Effect of Injectable Valproate Loading in Addition to Oral Valproate in Acute Mania - Observational Study

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ABSTRACT

Introduction: Injectable valproate loading has been used in control of status epilepticus. Its use in mania is very limited and is not explored adequately. Injectable valproate is used sparsely in clinical setting to control mania. Present research was planed to study the effect of Injectable valproate loading in addition to Oral valprote in acute mania patients and compare its effects with only oral valproate use.

Material and Methods: The observational study was conducted on patients between 18 to 65 years of age, who fulfilled the criteria for bipolar disorder current episode mania, according to International classification for diseases 10th ed. (ICD-10) in visiting the Department of Psychiatry M.G.M medical college Indore and Mental Hospital, Indore. In this study Injectable valproate was used in addition to oral valproate to achieve faster serum concentration and faster results.

Results: Control of manic symptoms (fall in YMRS score) was faster in patients loaded with additional injectable valproate and oral dosing when compared with only oral dosing and this was statistically significant from day 3. Minimal side effects of nausea and somnoloscence were seen and there was no statistically significant difference between the two groups in this regard. No sever adverse events were reported. Limitations of the study are being discussed.

Conclusion: Injectable Valproate loading, with oral dosing is faster and has robust antimanic action when compared with oral valproate alone. It is not associated with additional adverse effects.

Keywords: Valproate, Injectable Valproate, Oral Valproate, Mania

INTRODUCTION

Valproate has emerged as a drug of primary choice for the treatment of acute mania. It can be administered in high doses as an oral loading therapy.[1] In some studies injectable valproate was found to be more efficacious and better tolerated than oral valproate, as it reduced manic symptoms more rapidly than oral valproate.[2] Achieving therapeutic level of valproate by oral rout in blood may need many days. Injectable valproate loading in addition to Oral valprote in acute mania may be helpful in rapidly achieving therapeutic level in blood for early response. Therapeutic levels of valproate needed to control mania are not well established, but clinical observation is that higher the dose of valproate better is the control. Side effects of valproate often limit its dose escalation.

Research was aimed to study the effect of Injectable valproate loading in addition to Oral valprote in acute mania patients and compares its effects with only oral valproate use. Further objectives were

- To study socio demographic profile of the sample and compare to find any statistical differences.
- To study the Clinical profile of sample and compare illness characteristics in both groups.
- To study the Efficacy of Injectable valproate loading in addition to Oral valproate over oral valproate in acute mania patient by YMRS.
- To study the adverse effect profile of Injectable valproate loading in addition to Oral valprote over oral valproate in acute mania patient and compare the differences between the two study groups.

MATERIAL AND METHODS

This was an Observational study. Oral valproate and injectable valproate in addition to oral valproate was used alternately in admitted new acute mania patients to make two groups of patients.

Study population: 10 Patient between 18 to 65 years of age, who fulfilled the criteria for bipolar disorder current episode mania, according to International classification for diseases 10th ed. (ICD-10) in Department of Psychiatry M.G.M medical college Indore and Mental Hospital, Indore. Saple size was based on the inclusion and exclusion criteria.

Inclusion criteria: Ten consecutive patients that presented to the department with mania, of 18-65 years age group, who fulfilled the ICD-10 criteria for bipolar affective disorder, manic episode and who or their legally acceptable representatives (LAR) provided written informed consent were included.

Exclusion criteria: Patients with an organic brain syndrome, patients with a significant history of previous liver and renal diseases, sever medically ill patient and patients with deranged liver and kidney functions, intoxicated patients, and pregnant and lactating women were excluded.

Tools

1. Semi-structured data entry Performa
2. ICD-10.MINI-6 - for diagnosis
3 Young mania rating scale (YMRS) and clinical global impression (CGI) -for severity assessment:

Procedure

Protocol was approved by departmental scientific committee. Patient meeting inclusion criteria were admitted in hospital and after detailed evaluation diagnosis was conformed

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in each case. Alternate patients were advised injectable valproate and oral valproate in dose 20mg/kg/day in one group and only oral valproate in same dose in other group, for first 2days. Injectable valproate was given intravenously in a drip of normal saline over six hours and oral valproate was given PO in two divided dosage as CR preparation. After day two, oral valproate was given in dose 20mg/kg/day for next5days. Olanzepine 10mg/day was given for 7days.During Hospital stay, if needed, injectable antipsychotic (Haloperidol) and injectable Benzodiazepines (Lorazepam) were given in emergency to manage patient on basis of clinical judgment. Young mania rating scale (YMRS) was administered at admission and on day 3 day 5 and day 7 where as clinical global impression (CGI) was administered at admission and day 7.

STATISTICAL ANALYSIS

The analysis was done using computer program SPSS v16 and ANOVA was applied to find statically significant differences in two the groups.

RESULTS

All patients were male with mean age of 34.2 years, most of them married, employed, literate, belong to middle socioeconomic status and reside in urban setting. There were no statistical differences in these parameters between the two groups. (table-1)

Clinical profile: Average total duration of illness was 7.2yearsand current episode duration was 1 month with past history of >3 episodes in 5 patients (50%). Average YMRS score was36.9 and CGI score was5.2 at onset. In clinical course of study most of patient required 1wk hospital stay. All above parameters matched statistically in both groups. (Table-2)

Outcome: Maximum reduction in YMRS score was on 2nd day of injectable plus oral valproate use. During this period oral Olanzepine 10mg/day was used in all patients and injectable Antipsychotic (Haloperidol) was used in 7 out of 10 (70%) individuals. Injectable Lorazepam was needed in 6 patients (60%). Use of injectable haloperidol and lorazepam was statistically higher in the oral group. Adverse effect e.g. nausea, and somnolence were reported in 5 out of 10 (50%) patients and no serious adverse effect were reported in any individual. There was no statistical difference in adverse events between the two groups (table-3). Reduction in YMRS between 1 to 3days in injectable plus oral valproate treatment group was 22.4 $\pm$2.6 points and maximum reduction in symptoms was seen on day two. Reduction in YMRS between 1 to 3days in oral valproate treatment group was 10.0 $\pm$3.2 points. This difference was statistically significant. Reduction in YMRS between 3 to 5 days in injectable plus oral valproate treatment group was 7.2 $\pm$1.0 points. Reduction in YMRS between 3 to 5days in oral valproate treatment group was 3.2 $\pm$ 1.8 points. This difference was statistically significant. Reduction in YMRS between 5 to 7 days in injectable plus oral valproate treatment group was 3.8 $\pm$ 1.3 points. Reduction in YMRS between 5 to 7 days in oral valproate treatment group was 5.4 $\pm$ 0.9 points. This difference was statistically significant and the drop was more in oral valproate treatment group, meaning oral valproate started its action between 5 to 7 days. (Table-3; Figure - 1)

DISCUSSION

Antimanic efficacy of oral valproate has been apparent on the fourth day of treatment in some studies[3] and in single dose in some reports.[4] In our study statistically significant effects were seen between days 5 to 7 for oral valproate when compared with use of injectable valproate along with oral

	IV Valproate Loading with oral valproate (N=5)	Oral Valproate	p value	Level of significance (p value <0.05)
Age (mean age)	34.2±4.5	31.4±11.30487	0.621	N.S.
Sex Male Female	 4(80%) 1(20%)	 4(80%) 1(20%)	1.000	N.S.
Marital status Married Unmarried	 4(80%) 1(20%)	 3(60%) 2(40%)	0.545	N.S.
Education Status Primary Higher secondary	 3(60%) 2(40%)	 2(40%) 3(60%)	0.580	N.S.
Occupation Unemployed Self employed Unskilled	 1(20%) 3(60%) 1(20%)	 1(20%) 0(0%) 4(80%)	0.608	N.S.
Residence Rural Urban	 1(20%) 4(80%)	 2(40%) 3(60%)	0.545	N.S.
Family type Nuclear Joint	 2(40%) 3(60%)	 3(60%) 2(40%)	0.580	N.S.
Total family Income <5000 >5000	 3(60%) 2(40%)	 2(40%) 3(60%)	0.580	N.S.

Table-1: Socio-demographic characteristic

S.N.	IV Valproate Loading (N=5)	Oral Valproate	p value	Level of significance (p value <0.05)
Total duration of illness(In Year)	7.2±1.3	31.4±11.3	0.667	N.S.
Duration of current episode			1.000	N.S.
<1month	4(80%)	3		
>3month	1(10%)	2		
H/o manic episode in past			0.580	N.S.
>3eposode	3(60%)	2		
<3episode	2(40%)	3		
Family H/O psychiatric illness			1.000	N.S.
No	4(80%)	4		
Yes	1(20%)	1		
H/o Rapid cycling			0.347	N.S.
No	4(80)	5		
Yes	1(20%)	0		
YMRS score at onset	37.2±5.4	36.6±4.7	0.856	N.S.
CGI score at onset	5.0±0.7	5.4±0.8	1.000	N.S.

Table-2: Clinical Profile

S.N.	IV Valproate Loading (N=5)	Oral Valproate	p value	Level of significance (p value <0.05)
Reduction in YMRS1(1-3days)	22.4±2.6	10.0±3.2	0.0001	Significant
Reduction in YMRS(3-5days)	7.2±1.0	3.2±1.8	0.003	Significant
Reduction in YMRS(5-7days)	3.8±1.3	5.4±0.9	0.053	Significant
Reduction in CGI(1-7days)	3.8±0.8	2.2±0.8	0.016	Significant
Antipsychotic use			0.040	Significant
No	3(60%)	0		
Yes	2(40%)	5		
Antipsychotic dose	12.0±5.7	20.0±3.5	0.029	Significant
BZP use			0.004	Significant
No	4(80%)	0		
Yes	1(20%)	5		
BZP dose	4.4±2.6	9.6±2.2	0.009	Significant
Duration of Hospitalization			0.009	Significant
<1wk	3(60%)	2		
>2wk	2(40%)	3		
ADR			0.580	N.S.
No	3(60%)	2		
Yes	2(40%)	3		

Table-3: Outcome measures

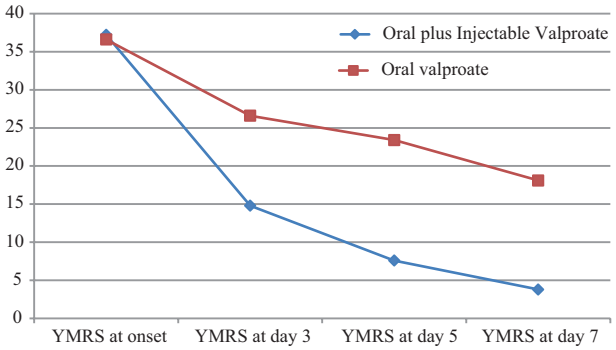

Figure-1: Comparison of YMRS scores from onset to day 7, between oral plus injectable valproate and oral valproate treatment groups

valproate dosing where clinical and statistical improvement in control of mania was seen between 1 to 3 days.

It has been observed that injectable valproate is more efficacious and better tolerated than oral valproate as it reduces manic symptoms more rapidly than oral valproate i.e. on day 3 and day 7.[2,6] Injectable valproate in addition to oral dosing has not been studied previously.

Our study show similar outcome like previous studies on cursory look, but reduction of symptom on clinical rating score is more robust in this observational study without any increase in adverse effect. This is apparently because of addition of effects of oral as well as injectable valproate and the fact that total per day dose was much higher, in fact double than in other studies. Maximum loading Dose of 30mg/kg/day of valproate has been recommended.[10] Paucity of side effects in this study is also remarkable and is attributable to use of injectable valproate.

Pharmacokinetic profile of intravenous loading, a quick saturation of plasma binding of proteins and a rapid achievement of peak concentration of valproate which is 22% higher than those obtained with equivalent oral dose, have been proposed reasons for its rapid onset of action over oral valproate loading.[1]

A rapid initial increase in peak concentration might be needed to reduce certain intracellular changes before compen-

satory down regulation of synaptic receptor and transmebranous transducing system can occur.[5] Therapeutic serum levels of 50 micrograms /dl have been achieved on day 3 and day 4 of oral valproate loading.[7,8]

Further intravenous valproate may cause a rapid saturation of plasma binding protein which could increase the initial serum concentration of the unbound drug and thus result in rapid attainment of high cerebral valproate level.[1] This is better alternative to usual saturation schemes used in oral valproate loading.[9]

Initial load of oral valproate is bound to carnetine in liver to form a valproate carnetine complex, which is responsible for valproate's hepatotoxicity. Injectable valproate loading bypasses this to rapidly increase serum levels, where oral dosing of valproate traps the valproate in liver.

In summary, injectable valproate loading with oral valproate is more efficacious and well tolerated when compared with oral valproate loading alone.

Limitations of study

Although stastical significances were obtained, this is a small sample size. A study with larger sample size is awaited.This is a short term study and clinical outcome for oral valproate needs to be studied over longer periods till robust clinical improvement is also seen in this group.This study is observational clinical study, for more evidence a double blind randomized control study is needed alongwith comparisonof oral valproate loading and injectable valproate separately (three groups).

Serum valproate level wasnot measured in this study.Effects of oral olanzepine and injectable haloperidol and lorazepam were not studied in this study. They must have contributed to effect as well as side effect in this study.Hepatic profile before and after administration of valproate was also advisable in any further planned study.

CONCLUSION

Injectable valproate loading in addition to oral valproate dosing starts its action on day two and is superior to only oral valproate dosing. It continues to be superior in action over day 3 to 5 and produces statistically significant better outcome in control of mania. Oral valproate dosing starts its action between 5 to 7 days and improvement during this period is statistically better than injectable plus oral group but injectable plus oral group is still superior in total drop in YMRS. Both treatments are associated with minimal adverse events and well tolerated with no severe adverse events.

REFERENCES

1. Grunze, Heinz; Erfurth, Andreas; Amann, Benedikt; Giupponi, Giancarlo; Kammerer, Christine; Walden, Jorg. Intravenous Valproate Loading in Acutely Manic and Depressed Bipolar Patients. Journal of Clinical Psychopharmacology: 1999;19:95-100.
2. R. K. Solanki, Paramjeet Singh, Renu Khandelwal, and Aarti Midha. Efficacy and tolerability of injectable sodium valproate in patients with mania. Indian J Psychiatry. 2006;48:118–120.
3. Pope HG Jr, McElroy SL, Keck PE Jr, Hudson JI. Valproate in the treatment of acute mania. A placebo controlled study. Arch Gen Psychiatry. 1991;48:628.
4. Phrolov K, Applebaum J, Levine J, Miodovnick H, Belmaker RH. Single dose intravenous valproate in acute mania. J Clin Psychiatry. 2004;65:6870.
5. Andreas Erfurth, Heinz Grunze. New perspectives in the treatment of acute mania: A single case report. Progress in Neuro Psycho-pharmacology and Biological Psychiatry 1998;22:1053–1059.
6. Duggal HS, Jagadheesan K, Gupta S, Basu S, Akthar S, Nizamie HS. Intravenous valproate: A New perspective in the treatment of Manic Symptoms. Indian Journal of Psychiatry 2002;44:173-6.
7. McElroy SL, Keck PE. Valproate as loading treatment in acute Mania. Neuropsychobiology 1993,27:146-9.
8. Keck PE, McElroy SL, Tugrul KC, Bennett JA. Valproate oral loading in treatment of acute mania. J Clin Psychiatry. 1993;54:305-8.
9. Thorsten Gerstner, Nellie Bell, S. A. Kenig, Seizure. Oral rapid loading of Valproic Acid- An alternative to the usual saturation scheme? 2006;15:630-632.
10. Nassir Ghaems. Mood Disorders: A practical Guide S. Lippincott Williams and Wilkins: 2003; Pg 130

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