Current Trends in the Drug Therapy of Parkinson Syndrome

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1. INTRODUCTION

Parkinson's disease is the major example of a central nervous system disorder that can be subject to a specific treatment by substituting the underlying neurotransmitter defect. Following the findings of EHRINGER and HORNYKIEWICZ [1] of a severely lowered striatal dopamine content in the parkinsonian brains, Levodopa substitution has become the principal form of drug treatment of Parkinson Syndrome some 20 years ago [2,3,4,5,6]. The therapeutic effects of Levodopa turned out to be highly superior to those of any other type of Parkinsonian treatment that had hitherto been employed. Unfortunately, the good response seen in most parkinsonian patients when first given Levodopa can usually not be maintained during chronic Levodopa-treatment. More than 50% of the patients show a declining total efficacy of the drug, frequently accompanied by a shortening of the duration of action of oral Levodopa ("wearing off" response), Levodopa-induced abnormal involuntary movements(AIM's) and pharmacogenic psychoses at increasingly lower dosage-levels of Levodopa (Table 1). Such changes in drug response usually become apparent after 3 to 5 years of chronic Levodopa substitution [7,8,9]. Probably the most disabling phenomenon developing during long-term Levodopa treatment of Parkinson's disease are the fluctuations in motor performance termed "on-off" effects [10,11].

el Biochemical Pharmacolo ical and Clinical Aspects of Cytidinediphosphocholine
ippia, E. P. Kennedy, S. I. Nilsson, and P. Galletti, Editors

TABLE 1 THERAPEUTIC PROBLEMS IN THE LATE PHASE OF PARKINSONISM

1) Declining efficacy of Levodopa "Wearing-off" reactions
2) Increasing incidence of drug-induced abnormal involuntary movements (AIM's)
3) Fluctuations in drug response ("on-off" reactions)
4) Increasing incidence of drug-induced psychoses

Whether these late management problems in Parkinson therapy actually are due to chronic exposure of striatal dopamine receptors to Levodopa or whether they are symptoms of the disease progress (or both) still remains controversial [8]. However, in the current concept of drug treatment for parkinsonism there is a growing tendency to either employ drugs alternative to Levodopa itself or to use Levodopa in combination with substances allowing lower Levodopa-dosages with fewer side effects or a more constant action of Levodopa. Some of these current trends in parkinsonian drug treatment will be briefly reviewed in this article.

2. "POST-LEVODOPA" TRENDS IN PARKINSONIAN DRUG THERAPY

In view of the lack of substances that may stop or prevent the underlying disease process of Parkinson Syndrome current efforts to improve anti-parkinsonian therapy are aiming to overcome the long-term problems of Levodopa treatment. At present however, the only class of substances that may be a true alternative to Levodopa substitution with possibly fewer long-term complications are the dopaminergic ergots. All other antiparkinsonian drugs introduced in the post-Levodopa era have their optimal effects only when combined with Levodopa itself. The classical example in this respect is L-deprenil, a selective inhibitor of MAO-B now widely used in clinical practice. Less well defined, but of considerable scientific interest is the role of neuropeptides, such as the tripeptide M.I.F. (PLG), and the phospholipid precursor Cytidine diphosphocholine (CDP-Choline) as anti-parkinsonian agents.

2.1 CURRENT STATUS OF DOPAMINOMIMETICS IN PARKINSON THERAPY

Dopaminergic ergots are in wide clinical use for more than 10 years now and there is no doubt about their effectiveness as antiparkinsonian agents. The broadest experience has accumulated with Bromocriptine [12,13,14,15], more recently equally favourable or even better results were reported with Mesulergine [10,17,18], Lisuride [19,20] and Pergolide [21,22]. In most clinical studies these dopamine agonists have been employed in combination with Levodopa and there is a prevailing view in the literature that in monotherapy these agents are not quite as effective as Levodopa [23]. However, in long-term studies of patients treated with Bromocriptine as monotherapy there has clearly been less development of AIM's and also of fluctuations in motor performance [13,15]. Furthermore the addition of a dopamin-

ergic ergot in advanced disease stages of Parkinsonism with a declining response to Levodopa frequently leads to some restoration of clinical improvement with reduction of pre-existing AIM's as is depicted in the example of Figure 1 for 10 patients with advanced parkinsonism treated with Lisuride.

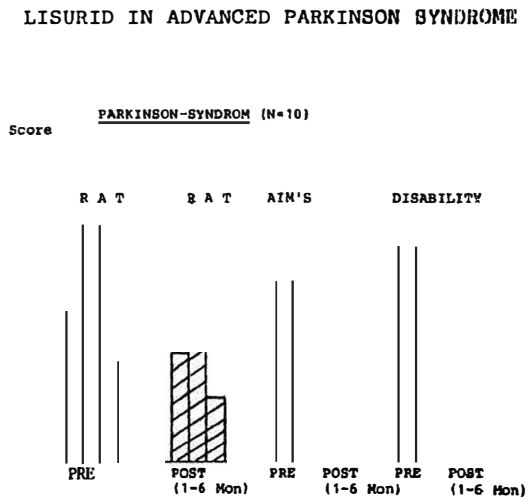

FIG. 1 Results of treatment with Lisuride (0.8 to 3.2 mg/d, mean 1.75 mg/d) in 10 patients with advanced Parkinson's disease (mean duration 13.2 years) in combination with pre-existing L-Dopa treatment (mean daily dose 540 mg)
R = Rigidity, A = Akinesia, T = Tremor.

Despite the numerous clinical reports on the anti-parkinsonian effects of dopaminomimetic agonists it is still controversial whether these agents can be employed as the primary treatment for Parkinson's disease resulting in fewer long-term complications than are now seen with Levodopa. Further long-term studies with dopamine agonists as monotherapy are clearly needed.

2.2 ANTIPARKINSONIAN EFFECTS OF CDP-CHOLINE - A CLINICAL STUDY

CDP-Choline, an intermediate compound in the bio-synthesis of brain phospholipids, has been shown to enhance striatal dopaminergic activity in various experimental settings [24,25]. Several clinical trials of CDP-Choline have clearly

indicated its antiparkinsonian efficacy [26,27,28]. Based on our own observations that a dosereduction of Levodopa seems possible after addition of CDP-Choline [29] we conducted a 5 week-trial with CDP-Choline in 20 patients (mean age 62 years, mean duration of disease 5,2 years) who had been on a stable Levodopa-substitution therapy for at least 6 months. The severity of disease as assessed by the scale of HOEHN and YAHR was grade 1 in one patient, grade 2 in eight patients, grade 3 in ten patients and grade 4 in one patient.

For the trial, patients were left on their previous Levodopa substitution therapy without any other concomitant anti-parkinson medication. They were randomly assigned to one of two equal treatment groups. During the first week the base-line values under individual L-Dopa therapy were evaluated in both groups. In group 1 daily i.v. injections of physiological saline were added during the second week. From week 3 to 5, placebo injections were replaced by 1000 mg of CDP-Choline given i.v in addition to the unchanged L-Dopa therapy. In group 2 L-Dopa dosage was reduced by 50% with replacement of capsules by placebo. Additional daily i.v. injections of saline were given as in group 1. From weeks 3 to 5, daily saline injections were replaced by 1000 mg of CDP-Choline given intravenously.

To evaluate the parkinson symptoms and psychological status of the patients during the trial, the following procedures were used: the clinical and disability status of the patients were assessed by a 5-point physician's and nurse's rating performed at weekly intervals.
In addition, motor function was evaluated by a test battery consisting of 3 subunits - a modified tapping and tread test and Grünberger's test of skilled hand use (6), which were performed at weekly intervals, and a drawing and writing test which had to be performed 3 times daily.

The patients' overall psychological status as well as concentrational power and depression were assessed by a 100 mm-test, which the patients performed 3 times daily, Brickenkamp's d_2-Test and the Hamilton depression rating scale, which were performed at weekly intervals.

The results obtained in this trial were in favour of a "Levodopa-saving" effect of CDP-Choline [30]. In the 5-point-clinical rating scale used in the study there was a significant improvement from baseline values and score values of week two respectively to week 5 indicating additional improvement in parkinsonian symptoms achieved by the addition of CDP-Choline. In group 2 CDP-Choline prevented deterioration of symptoms after the 50% reduction of Levodopa dosage (Fig. 2).

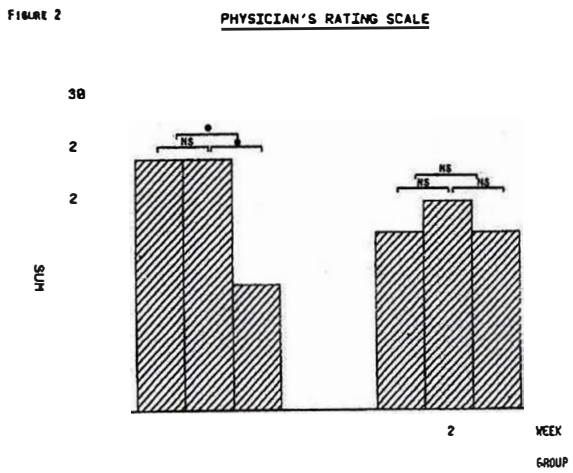

FIG. 2 Ranked score sums in the 5-point clinical rating scale during treatment with L-Dopa (week 1, baseline), Levodopa + i.v. Placebo (week 2) and L-Dopa + i.v. CDP-Choline (weeks 3 through 5). L-Dopa had been reduced by 50% after week 1 in group. (NS = not significant, * = significant with $p < 0.05$, Friedman's analysis of variance)

Similar results were obtained in different motoric tests in this trial of which an example is depicted in Figure 3.

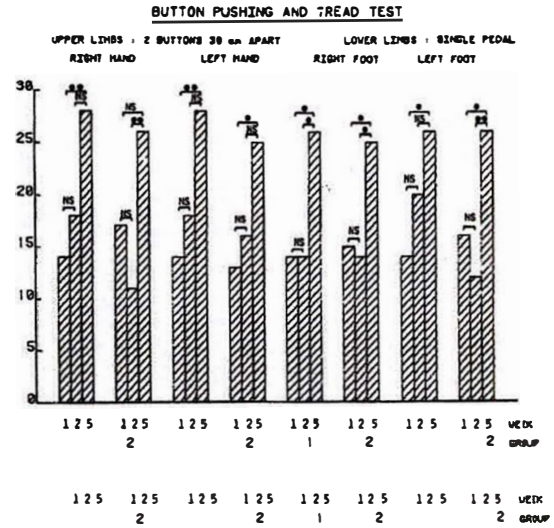

FIG. 3 Ranked score sums for number of response obtained when patients alternatingly had to press two buttons 30 cm apart or one foot-pedal for 20 seconds. Treatment groups as in Fig. 2, note improvement in both treatment groups by week 5 (NS = not significant, * = significant with $p < 0.05$, ** = significant with $p < 0.01$, Friedman's analysis of variance)

Despite the favourable results observed with CDP-Choline as an additive drug in Parkinson therapy by several authors, the substance so far has not been used on a broad clinical basis. This may be due to the effect that parenteral forms of therapy are of limited value in chronic illnesses as Parkinson's disease. On the other hand we feel that the possible role of CDP-Choline in the management of certain late problems in Parkinson-therapy, for instance fluctuations in motor performance deserves further interest.

2.3 MANAGEMENT OF FLUCTUATIONS IN MOTOR PERFORMANCE IN LATE PHASES OF PARKINSONISM

As has been pointed out earlier in this chapter fluctuations in motor performance or so-called "on-off" reactions constitute one of the major challenges in current Parkinson therapy. The therapeutical strategies in Parkinson patients experiencing such fluctuations in motor performance

have to be based on the type of fluctuation being present. In accordance with MARSDEN and PARKES [11] these fluctuations may be classified as shown in table 2.

TABLE 2 FLUCTUATION IN MOTOR PERFORMANCE IN L-DOPA TREATED PARKINSON PATIENTS

A. Relation to L-Dopa Plasma Level
- "wearing off" reaction, nocturnal akinesia
- early morning akinesia, early morning dystonia
- peak-dose dyskinesia
- dyskinesia - improvement - dyskinesia cycles

B. Seemingly unrelated to L-Dopa Plasma Level
- rapid oscillations ("yo-yoing")

C. Possibly independent of L-Dopa Treatment
Freezing episodes

In general, fluctuations with some relation to L-Dopa plasma levels are more favourable to treat than those without such a relation. As was mentioned before in this chapter dopaminomimetic ergots may reduce fluctuations in motor performance in Parkinson patients, possibly due to their longer plasma half-lives when compared to L-Dopa. End-of-dose deterioration phenomena are particularly responsive to the addition of the MAO-B inhibitor L-deprenil (Selegiline) to L-Dopa [31,32] especially if L-Dopa is simultaneously given in small and frequent doses in an effort to achieve more constant plasma levels of Levodopa. The latter may obviously be guaranteed by intravenous infusions of Levodopa, a therapeutic strategy which is currently finding renewed interest in clinical research with some promising results in patients with "on-off" phenomena [33,34].

Fluctuations of the "yo-yoing" type and freezing episodes are - at least at present - virtually impossible to treat successfully despite some favourable results obtained with L-Threo-DOPS, the precursor of noradrenaline, in the treatment of freezing-phenomena [35].

3. FUTURE PERSPECTIVES

Summarizing the current status of research in Parkinson-therapy there presently seem to be three major fields for future developments.

One certainly is the field of dopamine receptor agonists where the ongoing development may supply us with even more potent and more selective agonists than we presently possess and which may eventually be devoid of such distressing properties as inducing AIM's or hallucinosis or may show less decline in long-term efficacy. It also remains to be seen which role specific agonists and antagonists of presynaptic dopamine receptors may gain in Parkinson therapy with their property of influencing feed-back control of nigro-striatal neurons [36].

A second area for future progress in Parkinson therapy is the research in the field of peptide neurotransmitters and neuromodulators. Along with others we were able to demonstrate the antiparkinsonian efficacy of the tripeptide PLG (M.I.F.) [37,38] (see Fig. 4).

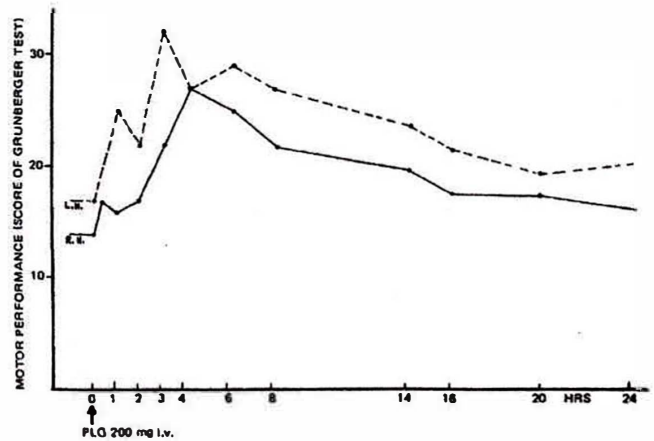

FIG. 4 Acute effect of a i.v. bolus injection of the tripeptide PLG in a 61 year old parkinsonian patient under chronic Levodopa-substitution. (Horizontal axis = time scale, vertical axis = motor performance score; R.H. = right hand, L.H. = left hand)

The development of orally active analogues of this peptide may well offer new aspects in antiparkinsonian therapy.

The clinical research currently going on to evaluate the benefits of intravenous infusion of Levodopa or dopamine agonists in patients with late complications of chronic dopaminergic treatment may finally lead to the advent of implantable supply systems of Levodopa or other dopaminergic drugs. Parkinson patients may then be submitted to a more physiological way of dopamine receptor stimulation provided penetration into the brain can be made constant.

Despite all their possible advantages these future developments would still only be a partial substitution of a transmitter defect in the brain. The ultimate goal of Parkinson therapy must be to halt the underlying disease process.

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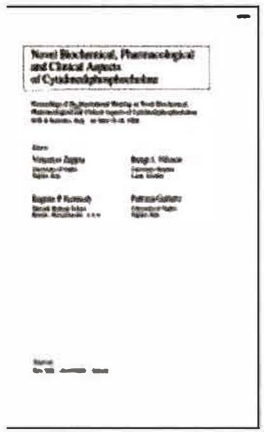
Novel Biochemical, Pharmacological, and Clinical Aspects of Cytidinediphosphocholine: Proceedings of the International Meeting on Novel Biochemical, Pharmacological, and Clinical Aspects of Cytidinediphosphocholine Held in Sorrento, Italy on June 12-14, 1984 ; Editors, Vincenzo Zappia ... [et Al.].



Vincenzo Zappia

Elsevier, 1985 - 406 Seiten

★★★★★

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Product details

Format: Hardback | 424 pages

Dimensions: 150 x 230mm

Publication date: 01 Apr 1985

Publisher: ELSEVIER SCIENCE & TECHNOLOGY

Imprint: Elsevier Science Ltd

Publication City/Country: Oxford, United Kingdom

ISBN10: 0444009671

ISBN13: 9780444009678