A double-blind study of the effects of levodopa in Parkinson's disease

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THERE IS CONSIDERABLE EVIDENCE suggesting that the symptoms of parkinsonism are related to a depletion of striatal dopamine.[1–4] Since oral dopamine does not cross the blood-brain barrier, efforts have focused on the systemic administration of L-dopa, dopamine's immediate precursor, which appears to pass through the barrier. Recent studies indicate that L-dopa is rapidly becoming the treatment of choice in parkinsonism.[5–8]

In the present study, a double-blind therapeutic trial has been used in the treatment of Parkinson's syndrome. The purpose of the study is to compare L-dopa to a conventional antiparkinsonian medication (procyclidine hydrochloride) and a placebo (lactose). Additionally, this study has been designed to determine whether a two- to six-week period is an adequate length of time to see the benefits of L-dopa therapy in parkinsonian patients receiving no other medication. It was also designed so that a patient could continue to take any drug that brought about significant improvement; in such cases, he was not required to try the other drugs in the study.

METHODS

Thirty patients (15 men and 15 women), aged 42 to 76 years, with well-established parkinsonism took part in the study. The population studied included 2 patients under 45 years of age and none over 80 years of age; the majority of patients were in the 61- to 70-year age group. The distribution follows:

Age	*Men*	*Women*	*Total*
Under 45	1	1	2
46 to 60	3	6	9
61 to 70	5	6	11
Over 70	6	2	8

The group studied was primarily Caucasian, with only 2 Negroes and no Orientals. Three patients had had stereotaxic surgery.

Patients accepted for the study were seen as outpatients, examined, and tested. This initial evaluation served as a basis for future comparisons and represented their status under optimal medical treatment prior to hospitalization for the double-blind drug study. The severity of their disease was graded as follows: [1] stage 1, unilateral involvement; [2] stage 2, bilateral involvement; [3] stage 3, first evidence of impaired balance and righting reflex; [4] stage 4, fully developed severe disease; and [5] stage 5, confinement to bed or wheelchair unless aided.[9] Grades III and IV were the degrees of severity most often reported in the study; 3 patients had stage 1 while 5 had stage 5, the most severe form of the disease.

Ten to fourteen days before hospitalization the patients stopped taking all medication, and no other maintenance medication was utilized throughout the study. Six patients with severe nursing problems were hospitalized during the two-week withdrawal period. At the end of the two-week period, all patients were hospitalized, fully reevaluated clinically, and tested for evidence of cardiovascular, hepatic, or renal disease. Routine clinical examinations, tests of motor and performance skills, blood tests, movies, tape recordings of speech, electroencephalograms, and pulmonary function studies were taken on every patient in the predrug period, during each drug trial, and at the end

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of the period. One of three medications, placebo, procyclidine hydrochloride, or L-dopa, was then given to each individual patient for a two-week trial in the hospital. The medications were randomly chosen in a double-blind protocol. If at the end of two weeks there had been no effect, the patient could elect to try the second drug. If there had been some effect, the patient was sent home and the medication continued for four more weeks. At the end of the two- to six-week period, the patient was fully evaluated with appropriate testing. At this point, the patient was given the option of either continuing treatment with the drug he first selected or electing to try one of the other two he had not received.

The patient who elected to try another drug would then again discontinue all medicine for two weeks and was readmitted to the hospital for the trial of the second medicine. At the end of two weeks' hospitalization, the same options were offered as existed in the first period. In a similar fashion, the patient could try the third medicine. Each patient was hospitalized in the clinical research center of the hospital where physical therapy, special nursing care, frequent records of blood pressure, and metabolic studies were readily accessible.

At the end of the three trials, both the patient and his physician decided on which medication was best and on the order in which they would be taken. The physician treating the patient did not know whether the capsules contained lactose (A), 1.25 mg. of procyclidine hydrochloride (B), or 500 mg. of L-dopa (C). When each patient completed all his trials and had rated the medications, the capsules were identified as A, B, or C. Only after the study was terminated were the investigators informed of the nature of capsules. L-dopa was, therefore, compared against a placebo and a widely accepted antiparkinsonian drug, procyclidine hydrochloride.

Each patient was his own control in this study. A rated neurological examination[10] was utilized as a measure of effectiveness of drug therapy. All of the major symptoms of parkinsonism, including mental status, postural stability, sialorrhea, sweating, facial expression, bradykinesia, finger dexterity, tremor of each limb and face, rigidity of each limb and neck, and posture, were evaluated. Each symptom

TABLE 1

RESULTS OF PREFERENCE FOR L-DOPA, PROCYCLIDINE, AND PLACEBO AND STATISTICAL COMPARISONS

Drug order	*Number of patients preferring drug* L-dopa	Procyclidine	Placebo
L-dopa	10	–	–
Placebo, L-dopa	4	–	–
Procyclidine, L-dopa	6	–	–
Placebo, procyclidine, L-dopa	5	1	–
Procyclidine, placebo, L-dopa	4	–	–
Total	29	1	–

Statistical comparisons

I. Independent samples analysis—analysis restricted to results of first drug period
   A. Data
      1. Of 10 patients on L-dopa first, all 10 chose to go no further.
      2. Of 10 patients on procyclidine first, none chose to go no further.
      3. Of 10 patients on placebo first, none chose to go no further.
   B. Null hypotheses
      1. Proportion choosing to go no further at end of first drug period is the same for L-dopa and procyclidine.
      2. Proportion choosing to go no further at end of first drug period is the same for L-dopa and placebo.
   C. Results of two-tailed test of significance (Fisher's exact test)
      1. Difference is highly significant ($p < 0.0001$).
      2. Difference is highly significant ($p < 0.0001$).

II. Paired samples analysis—analysis restricted to patients receiving 2 or 3 of the study drugs
   A. Data
      1. Of 16 patients on both L-dopa and procyclidine, 15 preferred L-dopa and 1, procyclidine.
      2. Of 14 patients on both L-dopa and placebo, 13 preferred L-dopa and 1, neither drug.
   B. Null hypotheses
      1. L-dopa and procyclidine are equally preferable.
      2. L-dopa and placebo are equally preferable.
   C. Results of two-tailed test of significance (binomial distribution used)
      1. Difference is highly significant ($p < 0.001$).
      2. Difference is highly significant ($p < 0.001$).

was measured on a five-point scale, and the sum of the scores for each patient provided an index of the severity of his illness. Each symptom was rated from 0 to 4, with 0 indicating an absence of that particular symptom and 4 indicating the most severe form of the respective symptom. The Northwestern University Disability Scale[10] was utilized in each period as an assessment of the performance of daily living activities. This scale enabled the clinician to measure such common activities as walking, dressing, eating, feeding, hygiene, and speech. Activities with a score of 0 indicated no impairment of that particular function, while a score of 10 indicated the most severe restriction of the activities of walking, dressing, hygiene, and speech. In grading the severity of the activities of feeding and eating, however, a score of 5 indicated the most severe restriction. The sum of the scores of the various activities was considered the disability index for each patient.

Since the formal neurological examination alone often did not reflect the overall functional improvement of each patient, an index combining the neurological and disability examinations was calculated. The scores of the neurological and disability examination added together were taken as an index of function. This index has proved to be a somewhat quantitative measure of the return of function. The overall clinical assessment by the clinician has remained the most practical and useful overall gauge of improvement.

Treatment with each medication was begun with a dose of 2 capsules and increased according to each patient's tolerance until optimal clinical response or disturbing side effects became apparent. Maximum dosage of L-dopa was 7.5 gm.; of procyclidine hydrochloride, 20 mg.; and of lactose, 16 capsules.

RESULTS

The independent samples analysis (restricted to patients' choices at conclusion of first drug period) as well as crossover analysis (restricted to patients on more than one drug) arrived at the same inescapable conclusion: L-dopa was the drug of preference in this study. Table 1 summarizes the results, and the p values are calculated for comparison. It is of interest that 29 of 30 patients chose to discontinue the study the first time they were treated with L-dopa, indicating that they were so satisfied with this particular drug that they saw no need to give it up for the remaining ones.

As L-dopa was continued, there was a marked improvement after seven to ten days in responsive patients. This dramatic, sharp improvement was then usually followed by a continued but more gradual improvement. All of the activities of daily living progressively improved until side effects became apparent, at which time certain activities deteriorated, e.g., facial grimacing made eating difficult in cases in which this function had been improving. The percentage of improvement in the examination of the activities of daily living was computed for each period and during each drug trial. The average improvement seen in the 29 patients who chose L-dopa was striking. However, some improvement also occurred in patients who tried procyclidine hydrochloride, and 1 patient chose this drug over L-dopa and

TABLE 2

COMPARISON OF CHARACTERISTICS OF PATIENTS BY FIRST DRUG ADMINISTERED

	First drug			*Total (all patients)*
	Placebo	*Procyclidine*	*L-dopa*	
Total patients	10	10	10	30
Sex				
Men	6	5	4	15
Women	4	5	6	15
Age (years)				
≤60	3	4	3	10
61-70	5	2	5	12
71-80	2	4	2	8
Severity (grade)				
I	1	0	2	3
II	2	2	1	5
III	2	3	2	7
IV	4	2	4	10
V	1	3	1	5
Duration of disease (years)				
≤5	7	5	7	19
6-10	3	3	1	7
11-15	0	2	1	3
16-20	0	0	1	1

lactose. On the average, facial expression improved more with procyclidine hydrochloride than with L-dopa or lactose. Posture was the only finding which worsened with procyclidine hydrochloride. In general, the symptoms of parkinsonism became worse on lactose; however, mild improvement was seen in tremor, rigidity, and speech in some patients who tried lactose. The improvement in these patients may represent the benefit seen with physical therapy or the "placebo effect." None of the patients selected lactose as the drug of choice. Table 2 shows the distribution characteristics of patients on the first trial of each medication.

Side effects which occurred in this study are summarized in Table 3. As evident from this table, L-dopa has considerable undesirable side effects. Four patients chose to discontinue the medication after six weeks; 2 patients became frightened with the mental changes (psychoses and hallucinations), 1 patient had marked dystonia and abnormal movements, and 1 patient had persistent nausea and emesis. However, none of our patients had nonreversible side effects and no deaths or cardiac arrhythmias occurred among the 30 patients. Table 4 summarizes the alterations in laboratory tests; there was a transient elevation in the BUN, SGOT, and alkaline phosphatase, while the white blood count decreased in a few. No appreciable change occurred on serial EEG tracings.

The side effects induced by L-dopa had little effect on the neurological rating scale but often had a significant effect on the disability rating scale. Involuntary movements hampered the improvement of walking, dressing, and speech. There appeared to be no correlation between optimal daily dose of 3 to 6 gm. of L-dopa per day and the degree of response. On the other hand, doses lower than 3 gm. per day resulted in a greater percentage of poor response. The average dose of L-dopa in this study was 4 gm. per day. The duration of Parkinson's disease prior to L-dopa therapy tended to have a slight influence on the degree of improvement; there were no failures among patients who had had their illness for less than two years. Those patients whose disease spanned more than fifteen years had minimal improvement of function. Although sex played no apparent role in the effectiveness of L-dopa, age did, i.e., the younger the patient, the better his response to L-dopa. Of the individual neurological components tested, the greatest average improvements occurred in sialorrhea, sweating, and finger dexterity. All three of the

TABLE 3
SIDE EFFECTS

	L-dopa	*Procyclidine hydrochloride*	*Lactose*
Gastrointestinal			
Nausea	30	5	1
Vomiting	30	1	0
Diarrhea	3	1	1
Dyspepsia	5	2	0
GI bleeding	0	0	0
CNS			
Dystonia	3	0	0
Abnormal movements	10	0	0
Choreoathetosis	6	0	0
Seizures	1	0	0
Confusion	12	6	0
Nervousness, anxiety	11	4	2
Depression	9	1	1
Abnormal dreams	6	1	0
Hallucinations	6	0	0
Paranoid feelings	3	1	0
Overt psychosis	7	3	1
Insomnia	12	0	0
Drowsiness	3	0	0
Blurred vision	0	7	0
Dry mouth	0	11	0
Cardiovascular			
Hypotension*	30	1	1
Chest pains	1	0	1
Hypertension	0	0	0
Mitral insufficiency	0	0	0
Arrhythmias	0	0	0
ECG changes	0	0	0
Dermatologic			
Flushing of skin	1	1	0
Dermatitis	0	0	0
Miscellaneous			
Malaise	3	0	0
Hyperventilation	2	0	0
General pain	0	1	1
Myalgia	2	0	0
Urinary urgency	1	0	0
Increased libido	5	0	0

* Included any drop in blood pressure

cardinal symptoms of Parkinson's disease—rigidity, tremor, and bradykinesia—improved by approximately 60%. The improvement in bradykinesia was especially significant in 25 patients. Twenty-one of 30 patients enjoyed a 50% or greater improvement after the initial period of six weeks. Walking and posture responded the least. Seven patients who had had minimal improvement (15% or less) after six weeks of L-dopa therapy experienced a 19% or greater improvement with prolonged therapy. Three patients remained minimally responsive even after more than five to six months of L-dopa therapy. This minimal improvement (15% or less) was considered to be greater than that obtained with prior antiparkinsonian medical therapy. In the patients with minimal improvement, both patient and doctors recognized some immeasurable response which made it clear to both that this drug trial with drug C, or L-dopa, was significantly better than with the other two. Of the disability components tested, the greatest average improvement occurred in feeding and eating. All of the disability categories measured showed a mean response of greater than 40% and most were close to or above the 50% level. Two people completely recovered from their disabilities in the first six weeks, and 1 more recovered completely in the subsequent month. All 3 patients who had had a previous thalamotomy improved considerably; however, 1 decided to stop L-dopa therapy owing to mental changes (hallucinations and psychosis). Of the 2 other patients, both improved with procyclidine hydrochloride (45 and 41%, respectively) as well as with L-dopa (73 and 93%, respectively). One of the patients with mild right hemiparesis after his surgery became significantly worse after L-dopa therapy.

TABLE 4

LABORATORY SUMMARY

	L-dopa	*Procyclidine hydrochloride*	*Lactose*
Increased alkaline phosphatase	5	0	0
Increased SGOT	4	1	0
Increased BUN	12	1	1
Darkened urine	23	0	0
Decreased white blood count	2	1	0

DISCUSSION

When the double-blind technique is utilized, there is little doubt that L-dopa is better than placebo or procyclidine hydrochloride in the treatment of parkinsonism. Twenty-nine of 30 patients selected L-dopa, while 1 patient chose procyclidine hydrochloride. None felt lactose to be of significant benefit compared with the other two drugs. Previous reports have also verified that L-dopa is the drug of choice in Parkinson's disease;[5–8] however, double-blind methods were not used to compare L-dopa with another conventional antiparkinsonian drug.

Previous reports have indicated that the dosage must be increased very gradually and that improvement in symptoms might, in some patients, be delayed for months. However, our study has shown that a therapeutic response to L-dopa often occurred in less than two weeks and usually by six weeks if the drug was to be effective. In 7 of 30 patients who had minimal improvement, significant additional progress did occur when the drug was continued for a further six- to twelve-week period. This suggests that a trial of this medication should be at least three months long before it is discontinued. More patients tolerated the optimal dose by the end of six weeks. Other reports have indicated that in rare patients improvement may not occur in this period, but this has not been our experience so far.

Movies, handwriting, speech evaluation, and pulmonary function tests revealed the most consistent improvement, while the EEG and blood studies were of little assistance. Many patients receiving L-dopa showed increased intelligibility and decreased tremor by tape recordings of speech. This was not evident with either procyclidine hydrochloride or lactose. In addition, there was increased respiratory flow rates during pulmonary function tests with L-dopa which did not occur with placebo or procyclidine hydrochloride. Improved handwriting often correlated with improved speech. Movies offered an excellent mode of recording serial improvement and side effects of the various drugs on the patients. These studies were all evaluated while the physicians were

still working within the double-blind protocol.

Side effects were frequent with L-dopa, especially related to gastrointestinal (nausea and emesis), CNS (confusion, movement disorders, and psychic changes), and cardiovascular (hypotension) systems. However, side effects also occurred with the other drugs, but to a much lesser degree. There were no deaths or nonreversible problems. With gradual reduction of the medication, the side effects abated, often with a recurrence of some parkinsonian symptoms at the lower dosage, however. The question of whether the marked improvement from L-dopa is worth the frequent side effects seems to be answered in our double-blind study in that patient acceptability and choice were the prime criteria for final selection of the drug.

SUMMARY

Both the independent analysis and the crossover analysis have shown that L-dopa was preferred over procyclidine hydrochloride and lactose in this double-blind study. Although side effects were frequent and caused 4 patients to discontinue L-dopa, nevertheless, the remaining 25 patients readily accepted this medication. Twenty-one of 30 patients enjoyed a 50% or greater improvement after the initial period of six weeks. An additional 7 patients who had less impressive early responses demonstrated a 19% or greater improvement after prolonged therapy. Patients given placebo or standard antiparkinsonian medicine on the first trial always were willing to give it up to try "something else." Twenty-nine of 30 patients were satisfied with L-dopa the first time they received it and had no interest in giving it up to try the other drugs in the study.

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REFERENCES

1. Ehringer A, Hornykiewicz O: Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. Klin Wschr 38: 1236-1239, 1960
2. Bernheimer H, Birkmayer W, Hornykiewicz O: Zur Biochemie des Parkinson-Syndrome des Menschen, Einfluss des Monoaminoxydase-Hemmer-Therapie auf die Konzentration des Dopamins, Noradrenalins und 5-Hydroxytryptamins im Gehirn. Klin Wschr 41:465-469, 1963
3. Hornykiewicz O: Die topische Lokalisation und das Verhalten von Noradrenalin und Dopamin (3-Hydroxytyramin) in der Substantia nigra des normalen und parkinsonkranken Menschen. Wien Klin Wschr 75:309-312, 1963
4. Hornykiewicz O: Dopamine (3-hydroxytyramine) and brain function. Pharmacol Rev 18:925-964, 1966
5. Cotzias GC, Van Woert MH, Schiffer LM: Aromatic amino acids and modification of parkinsonism. New Eng J Med 276:374-379, 1967
6. Cotzias GC, Papavasiliou PS, Gellene R: Modification of Parkinsonism—chronic treatment with L-dopa. New Eng J Med 280:337-345, 1969
7. Yahr MD, Duvoisin RC, Hoehn MM, et al: L-Dopa (L-3,4-dihydroxyphenylalanine): Its clinical effects in parkinsonism. Trans Amer Neurol Ass 93:56-60, 1968
8. McDowell F, Lee JD, Swift T, et al: Treatment of Parkinson's syndrome with L-dihydroxyphenylalanine (Levodopa). Ann Intern Med 72:29-35, 1970
9. Hoehn MM, Yahr MD: Parkinsonism: Onset, progression and mortality. Neurology (Minneap) 17:427-442, 1967
10. Canter DJ, De La Torre R, Mier M: A method for evaluating disability in patients with Parkinson's disease. J Nerv Ment Dis 133:143-147, 1961

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