Single-Dose Intravenous Valproate in Acute Mania

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Objective: High-dose loading with oral and intravenous valproate has been reported to be therapeutic in mania over 48 to 72 hours. We hypothesized that very high dose intravenous (IV) valproate might have even more rapid effects equivalent to effects in status epilepticus that occur within 20 minutes.

Method: Seven patients with mania (Young Mania Rating Scale score > 20) and minimal prior drug treatment were given valproate 20 mg/kg IV over 30 minutes.

Results: No antimanic effects were observed during 120 minutes of observation. There were no side effects.

Conclusion: Slowly evolving biochemical changes, perhaps at the gene level, may be required for the antimanic effect of anticonvulsants.

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The role of anticonvulsants in the treatment of mania and bipolar disorder is increasingly prominent. While many studies rightly emphasize the key importance of prophylaxis and long-term maintenance, the treatment of acute mania is far from optimal. Lithium, carbamazepine, and valproate work slowly when given under usual oral dosing schedules. Modern pressure for early hospital discharge often leads to premature discharge of a still hypomanic patient, who then ceases medication and rebounds, sometimes thereby becoming medication resistant. Rapid oral lithium loading is a little tried option for acute mania and may be more possible than previously thought.[1]

Oral valproate loading (20 mg/kg/day of divalproex sodium in 2 or 4 doses for 5 days) was studied by Keck et al.[2] Ten of 19 manic patients responded with more than 75% reduction in mania ratings by study termination with the greatest improvement within the first 72 hours. Grunze et al.[3] reported that 4 of 5 manic patients showed substantial improvement on the Bech-Raphaelsen Mania Scale (> 50%) after 48 hours of intravenous valproate loading in 3 times daily divided doses of 600 mg each dose.

In patients suffering from status epilepticus, valproic acid was reported to exert central biological effects in less than 20 to 30 minutes after initiation of intravenous administration of 15 mg/kg in a bolus.[4] Similar results were reported by Kaplan[5] while administering intravenous valproate, 500 mg, at a rate of 20 mg/min. While effectiveness in status epilepticus does not prove effectiveness in mania, it certainly does prove that valproate can have major neurobiological effects almost immediately. We therefore hypothesized that intravenous valproate could have major antimanic effects within 1 hour.

METHOD

Methods were based on our recent study of intravenous fosphenytoin in acute mania.[6] Acutely manic patients aged 18 to 50 years able to give written informed consent and in need of immediate acute treatment were eligible for study. In general, newly admitted unmedicated patients were the subjects for this study. Patients who had any medication in the previous 6 hours were excluded. Patients who had taken more than 10 mg of haloperidol or 20 mg of diazepam or their equivalent in the last 24 hours were excluded, as were those who had taken more than 30 mg of haloperidol or 60 mg of diazepam or their equivalent over the last week. Patients treated with a mood stabilizer in the last 3 days were excluded. Extreme attention was given to prevent the conduct of the study from delaying standard treatment. For instance, patients admitted at night were not to be deprived of sleep medication or initial neuroleptic treatment in order to meet entrance criteria for admission to the study. An outside monitor was appointed to supervise this aspect of the study.

Acutely manic patients (Young Mania Rating Scale [YMRS][7] score > 20) who consented to intravenous valproate were attached to cardiac monitoring (as requested by our Helsinki Committee) while in a comfortable room and reclining chair designed for interviewing during infusion. An internal medicine consultant was present during each infusion. Valproate was given intravenously, 20 mg/kg in 250 cc of 0.9% NaCl solution at 50 mg/min (1400 mg for a 70-kg person [156 lb]). Saline was used as

Table 1. Lack of Effectiveness of Intravenous Valproate in Acute Mania During 120-Minute Observation

			Change From Baseline in 6-Item Young Mania Rating Scale					Change From Baseline in Clinical Global Impressions Scale					Change From Baseline in Repeatable Modified MMSE				
Patient	Age (y)/ Sex	Baseline YMRS	6-Item YMRS	30 min	45 min	60 min	120 min	Baseline CGI	30 min	45 min	60 min	120 min	Baseline MMSE	30 min	45 min	60 min	120 min
1	28/M	39	25	0	0	0	0	5	0	0	0	0	7	0	0	+1	0
2	37/M	25	19	0	0	0	0	4	0	0	0	0	7	0	0	–1	0
3	26/M	24	20	0	0	0	0	4	0	0	0	0	9	+1	0	0	0
4	61/F	26	20	0	0	0	0	4	0	0	0	0	11	0	0	0	0
5	40/M	27	19	0	0	0	0	4	0	0	0	0	10	+1	0	0	0
6	56/F	31	20	0	0	0	0	4	0	0	0	0	9	0	0	0	0
7	54/M	31	22	0	0	0	0	5	0	0	0	0	11	0	0	0	0

Abbreviation: MMSE = Mini-Mental State Examination.

placebo. An infusion bag of valproate in saline or saline IV infusion was prepared by a nonblinded supervising physician (J.L.). The patient was rated on a modified 6-item YMRS for repeated measures, Clinical Global Impressions scale (CGI),[8] and a modified Mini-Mental State Examination (MMSE)[9] for repeated administration at baseline, 30 minutes, 45 minutes, 60 minutes, and 120 minutes by a blinded rater (K.P.). The YMRS items chosen for repeated measures were elevated mood, increased motor activity-energy, speech, language-thought disorder, content, and disruptive-aggressive behavior, as in our previous study.[6] The protocol was approved by our institutional review board in accordance with the Declaration of Helsinki.

According to DSM-IV, 4 of these patients had bipolar affective disorder with a preponderance of manic episodes, whereas the 3 other patients had schizoaffective disorder mainly characterized by manic episodes. Only 1 of the patients exhibited a rapid cycling pattern. Three patients were previously treated successfully with valproic acid in therapeutic doses, while the other 4 were not previously treated with valproic acid. No patient was treated with valproic acid in the 2 months' period prior to the study.

The patient, the clinical rater (K.P.), and the nursing staff believed that the patient could receive valproate or placebo. In fact, as part of a run-in plan, the supervising physician gave the first 7 patients studied all active valproate. There were 5 men and 2 women, aged 26 to 61 years.

RESULTS

No subject had any clear improvement in manic symptoms on the YMRS at any study time point after intravenous valproate administration (Table 1). No sedation or confusion was noted on the modified MMSE after valproate administration (Table 1). There were no side effects. In the 2 days following the study, 6 of the 7 patients were treated by independent psychiatrists with oral valproic acid in doses of 1000–1500 mg/day in combination with neuroleptic treatment. (One patient was administered chlorpromazine, 300 mg/day, and the other 5 received haloperidol, 5–10 mg/day). None of these 6 subjects showed any significant improvement after 2 days of oral valproic acid administration. A seventh patient was treated with haloperidol only, in a dose of 15 mg/day, and also showed no significant response within 2 days of treatment.

DISCUSSION

It has been hypothesized that the biochemical basis of antimanic treatment involves changes in gene expression that take days or weeks.[7] The absence of antimanic effects in 120 minutes after maximal doses of valproate supports the concept that the biochemical action of currently available mood stabilizers requires a time interval, even though the anticonvulsant effect in status epilepticus can be achieved in minutes. Similar negative results in mania were obtained with intravenous fosphenytoin,[6] an effective rapid agent against status epilepticus. Because valproate is a much more established antimanic agent, it seemed important to study the acute effects of intravenous valproate as well. Doses in the present study of about 1400 mg in 30 minutes are more than double those reported by Kaplan[5] to be effective in status epilepticus within 30 minutes.

Cloyd et al.[10] reported valproate pharmacokinetics after intravenous rapid infusion similar to that used in the present study. Standard plasma valproate levels are meaningful only when trough levels are drawn 8 to 14 hours after the last dose and equilibration with brain levels can be implied. No level of valproate after rapid infusion has been shown to be related to efficacy in status epilepticus.

This article clearly does not contradict previous reports of effective and safe treatment of mania with rapid oral or intravenous valproate.[2,3] Such rapid loading can lead to improvement within a few days. In our sample, follow-up treatment with oral valproate did not lead to improvement within 48 hours, but only standard doses were used and not the high-dose loading strategy of Grunze et al.[3] The present study reinforces the distinction between the time course of the antiepileptic effects of anticonvulsants and

that of the antimanic effects. An initial mechanism, such as blockade of activated sodium channels, may be common to both therapeutic mechanisms; however, to achieve an effect on mood, the initial biochemical effect must perhaps over time cause secondary changes such as in gene expression.[11]

Drug names: carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), diazepam (Valium and others), divalproex sodium (Depakote), fosphenytoin (Cerebyx), haloperidol (Haldol and others), valproic acid (Depakene and others).

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