A TRIAL OF SODIUM VALPROATE IN TARDIVE - DYSKINESIA

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SUMMARY

This study reports the results of an open trial of Sodium Valproate in tardive-dyskinesia. Fifteen patients identified having tardive dyskinesia by two psychiatrists independently were treated with Sodium Valproate in dosage of 1200 mg/day for 4 weeks. Assessments were made on abbreviated Dyskinesia Scale. There was statistically significant improvement after 2 and 4 weeks of treatment. Authors found Sodium Valproate quite effective in the management of tardive-dyskinesia.

Introduction

Neuroleptic therapy is associated with a number of complications which may appear in the beginning or after years of treatment. Tardive-dyskinesia is one of the important and most distressing complications of neuroleptic therapy. Initially considered to be a rare entity, a number of prevalence studies have demonstrated that it is relatively common condition. Many treatment strategies have been tried for it but none is satisfactory.

In its typical form tardive dyskinesia is seen after long term neuroleptic therapy as is suggested by its name i.e. tardive, but it may appear as early as 3-6 months of treatment with neuroleptics (Tarsy 1984).

Tardive dyskinesia is characterised by abnormal involuntary movements of orofacial region, extremities and trunk. The most common presentation is of bucco-linguomasticatory triad which consists of sucking and smacking movements of lips, lateral jaw movements, puffing of cheeks, thrusting, rolling or fly catching movements of tongue and chewing movements etc. This bucco-linguomasticatory triad is sometimes accompanied by choreo-athetoid movements of limbs and trunk, axial hyperkinetics, ballistic movements, rhythmic and swaying movements of body from side to side and akathisia. All these features together are seldom present in a patient at a particular time and all of these involuntary movements disappear during sleep.

The prevalence of tardive dyskinesia among chronically ill psychiatric inpatients has shown an increase from 1960 through 1980. Various studies of prevalence of tardive dyskinesia in chronically ill psychiatric inpatients have shown prevalence varying from 2.9-42.4%, the weighted mean prevalence being 17.5%. The prevalence of tardive dyskinesia in psychiatric outpatients on long term neuroleptic therapy varies from 0 to 34.4% in different studies (Jeste and Wyatt 1981).

The underlying biochemical disturbance in tardive dyskinesia is a state of relative dopaminergic overactivity. Chronic blockade of dopaminergic receptors leads to denervation supersensitivity (Burt et al 1977). Another mechanism that can lead to dopaminergic overactivity is the impairment of other modulating systems that interact with dopamine mechanisms in basal ganglia. It is possible that damage to the striatal interneurons that regulate activity of dopamine neurons by feedback mechanisms using acetylcholine, gamma amino butyric acid (GABA) or peptides as neurotransmitters leads to tardive-dyskinesia (Tarsy 1984). Based on the above mentioned mechanism, a number of drugs have been used in tardive dyskinesia varying from dopamine antagonists to dopaminergic...
drugs through cholinergic, GABA ergic and anticholinergic drugs, noradrenergic blockers and neuroleptic withdrawal (Jeste and Wyatt 1982, Simpson et al 1982). Till now there is no satisfactory treatment for tardive-dyskinesia. Neuroleptic withdrawal reverses dyskinesia in 37% of cases, rest of cases belonging to persistent tardive dyskinesia (Jeste and Wyatt 1982). In two excellent reviews on the treatment of tardive dyskinesia, Jeste and Wyatt (1982) and Simpson et al (1982) opine that neuroleptics are superior to all other drugs in suppressing tardive dyskinesia, while among non-neuroleptic drugs GABA-ergic drugs and putative nor-adrenergic blockers appear to be promising at this time. Among putative nor-adrenergic blockers, clonidine was reported to suppress psychotic and dyskinetic symptoms in two patients with tardive dyskinesia (Freedman et al 1980). However, this needs further investigation. Propranolol, a beta-adrenergic blocker has also been found to be useful in suppressing tardive dyskinesia (Bacher and Lewis 1980, Kulik and Wilbur 1980).

Amongst GABA-ergic agents-benzodiazepines and Sodium Valproate have been tried in tardive-dyskinesia with varying degree of success.

Linnola et al (1976) in a two week trial of Sodium Valproate in tardive dyskinesia reported significant improvement in 17 patients out of a total of 32 with oro-facial dyskinesia. Involuntary movements of extremities and dystonic spasms were also significantly reduced in 7 out of 9 patients. Gibson (1978) did not find any change in tardive dyskinesia in 25 schizophrenic patients, given Sodium Valproate for one month. Casey and Hammers- tud (1979) and Crowe (1983) found it useful in tardive-dyskinesia.

Various studies of drug trials in tardive-dyskinesia suffer from a number of deficiencies. These have been discussed in detail by Jeste and Wyatt (1982).

Despite considerable use of neuroleptics in our country and recognition that many of our patients have tardive dyskinesia, there is no report of any significance from our country regarding its management. Therefore, we studied the effect of Sodium Valproate on tardive-dyskinesia in psychiatric outpatients on long term antipsychotic therapy. An attempt was made to circumvent limitations of earlier studies.

Material and Methods

The patients having tardive dyskinesia diagnosed by two independent psychiatrists form the sample of study. It was ensured that each subject had received at least 100 gms of Chlorpromazine equivalents of antipsychotics in total and was on antipsychotic therapy for at least three months. Patients having any uncontrolled organic brain illness were excluded from the study.

Assessments of tardive-dyskinesia were made on Abbreviated Dyskinesia Scale (ADS) of Simpson et al (1979).

A total of fifteen patients were found suitable for the study. Informed consent was taken from all the patients. All the subjects were assessed on three subsequent occasions over a period of one month to further ensure the diagnosis.

Sodium Valproate was given in tablet form in fixed dosage of 1200 mg/day (400 mg t.i.d.) for four weeks. Assessments were done at 0, 2 and 4 weeks of trial. Maintenance medication of antipsychotics and anti-parkinsonian agents was continued without any change in the dosage during trial period.

Results

Sample consisted of fifteen subjects, twelve males and three females, with mean age of 37.67 years (S. D 14.28 yrs). They
### TABLE

Scores on Abbreviated Dyskinesia Scale (ADS) after 0.2 and 4 weeks of treatment with Sodium Valproate

| Patient No. | 0 week | 2 weeks | 4 weeks | % reduction in scores after 4 weeks |
|-------------|--------|---------|---------|-----------------------------------|
| 1*          | 17     | 8       | 6       | 64.71                             |
| 2*          | 23     | 17      | 11      | 62.17                             |
| 3*          | 11     | 5       | 3       | 72.73                             |
| 4*          | 39     | 27      | 5       | 87.79                             |
| 5*          | 30     | 13      | 12      | 60.00                             |
| 6*          | 10     | 4       | 0       | 100.00                            |
| 7           | 33     | 19      | 23      | 30.30                             |
| 8*          | 9      | 5       | 4       | 55.55                             |
| 9           | 26     | 21      | 18      | 30.77                             |
| 10*         | 17     | 11      | 7       | 58.82                             |
| 11          | 24     | 26      | 14      | 41.67                             |
| 12          | 29     | 8       | 16      | 44.83                             |
| 13          | 13     | 10      | 7       | 46.15                             |
| 14*         | 41     | 18      | 18      | 56.98                             |
| 15*         | 21     | 20      | 8       | 61.90                             |

**MEAN**

|           | 22.867 ± 10.211 | 14.800 ± 6.085 | 10.133 ± 6.556 | 57.625 ± 18.883 |

* Patients, who showed more than 50% improvement
** t = 5.0603, p < .01 at df = 14
*** t = 4.8308, p < .001 at df = 14

had been on neuroleptic therapy for a duration varying from 11 months to 20 years (mean 8.195 yrs, S.D. 4.026 yrs).

The Table shows scores of the patients on Abbreviated Dyskinesia Scale (ADS) at 0, 2 and 4 weeks and percentage improvement in tardive-dyskinesia after 4 weeks of trial with Sodium Valproate.

There was a significant improvement in tardive dyskinesia both after 2 and 4 weeks of trial ( $P < .01$ and $< .001$ at 2 and 4 weeks respectively).

### Discussion

Sodium Valproate was found effective in tardive-dyskinesia. Ten out of the fifteen patients showed more than 50% reduction in ADS ratings, while in one of the patients, complete remission of dyskinesia symptoms was achieved.

In our study, we used relatively strict criteria for diagnosis of tardive dyskinesia (criteria as recommended by Jeste and Wyatt 1981). In addition, we made assessments on ADS, which has been shown to have good reliability and validity (Simpson et al 1979). The only limitation of our study is that ours is an open trial. But if we take Jeste and Waytt's (1982) suggestion of taking a patient in an open trial as improved only if improvement is more than 50%, 66.67% of our sample showed improvement in 4 weeks.

In earlier studies, Linnoila et al (1976), Casey and Hammerstad (1979) and Crowe (1983) found Sodium Valproate useful in tardive-dyskinesia, while Gibson (1978) failed to find any significant improvement in tardive-dyskinesia with Sodium Valproate in their sample. The main criticism against Gibson's study is that inadequate doses of Sodium Valproate (600 mg/day) was used and only clinical global assessments of dyskinesia were made.

In the study by Linnoila et al (1976),
Oro-facial dyskinesia were totally or significantly relieved with Sodium Valproate in dosage of 900 mg/day. No correlation was found between blood levels of valproate and improvement. However, Casey and Hammerstad (1979) in a nine week trial on one patient found modest improvement in dosage of 900-2100 mg/d and a greater improvement with dosage above 2100 mg/day and dyskinetic symptoms increased when blood levels of Valproate went below 65 µg/ml and decreased with levels above 65 µg/ml. This suggests that a sustained minimal blood level may be necessary for improvement.

Crowe (1983) found improvement in dyskinesia with Sodium Valproate in dosage above 400 mg/day concurrently with existing neuroleptic treatments in 8 patients. In most cases, control of symptoms could be achieved within two weeks with the dose and could be maintained, provided dose was not altered. Patients were followed-up for a period of 2½ years, while on Sodium valproate.

Conclusion

This open trial of Sodium Valproate, though limited in scope found Sodium Valproate quite effective in tardive dyskinesia. Our results suggest that it can be used along or concurrently with neuroleptics in tardive dyskinesia.

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