Short report

Oxpentifylline in Parkinson's disease

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SUMMARY   The effects of oxpentifylline were assessed in a double blind trial in 11 patients with Parkinson's disease already under treatment. No significant improvement was noted. Eight patients developed involuntary movements or a worsening of movements if already present. The significance of this unexpected finding is discussed.

The modern treatment of Parkinson's disease is with drugs aimed at enhancing dopaminergic activity in the striatum. There is evidence that there are two types of dopamine "receptor" and that one receptor is dependent on cyclic AMP (adenosine 3'5' monophosphate) which acts as a "second messenger."[1-3] The precise role and importance of the two dopamine receptors in Parkinson's disease and in the receptor hypersensitivity phenomena that complicate treatment is at present uncertain but compounds which affect dopamine receptor sensitivity are of great interest and might introduce new possibilities in the management of patients with Parkinson's disease.

Inhibition of cyclic AMP phosphodiesterase raises the intracellular levels of cyclic AMP and should therefore enhance dopaminergic activity. Some experimental work in animals has supported this hypothesis[4 5] although no enhancement of therapeutic benefit was found in patients treated with caffeine (which is a moderate phosphodiesterase inhibitor) and the dopamine agonist bromocriptine.[6] Arbuthnott and his colleagues[7] showed that aminophylline potentiated the effects of apomorphine-induced turning in a denervation animal model (6-hydroxydopamine lesioned rats) but concluded that, as this was the only central stimulant amongst the drugs they tested, the effects observed were related to the known central stimulatory actions of aminophylline rather than to its phosphodiestrase inhibitory activity.

Oxpentifylline is a methylxanthine derivative related to theophylline. This is a widely used group of pharmacological agents of which oxpentifylline is the most recent addition. It has been shown to inhibit phosphodiesterase in a wide variety of tissues[8] including brain.[9] In addition oxpentifylline has been shown to reduce blood viscosity[10] and to increase red cell flexibility, probably as a result of its effects on cyclic AMP in the red blood cell.[11] Oxpentifylline is currently used for the treatment of peripheral vascular disease.

In view of its potent effect on phosphodiesterase, oxpentifylline was examined in various animal models to see whether it would potentiate the effects of dopaminergic agonists (B Costall and R Naylor, personal communication). The only situation in which a potentiation was found was in a "denervation animal model" using rats with 6-hydroxydopamine lesions in the striatum and mesolimbic areas. Arbuthnott and his colleagues[7] had obtained similar results with aminophylline. The present study was designed to investigate whether oxpentifylline had a potentiating effect in patients with Parkinson's disease who were receiving treatment with dopamine agonists. Since oxpentifylline, in common with other xanthine derivatives, has a mild central stimulating effect, an attempt was made to monitor this effect in the study so that any specific potentiation of an anti-Parkinsonian effect could be identified.

Patients and methods

The study was conducted on patients with established Parkinson's disease already receiving

treatment. Criteria for inclusion in the trial were
"on-off" attacks, unsatisfactory response to levo-
dopa or deterioration while on levodopa following
an initial improvement. On admission to the trial
all patients continued on their current therapy
of levodopa alone, levodopa plus a decarboxylase
inhibitor (Sinemet), anticholinergics (either benz-
hexol or orphenadrine), bromocriptine or a com-
bination of these agents. The study had the con-
sent of the ethics committee and the purpose of
the trial was explained fully to all patients who
were asked to participate. Patients with signific-
ant renal, hepatic or ischaemic heart disease were
excluded.

The study was designed as a double-blind,
within-patient comparison of oxpentifylline and
placebo added to their existing therapy. Before
entering the trial each patient was assessed using
the rating scale previously described.[12] Oxpen-
tifylline in large doses has been associated with
upper gastrointestinal side effects, notably nausea
and epigastric discomfort. All patients were there-
fore initially titrated to a maximum tolerated
dose, up to 1200 mg a day in divided doses, over
the course of two to six weeks. Patients were
then randomly allocated to treatment with either
oxpentifylline, in the maximum dose achieved,
or placebo. The drugs were presented in film
coated tablets matched for size, shape and colour
and patients took each drug for six weeks and
were then crossed over to the alternative treat-
ment.

The patients were assessed at two-weekly
intervals by two independent observers, one
(RGA) "blind" who completed the clinical assess-
ment and the other (JAT) who undertook the
routine supervision of patients and recorded any
adverse effects.

In addition to the clinical assessment an objec-
tive measure of the effects of the drugs on central
(cortical) arousal was carried out by measuring
critical flicker fusion threshold (CFFT) using the
Leeds Psychomotor Tester. This apparatus uses
four light emitting diodes and the frequency at
which the diodes cease to be seen flickering and
appear stable is the CFF threshold. Using the
psychophysical method of limits for ascending
and descending scales[13] the mean value of six
measures (ascending and descending) of the
threshhold is used as the performance level.
CFFT has been shown to be a useful and sensi-
tive measure of CNS arousal.[14 15] In addition
each patient was furnished with a diary card
which they filled in daily recording abnormal
movements, bradykinesia and frequency and
severity of "on-off" attacks if present.

Results

Thirteen patients were included in the trial. Two
patients were withdrawn during the dose titration
period on oxpentifylline; one developed severe
nausea, and the other complained of nausea and
developed dyskinetic movements. The remaining
11 patients completed the trial and their results
are summarised (see table). Of these patients,
two complained of transient nausea which did
not persist but no other significant side effects
were encountered. Ten of the 11 patients were
able to tolerate the maximum doses of oxpen-
tifylline (1200 mg/day). This was a small sample
of patients and as can be seen the results were
variable. Although some patients were improved
by the addition of oxpentifylline to their existing
therapy, this followed no clear pattern and was
not statistically significant (using the Wilcoxon
signed rank test). However, eight patients experi-
enced abnormal involuntary movements, or a
striking worsening of movements if previously
present, while on oxpentifylline. Dyskinetic
movements were not altered in patients number
2 and 11 while on the active agent, and patient
number 10 showed a reduction in respect to her
dyskinesias. The latter was the only patient being
treated with bromocriptine during the trial
period. The significance of these results is dis-
cussed below. Oxpentifylline did not produce any
significant change in critical flicker fusion thres-
hold either in individual patients or when the
group was considered as a whole.

Discussion

The results of this investigation demonstrate no
change in the therapeutic response to levodopa
either subjectively or objectively when oxpen-
tifylline was added to the treatment regimen.
There was, however, a significant increase in the
incidence of abnormal involuntary movements
during treatment with oxpentifylline. This drug
therefore appears to have a differential effect on
these two manifestations of levodopa treatment.

Oxpentifylline, in common with other xanthine
derivatives, might be expected to have some
degree of central stimulating effect.[16] However
the results of the critical flicker fusion threshold
test reveal no significant change in levels with
oxpentifylline. Our patients did not report any
symptoms that might be interpreted as indicative
of an alerting or stimulating effect (insomnia,
tremor, nervousness or agitation). We believe
therefore that at the doses used the effects of
oxpentifylline which we observed are not attribut-

Table   *Clinical details and response to oxpentifylline*

Patient	Sex	Age (yr)	Length of history (yr)	Drugs on admission to trial	Oxpentifylline (mg/day)	Functional capacity	Rigidity	Hypokinesia	Abnormal movements
1	M	66	13	Sinemet (275) ½ tds Benzhexol 2 mg bd	1200	0	+	0	−
2	M	66	14	Sinemet (275) ½ 5 daily Orphenadrine 50 mg tds Amantadine 100 mg tds	1200	+	+	0	0
3	F	68	7	Sinemet (275) ½ 7 daily Benzhexol 2 mg tds	1200	0	0	+	−
4	F	66	6	Sinemet (110) 1 tds Benzhexol 2 mg tds	1200	0	0	+	−
5	F	52	10	Sinemet (110) ½ tds	1200	0	−	−	−
6	F	67	12	Levodopa 500 mg 8 daily	1200	+	+	+	−
7	F	57	6	Sinemet (110) 1 tds Orphenadrine 50 mg tds	1200	+	0	+	−
8	M	51	7	Sinemet (110) ½ bd Benzhexol 2 mg qds	1200	−	0	−	−
9	F	42	10	Sinemet (275) 1 qds Benzhexol 2 mg qds	1200	0	+	+	−
10	F	48	14	Sinemet (110) ½ 7 daily Benzhexol 2 mg tds Bromocriptine 2·5 mg 6 daily	1200	−	−	+	+
11	M	75	6	Sinemet (110) 3½ daily Benzhexol 5 mg bd	900	0	0	0	0
Significance						N.S.	N.S.	N.S.	$p < 0.01$

+ Improved, − Worsened, 0 No change. N.S. Not significant.

able merely to a non-specific central stimulating effect. Acting via catecholamine sensitive adenylate cyclase[17] oxpentifylline may cause sympathetic stimulation. However animal work and previous studies in human subjects[18] as well as prolonged usage in clinical practice have not been associated with tremor or abnormal movements. If the abnormal movements observed in our study derived from a noradrenergic mechanism they must therefore only develop in patients with the specific neurochemical defect of Parkinson's disease. There is no published evidence to suggest that dopa-induced dyskinesia is mediated via a noradrenergic mechanism.

There is considerable evidence that dopamine receptors may be differentiated into two types depending on their association with adenylate cyclase. Thus the D1 receptor causes the accumulation of cyclic AMP through the mediation of adenylate cyclase whereas in the D2 receptor no such involvement of adenylate cyclase can be demonstrated.[19] In the striatum three dopamine receptor groups can be identified: (a) presynaptic receptors which are unassociated with adenyl cyclase, (b) post synaptic receptors also unrelated to adenyl cyclase, (c) post synaptic

receptors associated with dopamine adenyl cyclase.[20] Oxpentifylline is only to be expected to have an action on the post synaptic receptor (c) which is associated with adenyl cyclase. The increase in abnormal involuntary movements of patients treated with oxpentifylline suggests that this hypersensitivity effect of dopa treatment (and treatment with synthetic dopamine agonists such as bromocriptine) may be partly or wholly dependent on this D1 receptor site in the striatum. However this conclusion is in direct conflict with the evidence presented by Price and his colleagues.[21] In their study of tiapride in the treatment of Parkinson's disease evidence is presented to suggest that the D2 receptor is responsible for dopamine induced dyskinesia.

Dopamine agonists that have been shown to be clinically useful and active in vivo have been shown to have little agonist activity on striatal adenyl cyclase.[22] [23] It is thus likely, although unproven, that the motor effects of dopa in Parkinson's disease are mainly dependent on the D2 receptor. Our results using oxpentifylline during treatment of patients with Parkinson's disease with levodopa would be compatible with this hypothesis.

Only one of our patients was taking bromocriptine during this trial but her response to treatment was different from all the other patients. Thus her symptoms and signs of Parkinsonism deteriorated but there was no increase in abnormal movements. Clearly no conclusions can be drawn from this single case but the response was similar to that reported by Kartzinel and his colleagues.[6] This patient had probably not developed dopamine hypersensitivity at the D1 receptor the potentiation of which by oxpentifylline would have resulted in abnormal movements and there is some evidence to suggest that such hypersensitivity is less common in patients treated with bromocriptine.[24][25] But at the same time the beneficial effects of bromocriptine were reduced by the potentiating effect of oxpentifylline either at the D1 receptor or elsewhere.

These results raise the important possibility of utilising the differential action of the two dopamine receptor types to avoid some of the late hypersensitivity phenomena (dyskinesias, dystonias and possibly "on-off" attacks) of dopa treatment. If a selective blocker of the D1 receptor could be identified—or a selective D2 agonist—these side effects might be avoidable.

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