Safety and Tolerability of Oral Loading Divalproex Sodium in Acutely Manic Bipolar Patients

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Background: Achieving therapeutic blood levels of a mood stabilizer as quickly as possible is desirable in patients with acute mania. We examined the feasibility and safety of an accelerated oral loading strategy (divalproex, 30 mg/kg/day, on days 1 and 2, followed by 20 mg/kg/day on days 3–10) designed to bring serum valproate concentrations to therapeutic levels (i.e., above 50 μg/mL).

Method: Fifty-nine patients who met DSM-IV diagnostic criteria for current manic episode and who had a Mania Rating Scale score ≥ 14 were randomly assigned on a double-blind basis to receive divalproex oral loading (N = 20); divalproex nonloading (N = 20) at a starting dose of 250 mg t.i.d. on days 1 and 2, followed by standard dose titration for days 3 to 10; or lithium carbonate (N = 19) at a starting dose of 300 mg t.i.d., followed by standard dose titration for days 3 to 10.

Results: Eighty-four percent of the divalproex-loading patients, but only 30% of the divalproex-nonloading patients, had valproate serum levels above 50 μg/mL at day 3 of the study. None of the lithium-treated patients had serum lithium levels above 0.8 mEq/L at study day 3. No patient was removed from the study because of an adverse event. There were no significant differences between the groups in the frequencies or types of adverse events.

Conclusion: Accelerated oral loading with divalproex sodium is a feasible and safe method to bring serum valproate concentrations to effective levels rapidly.

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The risks of morbidity and mortality from episodes of acute mania associated with bipolar disorder often necessitate hospitalization. Rapid and safe reduction of manic symptoms is an important initial goal in the management of acute manic episodes. The safety and effectiveness of divalproex in the treatment of mania has been demonstrated in double-blind, placebo-controlled trials.[1,2] Data from these studies suggested that clinical response is more likely at serum valproate concentrations above 50 μg/mL.[1]

To enhance symptom stabilization, initial pharmacologic treatment of acute mania often consists of a mood stabilizer plus an antipsychotic.[3–5] However, there are a number of drawbacks to the use of antipsychotics either adjunctively or alone.[6] These include risks of extrapyramidal and other side effects, especially tardive dyskinesia. The extent to which this holds true for the newer atypical antipsychotics is unclear. An alternative clinical approach is to initiate treatment with higher doses of a mood stabilizer in an attempt to achieve a therapeutic plasma concentration earlier in the course of the hospitalization.

The safety and efficacy of divalproex loading strategies have been examined in several open-label trials. Rapid stabilization with divalproex initiated at 20 mg/kg/day was well tolerated and effective in reducing manic symptoms.[7,8] All patients achieved serum concentrations above the therapeutic threshold of 50 μg/mL by the second or third day of treatment. In the initial trial,[7] 10 (53%) of the 19 patients who received at least 1 dose of valproate had a reduction of at least 50% in mean Young Mania Rating Scale scores compared with baseline. Among responders, the greatest rate of improvement occurred during the first 3 days of treatment.

In a second trial,[8] divalproex (20 mg/kg/day) was administered in combination with other agents such as antipsychotics and benzodiazepines. In this naturalistic study, 77% of the patients had a moderate or marked response.[8] Divalproex oral loading, when administered with antipsychotics and/or benzodiazepines, was well tolerated in this series of patients. These data suggest that higher initial doses (20 mg/kg/day) can be administered safely to hospitalized patients with acute mania. The authors of these

and other open studies clinically observed a more rapid onset of action among divalproex-loading patients.[7–9] However, controlled studies would be essential to draw this conclusion definitively.

In view of the apparent safety of the 20 mg/kg/day dose and the desire to hasten the antimanic effect, a preliminary trial[10] explored the tolerability of dosing initiated at 30 mg/kg/day for 2 days followed by 20 mg/kg/day in 9 acutely manic patients. All patients tolerated this loading dose well. Two patients reported sedation and gastrointestinal complaints. Another patient had a decrease in leukocyte count and low granulocyte count (38.2%) after 2 loading doses. These adverse events resolved in spite of continued divalproex sodium at 20 mg/kg/day. All 6 of the patients in whom serum drug concentrations were measured 48 to 72 hours after the start of treatment had values within the therapeutic range (mean = 93.5 μg/mL; range, 56–124 μg/mL).

In another study,[4] the antimanic and antipsychotic effect of divalproex loading was compared with haloperidol in a randomized open trial in hospitalized patients with acute mania. Interestingly, oral loading of divalproex at 20 mg/kg/day and haloperidol yielded comparable rates and degrees of improvement in both manic and psychotic symptoms. The greatest rate of improvement for both groups was again evident over the first 3 days of treatment. These findings suggest that a dosing regimen that provides rapid stabilization may allow clinicians to reduce the use of antipsychotic agents in patients with acute mania.

To date, no prospective, double-blind, controlled trials examining the safety and tolerability of oral loading divalproex in acutely manic patients have been reported. We report the findings from a double-blind, randomized, parallel-group, 10-day trial designed to examine the safety and tolerability of divalproex oral loading compared with standard titration of divalproex or lithium in the treatment of acutely manic patients.

PATIENTS AND METHOD

Study subjects consisted of 59 patients, aged 18 to 60 years, with a DSM-IV diagnosis of bipolar disorder (manic or mixed) and hospitalized for treatment of an acute manic episode. Patients were required to have manic symptoms of sufficient severity to have a total Young Mania Rating Scale (YMRS)[11] score ≥ 14, as assessed by the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-C).[12] Patients were excluded if they had any of the following conditions: known intolerance to either of the test drugs; other central nervous system disease; uncontrolled gastrointestinal, hepatic, renal, cardiovascular, endocrine, pulmonary, immunologic, or hematologic disease; a substance-dependence disorder for which acute treatment was being given; a urine screen positive for phencyclidine or amphetamine; hyperthyroidism; a low platelet count; a serious risk of suicide; or pregnancy. Patients were also excluded if they had received a depot antipsychotic drug or any experimental drug within the previous 4 weeks or if they were receiving any medication that might interfere with evaluation of the safety or efficacy of divalproex. Women of childbearing age were required to use an effective means of birth control during the study. All patients provided written informed consent for study participation and underwent a thorough history and physical, laboratory, and psychiatric examinations before study admission and at the conclusion of the trial.

After a drug washout period of no more than 72 hours and confirmation of the diagnosis of acute mania and of subtherapeutic serum concentrations of valproate (≤ 20 μg/mL) and lithium (≤ 0.2 mEq/L), patients were randomly assigned to 1 of 3 groups. The divalproex loading group (N = 20) received oral divalproex administered via a rapid stabilization schedule: 30 mg/kg/day on days 1 and 2 and 20 mg/kg/day on days 3 through 10. The divalproex nonloading group (N = 20) received oral divalproex at the usual dose of 250 mg t.i.d. on days 1 and 2 followed by gradual dose titration for the remaining 8 days. The lithium group (N = 19) received lithium carbonate at the usual initial dose of 300 mg t.i.d. on days 1 and 2 followed by gradual dose titration on days 3 through 10. Blinded medication was provided in identical-appearing gray capsules so that all patients received the same total number of capsules. Lorazepam was allowed to manage agitation, insomnia, restlessness, irritability, and hostility (4 mg/day on days 1–4 and 2 mg/day on days 5–7).

Adverse event profiles and records of concomitant medications were obtained every day throughout the study. Blinded raters evaluated the patients with the SADS-C and the Global Assessment Scale (GAS)[13] on days 2 through 6 and on days 8 and 10. Serum concentrations of valproate and lithium were obtained on days 3, 5, 7, and 10, before the first morning dose of the assigned drug was given.

This study was not designed to evaluate the relative efficacy of rapid loading compared with nonloading strategies. However, it was hoped that the results of this study would provide data to assist in the design of an efficacy study.

RESULTS

The 3 treatment groups were similar in demographic characteristics and illness severity (Table 1). The baseline YMRS and GAS scores are similar to those in other treatment studies of acute mania.[2,14] Approximately half of the patients had 1 to 5 previous manic episodes, and 7 (2 each in the divalproex loading and the divalproex nonloading groups and 3 in the lithium group) had more than 20 such episodes.

Table 1. Characteristics of Randomized Patients[a]

Characteristic	Divalproex Loading (N = 20)	Divalproex Nonloading (N = 20)	Lithium (N = 19)
Sex (M/F)	11/9	12/8	11/8
Age, y, mean (SD)	36.0 (9.4)	32.4 (9.1)	36.4 (8.4)
Race (white/black/other)	11/7/2	11/6/3	13/6/0
Height, in, mean (SD)	68.0 (3.3)	67.2 (5)	67.1 (4.5)
Weight, kg, mean (SD)	87.5 (28.3)	80.0 (21.9)	76.6 (17.3)
No. with family history of psychiatric illness	13	11	11
Years since first manic episode, mean (SD)	19.5 (23.4)	19.9 (28.9)	8.7 (7.3)
Baseline YMRS score[b]	24.5	26.2	25.1
Baseline GAS score[b]	36.2	35.7	33.0

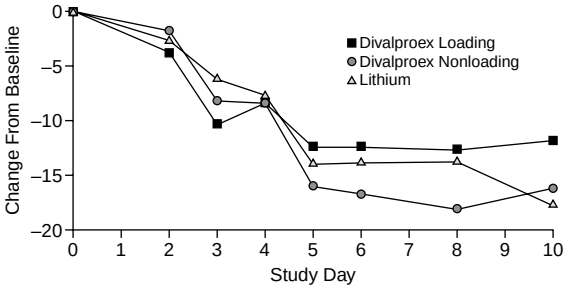
[a]Abbreviations: GAS = Global Assessment Scale, YMRS = Young Mania Rating Scale.
[b]Model-based mean. No significant differences were noted among the treatment groups.

Seven patients (35%) in each of the divalproex-treated groups and 9 (47%) in the lithium standard-titration group discontinued the study medication before the conclusion of the trial. In no case was an adverse event cited as the reason for discontinuation of the study medication. Nine patients (2 in the divalproex loading group, 4 in the divalproex nonloading group, and 3 in the lithium group) discontinued because of lack of efficacy, and 3 patients (1 in the divalproex loading group and 2 in the lithium group) discontinued because of noncompliance. Miscellaneous other reasons such as discharge from the hospital or recovery accounted for the remaining withdrawals.

Adverse events were reported by 60% (N = 12) of the patients in the divalproex loading group, 75% (N = 15) of those in the divalproex nonloading group, and 74% (N = 14) of those in the lithium group. None was serious and no patient withdrew from the study because of an adverse event. The most common adverse events were dyspepsia, nausea, headache, and constipation. No statistically significant differences were found among the groups in the number and type of adverse events.

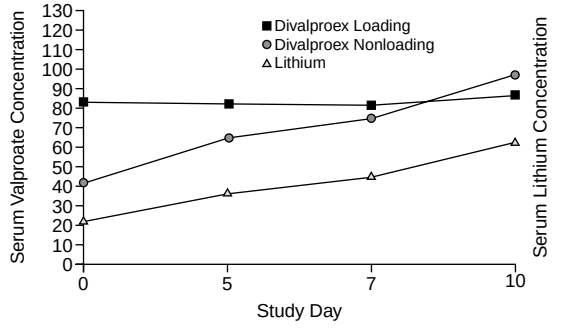
Similar degrees of improvement were seen in all 3 groups on the YMRS (including subscales) and GAS at most timepoints in observed cases (Figure 1). On day 3, there was a trend toward more rapid efficacy in patients assigned to the divalproex loading regimen. The mean change from the baseline YMRS score at that time was –10.3 in the divalproex loading group versus –8.1 in the divalproex nonloading group and –6.1 in the lithium group ($p = .467$ divalproex loading vs. divalproex nonloading; $p = .152$ divalproex loading vs. lithium). At least 70% of the patients in all 3 treatment groups received adjunctive lorazepam at some point, with no significant differences among the groups. Fourteen of 20 patients in the divalproex loading group received adjunctive lorazepam, 15 of 20 patients in the divalproex nonloading group received adjunctive lorazepam, and 15 of 19 patients in the lithium group received adjunctive lorazepam.

Figure 1. SADS-C Evaluation of Young Mania Rating Scale Using Observed Cases (change from baseline)[a]



[a]Abbreviation: SADS-C = Schedule for Affective Disorders and Schizophrenia-Change Version.

Figure 2. Mean Mood Stabilizer Serum Concentration[a] at Each Evaluation



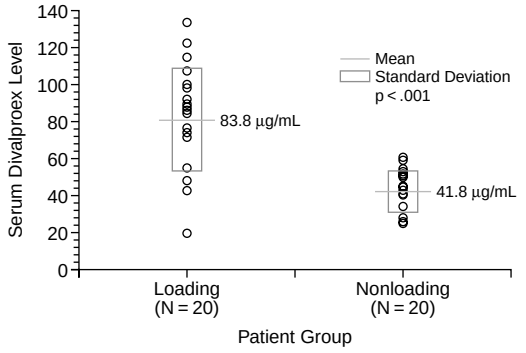
[a]Valproate concentration measured as μg/mL; lithium concentration measured as mEq/L.

As expected, the serum concentration of valproate rose more quickly in patients receiving the rapid-stabilization dose (Figure 2). By day 3, the mean serum concentration of divalproex in the divalproex loading group (mean ± SD = 83.8 ± 27.6 μg/mL; range, 19.3–132.7 μg/mL) was well above the accepted threshold of the therapeutic range of 50 μg/mL, whereas this concentration had not yet been reached in the divalproex nonloading group (41.8 ± 11.3 μg/mL; range, 24.3–71.4 μg/mL). Figure 3 depicts the actual serum levels of divalproex on day 3 for both treatment groups, showing a lower mean and restricted range for the nonloading group, and higher mean and larger range for the loading group ($p < .001$). Therapeutic range was achieved by day 3 for 84% (16/19) of the loading group subjects compared with only 30% (6/20) of the nonloading group subjects.

DISCUSSION

This is the first prospective, randomized, double-blind, parallel-group trial comparing oral loading of divalproex with standard titration of either divalproex or

Figure 3. Serum Divalproex Level on Day 3 for Loading and Nonloading Patients



lithium. A loading dose of divalproex of 30 mg/kg/day for 2 days followed by 20 mg/kg/day was as well tolerated as the usual divalproex and lithium dosing. In addition, the loading dose group attained therapeutic concentrations more rapidly than the other groups. A minority of patients (16%) did not attain therapeutic levels by day 3, even with rapid loading. The proportion of patients reporting various adverse events was similar in the 2 divalproex groups and did not differ significantly from that in the patients receiving lithium. Moreover, no patients in any of the 3 arms discontinued treatment because of adverse events.

The objective of the current study was to evaluate the safety and tolerability of an oral loading dose of divalproex. This study was not powered to detect a difference in efficacy. Using the day-2 model-based mean and variance estimates from the study, a sample size of approximately 105 patients per arm would be required to achieve 80% power of detecting statistically significant ($p < .05$) differences between treatment groups. Nevertheless, these data suggest an earlier onset of action in patients who received the higher initial dose, with a greater change in baseline YMRS score on day 3. A key next step will be to assess the efficacy of rapid loading of divalproex in a controlled fashion. Rapid acceleration of dosing may be considered a safe alternative in this patient population.

Drug names: divalproex sodium (Depakote), haloperidol (Haldol and others), lorazepam (Ativan and others).

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