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Effects of tiapride in tardive dyskinesia

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Abstract. Tiapride, a selective D2 dopaminergic receptor blocking agent from the substituted benzamide class, was evaluated in a blind video-controlled trial in 10 psychiatric patients with tardive dyskinesia. There was a significant decrease in dyskinesia with a parallel increase in parkinsonism. This relationship between two opposite effects on movement suggests a common pathophysiological basis lying on a reciprocal hyper- and hypoactivity of the dopaminergic striatal system. Nevertheless, other mechanisms may be involved, for the evolution of individual parkinsonian and dyskinesia scores is not necessarily opposite: the tiapride-induced parkinsonism was generally acceptable and in two cases, the dyskinesia scores were reduced without an increase in parkinsonism. Therefore, more dyskinetic patients have to be evaluated in long-term studies with tiapride, before this drug could be recommended in tardive dyskinesia, when dyskinetic movements become intolerable.

Key words: Tiapride – Tardive dyskinesia – Parkinsonism – Dopamine receptors

Tardive dyskinesia (TD), consisting of involuntary abnormal movements, results from long-term neuroleptic (NL) therapy (Klawans 1973). The exact pathological basis of TD is not known, but the most widely accepted theory is thought to be striatal dopaminergic receptor hypersensitivity following chronic blockade by NL. TD can be temporarily alleviated with classical NL (butyrophenones or phenothiazines), although these may aggravate parkinsonism (Kazamatsuri et al. 1972).

According to the hypothesis of multiple dopaminergic receptors (Kebabian and Calne 1979), classical NL are non-specific blocking agents. Tiapride, an atypical NL of the substituted benzamide class, which selectively blocks D2 dopaminergic receptors (Jenner and Marsden 1981) is known to suppress stereotypies in animals without altering locomotor hyperactivity (Costall and Naylor 1977). Since this drug seems to have behavioural and biochemical particularities regarding dopaminergic function, we evaluated tiapride in TD.

Patients and methods

Ten psychiatric patients (inpatients our outpatients) who were physically healthy and had stable dyskinesia for at least 6 months prior to the study gave informed consent to participate in his study. Individual patient data are shown in Table 1. Medication that was taken at the beginning of the

Table 1. Patient data and drugs used

No.	Sex	Age (years)	Psychiatric diagnosis	Duration of previous neuroleptic treatment (years)	Treatment during investigations		
					Neuroleptic drugs and dose	(mg/day)	Tiapride Final dose (mg/day)
1	F	58	Cyclothymic disorder	15	Propericiazine	15	600
2	M	28	Paranoïd schizophrenia	4	Haloperidol	5	450
3	F	84	Hebephrenic schizophrenia	19			300
4	M	66	Residual schizophrenia	5			600
5	F	63	Paranoïa	6			450
6	F	70	Paranoïd schizophrenia	10	Pimozide	4	600
					Pipamperone	80	
7	F	74	Paranoïd schizophrenia	12	Chlorpromazine	35	600
					Pipamperone	40	
8	F	81	Atypical depression	4			600
9	M	57	Residual schizophrenia	15			600
10	F	85	Paranoïd schizophrenia	10			300
Means		66.6 ± 16		10 ± 4.9			510 ± 120

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study had been in use at the same dosage for at least 3 months and was continued throughout the entire evaluation. No patient was receiving anticholinergics and six patients (nos. 3, 4, 5, 8, 9, 10) were off neuroleptic drugs for 1–3 years owing to their stable psychiatric state.

The placebo and active drugs were administered blindly according to the schedule of 2 weeks of placebo (weeks 1, 2), 4 weeks of tiapride and 2 weeks of placebo (weeks 7, 8). During the final placebo period, patients received the same number of tablets as they had received during the last week of active drug treatment.

Tiapride or placebo was given three times daily. The initial dose was 150 mg/day and increased by 150 mg/day each week until maximum benefit or side-effects developed. If side-effects occurred, the dose was reduced to the level at which the side-effects were resolved. TD and parkinsonism symptoms were recorded weekly at the same time of day on videotape during a 10-min standardized examination. Scoring of symptoms was done on TV screen by the same person, blind to the treatment, at the end of the study after randomisation of each taping session. The rating scale for TD included evaluation of 10 body regions (ocular and peri-ocular region, jaw, lips, tongue, upper trunk, lower trunk, and each of the extremities). Two global judgements, global severity, and incapacity, were included. Scoring ranged from 0 to 4 for each item according to its intensity (0 = none, 1 = minimal, may be extreme normal, 2 = mild, 3 = moderate, 4 = severe). Parkinsonian symptoms were rated using 22 items, each one scored also from 0 to 4 (Lhermitte et al. 1977a).

Statistical analysis of the effects of tiapride on TD and parkinsonism was made using Newman-Keuls test for individual scores, and Student's *t*-test for global scores.

Results

On the whole, tiapride significantly diminished TD ($P < 0.01$) at weeks 3 and 4 of the active treatment period, but at the same time, parkinsonism was significantly increased (Fig. 1). TD and parkinsonism scores were not significantly different between the initial and the final placebo periods. The individual patient scoring (Table 2) showed that the decrease in TD ranged from no change to greatly improved. Among the seven improved dyskinetic patients, five worsened their parkinsonism and one patient (no. 5), whose TD was unchanged, became more parkinsonian.

The decrease in TD scores and the increase in parkinsonian scores was attained with doses of tiapride ranging from 450 to 600 mg/day (mean 510 mg/day). In only one case (patient no. 3), did 300 mg suffice. There was no topographic selectivity with regard to dyskinetic syndrome or its improvement. Besides extrapyramidal symptoms, no other effects were observed.

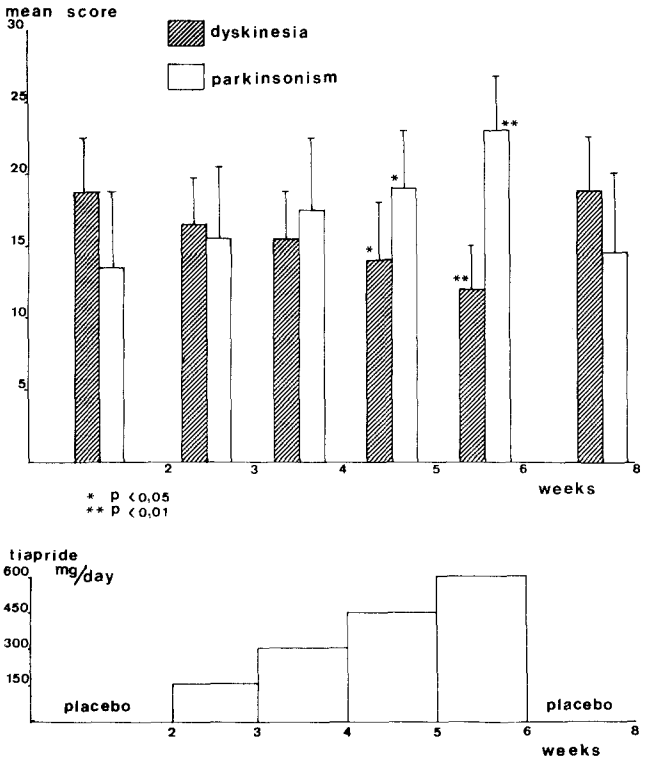

Fig. 1. Mean TD and parkinsonian scores. The TD score during weeks 3 and 4 of tiapride administration is significantly lower than the corresponding placebo scores before and after, whereas the parkinsonian score is significantly higher in the same period

Table 2. TD and Parkinsonian scores

Case	Tardive dyskinesia scores			Parkinsonism scores		
	Placebo[a] before tiapride	Tiapride at 4 weeks	Placebo[b] after tiapride	Placebo[a] before tiapride	Tiapride at 4 weeks	Placebo[b] after tiapride
1	19	17.5	17.75	16	20.5	19.5
2	18.66	9.5*	15.25	3.2	3	2.5
3	21.16	12*	19.5	17.66	33*	14.75
4	16.3	7*	18	18.33	23.5*	14.5
5	13	16.5	14.5	10	20*	13.75
6	20	12.5*	19.5	6.66	15.5*	8
7	29.66	20.5*	28	19.5	30*	20.5
8	17.16	4.5*	19	18	28*	22.25
9	16.5	8*	18.75	3.16	24*	6.5
10	15.9	12	18.25	21.25	20	20.75
Mean ± SD	18.45 ± 4.4	12 ± 4.5	18.85 ± 3.5	13.72 ± 6.5	22.25 ± 4.01	14.35 ± 6.5

[a] Calculated as the mean of three scores (weeks 0, 1, 2 of the initial placebo period)
[b] Calculated as the mean of two scores (weeks 7 and 8 of the final placebo period)
* Individual score = $P < 0.05$ versus the initial placebo period score (Newman-Keuls test)

Discussion

The results of this study suggest that an antidyskinetic effect of tiapride is related to the induction of a hypokinetic, i.e., parkinsonian syndrome. This relation is dose-dependant and evident when the mean of all the patients scores is considered. This effect is similar to those of classical NL derived from phenothiazines and butyrophenones (Claveria et al. 1975; Gerlach and Simmelsgaard 1978; Kazamatsuri et al. 1972). However, in our study, tiapride-induced parkinsonism is generally tolerable and in two patients TD improved without worsening parkinsonism. Whereas such as dissociation is possible but rare with thiopropazate (Kazamatsuri et al. 1972), a classical NL, it appears much more frequently with atypical NL such as oxiperomide (Casey and Gerlach 1980), clozapine (Simpson et al. 1979), and sulpiride (Casey et al. 1979), a drug closely related to tiapride and belonging to the substituted benzamide class.

Many animal experiments may suggest atypical mechanisms of action for the latter drugs: a selective activity on D2 (Kebabian and Calne 1979) or D4 (Sokoloff et al. 1980) dopaminergic sites with in vitro binding studies, a preferential bioavailability for meso-cortical rather than striatal dopaminergic areas (Bartholini 1976), no induced cataleptic effect (Niemegeers and Janssen 1979), and a reduction of apomorphine-induced stereotypy without reverse of locomotor hyperactivity (Costall and Naylor 1977). In man, it is not yet possible to distinguish clinical sub-types of hyperkinetic movements related to different dopaminergic activities: acute studies using dopaminergic agonists and antagonists known to act at D1 and/or D2 dopaminergic binding sites do not show any specific action on movement or endocrinologic function (Pollak et al. 1982; Schachter et al. 1980). Therefore, it seems likely that other factors such as dosage, blood-brain barrier crossing and bioavailability among different brain areas should be the major parameters for NL effects in human studies: for example, (a) the beneficial effect of apomorphine on parkinsonian symptoms can be reversed by sulpiride if a sufficient dose is administered (Pollak et al. 1982) but not by a lower dosage, efficient against emesis (Corsini et al. 1976); (b) substituted benzamides easily prevent emesis or induce hyperprolactinemia through an action on the area postrema and the hypothalamo-hypophysis axis respectively, structures outside the blood-brain barrier, whereas higher doses are necessary to achieve an antipsychotic action (Borenstein et al. 1969); (c) tiapride reduces levodopa-induced peak-dose involuntary movements in parkinsonian patients at the price of an unacceptable increase in parkinsonism (Lees et al. 1979), whereas very low doses have been reported to be beneficial (Lhermitte et al. 1977b).

Since tiapride and other atypical NL are presumed to diffuse unevenly in the central nervous system, it is possible that a return of the dopaminergic hyperactivity to a normal level could be achieved in the structures responsible for TD, without blocking dopaminergic receptors located in other structures. This action is only relatively specific and could not totally avoid a dopaminergic hypoactivity causing parkinsonism, as in the present study.

In this study concerning only 10 patients, tiapride-induced parkinsonism remains tolerable and a pure antidyskinetic effect can sometimes be expected. If this conclusion is achieved with a larger group of patients, tiapride may be considered as one of a few potential treatment in severely disabled TD patients. However, its long-term use has also to be evaluated, because of the risk of tolerance and even aggravation of TD as has been reported during extended treatment with classical NL (Barnes et al. 1983). As tiapride may aggravate parkinsonism, it can be partly assimilated to classical NL and the same risks might be raised for both. Moreover, TD has been induced by metoclopramide, another substituted benzamide (Lavy et al. 1978).

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