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Oxypertine in Tardive Dyskinesia: An 8-week Controlled Study

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Summary: In a double-blind placebo controlled trial of oxypertine in the treatment of tardive dyskinesia, 33 patients with chronic schizophrenia received either oxypertine or placebo. At the end of eight weeks, the results showed that oxypertine was superior to placebo at a statistically significant level.

In a previous paper (Freeman *et al*, 1980) we reported a trial of oxypertine versus placebo in 28 patients with tardive dyskinesia (TD) who received medication for four weeks: more patients improved on oxypertine than on placebo (71.4 per cent v. 50 per cent), but the results did not reach statistical significance. The rationale for using oxypertine was that dopamine (DA) is one of the transmitters prominent in the extrapyramidal pathways, and dysfunction in these is thought likely to be a cause of TD. If dopamine-blocking neuroleptics cause TD by making the nigrostriatal pathway supersensitive and so upsetting the delicate inhibitory control of the extrapyramidal system over involuntary movement; the pre-synaptic depletion of dopamine may compensate for the post-synaptic supersensitivity and thus improve the TD. Reserpine (Villeneuve *et al*, 1970) and tetrabenazine (Bandtup, 1961), which have this effect, have been shown to benefit TD, but they also cause depression. Oxypertine is thought to deplete pre-synaptic neuronal stores of neurotransmitters, and there is no evidence that it causes depression.

Oxypertine is an indole derivative, based on the serotonin molecule, with the addition of a phenylpiperazine side-chain which confers lipid-solubility, thus enabling the substance to cross the blood–brain barrier and enhancing its effect on brain amines. It is more potent at depleting brain noradrenaline than brain dopamine, and its antipsychotic effect is approximately equal to that of chlorpromazine. A therapeutic effect on involuntary movements was first reported by Eckmann (1968). When Chien *et al* (1978) compared its efficacy in the control of TD with that of sodium valproate and dimethylaminothanol in a double-blind study, only oxypertine was found to be significantly superior to placebo on all assessments, though the number of patients (17) was too small to prove its value conclusively. Kazamatsuri (1980) has reported an open study of oxypertine in ten chronic patients in a mental hospital, all of whom showed clear evidence of TD. The neuroleptic drugs that were being given before the trial started were continued, and in seven patients there was disappearance of their involuntary movements while they were receiving oxypertine.

In our previous investigation, the neuroleptics that were being given to the patients involved were withdrawn completely, starting two weeks before the oxypertine trial. However, this wash-out period may have been insufficient to achieve a stable baseline of TD following abrupt drug withdrawal: in the present study, therefore, it was decided that there would be no change in patients' neuroleptic regimens during the period of oxypertine treatment.

Method

Trial design

This was a double-blind, between-patient study: subjects received either oxypertine or a matched placebo for an eight-week period.

Subjects

Our sample was selected from among the more cooperative in-patients of a psychiatric hospital (Prestwich Hospital, Manchester), aged between 18 and 70, and of either sex. We requested that their psychiatric condition was stable and such that they were capable of giving informed consent to the study, and that they were diagnosed as having tardive dyskinesia of at least three months' duration prior to the study. Patients were excluded if they weighed below 50 kg or above 110 kg; if they were pregnant; or if they suffered from dementia, other organic brain

disease, or known renal or hepatic dysfunction.

The sample thus selected consisted of 33 patients, all diagnosed as suffering from chronic schizophrenia. All completed the full eight weeks of treatment, 15 of them receiving oxypertine and 18 placebo. One of the patients of the oxypertine group was subsequently excluded from the analysis of results as his weight was found to fall below the limit set by the protocol. Nineteen males and 13 females completed the study, with both treatment groups being balanced in terms of sex. The age-range was 35–70, with no significant differences between the two treatment groups in mean age (oxypertine 56.64, SD 10.36; placebo 58.33, SD 8.05) or mean duration of schizophrenia (oxypertine 24.43, SD 11.88; placebo 27.67, SD 9.85). Similarly, no significant differences were found between the two groups in height or weight.

Medication

The design of the trial allowed for dosage to be varied according to therapeutic effect, the permitted range being between 80 mg (two tablets) and 240 mg (six tablets) daily. For the *first* week, the dosage was 40 mg *t.d.s.* For the *second* week, it was 40 mg *q.d.s.* or *b.d.*, according to therapeutic response or appearance of side-effects in the first week. In the *third* week, those on 40 mg *q.i.d.* had their dose increased to 80 mg *q.i.d.*, if their TD had not responded adequately, provided that agitation or overactivity was not a problem; otherwise, the dose was maintained at the previous level. The dose level achieved by the fourth week was maintained until week 8. The control group received medication in the same manner, but a matched placebo was substituted for oxypertine.

Anticholinergic or antiparkinson drugs, where already prescribed, were maintained throughout the trial. However, no subjects were started on such drugs in the four weeks before the trial commenced, and none were given on a *p.r.n.* basis during the study.

Assessments

Assessment of tardive dyskinesia was made using the Abnormal Involuntary Movements Scale (AIMS) devised by the US National Institute of Mental Health. The AIMS scale subdivides tardive dyskinesia into seven areas:

a. Muscles of facial expression
b. Lips and perioral area
c. Jaw
d. Tongue
e. Upper extremities—arms, wrists, hands, fingers
f. Lower extremities—legs, knees, ankles, toes
g. Trunk—neck, shoulders and hips (including rocking movements)

There are three global judgements:

1. Severity of abnormal movements
2. Incapacitation due to abnormal movements
3. Patient's awareness of abnormal movements

The BPRS (Brief Psychiatric Rating Scale) was used to assess the patient's psychiatric condition. This 16-point scale assesses:

a. Somatic concern
b. Anxiety
c. Emotional withdrawal
d. Conceptual disorganisation
e. Guilt feelings
f. Tension
g. Mannerisms and posturing
h. Grandiosity
i. Depressive mood
j. Hostility
k. Suspiciousness
l. Hallucinatory behaviour
m. Motor retardation
n. Uncooperativeness
o. Unusual thought content
p. Blunted affect

Assessments with AIMS and BPRS were made at regular intervals, as shown in the Fig.

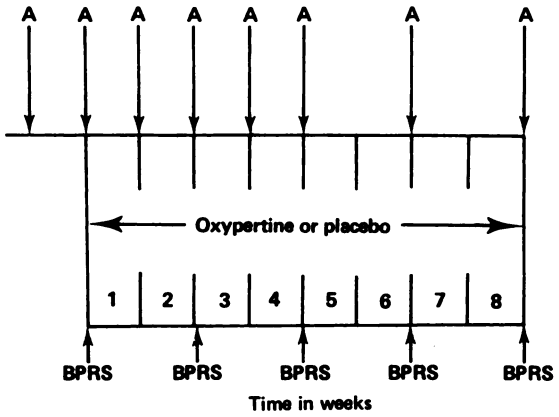

FIG.—A = Abnormal involuntary Movement Scale assessments BPRS = Brief Psychiatric Rating Scale assessments

Results

Abnormal involuntary movements

The results of the assessments of tardive dyskinesia made with the AIM scale at the beginning, mid-point and end of the trial (weeks 0, 4 and 8) are shown in Table I. For each bodily region and global rating specified in the AIMS, we made comparisons between week 0 and week 4, and between week 0 and week 8, of the numbers of affected subjects in each group (oxypertine and placebo). The number affected fell

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TABLE I

Number of subjects affected by tardive dyskinesia, as assessed by the AIMS scale, at the beginning, mid-point and end of the 8-week study. Statistically significant improvements within each group (compared with week 0) are given in brackets; n.s. = not significant

AIM assessment	Oxypertine (n = 14)			Placebo (n = 18)		
	Week 0	Week 4	Week 8	Week 0	Week 4	Week 8
Regional ratings:						
a. Muscles of facial expression	6	0 (P <0.02)	0 (P <0.02)	13	6 (P<0.05)	8 (n.s.)
b. Lips & perioral area	14	4 (P <0.002)	1 (P <0.002)	18	13 (P <0.006)	8 (P <0.003)
c. Jaw	11	3 (P <0.01)	1 (P <0.001)	15	14 (n.s.)	12 (n.s.)
d. Tongue	14	12 (P <0.0001)	10 (P <0.00001)	17	17 (n.s.)	11 (n.s.)
e. Upper extremities	14	6 (P <0.001)	3 (P <0.001)	18	13 (P <0.025)	9 (P <0.01)
f. Lower extremities	14	7 (P <0.01)	4 (P <0.0001)	18	13 (P <0.05)	12 (n.s.)
g. Trunk	11	1 (P <0.001)	1 (P <0.001)	16	13 (n.s.)	11 (n.s.)
Global ratings:						
1. Severely abnormal movements	14	7 (P <0.0002)	4 (P <0.00001)	18	17 (P <0.02)	13 (P <0.01)
2. Incapacitation	2	0 (n.s.)	0 (n.s.)	5	1 (n.s.)	1 (n.s.)
3. Awareness	1	0 (n.s.)	0 (n.s.)	2	1 (n.s.)	0 (n.s.)

TABLE II

Abnormal involuntary movements: statistical comparison of improvements in oxypertine and placebo groups. Improvement was greater with oxypertine in every case

AIMS assessment	Week 0	Week 4	Week 8
Regional ratings:			
a. Muscles of facial expression	n.s.	P <0.05	P <0.01
b. Lips and perioral area	n.s.	P <0.05	P <0.05
c. Jaw	n.s.	P <0.01	P <0.002
d. Tongue	n.s.	n.s.	P <0.02
e. Upper extremities	n.s.	n.s.	n.s.
f. Lower extremities	n.s.	n.s.	n.s.
g. Trunk movements	n.s.	P <0.001	P <0.005
Global ratings:			
1. Severity of abnormal movements	n.s.	P <0.025	P <0.05
2. Incapacitation due to abnormal movements	n.s.	n.s.	n.s.
3. Patients' awareness of abnormal movements	n.s.	n.s.	n.s.

progressively in *every* case. Where a statistically significant improvement was found within a group (chi-squared test), the probability level is indicated in Table I.

For several regions (a, b, e and f) there were statistically significant improvements in both groups, although improvement was always more marked in the oxypertine group. When the two groups were compared directly (Table II), it was found that the improvements in the oxypertine group were significantly greater than those in the placebo group in five of the seven regions specified in the AIMS.

The same effect occurred in the *global rating of severity of abnormal movements:* before the study, all 32 subjects were rated as 'mild' or worse, whereas after treatment, twelve of the oxypertine group and five of the placebo group were rated at 'zero' or 'minimal severity'—a significant improvement in each group (Table I) but significantly *greater* in the oxypertine group (Table II).

Because of the small numbers of patients involved, no statistical significance could be assigned to the improvements in the numbers of patients *incapacitated* by their abnormal movements, nor could any difference be detected between the two groups. The same applied to our measurements of patients' *awareness* of their abnormal movements.

BPRS results

Using the chi-squared test, we found that only the 'mannerisms and posturing' assessment (g) showed statistically significant improvement between weeks 0 and 8. This improvement was recorded in both groups (P <0.001 and P <0.01 for oxypertine and placebo respectively).

Using the Wilcoxon signed rank sum test, we found more differences, probably due to the increased sensitivity of the test. All represented improvement: for the oxypertine group only, in the categories of emotional withdrawal (c) and conceptual disorganisation (d); for both groups, in mannerisms and posturing (g); and, for the placebo group only, in blunted affect (p).

There was no statistically significant difference

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between the oxypertine and placebo groups at any assessment.

Adverse reactions

No patient in either the oxypertine or the placebo group failed to complete the study. Only one patient, in the oxypertine group, experienced any side-effects – drowsiness and a fruity taste in the mouth in week 1, and just drowsiness in weeks 2, 6 and 8.

There were no reports of suspected drug dependence, habituation or tolerance.

Discussion

No general discussion of tardive dyskinesia or its treatment has been attempted in this paper because of the very substantial literature that already exists on these questions. However, the results of the present study have shown that there is a good therapeutic response to the use of oxypertine in the treatment of TD. In most sections of the AIMS assessments, a statistically significant improvement was obtained after four weeks of oxypertine treatment, and this was maintained through to the final assessment four weeks later. The only AIMS assessments not to show statistically significant improvement were patients' awareness of abnormal movements, and their incapacitation due to abnormal movements. However, there were very small numbers in these two groups, and thus the improvements which did occur did not show statistical significance.

There was a very large placebo effect in the AIMS assessments, but nevertheless oxypertine was shown to be greatly superior in reduction of tardive dyskinesia: the improvement in the oxypertine group was significantly better than for the placebo group in all divisions of the AIMS except regions (e) and (f) and global ratings (2) and (3). The large placebo effect in the (e) category (upper extremities) cannot be explained on the basis of our data.

The results from the BPRS did not show differences as clear as those from the AIMS, but sensitive statistical methods detected some improvement. There was, however, no significant difference between the two groups.

Overall, therefore, the results of this trial have confirmed those of our previous study and provide statistically significant support for the view that oxypertine is therapeutically active in controlling tardive dyskinesia. This condition is an extremely complex one, and great caution is needed in the evaluation of any possible methods of treatment, but at the same time, its importance is such that the development of effective therapeutic agents is a matter of the greatest priority for psychopharmacology.

In our previous study, we found that the beneficial effect of oxypertine was confined to those manifestations located from the neck upwards. This time, the pattern of results has been substantially the same, except that improvement in trunk movements was also seen in patients on oxypertine. We also noted in the previous study that patients receiving oxypertine were still improving at week 4, and postulated that further observation might show a pattern of increased statistical significance over placebo; this has generally been confirmed by the results at week 8.

In both studies, placebo improvement has been considerable, and it may well be that a substantial period of observation is needed to demonstrate unequivocally the superiority of a therapeutically active agent. Another possible criticism of this study is that the additional *neuroleptic* effect from administration of oxypertine in addition to the patient's existing neuroleptic medication may have resulted in some temporary improvement in TD. However, it is likely that any such effect would have disappeared before the end of the study period, though the precise time relationships of this effect are not fully known. The possibility cannot be ruled out that oxypertine was blocking the metabolism of other neuroleptics in use, and so increasing their effective levels. We are therefore carrying out a much longer controlled trial in which any such phenomena should have no influence on the results, so that we should find whether there is a likelihood of subsequent re-emergence of TD. This study may also help to establish whether depletion of pre-synaptic dopamine stores by oxypertine is read differently by the post-synaptic neurone from blockade due to increased doses of conventional neuroleptics.

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