mother committed suicide under treatment for a gastrointestinal tumor.

Although the hypothesis of multiple endocrine neoplasia type 1 and schizophrenia comorbidity could not be ruled out completely, the patient's psychiatric symptoms differed from those typical of schizophrenia. These clinical features seemed to be one of the psychiatric manifestations of multiple endocrine neoplasia type 1. We concluded that the psychiatric manifestations of our patient could be linked with multiple endocrine neoplasia type 1.

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Liepmann's Phenomenon During Benzodiazepine Withdrawal

TO THE EDITOR: Liepmann's phenomenon has been described in the context of alcohol-related delirium (1). We present a case of Liepmann's phenomenon apparently occurring with excessive use of diazepines.

Mr. A, a 44-year-old man, was admitted to the gastroenterology unit of Kitasato University for general fatigue of 1 week's duration. He had been followed since he was 29 for ulcerative colitis and had undergone a total proctocolectomy with an ileal pouch and anastomosis at 37 years of age. On admission, he was alert, and the results of a physical examination, routine blood tests, and X-ray radiographs of his chest and abdomen were within normal limits. Brotizolam, 0.25 mg/day, was prescribed for insomnia.

On the second hospital day, a colorectal fiberscopy revealed no substantial worsening of the mucosal lesions. At 3:00 a.m. on the fourth day, Mr. A began to wander about the ward, saying, "Many strange little people are walking around," "I'm coming home," and "I must meet an appointed user now." His restlessness alternated with sleeping every few minutes. A diagnosis of delirium was made, and haloperidol, 5 mg, was injected intramuscularly at 5:30 a.m. and had little effect on him. At 11:00 a.m., when a consultant psychiatrist gently closed Mr. A's eyes and asked if he could see birds, Mr. A replied, "That's right, I can see birds (*Hontoda, tori ga mieru*)." He also exhibited Liepmann's phenomenon (1) in relation to a whale (i.e., he said that he could see a whale when the psychiatrist closed his eyes and asked if he could see a whale). A brain computed tomography scan revealed normal findings, and an EEG showed a low-voltage fast pattern with no paroxysmal discharges.

At 11:30 a.m., Mr. A's father informed his psychiatrist by telephone that Mr. A consumed "too much alcohol and hypnotics" every night, but later, the "too much alcohol" was confirmed to be 350 to 500 ml of beer. At the time, Mr. A was unable to answer when asked whether he used any hypnotics. At around 2:00 p.m., while exhibiting Liepmann's phenomenon in regard to an airplane, he repeated the names of the psychiatrists whom he usually consulted. The psychiatrists were contacted and informed us that Mr. A was taking 2.4 mg/day of alprazolam, 1.5 mg/day of etizolam, 0.5 mg/day of triazolam, 2 mg/day of estazolam, 0.25 mg/day of brotizolam, 2 mg/day of flurazepam, and 10 mg/day of zolpidem.

Oral diazepam, 20 mg over 24 hours, and drip infusion of flunitrazepam, 2 mg at night, was started. Since then, Mr. A has not exhibited Liepmann's phenomenon. This delirious episode resolved in 5 days. His dose of diazepam was reduced to zero in 8 weeks. The episode of delirium may have been attributable to withdrawal from excessive use of sedative drugs. Liepmann's phenomenon in Mr. A was observed exclusively during the delirium.

To our knowledge, few reports, other than the report by Miura et al. (2) on withdrawal from meprobamate (3000 mg/day) have described Liepmann's phenomenon in conditions besides alcoholism. However, this case clearly demonstrates that it is necessary to be alert to the "concealed" or possible use of excessive diazepines underlying Liepmann's phenomenon.

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Increase in Risperidone Plasma Level With Lamotrigine

TO THE EDITOR: A combination of clozapine and risperidone is effective in treating patients with schizophrenia who are unresponsive to other atypical antipsychotics or monotherapy with clozapine (1). Nevertheless, there are patients who respond only partially or even fail to respond to this combination. Saba et al. (2) and Dursun et al. (3) reported on patients who showed a substantial improvement of persistent positive symptoms when lamotrigine was added to clozapine therapy. There is evidence supporting the positive effects of lamotrigine based on its glutamate excess-release inhibition (4).

Because of these interesting reports, we decided to supplement the clozapine-risperidone combination of Ms. A, a 26-year-old inpatient who suffers from therapy-resistant schizophrenia with imperative auditory hallucinations, with lamotrigine. She had been taking clozapine, 550 mg/day, for 5 years and risperidone, 8 mg/day, for 4 weeks and had only responded partially. Her plasma levels of ris-