Effects of Levodopa on Systolic Preejection Period, Blood Pressure, and Heart Rate during Acute and Chronic Treatment of Parkinson’s Disease

By Thomas L. Whitsett, M.D., and Leon I. Goldberg, Ph.D., M.D.

SUMMARY
The effect of levodopa on the externally recorded preejection period (PEP), blood pressure, and heart rate was evaluated in patients with Parkinson’s disease during the first 2 weeks of therapy and after 3 months of continuous therapy. During the same time periods, the response of these parameters to graded intravenous doses of dopamine and epinephrine was determined. During the first 2 weeks, levodopa (1.5 g) produced a dose-related shortening of the PEP which was maximal at the time of the 30 or 60-min recordings and remained significant (P < 0.05) for 90 min following the 1.0-g dose and for 120 min after the 1.5-g dose. The drug had no effect on heart rate and reduced arterial blood pressure minimally. Propranolol (10 mg by mouth) prevented the shortening of PEP produced by levodopa. After 3 months of therapy, levodopa (1.5 g) failed to shorten the PEP significantly. However, the effect of dopamine and epinephrine on PEP was not significantly different from that obtained during the first 2 weeks of treatment with levodopa. It is concluded that levodopa exerts a positive inotropic effect which is mediated via beta-adrenergic receptors and that tolerance develops by 3 months of continuous administration. The tolerance does not appear to be caused by impaired responsiveness of the heart since the effect of graded doses of dopamine and epinephrine on the PEP was similar during both acute and chronic administration.

Additional Indexing Words:
Dopamine Epinephrine Tolerance Positive inotropic action Propranolol

INTRAVERNIOUS injections of levodopa markedly increase myocardial contractility in the anesthetized dog. This effect can be completely eliminated by prior administration of the dopa decarboxylase inhibitor, methyl-dopa, and by the beta-adrenergic blocking agent, propranolol. Thus, the positive inotropic effect of levodopa appears to be due to production of a cardioactive catecholamine. A preliminary investigation demonstrated that levodopa exerted a positive inotropic effect on patients with Parkinson’s disease during the first 3 weeks of therapy; however, this effect was attenuated in individuals who had been on treatment for at least 7 weeks.

Because levodopa is now extensively used in the treatment of Parkinson’s disease, it was...
important to determine (1) the magnitude and duration of action of the positive inotropic effect, (2) the dose of the beta-adrenergic blocking agent, propranolol, required to inhibit this effect, and (3) the degree of tolerance to the positive inotropic action, including possible causative mechanisms.

In the present investigation, the effects of oral administration of 1 and 1.5 g of levodopa on the pre-ejection period (PEP), blood pressure, and heart rate were determined in patients being treated for Parkinson’s disease. The PEP was used as an index of myocardial contractility on the basis of a previous study by Harris and others who demonstrated that this measurement was a valid method of ascertaining beta-adrenergic receptor activation and blockade in man. Our studies were carried out during the first 2 weeks and also after 3 months of continuous therapy. The effects of three doses each of dopamine and epinephrine on the PEP were determined prior to the administration of levodopa and again after tolerance developed.

Methods

Group Studied

Patients with idiopathic or postencephalitic Parkinson’s disease of varying clinical severity were chosen for this study. Only patients found to be free of active cardiovascular disease by physical examination, electrocardiogram, and chest X-rays were permitted to participate. All patients were admitted to the Emory University Clinical Research Facility, where they underwent routine neurologic and cardiovascular evaluations and the laboratory studies required for patients receiving levodopa. The nature of the study was explained to each participant and an informed consent form was signed. Previously prescribed antiparkinsonism medications, for example, benztopine (Cogentin), procyclidine (Kemadrin), and trihexyphenidyl (Artane), were discontinued at least 12 hours prior to beginning of an experimental procedure.

Recordings

All investigations were carried out at approximately 7:30 a.m., after an overnight fast. Patients were maintained in the supine position for at least 5 min prior to measurement of the PEP, blood pressure, and heart rate. An individual study required from 2 to 3 hours. The systolic time intervals were measured by simultaneously recording the carotid pulse contour, phonocardiogram, and electrocardiogram on a Honeywell 1108 Visicorder at a paper speed of 200 mm/sec with 0.01-sec time markers. The carotid pulse contour was obtained with a stethoscope bell connected to a Statham P 23 D transducer by a short length of small-gauge polyethylene tubing. The bell was placed over the point of maximal pulsation of a carotid or subclavian artery, and this area was noted so that it could be used for subsequent determinations. The microphone for the phonocardiogram was placed where the second heart sounds were most clearly defined. The measurements included (1) the interval from the onset of the QRS complex of the electrocardiogram to the peak of the first major vibration of the second heart sound (Q-S2 interval); the latter end point was utilized rather than the beginning of the second sound because it was consistently well defined and is less subject to baseline variation and background interference; (2) the interval from the beginning upstroke of the carotid pulse contour to the trough of the incisura (left ventricular ejection time, LVET); and (3) the R-R interval, which was used to determine heart rate (heart rate = 120/R-R interval). Ten consecutive heart beats were measured and taken as the mean only when the previously described end points were well defined. The PEP was determined by subtracting the LVET from the Q-S2 intervals. The LVET was corrected for heart rate by the following: LVET - 1.7 x heart rate = ejection-time index. This correction eliminates

"Typical tracing demonstrating the carotid pulse contour, electrocardiogram (ECG), phonocardiogram (PCG), and heart rate which were simultaneously recorded at a paper speed of 200 mm/sec. The reference points for measuring left ventricular ejection time (LVET) and electromechanical systole (QS2) and technic used in calculating the pre-ejection period (PEP) are shown."
heart rate as a significant variable influencing the duration of ventricular ejection. The ejection-time index was calculated and analyzed for each portion of the study, and there was no consistent change. Therefore, the results will not be discussed further. A tracing of a typical recording is shown in figure 1. Blood pressure was measured indirectly by means of a mercury sphygmomanometer. Mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure.

Administration of Drugs

Oral Administration of Levodopa and Propranolol

Levodopa was always administered with a glass of milk to minimize nausea and vomiting which some patients have during initial levodopa therapy. Before the cardiovascular studies, levodopa was administered by gradually increasing the dose over 2 to 5 days beginning with 250 mg every 6 hours until the patient could tolerate a dose of 1.0 g with no side effects. At this point, the initial studies were carried out in a number of patients. The dose was then gradually increased during the next 7 to 10 days. Thus, the daily dose of levodopa obtained on the day before the cardiovascular study ranged from 1.5 to 4.5 g. PEP, blood pressure, and heart rate were determined before and at 30, 60, 90, and 120 min following placebo. 1.0 and 1.5 g of levodopa administered orally on successive days. In some patients, the effect of 0.5 g was also recorded. In six of the patients, the effects of 1.5 g of levodopa were studied again on the following day 45 min after oral administration of propranolol (10 mg).

No patient experienced nausea or vomiting or appeared to be anxious during the cardiovascular studies.

Intravenous Infusions of Dopamine and Epinephrine

Effects of intravenous infusions of dopamine and epinephrine on PEP, blood pressure, and heart rate were measured in five patients prior to administration of levodopa. These data were obtained before and during the final minute of a 5-min infusion at each of three infusion rates of dopamine (1, 2, and 4 µg/kg/min) and epinephrine (0.01, 0.02, and 0.04 µg/kg/min). At least 5 min were allowed between infusions for reestablishing baseline values. A Harvard variable-rate infusion pump was used for administering the amines.

After completion of these studies, the patients were discharged from the hospital and followed at biweekly intervals in an outpatient clinic. The dose of levodopa was gradually increased as clinically indicated. The five patients who had been previously studied with dopamine and epinephrine infusions and one additional patient were readmitted to the Clinical Research Facility after at least 3 months of continuous levodopa therapy. The effects of levodopa, dopamine, and epinephrine on the PEP, blood pressure, and heart rate were again determined in the same way as during the first week of therapy.

Materials and Analysis of Data

The following drugs were used: levodopa hydrochloride (3,4-dihydroxyphenylalanine, Levodopa*), dopamine hydrochloride (Intropin), epinephrine hydrochloride (Adrenalin†), and propranolol hydrochloride (Inderal‡). All results are expressed as the mean ± standard error (SE). The paired t-test was used for statistical analysis by comparing each treatment response to the appropriate control (pretreatment value).

Results

Effects of Placebo on PEP, Blood Pressure, and Heart Rate

The effects of a placebo resembling the levodopa capsule on the average PEP of six patients is shown in figure 2. During the 2-hour period of observation, PEP was shortened by 2 msec in one patient, but was either unchanged or prolonged in the other five. The average values following the placebo were more prolonged than the recordings obtained before administration. This prolongation, however, was statistically significant (P < 0.05) only at the 90-min recording. Blood pressure and heart rate were not statistically changed.

Effects of Levodopa on PEP, Blood Pressure, and Heart Rate during the First 2 Weeks of Therapy

PEP was not significantly altered after administration of 0.5 g of levodopa to four patients. Accordingly, all subsequent studies were carried out with either 1.0 or 1.5 g of the drug.

The effects of 1.0 and 1.5 g of levodopa on PEP were determined in eight and nine patients, respectively (seven patients received both doses). PEP was maximally shortened 30 to 60 min after administration of both doses.

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*The levodopa used in this study was kindly supplied by Dr. William B. Abrams, of Hoffmann-LaRoche, Nutley, New Jersey, and the dopamine by Dr. Kane Zelle, of Armar-Stone Laboratories, Mt. Prospect, Illinois.
†Parke Davis.
‡Ayerst.
At 90 min PEP was still significantly shortened, but less so than during the 30 and 60-min periods. At 120 min, PEP was not significantly different from control values after the 1-g dose, but was still significantly shorter than control values after the 1.5-g dose.

The effects of levodopa on heart rate and blood pressure are shown in table 1. Heart rate was not significantly altered. Slight but significant reductions in arterial pressure were measured, however, at several time intervals with both doses.

**Table 1**

<table>
<thead>
<tr>
<th>Effect of Levodopa on Heart Rate and Blood Pressure in 13 Patients*</th>
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<tbody>
<tr>
<td>Minutes after 1.5 g of levodopa</td>
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<tr>
<td>---------------------------------</td>
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<tr>
<td>Systolic (mm Hg)</td>
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<td>Diastolic (mm Hg)</td>
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<td>Mean BP (mm Hg)</td>
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<td>Heart rate (beats/min)</td>
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*All values are mean ± se. *P < 0.05 compared to appropriate control.
Levodopa did not significantly affect the heart rate or blood pressure, either before or after propranolol (table 2). However, the control systolic and diastolic blood pressures were significantly higher ($P < 0.05$) and the heart rate was significantly lower ($P < 0.05$) after propranolol. The control PEP, however, was not significantly altered by propranolol. This last finding is consistent with previous observations.6

Effect of Levodopa on PEP during the Initial 2 Weeks of Therapy and after 3 Months of Continuous Administration

The effects of levodopa (1.5 g) on PEP were determined in six patients during the first 2 weeks of therapy, and again after the drug was administered for 3 months. Comparison of the results is shown in figure 4. During the initial 2 weeks of therapy, the PEP was maximally reduced at the 30-min interval and remained significantly less than the control values at 120 min. After 3 months of therapy, the same dose of levodopa did not significantly shorten the PEP at any time interval. The average daily dose of levodopa

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Before levodopa (1.5 g by mouth)</th>
<th>After levodopa (0.5 g by mouth)</th>
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<tbody>
<tr>
<td>Systolic (mm Hg)</td>
<td>128 ± 4.0</td>
<td>124 ± 5.2</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>67 ± 2.9</td>
<td>68 ± 3.3</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>70 ± 4.9</td>
<td>70 ± 3.3</td>
</tr>
</tbody>
</table>

All values are mean ± se. The significant differences ($P < 0.05$) are higher control systolic and diastolic blood pressures and lower heart rate after propranolol.
prior to the second testing period was 5.1 g with a range between 3.0 and 7.5 g.

Control PEP and Heart Rate during the Acute and Chronic Administration of Levodopa

In the five patients who were studied during the initial 2 weeks and following 3 months of therapy with levodopa, multiple control PEP measurements were recorded prior to various procedures, e.g., one or two doses of levodopa and three doses each of dopamine and epinephrine. The control values during the initial 2 weeks were compared to those obtained after 3 months of therapy (31 paired observations). The PEP during chronic administration was significantly longer than that measured during the initial treatment period, being 95.6 ± 1.8 and 85.8 ± 2.8 msec, respectively (P < 0.001). Heart rate was significantly slower after chronic administration when compared to the initial period, being 61 ± 2.3 and 72 ± 3.0 beats/min, respectively (P < 0.001). There was no significant difference in blood pressure during chronic and acute periods (range, 124 ± 1.5 to 72 ± 1.5 mm Hg, and 126 ± 1.5 to 74 ± 1.7 mm Hg, respectively).

Figure 4
PEP (msec) in six patients during the control period and 30, 60, 90, and 120 min following levodopa (1.5 g). Responses are shown during the first 2 weeks (acute) and after 3 months (chronic) of levodopa therapy. Values are mean ± se. * = P < 0.05; ** = P < 0.01.

Figure 5
PEP (msec) in five patients during the control period (C) and after a 5-min infusion of three doses of dopamine (D). Responses are shown before levodopa was administered and after 3 months of therapy. The horizontal lines represent the se of the mean PEP values. The numbers above the dopamine (D) column were obtained by subtracting the dopamine PEP values from the control (C) PEP values. * = P < 0.05; ** = P < 0.01.

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Effects of Intravenous Infusions of Dopamine and Epinephrine on PEP, Before and After 3 Months of Levodopa Therapy

The effects of dopamine and epinephrine before and after administration of levodopa on five patients are shown in figures 5 and 6. The control PEP values were longer after administration of levodopa (see preceding paragraph). Dopamine significantly shortened the PEP ($P < 0.05$) when the amine was infused at rates of 2 and 4 $\mu$g/kg/min before and after 3 months of levodopa therapy. The average PEP was also shortened by the infusion of 1 $\mu$g/kg/min, but the change was not statistically significant. Statistical analysis of the changes produced by dopamine indicated no significant difference between values obtained before and after levodopa. Comparison of the PEP changes produced by dopamine in figure 5 with those produced by levodopa during the initial days of therapy (fig. 2) suggests that the equivalent of at least 4 $\mu$g/kg/min of dopamine was being generated 30 to 60 min after oral administration of levodopa.

Infusions of epinephrine at 0.01, 0.02, and 0.04 $\mu$g/kg/min resulted in significant shortening of the PEP in a dose-related fashion before and after administration of levodopa. Shortening of the PEP during administration of epinephrine has previously been reported.4-6,8 Statistical comparison of the changes before and after levodopa indicated that the changes were not significantly different except for those obtained after the infusion of 0.01 $\mu$g/kg/min. With this infusion rate of epinephrine, the PEP was reduced by 6.7 $\pm$ 0.5 msec before levodopa and 4.5 $\pm$ 0.7 msec after levodopa ($P < 0.05$).

The only significant blood pressure change which occurred with infusion of the amines
was with the 0.04-μg/kg/min infusion of epinephrine. Average systolic blood pressure increased from 128 ± 5.3 to 137 ± 7.4 mm Hg before levodopa and from 126 ± 2.2 to 131 ± 4.8 mm Hg after levodopa. Only the highest infusion rates of dopamine and epinephrine affected heart rate. With infusion rates of 4 μg/kg/min of dopamine and 0.04 μg/kg/min of epinephrine, heart rate was increased an average of 5 beats/min both before and after levodopa therapy.

**Side Effects**

Three patients who participated in the initial phase of this study were not investigated the second time because levodopa had to be discontinued because of adverse effects. Two of these patients experienced nausea and vomiting to a greater degree than the antiparkinsonian effect, and the third developed symptomatic orthostatic hypotension and acute myocardial infarction from which he had an uneventful recovery. Other side effects did not require discontinuation of the drug. Four patients developed dyskinesia; three experienced akathisia, and one noted intermittent torsion dystonia of the neck, puckering of the lips, and abdominal muscle contractions. One patient who had been totally bed-fast prior to levodopa therapy experienced symptomatic orthostatic hypotension and intermittent episodes of hypertension and flushing which lasted for approximately 1 hour.

**Discussion**

This study has demonstrated that oral administration of levodopa (1.0 and 1.5 g) significantly shortens the PEP in patients with Parkinson’s disease during the first 2 weeks of therapy. Thus, it appears that sufficient amounts of a cardioactive catecholamine are generated to increase myocardial contractility. This conclusion is supported by the following data: (1) Shortening of PEP was observed in the absence of significant change in blood pressure. Previous studies have shown that such a change correlates well with other methods of detecting a positive inotropic effect.9-12 (2) Other drugs with positive inotropic effects shorten the PEP.4, 6, 13 (3) The administration of the beta-adrenergic blocking agent, propranolol, completely prevented the shortening of the PEP by levodopa.

This study does not indicate which of the products of levodopa metabolism, dopamine or norepinephrine, was responsible for the increase in myocardial contractility. However, measurements of renal plasma flow in patients with Parkinson’s disease treated with the same dose of levodopa indicated that renal vascular resistance significantly decreases.14 Such an effect is characteristic of the action of dopamine15, 16 and does not appear with norepinephrine, which increases renal resistance.17 Furthermore, dopamine, unlike other sympathomimetic amines, may increase myocardial contractility to a greater degree than it increases heart rate.18 The response to levodopa in our study followed this pattern. Thus, dopamine appears to be the major cardioactive catecholamine produced by decarboxylation of levodopa. However, dopamine stimulates the myocardium both by a direct action of beta-adrenergic receptors and indirectly by releasing norepinephrine from sympathetic stores.19, 20 Thus, released norepinephrine may have contributed to the positive inotropic effect.

The action of dopamine on the myocardium may have both beneficial and detrimental consequences. The positive inotropic effect could be helpful to patients with congestive heart failure, and, in fact, levodopa has been shown to produce a positive inotropic effect and an increase in sodium excretion in such patients.14 On the negative side, drugs with a positive inotropic action increase myocardial oxygen requirements, and this could produce coronary insufficiency in a patient with limited coronary reserve. Action on beta-adrenergic receptors also increases ectopic activity, especially in the presence of sensitizing agents such as cyclopropane and halothane,21 or in the ischemic heart. The development of disturbances in cardiac rhythm have been reported in the treatment of Parkinson’s disease with levodopa.22-25 In addition, drugs acting on beta-adrenergic receptors increase
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transmission through the atrioventricular node, and patients with atrial fibrillation could have a rapid increase in ventricular rate.

The results of this study suggest several means by which potentially detrimental effects can be minimized. First, since shortening of PEP was blocked by relatively small doses of propranolol, this drug could be used to prevent cardiac stimulation and, in fact, has been beneficial in treating cardiac arrhythmias produced by levodopa. Propranolol has also been used to treat the orthostatic hypotension produced by levodopa. In that report, the use of propranolol did not appear to reduce the efficacy of levodopa in the therapy of Parkinson’s disease. In this regard, it was interesting to note that the blood pressure of our patients recorded in the supine position was higher after administration of propranolol. Secondly, there appears to be tolerance to the positive inotropic effect of levodopa after 3 months of continuous therapy. Therefore, it is possible that undesirable cardiac stimulation could be prevented by building the dose up gradually over a prolonged period, as suggested by Cotzias and associates.

We did not discover the mechanism responsible for the failure of levodopa to shorten the PEP after continued therapy. Since dopamine and epinephrine produced similar shortening of PEP before and after continuous therapy with levodopa, beta-adrenergic blockade cannot be the responsible mechanism. Since gastrointestinal absorption of levodopa is not affected by prolonged administration of the drug, decreased absorption cannot explain the phenomenon. A more plausible explanation is that continuous therapy with levodopa results in decreased activity of the enzyme required to convert levodopa to dopamine. This concept is supported by a preliminary study of Dairman and others, which demonstrated that administration of levodopa to rats resulted in reduced levels of aromatic l-amino acid decarboxylase in the liver but not in the brain. Such a mechanism is compatible with the observations that there is tolerance to the cardiac effect of levodopa, but not to the antiparkinsonian action.

Several mechanisms could be responsible for the significant prolongation of the resting PEP after continuous administration of levodopa. Experimental studies have shown that levodopa attenuates the function of the sympathetic nervous system by both central and peripheral actions. Furthermore, chronic administration of levodopa to the rat results in reduced concentration of norepinephrine in the heart but not in the brain.

Acknowledgments

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