SHORT REPORT

Sulpiride in tardive dyskinesia^{*}

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Abstract

The abnormal involuntary movements in tardive dyskinesia can be reduced by the dopamine antagonist drugs, phenothiazines and butyrophenones, but most cause an increase in Parkinsonian signs. Sulpiride, a benzamide derivative, and selective antagonist of D2 receptors had a significantly beneficial effect on most of 15 patients ($p < 0.01$). In 12 patients the improvement was marked. The reduction of abnormal movements was observed even with low doses, and it was not necessary to increase the dose of sulpiride above 600 mg daily. There were no significant side effects during the trial nor during an additional three months of treatment.

Tardive dyskinesia is an iatrogenic syndrome caused by long term use of neuroleptic drugs.¹ The movements are often irreversible.² The neurophysiological mechanism of this syndrome remains unclear. Development of dopamine receptor hypersensitivity in the striatum after prolonged neuroleptic treatment might be the cause.^{3,4} Tardive dyskinesia can be suppressed by postsynaptic dopaminergic receptor blockers, such as phenothiazines or butyrophenones, but this blockade may induce Parkinsonism.⁵ Otherwise, the treatment with neuroleptic drugs appears a trap: withdrawal, or reducing the dose of these drugs exacerbates the hyperkinetic movements and a patient might thus remain on neuroleptic treatment for several years, despite improvement of the psychiatric illness.

Two different dopaminergic receptors have been identified in the striatum: D1 and D2.^{6,7} Most neuroleptic drugs block both. Sulpiride, a benzamide derivative, is a selective antagonist of D2 receptors only. It does not block the D1 receptors, except in high concentrations. This selective action may provide an advantage in tardive dyskinesia.^{2,7-11}

In this study we have therefore evaluated the clinical efficacy of sulpiride in patients on long term neuroleptic treatment and tardive dyskinesia.

Method

Fifteen psychiatric inpatients with tardive dyskinesia (eight female, seven male) were included in the study. Their ages ranged from 37-80 years (mean 67 years). Individual patient

characteristics are listed in the table. All the patients had been treated over the past five years with neuroleptic drugs and there was no change of drugs or their dose during the six months preceding or during the trial.

The duration of the neuroleptic treatment varied between 17 to 42 years (mean 28.3) and the tardive dyskinesia appeared at least several months before the start of the sulpiride treatment. All the patients were treated with anticholinergic drugs.

During the study sulpiride or placebo was added to the daily treatment. A single blind crossover placebo controlled design was used, with the patients receiving placebo or sulpiride in a randomised fashion. The initial dose of sulpiride for all the patients was 100 mg/day orally (50 mg twice a day), and increased weekly by 100 mg/day until a marked clinical improvement, without side effects, was achieved ("optimal dose"). Two weeks after reaching the optimal dose in the sulpiride group (average duration of active treatment with sulpiride was four weeks), the sulpiride was stopped and switched to placebo. At that time patients receiving placebo were switched to sulpiride. Movement patterns and quantity were scored at baseline, at two weeks and two weeks after termination of sulpiride treatment. After completion of this first phase of the study, sulpiride was reintroduced to all patients at the optimal dose for three months and then stopped. The patients were then reassessed nine to 12 months after stopping. The scores were estimated according to a rating scale of tardive dyskinesia and neurological side effects, modified from Gerlach¹² (fig 1). Validation of

Table Patient data, diagnosis and duration of the neuroleptic treatment

No	Sex	Age	Diagnosis, duration of neuroleptic treatment years	Treatment* (last 5 years)**
1	F	77	Schizophrenia 33	H, T
2	F	80	Schizophrenia 40	Ch
3	F	75	Schizophrenia 42	T, Ch, H
4	M	63	Schizophrenia 18	H, Ch
5	M	64	Schizophrenia 34	Ch, L, F
6	M	62	Schizophrenia 30	H, Ch, L
7	F	80	Schizophrenia 28	Ch, L
8	F	62	Schizophrenia 18	T
9	M	64	Schizophrenia 29	H, Ch, L
10	M	66	Schizophrenia 42	Ch
11	M	37	Schizophrenia 15	H, L
12	F	70	Schizophrenia 34	H, Ch, L
13	F	68	Schizophrenia 27	Ch, L, F
14	F	64	Schizophrenia, Epilepsy 18	H, L
15	M	77	Schizophrenia 17	H, T, L

*H = haloperidol; Ch = chlorpromazine; L = levomepromazine; T = thioridazine; F = fluphenazine.

**All patients were also treated with anticholinergic drugs.

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Figure 1 Rate scale of tardive dyskinesia and neurological side effects (modified from Gerlach's rating scale¹²).

Oral tardive dyskinesia	Hyperkinesia Score 0-6 Passive - active		Amplitude Score 0-6 Passive - active		Duration Score 0-3 Passive - active	
Jaw						
Tongue						
Total						

	Score 0-6 Passive - active	
Jaw		
Tongue		
Lips		
Face		
Head		
Trunk		
Upper extr.		
Lower extr.		
Total		

Parkinsonism Score 0-3	
Facial expr.	
Bradykinesia	
Tremor	
Posture	
Arm swing	
Gait rigidity	
Salivation	
Total	

the evaluation of the results was effected according to the Wilcoxon's test.

Results

All the patients completed the trial. Individual patient scores of treatment with sulpiride and placebo are presented in fig 2 and 3. Patients treated with sulpiride showed significantly lower tardive dyskinesia scores ($p < 0.01$) than during placebo treatment. In six patients (1, 2, 3, 8, 13 and 15—table), the improvement was marked; the movements diminished or stopped completely. In six other patients (6, 7, 9, 10, 11 and 14) the improvement was less marked, with movements of body and perioral regions remaining. In two of those patients (9 and 10), doses of sulpiride were not increased due to a slight increase of pre-existing Parkinsonism and in one patient (14), an increase of sulpiride over 600 mg daily, aggravated pretreatment epileptic seizures. In three patients there was no real improvement. Of those, one patient (12) showed slight Parkinsonism on 300 mg daily of sulpiride, and patients 4 and 5 did not benefit from doses of 300 to 600 mg sulpiride daily. Female patients generally responded better than males. Five of the six patients with marked improvement were females.

Side effects were observed in six patients: one patient had convulsions as mentioned above; five patients had slight Parkinsonism:

Figure 3 Tardive dyskinesia scores: body movements.

two had not shown any Parkinsonian signs before the start of the trial. This side effect appeared mostly with doses of 200 to 400 mg of sulpiride without significant difference to the sex of the patients. These Parkinsonian signs did not interfere with overall functioning of the patients.

Treatment with sulpiride was continued for three additional months after the completion of the trial, without side effect after that: treatment with sulpiride was eventually stopped in all the patients. The involuntary movements did not reappear except in four patients. In these patients, the treatment with sulpiride was restarted on the optimal dose found during the trial.

Discussion

It appears from this study that sulpiride reduced abnormal movements of mouth, trunk and limbs in patients with tardive dyskinesia. The improvement was observed even with low doses. Contrary to results in previous publications,^{2,8,9,11} it was not necessary to increase the dose of sulpiride above 600 mg daily. Most of the patients received 200–400 mg daily and the side effects were insignificant.

We found it surprising that in most of the patients, tardive dyskinesia disappeared after a treatment period of three months and in some, the movements did not reappear after sulpiride was stopped. Such results have not been reported before. The question arises, was it the result of loss of hypersensitivity in the dopamine receptors of the striatum or that sulpiride reinstated the normal function of the receptors in these patients?

The wide variation in clinical presentation of tardive dyskinesia is hard to explain by denervation of dopamine receptors alone. Possibly other neurotransmitters like acetylcholine, gamma-amino-butyric acid (GABA), norepinephrine and serotonin are involved in this disorder.¹²⁻¹⁴

Figure 2 Tardive dyskinesia scores: oral dyskinesia.

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