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CDP-CHOLINE IN THE TREATMENT OF PARKINSON SYNDROME

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SUMMARY

The aim of this paper was to summarize our experience in the use of CDP-Choline in treatment of patients with Parkinson's disease within the last ten years.
"Cytidine 5"-Diphosphocholine (CDP-Choline) is a precursor essential for the synthesis of phosphatidylcholine. The substance was found to increase axonal levodopa-flow, levodopa-uptake at the synapse, and the activity of tyroxin-hydroxilase. Furthermore, the substance may act through induction of hypersensitivity in the dopamin receptors which are down regulated during long-term levodopa treatment.
The results of the first two studies demonstrate that CDP-Choline is an effective substance in the treatment of Parkinson's disease when given intravenously. Study II, that the combination of levodopa plus DCI and CDP-Choline is superior to levodopa plus DCI monotherapy. The results in group II of study II indicate that CDP-Choline exhibits a levodopa sparing effect.
Therefore, CDP-Choline may be regarded as a novel "substance combining classical dopaminergic effect with a new effect on the signal transfer at the cell-membrane".

INTRODUCTION

"Cytidine 5"-Diphosphocholine (CDP-Choline) is a precursor essential for the synthesis of phosphatidylcholine (Kennedy 1957; Shimamoto et Al. 1975).
The substance was found to increase axonal levodopa-flow, levodopa-uptake at the synapse, and the activity of tyroxin-hydroxylase (Martinet et Al. 1978).
Furthermore, the substance may act through induction of hypersensitivity in the dopamine receptors which are down-regulated during long-term levodopa treatment.
The present publication summarizes the results of pharmacological studies on the efficacy of CDP-Choline in the treatment of Parkinson's disease.

PATIENTS AND METHODS

The first study was performed in 1977 (Gerstenbrand et Al. 1973). Five male and five female patients (aged between 50 and 72 years) suffering from Parkinson syndrome (9 from Parkinson disease and one from postencephalitic Parkinson syndrome) of various severity (5 with mild, 2 with medium and 3 with severe symptomatology) were randomly assigned to one of two treatment groups after a washout period.
There was no difference with respect to the disease duration and age between the two groups. In the first group 5 patients received 500 mg CDP-Choline daily intravenously during the first 10 days, and 1000 mg daily during the following 20 days.
The second group received 1000 mg CDP-Choline intravenously during the 30 days of the study, and on the last 10 days, in addition to CDP-Choline, L-Dopa 100 mg daily intravenously. For evaluating the patients at weekly intervals, the following scales and tests were used: a 10- items rating scale ranging from 0 to 5 to evaluate the severity of motor and vegetative symptoms, a walking test (the time required for walking 10 meters).
The Grünberger-Gerstenbrand (Gerstenbrand et Al. 1973) motor battery for skilled hand movements, the concentration test of Brickenkamp (d2-test), various tapping and tread tests and a 100 mm analogue scale for self-evaluation from the patient of general clinical state.
The second, single blind, placebo-controlled study was performed in 1981 (Rainer et Al. 1977). 20 levodopa-treated parkinsonian patients without levodopa-dependant clinical fluctuations except for mild wearing-off phenomenon were included in the study.
The ages of the patients ranged from 48 to 71, mean 62 years, disease duration from 4 to 6.5 years, mean 5.2 years, the stage of the disease according to Hoehn and Yahr from I to IV (I - 1pt, II - 8 pts, III - 10 pts, IV - 1 pt) and daily levodopa dosage from 300 to 800 mg.
The patients were randomly assigned to one of two treatment group.
There was no difference between the two groups with respect to age, disease duration, daily levodopa dosage and severity of the disease. During the first week of the study, both groups received their optimum levodopa plus DCI-dosage.
During the remaining four weeks of the study, the patients of group I continued to receive the optimum levodopa plus DCI-dosage, whereas in group II 50% of the daily levodopa plus DCI-dosage was replaced by placebo-capsules.
Both groups received intravenous placebo injections in addition to levodopa plus DCI in the second week of the study and 1000 mg CDP-Choline daily intravenously from the third to the fifth week.
To evaluate the parkinsonian symptoms and the psychological aspects of the patients the following procedures were used: a 5-points physicians' rating scale consisting of 10 items to assess the motor symptoms and disability, a motor-battery assessing the performance in tapping and treading, Gerstenbrand-Grünberger's test of skilled hand use, drawing and writing test.

The patient's concentration was tested by means of the Brickenkamp's d2-test. Depression was assessed by means of analogue scale (100 mm-test) and the Hamilton Depression scale.
In 1985, a pilote study was performed, comprising 15 parkinsonian patients suffering from severe levodopa-induced side effects like dyskinesias (6 pts) and pharmacotoxic psychosis (5 pts). The patients were given CDP-Choline intravenously, at dosages between 250 mg and 500 mg daily during three to four weeks. Levodopa plus DCI-dosage was reduced by mean 50%.
The mean age of the patients was 69 (± 4.5) years, mean disease duration was 7.5 years.
The Hoehn and Yahr score ranged from three to five. The Columbia rating scale mean scores before treatment was 46 (± 12.6).

RESULTS

Study 1

30 days of treatment with CDP-Choline in group one (10 days of therapy at a dosage of 500 mg/day, 20 days at 1000 mg/day) yielded an improvement of rigidity in 3 pts (Fig. 1), of akinesia in 3 pts (Fig. 2) and of tremor in 1 pt. In group two, all 5 pts improved with respect to rigidity with CDP-Choline monotherapy (1000 mg iv/day, Fig. 1), 4 pts with respect to akinesia (Fig. 2) and 2 pts for tremor. Additional levodopa treatment in group two after 20 days of CDP-Choline monotherapy resulted in a marked improvement of rigidity in 3 pts (Fig. 1), akinesia in 4 pts (Fig. 2) and of tremor in 3 pts.
No side effects were observed.

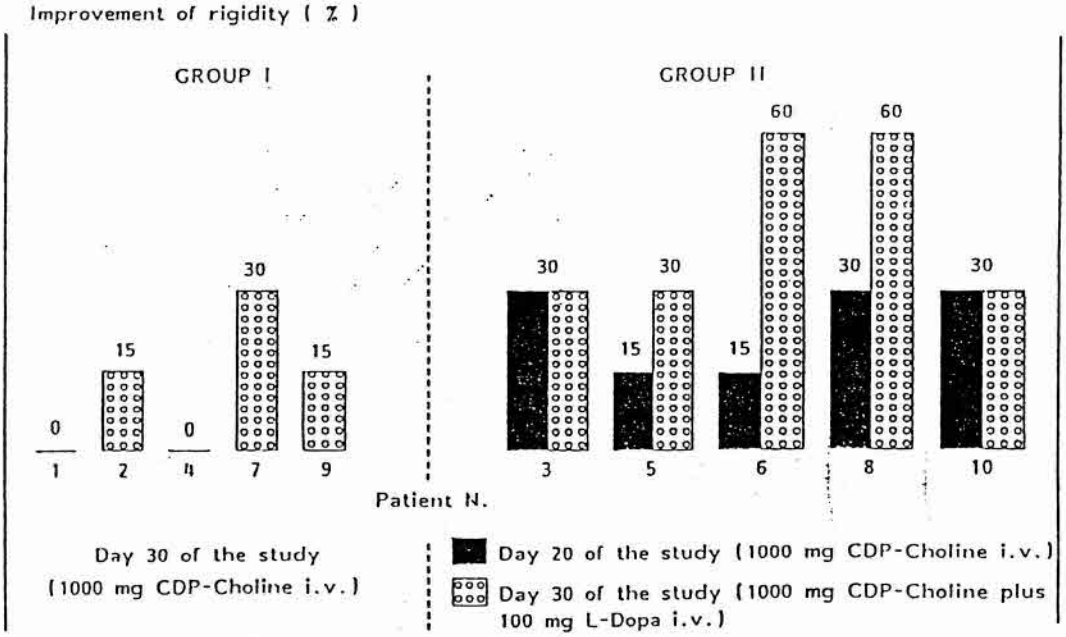

Fig. 1 - Effect of CDP-Choline on status of rigidity. Study n. 1 - N = 10.

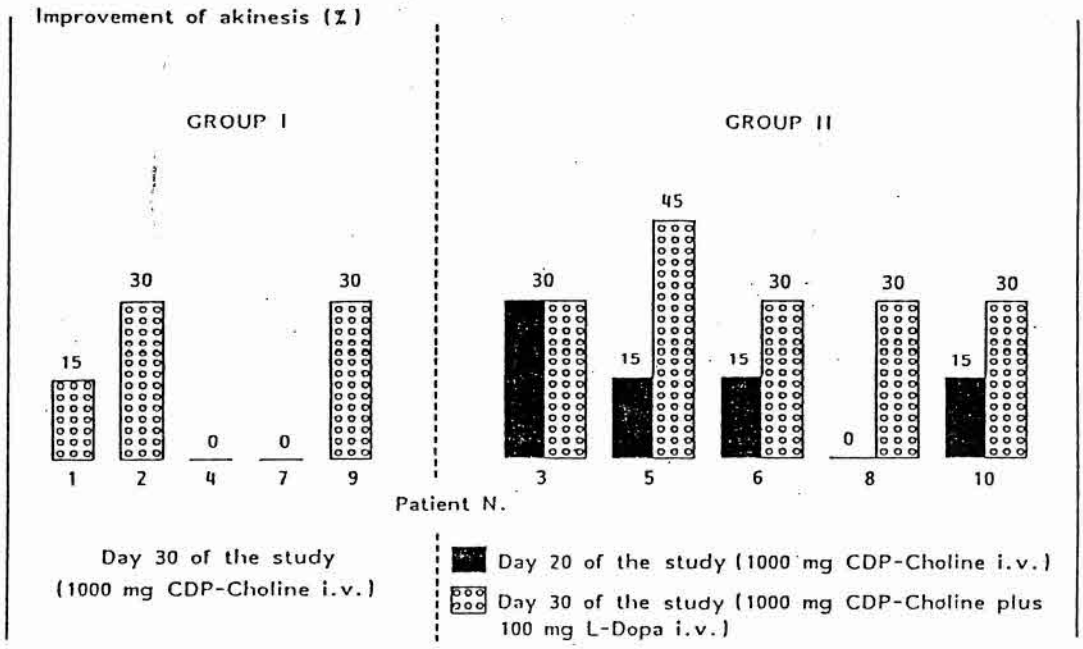

Fig. 2 - Effect of CDP-Choline on status of akinesia. Study n. 1 - N = 10.

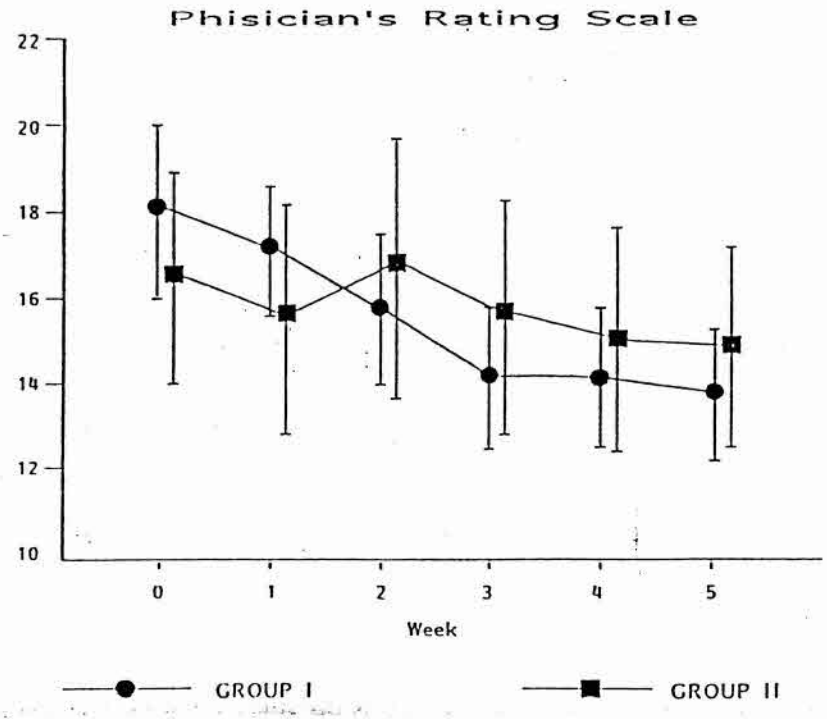

Fig. 3 - Mean scores of the clinical rating scale before and during the study of group I and II with standard deviations.

Study 2

Friedman's ANOVA revealed a significant improvement in the clinical rating scores of group I from the first to the fifth and from the second to the fifth week ($p \leq 0.05$) and no difference of the rating scores between the first and the second week of the trial.
No significant changes in the clinical rating scores were observed in group II between the first, second and fifth week of the trial (Fig. 3).
In the majority of the motor tasks, significant improvements were found in both groups between the first and the second and the first and the fifth week of the trial (group I in all of eight motor tasks, group II in seven of eight motor tasks).
In group I a significant improvement was found in the self-rating analogue scale for mood and in the Hamilton Depression scale between the first and fifth ($p \leq 0.01$) and the second and the fifth ($p \leq 0.05$) week.
There were no changes in the analogue scale scores and the Hamilton scores in group II between the first, second and the fifth week. No side effects attributable to CDP-Choline were observed. Two patients complained of headache, which disappeared spontaneously in the further course of the treatment without any change in the dosage of CDP-Choline. Two patients experienced transitory dizziness and one patient nausea. One patient related an increase of tremor probably due to the treatment with CDP-Choline.

Study 3

In the pilote study including 15 patients with advanced Parkinson's disease suffering from levodopa-induced side effects, three of six patients with levodopa-induced confusion and two of five patients with levodopa-induced pharmacotoxic paranoid-hallucinatory states showed an improvement.
In three of four non-confused patients, an improvement of cognitive processes was noted.
There was no significant deterioration in the mean Columbia rating scale scores.

DISCUSSION

The results of the first two studies demonstrate that CDP-Choline is an effective substance in the treatment of Parkinson's disease when given intravenously.
Study 2 showed that the combination of levodopa plus DCI and CDP-Choline is superior to levodopa plus DCI monotherapy. The results in group II of study 2 indicate that CDP-Choline exhibits a levodopa sparing effect.
The pilote study in 15 patients (study 3) with patients in late stages of the disease demonstrated that CDP-Choline is effective in the treatment of levodopa induced pharmacotoxic psychoses (confusion and paranoid-hallucinatory states).
The side effects of the substance are negligible.

Dopaminergic effects of the substance may be assumed.
Furthermore, a membrane stabilizing effect of the substance is possible. Preclinical studies have demonstrated that CDP-Choline protects the integrity of cell-membranes (Arienti et Al. 1979) by accelerating the resynthesis of phospholipids after damage to the neurons.
Therefore, CDP-Choline may be regarded as a novel "substance combining classical dopaminergic effect with a new effect on the signal transfer at the cell-membrane".

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