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# Piribedil in Parkinson's Syndrome: A Clinical Study

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*Summary.* The effect of a new dopamine receptor stimulating agent, piribedil (ET 495), was studied in 10 patients with Parkinson's syndrome, who had had no or a poor response to previous L-DOPA treatment, or had displayed marked side effects during L-DOPA administration. Piribedil produced significant improvement of the functions of activity of daily living (ADL), and appeared to have a preferential effect on parkinsonian tremor. However, treatment was difficult to control primarily because of severe psychiatric side effects.

*Key words:* Parkinson's syndrome, dopamine receptor stimulating agent, clinical trial, piribedil, L-DOPA.

From the results of animal studies, Carlsson (1959) suggested that dopamine (DA) had a role in extrapyramidal function and in neurological disorders, such as Parkinson's syndrome. Today, the aromatic amino acid precursor of DA, L-3, 4-dihydroxyphenylalanine (L-DOPA), is widely accepted as the basic treatment for Parkinson's disease. The antiparkinsonian actions of L-DOPA are very probably due to the activation of neostriatal dopamine receptors by DA formed from the administered L-DOPA (for review see Barbeau and McDowell, 1970; McDowell and Fletcher, 1972). Consequently, the search for new antiparkinsonian drugs has been concentrated on the development of drugs acting more or less selectively on central DA receptors.

Apomorphine has been shown directly to activate central DA receptors (Andén *et al.*, 1967; Ernst, 1967), and to be of some value, although only for a short time, in the relief of akinesia, rigidity and especially tremor in parkinsonian patients (Schwab *et al.*, 1951; Cotzias *et al.*, 1970; Castaigne *et al.*, 1971; Duby *et al.*, 1971; Strian *et al.*, 1972). Recently, a new DA-receptor stimulating agent has been discovered, with a longer duration than apomorphine, 1-(2-pyrimidyl)-4-piperonylpiperazine (ET 495, piribedil; Corrodi *et al.*, 1971; 1972). It had previously been used as a vasodilator (Regnier *et al.*, 1968).

In the present study the effect of piribedil on Parkinson's syndrome has been investigated in ten patients who showed no or a poor response to previous L-DOPA treatment, or displayed marked side effects during L-DOPA administration.

## *Patient and Methods*

The clinical study was performed on ten patients with idiopathic Parkinson's syndrome, six women and four men, aged 73.0 ± 9.0 years (mean ± S.D.). The duration of their symptoms was from 4 - 33 years and nine of the ten had advanced handicaps (Table 1). Three patients had previously undergone stereotactic surgery, but with persistent effect on tremor in only one patient (K.L.).

Eight patients were on L-DOPA treatment, but the effect of the treatment was rather poor. Doses of L-DOPA and the duration of treatment are shown in Table 1. Two patients had been treated previously with L-DOPA, but it had been stopped because of side effects, i.e. postural hypotension (H.D. and K.L., Table 1). Nine of the patients had been on constant antiparkinsonian therapy (see Table 1) for a long time, during which they had displayed a constant clinical picture of their parkinsonian symptoms. Thus, the performance level at the start of the present study provided a stable base line from which drug-induced changes could be measured.

Piribedil, 1-(2-pyrimidyl)-4-piperonylpiperazine (ET 495, Trivastal®, Serviér, kindly supplied by ASTRA AB), was given orally as tablets of 20 mg, three times daily for one week. Thereafter, the dose was increased by 20 mg every week until side effects occurred, or the maximum daily dose of 240 mg was reached.

The symptoms of tremor, rigidity and hypokinesia were rated according to a four-point scale from very severe to absent. Hypokinesia was considered

severe when voluntary hand movements or walking were impaired. Ridigity was considered severe when continuous muscular resistance during passive extension of the elbow, wrist or knee joints could only be overcome by a certain degree of force. Tremor was evaluated as severe when it obviously interfered with voluntary motor actions. The patients were investigated once a week by a physician and by a physio-therapist in order to evaluate the clinical picture and the functions of activity of daily living (ADL). The ADL-functions, scored according to a four-point scale described earlier (Granerus *et al.*, 1972), ranged from 0 (absence of parkinsonian symptoms during most of the day) to 4 (complete handicap). Blood pressure and heart rate were followed daily and electrocardiogram was recorded once a week.

The following laboratory tests were performed at regular intervals during treatment; blood - Hb, WBC and differential count and thrombocytes; serum - electrolytes, creatinine, bilirubin, alkaline phosphatase, thymol turbidity, GOT and GPT.

Statistical comparisons were performed by the nonparametric Wilcoxon test for paired data and the Mann-Whitney U-test (Siegel 1956).

Table 1. Therapeutic and side effects of treatment with piribedil in 10 patients suffering from parkinsonism

| Case | Sex | Age (years) | Duration of parkinsonism (years) | Antiparkinsonian treatment | | | | | | | Treatment with other drugs | | Therapeutic effects on parkinsonian symptoms | | | | | | | | Side effects | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Piribedil maximum dose (mg/day) | Piribedil dose (mg/day) | Duration of treatment with piribedil | | L-DOPA dose (g/day) | Duration of L-DOPA treatment (months) | Anticholinergic drugs | Tricyclics | Neuroleptics | ADL-group[a] Without | ADL-group[a] With piribedil | Tremor Without | Tremor With piribedil | Rigidity Without | Rigidity With piribedil | Hypokinesia Without | Hypokinesia With piribedil | Mental symptoms | Vestib. nerve lesion | Alk. phosphatase | SGOT, SGPT | Nausea | Flushing | Hypotension | Heavy legs |
| A.A. | M | 60 | 13 | 100 | 0 | | 5d | 6.0 | 52 | + | + | 0 | 3 | 1 | 3 | 0 | 2 | 1 | 3 | 1 | + | – | – | – | – | – | – | – |
| M.S. | M | 68 | 10 | 220 | 0 | 3m | 14d | 4.6 | 50 | + | + | 0 | 4 | 4 | 2 | 2 | 4 | 4 | 4 | 4 | + | – | + | – | – | – | – | – |
| H.F. | F | 76 | 8 | 240 | 120 | 16m | | 4.4 | 13 | + | 0 | 0 | 3 | 2 | 2 | 1 | 3 | 2 | 3 | 2 | + | – | – | – | – | – | – | – |
| D.P. | F | 84 | 17 | 200 | 0 | 8m | | 3.2 | 33 | + | + | + | 3 | 2 | 3 | 1 | 3 | 2 | 3 | 2 | – | – | – | – | + | – | – | + |
| F.L. | F | 78 | 33 | 240 | 0 | 5m | | 3.0 | 32 | + | 0 | 0 | 4 | 4 | 1 | 1 | 4 | 4 | 4 | 4 | – | – | – | – | – | – | – | – |
| K.B. | M | 55 | 4 | 200 | 0 | 1m | 14d | 4.0 | 30 | 0 | 0 | 0 | 2 | 1 | 2 | 0[b] | 0 | 0 | 1 | 1 | – | – | – | – | + | – | – | – |
| A.M. | F | 74 | 14 | 200 | 0 | 4m | | 1.8 | 46 | 0 | + | 0 | 4 | 4 | 1 | 1 | 4 | 4 | 4 | 4 | + | – | – | – | – | + | – | – |
| S.S. 1) | F | 75 | 6 | 100 | 0 | | 12d | 1.8 | 24 | 0 | 0 | + | 4 | 3 | 4 | 2 | 4 | 3 | 4 | 3 | – | – | – | +[c] | – | – | – | – |
| 2) | | | | 120 | 120 | 9m | | 1.8 | 30 | 0 | 0 | + | 4 | 3 | 4 | 2 | 4 | 3 | 4 | 3 | – | – | – | – | – | – | – | – |
| H.D. | M | 84 | 12 | 200 | 180 | 16m | | 0 | – | + | 0 | 0 | 4 | 0 | 4 | 0 | 4 | 0 | 4 | 0 | – | +[d] | – | – | +[d] | – | – | – |
| K.L. | F | 76 | 22 | 240 | 0 | 4m | 14d | 0 | – | 0 | 0 | 0 | 4 | 4 | 0 | 0 | 4 | 4 | 4 | 4 | + | – | – | – | – | – | + | – |

[a] ADL: Activity of daily living

[b] Effect of tremor suddenly disappeared after 4 weeks of treatment

[c] Interaction between piribedil and chlopenthixol? (see text)

[d] Effect of piribedil and/or nitrofurantoin? (see text)

*Results*

(see Table 1)

Therapeutic Effects

The results shown in Table 1 represent the clinical symptoms before and during piribedil treatment. Piribedil caused a slight but significant improvement in the ADL-function ($p<0.05$), and of the main parkinsonian symptoms (tremor, rigidity, hypokinesia). Tremor seemed to improve more than rigidity or hypokinesia.

The duration of treatment with piribedil varied from 5 days to 16 months. Treatment was discontinued in eight of the ten patients because of side effects, or for lack of effect. Only two patients received piribedil continuously from the start of treatment. In a third patient (S.S.), who responded well initially, treatment was discontinued because of increased transaminase activity in the serum. Piribedil was reintroduced after six months of withdrawal and there was no further sign of this side effect (see below). The patients on piribedil at present receive maintenance doses of 120 to 180 mg per day.

Of the ten patients, one showed marked improvement, one a moderate, and in four patients ADL-functions slightly improved.

On the main parkinsonian symptoms (tremor, rigidity, and hypokinesia), no effect at all was seen in four of the ten patients. In two of nine patients with tremor (A.A. and H.D.) this symptom improved markedly, in three (K.B., D.P., and S.S.), there was a moderate effect, and in one (H.F.) a mild effect was seen. In patient K.B. the effect lasted only for four weeks. In the nine patients with rigidity before treatment, marked improvement was seen in one (H.D.) and a little effect in four. All the ten patients had hypokinesia before treatment. One of them (H.D.) improved markedly, one (A.A.) moderately, and three of them (H.F., D.P., and S.S.) only a little.

Side Effects

*Mental symptoms* were seen in 5 of the 10 patients treated with piribedil, four of whom were treated simultaneously with L-DOPA. All of them became confused and displayed symptoms such as dizziness, restlessness, anxiety, behavioural disorders, delusions and hallucinations. In addition, two patients showed a stereotyped pattern of behaviour; one of them repeatedly wound up his alarm clock. All the mental symptoms disappeared when the dose of piribedil was reduced or when the drug was discontinued. Two of the 5 patients had shown similar symptoms on a L-DOPA dose higher than that which they received at the time of the present study.

*Neurological symptoms* were seen in one patient. After three months of treatment with piribedil, 200 mg per day, a patient suddenly developed severe nausea, and bilateral nystagmus due to bilateral peripheral vestibular nerve lesion. However, at the same time the patient was given nitrofurantoin for nine days, because of a urinary tract infection, a drug that can induce peripheral neuritis, but not to our knowledge vestibular nerve lesion. Thus, the possibility cannot be excluded that piribedil contributed to the development of this symptom.

*Alkaline phosphatase* activity in serum increased progressively in one patient after treatment with piribedil for 2.5 months. No other signs of cholestasis were observed in the patient. The phosphatase activity fell to normal when piribedil treatment was discontinued.

*Transaminase activity* increased to a pathological level in one patient after 12 days of treatment with piribedil. However, she was being treated simultaneously with clopenthixol for a latent paranoid psychosis. The transaminases fell to normal upon withdrawal of the drugs. When piribedil was reintroduced subsequently, no change in the transaminases was observed during a further nine months of treatment.

Patients who experienced nausea, flushing and arterial hypotension during treatment with piribedil had all displayed the same symptoms previously while receiving L-DOPA, although the dose of the latter was higher than the present one. One patient complained of a feeling of heavy calves.

*Discussion*

This study was originally planned as a pilot experiment, which was to be followed by a broader trial with a double-blind cross-over design. However, owing to the frequent and severe mental side effects the intention was not fulfilled.

In the present study, which was not of double-blind cross-over design, piribedil caused a definite, objectively demonstrable improvement of Parkinsonian symptoms in the majority of patients. It had a beneficial effect on parkinsonism either given alone or in combination with L-DOPA and/or anticholinergic drugs. Tremor was relieved to a greater extent than rigidity or hypokinesia.

Five of the six patients with improvement of tremor had been treated with L-DOPA for a long period without notable effect on the tremor. As has been shown in several investigations (Granerus *et al.*, 1972) tremor responds less promptly than rigidity and hypokinesia to L-DOPA. Thus, piribedil appears to have a somewhat different effect on parkinsonian symptoms than L-DOPA, although the exact mechanism of the differential actions remains to be clarified.

In one patient the beneficial effect on tremor suddenly disappeared after 4 weeks of treatment. One possible explanation for this could be that direct activation of central dopamine receptors by piribedil might lead to decreased sensitivity of the receptors.

It should be emphasized that no less than half the patients had severe mental symptoms during piribedil treatment. In all them the side effects were reversible. For comparison, it may be mentioned that mental symptoms, such as restlessness,

irritability, anxiety, delusions, hallucinations etc. occur in about 15 % of L-DOPA treated patients (Granerus *et al.*, 1972). The limited number of patients, who were selected for piribedil treatment on other indications than those of the larger L-DOPA-treated patient groups, does not permit quantitative comparison of the mental side effects. Qualitatively, however, many of the symptoms provoked by piribedil have also been observed during L-DOPA treatment.

The markedly stereotyped behavioural pattern seen in two of the patients receiving piribedil was very similar to that seen after high doses of amphetamine, which has also been called "punding" (Rylander 1970), The "punding" phenomenon is thought to be elicited by central catecholamines, particularly dopamine, released by amphetamine (Carlsson, 1970). Recently, it has been shown (Corrodi *et al.*, 1972) that piribedil, besides its direct effect on central DA-receptors, like amphetamine can also release DA from presynaptic structures. In view of this indirect effect of piribedil, combined treatment with piribedil and L-DOPA would be expected to result in potentiation. This may explain why so many patients displayed mental side effects, since 4 of the 5 patients affected in this way were also treated with L-DOPA.

The present study illustrates both that considerable benefit can be gained by administration of a DA receptor activating drug to parkinsonian patients who have not responded adequately to other treatment methods, and that the risks of serious side effects may be marked in such patients.

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