Oxiperomide in tardive dyskinesia

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SUMMARY Tardive dyskinesia can be suppressed by dopaminergic receptor blockers, but often at the cost of a reciprocal increase in Parkinsonism. Oxiperomide, a dopaminergic antagonist that has been shown to reduce levodopa-induced dyskinesias without producing an equal aggravation of Parkinsonism, was evaluated in a blind placebo-controlled trial in 10 patients with tardive dyskinesia. It decreased tardive dyskinesia significantly ($p < 0.01$) without significantly provoking or increasing Parkinsonism. There was no relationship between either tardive dyskinesia or Parkinsonism and eye blinking rates. These results can be interpreted as additional evidence for the existence of more than one population of dopamine receptors involved in controlling extrapyramidal function. Although oxiperomide is only a palliative suppressing agent in tardive dyskinesia, as the symptoms returned when the drug was stopped, it is an interesting agent in the search for selective dopaminergic receptor blockers.

Tardive dyskinesia is a syndrome of involuntary hyperkinetic movements in the oral, facial, limb, and truncal regions. The pathophysiological basis of tardive dyskinesia is thought to involve the development of dopaminergic receptor hypersensitivity in striatal neurones that results from long-term neuroleptic treatment.¹ Increasing the neuroleptic dose can suppress tardive dyskinesia temporarily but may aggravate or precipitate drug-induced Parkinsonism.^{2–4} Oxiperomide, a dopaminergic antagonist, reduced levodopa-induced hyperkinesias—which are clinically similar to tardive dyskinesia—in idiopathic Parkinsonism and other spontaneous dyskinesias without producing incapacitating symptoms of Parkinsonism.⁵ It also inhibited dopaminergic agonist-induced stereotypic behaviour more than the locomotor activity in guinea pigs.⁶ These results from clinical and animal studies are consistent with the hypothesis that there are different types of dopaminergic receptors modulating extrapyramidal function.^{1, 6–9} We, therefore, studied the antihyperkinetic and Parkinsonism effects of oxiperomide in 10 patients with tardive dyskinesia. Furthermore, as eye blinking has been suggested to be associated with extrapyramidal functions,¹⁰ we also assessed eye blink rates during the study.

Patients and methods

Ten psychiatric inpatients who were physically

healthy and had stable tardive dyskinesia for at least six months before the study gave informed consent to participate in this placebo-controlled trial. Pertinent data for each patient are shown in the table.

Medications, if any, that were being taken at the beginning of the study were continued throughout the entire evaluation. Patient 3 received chlorimipramine 100 mg/day and patient 7 received amitriptyline 100 mg/day. Oxiperomide was given in 5 mg tablet doses twice daily, starting at 10 mg/day and increasing weekly by 5–10 mg/day intervals, up to 40 mg/day, until an optimal dose was achieved or side effects developed. Dosage was adjusted individually and in the case of side effects, was reduced to a level at which no side effects occurred. Dosage range was 5–40 mg/day and the final dose is shown in the table.

The placebo and active drugs were administered according to the schedule of four weeks of placebo, six weeks of oxiperomide, and four weeks of placebo. The patients' hyperkinesias were recorded biweekly on videotape during a standardised examination that included sitting, standing, walking, distraction by conversation, and performing voluntary movements of non-affected muscle groups, such as writing. Recordings were made at the same time of day and lasted approximately five minutes. Scoring of symptoms was done by an independent psychiatrist who viewed the videotapes in random order and who was blind to the status of drug treatment. The rating scale for tardive dyskinesia included evalua-

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Accepted 20 June 1979.

Figure Mean hyperkinesia (●—●) and Parkinsonism (○---○) scores during the whole trial. The hyperkinesia score during oxiperomide was significantly lower than the corresponding placebo scores before and after ($p<0.01$, Wilcoxon's test for paired differences). The Parkinsonism score did not change significantly.

tions of the eight body regions of the jaw, tongue, lips, face, head, trunk, and lower and upper extremities. Scores ranged from 0-6 (absent-severe) for each body region assessed during the standardised examination.¹¹ Symptoms of Parkinsonism were rated with a modified Webster scale that comprised eight items: facial expression, bradykinesia, tremor, posture, arm swing, gait, rigidity, and salivation, and

were scored 0-3 (absent-severe).¹² Eye blink rates were determined by doubling the total number of eye blinks in 30 seconds during the same part of the standardised examination.

Statistical analysis of the effects of oxiperomide on tardive dyskinesia and Parkinsonism was made with Wilcoxon's test for paired differences.

Results

Oxiperomide suppressed tardive dyskinesia significantly for the group ($p<0.01$) while having no significant effect on Parkinsonism (fig). The table shows the individual patient scores demonstrating that the decrease in tardive dyskinesia ranged from no change to greatly improved. Parkinsonism scores also varied, but with only minimal aggravation of Parkinsonism in five of 10 patients. A strong dose-response relationship was seen with the decrease in tardive dyskinesia, whereas there was only a trend toward a dose-response relationship with Parkinsonism.

During the second placebo phase, tardive dyskinesia promptly returned to the pretreatment level for the group (fig). However, some patients had an increase in tardive dyskinesia above the pretreatment scores (table, cases 5, 6, 7, 8) while others showed no change or a slight continued improvement from pretreatment scores. Parkinsonism scores returned to pretreatment levels.

Eye blink rates ranged from 2-64/min across the group. However, blinking rates tended to stay the same for each patient throughout the study, and there was no correlation between blinking rates and changes in tardive dyskinesia or Parkinsonism.

Side effects with oxiperomide were troublesome

Table Patient data, drug used, and tardive dyskinesia scores

Case	Sex	Age (yr)	Diagnosis	Duration of illness (yr)	Duration of tardive dyskinesia (yr)	Duration of previous neuroleptic treatment (yr)	Treatment during investigation				Tardive dyskinesia scores		
							Neuroleptic drugs	Oxiperomide			Placebo before oxiperomide	Oxiperomide at 6 wk	Placebo after oxiperomide 4 wk
							Drug	Dose (mg/d)	Duration (yr)	Final dose (mg/d)			
1	M	55	MD	16	5	5	Hal	6	5	30	8	8	8.5
2	M	59	MD	24	4	15				20	7.5	3.5	5.5
3	M	62	MD	32	3	16				20	11	3	10
4	M	63	SS	32	1	18				15	12	4.5	8
5	M	67	SH	44	12	24	CPZ	105	12	20	8	4	10
6	M	68	SP	42	4	22				30	6	0.5	8
7	M	69	DA	4	2	2				10	8	5	9.5
8	M	70	SH	48	4	20				40	11.5	6.5	19
9	F	71	DA	18	5	16	Thior	100	2	10	7.5	7	7
10	F	82	DO	30	3	16	Thior	100	6	5	7	1	7
Means		66.6		29	4.3	15.4				20	8.65	4.3	9.25

MD=manic depressive psychosis; SS=simple schizophrenia; SH=hebephrenic schizophrenia; SP=paranoid schizophrenia; DA=alcoholic dementia; DO=organic dementia; Hal=haloperidol; CPZ=Chlorpromazine; Thior=thioridazine. The differences in tardive dyskinesia scores between "oxiperomide at 6 wk" and placebo before and after oxiperomide are significant ($p<0.01$, Wilcoxon's test for paired differences).

for some patients, but were managed successfully with a dosage reduction. Depression occurred in two patients (cases 4 and 9), two patients (cases 4 and 7) became slightly sedated, and one patient (case 5) had a recrudescence of paranoia, hallucinations, and psychomotor restlessness. There were no anticholinergic side effects of dryness of mouth, blurred vision, or constipation. Laboratory assessments remained within the range of normal throughout the evaluation.

Discussion

The results of this study suggest that the mechanisms responsible for the hyperkinetic symptoms of tardive dyskinesia are not necessarily the opposite of those processes involved in the hypokinetic symptoms of Parkinsonism. The clinically obvious and significant antihyperkinetic effects of the neuroleptic oxiperomide were dose-dependent, whereas the Parkinsonism effects of oxiperomide, although associated with increasing drug doses, were minimal and present in only five of the 10 patients. These findings are consistent with the earlier report that oxiperomide preferentially reduced levodopa-induced hyperkinesias without producing a concomitant aggravation in disability from Parkinsonism.⁵ Although oxiperomide is clearly not a pure antihyperkinetic drug, it does offer a potential advantage in managing hyperkinesias because previous trials with other neuroleptics in tardive dyskinesia²⁻⁴ and levodopa-induced hyperkinesias^{13, 14} have shown an inseparable relationship between antihyperkinetic and Parkinsonism effects.

Our findings are consistent with the hypothesis that there is more than one dopaminergic mechanism in nigrostriatal function that may be selectively involved in the pathophysiology of tardive dyskinesia.^{1, 8-9} Oxiperomide has been shown strongly to inhibit stereotypic behaviour induced by intrastriatal injections of dopamine agonists in rodents with much less inhibition of locomotor activity, suggesting that different mechanisms underlie these behavioural phenomena.⁶

These and other findings have contributed to oxiperomide being classified as a selective antagonist to type 2 dopamine receptors (D-2).¹⁵ We have found similar antihyperkinetic effects with sulpiride,¹⁶ which is also classified as a selective D-2 receptor blocker.¹⁵

While oxiperomide offers a few advantages over other neuroleptics, some effects can be troublesome. The rebound above baseline levels in some tardive dyskinesia symptoms suggests that oxiperomide has the potential to aggravate further the development of tardive dyskinesia. This most probably occurs through its effect of dopamine receptor blockade.

On the other hand, these findings of increased hyperkinesias could be interpreted as spontaneous fluctuations that can be seen in long-term evaluations of tardive dyskinesia. Side effects of drowsiness and depression are manageable by a decrease in dosage, but limit the clinical versatility of oxiperomide. Parkinsonism, although occurring in mild forms, can develop in some patients.

The absence of a correlation between changes in eye blink rate and tardive dyskinesia or Parkinsonism does not clarify the proposed relationship between blinking and dopaminergic function in schizophrenia or tardive dyskinesia.¹⁰ However, the results of this study are consistent with the previous observation of a wide range of blinking rates in patients with tardive dyskinesia.¹⁰ Since disturbances in eye blinking or eye movement are involved in a number of syndromes involving dopaminergic function (Parkinsonism, levodopa-induced dyskinesias, schizophrenia, tardive dyskinesia, blepharospasm, and so on), further investigations between the easily quantifiable eye blink rate and disorders of cognition and movement are worthwhile.

In summary, oxiperomide had an antidyskinetic effect in tardive dyskinesia without producing a reciprocal increase in Parkinsonism. Although some manageable side effects limit the dosage flexibility, oxiperomide offers encouraging leads in the search for dopaminergic antagonists that are selectively antidyskinetic.

This work was supported, in part, by the Danish Medical Research Council, the United States Veterans Administration Career Research Award, NINCDS Grant 14081, and The Grass Foundation. Oxiperomide was generously supplied by Janssen-pharma.

References

- 1 Klawans HL. *The Pharmacology of Extrapryramidal Movement Disorders*. Basel, Karger: 1973.
- 2 Kazamatsuri H, Chien C, Cole JO. The treatment of tardive dyskinesia. II. Short-term efficacy of dopamine-blocking agents haloperidol and thiopropazate. *Arch Gen Psychiatry* 1972; 27:100-3.
- 3 Claveria LE, Teychenne PF, Calne DB *et al*. Tardive dyskinesia treated with pimozide. *Neurol Sci* 1975; 24:393-401.
- 4 Gerlach J, Simmelsgaard H. Tardive dyskinesia during and following treatment with haloperidol, haloperidol + biperiden, thioridazine, and clozapine. *Psychopharmacology* 1978; 59:105-12.
- 5 Bedard P, Parkes JD, Marsden D. Effect of new dopamine-blocking agent (oxiperomide) on drug-induced dyskinesias in Parkinson's disease and spontaneous dyskinesias. *Br Med J* 1978; 1:954-6.

- 6 Costall B, Naylor RJ. Cholinergic modification of abnormal involuntary movements induced in the guinea pig by intrastriatal dopamine. *J Pharmacol Pharmacol* 1975; **27**:273–5.
- 7 Marsden CD. The neuropharmacology of abnormal involuntary movement disorders (the dyskinesias). In: D Williams, ed. *Modern Trends in Neurology*. London: Butterworth, 1975; **6**:141–66.
- 8 Cools AR, Van Rossum JM. Excitation-mediating and inhibition-mediating dopamine-receptors: a new concept towards a better understanding of the electrophysiological, biochemical, pharmacological, functional, and clinical data. *Psychopharmacologia* 1976; **45**:243–54.
- 9 Casey DE, Denney D. Pharmacological characterization of tardive dyskinesia. *Psychopharmacology* 1977; **54**:1–8.
- 10 Stevens JR. Eye blink and schizophrenia: psychosis or tardive dyskinesia? *Am J Psychiatry* 1978; **135**:223–26.
- 11 Gerlach J. A rating scale for tardive dyskinesia. *Dan Med Bull* 1979; **26**:209–45.
- 12 Webster DD. Critical analysis of the disability in Parkinson's disease. *Modern Treatment* 1968; **5**:257–82.
- 13 Klawans HL, Weiner WJ. Attempted use of haloperidol in the treatment of L-dopa induced dyskinesias. *J Neurol Neurosurg Psychiatry* 1974; **37**:427–30.
- 14 Tarsy D, Parkes JD, Marsden CD. Metoclopramide and pimozide in Parkinson's disease and levodopa-induced dyskinesias. *J Neurol Neurosurg Psychiatry* 1975; **38**:331–35.
- 15 Iversen LL. More than one type of dopamine receptor in brain? *Trends in Neuroscience* 1978; **5**:5–6.
- 16 Casey DE, Gerlach J, Simmelsgaard H. Sulpiride in tardive dyskinesia. *Psychopharmacology* 1979; **66**: 73–77.