NEW TRENDS IN THE THERAPY OF PARKINSON'S SYNDROME

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For about twenty years drug therapy of Parkinson's syndrome is centering around high-dose oral levodopa substitution, which has brought about a major advance in the control of specific symptoms (2, 3, 4, 13). However, long-term administration of levodopa in Parkinson's syndrome has proven to be associated with a variety of shortcomings. Together with declining efficacy, which usually becomes evident after 3 to 5 years of chronic levodopa treatment, the frequency and severity of drug-related side-effects increases. These include the "on-off" phenomenon, dyskinesias as well as paranoid hallucinatory syndromes and may often lead to dose reduction of levodopa below the required level (9, 23).

Much of current investigation in the field of parkinsonism is related to the control of these long-term problems in levodopa therapy and some new trends in the therapy of Parkinson's syndrome have evolved in the past ten years without, however displacing levodopa as the central therapeutic agent. Among the new substances introduced into parkinsonian therapy dopaminergic agonists out of the ergot alkaloids family seem to play the most important role in current clinical practice (5, 6, 17, 18, 19, 20). In this paper focus shall be put on some other substances which either have already come to a broader clinical use or may be of future importance in the treatment of parkinsonism.

β-*Adrenergic blocking agents in parkinsonian therapy*

In order to optimate drug therapy of parkinsonism it proves useful to differentiate between subtypes of the disease on the basis of differences in clinical symptomatology (Tab. 1). Especially in the tremor-dominant type of Parkinson's syndrome oral levodopa substitution alone often fails to provide sufficient control of symptoms. Based on a number of contradictory reports in the literature indicating a positive influence of β-adrenergic blocking agents on parkinsonian tremor (1, 15, 24, 29) as well as their ineffectiveness (28, 30) we further evaluated the efficacy of combined treatment of tremor-dominant Parkinson's syndrome with levodopa and β-adrenergic blocking agents in 25 patients with insufficient control of tremor by levodopa. The patients were kept on their basic therapy with L-Dopa and bupranolol or propranolol was added in a double-blind cross-over fashion for four weeks. In five patients a new compound with potent nonselective β-adrenergic blocking properties of prolonged duration (LT 31-200, Sandoz, Basle) was added to levodopa in an open trial.

TABLE 1

SUBTYPES OF PARKINSON'S SYNDROME ACCORDING TO CLINICAL SYMPTOMATOLOGY

Type 1:	Equivalence type (R = T = A)
Type 2:	Akinesia-rigidity type
Type 3:	Tremor-dominant type
Type 4:	Parkinson's syndrome with pronounced depressive psychosyndrome
Type 5:	Parkinson's syndrome with pronounced vegetative symptoms (Borderline cases of Shy-Drager-syndrome)
Type 6:	Parkinson's syndrome with pronounced optomotoric disturbances (Borderline cases of Steele-Richardson-Olszewski syndrome)
Type 7:	Parkinson's syndrome with dementia (Dementia - type; Borderline cases of parkinsonism - dementia - als - complex)

The effects of combined treatment with levodopa and bupranolol or propranolol on tremor, rigidity, akinesia and on the emotional condition are displayed in Figures 1 - 5 for the first twenty patients. Tremor was markedly reduced in six of the ten patients receiving bupranolol and seven of the ten patients receiving propranolol (Fig. 1). Concerning rigidity and akinesia some improvement occurred in individual cases of both groups (Figs 2 and 3); the majority of patients did not show improvement of these symptoms.

Emotional condition as assessed by the Hamilton scale and the 100 mm test improved remarkably in 3 patients of group one (cases 1, 4 and 6; Fig. 4), while four patients showed slight im-

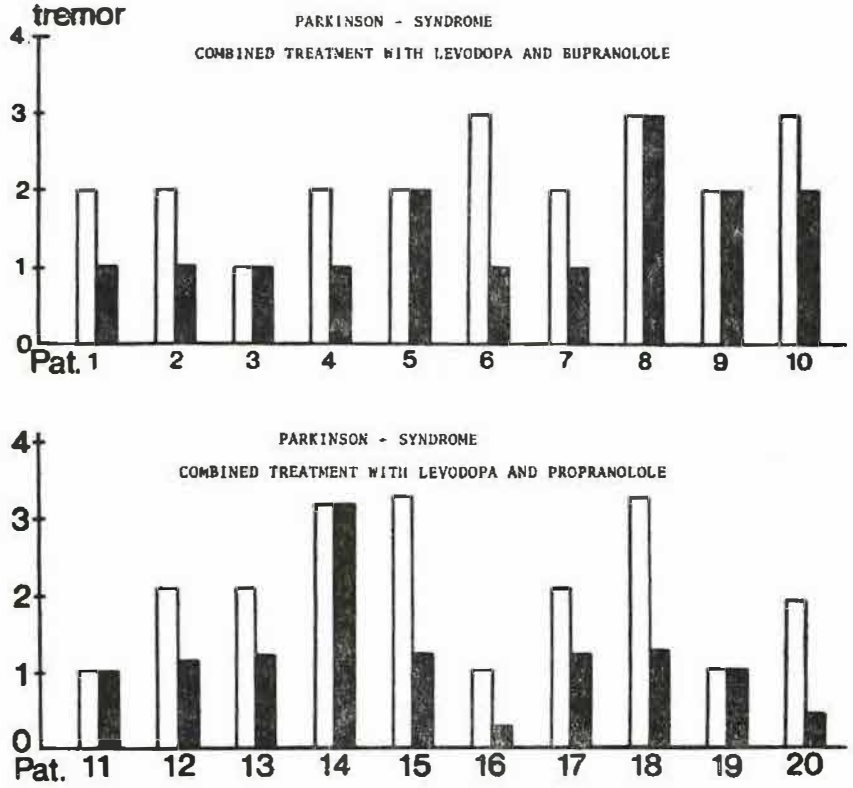

Fig. 1: Tremor-score in 20 patients with tremor-dominant Parkinson's syndrome treated with a combination of L-Dopa and a β-adrenergic antagonist (□ = before addition of ß-adrenoceptor antagonist, ◆ = 4 weeks after addition of β-adrenoceptor antagonist).

provement (Fig. 4). In group two eight of ten patients showed improvement of their emotional condition (Fig. 5). Concerning the new β-blocker LT the 5 patients already evaluated, all showed a significant reduction of tremor scores from week 0-4 (Fig. 6). At the same time motor performance scores increased (Fig. 7).

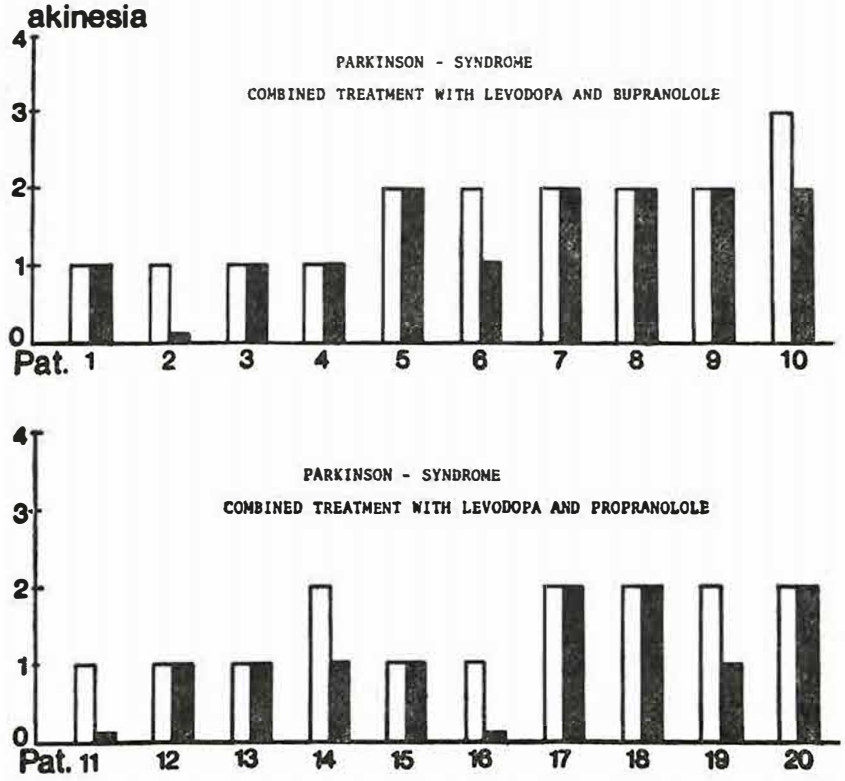

Fig. 2: Rigidity-score in 20 patients with tremor-dominant Parkinson's syndrome treated with a combination of L-Dopa and a β-adrenergic antagonist (□ = before addition of β-adrenoceptor antagonist, ◆ = 4 weeks after addition of β-adrenoceptor antagonist).

These results indicate that the combination of L-Dopa with β-blocking agents does provide a better control of symptoms in the tremor-dominant form of Parkinson's disease than does levodopa alone.

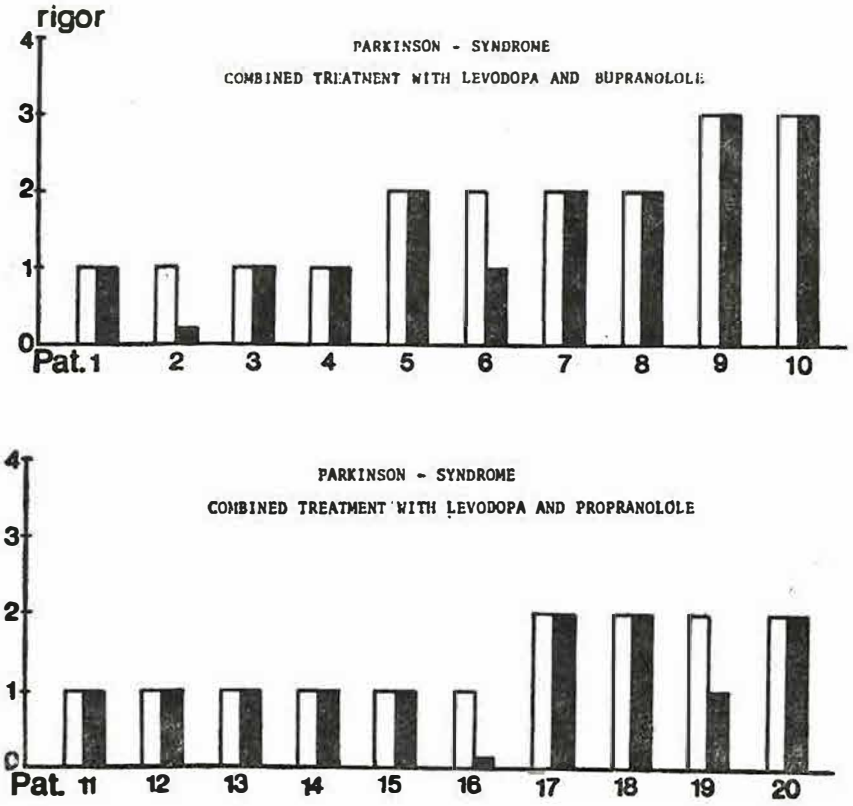

Fig. 3: Akinesia-score in 20 patients with tremor-dominant Parkinson's syndrome treated with a combination of L-Dopa and a β-adrenergic antagonist (□ = before addition of ß-adrenoceptor antagonist, ◆ = 4 weeks after addition of β-adrenoceptor antagonist).

The role of MIF

Much of present experimental work in neurochemistry and neuropharmacology is devoted to the role that peptides may play as neurotransmitters or neuromodulators in the normal brain as well as in certain disease states.

The first peptide that was clinically tested for its therapeutic efficacy in an extrapyramidal disorder was the tripeptide (PLG [Pro-leu-gly-NH_2]) wich has MSH-release-inhibitory properties and is therefore referred to as melanocyte-inhibiting-factor (M.I.F.).

After a deterioration of parkinsonian symptoms had been obser-

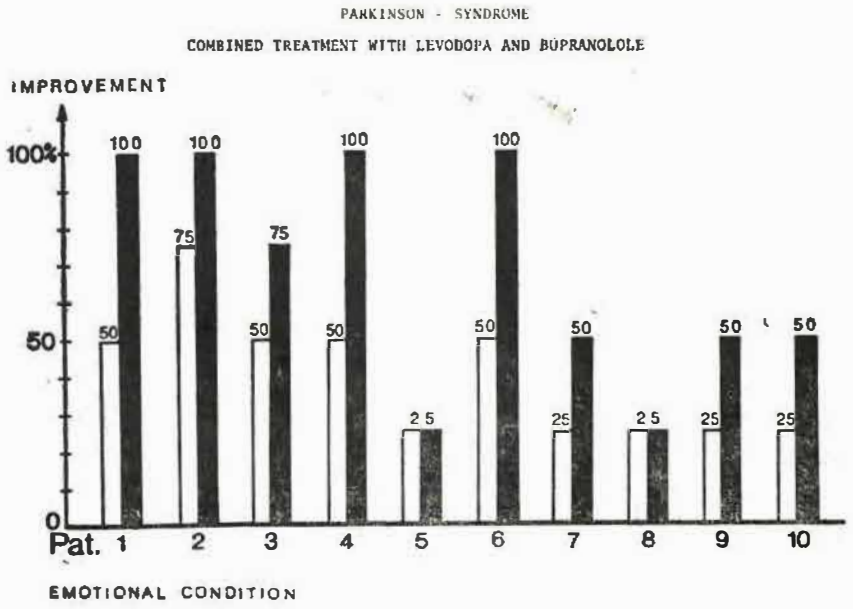

Fig. 4: Emotional condition in 10 patients with tremor-dominant Parkinson's syndrome treated with a combination of L-Dopa with Bupranolol (□ = before addition of Bupranolol, ◆ = 4 weeks after addition of Bupranolol).

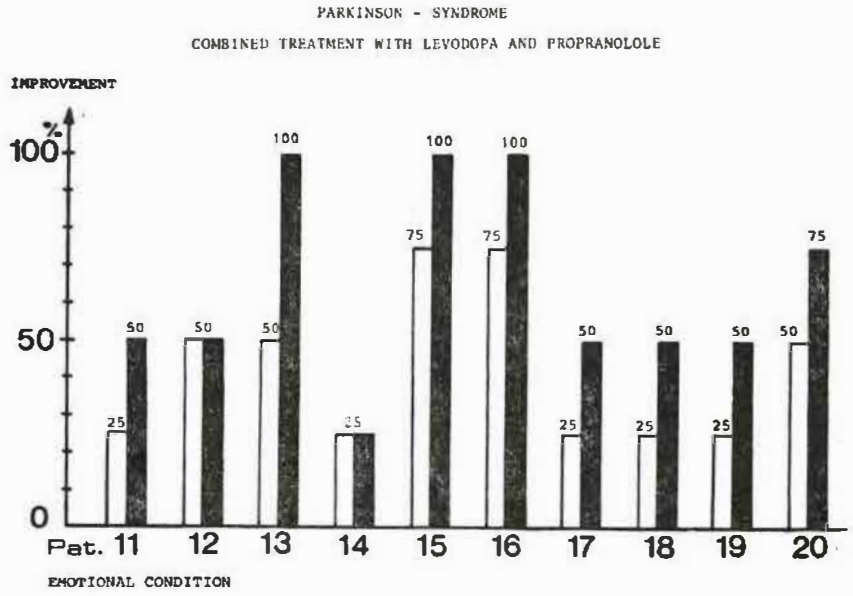

Fig. 5: Emotional condition in 10 patients with tremor-dominant Parkinson's syndrome treated with a combination of L-Dopa with Propranolol (□ = before addition of Propranolol, ◆ = 4 weeks after addition of Propranolol).

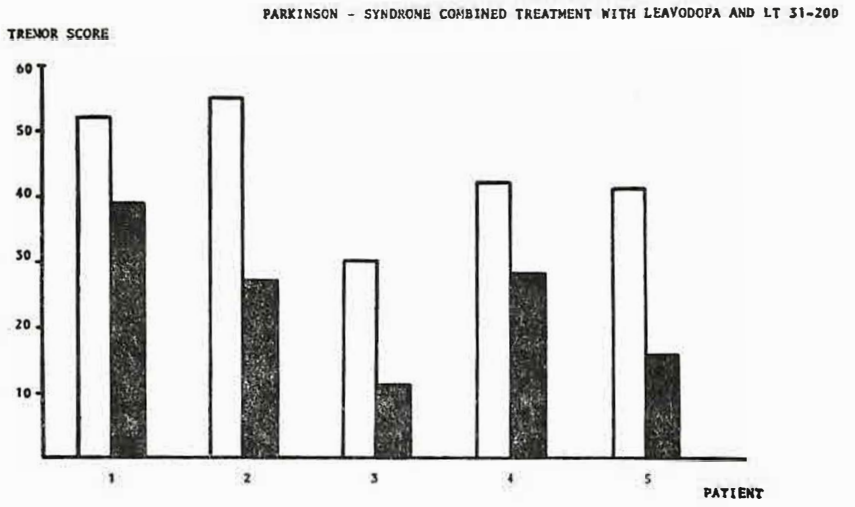

Fig. 6: Tremor-scores in 5 patients with tremor-dominant Parkinson's syndrome treated with L-Dopa + LT 31-200, (□ = before addition of LT 31-200, ◆ = after addition of LT 31-200).

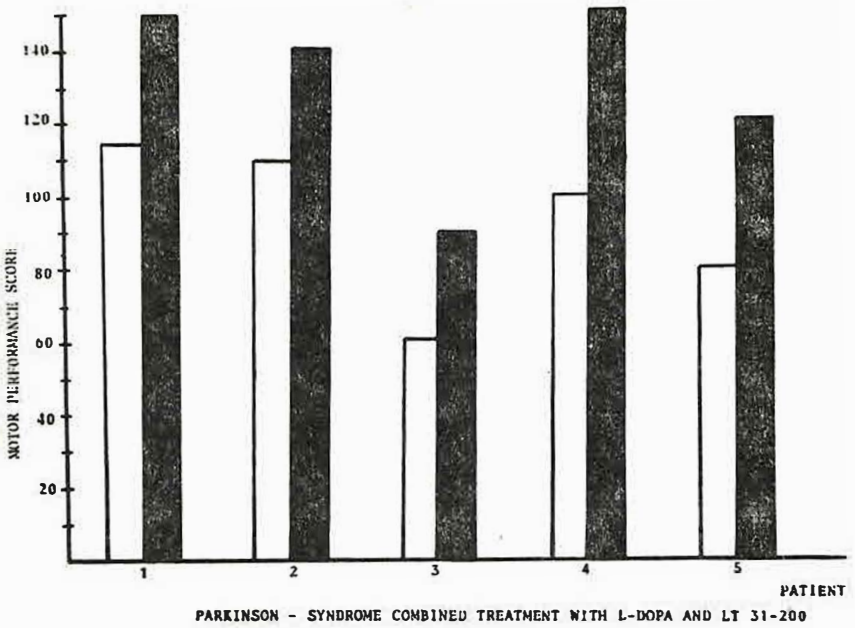

Fig. 7: Motor performance scores in 5 patients with tremor-dominant Parkinson's syndrome treated with L-Dopa + LT 31-200 (□ before addition of LT 31-200, ◆ = after addition of LT 31-200).

ved after injections of MSH to patients by Cotzias and co-workers (8) and elevated MSH plasma-levels in Parkinson's disease had been measured by Shuster and collaborators (27), PLG was soon tested in animal experiments, where an oxotremorine antagonism and L-Dopa potentiation could be observed (25, 26) and in clinical trials in Parkinson's syndrome, where positive effects were first reported by Kastin and Barbeau (16). Similar observations were made by Fischer and collaborators (10). In our own studies with PLG in Parkinson's syndrome in 1976 we started to use higher dosages than Barbeau and Fischer and applied 400 mg daily as a continuous 24 - hr i.v. infusion (11).

In a 10 day treatment period with PLG as the sole anti-parkinsonian agent there was global clinical improvement in nine of ten patients. Rigidity and akinesia were influenced more than tremor. There was mood brightening in 5 of 10 patients (Tab. 2).

TABLE 2

EVALUATION OF TREATMENT WITH M.I.F.
(400 mg i.v. / 24 hrs) of 10 patients with Parkinson's syndrome.

No. of patient	Initials	Age	Sex	Diag-nosis	Degree pre A R T	post A R T	Global clinical improve-ment %	Psychol. state pre	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 2nd 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

Psychological state: D = depressed, N = normal, Hm = hypermanic.
P.a. = paralysis agitans A = akinesia M = male
T = tremor R = rigidity F = female

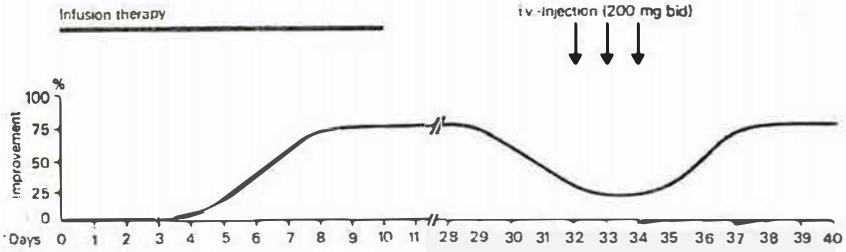

Fig. 8: Course of treatment in a 47 yrs. old parkinsonian patient with M.I.F.

A depot effect with continuing improvement of up to four weeks after cessation of the infusion series was observed in eight patients. When deterioration finally occurred it was possible to restore the original improvement by a series of three to five bolus injections of 400 mg of M.I.F. in three of them (Fig. 8). Giving PLG as i.v. bolus injections of 200 to 400 mg daily in combination with a stable L-Dopa therapy we could confirm the L-Dopa potentiation seen by Barbeau (14). Again tremor was influenced less then akinesia and rigidity (Fig. 9). Improvement in motor performance scores averaged between 20% and 40%. The effect of a single PLG-injection became evident within 15 minutes and lasted up to 24 hours.

The mechanism by which PLG might influence parkinsonism still remains uncertain. A postsynaptic site of action of PLG would most conveniently explain the clinical observations made by several

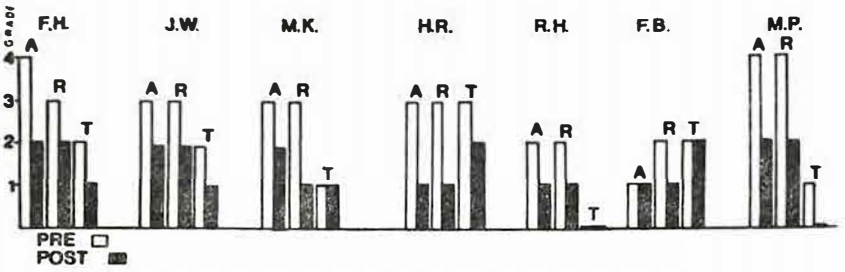

Fig. 9: Combined treatment with Levodopa and MIF (200 mg i.v. twice daily) in 7 parkinsonian patients. Treatment period with MIF from 10 to 15 days.

authors. The demonstration of specific binding sites for PLG in the rat striatum (7) points to a postsynaptic site of action, maybe via modulation of dopamine receptors.

CDP-choline

Among the substances investigated for their capacity to influence parkinsonism in the past ten years CDP-choline deserves special interest. The substance serves as an important co-enzyme in the synthesis of brain phospholipids and could be shown to exert a protective effect against dopamine loss in the caudate nucleus in lesion experiments in cats (21).

Intravenous administration of CDP-choline could be shown to lead to a significant increase in dopamine concentration in the rat striatum (22). Several clinical studies have meanwhile been published indicating a positive effect of CDP-choline in Parkinson's syndrome, our own first positive results of a clinical trial with CDP-choline as monotherapy for parkinsonism not only showed positive effects of the drug but indicated a possible "levodopa-saving" effect of CDP-choline when used together with L-Dopa (12). To further investigate the clinically most important question if levodopa dosage could be reduced when applying CDP-choline ** concomitantly we conducted a controlled study in 20 patients with idiopathic Parkinson's syndrome in cooperation with the IPHAR Institute, Munich, and the Neurological departments of the General Hospital of Salzburg and Linz, Austria. The patients, 12 males and 8 females, aged 48-71 years (mean 62) had been on a stable substitution therapy with levodopa and DCI * for at least 6 months. For the trial they were left on their previous levodopa substitution therapy without any other concomitant anti-parkinsonian medication and were randomly assigned to one of two treatment groups. The study design is displayed in Figure 10.

To evaluate the parkinsonian symptoms and psychological status of the patients during the trial, clinical rating scales were employed together with a motoric test battery consisting of three subunits and the 100 mm-test, Brickenkamp's d_2-test and the Hamilton Scale for assessment of depression. Clinical assessment of the patients in a 5-point rating scale revealed the results displayed in

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(*) DCI = Decarboxylase inhibitor.
(**) Nicholin-Rexort (trade marks).

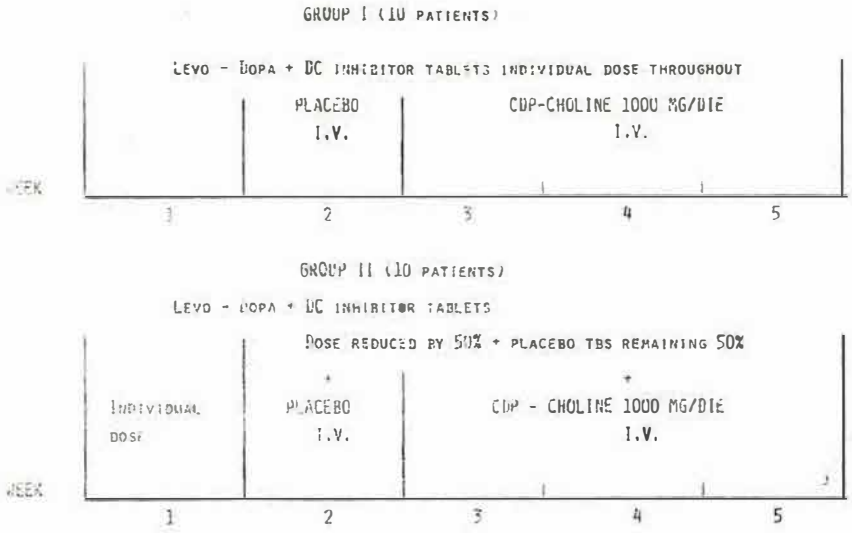
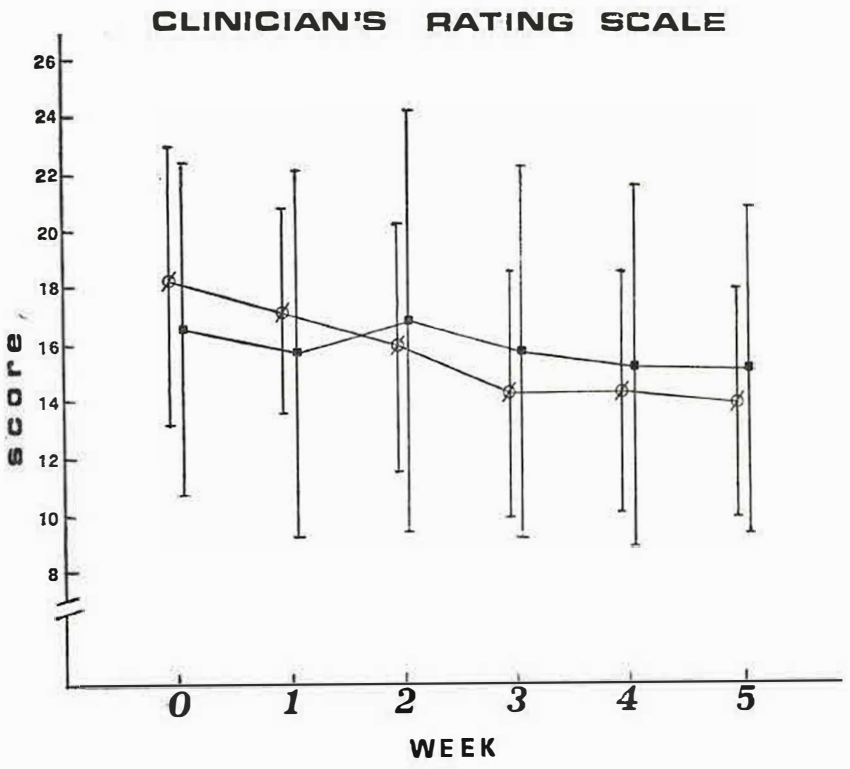


Fig. 10: Study design of combined treatment with Levodopa and CDP - Choline in 20 parkinsonian patients.

the following two figures. In both groups, mean scores from physicians rating decreased from weeks 0 to 5 expressing clinical improvement. There was no significant difference between the two groups at any of the weekly measurement points (Fig. 11).

When comparing the ranked score sums of the clinical rating there was a significant improvement from the end of week two (LD/DCI or LD/DCI plus placebo) to week 5 (LD/DCI) in group one while no significant changes occurred in group two (50% reduction of LD/DCI after the first week) (Fig. 12). However, when comparing the changes from week 2 to week 5 there was no significant difference between the two groups. The same result was also obtained when comparing the scores of nurse's rating of week 2 and 5 in both groups.

In the motor performance tests, analogous trends were evident. The ranked score sums of weeks 1, 2 and 5 in the button pushing and tread test are displayed in the following figures 13 and 14 for the test part of the upper extremities. Statistically significant improvement from week 1 to week 5 is evident for all test parts in group one and for some parts in group two. Again no significant difference between the two groups could be detected when comparing the changes from week 2 to 5 using the Mann-Whitney-U-test. The latter was also true when comparing the respective scores



Legend: ø = group I

▪ = group II

Fig. 11: Mean scores from the clinician's rating scale before and during the study for group I and II with standard deviations.

of Grunberger's motor function test, while there was a significant increase in total score of this test from week 1 to 5 in group one.

The patients' overall psychological conditions as assessed by a 100 mm scale significantly improved by week 5 in the first group, while improvement in group two was not statistically significant. Again no significant difference in the change from week two to five was found between groups one and two (Fig. 15). The results obtained in the present study again demonstrate the clinical effectiveness of CDP-choline in Parkinson's syndrome. The combined therapy of Parkinson's syndrome with "levodopa" plus decarboxylase inhibitor and CDP-choline as administered in group one brought

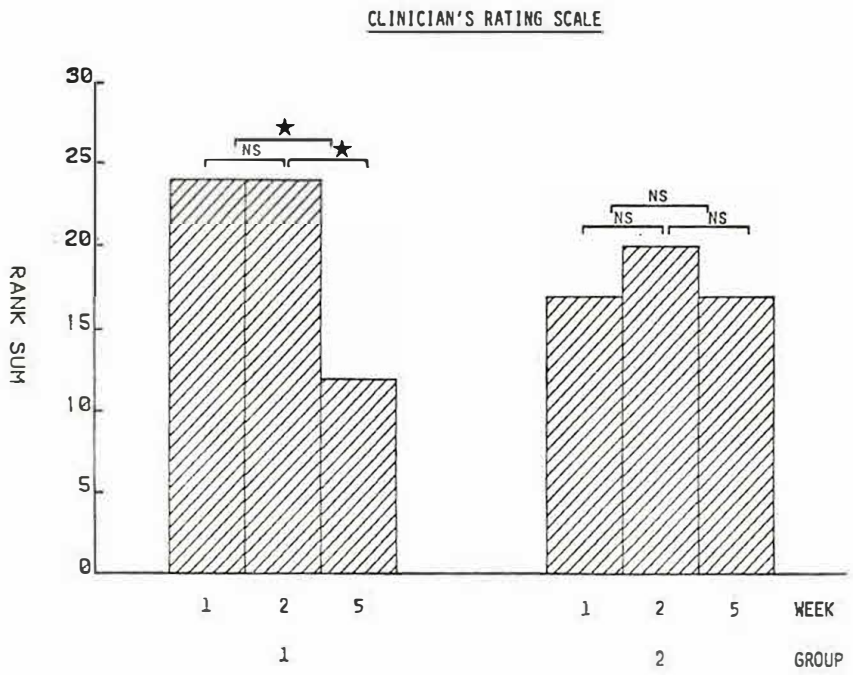
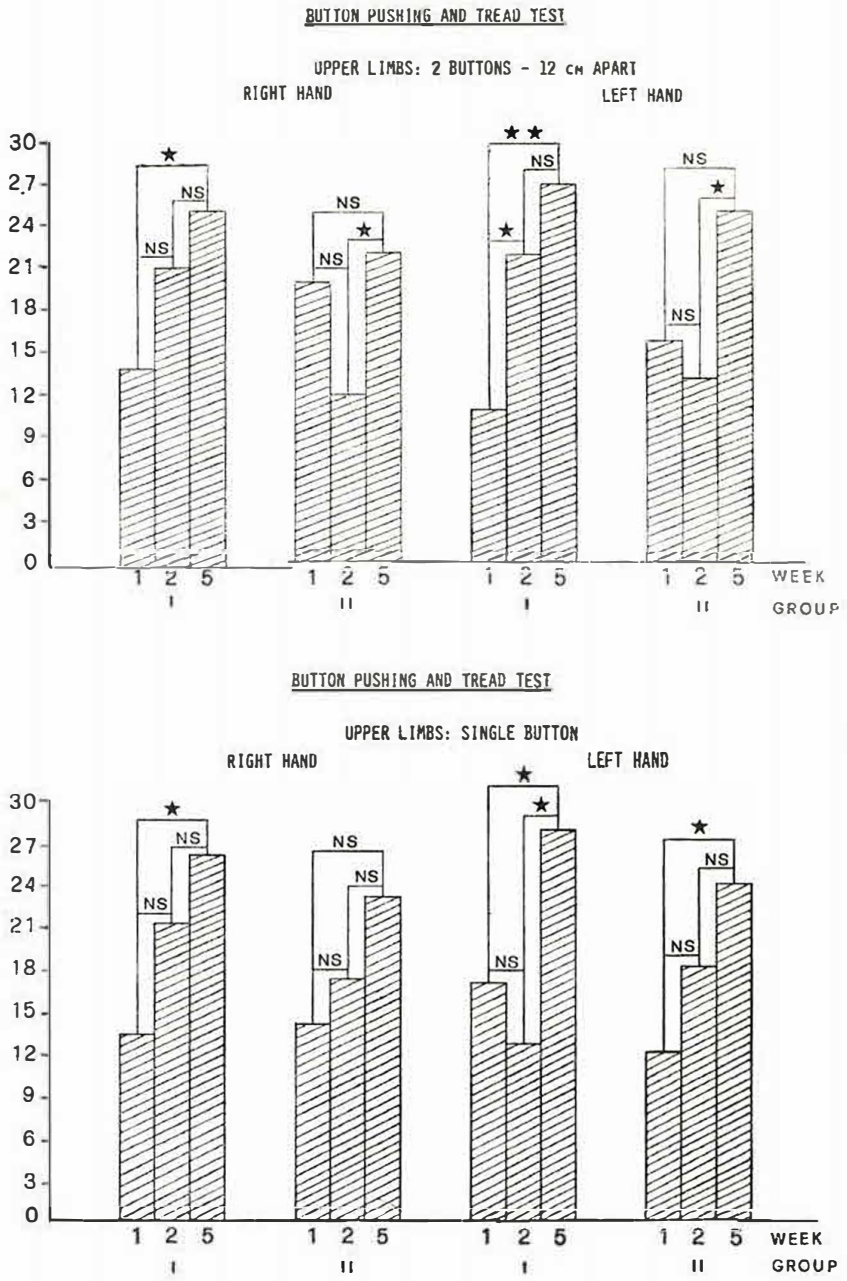


Fig. 12: Ranked score sums in the clinician's rating scale in two groups of parkinsonian patients following treatment with Levodopa (week 1) Levodopa + Placebo (week 2) and Levodopa + CDP-choline (week 5). Patients in group I received their normal maintenance dose of Levodopa throughout whilst those in group II received half their normal maintenance dose during weeks 2-5 of the study. Results of the Friedman's analysis of variance are shown as NS = not significant, * = significant with $p < 0.05$.

significant further improvement in the different tests applied, suggesting that treatment with CDP-choline plus levodopa/DCI is superior to LD/DCI-monotherapy. What seems most important is that in group two there was no significant difference in the change of scores of all tests performed from week 2 to 5 as compared to group one. Since dosage of LD/DCI was reduced by 50% after week one in this group CDP-choline must have been able to compensate this dose reduction of LD/DCI. In clinical practice CDP-choline should thus be a useful alternative drug in parkinsonian patients requiring dose reduction of levodopa due to central side effects. Furthermore, additional CDP-choline to prior levodopa - treatment may be a way to overcome "decompensation states" in the course of parkinsonism.



Figs. 13-14: Ranked score sums for number of responses in the button pushing and tread tests in two groups of parkinsonian patients following treatment with Levodopa (week 1), Levodopa + Placebo (week 2) and Levodopa + CDP-choline (week 5). Patients in group I received their normal maintenance dose of Levodopa throughout whilst those in group II received half their normal maintenance dose during weeks 2-5 of the study. Results of the Friedman's analysis of variance are shown as NS = not significant, * = significant with $p < 0.05$, ** = significant with $p < 0.01$.

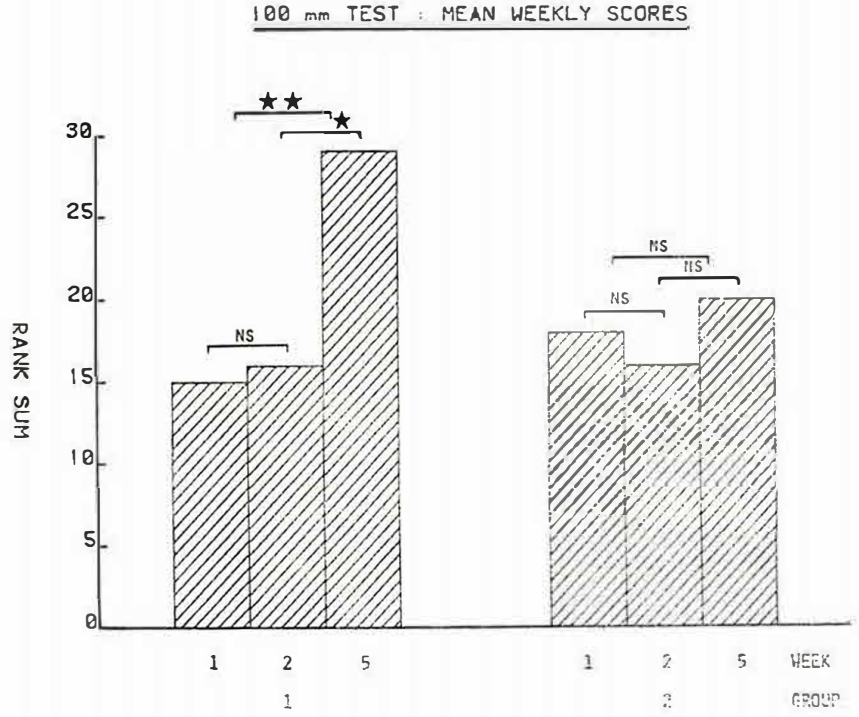


Fig. 15: Ranked score sums in the 100 mm test in two groups of parkinsonian patients following treatment with Levodopa (week 1), Levodopa + Placebo (week 2) and Levodopa + CDP-choline (week 5). Patients in group I received their normal maintenance dose of Levodopa throughout whilst those in group II received half their normal maintenance dose during week 2-5 of the study. Results of the Friedman's analysis of variance are shown as NS = not significant, * = significant with $p < 0.05$, ** = significant with $p < 0.01$.

Conclusion

At present, drug therapy of parkinsonism is still centering around oral levodopa substitution. The shortcomings and long-term problems of this form of therapy, however, have led to some new trends and modifications aiming at more constant efficacy and less central side-effects in anti-parkinsonian treatment. The dopaminergic agonists of the ergot alkaloid family currently play the most important role in clinical praxis as adjuvants to levodopa or even as monotherapy. Some other alternatives in drug therapy of parkinsonism are of similar importance in certain clinical situations.

In this context β-blocking agents have emerged as useful adjuvants to levodopa treatment in the tremor-dominant type of parkinsonism.

In patients with side-effects requiring dose-reduction of levodopa CDP-choline may be an adjuvant preventing decompensation of parkinsonian symptoms. The possible future role of neuropeptides in parkinsonian therapy remains undertermined. What has to be stated despite all new developments in drug therapy for parkinsonism is, however, that we are still lacking a causally acting drug, one that would prevent degeneration of the nigrostriatal tract.

ABSTRACT

For two decades drug therapy of parkinsonism has been centering around oral levodopa substitution. Modifications and new trends in parkinsonian therapy have evolved in recent years certainly due to some shortcomings and long-term problems of levodopa treatment.

Dopaminergic agonists already play an important role in clinical praxis either as adjuvants to levodopa or as monotherapy for parkinsonism. In the tremor-dominant type of Parkinson's syndrome — one of seven clinically identificable subtypes of the disease — levodopa treatment often fails to provide sufficient control of symptoms.

Results with three different β-adrenoceptor antagonists given as adjuvants to L-Dopa 25 parkinsonian patients are reported, showing the superiority of this combined therapy versus L-Dopa alone in the control of tremor in the majority of patients. A favourable response of the emotional condition of the patients has also been observed.

In a controlled study of 20 parkinsonian patients the question of a possible levodopa dose-reduction by applying CDP-choline concomitantly has been evaluated.

The results reported show no significant differences between the patient group reveiving CDP-choline together with an unchanged levodopa - dose and the group of 10 patients receiving only 50% of their previous levodopa dosage. These observations point to a « levodopa-saving » effect of CDP-choline, which may be important in clinical situations requiring dose-reduction of levodopa.

The results with M.I.F. in the treatment of Parkinson's disease are reviewed and the role of peptides in parkinsonian therapy is re-evaluated.

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