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An Alternative Medicine Treatment for Parkinson's Disease: Results of a Multicenter Clinical Trial

HP-200 in Parkinson's Disease Study Group

ABSTRACT

The natural occurrence of antiparkinsonian drugs in plants—anticholinergics in *Datura stramonium*, levodopa in *Mucuna pruriens* and *Vicia faba*, dopamine agonist activity in *Claviceps purpura*, and MAO inhibitor activity in *Banisteria caapi*—are known. Our study examined the efficacy and tolerability of HP-200, derived from *Mucuna prurient*, in patients with Parkinson's disease. Sixty patients with Parkinson's disease (46 male and 14 female) with a mean (±SD) age of 59 ± 9 years were treated in an open study for 12 weeks. Of these, 26 patients were taking synthetic levodopa/carbidopa formulations before treatment with HP-200, and the remaining 34 were levodopa naive. HP-200, a powder (supplied as a 7.5 g sachet), was mixed with water and given orally. The Unified Parkinson's Disease Rating Scale (UPDRS) was used at baseline and periodically during the 12-week evaluation. Statistically significant reductions in Hoehn and Yahr stage and UPDRS scores were seen from baseline to the end of the 12-week treatment ($p < 0.0001$, *t*-test). The group mean (±SD) dose for optimal control of symptoms was 6 ± 3 sachets. Adverse effects were mild and were mainly gastrointestinal in nature. No adverse effects were seen in clinical laboratory reports. HP-200, developed from an alternative medicine source, Ayurveda, was found to be an effective treatment for patients with Parkinson's disease.

INTRODUCTION

Drugs derived from plant sources that have been found to be effective in the treatment of Parkinson's disease are well known. For example, the seeds of the *Datura* plant have an anticholinergic effect and have been used for several decades as an antiparkinsonian drug. The beans of *Mucuna pruriens* and other members of the *Mucuna* genus (Bell and Janzen, 1971; Damodaran and Ramaswamy, 1937; Natelson, 1969) and *Vicia faba* (Lattanzio et al., 1982) contain levodopa, a major drug used in the treatment of Parkinson's disease. A dopamine agonist, bromocriptine, is extracted from ergot (*Claviceps purpura*), a fungus (Parkes, 1977). Monoamine oxidase inhibitors are known to exist in plant sources, such as *Banisteria Caapi* (banisterine) (Sanchez-Ramos, 1991) and *Nicotiana tabacum* (the common tobacco plant) (Norman et al., 1982).

The ancient Indian medical system, Ayurveda, now considered to be a form of alternative medicine, offers a large number of thera-

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peutics for the treatment of many different diseases (Dash and Kashyap, 1980). Parkinson's disease is described in Ayurveda as *Kampavata* (*kampa* means tremor, and *vata* refers to the metabolic derangement that causes neurological or mental disease) (Manyam, 1990). The Ayurvedic Materia Medica mentions treatment of Parkinson's disease with *M. pruriens* (*Atmagupta* in Sanskrit) (Manyam, 1990). In addition, *M. pruriens* has been described as a useful therapeutic agent for treating various diseases of the endocrine, reproductive, and nervous systems (Nadkarni, 1908; Singhal et al., 1979; Vaidya, 1925; Vaidya et al., 1978a, b). The *M. pruriens* plant is a twiner with trifoliate leaves, purple flowers, and turgid S-shaped pods covered with hairs that cause intense itching on contact with the skin. The plant belongs to the family Leguminosae, is indigenous to India and other parts of the world, and has been used in Ayurveda from ancient times (Manyam, 1990). The overdose effects of *Mucuna* are recognized in Ayurveda and include headache (*Sirah suta*), dystonia (*manyastambha*), fatigue (*srama*), tremor (*kampa*), syncope (*murcha*), and thirst (*trsa*) (Dutt, 1980). Many of the same adverse effects occur from synthetic levodopa and other drugs used in treating Parkinson's disease.

In 1937, Indian scientists isolated levodopa from the beans of the *Mucuna* (Damodaran and Ramaswamy, 1937). However, its importance in the treatment of Parkinson's disease was unknown at that time. Following the establishment of the role of levodopa in the treatment of Parkinson's disease, a screening of more than 1000 species of 135 plant families revealed that only plants from the genus *Mucuna* contained levodopa in sufficient amounts to consider commercial development (Daxenbichler et al., 1971). Vaidya et al. (1978a), in a study using the Northwestern University Disability Scale (Canteb et al., 1961), treated patients with Parkinson's disease with a powder made from the whole bean of *Mucuna*. The results indicated a decreased incidence of adverse effects from treatment with *Mucuna* powder when compared with the synthetic levodopa patients were receiving before entering the trial.

Our studies (unpublished) show that the levodopa content (dry weight) of a whole *Mucuna* bean is 4.02%, the endocarp containing 5.28% and the pericarp (skin) 0.09%. Vaidya et al. (1978b) showed *Mucuna* to be effective in the treatment of galactorrhea, suggesting that *Mucuna* may have direct dopamine agonist activity. As *Mucuna* is a legume, it is a rich source of tocopherol (vitamin E). Vitamin E is known to play an important role in both humans and animals (Kayden, 1993). However, the importance of vitamin E in Parkinson's disease is not proven (The Parkinson's Disease Study Group, 1993). Because of its bulk, *Mucuna* is likely to aid excretion, thus lessening constipation, which is common in Parkinson's disease. As a single drug, it may benefit many symptoms of Parkinson's disease and may contain other unidentified antiparkinson compounds in addition to the amino acid, levodopa. We are reporting the first open trial of HP-200, a formulation prepared from the endocarp of *M. pruriens* beans, in Parkinson's disease to evaluate efficacy and tolerability in patients with Parkinson's disease.

PATIENTS AND METHODS

Study population

Sixty patients with known idiopathic Parkinson's disease participated in the study after giving informed consent for the protocol approved by each of the four participating institutions: Jaslok Hospital and Medical Research Center, Sir J.J. Group of Hospitals of Grant Medical College, Hinduja National Hospital and Medical Research Center, Bombay, and Public Health Center, Madras. Forty-six patients were male, and 14 were female. The mean (±SD) age was 59 ± 9 years. The duration of illness was a mean (±SD) of 4.1 ± 3.4 years. Eight patients were in Hoehn and Yahr stage I, 27 in stage II, 17 in stage III, and 8 in stage IV (Hoehn and Yahr, 1967). Thirty-four patients were levodopa naive, and 26 were being treated with carbidopa/levodopa in varied doses. Thirty-two of these 60 patients were taking anticholinergics, 9 amantadine, and 9 selegiline. The diagnosis of Parkinson's disease was based on having two or more of the following symptoms or signs: resting tremor,

rigidity, postural change, bradykinesia, and gait disturbance. Patients with a past or present history of treatment with neuroleptic drugs, surgery for parkinsonism, severe head injury, cerebral infarction, or unstable cardiovascular, renal, hepatic, or pulmonary disease were excluded. No change in diet was made, and other medications for systemic disease, such as insulin, antihypertensives, and analgesics, were continued during the trial.

Study protocol

Carbidopa/levodopa was discontinued in those who were taking the drug before entering the study ($n = 26$). Other antiparkinson drugs, such as amantadine, anticholinergics, and selegiline, were continued. HP-200 doses were initiated at one sachet thrice daily and increased at the week 2 and week 4 visits to obtain the optimal response. The efficacy and adverse reactions were assessed at weeks 2, 4, 8, and 12. Laboratory studies included complete blood count (CBC), blood chemistry, chest x-ray, and electrocardiogram at baseline and at week 12.

Study outcome measurements

Parkinsonism was scored using the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1988). UPDRS I evaluates mentation, behavior and mood, with a maximum score of 16 for 4 items. UPDRS II evaluates activities of daily living, with a maximum score of 52 for 13 items. UPDRS III evaluates motor examination components, with a maximum score of 56 for 14 items. Reduction in the score indicates improvement. Baseline scores were obtained 12 hours or more after the last dose of carbidopa/levodopa was taken, and the subsequent scores were determined following a dose of HP-200. Total scores at the baseline and week 12 were compared to evaluate the efficacy of the drug.

Drug

HP-200 was prepared from the beans of *M. pruriens* and was supplied in the form of 7.5 g powder sachets. The levodopa content in HP-200 was determined for standardization of the preparation, since it is of plant origin, and correction for seasonal variation and other natural causes that may have an impact on the chemical content of the product must be made. Adjustments to maintain levodopa content at 33.33 mg/g of HP-200 were undertaken by adjusting the amount of *Mucuna* endocarp powder in HP-200. The product was tested for stability for 36 months and was found to be stable. When mixed with water, the powder mixture was found to be stable for 24 h at refrigerator temperature (12° C), room temperature (18° C), and human body temperature (37° C).

Safety studies

Despite the use of *M. pruriens* in humans for centuries (Manyam, 1990), an additional safety measure in the form of an acute oral toxicity study of the HP-200 powder was conducted. Single doses of 2.5, 5, 7.5, and 10 g/kg were administered to male and female mice ($n = 10$ each, 20–25 g body weight) and male and female albino rats ($n = 10$ each, 125–150 g body weight) by gavage using a 14-gauge intragastric feeding tube. The dose of 10 g/kg was the highest feasible dose that could be administered with the use of the intragastric feeding tube. The animals were observed for signs of toxicity, change in behavior, and mortality for a period of 48 hours. No morbidity or mortality occurred in any of the animals, and the LD_{50} of HP-200, when administered in a single dose by the oral route, is greater than 10 g/kg body weight. The reported LD_{50} of synthetic levodopa under similar conditions is 3650 mg/kg in mice and 4000 mg/kg in rats (Budavani, 1980). Since the levodopa content of HP-200 is approximately 3%, the LD_{50} of HP-200 would, therefore, be approximately 100 g/kg, an amount not feasible for administration in a single dose. Long-term toxicological studies of similar doses in male and female albino rats ($n = 100$) for 52 weeks did not reveal any significant change in CBC, blood chemistry, urinalysis, gross pathology, and histology of vital organs.

Data management and statistical analysis

Demographic and clinical characteristics of the patient population are included in Tables 1 and 2. The mean ± SD of the total scores on

TABLE 1. PATIENT CHARACTERISTICS

Characteristic	*Baseline*	*Week 12*
No. of patients	60 (46 M/14 F)	–
Age (years)	59 ± 9[a]	–
Duration of illness (years)	4.1 ± 3.4	–
Levodopa naive	34	–
Carbidopa/levodopa treated	26	–
Hoehn and Yahr stage	2.5 ± 1	1.6 ± 1[b]
UPDRS I	2.2 ± 1.5	1.1 ± 1.8[b]
UPDRS II	12.8 ± 6.4	7.6 ± 6.4[b]
UPDRS III	18.2 ± 8.1	9.8 ± 7.4[b]
Other anti-PD medications[c]		
Anticholinergics	32	32
Amantadine	9	9
Selegiline	9	9
HP-200 dosage/day	None	6 ± 3[d]

[a]Values are means ± SD.
[b]Significance by paired *t*-test, $p = 0.0001$.
[c]Either alone or in combination with others.
[d]No. of sachets of 7.5 g each.

the UPDRS were determined at the baseline period and at the end of weeks 4, 8, and 12 of HP-200 treatment. The data of baseline and week 12 on HP-200 treatment were used for statistical analysis, as the dosage was stabilized by week 12 and adequate time was allowed to assess any adverse reactions. Comparisons were done using the Statistical Analysis System procedure (SAS Institute, 1982) to estimate means, SDs, and significance. All group values were reported as mean ± SD, and significance was expressed as *p* value. The paired *t*-test was applied to compare the effect of HP-200 on scores at week 12 with baseline scores. Two by two split plot analysis of variance (ANOVA) was applied to compare the subgroups of levodopa-treated vs. levodopa-naive patients over the two time periods (0–12 weeks).

RESULTS

The daily dose of HP-200 employed was a mean (±SD) of 6 ± 3 sachets at the end of 12 weeks. The frequency of dosing was a median of three times daily (9 patients b.i.d., 37 patients t.i.d., 11 patients q.i.d., 3 patients 5 times/day). Slight variation in dosage occurred among the four centers, but this was not statistically significant. During this period, no change was made in the patients' other antiparkinson medications, such as anticholinergics, amantadine, or selegiline, nor did the patients receive any other synthetic levodopa preparations.

Efficacy

The Hoehn and Yahr stage decreased from a mean (±SD) of 2.5 ± 1 at baseline to 1.6 ± 1 at week 12. The difference was significant by the paired *t*-test ($p = 0.0001$). UPDRS I (mentation, mood, and behavior) scores at baseline were 2.2 ± 1.5 and fell to 1.1 ± 1.8 at week 12. UPDRS II (activities of daily living) scores fell from 12.8 ± 6.4 at baseline to 7.6 ± 6.4 at week

TABLE 2. LEVODOPA NAIVE VS. CARBIDOPA/LEVODOPA TREATED: PATIENT CHARACTERISTICS

Characteristic	*Levodopa naive*	*Carbidopa/Levodopa treated*
No. of patients	34 (26M/8F)	26 (20M/6F)
Age (years)	60.1 ± 9.3[a]	57.5 ± 7.5
Duration of illness (years)	3.9 ± 3.2	4.4 ± 3.7
Hoehn and Yahr stage		
Baseline	2.4 ± 0.9	2.7 ± 0.9
Week 12	1.6 ± 0.9	1.5 ± 0.6
UPDRS I		
Baseline	2.2 ± 1.8	2.3 ± 1.9
Week 12	0.8 ± 1.5	1.3 ± 2.0
UPDRS II		
Baseline	11.6 ± 5.6	14.4 ± 7.1
Week 12	8.0 ± 10.3	7.1 ± 5.8
UPDRS III		
Baseline	17.3 ± 7.6	19.3 ± 8.7
Week 12	9.9 ± 8.1	9.7 ± 6.6
Other anti-PD medications[b]		
Anticholinergics	20	13
Amantadine	2	7
Selegiline	2	7
HP-200 dosage/day (week 12)	5 ± 2	7 ± 3[c]
Adverse reaction		
Nausea	4 (11.8)[d]	3 (11.5)
Vomiting	1 (2.9)	0
Sensation of abdominal distention	1 (2.9)	3 (11.5)
Dyskinesia	0	2 (7.7)
Insomnia	1 (2.9)	1 (3.8)

[a]Values are means ± SD.
[b]Either alone or in combination with others.
[c]$p = 0.0095$ by ANOVA.
[d]Parenthesis indicate percent.

TABLE 3. ADVERSE REACTIONS

Adverse reaction	*Frequency*	*Percent*
Vomiting	1	1.7
Nausea	7	11.7
Sensation of abdominal distention	4	6.7
Dyskinesia	2	3.3
Insomnia	2	3.3

12, and UPDRS III (motor examination) scores fell from 18.2 ± 8.1 at baseline to 9.8 ± 7.4 at week 12. All of these effects were significant according to the paired *t*-test ($p = 0.0001$). The details are included in Table 1. In all of these scales, a reduction in score indicates improvement.

Adverse reactions

During the treatment with HP-200, nausea was reported in 7 patients, transient vomiting in 1, and a sensation of abdominal distention in 4 (Table 3). Two patients who did not have dyskinesia on synthetic levodopa developed dyskinesia on HP-200, and insomnia was reported by 2 others. The degree of these adverse reactions was mild. No significant abnormalities attributable to the drug were noted on the laboratory reports, such as CBC and blood chemistry.

Levodopa naive vs. carbidopa/levodopa treated

The effect of HP-200 was compared between levodopa naive and those who were treated with carbidopa/levodopa (Table 2). The dosage of HP-200 in the levodopa-naive group (5 ± 2 sachets) was significantly lower than that of those previously treated with carbidopa/levodopa (7 ± 3 sachets) ($p = 0.0095$). No significant differences in the duration of illness, age, Hoehn and Yahr stage, or UPDRS I, II, and III scores were seen either at the baseline or at week 12 when the subgroups were compared. When the adverse reactions were compared, the levodopa-naive patients tolerated the preparation better.

DISCUSSION

An ideal drug for Parkinson's disease remains a dream. Most patients with Parkinson's disease are often on polypharmacy. Adjuvant drugs include anticholinergics, dopamine agonists, amantadine, antidepressants, and sometimes tranquilizers. The concept of retarding the progression of the disease has stimulated the use of monoamine oxidase inhibitors (Elizan et al., 1989; The Parkinson's Disease Study Group, 1993; Tetrud and Langston, 1989), but evidence of their effectiveness remains controversial (Elizan et al., 1989; Landau, 1990; Shoulson, 1993). To counteract secondary effects of parkinsonism, additional drugs, such as stimulant laxatives, may be necessary. Complicating this, the cost of antiparkinson drugs is high. For example, in 1991, the mean cost of an antiparkinson drug was $3099 per year per patient, with a range of $1284 to $5400 (R.B. Harris and B.V. Manyam, 1991, unpublished observations). Parkinson's disease is present worldwide, and with the increasing age of the global population, the number of patients with the disease is likely to be a major concern in geriatric medicine. Although many antiparkinson drugs are available, their costs are too high for a minority of the population in developed countries and the majority of patients in developing countries. Thus, a drug that is effective and inexpensive is needed. The naturally occurring drugs are likely to be less expensive than synthetic ones. HP-200 developed from *M. pruriens* may be a good drug to use because it may have more than one active ingredient, and it could be made available at an affordable cost.

Because the natural seed powder (as opposed to isolated active ingredients) was administered, this study will be useful to the investigation of a fundamental premise of herbal medicine that synergistic action of various components of the plant material in its natural state may enhance therapeutic effects and reduce side effects, which may not occur when one or more isolated chemical components, or active ingredients, are used alone. Unlike synthetic drugs where one specific molecule or compound is generally used, herbal remedies may include a mixture of several compounds having major therapeutic effects. It may be argued that the mixture of compounds could contain ingredients that may act as either an adjuvant or an an-

tidote for some of the adverse effects produced by the main intended compound. To illustrate this concept, when reserpine, the alkaloid derived from *Rauwolfia serpentina*, was used in the treatment of depression, extrapyramidal adverse effects were known to have occurred (Chase, 1972). On the other hand, when an extract of the root of *R. serpentina* was used, which contains reserpine and a host of other alkaloids, no such side effects were reported (Manyam, 1990). The possibility of unidentified compounds in a herbal remedy having toxic effects should also be considered. When considering the use of natural remedies, one should thoroughly review available literature, both ancient and modern, to be aware of any known toxic effects. For example, *V. faba* beans, which contain levodopa, can induce the hemolytic disease of favism in individuals with a hereditary deficiency of red cell glucose-6-phosphate dehydrogenase (Lattanzio et al., 1982) because of the action of some constituents other than levodopa.

M. pruriens has been used in humans in the Indian system of medicine for several centuries, and no serious adverse reactions have been reported (Manyam, 1990). Our acute and chronic toxicity studies (unpublished) in rats and mice did not reveal any significant abnormalities even when administered for up to 1 year at up to 10 g/kg body weight. A few side effects in this 12-week study are similar to those experienced from synthetic levodopa preparations (Martin, 1971). The data reported in this study using UPDRS show significant improvement in all the major components of parkinsonism. HP-200, developed from a naturally occurring plant product, has been used as an herbal medicine for several centuries and qualifies as an alternative medicine for the treatment of Parkinson's disease, as it has shown efficacy and safety in this initial open trial of 60 patients. There is an enormous problem when comparing a natural product, which has significant bulk, to a synthetic compound, which because of its "purity" and potency, has a smaller volume. A carefully planned double-blind study has been designed to further compare the adverse effects.

REFERENCES

Bell EA, Janzen DH. Medical and ecological considerations of L-dopa and 5-HTP in seeds. Nature 1971;229:136–137.

Budavani S, ed. The Merck index, 11th ed. Rathway: Merck Research Labs, 1989:860.

Canteb GJ, De La Torre R, Meir M. A method for evaluating disability in Parkinson's disease. J Nerv Ment Dis 1961;133:143–147.

Chase TN. Drug-induced extrapyramidal disorders. Proc Assoc Res Nerv Ment Dis 1972:448–466.

Damodaran M, Ramaswamy R. Isolation of L-dopa from the seeds of *Mucuna pruriens*. Biochemistry 1937;31: 2149–2151.

Dash VB, Kashyap VL. Materia medica of Ayurveda. New Delhi: Concept of Publishing, 1980.

Daxenbichler ME, VanEtten CH, Hallinan EA, Earle FR. Seeds as sources of L-dopa. J Med Chem 1971;41: 463–465.

Dutt VS. Materia medica of the Hindus (Krisnadas Sanskrit Studies, Vol II). Varanasi: Chaukhambha Orientalia, 1980:148–149.

Elizan TS, Yahr MD, Moros DA, Mendoza MR, Pang S, Bodian CA. Selegiline use to prevent progression of Parkinson's disease. Arch Neurol 1989;46:1275–1279.

Fahn S, Elton RL, Members of UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale, In: Fahn S, Marsden DD, Calne DB, Goldstein M, eds. Recent developments in Parkinson's disease. New York: McMallen Health Information, 1988:153–163, 293–304.

Hoehn MM, Yahr MD. Parkinsonism: Onset, progression, and mortality. Neurology 1967;17:427–442.

Kayden HJ. The neurologic syndrome of vitamin E deficiency: A significant cause of ataxia. Ann Neurol 1993;43:2167–2169.

Landau WM. Pyramid sale in the bucket shop: DATATOP bottoms out. Neurology 1990;40:1337–1339.

Lattanzio V, Bianco VV, Laflandra D. High-performance reversed-phase liquid chromatography (HPLC) of favism-inducing factors in *Vicia faba* L. Experientia 1982;38;789–790.

Manyam, BV. Paralysis agitans and levodopa in "Ayurveda," ancient Indian medical treatise. Movement Disorder 1990;5:47–48.

Martin WE. Adverse reactions during treatment of Parkinson's disease with levodopa. JAMA 1971;216: 1979–1983.

Nadkarni KM. Indian plants and drugs. Madras: Norton & Co, 1908:242.

Natelson BH. Beans a source of L-dopa. Lancet 1969;1:640–641.

Norman TR, Chamberlain KG, French MA, Burrows GD. Platelet monoamine oxidase activity and cigarette smoking. J Affective Disord 1982;4:73–77.

Parkes D. Bromocriptine. Adv Drug Res 1977;12:248–331.

The Parkinson's Disease Study Group. Effects of tocopherol and deprenyl on the progression of disability in

early Parkinson's disease. N Engl J Med 1993;328: 176–183.
Sanchez-Ramos JR. Banisterine and Parkinson's disease. Clin Neuropharmacol 1991;14:391–402.
SAS Institute. SAS user's guide: Statistics. Cary, NC: SAS Institute, 1982.
Shoulson I, Parkinson Study Group. The impact of extended deprenyl treatment in Parkinson's disease patients not requiring levodopa therapy. Ann Neurol 1993;34:263 (Abst.).
Singhal GD, Singh RH, Shukla KP. Non-operative considerations in ancient Indian surgery (based on Susruta Samhita, Cikitsa-Sthana, chapters 24–40). Varanasi: Singhal Publications, 1979:76.
Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. Science 1989;245:519–522.
Vaidya ND. A treatise on experienced remedies. Ahmeabad: Vaidya-Kalapataru, 1925:100.
Vaidya AB, Rajogopalan TG, Mankodi NA, Antarkar DS, Tathed PS, Purohit AV, Wadia NH. Treatment of Parkinson's disease with the cowhage plant—*Mucuna pruriens* bak. Neurol India 1978a;26:171–176.
Vaidya RA, Sheth AR, Aloorkar SD, Rege NR, Bagadia VN, Devi PK, Shah LP. The inhibitory effect of the cowhage plant—*Mucuna pruriens*—and L-dopa on chlorpromazine-induced hyperprolactinaemia in man. Neurol India 1978b;26:177–182.

APPENDIX

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