

INTRAVENOUS VALPROATE: A NEW PERSPECTIVE IN THE TREATMENT OF MANIC SYMPTOMS

HARPREET S.DUGGAL, K. JAGADHEESAN, SUBHASH GUPTA, SOUMYA BASU, SAYEED AKHTAR & S.HAQUE NIZAMIE

ABSTRACT

Over the last few years, the use of valproate in psychiatry has increased considerably. With the advent of oral loading dose strategy, its role in rapid treatment of acute mania has been demonstrated. The intravenous formulation of valproate, while retaining the rapidity of action of oral loading, also avoids some of the adverse effects of the oral preparation. Moreover, reports are pouring in that intravenous valproate loading may be more efficacious than oral valproate loading in the treatment of acute mania. We report two patients whose manic symptoms showed a dramatic response to intravenous valproate without adverse effects. The pharmacology of intravenous valproate and its clinical relevance to psychiatry are discussed.

Key words: Intravenous valproate, manic symptoms, pharmacology

Studies in the last decade have demonstrated that oral loading doses of sodium valproate is effective in controlling symptoms of acute mania (Keck et al., 1993; Martinez et al., 1998). Although intravenous formulation of valproate is in use in Europe for over a decade, much of its initial literature was limited to treatment of epileptic patients, especially those with status epileptics (Hovinga et al., 1999). Its use in neuropsychiatry is more recent with reports of its effectiveness in acute mania (Erfurth & Grunze, 1998; Norton & Quarles, 2000; Norton, 2000), agitation of autism (Hilty et al., 1998) and bipolar disorder with Alzheimer's dementia (Herbert & Nelson, 2000). It has not been effective in bipolar patients with pure depression (Grunze et al., 1999). Further, intravenous valproate appears suitable for those manic patients who refuse oral medications or cannot tolerate oral medicines due to adverse effects, especially gastrointestinal symptoms after gastric bypass

surgery (Kaltsounis & De Leon, 2000). In line with the growing interest, we present two cases in which acute manic symptoms responded well to intravenous valproate and discuss the pharmacological and clinical perspectives of this new modality of treatment of acute mania.

CASE REPORT

Case 1: D.K., a 36-year-old male, diagnosed with bipolar disorder was admitted for third episode of mania with psychotic symptoms and comorbid cannabis harmful use as per the ICD-10 diagnostic criteria (World Health Organisation, 1992). The present episode was of 10 days duration and it was consequent to poor compliance with lithium. On admission, the patient was very hyperactive and aggressive and had overtalkativeness, flight of ideas, elated affect, increased libido, delusions of grandeur and persecution and poor insight. He refused oral medications and was considered for

valproate infusion. After baseline liver function tests (LFT) and platelet counts, he was started on 550 mg of i.v. valproate twice/day. The dose was calculated at 20 mg/kg body weight. The rate of infusion was not to exceed 20mg/min and the dose of valproate (550 mg) was mixed with 100ml of 5% dextrose to be infused over one hour (Facts & Comparison, 1998; Norton & Quarles, 2000). A total of six doses were administered over three days after which the patient was switched to equivalent doses of oral valproate. His baseline score on a scale for manic symptoms (Cassidy *et al.*, 1998) before the start of treatment with i.v. valproate (day 0) was 47, which dropped to 34 on day 3 and to 9 on day 6. The domains showing maximal improvement within three days of starting the treatment with i.v. valproate included increased motor activity, paranoia, aggression and irritability. This improvement continued when the patient was switched to oral valproate so that by day 9, his score on the mania rating scale was zero. The patient was not prescribed any concomitant neuroleptics and parenteral lorazepam was prescribed on prn basis, the total dose not exceeding 4 mg/day. Adverse effects due to valproate were rated using a checklist and the patient did not report any of these, including injection site reactions. His LFT and platelet counts a week after the start of valproate were within normal limits.

Case2: D.S., a 38-year-old male was admitted with a diagnosis of schizoaffective disorder, manic type (as per ICD-10) of 17 years duration. The patient was initially treated with oral neuroleptics but due to poor compliance was commenced on depot neuroleptics. However, he continued to deteriorate while continuing this medication and his present admission was prompted by an acute exacerbation of symptoms. On admission, he had mannerisms, over talkativeness, irritable and elated affect, racing thoughts, loosening of association, delusions of grandeur, persecution and reference and poor insight. It was decided to start the patient on clozapine but for the stabilization of acute phase, i.v. valproate was chosen which was to be

continued in oral form along with clozapine. After baseline investigations as for case 1, the patient was treated with 750 mg twice/day of i.v. valproate, the dose being infused with 150ml of normal saline at a similar rate as in the previous case. Patient received six doses of i.v. valproate and it was converted to equivalent doses of oral valproate. The patient's baseline score (day 0) on the mania rating scale was 51 while that on Brief Psychiatric Rating Scale was 63. On day 3, the respective scores were 29 and 40 and on day 6 these were 21 and 33. The areas showing maximal improvement within three days of valproate infusion were increased motor activity, decreased sleep, irritability and aggression on the mania rating scale and anxiety, grandiosity, tension, excitement, mannerism and uncooperativeness on the BPRS. He did not experience any side effects while being on i.v. valproate and other laboratory tests were also normal.

DISCUSSION

This report demonstrates that intravenous valproate is effective in controlling manic symptoms in bipolar disorder and schizoaffective disorder. There was a rapid response in either case, with the second patient showing more than 40% improvement in manic symptoms within three days of treatment with i.v. valproate with the improvement continuing with oral valproate. This in fact is comparable or even faster than the response obtained with oral valproate loading (Keck *et al.*, 1993). Moreover, to our knowledge this is the first report to show effective treatment of manic symptoms in a case of schizoaffective disorder, manic type, with i.v. valproate, which is in contrast to an earlier report that had failed to show improvement in schizoaffective disorder (Grunze *et al.*, 1999). A notable observation was that both the patients had responded to valproate alone without concurrent neuroleptics though both had psychotic symptoms at presentation. Although regarded as safer than other anticonvulsants, i.v. valproate is not entirely free from side effects. The more common of these

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included nausea, vomiting, headache, somnolence, dizziness, injection site reactions and taste perversion (Devinsky et al., 1995). However, neither patient showed any adverse reactions to i.v. valproate.

Pharmacokinetic profiles of intravenous loading, a quick saturation of plasma binding of proteins and a rapid achievement of peak concentrations of valproate, which is about 22% higher than those obtained with the equivalent oral dosage, have been the proposed reasons for its rapid onset of action over oral valproate loading (Wangemann et al., 1997; Grunze et al., 1999). A rapid initial increase in peak concentration might be needed to induce certain intracellular changes before compensatory down-regulation of synaptic receptors and transmembranous transducing systems can occur (Erfurth & Grunze, 1998). Further, intravenous valproate may cause a rapid saturation of plasma-binding proteins, which could increase the initial serum concentration of the active unbound drug and thus result in rapid attainment of high cerebral valproate levels (Grunze et al., 1999). In line with this, a study cites greater unbound fraction of the drug than expected in patients of status epilepticus treated with i.v. valproate (Hovinga et al., 1999).

In sum, i.v. valproate is a promising and safe drug, which expands the spectrum of treatment options available for acute manic symptoms. However, before its widespread use in psychiatry, more studies are required to establish the optimal initial dosage and administrating rate. In this direction, a controlled study with a larger sample size and concurrent monitoring of serum valproate levels would overcome some of the limitations of our endeavor.

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HARPREET S. DUGGAL, D.P.M., Resident, K.JAGADHEESAN, M.D., Senior Resident, SUBHASH GUPTA, D.P.M., Resident, SOUMYA BASU, D.P.M., Resident, SAYEED AKHTAR, M.D., D.N.B., Chief Medical Officer, S.HAQUE NIZAMIE*, M.D., D.P.M., Professor of Psychiatry & Director, Central Institute of Psychiatry, Kanke, Ranchi-834006 (Email: jagpsy@yahoo.co.in).

*Correspondence