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Amphetamines in the treatment of Parkinson's disease

J. D. PARKES, D. TARSY[1], C. D. MARSDEN, K. T. BOVILL, J. A. PHIPPS, P. ROSE, AND P. ASSELMAN

From the Parkinson's Disease Clinic, King's College Hospital, London

SYNOPSIS Twenty-two patients with Parkinsonism were treated with levoamphetamine and 12 of these with dextroamphetamine. Levoamphetamine resulted in a significant improvement in disability from Parkinsonism, although the reduction in total disability, tremor, akinesia, and rigidity scores was slight (*ca* 20%). Dextroamphetamine in lower dosage also reduced disability by some 17%. The most disabled patients, including those also on levodopa, showed the greatest response to amphetamines. Previously, amphetamines have been reported to be a selective treatment for the oculogyric crises of post-encephalitic Parkinsonism. Amphetamines are thought to cause the release of catecholamines from central neurones. Their action in Parkinson's disease may be limited because of pre-existing striatal dopamine deficiency. Side-effects of amphetamines, anorexia, and CNS stimulation are different from those caused by levodopa in patients with Parkinson's disease.

Amphetamines were widely used to treat patients with post-encephalitic Parkinsonism in the 1930s (Finkelman and Shapiro, 1937; Davis and Stewart, 1938). Subjective improvement in mood and energy was often considerable, with reversal of disordered sleep rhythms, but there was little or no objective improvement in the symptoms of Parkinsonism. Rigidity was sometimes slightly lessened, but akinesia and tremor were not altered. The total reduction in disability was probably less than that obtained from anticholinergic drugs (Solomon *et al.*, 1937). Amphetamines, however, had a dramatic effect on the oculogyric crises of post-encephalitic Parkinsonism, which were often abolished (Davis and Stewart, 1938; Matthews, 1938). There was no evidence that patients with post-encephalitic Parkinsonism developed tolerance or became addicted to amphetamines (Solomon *et al.*, 1937), but because of the very slight therapeutic effect, and the possibility of drug misuse, these compounds have rarely been used in the treatment of idiopathic paralysis agitans (Calne and Reid, 1972). Birkmayer and Hornykiewicz (1962) gave amphetamines intravenously to Parkinsonism patients with little clinical improvement but there have been few further trials of amphetamines in Parkinson's disease since the discovery of striatal dopamine deficiency in this condition. Amphetamines, however, might have some therapeutic effect in Parkinsonism, since, like levodopa, they potentiate dopamine mechanisms in the striatum (Stein, 1964; Glowinski and Axelrod, 1965; Randrup and Munkvad, 1970).

Dextroamphetamine and levoamphetamine in low doses will release dopamine and noradrenaline from neurones containing these catecholamines (Carlsson, 1970). D-amphetamine is more potent in this respect, as well as inhibiting dopamine reuptake in striatal dopaminergic neurones (Harris and Baldessarini, 1973; Thornburg and Moore, 1973). Amphetamines and levodopa both reverse reserpine akinesia in rodents (Carlsson, 1970).

These considerations called for further study of amphetamines in Parkinson's disease. We describe here a double-blind controlled trial of levoamphetamine treatment and an open trial to determine the effects of dextroamphetamine.

METHODS

PATIENTS Twenty-seven patients with idiopathic Parkinson's disease and one with post-encephalitic Parkinsonism attending the Parkinson's disease

[1] Present address: Department of Neurology, Boston University School of Medicine, Boston, Mass., U.S.A.

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clinic of King's College Hospital were invited to take part in the trial. Patients were included irrespective of age, sex, severity; or duration of disease, but excluded if they had any history of cardiac illness, abnormal electrocardiograph, or a resting diastolic blood pressure above 100 mmHg. Six patients did not complete the trial because of side-effects from amphetamines or placebo. The remaining 22 patients completed the trial and are described below. Eleven were male and 11 female, aged from 51 to 82 years (mean 63). The duration of disease was from three to 24 years (mean 9.9) except for the single patient with post-encephalitic Parkinsonism. Three patients had had a thalamolysis, bilateral in two. Thirteen were mildly disabled, seven had a moderate degree of disability, and two were largely chair-bound. Five had involuntary movements as a result of levodopa treatment.

MEDICATION Three patients were taking no other treatment. Fifteen were established on stable levodopa dosage (500 mg–4.5 g daily, mean 2.8 g), 16 were taking amantadine, 200 or 300 mg daily, and 10, anticholinergic drugs. These were continued unchanged throughout the trial of amphetamines. The daily dosage of levoamphetamine was 50 mg, and dextroamphetamine, 15 mg. These dosages were decided on the basis of previous experience in patients with narcolepsy in which they produced increased alertness with few side-effects (Parkes *et al.*, 1974).

DESIGN OF TRIAL Each patient was given either amphetamine or placebo capsules for two weeks followed by the alternative preparation for a further two weeks. Random allocation to the treatment period was made. Levoamphetamine was given twice daily, 30 mg at 8 a.m. and 20 mg at 12 midday in capsules identical in appearance with those containing placebo. Twelve patients who had not developed any side-effects on either levoamphetamine or placebo were given dextroamphetamine, 10 mg at 8 a.m. and 5 mg at 12 midday, for a further two week period. Patients were examined at the beginning of the trial and after two, four, and (for those patients on dextroamphetamine) six weeks by examiners not aware of whether patients were taking active medication or placebo. Patients were evaluated for disability, tremor, posture, akinesia, and rigidity by a scoring system previously described (Marsden *et al.*, 1973).

Because the changes in scores produced by placebo or active drug were not normally distributed, pair differences were analysed for statistical significance using the sign test and Wilcoxon's test for paired observations.

TABLE 1

PATIENTS' SUBJECTIVE RESPONSE TO LEVOAMPHETAMINE, DEXTROAMPHETAMINE, OR PLACEBO

	No.	*Better*	*Worse*
Placebo	22	0	1
Levoamphetamine	22	8	1
Dextroamphetamine	12	5	0

RESULTS

OBSERVERS' SUBJECTIVE IMPRESSION The side-effects of amphetamine treatment were common and it was therefore not always possible to preserve the double-blind nature of the trial. The clinical impression was that, apart from a modest improvement in three patients, little or no change occurred in the severity of the disease. No patient showed a marked or dramatic response and, at the conclusion of the trial, only two patients were continued on amphetamine treatment, both of whom appeared more cheerful on this. The severity of involuntary movements increased in two patients on levoamphetamine.

TABLE 2

RESPONSE IN PARKINSON'S DISEASE TO AMPHETAMINES AND PLACEBO

	Total disability	*Tremor*	*Posture*	*Rigidity*	*Akinesia*
Pre-trial scores	30.5 ± 3.3	2.4 ± 0.6	2.4 ± 0.8	2.8 ± 0.6	8.1 ± 0.9
Placebo	27.8 ± 3.8	1.9 ± 0.4	2.6 ± 0.6	2.7 ± 0.6	6.6 ± 0.9
Levoamphetamine (50 mg)	22.1 ± 3.1†	1.2 ± 0.3*	1.6 ± 0.5	1.6 ± 0.5*	6.2 ± 1.1
Dextroamphetamine (15 mg)	23.0 ± 4.5	1.7 ± 0.6	2.2 ± 0.7	2.4 ± 0.6	6.6 ± 1.7

Mean total disability scores and sub-scores before treatment, on placebo and L- and D-amphetamine.
Difference from placebo significant * $P < 0.05$, † $P < 0.01$, Wilcoxon's paired rank test.

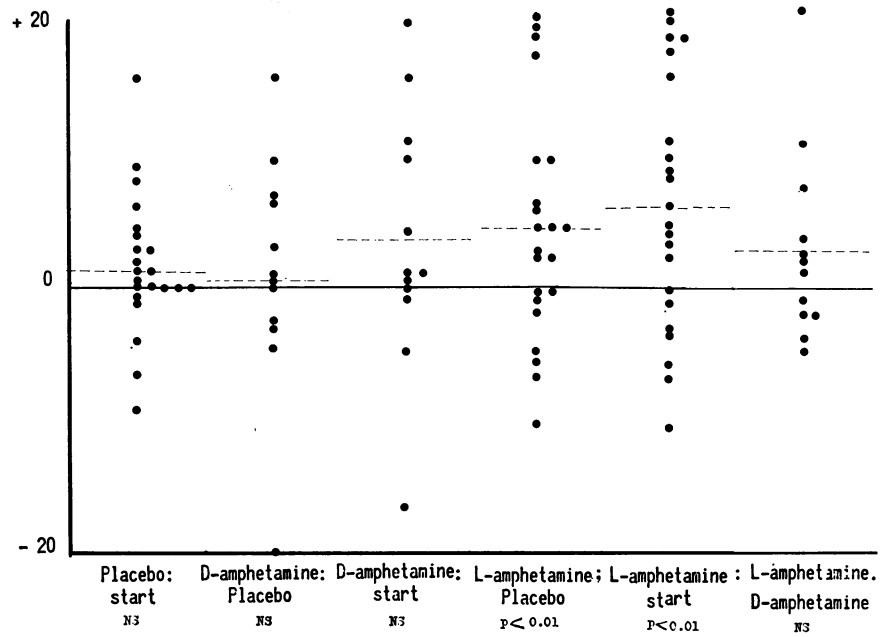

FIG. 1 *Placebo and amphetamine periods compared with start of trial and one another. Mean change in score is shown by a broken horizontal line.*

PATIENTS' SUBJECTIVE IMPRESSION The patients' preferences, in response to direct questioning, for levoamphetamine, dextroamphetamine, or placebo are shown in Table 1. Eight patients described benefit from levoamphetamine, two with reduced tremor, and one with lessened rigidity, while the others felt generally better ($P > 0.05$, sign test). Five of these patients described improvement with dextroamphetamine, one with reduced tremor. In contrast, side-effects from levoamphetamine led to four patients stopping the trial.

EFFECT OF TREATMENT ON SCORES Scores at the start of the trial were compared with the scores after placebo treatment. No significant differences were found. Mean total disability score was reduced during levoamphetamine treatment, as compared with placebo by 5.7 score units, an improvement of 20.5% ($n=22$, $t=45$, $P<0.01$). During dextroamphetamine treatment mean total disability score was reduced by 4.8 or 17.3% ($n=12$, $t=24$, NS). Both isomers also resulted in a reduction of mean tremor, rigidity and posture scores (Table 2). The improvement in tremor and rigidity scores after levoamphetamine, as compared with scores on placebo, was slight but statistically significant at 5% level ($n=18$, $t=37$, $P<0.05$; and $n=20$, $t=44.5$, $P<0.05$; respectively).

FACTORS INFLUENCING RESPONSE TO TREATMENT The three patients taking levoamphetamine as the single treatment showed an insignificant reduction in total disability score compared with placebo (mean scores: no treatment 21, placebo 21, levoamphetamine 18). The percentage reduction in mean score of the 15 patients on levodopa, with additional levoamphetamine, was greater than that of those patients not on levodopa. The first group was initially more disabled. However, the difference in response between the two groups was not statistically significant.

The 16 patients on amantadine, 13 also taking levodopa, had a mean total disability score at the commencement of the trial of 30, on placebo 29, and on levoamphetamine 24. This response did not differ significantly from patients not on amantadine. The four most disabled patients all

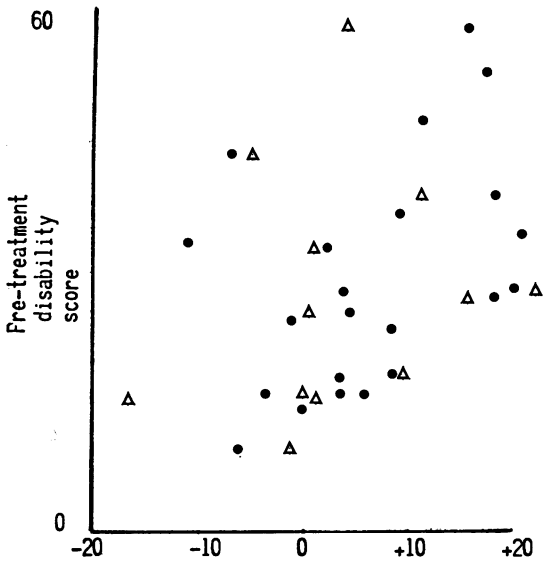

FIG. 2 *Relationship between changes in individual total scores (ordinate) after* L- *and* D-*amphetamine treatment, and initial disability. For* L-*amphetamine, r=0.6, P<0.01; for* D-*amphetamine, r=0.26, NS. ● = L(⁻)amphetamine. △ = D(⁺)amphetamine.*

showed a considerable improvement with levoamphetamine, while the four least disabled did not respond. The relationship between initial disability and amphetamine response, is shown in Fig. 2 (in the case of levoamphetamine, r=0.6, P<0.01). The patients with a previous thalamolysis all responded to levoamphetamine. The result of treatment did not show a significant relationship with the patient's age, sex, or duration of disease. The patient with post-encephalitic Parkinsonism had a slight reduction in total disability score while on levoamphetamine (28%) and oculogyric crises did not occur on this medication. Nine of 12 patients given dextroamphetamine had a reduction of total disability score on this treatment as compared with placebo, and all but one of these patients responded to both dextro- and levoamphetamine.

SIDE-EFFECTS Side-effects from levoamphetamine prevented continued treatment in four patients, palpitations occurring in three and

TABLE 3

NUMBER OF PATIENTS REPORTING SIDE-EFFECTS DURING LEVOAMPHETAMINE, DEXTROAMPHETAMINE, AND PLACEBO TREATMENT

Side-effect	*Placebo (22)*	*Levoamphetamine (22)*	*Dextroamphetamine (12)*
Palpitations	0	2	0
Insomnia	0	4	0
Jitteriness	0	1	0
Headaches	0	2	2
Hallucinations	0	2	0
Tremor worse	0	2	0

headache in two. Two patients on placebo described malaise. In 10 of the remaining patients less severe side-effects occurred (Table 3). In the 12 patients without side-effects on levoamphetamine and subsequently given dextroamphetamine, only two complained of headaches and no other side-effects were reported. Four patients on levoamphetamine complained of insomnia, two described a definite elevation of mood, and lesser degrees of well-being with more drive occurred in seven.

Mean systolic and diastolic blood pressures at the start of the trial were 137 and 88 mmHg respectively: on placebo, 132 and 81; on levoamphetamine 128 and 80; and on dextroamphetamine, 135 and 85 mmHg.

DISCUSSION

Dextro- and particularly levoamphetamine given for a short time cause a slight reduction in the disability of patients with Parkinson's disease, although side-effects are common, and both isomers are of little value in routine treatment. Benzedrine (D, L-amphetamine) was first used for its alerting effect in patients with post-encephalitic Parkinsonism, many of whom were somnolent. This treatment caused a subjective improvement in energy and mood, but little objective change in signs of Parkinsonism (Solomon *et al.*, 1937), although some patients showed a slight lessening of rigidity comparable with that produced separately by anticholinergic drugs. The combination of these with benzedrine resulted in considerable subjective improvement in most patients. Similar results were described by Davis and Stewart (1938). Patients showed

little improvement in the motor features of Parkinsonism, but oculogyric crises were abolished or reduced in all those with this symptom. Other drugs that stimulate the central nervous system have not proved of greater value than amphetamines in Parkinsonism, although methylphenidate given intravenously may reduce rigidity in some patients (Halliday and Nathan, 1961).

The failure of amphetamines to produce much improvement in Parkinson's disease may be due to the fact that these drugs cause the release of endogenous neuronal catecholamines, as well as blockade of catecholamine re-uptake. Both these effects depend on neuronal stores of dopamine, known to be depleted in Parkinson's disease. Levodopa in contrast appears to be converted to dopamine largely by extraneuronal aromatic acid decarboxylase, and dopamine may have a direct post-synaptic effect in the striatum in spite of degeneration of nigrostriatal dopamine neurones. An increase in cerebral dopamine synthesis as the result of levodopa treatment may be necessary in patients with Parkinson's disease before an additional effect of amphetamines is apparent; patients on levodopa had the greatest benefit from amphetamines in the present trial. Amphetamines have no effect in reversing reserpine akinesia in animals who are also treated with alpha-methyl-para-tyrosine, a drug which prevents the synthesis of catecholamines. However, the activity of D-amphetamine may be restored by a very small dose of dopa which is ineffective *per se* (Carlsson, 1970).

Choreiform and other movements are common side-effects of levodopa treatment but are rarely produced by amphetamines, although orofacial movements, tics, and seemingly compulsive motor behaviour may occur in amphetamine addicts as well as in hyperkinetic children on chronic high amphetamine dosage (Ashcroft *et al.*, 1965; Mattson and Calverley, 1968; Rylander, 1972). This difference may be related to the different diseases treated, and to a greater effect of levodopa than amphetamines on cerebral dopamine systems. Amphetamines increased levodopa-induced movements in two patients. Nausea and vomiting may occur during initial treatment in most patients given levodopa but are less common side-effects of amphetamine, although both drugs cause anorexia. The central stimulant effects of amphetamines, in particular insomnia and jitteriness, do not occur to the same extent with levodopa. Stimulant effects may be partially due to potentiation of central noradrenaline, rather than dopamine, mechanisms by amphetamines (Stein, 1964), whereas levodopa has little effect on cerebral noradrenaline concentration (Everett and Borcherding, 1970).

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