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SHORT COMMUNICATION

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Clozapine efficacy in tardive dyskinesia in schizophrenic patients

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Abstract Tardive dyskinesia (TD) is a long-term severe complication of antipsychotic treatment, with mean prevalence of 20–35%. The aim of this study was to evaluate effects of clozapine in severe TD. In an open trial seven patients with schizophrenia and severe TD were given clozapine for 6 months. Tardive dyskinesia severity was evaluated with AIMS and ESRS and schizophrenic psychopathology with PANSS. Clozapine mean dose at the end of the study was 392.86 mg/day. A mean reduction of 52% was observed in ESRS scores for TD. Two patients also had dystonic movements, and there was 50% reduction in one of them and complete remission in the other. There was also a 27% mean reduction in PANSS scores. Clozapine seems to be an alternative in the treatment of schizophrenic patients with severe TD.

Key words Tardive dyskinesia · Treatment · Clozapine · Schizophrenia

Introduction

Tardive dyskinesia (TD) is a drug-induced movement disorder associated with prolonged administration of antipsychotics. It is usually mild and may improve over time but in some patients is disabling and irreversible. Its incidence is cumulative, approximately 5% a year until the fourth year of continuous use of antipsychotics [1], and the mean prevalence in psychiatric patients using antipsychotics is approximately 25% [2]. It may not require any specific treatment other than antipsychotic withdrawal or dosage reduction, but this is not always feasible due to high risk of psychotic relapse. There are also other drug therapies, but none are clearly effective in all patients with TD [3].

Clozapine is an atypical antipsychotic drug associated with very few acute extrapyramidal symptoms (EPS) and there are a few reports of TD associated with its use [4]. In addition, TD's incidence in patients taking clozapine is significantly lower than in patients taking typical antipsychotics [5], and in all studies relationship between clozapine and TD is not clear, since all patients had taken typical antipsychotics before they used clozapine. There are studies on clozapine effects in TD, including case reports, open trials [6] and one controlled study [7], and they report complete or partial TD remission with clozapine's use.

We studied the effect of clozapine in TD and psychotic symptoms on patients with schizophrenia and severe and persistent TD.

Methods

Seven patients (5 women and 2 men) were recruited from the outpatient clinic from the Institute of Psychiatry for an open trial of clozapine. Selection criteria were as follows: (a) age between 17 and 55 years; (b) diagnosis of chronic exacerbated schizophrenia (DSM-III-R); (c) previous use of antipsychotic for more than 6 months; (d) presence of severe TD (rated above 13 in AIMS [8]); (e) no current or past history of serious medical illness, particularly blood dyscrasias; (f) no pregnancy or breast feeding; and (g) no history of drugs or alcohol abuse. After complete description of the study to the subjects, written informed consent was obtained.

Patients were then admitted to the inpatient service and submitted to CT, ECG, EEG and blood tests (haemogram, serum sodium, potassium, urea, creatinine, glucose, chloride, protein electrophoresis, bilirubin, alkaline phosphatase, GGT, ALT/AST and uric acid) and then were withdrawn from antipsychotic medication for 1 week. Baseline evaluations were performed using the Positive and Negative Syndrome Scale (PANSS) [9] to assess mental status and AIMS and ESRS [10]) to rate TD. Treatment with clozapine was initiated, and patients were followed-up as outpatients. Patients received clozapine for 24 weeks up to a maxi-

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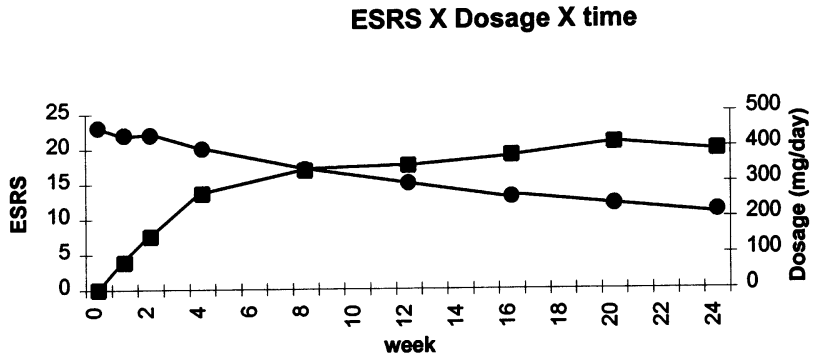

Fig. 1 Clozapine dosage: ESRS total scores for tardive dyskinesia and tardive dystonia during the treatment. ● ESRS scores; ■ Clozapine dosage

mum of 500 mg/day. At the endof the study blood tests, EEG and ECG were performed again. Haemograms were repeated weekly for 18 weeks and then monthly. Outcome measures were made with PANSS at baseline and weeks 2, 4, 8, 16 and 24, and AIMS and ESRS at baseline and weeks 1, 2, 4, 8, 12, 16, 20 and 24, always by the same evaluator. Adverse effects were evaluated monthly.

Results

The patients had a relatively low age (mean age 28.5 years, range 16–46 years). They had been schizophrenic for a mean of 10.9 years (range 3–30 years) and they had a mean of 2.14 previous admissions. Tardive dyskinesia was present for a mean of 16.71 months (SD 14.14 months). Mean clozapine dosage at the end of the study was 393 mg/day, ranging from 200 to 500 mg/day (Fig. 1).

There was a mean reduction of 52% in ESRS scores for TD (Fig. 1) and tardive dystonia, whereas there was a mean reduction of 49% in axial movements, 60% in limb movements and 75% in dystonic movements. In AIMS scores observed mean reduction was 41%. Four patients showed an improvement greater than 50% in TD's ESRS scores. Two patients also had dystonic movements: these remitted completely in one patient and were reduced to 50% in the other. There was also a mean reduction in parkinsonism of 73% (SD 26%), and the item with the smallest reduction was rigidity.

Most patients presented at baseline severe psychiatric symptomatology (mean ± SD baseline global PANSS: 98.6 ± 14.1), despite previous treatment with typical antipsychotics. There was a mean reduction of 27% in PANSS scores, which was more marked for positive symptoms (35%) and less marked for general symptoms (23%), and 28% for negative symptoms.

A patient received diazepan for 1 month (weeks 10–14) to prevent recurrence of a partial convulsive crisis presented in the tenth week. Other observed side effects were sialorrhoea, excessive somnolence, obstipation and blurred vision; all were moderate and remitted during treatment.

There were no abnormalities in the laboratory tests, except in computed tomography, which showed enlargement of cortical sulci in two patients and of left temporal horn in another.

Discussion

We observed a significant improvement of TD (mean reduction of 52%), and improvement was greater than 50% in four of the seven patients. The rate of improvement varied widely (33–76%) among TD symptoms and was more marked for dystonic movements. According to the literature, TD's remission rates after antipsychotic withdrawal ranges from 0 to 90%, and the mean remission rate 3 months after antipsychotic withdrawal is approximately 57% [11]. On the other hand, an improvement of more then 50% was observed in only 26% of patients with persistent and severe TD with various treatments (including antipsychotic withdrawal when feasible) [12]; thus, TD's remission rate observed in this study is significant.

There are many studies on clozapine effects in TD, including case reports, open trials [6] and one controlled study [7], and they report complete or partial TD remission with clozapine's use. In general, improvement is greater and more persistent with larger dosages and longer use of clozapine. Tardive dyskinesia's partial and complete remission rates with clozapine are greater than with typical antipsychotics, and most consistent and larger improvements were observed in patients with severe TD and dystonic symptomatology. With regard to tardive dystonia, there are case reports and an open trial [13] where improvement, sometimes lasting, is observed after months of treatment with clozapine.

There are two main hypotheses about the mechanism of improvement of TD:

1. Reduction in D2 striatal supersensitivity because clozapine has little effect in striatum, where there is a high concentration of D2 and low density of D4 [14]
2. Action on TD pathophysiology by balanced blocking of D1 and D2 receptors, or acting in other neurotransmitter systems such as cholinergic, serotoninergic or noradrenergic systems [14].

Conclusion

Clozapine is effective in treating patients with schizophrenia and severe TD because, besides improving schizophrenic symptomatology, it improves TD, especially dys-

tonic movements. On the other hand, controlled and larger studies are necessary to confirm the effects of clozapine and other atypical agents in TD.

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References

1. American Psychiatric Association. Task Force on Tardive Dyskinesia (1992) Tardive dyskinesia: a task force report of the American Psychiatric Association. American Psychiatric Association, Washington, DC
2. Chouinard G, Ross-Chouinard A, Annable L, Jones BD (1980) The extrapyramidal symptom rating scale. Can J Neurol Sci 7: 233
3. Dave M (1994) Clozapine-related tardive dyskinesia. Biol Psychiatry 35: 886–887
4. Gardos G, Cole JO, Salomon M, Schniebolk S (1987) Clinical forms of severe tardive dyskinesia. Am J Psychiatry 144: 895–902
5. Gerlach J, Lublin H, Peacock L (1996) Extrapyramidal symptoms during long-term treatment with antipsychotics. Neuropsychopharmacology 14: 35–39
6. Guy W (1976) Assessment manual for psychopharmacology. U.S. Department of Health, Education and Welfare, ECDEU, Washington, DC, pp 534–537
7. Jeste DV, Caligiuri MP (1993) Tardive dyskinesia. Schizophr Bull 19: 303–315
8. Jeste DV, Potkin SG, Sinha S, Feder S, Wyatt RJ (1979) Tardive dyskinesia – reversible and persistent. Arch Gen Psychiatry 36: 585–590
9. Kane JM, Woerner M, Lieberman J (1988) Tardive dyskinesia: prevalence, incidence and risk factors. J Clin Psychopharmacol 8: 52S–56S
10. Kay SR (1991) Positive and negative syndromes in schizophrenia. Brunner/Mazel, New York
11. Lieberman JA, Saltz BL, Johns CA, Pollack S, Borenstein M, Kane J (1991) The effects of clozapine on tardive dyskinesia. Br J Psychiatry 158: 503–510
12. Tamminga CA, Thacker GK, Moran M, Kakigi T, Gao XM (1994) Clozapine and tardive dyskinesia: observation from human and animal model studies. J Clin Psychiatry 55 [Suppl b]: 102–106
13. VanHarten PN, Kamphuis DJ, Matroos GE (1996) Use of clozapine in tardive dystonia. Prog Neuropsychopharmacol Biol 20: 263–274
14. Wagstaff AJ, Bryson HM (1995) Clozapine: a review of its pharmacological properties and therapeutic use in patients with schizophrenia who are unresponsive or intolerant to classical antipsychotic agents. CNS Drugs 4: 370–400