Levodopa ameliorated anorectal constipation in *de novo* Parkinson's disease: the QL-GAT study

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Abstract

Background: Gastrointestinal tract (GIT) dysfunction is common in Parkinson's disease (PD) patients. However, it remains unclear whether levodopa affects GIT function in PD.

Objective: To perform an open study of levodopa's effects on anorectal constipation in *de novo* PD patients by the quantitative lower-gastrointestinal autonomic test (QL-GAT).

Methods: Nineteen unselected *de novo* PD patients (10 men, 9 women; mean age, 66 years; mean duration of the disease, 2.2 years) were recruited for the study. Eighteen of the patients reported constipation. These patients were treated with 200/20 mg b.i.d. of levodopa/carbidopa for 3 months. Pre- and post-treatment, objective parameters in the QL-GAT that comprised the colonic transit time (CTT) and rectoanal videomanometry were obtained.

Results: Levodopa was well tolerated by all patients. There was a trend toward subjective improvements in bowel frequency and difficulty defecating. Levodopa did not significantly change CTT of the total colon or any segment of the colon. During rectal filling, levodopa significantly lessened the first sensation ($p<0.05$). It also tended to augment the amplitude of spontaneous phasic rectal contraction (not statistically significant). During defecation, levodopa significantly lessened the amplitude in paradoxical sphincter contraction upon defecation (PSD) ($p<0.01$). It also tended to augment the amplitude of rectal contraction and lessen the amplitude of abdominal strain (not statistically significant). Overall, levodopa significantly lessened post-defecation residuals ($p<0.05$).

Conclusions: The QL-GAT in the present study showed for the first time that levodopa augmented rectal contraction, lessened PSD, and thereby ameliorated anorectal constipation in *de novo* PD patients.

Introduction

Parkinson's disease (PD) is a common movement disorder associated with the degeneration of dopaminergic neurons in the substantia nigra [1]. In addition to the motor components , patients with PD often have non-motor symptoms, of which gastrointestinal tract (GIT) dysfunction is one of the most common [2]. The various aspects of non-motor dysfunction differ from each other in their anatomy, pathology, and neurochemistry and also in their responsiveness to levodopa [3-5]. However, it remains unclear whether levodopa affects GIT function in patients with PD. We devised the quantitative lower-gastrointestinal autonomic test (QL-GAT), which proved useful for assessing drugs to treat constipation in PD [6-8]. In this study, we performed an open trial of levodopa's effects on anorectal constipation, a prominent lower-GIT symptom in *de novo* PD patients, using objective parameters given by the QL-GAT.

Materials and methods

Patients

We recruited 19 unselected *de novo* PD patients, irrespective of the presence of constipation, who had not taken any medication for PD, most of whom had been referred for treatment of their PD There were 10 men and 9 women with a mean age of 66 years [range 47-83 years]; the mean duration of the disease was 2.2 years (14 years). In all patients the diagnosis of PD was confirmed according to clinical diagnostic criteria, [1,9] findings from magnetic resonance imaging (MRI) scans, ^{99m}Tc- L,L-ethyl cysteinate dimer (ECD) single-photon emission computed tomography (SPECT), and ^{123}I-metaiodobenzylguanidine (MIBG) cardiac scintigraphy [10]. In 10 cases motor unit potential analysis of the sphincter electromyography [11] that was performed in order to confirm the diagnosis. Disease staging was assessed by Hoehn-Yahr, and the median score was 3 (1-4), with all subjects able to walk independently with the exception of a male patient who needed occasional assistance for walking. Sixteen of the patients also underwent Unified Parkinson's Disease Rating Scale (UPDRS), Part 3 Motor Function, and the mean value was 23 (9-30). None of the patients was taking anti-cholinergic agents, anti-depressants, GIT prokinetics such as mosapride citrate, or any other drugs that might have affected lower-GIT function.

Eighteen of the patients were found to have constipation according to a questionnaire on pelvic organ function [12]: Thirteen patients had decreased bowel frequency (11 < three times a week with/without enema, 2 > three times a week but with occasional laxative use), and 18 had difficulty with defecation (needing a long time, much straining, or needing to manually expel

residual stools; 11 > daily, 1 > weekly, 6 > monthly). One patient reported fecal incontinence (once per month). None of the patients had abnormalities in blood chemistry (including blood sugar) or urinalysis. None had a recent history of anal fissure or hemorrhoid that might affect lower-GIT function. Did you have institutional approval After being informed of the purpose of the study and the procedure, all patients gave informed consent before participating in the study. Seven patients were already taking occasional laxatives (magnesium oxide, Senna alexandrina [a herbal medicine], etc.) to treat their constipation. We instructed these patients not to change the frequency and quantity of laxatives they took throughout this study.

Treatment and assessment protocol

We performed the QL-GAT before and 12 weeks after administration (b.i.d.) of 200 mg/day levodopa and 20 mg/day carbidopa. This dose was chosen in order to avoid adverse events such as nausea, vomiting, or sleep attack, and because all patients, with one exception were able to walk independently . The dosage remained unchanged during the 12 weeks study period. The patients attended the Neurology outpatient clinic monthly and and completed the questionnaire each time. The QL-GAT [13,14] consisted of colonic transit time (CTT), which measures *colonic transport*, and rectoanal videomanometry, which measures *transient anorectal reservoir* and *defecation*. The CTT study was performed using the repetitive ingestion method. We asked the patients to ingest a small test capsule containing 20 circular radiopaque markers, once a day for 6 days shortly after breakfast. Following the administration of the sixth test capsule on the sixth day ,a plain abdominal X-ray was taken on day 7, The markers were counted in three segments of the large bowel: the right colon, the left colon, and the sigmoid colon and rectum. One marker corresponded to 1.2 hours (20 markers for 24 hours) of transit time. We counted the number of markers in each segment of the large bowel and then calculated the right CTT (normal values [hours]: mean 6.9, range 3.6-7.2), left CTT (14.1, 2.4-19.2), rectosigmoid CTT (18.0, 7.2-26.4), and total CTT (39.0, 16.0-48.0) (mostly reflecting *parasympathetic innervation*) [13,14].

Anorectal videomanometry was performed in the morning in all patients, using a urodynamic computer (Urovision; Lifetech Inc., Houston, TX, USA) and an electromyographic (EMG) computer (Neuropack M2, Nihon Kohden Inc., Tokyo, Japan). A triple-lumen 9F catheter (for use with contrast medium infusion, rectal and anal pressures) was inserted into the anus. An 8F catheter (for use with abdominal pressure) was inserted into the bladder. A concentric needle electrode was inserted into the external anal sphincter muscles. In the resting phase with the patient in a seated

position, we measured anal sphincter pressure (mainly *sympathetic* [13,14]) (normal value [cmH_2O]: mean 64, range 42-97) by pulling the catheter from inside the rectum (2 cm/min) throughout the anal canal while infusing sterile water at a rate of 1 ml/min [13,14]. At this point we stabilized the catheter with visual guidance under X-ray fluoroscope. We also measured anal squeeze pressure (*somatic* [13,14]) (96, 52-128) and the increase in abdominal pressure when the subject coughed (98, 63-156) and straining (71, 48-113) (*viscera-somatic reflex* [13,14]).

With the patient seated, we then performed medium-fill (50 ml/min) videomanometry by infusing contrast medium (20% amidotrizoic acid) into the rectum while simultaneously recording the rectal pressure (the difference between the naïve rectal pressure abdominal pressure) in addition to anal sphincter pressure, sphincter EMG activity, fecal flow, and fluoroscopic images of the sigmoid colon, rectum, and anus. In the filling phase the following parameters were measured: first sensation (normal value [ml]: mean 128, range 50-160), maximal capacity (302, 127-600), rectal compliance (the smaller number indicates tonic contraction; *parasympathetic*), i.e., Δinfused volume / Δrectal pressure (normal value [ml / cmH_2O]: mean 69.0, range 18-150), spontaneous phasic rectal contraction (SPRC) (normal value [cmH_2O]: mean 22.0, range 10-50) (*parasympathetic*), and phasic anal contraction (*somatic*) in response to the phasic rectal contraction (-11.0 [relaxation], -40 to +10). In the defecation phase following the maximum capacity volume, the following parameters were measured: rectal contraction (11.1, 0-40) (*parasympathetic*), anal contraction (19.6, -50 to +60) (iknown as a paradoxical sphincter contraction upon defecation (PSD) if exaggerated or anismus; *somatic*), abdominal straining (67.3, 0-125) (*somatic*), and post-defecation residuals (normal value [ml]: mean 10, range 0-15). Statistical analysis was made using Student's *t*-test and χ^2-test. All patients gave informed consent before participating in the study. This study was approved by the Sakura Medical Center Ethics Committee, Toho University.

Results

Levodopa was well tolerated by all patients. None had vomiting or other adverse GIT effects during the observation period. In addition, parkinsonian motor symptoms (resting tremor, rigidity, or gait disorder) responded well to levodopa treatment in all patients, as measured by UPDRS Part 3 Motor Function, with a mean value 23 (9-30) to 17 (7-23). However, there was no clear correlation between the improvement of UPDRS Part 3 Motor Function and each of the

following GIT parameters. Although a χ^2-analysis of the data from the questionnaire on pelvic organ function was not significant, there was a trend toward subjective improvements, e.g. after the administration of levodopa, 10 patients had decreased bowel frequency (7 < three times a week with/without enema, 3 > three times a week but occasionally using laxatives), and 15 had difficulty defecating (needing a long time, straining much, or manually expelling residual stools; 4 > daily, 7 > weekly, 4 > monthly). Accidental fecal incontinence in one patient resolved during the observation period. None developed new onset fecal incontinence.

The QL-GAT was well tolerated by all patients. None had infection, bleeding or other adverse events after the QL-GAT, and all patients were able to repeat the test. The results of the CTT study are shown in **Table 1**. Levodopa did not significantly change CTT of the total colon (49.3 to 56.7 hours) or CTT of the right, left, or rectosigmoid segment either before or after treatment. A representative case of the rectoanal videomanometry is shown in **Figure 1**, and the results are shown in **Table 2**. In the rectoanal videomanometry, in the resting state, levodopa did not change the anal sphincter pressure, anal squeeze pressure, or abdominal pressure with coughing or straining. During rectal filling, levodopa significantly lessened the first sensation (178.6 ml to 121.3 ml, $p<0.05$). It also tended to lessen the maximum rectal capacity and to augment the amplitude in SPRC, though these changes did not reach statistical significance. During defecation, levodopa significantly lessened the amplitude in PSD (29.7 cmH_2O to -7.1 cmH_2O, $p<0.01$). It also tended to augment the amplitude of rectal contraction and lessen the amplitude during abdominal strain, though these changes did not reach statistical significance. Overall, levodopa significantly lessened post-defecation residuals (142.2 ml to 53.9 ml, $p<0.05$).

Discussion

Constipation is a prominent lower-GIT disorder in patients with PD [2] The average Hoehn-Yahr stage of 3 in our patients seemed high for patients who have not yet begun treatment. This presumably depends on most patients having been referred from general physicians; and the study included patients over 80 years old. In the baseline assessment using a questionnaire, our *de novo* PD patients showed slightly more common bowel symptoms than those reported previously. ?Reference This presumably depends on the method we used, in which we asked patients to grade their bowel symptoms as monthly, weekly, and daily. In the baseline assessment using the QL-GAT, *de novo* PD patients showed slowed CTT and decreased SPRC, as have been seen in previous studies of PD as compared with normal subjects [13,14], both of which are major

causes of slow transit constipation. These findings mostly reflect peripheral enteric pathology in PD via an altered cholinergic enteric nervous system (ENS) circuit, which normally promotes peristalsis [13,14]. Our patients with PD also had weak strain and PSD, asseen in previous studies of PD [13,14]. Weak strain and PSD are major causes of anorectal constipation. Straining plays a physiological role in both coughing and defecation, which is achieved by co-contraction of the glottis, diaphragm and abdominal wall. Straining is associated with activation in brainstem nuclei such as the Kolliker-Fuse nucleus and medullary respiratory neurons [14]. The mechanism of impaired straining in PD may include rigidity and reduced contractability of the axial muscles, and a failure of coordinated glottis closure [15]. However, neuronal degeneration in the central nervous system (CNS) relevant to straining has yet to be clarified in PD. The precise mechanism of coordinated anal sphincter inhibition on defecation remains unknown. Mathers and colleagues [16] consider PSD a focal dystonia. PSD also occurs in spinal cord-injured patients, suggesting that dysfunction in the suprasacral descending pathway to the external sphincter is a contributing factor. Apomorphine is shown to lessen PSD [16]. This effect was not antagonized by domperidone, which does not cross the blood-brain barrier (BBB), suggesting that the CNS pathology may produce PSD [16]. Therefore, weak strain and PSD might be the results of altered somatic nerves that mainly result from brain pathology in PD [13,14]. As a result, PD patients had large post-defecation residuals, and our patients had both slow transit and anorectal constipation before levodopa treatment. While levodopa remains the mainstay in the treatment of motor symptoms in PD, the question of whether levodopa affects GIT function has not been answered definitively. To the best of our knowledge, this is the first study to assess levodopa's effects on anorectal constipation in *de novo* PD patients by using objective parameters given by the QL-GAT.

In the present study, levodopa ameliorated difficult defecation in *de novo* PD patients after a 3-month administration period. During rectal filling, levodopa significantly lessened the first sensation (178.6 ml to 121.3 ml, $p<0.05$) together with augmenting the amplitude of rectal contraction (not statistically significant). During defecation, levodopa significantly lessened the amplitude of PSD (29.7 cmH_2O to -7.1 cmH_2O, $p<0.01$) and also lessened post-defecation residuals (142.2 ml to 53.9 ml, $p<0.05$). Among these, decreased first sensation is most probably the result of augmented rectal contraction. In summary, levodopa augmented rectal contraction, lessened PSD, and thereby ameliorated anorectal constipation in *de novo* PD patients without serious adverse effects.

In experimental animals, the ENS plays the most important role in regulating the peristaltic

reflex of the lower GIT. The origin of the slow wave rhythmicity in lower GIT has been identified in the myenteric (Auerbach's) and submucous (Meisner's) plexuses, where interstitial cells of Cajal (ICC) exist [17]. 1-Methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP)/salsolinol-induced parkinsonian animals showed decreased GI motility [18] and decreased c-Kit expression in the ICC [19]. The strength of cholinergic transmission in the ENS is thought to be regulated by opposing receptors, serotonin 5-HT4 receptor-mediating excitation [20] and dopamine D2 receptor-mediating inhibition [21], based on tests with knock-out mice [20,21]. However, a number of studies have also demonstrated increased motility in the colon (in which dopamine receptors are scarce), but not in the stomach (rich in dopamine receptors), in response to externally administered dopamine, presumably mediated by other receptor populations such as adrenergic or serotonergic receptors, or by central mechanisms [22].

Similarly, clinical reports of dopamine's effect on GIT motility have produced conflicting results. Unlike levodopa, dopamine cannot cross the BBB. Dopamine is used as a peripheral vasoactive drug in intensive care units, where it has been shown to reduce gastric migrating motor complex [23]. In contrast, dopamine increases colonic motility in normal volunteers [4] and in patients with irritable bowel syndrome [24]. Dopaminergic blockers, e.g., domperidone (unable to penetrate the BBB) and metoclopramide (partially crossing the BBB) are widely used as upper-GIT prokinetics that prompted gastric emptying. [25,26] In contrast, they did not accelerate colonic transit significantly [27]. The basal ganglia modulate the bowel motility, with the main action apparently being inhibitory. Electrical stimulation or microinjection of dopamine into the striatum inhibits upper-GIT motility [28]. However, under stress conditions, intracerebroventricular administration of dopamine facilitates colonic spike bursts, presumably via the hypothalamus [29]. Although the connection has not been fully clarified, bowel function seems to be modulated by the central nervous system (CNS) structures [30]. Considering the above evidence, levodopa might have acted on the lower-GIT function by both the ENS and CNS mechanisms in our *de novo* PD patients.

A questionnaire on pelvic organ function showed that levodopa tended to improve defecation frequency. In contrast, the QL-GAT showed that levodopa did not significantly change CTT of the total colon or any segment of the colon. We do not know the exact mechanism for this discrepancy. However, augmented rectal contraction may well increase the rectal sensation, as occurs in the bladder. It is therefore possible that increased rectal sensation might have facilitated defecation frequency in our *de novo* PD patients.

Finally, some discussion is warranted regarding the interaction between somatic motor and anorectal function. In the healthy population, there have been conflicting reports about whether moderate exercise improves constipation, e.g., moderate exercise is reported to shorten mouth-to-anus transit time [31] whereas it did not [32]. Similarly, it remains uncertain whether exercise may improve bowel function in PD. In our patients, UPDRS, Part 3 Motor Function improved after administration of levodopa. Although there was no clear correlation between the improvement in motor function and each of the GIT parameters, it is possible that improved anorectal constipation might partly be a result of improved motor function. The limitation of our study is that it did not include controls. Future studies should be performed with a double blind design in order to confirm levodopa's effects on constipation in PD, the improvement of which is important for the patients' quality of life.

In conclusion, the QL-GAT in the present study showed for the first time that levodopa augmented rectal contraction, lessened PSD, and thereby ameliorated anorectal constipation in *de novo* PD patients without serious adverse effects.

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