

TRANSDERMAL DOPAMINE AGONIST AMELIORATES GASTRIC EMPTYING IN PARKINSON'S DISEASE

Hypothesis / aims of study

Slow gastrointestinal (GI) transport can be attributed to peripheral myenteric plexus pathology in Parkinson's disease (PD), where altered balance of cholinergic/ 5-HT₄ serotonergic excitation and D₂ dopaminergic inhibition might occur. This is further affected by ghrelin and other hormonal changes. It is recently reported that in PD patients, levodopa does not worsen gastric emptying (GE) or colonic transit time (CTT) while levodopa facilitates defecation. However, whether dopaminergic receptor agonist (DA) affects GI motility is not well known. To answer this question, we measured GE and CTT before and after DA administration in a single PD patients cohort.

Study design, materials and methods

We enrolled 9 PD patients (3 men, 6 women; age 65.0 ± 4.1 years (mean \pm standard deviation); disease duration, 2.6 ± 2.4 years; Modified Hoehn and Yahr (HY) stage, 1.9 ± 0.5 ; abdominal discomfort, one, bowel movement <3 times a week (constipation), 3). After the first measure, all started to take DA: 16.7 ± 11.5 mg/day rotigotine transdermal patch in 7; 3.8 ± 3.2 mg/day pramipexole extended release in 2 (dose titrated and fixed for the following months). Three (one rotigotine, 2 pramipexole) were also taking 366.7 ± 115.5 mg/day levodopa. Before and 182 \pm 238 days after DA, we measured GE using ¹³C-octanoic acid expiration breath test. We obtained T_{max} (¹³C), e.g., the peak time of the ratio of ¹³CO₂ / ¹²CO₂ ($\Delta^{13}\text{CO}_2(\text{‰})$). We also measured total CTT. After 6-day administration of Sitzmarks⁵ we took a plain abdominal X-ray. One marker corresponded to 1.2 hours of CTT. Statistical analysis was performed by Mann-Whitney's U test. None had comorbid diseases (diabetes, abdominal surgery, etc.) or drugs that might affect GE or CTT. Informed consent was obtained from all patients prior to participation in this study.

Results

After DA (mainly rotigotine patch), new onset of abdominal discomfort, constipation, or the other GI symptoms were not seen. All reported an improvement of motor disorder. After taking 182 days DA, mean T_{max} (¹³C) shortened significantly (55.6 ± 14.2 min to 46.1 ± 14.5 min) ($p < 0.05$) (Figure 1), which was marked particularly in delayed group (T_{max} (¹³C) ≥ 60 min) ($p < 0.05$) while this acceleration was not noted in normal group (T_{max} (¹³C) < 60 min) (Figure 1). In contrast, mean CTT did not change significantly (33.4 ± 37.9 hours to 47.5 ± 31.3 hours). There were no significant associations between the magnitude of the change in T_{max} (¹³C) and severity of abdominal symptoms, severity of T_{max} (¹³C), sex, Hoehn Yahr motor grade, illness duration, a period of DA administration, or concurrent levodopa use.

Interpretation of results

In PD we found a significant shortening of GE after DA (mainly rotigotine patch), suggesting that DA ameliorates GE in PD. Previously, Ramsbottom and Hunt reported that subnauseous doses (0.25 mg intravenously) of apomorphine slowed GE in PD patients 1. However, no reports are available whether routine doses (without vomiting or other significant GI symptoms) of DA affect GE in PD. We have shown in PD patients that levodopa does not affect GE or CTT significantly. On the contrary, subthalamic deep brain stimulation (DBS) can improve GE in PD, suggesting that central dopaminergic facilitation augments GI motility 2. One explanation for the discrepancy is as follows. Although levodopa is manufactured as a modern formula with carbidopa/benserazide (a dopa decarboxylase inhibitor that does not penetrate the blood-brain barrier), a small amount of dopamine might be produced peripherally. Woitalla et al. recently reported that a switch from oral anti-PD medications (levodopa, DAs, anticholinergics, etc.) to rotigotine transdermal patch improved GI symptoms among patients with PD 3. Rotigotine is absorbed through the transdermal system without passing the gut. It is reasonable to assume that the transdermal system might minimize D₂ dopaminergic inhibition of the myenteric plexus *per se*, and bring about central dopaminergic augmentation on GI motility, as reported in DBS. Limitations of this study include that we repeated the test after an interval of 182 days. However, it is unlikely that GE accelerates during a course of the disease. Delayed GE occurs very early in PD and may progress during a course of the disease. Therefore, disease-related progression of delayed GE might not have interfered the present study results. However, since this is an open-label, pilot study in a small number of patients, confirmatory studies are needed.

Concluding message

In a single PD patients cohort, we found a significant shortening of GE after DA (mainly rotigotine transdermal patch), suggesting that transdermal DA ameliorates GE in PD.

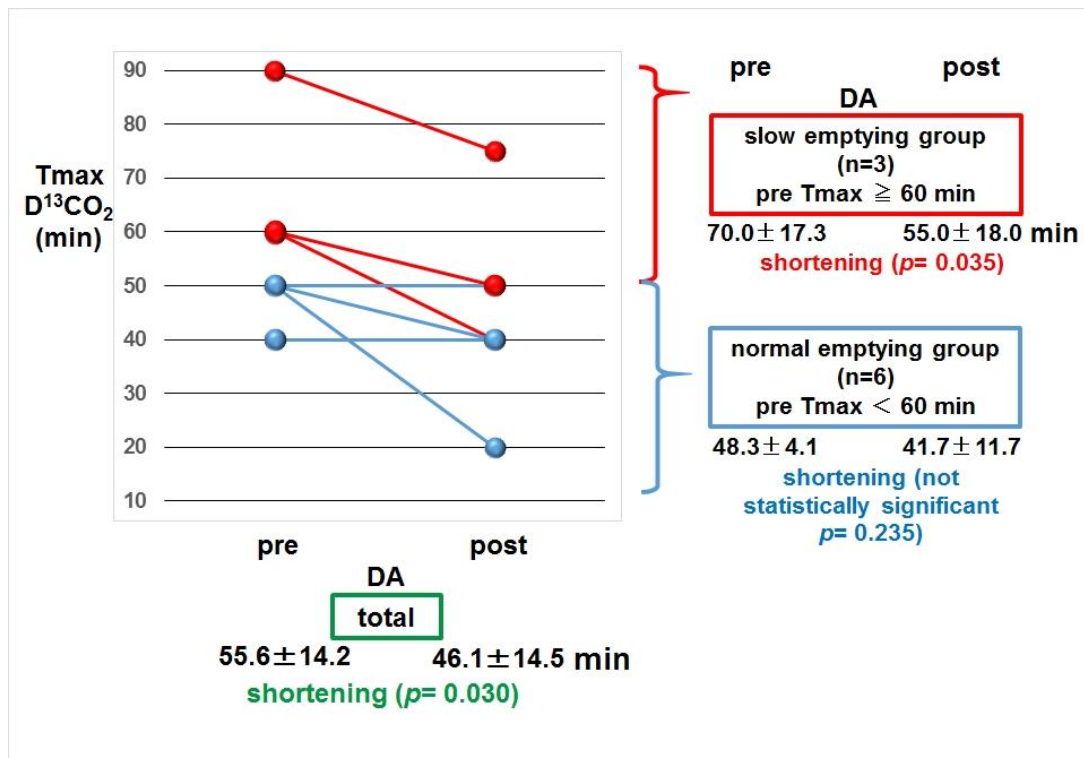


Figure 1 Effect of dopamine agonists on gastric emptying in Parkinson's disease patients.

The gastric emptying study showed that before and after dopamine agonists (mainly rotigotine transdermal patch), mean Tmax (¹³C) shortened significantly (55.6 ± 14.2 min to 46.1 ± 14.5 min) ($p < 0.05$). Since Tmax (¹³C) in PD patients before DA was diverse, according to the normative data (43.9 ± 10.3 min, $n=63$),⁴ we divided them into two groups; e.g., delayed group (Tmax (¹³C) ≥ 60 min) and normal group (Tmax (¹³C) < 60 min). As a result, DA shortened Tmax (¹³C) in delayed group ($p < 0.05$). This acceleration was not noted in normal group. After taking 182 days DA, mean total CTT did not change significantly (33.4 ± 37.9 hours to 47.5 ± 31.3 hours). There were no significant associations between the magnitude of the change in Tmax (¹³C) and severity of abdominal symptoms, severity of Tmax (¹³C), sex, Hoehn Yahr motor grade, illness duration, DA type, a period of DA administration, or concurrent levodopa use.

References

1. Ramsbottom N, Hunt JN. Studies of the effect of metoclopramide and apomorphine on gastric emptying and secretion in man. Gut. 1970; 11: 989-993.
2. Arai E, Arai M, Uchiyama T, et al. Subthalamic deep brain stimulation can improve gastric emptying in Parkinson's disease. Brain 2012; 135: 1478-1485.
3. Woitalla D, Kassubek J, Timmermann L, et al. Reduction of gastrointestinal symptoms in Parkinson's disease after a switch from oral therapy to rotigotine transdermal patch: a non-interventional prospective multicenter trial. Parkinsonism and Related Disorders 2015; 21: 199-204.

Disclosures

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