Central Nervous System Effects of Hypothalamic Hormones and Other Peptides, edited by Collu et al. Raven Press, New York © 1979.

Clinical Utilization of MIF-I

F. Gerstenbrand, W. Poewe, F. Aichner, and C. Kozma

Clinic of Neurology, University of Innsbruck, Innsbruck, Austria

After 15 years of clinical experience with levodopa substitution therapy for Parkinson syndrome, the implications and problems of this form of therapy require some fundamental reorientation in the management of this disease entity. The possible role of the tripeptide L-prolyl-L-leucyl-glycine amide (PLG), which has melanocyte-inhibiting factor (MIF) activity, is one of the items being discussed among neuropharmacologists (10,11) and clinicians (3,5,7,9).

Kastin and Barbeau (9) in 1972 were the first to use PLG in patients with Parkinson's syndrome. In their first set of studies they supplied the substance by i.v. infusion. Although rather low doses of 20 to 40 mg were used, clinical improvement of up to 20% was observed. However, when the same authors gave PLG orally in gradually increasing amounts up to 1.5 g daily, results were disappointing on a long-term basis, although initial improvement could be detected (4). Barbeau (1) then continued to use PLG intravenously with very good results when given as a potentiating agent with levodopa therapy. Although his patients had been under levodopa therapy for a mean of 4 years, additional PLG injection still produced improvement in motor performance of up to 44% (1). Concerning the different clinical manifestations of parkinsonism, no differentiation was done (3). According to Barbeau (2), akinesia and rigidity are more affected than tremor by PLG.

PLG was available to our own group in Vienna for clinical utilization first in 1975. Under the impression that the doses for infusion therapy used by Kastin and Barbeau in 1972 had been too low, we raised the PLG dosage to 400 mg daily and administered it as a 24-hr continuous i.v. infusion over 10 days. In total, 10 patients were treated, and PLG was given as sole therapeutic agent with no other antiparkinsonian therapy. After the 10-day period of clinical observation, the patients were controlled during a follow-up period of 4 weeks at weekly intervals (7,8).

As can be seen from Table 1, all 9 patients in whom MIF infusion therapy was completed—1 patient declined further treatment after the first day—showed global clinical improvement. In 5 patients this improvement averaged 75%, in 2 it was 50%, and 2 patients with severe clinical manifestations at

TABLE 1. *Evaluation of treatment with MIF-I (400 mg daily) i.v. in 10 patients with Parkinson syndrome*

No. of patient	Initials	Age	Sex	Diagnosis[a]	Degree[b] Pre- A R T	Degree[b] Post- A R T	Global clinical improvement (%)	Psychological state Pre-	Psychological state Post-	Depot effect	Remarks
1	F.R.	47	M	P.a.	3 3 0	1 1 0	75	D	N	+	—
2	J.F.	67	M	P.a.	3 3 3	1 2 2	50	D	N	±	—
3	J.K.	61	M	P.a./T	1 1 3	0 0 2	75	D	Hm	±	A second course of treatment produced the same effect
4	E.W.	70	M	P.a.	1 3 2	0 2 1	50	N	N	+	An i.v. injection course produced the same effect
5	J.D.	66	M	P.a.	4 4 1	3 3 1	25	D	N	−	—
6	P.K.	62	F	P.a.	3 3 0	1 2 0	75	N	N	+	—
7	M.S.	67	F	P.a./T	2 2 3	2 2 3	0	D	D	−	Interruption of study; patient declined further treatment
8	L.H.	64	M	P.a.	1 2 1	0 1 0	75	N	N	+	—
9	Th.Z.	60	M	P.a.	2 2 2	1 1 1	75	D	N	+	—
10	B.S.	68	F	P.a./T	2 1 4	1 1 3	25	D	D	±	Rapid deterioration of tremor after cessation of treatment

[a] P.a., paralysis agitans.

[b] A, akinesia; R, rigidity; T, tremor.

[c] Psychological state: D > depressed; N, normal; Hm, hypermanic.

the onset showed mild improvement of 25%. Regarding the cardinal symptoms, there was improvement of akinesia (Fig. 1) in all patients—significant in 3, moderate in 4, and mild in 2 patients. Rigidity (Fig. 2) was also improved in all patients, significantly in 1, moderately in 3, and mildly in 4 cases. Tremor (Fig. 3) was least affected.

The improvement in motor performance correlated with a remarkable improvement in handwriting, which is demonstrated in Figs. 4 and 5. The motor performance was controlled by a test battery consisting of six single test units in a fixed combination.

We paid particular attention to the time course of the PLG effect. In our first study, evaluation of the different rating systems had revealed a first positive effect after 48 hr with the maximum effect becoming evident on the 7th day. Remarkable was a depot effect, which could be observed in 8 patients and lasted for about 3 weeks after PLG treatment had been stopped, then a gradual deterioration of all symptoms became visible. Four weeks after maximum improvement had been reached, the therapeutic effect had disappeared. However, it was possible to restore the original clinical improvement by single i.v. injections of 200 mg PLG twice daily for 3 days. Again a depot effect was reached lasting shorter than after the infusion period. Like Barbeau (2) we could observe no significant side effects, apart from a positive influence on the patient's mood. Out of 7 patients with depression at the onset of treatment period, 4 achieved a normal psychological state, 1 showed hypomanic features, and 2 remained in an unchanged depressive mood (see Table 1).

Based on these encouraging results and Barbeau's clinical experience (1) about the DOPA-potentiating effect of PLG, we started another set of PLG studies in Innsbruck (6). In a group of 7 patients, consisting of 5 men and 2 women, with a mean age of 61 years and a Parkinson syndrome of grades 2 through 4, we applied PLG intravenously additional to oral levodopa

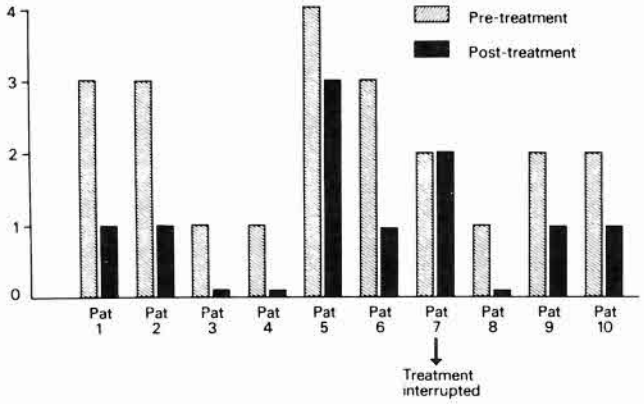

FIG. 1. Effect of MIF i.v. (400 mg daily through 10 days) on akinesia of 10 patients with Parkinson syndrome.

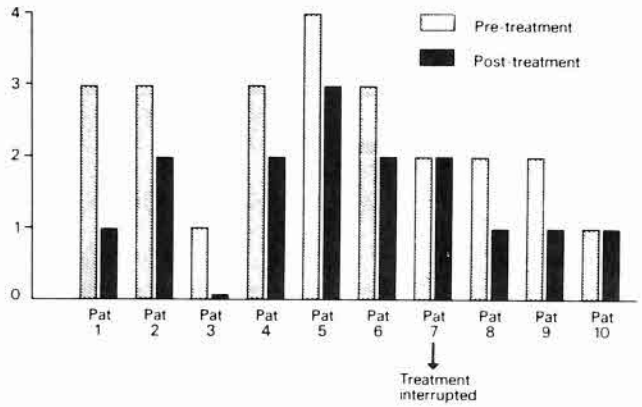

FIG. 2. Effect of MIF i.v. (400 mg daily through 10 days) on rigidity of 10 patients with Parkinson syndrome.

medication. All patients had been under levodopa for at least 6 months prior to the study, the mean duration of previous DOPA therapy being 3½ years. Levodopa had been given in a dosage from 400 to 750 mg either with benserazide (Madopar) or carbidopa (Sinemet). In 3 of the 7 patients PLG was given twice daily (as a 200-mg i.v. injection) over a period of 10 days. Four patients received PLG over 15 days. In this group we gave the substance in a crossover manner every second day for the first 6 days, alternating with placebo. In the crossover phase PLG was injected as a single 400-mg bolus, the following 9 days the administration was as in the first group. Another 2 patients had been under previous therapy with Budipine, a diphenylpiperidine derivative with anticholinergic and hypothetic dopaminergic properties. Additional PLG (200 mg i.v.) was given twice daily for 10 days.

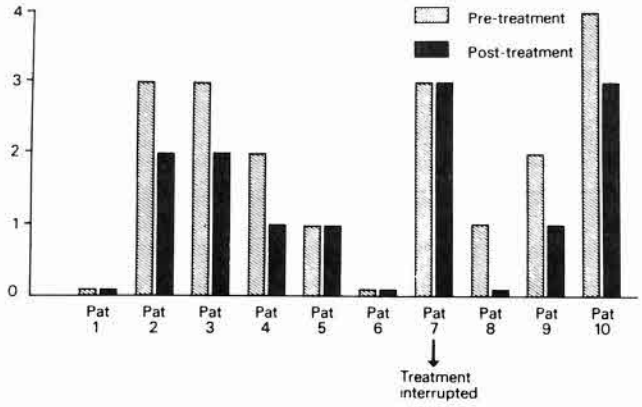

FIG. 3. Effect of MIF i.v. (400 mg daily through 10 days) on tremor of 10 patients with Parkinson syndrome.

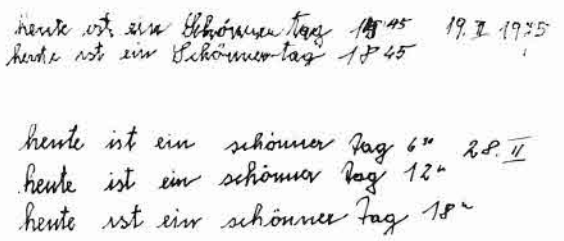

FIG. 4. Pattern of handwriting of a 61-year-old male patient, J. K., with paralysis agitans. Comparison before treatment and 9 days after infusion therapy (400 mg daily).

In 2 patients with a Parkinson syndrome of mild degree who had been without previous antiparkinson therapy, PLG was administered twice daily (200 mg i.v.) as sole therapy over 10 days. Finally, we administered PLG to 2 patients with Parkinson symptoms following a traumatic apallic syndrome.

Table 2 gives a synopsis of all patients studied. In the first group, all 3 patients had Parkinson's syndrome of grade 3, and in all of them akinesia and rigidity were more prominent than tremor. Their cumulative score in our test battery ranged from 226 to 480, the maximal score being 1,000. We also used the peg-board test, prosupination recording, button press test, and the motor performance test of Grünberger. In addition, each patient had to perform drawing and handwriting tests. Finally the patients were rated by doctors and nurses.

In all 3 patients there was global improvement of 25% to 50%. The additional improvement became evident already on the first day of treatment, improvement having reached the maximum after the 4th or 5th day. As in our first group, improvement was more prominent for akinesia and rigidity than for tremor. The motor performance score proved to be a particularly sensitive indicator of the PLG-induced effect. A depot effect was evident in our first set of studies, lasting between 10 days and 3 weeks. Again, restoring of the original improvement could be achieved with a second 3-day PLG period. Remarkable side effects were the influence on

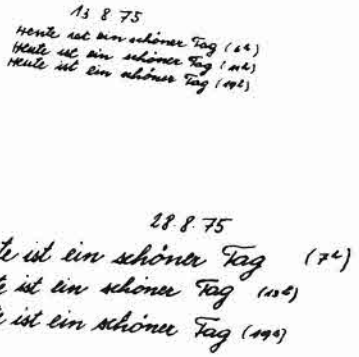

FIG. 5. Pattern of handwriting of a 67-year-old male patient, J. F., with paralysis agitans. Comparison before treatment and 5 days after infusion therapy with MIF (400 mg daily through 10 days).

TABLE 2. *Results of PLG studies (second series)*[a]

Name	Age	Sex	Diagnosis[b]	Levodopa	Other AP therapy	Degree[a]		Motor performance		Clinical improvement (%)	Psychological State		Remarks
						Pre-ART	Post-ART	Pre-	Post-		Pre-	Post-	
F.H.	63	M	PS/3	625 mg/S	—	432	221	226	488	50	D	N	Dyskinesia
J.W.	61	M	PS/3	750 mg/S	—	332	221	480	650	25	D	D	Dyskinesia
M.K.	61	F	PS/3	400 mg/M	—	331	221	420	532	25	N	Hm	—
H.R.	64	M	PS/3	750 mg/S	—	333	112	395	615	75	N	N	Dyskinesia
R.H.	58	M	PS/2	500 mg/S	—	220	110	526	730	50	D	N	—
F.B.	61	M	PS/2	400 mg/M	—	122	112	473	586	25	D	N	—
M.P.	72	F	PS/4	600 mg/M	—	441	220	160	356	50	N	Hm	—
G.W.	65	F	PS/3	—	Budipine	333	112	235	480	50	D	Hm	—
R.M.	59	F	PS/2	—	Budipine	220	120	368	475	25	N	N	—
S.J.	61	M	PS/2	—	—	221	121	375	492	25	N	N	—
J.M.	56	F	PS/2	—	—	220	110	486	640	50	D	N	—
H.Z.	30	M	TAS + PS/2	—	—	210	110	380	540	25	N	N	Cerebellar
M.S.	24	M	TAS + PS/2	—	—	310	210	245	456	25	N	N	Cerebellar

[a] Abbreviations as in Table 1.

[b] PS, Parkinson's syndrome; TAS, traumatic apallic syndrome.

preexisting dyskinesias which showed transient exacerbation in 2 patients during this series. This observation is in accordance with previously published studies (13). The effect on the psychological state was the same as reported earlier (7).

Four patients in whom the 9-day period was preceded by a crossover application of PLG and placebo during 6 days showed globally similar results, as can be seen in Table 2. The improvement ranged from 25 to 75%. There was no correlation between the severity of symptoms at onset and final improvement. The same effects on dyskinesia and mood could be observed. Figure 6 shows a patient before the study had started and at the end of the 15-day period.

Figure 7 summarizes the results of the clinical ratings of akinesia, rigidity, and tremor in all 7 patients treated with the combination of levodopa and PLG. Again, it is visible that tremor is less influenced than akinesia and rigidity.

The crossover trial in the second group revealed another remarkable aspect of the PLG effect. As can be seen from Fig. 8 there is an overhanging effect of PLG demonstrable during the placebo days. The graph represents the rigidity scores of all four extremities of one of the patients (case 4) of this group in a continuous 15-day rating period with 6 daily ratings during the first 7 days and 3 daily ratings thereafter. A daily profile with a minimum at 2 P.M. was evident on DOPA when placebo was added. A 400-mg bolus in the morning accentuated this profile. This PLG effect not only was maintained during the following placebo days but was still accentuated. Up to the 6th

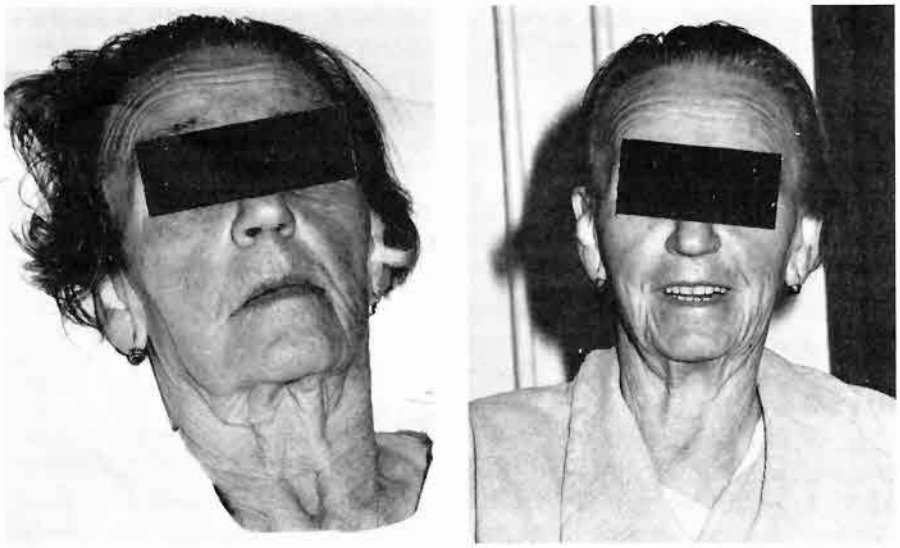

FIG. 6. Left: patient before the start of the study. Right: patient at the end of 15-day treatment period.

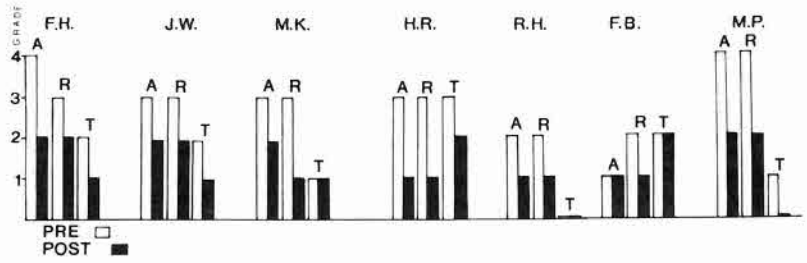

FIG. 7. Effect of treatment with PLG (200 mg) twice daily in addition to previous levadopa treatment on akinesia rigidity and tremor in 7 patients with Parkinson syndrome.

day an additional and cumulative effect became evident. In the permanent application period (with application of 200 mg PLG twice daily) only a slight further decrease in rigidity was reached, whereas the circadian profile was progressively lost.

In order to find out more details about the immediate effect of PLG and its time course as already examined by Barbeau and Kastin (3), we followed motor performance in one of the patients out of group 1 (case 3) in a continuous 24-hr rating after a single 200-mg dose of PLG i.v. It can be seen from Fig. 9 that a marked increase is reached after 1 hr, becoming maximal 3 to 4 hr after the injection, with a gradual decrease in the following 20 hr. After 24 hr performance score was still 20% higher than the control value.

Two patients who had been treated with an anticholinergic agent (Budipine) for 3 months received additional PLG 200 mg i.v. twice daily for 10 days. Potentiation of the Budipine effect could be demonstrated on a long-term basis as well as during an 8-hr rating period. Table 2 shows a global improvement of 25% in one patient (case 9) and of 50% in case 8. Figure 10 shows the result of 8-hr rating in such a patient.

With the fifth group, it was possible to confirm our previous results on the effect of PLG on Parkinson symptoms when used without any other antiparkinson therapy.

Based on the experience that PLG as the sole agent is effective in relieving Parkinson symptoms, we administered the substance to 2 patients in a deficiency state after a traumatic apallic syndrome with prominent Parkinson signs as well as cerebellar symptoms. Both showed mild clinical improvement approximating 25%. The drawing and writing performance of 1 of the 2 patients showed significant improvement under PLG. This effect was in part due to a diminution of the cerebellar symptoms.

In summarizing the results of our second set of studies with PLG, we confirm Barbeau's clinical observation of potentiation of levodopa effect by MIF (1). Although our first set of studies showed a dependence of PLG-induced improvement on the severity of parkinsonian symptoms, this correlation was not confirmed by the results of our second series.

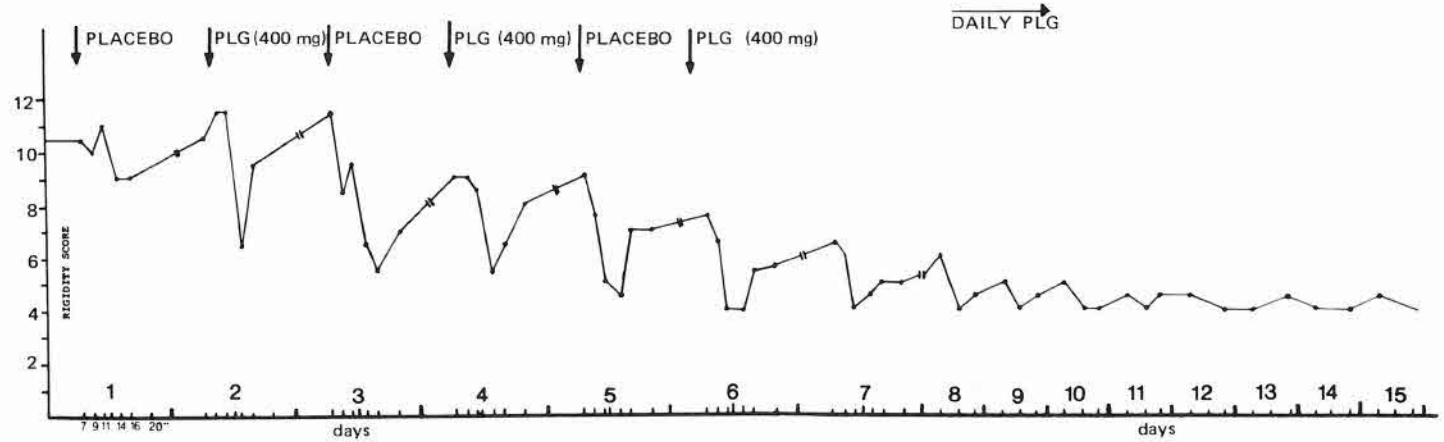

FIG. 8. Hans R., a 64-year-old male with Parkinson syndrome of grade 3. Oral levodopa therapy (Sinemet, 6 × ½, 1 year). Additional PLG treatment for 15 days. During first 6 days every second day 400 mg PLG i.v. as a bolus and from the 7th day 400 mg PLG i.v. daily. Rigidity, total score for all four extremities.

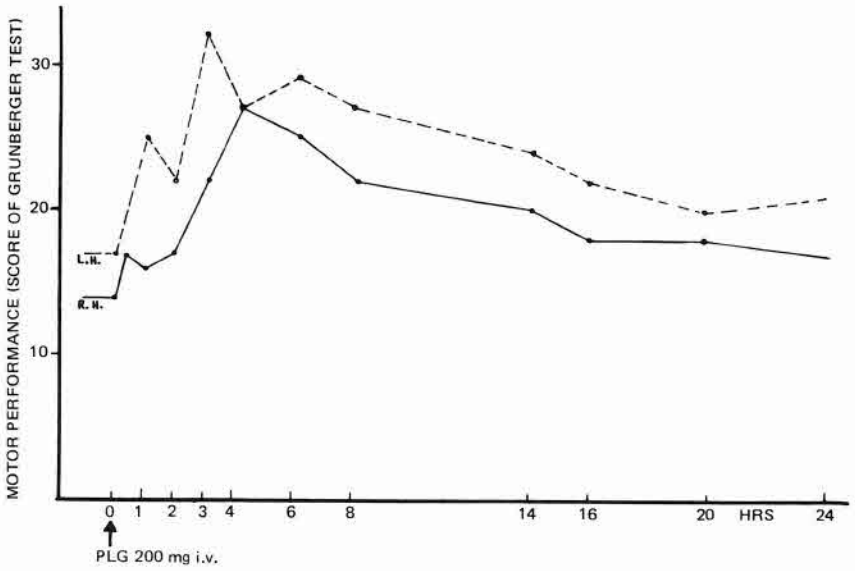

FIG. 9. Maria K., a 61-year-old female with Parkinson syndrome of grade 3. Oral levodopa therapy (Maldopar, 125 mg 4 × 1, 1½ years). Motor performance profile over 24 hours. Period after bolus injection of 200 mg PLG i.v. (L.H. = left hand; R.H. = right hand.)

In analyzing the clinical effect of PLG, it seems that the bolus injection of 200 or 400 mg is superior to the slow infusion. Whereas in the first series there was a delay of 3 days before the effects were visible, the bolus administration of the substance led to first effects after 10 to 15 min, with a maximum reached after 3 hr. When we used the bolus injection alternating with a placebo, a cumulative effect was discovered. From current experimental data, it thus seems that PLG acts as a receptor-activating substance at the postsynaptic site. From our clinical experience, we would suggest that this activation is dependent on dosage as well as on the factor of time. According to our experience, a dose of 200 mg PLG as a bolus (i.v.) is necessary for rapid clinical effects. Lower doses seem to be less effective. On the other hand, we could not increase the clinical improvement or its rapidity of onset with daily doses higher than 400 mg. It is our impression that a slow intravenous infusion needs the cumulative property of PLG to become clinically effective, and therefore onset of improvement is delayed.

The question whether PLG can cause dyskinesias or worsen preexisting levodopa dyskinesias is still unanswered. From our experience transient activation of dyskinesias seems possible. We could not find that PLG reduced the dyskinesias in our patients.

Cerebellar symptoms in one of our patients with a deficiency state from a traumatic apallic syndrome were diminished under PLG. The influence of

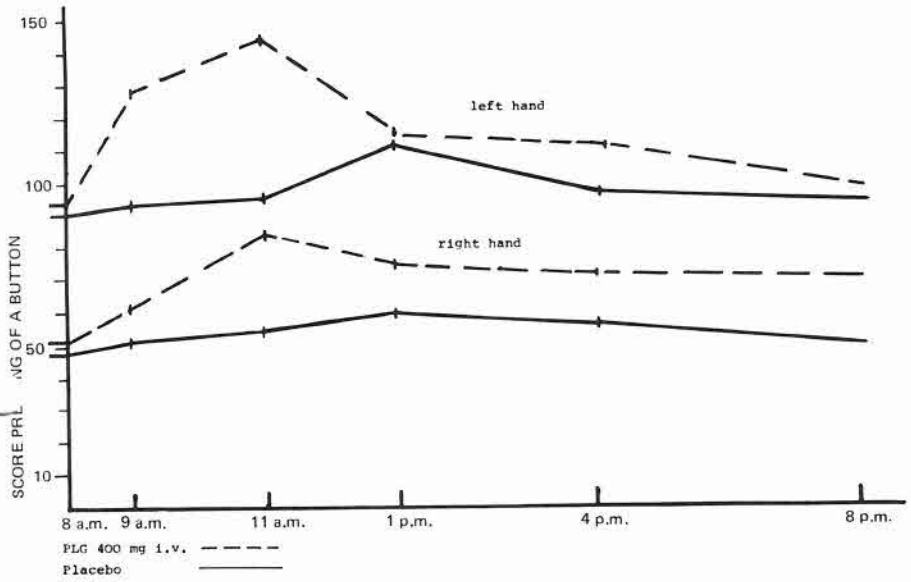

FIG. 10. Gertraud W., a 65-year-old female with Parkinson syndrome (Postenc.). Budipin therapy 80 mg (3 months). Motor performance (pressing a button) after PLG 200 mg i.v. as bolus (——) as compared to placebo (—).

PLG on the depressive state was reconfirmed, which suggests further clinical investigation in endogenous depression.

In closing, we would again like to emphasize that PLG is opening a new way in therapy for Parkinson's syndrome.

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