Original Article

Sodium Valproate as an Adjunctive Drug in Treatment of Schizophrenia

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Objective: Although sodium valproate came to the market as an anticonvulsant drug, nowadays it's wildly used in the management of psychiatric disorders. It is used as a mood stabilizer and as an adjunctive agent in treatment of depression and psychosis. There are controversies regarding sodium valproate efficacy in psychosis. Although some studies have reported that it is effective in the management of positive symptoms and aggression in acute psychosis, others have not found such an association. Our study aims to investigate the effects of adjunctive sodium valproate in the pharmacological management of patients with schizophrenia.

Method: In a double blind clinical trial, 32 schizophrenic patients (age 18 – 65), who were in immediate need of admission, were randomly allocated into two groups. The first group was treated by combination of sodium valproate and risperidone and the other by combination of placebo and risperidone. A diagnosis of schizophrenia was established based on DSM-IV-TR criteria. All patients were assessed by PANSS on the 1st, 14th and 28th days of the admission. The collected data were analyzed by Student and Paired T tests through SPSS.

Results: Comparison of PANSS mean score in two groups, before and after the trial, showed statistically significant differences. The reduction in PANSS score was significantly higher in the group treated with sodium valproate than in placebo group (P= 0.006). Although, there was a statistically significant reduction in positive symptoms in both group after 2 weeks of treatment (P= 0.048), the difference was not significant in the fourth week (P= 0.88).

Conclusion: Our study shows that if used as an adjunct to antipsychotic in the management of acute psychosis, sodium valproate will speed up the recovery of positive symptoms.

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Introduction

Although sodium valproate was first introduced as an anticonvulsant, it has been widely used as a mood stabilizer with a better effect than Lithium (1-4). According to the studies conducted in the last decade, sodium valproate has been used more than lithium in the management of bipolar and schizoaffective disorders (5).

Sodium valproate has been successfully used as an adjunctive drug with antidepressants and neuroleptics in the management of psychotic and depressive disorders (6-7). Its effect on aggression and impulsive behaviors has resulted in its use in schizophrenia (8-9).

Sodium valproate regulates the mesolimbic dopaminergic activity through voltage dependent ion channels and gabaergic effects. In many studies sodium valproate is suggested to be used in schizophrenic patient who have accompanying symptoms of restlessness, excitement, aggression and hostility (10). In a study conducted by Morinigo *et al*, four treatment resistant psychotic patients were treated with sodium valproate in addition to anti psychotic drugs. They showed a decline in the positive symptoms, disruptive behaviors, aggression and hostility (11). Afaq *et al* also showed that combination of valproate with an antipsychotic can decrease the aggression (12).

Other studies have suggested its efficacy in increasing the patients' response to antipsychotic (13).

However, some studies have indicated that sodium valproate is not more effective than placebo in controlling psychotic symptoms (14-18).

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Because some patients with schizophrenia do not show the expected response to anti psychotics, the researchers have, in recent years, attempted to study the effect of adjunctive medications in the pharmacological treatment of psychosis. To clarify this issue further, current study has been designed to investigate the effects of sodium valproate on clinical symptoms of patients with schizophrenia.

The present study is a randomized double blind clinical trail conducted in 2 mental health hospitals (Noor and Farabi) in Isfahan (Iran) during spring and summer of 2006.

Materials and Methods

The present study is a randomized double blind clinical trail conducted in 2 mental health hospitals (Noor and Farabi) in Isfahan (Iran) during spring and summer of 2006.

The patients were selected from those who had been referred to emergency department of both hospitals and who were in need of emergency admission and antipsychotic therapy. A diagnosis of schizophrenia was confirmed based on DSM-IV-TR criteria by a psychiatrist. To be included in the study, the subjects must not have taken any antipsychotic drugs (oral or parental) or mood stabilizer in the past month before the study.

The patients with pregnancy and breast feeding, co morbid illicit drug abuse and any history of severe adverse reaction to antipsychotic or valproate were excluded from the study. Those below 16 or above 65 were not included either.

The patients were then randomly divided into two groups of A and B after obtaining an informed written consent from a significant family member (based on Helsinki protocol). The groups were matched concerning the onset and length of the illness, subtype of schizophrenia, age and sex. Patients in group A were given a combination of risperidone and sodium valproate and group B the combination of risperidone and placebo.

Risperidone was started with a dose of 2mg/day and increased to 6 mg/day after a week in both groups. Sodium valproate was started with a dose of 600 mg/day and increased gradually aiming a maximum dose of 20 mg/kg if tolerated. On the average, sodium valproate dosage increased 400 mg every two days. Possible side effects of sodium valproate and risperidone were separately checked in each visit based on a devised check lists. In case of emergence of any side effects, the dosage was gradually decreased to a level that patient could tolerate. In group B, instead of valproate, placebo, which had the same appearance, was administrated by the staffs who were blind to the randomization. If needed, lorazepam was also prescribed in both groups, in the first week of treatment, up to 4mg/day.

All the subjects were evaluated on the 1st, 14th and 28th days of the study by different psychiatrists using positive and negative syndrome scales (PANSS). The psychiatrists who conducted the assessments were blind to randomizations. PANSS includes 30 items divided into three categories of positive syndrome, negative syndrome and general psychopathology. It has a high validity and reliability(19).

At the end, considering a *p value* of ≤ 0.05 as significant, the data were analyzed by Paired and Student t tests through SPSS.

Results

All subjects in both groups were unemployed. The mean age was 32 $\pm$ 8.3 years in group A and 34 $\pm$ 11.6 years in group B. There was no significant difference between the groups with regard to age (P=0.29) or onset of their illness (P=0.35). Mean number of hospitalization was 2.75 in group A and 3.06 in group B (P= 0.34).

There were 12 men and 4 women in group A and 13 men and 3 women in group B (P=0.50).The comparison between two groups showed no significant difference regarding their educational level (Mann- Whitney, P= 0.95).

There were 3 patients with paranoid schizophrenia and 13 with undifferentiated type in group A but 5 paranoid and 11 undifferentiated in group B. There were no disorganized or catatonic cases in either group.

PANSS mean score, positive syndrome score and negative syndrome score before treatment were respectively 94.93 ± 14.6, 24.31 ± 6.95 and 22.81 ± 4.6 in group A and 96.84 ± 18.9, 24.18 ± 7.3 and 23.87 ± 8 in group B.

Positive and negative syndrome mean scores and total PANSS score showed a significant decrease from the first day to the first two weeks and from the second weeks to the fourth weeks in both groups (P= 0.001, repeated measure ANOVA).

Mean total PANSS score was 62.06 ± 13.3 in group A and 10.68 ± 11.5 in group B after four weeks. The comparison of these figures showed a significant difference in both group (P= 0.03). Comparison of changes in PANSS score before and after treatment also showed a significant difference in both groups. A reduction in score was significantly higher in group A compared to group B (P= 0.006).

The change in positive symptoms score showed a significant difference in group A and B (P= 0.048) after two weeks but no significant difference at fourth weeks (P= 0.88). There was no statistical differences within and between the two groups regarding the change in negative syndrome score after two weeks and four weeks (P= 0.44, 0.09).

A statistically significant difference at fourth week was obvious when comparing the two groups with regard to a reduction in score of delusions, hallucinations and impulse control. The improvement in symptoms in group A was more than the improvement in group B (P= 0.01, 0.029, 0.029).

Discussion

Our results show that a combination of sodium valproate and risperidone is more effective than risperidone alone in the treatment of schizophrenia. This means that sodium valproate can be used as an adjunctive therapy to decrease psychotic symptoms if needed. These findings are consistent with those of wassef *et al* on the efficacy of sodium valproate as an adjunctive therapy in psychosis (7) and those of Morinigo *et al* in the management of positive symptoms, disruptiveness and hostile behaviors(10,19).

Our finding also reveals the positive effect of sodium valproate on the speed of recovery of the positive symptoms. This is consistent with the findings of *Berlo et al* (13).

Limitations of our study

In the present study, the number of our subjects was low due to the rigid inclusion criteria. We were also unable to find the optimum and effective dose of sodium valproate in improving the psychotic symptoms. The increased chance of adverse effects and drug interactions in such a combination have not been investigated either.

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References

1. Bowden CL, Brugger AM, Swann AC. Efficacy oF divalproex vs Lithium and placebo in the treatment of mania. J AMA 1994; 271: 918-924.
2. Gerner RH, Stanton A. Algorithm for patient management of acute manic statas: Lithium, valproate , or carbamazepine? Journal of Clinical Psychopharmacology 1992; 12: 57-83.
3. Chou JCY. Recent advances in Treatment of acute Mania. Jourrnal of Clinical Psychopharmacology 1991; 11: 3-21.
4. Sussman N. Background and rational for use of anticonvulsants in psychiatry. Cleveland Clinic Journal of Medicine 1998; 65: 7-14.
5. Fenn HH, Robinson D, Ludy V. Trends in pharmacotherapy of schizoaffective and bipolar affective disorders: a 5–year naturalistic study. Am J Psychiatry 1996; 153: 711-13
6. Heninger GR. Charney DS, Strenberg DE. Lithium carbonate augmentation of antidepressant treatments. Archives of General Psychiatry 1983; 40: 1335-1342.

7. Wassef A, Watson D, Morrison P. Nouroleptic-volproic acid combination in treatment of psychotic Symptoms; a three-case report. Journal of Chinical Psychopharmacology 1989; 9: 45-48.
8. Sheard MH, Marini JL, Bridges CI. The effect of lithium on Impulsive aggressive behavior in man. Am J Psychiatry 1976; 133: 1409-1413.
9. Luchins DL.Carbamazepine in violent non- epileptic schizophrenics. Psychopharmacology Bulletin 1984; 20: 569-571.
10. Mc Evoy JP, Scheifler PL, Frances A. The expert consensus Guideline series: Treatment of schizophrenia. J Clin Psych 1999; 60 (11): 43.
11. Morinigo A, Martin J, Gonzales S. Treatment of resistant schizophrenia with valproat and neuroleptic drugs. Hillside J Clinic Psych 1989; 11: 199- 207.
12. Afaq I, Riaz J, Sedky K, et al. Divalproex as a calmative adjunct for aggressive schizophrenic patient. Journal of the Kentucky Medical Association 2002; 100(1): 17-22.
13. Berle JO, Spigset O. Are mood stabilizers beneficial in the treatment of schizophrenia? Tidsskr Nor laegeforen 2005; 125(13): 1809 –12.
14. Basan A, Leucht S. Valproate for schizophrenia. Cochran Database of Syst Rev 2003;CD004028.
15. Basan A, Kissling W, Leucht S. Valproate as an adjunct to antipsychotic for schizophrenia: a systematic Review of randomized trial. Schizoph Ros 2004; 70(1): 33-70.
16. Dose M, Hellweg R. Combined treatment of schizophrenic psychoses with haloperidol and valproate. Pharmacapsychiatry 1998; 31: 122-125.
17. Fisk GG, York SM. The effect of sodium-valproate on tardive dyskinesia revisited. Brit J Psych 1987; 150: 540-542.
18. Wassef AA. Dott SG. Randomized placebo controlled pilot study of divalproex sodium in the treatment of acute exacerbition of chronic schizophrenic. J Clin Psychophar 2000; 357- 361.
19. American Psychiatric Association. Handbook of psychiatric measures, Washington, DC: The institute; 2000. P. 494-497.
20. Littrell KH, Petty RG, Hilligoss NM, et al. Valproate for hostility in schizophrenia patients. J Clin Psych 2004; 65: 134