

Tiapride in levodopa-induced involuntary movements

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SUMMARY Tiapride, a substituted benzamide derivative closely related to metoclopramide, reduced levodopa-induced peak dose involuntary movements in 16 patients with idiopathic Parkinson's disease. However, an unacceptable increase in disability from Parkinsonism with aggravation of end-of-dose akinesia led to its cessation in 14 patients. Tiapride had no effect on levodopa-induced early morning and "off-period" segmental dystonia. These results fail to support the notion that levodopa-induced dyskinesias are caused by overstimulation of a separate group of dopamine receptors.

It has been suggested that levodopa-induced involuntary movements result from stimulation of a subpopulation of hypersensitive striatal dopamine receptors (Klawans, 1973). This has been supported by the evolution of some dyskinesia sequences which are independent of therapeutic effects (Barbeau, 1975; Lees *et al.*, 1977) and emerging evidence for the existence of separate dopamine receptor mechanisms in the corpus striatum of animals (McLennan and York, 1967; Olson *et al.*, 1972; Cools and Van Rossum, 1976).

The therapeutic possibilities of selective dopamine receptor blockade led to the use of haloperidol (Klawans and Weiner, 1974) and pimozide (Tarsy *et al.*, 1975) in the treatment of levodopa-induced peak dose dyskinesias. Both drugs effectively suppressed involuntary movements but caused an unacceptable increase in disability from Parkinsonism. Another dopamine receptor blocking drug, oxiperomide, in a dose of 5-10 mg daily has recently been reported to possess promising selective action (Bédard *et al.*, 1978) but its sedative effect makes evaluation difficult.

The substituted benzamides (orthopramides) possess many of the behavioural and biochemical properties associated with dopamine receptor blockade, but in contrast to the phenothiazines and butyrophenones they fail to antagonise dopamine-stimulated elevations of striatal adenylyl cyclase activity (Jenner *et al.*, 1978). Thus the short-acting antiemetic metoclopramide in small doses has been used with benefit in the control of levodopa-

induced nausea and vomiting without substantially increasing Parkinsonism (Tarsy *et al.*, 1975), but it does not benefit levodopa-induced dyskinesias. However, the provocation of acute dystonic reactions in 2% of patients (Robinson, 1973) and tardive dyskinesias (Lavy *et al.*, 1978) indicate that metoclopramide can cross the blood brain barrier. Tiapride (N-diethyl aminoethyl methoxy-2-methylsulphonyl-5-benzamide hydrochloride) is closely related structurally to both metoclopramide and the antipsychotic drug sulpiride and in common with these produces almost no cataleptic effects in rats. It reduces perioral dyskinesias induced by the striatal injection of dopaminergic agonists but, unlike other dopaminergic antagonists, does not reverse the dopamine-induced increase in locomotor activity (Costall and Naylor, 1975, 1977). On the basis of this behavioural model, L'Hermitte *et al.* (1977) have reported that carefully titrated doses of tiapride are effective in selectively reducing peak-dose dyskinesias whereas biphasic dyskinesias were aggravated. In the present study the effect of tiapride in Parkinsonism patients with disabling abnormal involuntary movements has been investigated further.

Patients and methods

SINGLE DOSE STUDIES

Five inpatients with idiopathic Parkinson's disease (mean age 64.4 years, mean duration of disease 13.2 years, mean duration of levodopa treatment 5.8 years) agreed to take part. Four of them were considered to have stage 3 disability on the Hoehn and Yahr classification whereas the other was in stage 2. All were experiencing disabling peak dose

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chorea and end-of-dose akinesia despite optimum levodopa dosage. Levodopa was stopped for 12 hours when a baseline assessment was performed by scoring each patient (Columbia Disability Scale) at 15 minute intervals over four to six hours after a single morning dose of levodopa given at 0900; dyskinesia severity was also assessed using a four point rating scale at 15 minute intervals. On the next day each patient was given tiaprìde in a single oral dose 15 minutes before levodopa (three patients were given doses of 25, 50, and 100 mg of tiaprìde, two patients received 50 and 100 mg of tiaprìde) and the patient was again observed and scored over a similar four to six hour period. Three patients were also given chlorpromazine 50 mg after an interval of three days and were similarly assessed.

LONG-TERM STUDIES

Sixteen patients on levodopa, all of whom were experiencing distressing abnormal involuntary movements and disabling fluctuations in bradykinetic disability (14 end-of-dose akinesia, two on-off phenomenon, eight early morning dystonia) agreed to take part. Their clinical features are summarised in Table 1. Parkinsonism and dyskinesia disability were assessed using the Columbia and dyskinesia rating scales, and tiaprìde 12.5 mg twice daily was then introduced in an open manner, the patients being reassessed at intervals of 14 days by the same assessor. The dose of tiaprìde was titrated over several weeks to determine individual optimum requirements. Eight of the patients who considered tiaprìde beneficial (at a time unknown to them and after a minimum period of four weeks treatment) had placebo substituted for active drug.

Table 1 Clinical features of patients

Case	Age (yr)	Sex	Duration of Parkinson's disease (yr)	Disease severity (Hoehn and Yahr stage)	Mean dose levodopa + dopa decarboxylase inhibitor (mg)	Duration of levodopa treatment (yr)
1	53	M	13	2	1000	8
2	71	F	18	4	100	8
3	74	F	10	3	600	9
4	58	M	4	2	700	4
5	69	F	8	3	800	7
6	68	M	10	4	3000*	9
7	60	M	7	2	1000	5
8	65	F	9	3	400	7
9	57	M	14	4	800	8
10	56	M	6	3	600	5
11	59	M	9	2	750	7
12	67	M	11	4	300	2
13	40	M	10	4	1000	9
14	70	M	9	3	750	8
15	75	F	9	3	600	9
16	68	F	3	3	450	2

*Levodopa alone.

Results

SINGLE DOSE STUDIES

Tiaprìde in doses up to 100 mg daily caused no reduction in levodopa-provoked involuntary movements or increase in disability of Parkinsonism. In contrast, two of the three patients who took chlorpromazine 50 mg daily showed some reduction in dyskinesia, but with associated drowsiness and increased Parkinsonism disability.

LONG-TERM EFFECTS

Long-term effects are summarised in Table 2. Peak dose dyskinesias were moderately reduced in 11 patients, slightly reduced in a further three, and unaltered in two. There was no change in the severity of morning and off-period dystonia but end-of-dose akinesia was aggravated. Increase in Parkinsonism disability was marked in two patients, moderate in seven, slight in six, and negligible in one; four patients were obliged to increase their levodopa intake to offset disabling increases in bradykinesia. In a further four cases, increased Parkinsonism provoked by tiaprìde was prolonged, subsiding only gradually four to six weeks after withdrawal. Tiaprìde also increased Parkinsonism disability in three patients before any effect on abnormal involuntary movement was observed. None of the eight patients who thought they were improved on tiaprìde detected a prolonged switch to placebo (nor was this noticed by their relatives). To the observers, two patients had a moderate increase in involuntary movements and three had less disability due to Parkinsonism.

SIDE EFFECTS

Lethargy and tiredness were reported in four

Table 2 *Effect of optimum dose of tiapride*

Case	Optimum tiapride dose (mg)	Reduction in peak dose dyskinesia	Reduction in off-period dystonia	Increase in Parkinsonism	Increase in end-of-dose akinesia
1	25	Moderate	None	Slight	Moderate
2	50	Moderate	None	Slight	None
3	75	Slight	—	Slight	Moderate
4	37.5	None	None	Moderate	Moderate
5	50	Moderate	—	Moderate	Moderate
6	100	Moderate	—	Moderate	—
7	75	Moderate	None	None	None
8	37.5	None	—	Marked	Marked
9	50	Moderate	None	Moderate	Moderate
10	37.5	Slight	None	Moderate	Marked
11	75	Moderate	—	Marked	None
12	37.5	Slight	—	Slight	Moderate
13	50	Moderate	None	Moderate	—
14	37.5	Moderate	None	Slight	Slight
15	12.5	Moderate	—	Slight	Moderate
16	25	Moderate	—	Moderate	Slight

patients. Other side effects included “muzzy headedness” (two), anorexia (one), irritability and confusion (one), and blurred vision (one).

Discussion

In this study all the patients had taken levodopa for several years and were disabled by distressing bradykinetic and dyskinetic oscillations. They had been carefully titrated to the optimum dose of levodopa in combination with carbidopa in small doses distributed evenly throughout the day. On this regimen most had accepted disabling peak-dose involuntary movements as the price for increased general mobility. Differences in patient selection might explain the beneficial effects reported by L’Hermitte *et al.* (1977). It is also possible that a comparable method of assessment of disabilities might have revealed selective effects of tiapride at small doses. The conspicuous aggravation of Parkinsonism, however, with even small doses of tiapride, did not encourage us to embark on more detailed and extended controlled studies as it seemed unlikely that such meticulous attention to dose adjustments would be of practical value.

Early morning and “off-period” segmental dystonia is an increasingly frequent and disabling complication of long-term levodopa therapy (Lees *et al.*, 1977). It is usually confined to the lower limbs but in some patients oromandibular dystonia, spasmodic torticollis, or dystonic hand postures also occur. Although dystonic foot postures were occasionally reported in Parkinson’s disease before the advent of levodopa therapy (Duvoisin *et al.*, 1972) they are seen frequently in patients on long-term treatment, and their frequent cessation on withdrawal of the drug indicates a close link with therapy. Paradoxically, increasing the morning dose of levodopa, or the addition of the dopa-

minergic agonist bromocriptine, tends to ameliorate this disturbance and baclofen, a gamma aminobutyric acid analogue, may also be helpful (Lees *et al.*, 1978). The inability of tiapride to modify this complication suggests that a subpopulation of dopaminergic receptors or other neurotransmitter systems are involved in its pathogenesis. Despite the inability of tiapride to reduce levodopa-induced abnormal involuntary movements selectively it is possible that other components of the long-term levodopa syndrome, such as isolated visual hallucinations, may respond. The recent reports of selective blockade of dyskinesias in patients treated with oxiperomide (Bédard *et al.*, 1978) and the absence of dyskinesias in patients treated solely with bromocriptine, a dopamine receptor agonist (Stern *et al.*, 1979), should encourage further attempts to inhibit this disabling complication selectively.

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