Intravenous Fosphenytoin in Acute Mania

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Objectives: Since several anticonvulsants are therapeutic in mania and since acute mania requires rapid and intensive treatment, we hypothesized that intravenous high-dose phenytoin might be acutely antimanic. A new prodrug of phenytoin, fosphenytoin, which has few cardiac or local vein side effects, was used to test this hypothesis.

Method: Seven patients with a DSM-IV manic episode and minimal prior drug treatment were given intravenous fosphenytoin and were assessed at baseline and after 15, 30, 45, and 60 minutes with the Young Mania Rating Scale, the Clinical Global Impressions scale, and the Mini-Mental State Examination. Data were gathered in 2002.

Results: No antimanic effects were observed. No subject had any clear improvement in manic symptoms on the YMRS at any timepoint assessed.

Conclusion: Intravenous fosphenytoin at doses that are effective in status epilepticus appears to be ineffective in acute mania.

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Lithium, carbamazepine, and valproate work slowly when given under usual oral dosing schedules. Rapid oral lithium loading is a little-tried option for acute mania and may be more possible than previously thought.[1] Rapid oral and even intravenous valproate loading also seem feasible, although they have not been not studied in a controlled fashion.[2]

The anticonvulsant drug with by far the most clinical experience in acute intravenous administration is phenytoin. Intravenous phenytoin has been used for decades in status epilepticus. Numerous studies have shown that intravenous phenytoin penetrates brain within 1 to 2 minutes and may relieve status epilepticus within 15 minutes.[3]

Kalinowsky and Putnam[4] reported marked beneficial effects of phenytoin in mania in the 1940s. In a controlled, double-blind, add-on trial, Mishory et al.[5] in 2000 found significant benefit of phenytoin in mania. Mishory et al. found phenytoin to have significant prophylactic effects in a controlled double-blind add-on study of 23 bipolar patients over 1 year (A. Mishory, M.D.; M. Winokur, M.D.; R.H.B.; et al., manuscript submitted).

Thus, intravenous phenytoin could be a useful tool for rapid control of manic symptoms without sedation. Despite its wide use, a disadvantage of intravenous phenytoin is the need for cardiac monitoring and local vein irritation during intravenous use.[6] Therefore, a new phenytoin prodrug that converts to phenytoin in the blood within 15 minutes is a major practical advance.[7] Fosphenytoin is devoid of local vein irritation and of first-pass cardiac toxicity.[7] Effectiveness in status epilepticus is still very rapid.[7]

Effectiveness in status epilepticus proves that phenytoin can have major neurobiological effects almost immediately. Intravenous phenytoin is used outside the context of status epilepticus in the preparation of patients for emergency neurosurgery when antiepileptic prophylaxis must be induced immediately. In these conscious patients, even very high intravenous doses are known to be nonsedating. We therefore hypothesized that intravenous fosphenytoin could have major antimanic effects within 1 hour.

METHOD

Patients aged 18 to 50 years who were able to give written informed consent, were experiencing a manic episode (DSM-IV criteria), and were in need of immediate acute treatment were eligible for the study. In general, the subjects were newly admitted, unmedicated patients. Patients who had taken 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, or more than 30 mg of haloperidol or 60 mg of diazepam or their equivalent over the last week, were also excluded. Patients treated with a mood stabilizer in the last 3 days were excluded. Extreme attention was given to preventing 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.

Table 1. Change From Baseline in Total and 6-Item YMRS Scores in 7 Acutely Manic Patients Receiving Intravenous Fosphenytoin

Patient No.	Sex/Age (y)	Baseline Total YMRS Score	Baseline 6-Item YMRS Score	Change From Baseline in 6-Item YMRS Score				
				15 min	30 min	45 min	60 min	120 min
1	M/48	30	20	0	0	0	0	0
2	M/47	25	21	0	–1	–1	–1	–1
3	F/41	32	22	0	0	–1	–1	–1
4	M/30	30	19	–2	0	0	0	0
5	F/46	31	19	0	0	–3	0	–1
6	M/49	26	17	+2	+1	+1	–1	0
7	F/40	24	18	–2	–2	–2	–2	0

Abbreviations: F = female, M = male, YMRS = Young Mania Rating Scale.

Consenting acutely manic patients (Young Mania Rating Scale [YMRS][8] score > 20) were attached to cardiac monitoring. Fosphenytoin was given intravenously, 50 mg of phenytoin equivalents per minute, for a maximum total of 5 mg/kg (350 mg for a person weighing 70 kg [156 lb]). A syringe of fosphenytoin or saline was prepared by a nonblinded supervising physician (R.H.B.). The patient was rated on a modified 6-item YMRS for repeated measures, the Clinical Global Impressions scale (CGI),[9] and a modified Mini-Mental State Examination (MMSE) (available from the authors on request) for repeated administration, at baseline and after 15 minutes, 30 minutes, 45 minutes, and 60 minutes. The protocol was approved by the Helsinki Committee (institutional review board). Data were gathered in 2002.

The patients, the clinical rater (J.A.), and the nursing staff believed that the patients could receive either fosphenytoin or placebo. In fact, as part of a plan to obtain pilot data, the supervising physician gave all of the first 7 patients studied (4 men and 3 women, aged 30–49 years) active fosphenytoin. Since none of the first 7 consenting patients had any response, the nonblinded supervisor (R.H.B.) stopped the study after 7 patients and no patient actually received placebo.

RESULTS

None of the 7 subjects had any clear improvement in manic symptoms on the YMRS at any timepoint after intravenous fosphenytoin administration (Table 1). No sedation or confusion was noted on the modified MMSE after fosphenytoin administration (data not shown). One patient (#7), who had the lowest baseline YMRS score and had been awake all night, experienced some somnolence after 15 to 60 minutes in a reclining position for the infusion, but no change in her aggressive and sexual thought content. Three patients had itching in the groin during the first few minutes of the infusion, a known side effect of fosphenytoin, and 4 had no side effects whatsoever. Four of the patients did not require immediate antimanic treatment after the 120-minute formal observation period, and in none of the patients was improvement noted over the following 3 hours.

DISCUSSION

It has been hypothesized that the biochemical basis of antimanic treatment involves changes in gene expression that take days or weeks.[10] Since intravenous phenytoin is not sedative (unlike valproate), antimanic effects, if demonstrated, would suggest that the key biochemical effect of phenytoin, sodium channel blockade (without gene expression changes), is sufficient for an acute antimanic response. The absence of such antimanic effects supports the concept that the biochemical basis of currently available mood stabilizers requires a time interval, even though the anticonvulsant effect in status epilepticus can be achieved in minutes. Alternatively, other, more standard mood stabilizers such as valproate may be able to yield very rapid effects after intravenous administration at status epilepticus doses. We are planning a trial of valproate to explore such a possibility.

Drug names: diazepam (Valium and others), fosphenytoin (Cerebyx), haloperidol (Haldol and others), phenytoin (Dilantin).

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