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Pharmacokinetics of Levodopa before and after Gastrointestinal Resection in Parkinson's Disease

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Key Words
Parkinson's disease · Levodopa · Pharmacokinetics · Gastrointestinal resection

Abstract
Introduction: Levodopa (LD) is important in the clinical treatment of Parkinson's disease (PD), and the changes of its pharmacokinetics may affect the clinical outcome. LD is mainly absorbed in the upper intestine; thus, the pharmacokinetics of LD may change after gastrointestinal operation. Here, we present the case of a patient who underwent resection of the intestine and compared his LD pharmacokinetics before and after resection. ***Case Presentation:*** A 72-year-old Japanese male PD patient developed jaundice and was diagnosed with cholangiocarcinoma. Pancreaticoduodenectomy was performed and part of the stomach, total duodenum, and part of the jejunum were resected. The patient had been treated with LD, and his pharmacokinetics was checked twice at the age of 68 years. Because LD is absorbed in the duodenum and jejunum, we checked his pharmacokinetics again after the operation. The results before the operation were almost similar; however, in comparison, the area under the curve and peak drug concentration was reduced, and the time-to-peak drug concentration and elimination halftime were elongated after the operation. ***Conclusion:*** Physicians must pay attention to the change of LD pharmacokinetics after gastrointestinal operation.

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Introduction

Parkinson's disease (PD) is a rare neurodegenerative disorder in which a number of medications consistently improve the clinical symptoms. Levodopa (LD) is the most effective antiparkinsonian drug used for treatment. It is known that the change of LD pharmacokinetics is related to several factors such as wearing off and delayed action [1]. Understanding the pharmacokinetics of LD is important in the clinical treatment of PD because these changes may affect the clinical outcome [2]. LD is mainly absorbed in the upper intestine [3]. Maintaining good absorption in the intestine leads to good clinical outcome, and the change in intestine absorption may induce the alteration in LD pharmacokinetics. Thus, if gastrointestinal operation is performed in patients with PD, the pharmacokinetics of LD may change after the perioperative period. However, there were few reports that describe LD pharmacokinetics during the perioperative period. Here, we present the case of a patient who underwent resection of the intestine and compared his LD pharmacokinetics before and after resection.

Case Presentation

A 72-year-old Japanese male PD patient had experienced a slowly progressive gait disturbance and akinesia since 56 years of age. He was diagnosed with PD at 58 years. He had no history of any neurological disorders. His family history is unremarkable. During the next 15 years, he had been admitted to our hospital several times for drug control, and LD pharmacokinetics was checked twice when he was 68 years old. At the age of 71 years 10 months, although his parkinsonian features had not changed, he suddenly developed jaundice and he was diagnosed with cholangiocarcinoma. At this time, his Unified Parkinson's Disease Rating Scale (UPDRS) motor score (part III) was 28/108 [4], and his daily antiparkinsonian treatment was 500 mg/50 mg of LD/carbidopa, 0.5 mg of cabergoline, and 2.5 mg of selegiline.

In the next month (at the age of 71 years 11 months), pancreaticoduodenectomy was performed. In this operation, subtotal removal of the stomach (3 cm from the pylorus side), total removal of the duodenum, and subtotal removal of the jejunum (20 cm from the ligament of Treitz on the distal side) was performed (fig. 1a). Reconstruction was made by end-to-end anastomosis of the pancreas to the bile duct to the jejunum (fig. 1b). There were no surgical complications in his post-operative course, and he recovered without any surgical problems. After 5 days, he could take the same oral antiparkinsonian agents as before the operation (500 mg/50 mg of LD/carbidopa, 0.5 mg of cabergoline, and 2.5 mg of selegiline); however, his Parkinsonian features were gradually remarkable within 2 weeks after the operation. The patient did not receive any agents as chemotherapy. He was then transferred to our ward for parkinsonian drug treatment.

At this time, his height, body weight, and body mass index were 158.0 cm, 61.0 kg, and 24.4, respectively. His neurological examination revealed marked masked face, dysarthria, and dysphagia. Mild tremor at rest in the left upper extremity, severe rigidity in the bilateral upper and lower extremity, and poor finger taps on the dominant left side were also observed. Gait was unable without assistance. His parkinsonian features were obviously getting worse, and UPDRS motor score (part III) was 68/108. Thus, we checked whether this worsening of parkinsonian features was due to a change in LD absorption in the gastrointestinal tract by checking his LD pharmacokinetics.

Written informed consent was obtained from this patient, and the approval of the Institutional Review Board was obtained for the examination of LD pharmacokinetics. To assess LD pharmacokinetics, he took a tablet containing 100 mg of LD and 10 mg of carbidopa at 9:00 a.m. following an overnight fast and a medication-free period of at least 18 h. Blood specimens were collected through an intravenous catheter at 0, 15, 30, 60, 120, and 180 min after LD administration, and plasma LD concentrations were measured by high-performance liquid chromatography with electrochemical detection. The procedure of measurement of blood LD concentration has been described in our previous report [5]. Peak drug concentration (C_{max}), the time-to-peak drug concentration (T_{max}), elimination halftime (T1/2), and area under the curve (AUC) were determined. C_{max} and T_{max} were observed values, T1/2 was determined by linear regression analysis, and AUC was estimated from the area under the time concentration line up to 3 h.

In his LD pharmacokinetics at the ages of 68 years 11 months (and 68 years 1 month), body weight was 64.2 (and 64.8) kg, AUC was 1,782.5 (and 1,825.0) mg·h/ml, C_{max} was 1,500 (and 1,500) mg/ml, T_{max} was 30 (and 30) min, and T1/2 was 48 (and 47) min. In the postoperative assessment (at the age of 72 years 4 months), AUC was 1,148.8 mg·h/ml, C_{max} was 450 mg/ml, T_{max} was 60 min, and T1/2 was >120 min (fig. 2).

Discussion

This is a very rare case with making comparison of LD pharmacokinetics before and after intestinal resection. The time lag between the first and second examination and the operation was about 3 years. We believe this period was very important, because there may be no influences of cholangiocarcinoma for the examinations. Moreover, since his clinical picture did not change during this period, it may be difficult to consider there was a marked change of pharmacokinetics.

In this study, the pharmacokinetic parameters remarkably changed after gastrointestinal resection. AUC and C_{max} were reduced by two thirds and one third, respectively, T_{max} increased two fold, and T1/2 showed a greater than two fold increase over the values before the operation. To our knowledge, this is the first report that compares LD pharmacokinetics before and after gastrointestinal operation.

Oral drugs are metabolized after absorption in the gastrointestinal tract, and these are then excreted from the body. Pharmacokinetics is influenced by changes in these conditions. In healthy subjects, it was reported that LD was equally absorbed when it was administrated into the proximal or the distal part of the duodenum or into the upper part of the jejunum [3]. In this case, the pylorus side 3 cm of the stomach, total duodenum, and 20 cm from the ligament of Treitz to the distal side of the jejunum were resected. Furthermore, in the reconstruction, about 20 cm of the remaining jejunum was set as coecum. Thus, the function of the longer gastrointestinal tract was lost, and this may affect the pharmacokinetics of LD remarkably.

There are many factors that influence the pharmacokinetics of orally administrated LD [6] such as the changes in gastric emptying time [7], food intake (fat or large neutral amino acids) [8], advanced age [5], sex [9], and body weight [10]. Of these factors, the influence of food (fat or amino acids) on the pharmacokinetics of LD may be one possible explanation for the results in the present study. LD is transported across the intestinal mucosa by the large neutral amino acid transport system, where amino acids such as tyrosine, phenylalanine, tryptophan, leucine, isoleucine, and valine competitively inhibit LD membrane transport [11]. Thus, when LD is administrated with food that contains protein, C_{max} and AUC decrease

and T_{max} increases. In the patient described, the postoperative LD pharmacokinetics pattern is almost similar to the pattern of influence by food intake. The competitive inhibition of LD absorption in the intestine by the large neutral amino acid resembles the dysfunction of absorption after intestinal resection. Thus, this may be one explanation for the changes in C_{max}, AUC, and T_{max}.

In this case, T1/2 also increased; however, it has been reported that T1/2 does not change when LD is administrated with food [6, 8]. Although elongation of T1/2 was reported in the assessment of older subjects and in the use of catecholamine-O-methyltransferase [5, 12], this case was not applicable to such situations. The gastrointestinal tract is also one of the main regions affected in patients with PD [13], and in this case, the stomach-duodenum-jejunum was resected. Therefore, although the reason for the T1/2 increase in the present case remains unclear, the changes in the gastrointestinal tract may affect the results of T1/2.

In conclusion, we experienced a case of PD where a comparison of LD pharmacokinetics before and after gastrointestinal resection was made. In this case, LD pharmacokinetics was markedly changed after the operation, and the changes in the absorption ability were suspected as the cause for these results. Physicians must pay attention for the change of LD pharmacokinetics after gastrointestinal operation.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

None of the authors have conflicts of interest to disclose.

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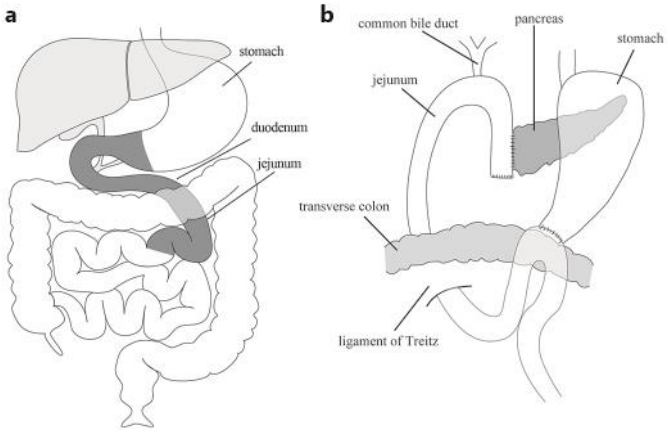

Fig. 1. Gastrointestinal resection and reconstruction. **a** The resected portion (a part of the stomach, total duodenum, and a part of the jejunum) is denoted in dark gray. **b** Gastrointestinal tract after reconstruction.

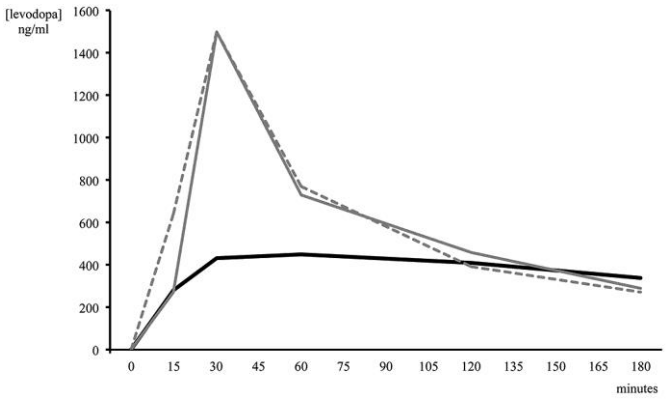

Fig. 2. LD pharmacokinetics before and after gastrointestinal resection. Solid black line represents the results at 72 years 4 months. Solid and broken gray lines represent the results at 68 years 11 months and 68 years 1 month, respectively.