Fatal Hepatic Failure and Valproate

TO THE EDITOR: Sodium valproate has been associated with acute hepatitis, including hepatic necrosis and death (1, 2). Risk factors include an age of less than 2 years, polytherapy, and neurological or metabolic abnormalities (1). Inspection of all published fatalities and reviews due to hepatic failure with valproate in the English, French, and Spanish literature revealed none in which an adult without preexisting hepatic or neurological disease was receiving valproate monotherapy (1, 2). We report what is to our knowledge the first such case.

Mr. A was a 51-year-old Hispanic man who had had 3 days of nausea, vomiting, and "orange urine." Three months previously, he began taking valproate as divalproex sodium, 125 mg t.i.d., for bipolar disorder not otherwise specified, consistent with the recent trend for the increasing use of alternatives to lithium as a first-line treatment for this disorder. He had a history of alcohol abuse (severity and duration unknown but no social or medical sequelae) and combat-related posttraumatic stress disorder; both had been in full, sustained remission for over 20 years. Mr. A smoked marijuana several times per week and had three drinks per week until treatment but ceased drinking alcohol after entering treatment. He had had several prior minor surgical procedures, but he had no current medical complaints and a normal primary care physical examination. His only medication was albuterol for asthma, as needed. Although no information on prior herbal or over-the-counter remedies was available, Mr. A agreed not to take any nonprescribed substances at the beginning of treatment. He had received no psychotropic medications since the 1970s. The results of screening laboratory tests before the administration of divalproex included normal aspartate aminotransferase (25 U/liter), alanine aminotransferase (22 U/liter), and total bilirubin (0.5 mg/dl) levels and a normal CBC.

After 1 month of minimal response, Mr. A's divalproex dose was increased to 250 mg t.i.d. with no ill effects; his psychiatrist endorsed continuation at this dose when his aspartate aminotransferase, alanine aminotransferase, bilirubin, γ-glutamyltransferase, and CBC were again normal and his divalproex level was 51.6 μg/ml. Five weeks later, Mr. A's symptoms had almost completely remitted; his psychiatrist increased his divalproex dose to 500 mg b.i.d.

After 3 months of divalproex treatment, Mr. A was icteric but had no hepatomegaly or tenderness. His divalproex level was 89.7 μg/ml, with total/direct bilirubin levels of 9.1/4.9 mg/dl (normal ranges=0.2–1.2/0.0–0.2, total/indirect), an aspartate aminotransferase level of 3330 U/liter (normal range=10–45), an alanine aminotransferase level of 3208 U/liter (normal range=7–52), a γ-glutamyltransferase level of 226 U/liter (normal range=10–65), an alkaline phosphatase level of 172 U/liter (normal range=30–115), an ammonia level of 162 μmol/liter (normal range=0–35), a prothrombin time of 18.8 sec (normal range=11–14), a partial thromboplastin time of 39 sec (normal range=27–37), an albumin level of 3.0 gm/dl (normal range=3.5–5.0), a ferritin level of 11,124 ng/ml (normal range=20–300), an iron level of 238 μg/dl (normal range=30–180); normal total iron-binding capacity, amylase, and hepatitis A/B/C serologies; noncontributory electrolyte levels; and a normal CBC. His urine toxicology was positive for cannabinoids; his blood alcohol level was nil.

Over his 10-day hospital course, as transfer for a liver transplant was being arranged, Mr. A became delirious but improved with lactulose and supportive care. His liver function worsened (a maximum aspartate aminotransferase level of 3645 U/liter, an alanine aminotransferase level of 3500 U/liter, a total bilirubin level of 19.7 mg/dl, a prothrombin time of 28 sec, a partial thromboplastin time of 48 sec, and an albumin level of 1.6 gm/dl); a biopsy was deferred pending transfer. Mr. A was transferred to a regional liver transplant center and died 1 month later.

The clinical diagnosis was unequivocally acute hepatitis, with the time course consistent with valproate monotherapy as the precipitant. No other risk factors were evident, although it is possible that this rare event was subserved by silent risk factors, such as characteristics of the cytochrome P450 system (e.g., reference 3). Thus, the risk of fatality from valproate monotherapy must be considered in the risk-benefit assessment during treatment choice, even in the absence of other manifest risk factors.

References

1. Bryant AE, Dreifuss FE: Valproic acid hepatic fatalities, III: US experience since 1986. Neurology 1996; 46:465–469
2. König SA, Schenk M, Sick C, Holm E, Heubner C, Weiss A, König I, Hehlmann R: Fatal liver failure associated with valproate therapy in a patient with Friedreich's disease: review of valproate hepatotoxicity in adults. Epilepsia 1999; 40:1036–1040
3. Neuman MG, Shear NH, Jacobson-Brown PM, Katz GG, Neilson HK, Malkiewicz IM, Cameron RG, Abbott F: CYP2E1-mediated modulation of valproic acid-induced hepatocytotoxicity. Clin Biochem 2001; 34:211–218

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Quetiapine-Induced Weight Gain and Escitalopram

TO THE EDITOR: Quetiapine-induced weight gain in an adolescent girl started with treatment with adjunctive escitalopram only. A slight decrease in weight gain was observed as antipsychotic treatment was shifted from quetiapine to amisulpride. However, reintroduction of quetiapine was followed by a novel spectacular increase in weight, confirming the potentiation of quetiapine-induced weight gain by escitalopram.

Weight gain induced by atypical antipsychotics is a well-known side effect (1), particularly damaging to an adolescent's self-image and related to an increase in the risk for diabetes mellitus (2). Among the atypical antipsychotics available in Europe, quetiapine seems to be associated with a lower weight gain (3).

Amy, a 16-year-old adolescent, was treated with quetiapine for a first psychotic episode over 5 months with an absence of weight gain. Because her depressive symptoms were pronounced after remission of her psychotic symptoms, the introduction of escitalopram was followed by a dramatic increase in weight (8 kg over 1 month). This worrisome side effect led to replacing quetiapine with amisulpride. Quetiapine discontinuation was followed by a transient decrease in weight gain. The reappearance of severe psychotic symptoms with amisulpride treatment led us to reintroduce quetiapine because Amy was previously re-

sponsive to this treatment. Unfortunately, a novel dramatic increase in weight was observed, with an additional 8-kg gain over 1 month. Discontinuation of escitalopram and replacement by topiramate was followed by weight stabilization.

A phasic craving for carbohydrate has been described with citalopram (4) and paroxetine (4, 5). As during escitalopram treatment, a decrease in weight gain followed transient discontinuation of quetiapine, so we may attribute the weight gain to the specific association rather than understand it as an unusual weight gain with escitalopram. As far as we know, a weight gain resulting from an association of quetiapine and escitalopram has not been reported.

Susceptibility to weight gain was obvious for this patient, and an overweight family trend could explain part of her predisposition. However, the weight gain induced by quetiapine was absent before the introduction of escitalopram. Therefore, the association of quetiapine and escitalopram appears to potentiate dramatically the neuroleptic-induced weight gain and should lead to further investigation. Antipsychotic-induced weight gain could be mediated by different factors, including important ones that are independent from the antipsychotic treatment itself.

References

1. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ: Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156:1686–1696
2. Sussman N: The implications of weight changes with antipsychotic treatment. J Clin Psychopharmacol 2003; 23:S21–S26
3. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC: Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998; 44:778–783
4. Bouwer CD, Harvey BH: Phasic craving for carbohydrate observed with citalopram. Int Clin Psychopharmacol 1996; 11:273–278
5. Harvey BH, Bouwer CD: Neuropharmacology of paradoxic weight gain with selective serotonin reuptake inhibitors. Clin Neuropharmacol 2000; 23:90–97

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Transcranial Magnetic Stimulation for Refractory Depression

TO THE EDITOR: Several studies have shown that repetitive transcranial magnetic stimulation is effective in the treatment of acute depressive symptoms (1). However, the maintenance effect of this technique has not yet been assessed. In this study, we sought to investigate the capability of repetitive transcranial magnetic stimulation, when administered regularly over a period of 3 months after an acute phase, in maintaining its efficacy with refractory treated depressed patients.

Eleven refractory depressed patients were included in this open study: six women and five men with a mean age of 47.18 years (SD=12.83) and a duration of illness of 9.03 years (SD=7.5). All participants gave their informed consent after receiving a detailed explanation of the study. Patients were recruited if they did not respond to at least two different antidepressants. Treatment parameters were as follows: stimulation over the left dorsolateral prefrontal cortex, 10 Hz, 80% of the motor threshold, 26 trains, 1600 pulses. They received one daily session over 2 weeks then three weekly sessions for 2 weeks. At the end of the first month, the patients received one weekly session over 1 month and then one session each fortnight.

The patients were assessed with the Hamilton Depression Rating Scale at baseline, after 1 month, and then after 4 months. Mean score on the Hamilton depression scale at baseline was 24.1 (SD=3.7).

Statistical analysis showed that mean Hamilton depression scale scores had decreased significantly by the end of the first month (mean=10.27, SD=3.87) (analysis of variance [ANOVA] for repeated measures followed by the Tukey-Kramer multiple comparison test, df=2, 30, p=0.003). At the end of the trial, the scores were maintained, and no statistical difference was found between the week 4 scores and the final scores (mean=10.36, SD=5.1) (ANOVA for repeated measures followed by the Tukey-Kramer multiple comparison test, df=2, 30, p=0.91). Moreover, eight patients were responders (with more than 50% reduction in Hamilton depression scale scores). Repetitive transcranial magnetic stimulation was well tolerated, and no side effects were noted.

All patients had improved after 4 weeks of treatment. This effect was maintained during the next 3 months. Even though our study was an open trial, the significance of these results are interesting regarding some difficulties found in the treatment of refractory depression.

The most robust findings were, first, the acute efficacy of repetitive transcranial magnetic stimulation with refractory depressed patients and, second, its maintenance effect over a period of 4 months. Nevertheless, only a few open studies are available concerning the maintenance effect of repetitive transcranial magnetic stimulation after the end of the cure (2 to 20 weeks) (2), and it deserves further double-blind studies.

References

1. Pascual-Leone A, Catala MD, Pascual-Leone Pascual A: Lateralized effect of rapid-rate transcranial magnetic stimulation of the prefrontal cortex on mood. Neurology 1996; 46:499–502
2. Boutros NN, Gueorguieva R, Hoffman RE, Oren DA, Feingold A, Berman RM: Lack of a therapeutic effect of 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. Psychiatry Res 2002; 113:245–254

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Evidence of Depressive Mixed States

TO THE EDITOR: The article on agitated depression in bipolar depression by Mario Maj, M.D., Ph.D., et al. (1) is a considerable contribution to our understanding of the nature and clinical implications of depressive mixed states in bipolar I disorder. The authors reported that manic symptoms during a depressive episode are considerably overlapping with agitated depression in bipolar I depressives. The data also implied that bipolar I depressives with and without depressive