Influence of moderate intensity exercise on Levodopa bioavailability in Parkinsonian patients

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ABSTRACT

Background: Parkinson’s disease (PD) is a slowly progressive disorder that affects men and women equally, and eventually leads to disability. Thus, its management is lifelong, including pharmacological and non-pharmacological interventions. Aim of work: This work was conducted to determine the effectiveness of moderate intensity exercises on levodopa bioavailability and the relationship between it and degree of motor impairment in PD patients. Methodology: The study included 20 patients with PD at stage (I) to stage (III) according to Hoen and Yahr classification, and were evaluated by the Unified Parkinson Disease Rating Scale (UPDRS) in two-days assessment “exercise day”, and “non-exercise day” at different intervals following drug intake. Results: Revealed significant increase in bioavailability of levodopa with receiving moderate intensity exercises at different intervals after drug intake, with subsequent improvement of motor impairment signs in exercise day compared with non-exercise day. Conclusion: Moderate intensity exercises have an important role in improving the degree of motor impairment signs, which could improve long-term functional prognosis of PD patients. (Egypt J. Neurol. Psychiat. Neurosurg., 2004, 41(1): 141-150).

INTRODUCTION

Parkinson’s disease (PD) is a neurodegenerative disorder with no identifiable cause resulting from basal ganglionic dysfunction, with subsequent progressive decrement in the concentration of the monoamine neurotransmitter dopamine⁴, with resultant loss of dopaminergic influence on other structures in the basal ganglia, which leads to the classic parkinsonian cardinal signs of bradykinesia, rest tremor, rigidity, and postural reflex impairment⁴.². Because there is no antemortem biological marker for PD, the diagnosis of PD is based entirely on neurological evaluation³, and hence, neurological signs suggesting more extensive injury of the motor or sensory pathways extending beyond the pigmented brainstem nuclei are not included in the diagnosis of PD. These signs are suggestive of other neurodegenerative disorder, often termed “atypical parkinsonism”, including progressive supranuclear palsy, striatonigral degeneration, and other less common conditions²⁴.².

The mainstay of the treatment of PD is levo-dopa therapy, which is the immediate precursor to dopamine⁵. Levo-dopa crosses the blood brain barrier where it is then converted to dopamine, thus helping
reestablishment of dopaminergic effect. The administration of levo-dopa could be associated with dramatic improvement in parkinsonian symptoms especially during early stages of the disease. Management of PD is life long including pharmacological therapy in form of drugs mainly levo-dopa, and non-pharmacological interventions that include physical rehabilitation protocols, occupational and speech therapy, and good nutrition. Many authors emphasized that moderate intensity exercise techniques are important adjunctive therapy in PD, and are needed to prevent or correct musculoskeletal impairment to improve range of motion, gait, endurance, and eventually the long-term functional prognosis. The exercise intensity is expressed as a percentage of maximum heart rate, which is based on the fact that heart rate is a linear function of exercise intensity; the maximum heart rate can be estimated by subtracting one’s age from 220. Low intensity exercise would be equal to 50% to 60% of individual’s maximum heart rate, while moderate intensity exercise is equal to 65% to 80% of individual’s maximum heart rate, whereas, 85% to 90% would relate to high intensity exercise.

Furthermore; Schenckman et al. and Olanow and Kaller reported that physical techniques should be tailored to the stage of the disease; the programs included in early stages of PD maintaining regular physical activities as daily walking concentrating on maintaining long strides, adequate ground clearance and cycling on bicycle ergometer. In more advanced stages, patients should maintain up right posture, strengthen back and hip extensors, also maintaining lower limb muscle force, practice standing up from seats of different heights. In later stages, patients should be educated to change their position in bed regularly to prevent pressure sores, daily standing and walking if possible and breathing exercises to maintain clear airways and vital capacity.

Furthermore, exercises could produce dramatic changes in the pharmacokinetic variables including bioavailability of the orally administered L-dopa resulting in altered clinical responses because the amount of drug reaching circulation and ultimately target tissues is excessively high or excessively low. The magnitude of these changes is dependent on factors that pertain to exercise related characteristics such as its intensity, mode, and duration. Moreover, Ciccone reported that exercise could produce such effects by altering drug absorption at the site of drug administration. This occurs in two primary ways; first, by increase tissue heat during exercise, which increases kinetic molecular movement and thus increase diffusion of drug molecules across biological membranes; second, by affecting drug dispersion away from the site of drug administration.

The aim of this study is to evaluate the effect of moderate intensity exercises on the bioavailability of L-dopa in patients with PD, determine the degree of improvement of motor impairment signs with and without exercises.

**Patients and Methods**

Patients:

The current study included a series of 20 patients; 15 (75 %) males, and 5 (25%) females with idiopathic Parkinson disease (PD) and on L-dopa therapy. They were recruited from the outpatient clinic of Neurology departments, Cairo University Hospitals. Diagnosis of idiopathic PD was based on presence of at least two of the three
cardinal signs of this disorder (bradykinesia, rest tremor, rigidity), observed good response to L-dopa therapy, and normal MRI of the brain\textsuperscript{19}. All patients were at stage (I) to stage (III) according to Hoen and Yahr classification\textsuperscript{20}. Exclusionary criteria included: evidence of secondary or atypical parkinsonism including presence of other clinically relevant neurological deficits such as pyramidal affection, dysautonomia, dementia, amyotrophy, hearing, sensory, or visual impairment; and presence of hepatic disease or other metabolic disorders.

**Methods:**

1. Full neurological evaluation including thorough history taking, and full neurological examination using the Minimental State Examination (MMSE), and those with total scores below 23 were excluded\textsuperscript{21}; the Unified Parkinson Disease Rating Scale (UPDRS)\textsuperscript{22}; and Hoen and Yahr classification\textsuperscript{20}.

2. Each patient was informed about objectives and steps of the work; and all patients were subjected to two sets of assessment (the exercise day, and non-exercise day).

3. The following strategies were performed for each patient:
   a. Each patient was refrained from eating or administering any drug at the day of conducting the study.
   b. Light breakfast was given to each patient consisting of juice and biscuits before administration of instructed dose of L-dopa, because ingestion of protein-containing diet interferes with drug absorption from gut\textsuperscript{23}. The instructed dose of L-dopa was previously determined according to clinical staging of each patient.
   c. In non-exercise day, blood samples (5 ml) in heparinized syringes were withdrawn at the time of administration of instructed dose of L-dopa to determine the baseline blood level, and at 30, 45, 60 and 75 minutes after drug intake to determine the blood levels at these times. Samples were collected in plastic tubes and were put on ice immediately to avoid oxidation of L-dopa\textsuperscript{23}.
   d. In the exercise day; the same procedures of the non-exercise day were undertaken but in this day the patient was requested to start pedaling exercise on bicycle ergometer, where the patient caught a modified handle bar, and an ear sensor was connected to ear lobe of the patient to measure pulse rate; the following criteria for exercises were adopted:
      - The exercises started 15 minutes after administration of the instructed dose of L-dopa.
      - The duration of exercises was 35 minutes according to Carter et al.\textsuperscript{17}.
      - The intensity of exercises was 70\% of predictive maximum heart rate (i.e., moderate intensity exercises)\textsuperscript{13}.
      - The test procedure was divided into three stages:
        **Stage I:** five minutes warming up of pedaling without resistance.
        **Stage II:** active stage lasted for 25 minutes and consisted of pedaling against resistance, which differed according to the patient's 70\% of his/her maximum heart rate.
        **Stage III:** five minutes cooling down of pedaling without resistance.
Patients were evaluated using UPDRS to assess rigidity, bradykinesia, and tremor and to correlate them with L-dopa level in two sessions: at the time of drug administration, and after 60 minutes of its intake, which is the time of maximum efficacy of L-dopa after oral intake.  

4. Laboratory analytic procedures:  
   - Each tube was put in the centrifuge for 2 to 3 minutes for the purpose of plasma separation.  
   - The supernatant fluid was sucked by plastic suction to be put in another plastic clean test tube and all tubes were placed in deep freezer at degree of – 20 °C till the time of analysis.  
   - High Performance Liquid Chromatography (HPLC) apparatus was used to detect L-dopa level, where it represented by peaks displayed on a computer screen, and expressed by mg/ml.

**RESULTS**

**Demographic Data:**  
The age of patients included in this study ranged from 45 to 65 years, with a mean of (53±8.8) years; out of them there were 15 males, and 5 females. Duration of illness ranged from 1 year to 3 years with a mean of (2.13±0.9) (Table 1).

**Comparison between Levodopa bioavailability without and with exercises:**  
Upon evaluating bioavailability of levodopa at different times of drug intake in both non-exercise day and exercise day, there was no statistical significant difference at the time of drug ingestion [zero time]. However, there was statistically significant increase in bioavailability of levodopa in the exercise day at 30, 45, 60, and 75 minutes after drug intake (Table 2 and Figure 1).

**Comparison between degrees of motor impairments without and with exercises at zero time and at 60 minutes after drug intake:**

**Degree of Tremor Severity:**  
There was no significant difference between degree of severity of tremor without and with exercise at zero time, however at 60 minutes after drug administration, the degree of severity of tremor showed improvement in exercise day compared to non-exercise day with a high statistical significant difference (Table 3, Figure 2).

**Degree of Rigidity:**  
There was no significant difference between degree of rigidity without and with exercise at zero time. Though there was a decline in degrees of rigidity in exercise day at 60 minutes after drug ingestion compared to non-exercise day, yet this improvement was not of statistical significant difference (Table 4).

**Degree of Bradykinesia:**  
There was no significant difference between degree of bradykinesia without and with exercise at zero time; but though results showed that there was a decline in the severity of bradykinesia in exercise day at 60 minutes after drug intake compared to non-exercise day, yet this decline was not of statistical significant difference (Table 5).
Table 1. General Characteristics of Patients.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Range</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45 – 65</td>
<td>53 ± 8.8</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Duration of Illness (Years)</td>
<td>Range</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>1 – 3</td>
<td>2.13 ± 0.9</td>
</tr>
</tbody>
</table>

Table 2. Mean of levodopa bioavailability without and with exercise at different times after drug intake.

<table>
<thead>
<tr>
<th></th>
<th>Without Exercise</th>
<th>With Exercise</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-dopa bioavailability at zero time</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>L-dopa bioavailability at 30 minutes after drug ingestion</td>
<td>0.029</td>
<td>0.009</td>
<td>0.032</td>
<td>0.008</td>
</tr>
<tr>
<td>L-dopa bioavailability at 45 minutes after drug ingestion</td>
<td>0.043</td>
<td>0.018</td>
<td>0.052</td>
<td>0.02</td>
</tr>
<tr>
<td>L-dopa bioavailability at 60 minutes after drug ingestion</td>
<td>0.054</td>
<td>0.026</td>
<td>0.071</td>
<td>0.035</td>
</tr>
<tr>
<td>L-dopa bioavailability at 75 minutes after drug ingestion</td>
<td>0.073</td>
<td>0.034</td>
<td>0.114</td>
<td>0.052</td>
</tr>
</tbody>
</table>

*: Significant.

Fig. (1): Mean of levodopa bioavailability (mg/ml) without and with exercise at different times after drug intake.
Table 3. Degree of Tremor Severity at zero time and at 60 minutes after drug administration.

<table>
<thead>
<tr>
<th></th>
<th>Without Exercise</th>
<th></th>
<th>With Exercise</th>
<th></th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor at zero time</td>
<td>1.8</td>
<td>0.09</td>
<td>1.7</td>
<td>0.11</td>
<td>0.042086</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Tremor at 60 minutes after drug intake</td>
<td>1.4</td>
<td>0.11</td>
<td>0.6</td>
<td>0.11</td>
<td>4.571</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*: Significant.

Fig. (2): Degree of Tremor Severity at zero time and at 60 minutes after drug administration.

Table 4. Degree of rigidity at zero time and at 60 minutes after drug administration.

<table>
<thead>
<tr>
<th></th>
<th>Without Exercise</th>
<th></th>
<th>With Exercise</th>
<th></th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigidity at zero time</td>
<td>1.00</td>
<td>0.15</td>
<td>0.91</td>
<td>0.12</td>
<td>0.7581</td>
<td>&gt;0.05</td>
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<tr>
<td>Rigidity at 60 minutes after drug intake</td>
<td>0.40</td>
<td>0.11</td>
<td>0.20</td>
<td>0.09</td>
<td>0.25845</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 5. Degree of bradykinesia at zero time and at 60 minutes after drug administration.

<table>
<thead>
<tr>
<th></th>
<th>Without Exercise</th>
<th></th>
<th>With Exercise</th>
<th></th>
<th>t-value</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradykinesia at zero time</td>
<td>1.40</td>
<td>0.11</td>
<td>1.20</td>
<td>0.09</td>
<td>0.258452</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Bradykinesia at 60 minutes after drug intake</td>
<td>0.80</td>
<td>0.17</td>
<td>0.60</td>
<td>0.09</td>
<td>1.000</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
DISCUSSION

Parkinson’s disease is the second most common neurodegenerative disorder, next to Alzheimer disease; it is characterized by tremor, rigidity, bradykinesia, and postural instability. Management of PD is life long that requires multiple interventions including pharmacological and non-pharmacological approaches. One of the most crucial non-pharmacological aspects of management is physical therapy.

Results of this study revealed non-significant difference in bioavailability of levodopa at the time of drug ingestion in both exercise and non-exercise days, which indicated that baseline levels of levodopa were consistent in both days. On the other hand, there was significant increase in levodopa bioavailability with receiving moderate intensity exercises at 30, 45, 60, and 75 minutes after drug intake. These findings could conclude that moderate intensity physical therapy intervention could augment the bioavailability of levodopa, which in accordance with Ciccon who reported that exercise can affect bioavailability by altering drug absorption at the site of drug administration through increased tissues heat during exercises, which increases kinetic molecular movement and thus increases diffusion of drug molecules across biological membrane. These findings were previously recognized by Carter et al. who found that exercises increased absorption of levodopa in PD patients. Moreover, the results of the present work are in agreement with Reuter et al. who found that the maximal levodopa concentration in plasma was higher with exercise.

On the other hand, these results were debated by Goetz et al. who concluded that vigorous exercise started one hour after levodopa ingestion did not influence levodopa plasma level in PD patients. This discrepancy between could be attributed to the intensity of exercise which was clarified by Carter et al. who reported that gastric emptying is accelerated by moderate exercises and delayed by severe exhausted exercises. These findings are in disagreement with VanBaak, 1990 who mentioned that exercises decrease absorption of orally administered drug because increased kinetic movement of the drug may be offset by the reduction in splanchnic blood flow commonly seen during moderate to high intensity exercise. Our results disagree with Mouradian et al. who studied the effect of different intensities exercises on bioavailability of infused intravenous levodopa in PD patients. Their results indicated that plasma levodopa level was unaltered by exercises. This discrepancy may be attributed to the using of intravenous levodopa, which enters directly to systemic circulation and does not be affected with factors that enhance or decrease absorption as in orally administered levodopa.

In addition the results of this work revealed that there was improvement of the motor impairment signs in exercise day compared with non-exercise day at 60 minutes after drug intake. This finding denotes that increase levodopa level is parallel to improvement of motor impairment signs, and support the role of exercise in improving motor impairment signs through their effect on levodopa bioavailability. These findings were previously supported by Jesse and Leonard, and also in accordance with Contin et al. who found that maximum motor response measured by finger tapping was positively correlated with matched duration of levodopa dose response. This was explained by relating the rate of motor response to oral levodopa to the rate of dopamine interaction with the post-synaptic receptors, which providing an index of pre-
synaptic dopaminergic homeostasis. In addition, our results showed that the most improving motor sign was tremor, and though there was improvement in both bradykinesia and rigidity at time of peak levodopa concentration in exercise day, yet this improvement was not statistically significant. These findings are in disagreement with Curtis$^{30}$ who reported that levodopa is effective in relieving bradykinesia. Also these results were debated by Jone and Godwin$^{31}$ who mentioned that the most effective treatment for the relief of most of motor impairment signs especially slowness and poverty of voluntary movement is levodopa. This controversy could be explained by the selection criteria in our work, as all patients participated in this work were mild cases at stage I to stage III according to Hoen and Yahr classification$^{20}$ and the most striking feature of our patients was tremor.

In conclusion, moderate intensity exercises have an important role in increasing the bioavailability of levodopa in PD patients in which consequently there is improvement in the degree of motor impairment signs (tremor, bradykinesia, and rigidity) with exercises. Thus exercise training programs could improve long-term functional prognosis of PD patients by minimizing incremental drug dosage increase.

REFERENCES


تآثير التمارين متوسطة الشدة على مستوى الليفوودوبا بالدم في مرضى الشلل الرعاش (باركنسون)

يعتبر مرض باركنسون من الأمراض العصبية الشائعة التي تصيب غالباً كبار السن، وتعتبر في أعراضها التي تؤدي في مآلها إلى درجة كبيرة من الإعاقة الحركية مما يضعف سلباً على إمكانية المريض بالقيام بوظائفه اليومية الروتينية. كما إن علاج هذا المرض هو علاج للأعراض المتمثلة أساساً في بعض الحركة وتيين العضلات والرعاش، ورغم إن هناك الكثير من التدخلات الدوائية وغير الدوائية للمرض إلا إنه عقار الليفوودوبا يشكل حجر الزاوية في العلاج والذي يستمر طوال الحياة. تهدف هذه الدراسة إلى بحث تأثير التمارين متوسطة الشدة على نسبة الليفوودوبا بالدم في مرضى الباركنسون وأثر ذلك في التحسن الحركي للمرضى. وقد أثبتت الدراسة زيادة في نسبة الدواء بالدم عقب التمارين متوسطة الشدة مما كان له الأثر في التحسن الحركي. وستنتج من هذا البحث أهمية العلاج الطبيعي والتمارين متوسطة الشدة لمرضى الباركنسون.