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Comparative Assessment in Effectiveness of Levodopa and Levodopa plus Pramipexole (Restin) in Treatment of Patients with Parkinson's Disease Referred to Hospital

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Abstract: One of the most common human neurodegenerative disorders, second only to Alzheimer disease, Parkinson Disease (PD) proves to be a diagnostic and therapeutic challenge in medical practice. Significant advances have been made in definin g its pathogenesis and pathology and in turn, in the development of therapeutic interventions designed to maximize control of symptoms while minimizing long-term disability and treatment related complications. The aim of this study was to comparative assessment in effectiveness of levodopa and levodopa plus restin in treatment of patients with Parkinson's disease referred to hospital. In this study, 40 patients with Parkinson disease were divided into 2 groups of 20. This study carried out from September until November, 2011 for 3 months. Based on data showed in the result, it has been revealed that combination use of levodopa plus restin showed better results than single use of levodopa. Finally can be state that the control of Parkinsonian symptoms in patients with dopamine agonists concomitant with levodopa therapy has been successful.

Key words: Levodopa, pramipexole, Parkinson disease, patients, Tabriz, Iran

INTRODUCTION

Parkinson's disease is a progressive, neuro-degenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Patients with Parkinson's disease suffer from both motor and non-motor symptoms. The cardinal motor symptoms include resting tremor, rigidity, bradykinesia and postural instability. Examples of non-motor symptoms are diminished sense of smell, depression and sleep disturbance.

Levodopa (LD), chemically known as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid was introduced in 1960's for the symptomatic treatment of Parkinson's disease. It remains the gold standard in the management of the motor symptoms of Parkinson's disease today. Nearly, all patients with Parkinson's disease eventually receive LD therapy at some stage of the disease. The active metabolite of LD, dopamine is responsible for the control of symptoms of Parkinson's disease, however it does not cross the Blood Brain Barrier (BBB). Since LD crosses BBB, it acts as a prodrug of dopamine. However, LD is rapidly decarboxylated to dopamine in extracerebral tissues, especially in the gastrointestinal tract following oral administrations and therefore, only a small portion of a given LD dose is transported across the BBB to the central nervous system. For this reason, LD is routinely administered with a decarboxylase inhibitor such as Carbidopa (CD) or benserazide to prevent the formation of peripheral dopamine. Currently, LD products are available as standard Immediate-Release tablet (standard or IR), Controlled-release tablet (CR), Orally Disintegrated Tablet (ODT) and immediaterelease CD-LD in combination with a fixed 200 mg dose of entacapone where entacapone inhibits the metabolism of LD mediated by Catechol-O-Methyltransferase (COMT). Additionally, a dual release formulation combining immediate and sustained-release of levodopa and benserazide is available in the Europe (Descombes *et al*., 2001; Ghika *et al*., 1997). A new product that delivers immediate and sustained release of LD and CD in a single formulation is currently under development. Since, the pharmacological effects of LD have been shown to be correlated with plasma concentrations of LD, this study reviews the Pharmacokinetics (PK) of LD and CD and the relationships between plasma concentrations of LD and the Pharmacodynamic (PD) effects of LD.

Pharmacokinetics of LD

Absorption: The absorption of LD is via the saturable L-neutral amino acid transport system for large amino acids. However, increasing LD dose resulted in a more

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than proportional increase of LD plasma concentrations probably because the major metabolism of LD in the GI tract is also by a saturable amino acid decarboxylation pathway (Muenter and Tyce, 1971).

Orally administered LD is almost completely absorbed with only 2% appearing in the feces (Nutt and Fellman, 1984; Sasahara *et al*., 1980). However, only about 30% of an oral LD dose reached the systemic circulation intact when not administered with CD. The oral bioavailability of LD is increased 2-3 times when co-administered with decarboxylase inhibitors. Bianchine *et al*. (1972) showed that following pretreatment with MK-486 (carbidopa), peak plasma LD concentration increased approximately 3-fold and plasma radioactivity half-life increased significantly from 3-15 h. Based on the data reported by Sasahara *et al*. (1980), it is possible to construct a plasma concentration-time profiles for levodopa in the absence and presence of carbidopa. In that regard, Nutt and Fellman (1984) also showed that the clearance of plasma LD after intravenous infusion of LD in the presence of CD were statistically significantly decreased by about 50% as compared to that determined in the absence of CD (Nutt *et al*., 1985). Thus, all current LD products are CDLD combination formulations. In healthy elderly subjects under fasting condition, the absorption of LD from an Immediate-Release (IR) CD-LD product is rapid with 60% of the dose absorbed in 30 min and the absorption was complete in 2-3 h (Yeh *et al*., 1989). Interestingly, although the currently available CD-LD entacapone combination product is an immediate-release formulation with the addition of entacapone to the formulation, the initial absorption rate for LD appeared to be decreased and the plasma concentration-time profiles of LD resembled that of the CR formulation (Le Witt *et al*., 2005). Similar outcomes, i.e., lower C_{max} and prolonged t_{max} were observed when Sinemet 50-200 was dosed in patients treated with entacapone (Piccini *et al*., 2000). These observations are somewhat consistent with the observations that the absorption rate of LD appeared to be affected by entacapone and the effect appeared to be a function of entacapone dose, probably due to competitive absorption (Keranen *et al*., 1993). It should be noted that there were also reports showing that the initial absorption rate of levodopa from an IR product was not delayed when coadministered with entacapone following a multiple dose regimen (Le Witt *et al*., 2005).

In general, co-administration of entacapone with CD-LD products tends to increase the total levodopa AUC by increasing the concentrations at the later time points after dosing. Since, the transport of LD is through the L-neutral amino acid transport system, studies have been conducted to evaluate the effect of dietary protein on the clinical response to LD. The results of these studies showed that the clinical effect of LD was reduced by a daily diet containing protein in excess of 1.6 g kg^{-1} or a single protein load of approximately 28 g. A protein containing diet tends to reduce the oral absorption of LD, however it should be noted that the decrease in response to LD did not appear to correlate with plasma LD concentrations (Carter *et al*., 1989). A study using positron emission to mography showed the decreased effect appeared to be correlated with a decrease in the uptake of LD into the brain probably due to competition from the increased plasma amino acid concentrations (Keranen *et al*., 1993).

For a Controlled-release (CR) LD product, the absorption was gradual and completed in 4-6 h under fasting conditions. The controlled-release CD-LD product has longer t_{max} and lower C_{max} in comparison to the immediate-release product b. A CR only product also reaches maximum concentration later that a product with the combination of an immediate and a controlled release properties (Descombes *et al*., 2001). Additionally in healthy elderly volunteers, the LD bioavailability of a CR formulation (Sinemet® CR 50-200 mg) and an IR formulation (Sinemet 2 tablets of 25-100 mg) administered under fasting conditions was reported to be 71 and 99%, respectively, therefore the bioavailability of a CR formulation has been estimated to be ~70% of an IR formulation under fasting conditions (Yeh *et al*., 1989). However, data from a recent randomized crossover study demonstrated that bioavailability of Sinemet 25-100 mg is comparable to that of Sinemet CR 25-100 mg suggesting caution should be exercised when extrapolating the relative bioavailability of LD between different formulations and/or different dose levels. Furthermore, it is important to note that Yeh *et al*. (1989) reported that the bioavailability of the CD-LD CR product increased 48% if taking after consuming a meal containing 2 eggs, toast, 8 ounces juice, 8 ounces milk and decaffeinated coffee, probably due to increased gastric retention which in turn allowed more complete absorption of LD in the upper GI (Bianchine *et al*., 1972). However, Mearrick showed that the absorption of LD from a standard release (IR) CD-LD product was increased during rapid gastric emptying under fasting conditions. Therefore, food effects on LD pharmacokinetics vary with formulations.

The pharmacokinetics of LD does not change after multiple days of dosing. Yeh *et al*. (1989) showed that LD plasma levels after every 8 h dosing for 10 days were essentially identical to those obtained after a single dose in healthy elderly volunteers for both Sinemet and a CR formulation.

Distribution of levodopa: Levodopa crosses the blood-brain barrier by stereospecific, saturable, facilitated process via the Large Neutral Amino Acid (LNAA) transport carrier system. Gey and Pletscher showed that 1 h after a 20 mg kg^{-1} 14 C-DL-DOPA subcutaneous dose in rats, only 0.1% of the radioactivity was found in the brain while most of the radioactivity was found in urine, skin, whole skeletal muscle, intestine and liver. After an intravenous dose of 50 mg LD alone, the V_{ss} (Volume of distribution at steady state) in young healthy volunteers was estimated to be 70% higher than that in elderly volunteers (Robertson *et al*., 1989). The V_{ss} of LD was estimated to be approximately 50% higher in young healthy volunteers than that in elderly volunteers when an intravenous LD dose was coadministered with CD. Kaakkola *et al*. (1985) reported similar V_{ss}/F for LD after oral dosing of 10-100 to 62.5-250 mg CD-LD in healthy volunteers. Levodopa is not highly bound to plasma proteins. The free fraction was found to be 76±8% at a concentration of 500 ng mL^{-1}.

Metabolism of levodopa: Nutt and Fellman (1984) conducted a comprehensive review of the metabolism of LD. Levodopa undergoes metabolism via four pathways: Decarboxylation by AAAD, 3-O-methylation by Catechol-O-Methyltransferase (COMT), transamination by tyrosine aminotransferase and oxidation by tyrosinase or other oxidants. AAAD, a nonspecific enzyme is widely distributed in gut, liver, kidneys, brain, lungs, adrenal, spleen and heart (Porter *et al*., 1973). Human brain capillaries also contain high concentrations of AAAD (Hardebo *et al*., 1680). The decarboxylation pathway is the major metabolic pathway for LD. About >95% of orally administered LD was decarboxylated peripherally and only 1% of the dose entered the brain. The initial product of decarboxylation is dopamine which may be further metabolized to form 3,4-Dihydroxyphenyl Acetic Acid (DOPAC), Homovanillic Acid (HVA) and to a lesser extent norepinephrine and vanillinemandelic acid. After intravenous dosing of LD, about 10% of the dose was accounted for by the 3-O-Methylation process (Goodall and Alton, 1972). The metabolic product via the COMT pathway is 3-O-methyldopa (3-OMD). About 3-OMD is further metabolized to vanilpyruvate by transamination and then reduced to vanillactate. COMT is primarily present in peripheral tissues, particularly liver, intestinal tract and kidneys; comparatively low activity is found in the brain and no activity is found in dopaminergic nigrostriatal neurons. The transamination pathway is reversible, therefore 3,4-dihydorxyphenyl-pyruvatemay serve as a precursor for LD. The presence of cysteinyldopa in the urine of parkinsonian patients suggests that oxidation of LD by tyrosinase or other oxidants to DOPA quinone intermediate does occur. DOPA quinone can be further metabolized to melanin (Nutt and Fellman, 1984).

In patients with Parkinson's disease when 100 mg 14 CLD was administered with a single 100 mg CD dose or after 100 mg CD t.i.d. for 7 days as compared to 100 mg 14 C-LD given alone, the majority of LD (~90%) was converted to 3-OMD by COMT in the peripheral tissues, peak plasma LD levels increased from non-detectable to 0.7 and 1.2 μg mL^{-1}, 2 h dopamine levels decreased from 0.3 μg mL^{-1} to nondetectable and peak HVA levels decreased 80%.

The corresponding decrease in urinary recovery of dopamine and DOPAC was approximately 3.5-fold and 2-fold, respectively (Bianchine *et al*., 1972). About 3-OMD has a 15 h plasma half-life is a poor substrate for AAAD and appears to compete with LD for transport to the brain via the large neutral amino acid transport carrier system. Steady-state plasma 3-OMD concentrations in Parkinsonian patients are correlated with LD dose and do not vary markedly during LD therapy. Although, oral challenges with 3-OMD reduce the clinical response to LD, 3-OMD is no more potent than phenylalanine in competing with LD for transport into the brain. Since 3-OMD makes a small contribution to the total concentration of large neutral amino acids competing with LD, Nutt and Fellman (1984) has concluded that 3-OMD is not an important determinant of clinical response to LD.

Excretion of levodopa: Following oral administration of a 100 mg dose of 14 CLD alone, 90% of the radioactivity (dose) was recovered in the 48 h urine. The dose recovered in the 48 h urine was reduced to about 60% when LD was coadministered with a single 100 mg dose of CD or with 100 mg CD t.i.d. for 7 days (Bianchine *et al*., 1972), probably because the majority of LD dose is converted to the long half-life 3-OMD during coadministration with CD. The inhibition of AAAD by CD was determined to be pseudo-irreversible. After an oral dose of 50-200 mg as an IR or a CR formulation, 7.2±2.4 and 3.0±1.4% of the LD dose was excreted in the urine as unchanged drug, respectively. This appeared to be consistent with the relative bioavailability of the respective formulations (Yeh *et al*., 1989). The plasma clearance of LD after intravenous administration in the presence of CD was reported to be age dependent, ranging from 781, 697 and 596 mL min^{-1} in 23-45, 55-76 and 56-67 years old healthy adults, respectively.

Renal clearance accounted for about 10% of the total body clearance (Yeh *et al*., 1989). Robertson *et al*. (1989) reported that the apparent plasma clearance (CL/F) of LD

averaged 9.3±1.0 mL/min/kg in young healthy volunteers and 5.8±0.9 mL/min/kg in elderly volunteers. The plasma half-life of LD when it is administered alone is about 50 min and increased to ~1.5 h when coadministered with CD.

Pramipexole in Parkinson's disease: This review will present the DA pramipexole in the treatment of PD, focusing on the latest developments.

Pharmacodynamics: Pramipexole is a non-ergotamine full agonist at the D_2 subfamily of dopamine receptors with higher selectivity for D_3 than for D_2 and D_4 dopamine receptors (Bennett and Piercey, 1999; Mierau and Schingnitz, 1992; Mierau *et al*., 1995; Mierau, 1995; Svensson *et al*., 1994). Thereby, pramipexole is able to simultaneously excite the direct striatopallidal pathway (by D_3 stimulation) and to inhibit the indirect striatopallidal pathway (by D_2 stimulation), alleviating PD symptoms by mimicking dopamine's effects in the striatum. Since the D_3 receptors enjoy greatest predominance in the limbic system (Bouthenet *et al*., 1991), pramipexole has the theoretical potential to also have an impact on psychiatric symptoms in PD (Bennett and Piercey, 1999). In addition, Pramipexole has a very low affinity for 5-HT2A, 5-HT2B and D_1 receptors, partly explaining its beneficial effects in the context of cardiac valvulopathy and dyskinesias.

Pharmacokinetics: Pramipexole has an absolute oral bioavailability >90% indicating good absorption and little first pass metabolism. It exhibits linear pharmacokinetics and <20% is protein bound, >90% of the absorbed dose is eliminated unchanged and almost exclusively by the kidneys, motivating a dose reduction with low creatinine clearance. Its elimination half-life is 8 h in young, healthy volunteers (Bennett and Piercey, 1999; Haselbarth *et al*., 1994a, b; Wright *et al*., 1997). In men and postmenopausal women with PD, gender had no impact on the pharmacokinetics of pramipexole and pramipexole did not alter levodopa's bioavailability (Kompoliti *et al*., 2002). In contrast to other DA, pramipexole has been found to exert no strong cytochrome P 450 inhibition *in vitro*, minimizing the risk for drug-drug interactions (Wynalda and Wienkers, 1997).

Clinical efficacy

Monotherapy in early Parkinson's disease (Previous results): The safety and efficacy of pramipexole as monotherapy in early PD were originally evaluated in 2 placebo-controlled clinical trials enrolling 599 PD subjects (Kieburtz, 1997). In addition, the Comparison of the Agonist pramipexole with Levodopa on Motor complications of PD (CALM-PD) study, conducted by the Parkinson Study Group (PSG), investigated initial treatment with pramipexole versus initial treatment with levodopa in 301 patients with early PD, requiring dopaminergic therapy. The subjects were randomly assigned to receive 1.5 mg pramipexole or 300 mg levodopa daily. The two treatment groups were of equal size. After the 1st 10 weeks of treatment, open-label levodopa (and during the last year of the study also other antiparkinsonian medication) could be added as needed, for better symptom control. The CALM-PD study design and the subsequent long follow up (up to 58 months), generated a wealth of data regarding the effects of pramipexole on a variety of PD features.

The combined results of these three pivotal studies showed that pramipexole started at low initial doses and up-titrated weekly was effective and well tolerated in mild to moderate PD. No differences in effectiveness based on age or gender were detected and no dose-response relationship could be demonstrated. Thus, doses of 1.5, 3, 4.5 and 6 mg day^{-1} did provide similar significant benefit in reducing PD signs and symptoms compared with placebo. However, several side effects were dose related. On the Unified Parkinson's Disease Rating Scale (UPDRS) (Lang and Fahn, 1989) significant improvement from baseline could be seen in both section II (around 2 points) and section III (around 5 points), compared with placebo (-0.6 points on both sections).

New studies: The 4 years results of the CALM-PD study showed that after 4 years, initial treatment with pramipexole resulted in a significant reduction of the risk for developing treatment fluctuations and dyskinesias but in a higher risk for freezing vs. initial treatment with levodopa. On the other side, a greater improvement in the total UPDRS score was seen in the levodopa group vs. the pramipexole group (2±15.4 vs. -3.2±17.3 points). More patients in the pramipexole group needed at 4 years open-label levodopa vs. the levodopa group (72 vs. 59%) but the mean daily levodopa dose was lower in the pramipexole group (434±498 vs. 702±461 mg day^{-1}). More pramipexole patients withdrew prior to the final follow-up visit than levodopa patients (45 vs. 33%) due to side-effects (Holloway *et al*., 2004). The aim of this study was to comparative assessment in effectiveness of levodopa and levodopa plus restin in treatment of patients with Parkinson's disease referred to hospital.

MATERIALS AND METHODS

This research was from case control types of studies. In this study, 40 patients with Parkinson disease were divided into 2 groups of 20. This study carried out from

September until November, 2011 for 3 months. In this study after obtaining of questionnaires, levodopa was administrated at the dose of 250 mg twice in day for group 1 and about group 2, levodopa with the same dose plus restin at the dose of 0.18 mg were administrated twice a day. Then clinical signs and disease progresses were recorded in the daily questionnaires.

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), Version 13.0 was used for statistical analysis. All data are presented as mean±SEM. Before statistical analysis, all variables were checked for normality and homogeneity of variance by using the Kolmogorov-Smirnoff and Levene tests, respectively. The data obtained were tested by ANOVA followed by Tukey's post-hoc multiple comparison test. The Kruskal-Wallis test followed by Mann-Whitney U post-test was used for the analysis. $p<0.05$ was considered statistically significant.

RESULTS

In this study after treatment period, some clinical signs were measured include Bradykinesia in hands, rigidity, posture, upper extremely swing, gait, tremor, facies, seborrhea, speech and self-care. Related data was shown in Table 1 and Fig. 1. Based on data showed in Table 1, it has been revealed that combination use of levodopa plus restin showed better results than single use of levodopa.

Table 1: data obtained from questionnaires during the study

	Mean value		
Parameters	Group 1	Group 2	p-values
Bradykinesia in hands	5.10	3.35	0.005
Rigidity	3.90	3.85	0.005
Posture	3.60	1.85	0.013
Upper extremely swing	5.15	3.15	0.003
Gait	2.30	4.00	0.017
Tremor	4.20	2.40	0.000
Facies	3.50	1.25	0.000
Seborrhea	1.15	1.00	0.796
Speech	4.10	1.70	0.000
Self-care	3.70	1.60	0.005
Total	36.70	24.15	0.005

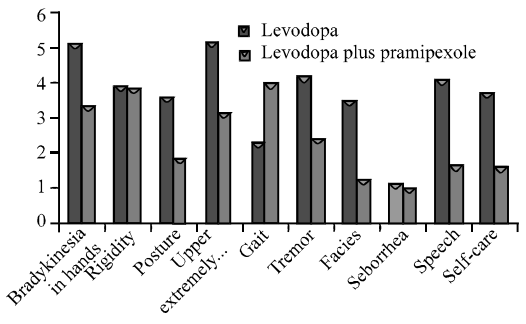

Fig. 1: Comparative diagram of data obtained from two understudying groups

DISCUSSION

The objective of this investigation was to analyze the effects of Parkinson's disease and of levodopa on a variety of cognitive and motor functions.

Effects of Parkinson's disease: The results obtained by cognitive tests before treatment did not confirm recent findings of the detrimental effect of Parkinson's disease on intelligence (Asso *et al*., 1969; Loranger *et al*., 1972a) and on memory (Marsh *et al*., 1971; Warburton, 1967). Patients did not differ significantly from the control group in any of the intelligence and memory tests used. The reason for the discrepancy in results may lie in the makeup of the groups, for a large number of the older subjects were of European origin and had received their education which in some cases was rather limited, in a variety of European countries.

English was therefore not their first language. Also owing to a time factor, an abridged form of the WAIS was used in the study. On paper and pencil tasks, the patients' designs and handwriting were consistently smaller than those of the controls, though they did not differ significantly in accuracy except for the obvious tremor of the patients.

The effects of Parkinson's disease on all psychomotor tasks were readily apparent and the patients showed significant impairment in performance when compared with the controls on measures of rigidity, tremor and finger dexterity and forearm strength.

Correlational analyses were carried out in order to evaluate the effects of certain factors such as age, intelligence, duration of illness, severity of impairment and drug dose on the subjects' performance of the various tasks. A relationship between the severity of symptoms and intellectual impairment has been reported previously (Christensen *et al*., 1970; Loranger *et al*., 1972b; O'Brlen *et al*., 1971).

Age was a consistently significant factor in normal subjects' performance in motor tasks while for the patients this correlation was not consistent. Understandably, the degree of neurologic impairment once again had significant negative effects on patients' performance on the various motor tasks. Duration of illness was also found to affect patients' performance of the various psychomotor tasks. No significant correlation existed between age and duration of illness in the experimental group.

Effects of levodopa: The comparison of the post-treatment with pretreatment scores showed that levodopa did not affect intelligence or memory functions and only the more difficult task of reproducing Rey's complex figure from memory improved significantly after treatment. Researchers were not able to confirm recent findings (Loranger *et al*., 1972a; Meier and Martin, 1970) of a significant increase on all WAIS measures following levodopa therapy. The finding of lack of memory improvement is in agreement with previous research (Marsh *et al*., 1971; O'Brlen *et al*.,1971; Puca *et al*., 1971). Thus while differences in procedure may partly account for the discrepant findings in levodopa-related intellectual changes, there appears to be fairly good agreement on the lack of drug effect on conventional memory tests. Furthermore, the WAIS improvements found by Loranger *et al*. (1973) after an average of 8 months were not maintained so that pretreatment levels were found on retesting 30 months later.

It is noteworthy that three of the patients did show a 13-point increase in IQ at retest, however they were of superior intelligence and in the under 65 age group. Here again age emerges as a major factor facilitating cognitive improvement after treatment. The beneficial effect of levodopa on a variety of motor functions has been well established by clinical observation (Mcdowell *et al*., 1970) by rating scales (Nakano and Tyler, 1971) and by objective measurements. Motility was assessed by Meier and Martin (1970) with a pegboard task and a two-hand coordination test and by Stern *et al*. (1970) by means of a Motility index apparatus. Reports of improved handwriting are frequent in the literature (Blonsey, 1971; Godwin-Austen *et al*., 1969) and were confirmed by researchers findings. Hand writing changes have also been investigated by Nakano and Tyler (1971) in a double-blind study. They found hand writing one of the most consistent indices of improvement. Marsh and Kravitzm (1971) found both legibility and speed significantly increased after a mean daily medication level of 4.48 g had been reached.

By increasing the size of their writing laterally, the patients also improved legibility. We have been able to confirm previous clinical reports describing the areas and extent of improvement in parkinsonian patients' motor functions with levodopa treatment. By means of objective tests and apparatus, researchers have shown that rigidity, strength of grip, finger dexterity and intention tremor significantly improve by 5 weeks after initiation of treatment and that this change is maintained for at least 6 months while a reduction in resting tremor only begins after 6 months of drug administration. The findings of some investigators of cognitive changes in patients with Parkinson's disease both before and after levodopa have not been confirmed by the study but factors such as ageing, cortical atrophy and cerebrovascular disorders as well as variation in research procedures, tend to contribute to the complexity of the problem.

CONCLUSION

It can be stated that the control of Parkinsonian symptoms in patients with dopamine agonists concomitant with levodopa therapy has been successful.

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