Movement Disorders
Vol. 12, No. 6, 1997, pp. 952–957

Effect of Chronic Oral Domperidone Therapy on Gastrointestinal Symptoms and Gastric Emptying in Patients With Parkinson's Disease

Irfan Soykan, †Irene Sarosiek, Jeannie Shifflett, *George F. Wooten, and Richard W. McCallum

*Departments of Medicine and *Neurology, Health Sciences Center, University of Virginia, Charlottesville, Virginia; and †Kansas University Medical Center, Kansas City, Kansas, U.S.A.*

Summary: This study investigated whether domperidone could improve gastrointestinal symptoms in patients with Parkinson's disease who were receiving levodopa therapy. A total of 11 patients were studied. Following a baseline gastric emptying test, patients were treated with a starting dose of domperidone 20 mg p.o. q.i.d. A follow-up gastric emptying test was repeated at least 4 months after starting domperidone therapy. At the beginning and at each 3-month follow-up visit, symptoms of nausea, vomiting, anorexia, abdominal bloating, heartburn, regurgitation, dysphagia, and constipation were evaluated and scored on a scale of 0–3. The overall mean follow-up period was 3 years. Compared with their baseline evaluation, patients experienced a significant improvement in all symptoms ($p < 0.05$) except dysphagia and constipation. Gastric emptying of an isotope-labeled solid meal was significantly faster, with a baseline result of 60.2 ± 6.4% retention of isotope 2 h after the meal compared with 37.0 ± 2.2% retention during domperidone therapy ($p < 0.05$). Patients' global assessment of Parkinson's disease remained stable or improved. Serum prolactin was elevated in all patients after domperidone therapy ($p < 0.05$). Domperidone therapy significantly reduces upper gastrointestinal symptoms and accelerates gastric emptying of a solid meal, but does not interfere with response to antiparkinsonism treatment. **Key Words:** Parkinson's disease—Domperidone—Gastric emptying—Prokinetic agent—Gastrointestinal motility disorder—Gastrointestinal symptoms.

Patients who have Parkinson's disease (PD) may experience various gastrointestinal (GI) symptoms, such as nausea, vomiting, anorexia, abdominal bloating, heartburn, dysphagia, and constipation (1). Disorders of motility result in the most frequent complaints. In PD, GI motility abnormalities are principally of three types: dysphagia, disordered gastric emptying, and constipation. Nausea and vomiting are not typical complaints in untreated patients with PD, but are common enough in patients receiving antiparkinsonism medications to warrant discussion (2). Some GI symptoms in PD are a reflection of the primary disease process (3). The most common GI symptoms in PD—dysphagia and constipation—are most likely a direct result of the PD process, whereas nausea and vomiting are clearly related to dopaminergic medications (4). Abdominal bloating is particularly likely to occur during "off" periods in individuals with motor fluctuations and can actually dominate the clinical picture for these patients. The use of dopaminergic drugs such as levodopa and bromocriptine can be limited by peripheral side effects such as nausea and vomiting (5). Delayed gastric emptying, which may be produced by dopamine or dopamine-stimulating agents, is associated with a poor therapeutic response to levodopa in patients with PD (6,7).

Domperidone, a benzimidazole derivative, is a specific dopamine antagonist that stimulates the GI tract and has antiemetic properties. Unlike most other dopamine receptor-blocking drugs, it does not readily cross the blood–brain barrier (8). This attribute is particularly important in patients with PD, in whom central dopamine deficiency is characteristic. Domperidone-induced extrapyramidal side effects are rare, but have been reported (9–12). The drug is extensively used outside the United States for its antiemetic effects and its prokinetic effect on upper GI smooth muscle (5,8). Some reports from Europe regard the use of domperidone as adjunctive therapy in the treatment of PD (13–15). Therefore, this

Received April 15, 1996; revision received March 19, 1997. Accepted March 19, 1997.

Address correspondence and reprint requests to Dr. R. W. McCallum at University of Kansas Medical Center, 3901 Rainbow Boulevard, Department of Medicine–4035D, Kansas City, KS 66160-7350, U.S.A.

study investigated whether domperidone could improve GI symptoms in patients with PD receiving therapy with levodopa.

MATERIALS AND METHODS

Patients

Patients who had GI symptoms while using levodopa and who agreed to undergo a gastric emptying study were invited to enroll into the project. A total of 11 patients (two men and nine women) with PD and GI symptoms were referred from the PD specialty clinic at the University of Virginia Health Sciences Center. All were receiving levodopa as antiparkinsonism therapy. All 11 were experiencing abdominal bloating and constipation. Ten patients reported nausea; six, anorexia; five, heartburn; four, dysphagia; four, vomiting; and two, regurgitation. Table 1 lists the patients' demographic characteristics and clinical information. Informed consent was obtained from all patients prior to enrollment.

TABLE 1. *Patient information, PD severity, and antiparkinsonian therapy before and during the course of follow-up and domperidone doses of patients*

Patient	Sex	Age (years)	Disease duration (years)	Weight	Degree of PD	Therapy before starting domperidone	Therapy during the highest dose of domperidone	Domperidone dose (mg/day)
1	M	77	20	Gained	Severe	Carbidopa–levodopa 25/100 6 tab/day	Carbidopa–levodopa 25/100 6 × ½ Carbidopa–levodopa CR 5 × ½ Mineral oil (1–2 oz)	80
2	F	80	15	Lost	Moderate	Carbidopa–levodopa 25/100 t.i.d. Mineral oil (1–2 oz/day)	Carbidopa–levodopa 50/200 b.i.d. Selegiline 6 mg b.i.d. Mineral oil (1–2 oz/day)	80–100
3	F	87	7	Same	Mild	Selegiline 5 mg b.i.d. Carbidopa–levodopa 25/100 t.i.d.	Selegiline 5 mg b.i.d. Carbidopa–levodopa 25/100 1½ tab t.i.d.	50–80
4	F	66	6	Same	Mild	Carbidopa–levodopa 25/100 4½ tab/day Selegiline 5 mg b.i.d.	Carbidopa–levodopa 25/100 t.i.d. Selegiline 5 mg t.i.d.	50–80
5	F	74	6	Same	Mild	Selegiline 5 mg/day Carbidopa–levodopa 25/100 q.i.d. (½)	Selegiline 5 mg/day Carbidopa–levodopa 25/100 q.i.d. (½)	80
6	F	66	9	Stable	Mild	Selegiline 5 mg b.i.d. Carbidopa–levodopa 25/100 (1½ b.i.d.)	Selegiline 5 mg b.i.d. Carbidopa–levodopa CR 50/200 t.i.d.	80
7	F	63	2	Lost	Mild	Carbidopa–levodopa 25/100 (½ t.i.d.)	Carbidopa–levodopa 25/100 (½ t.i.d.) Selegiline 5 mg/day Cimetidine 400 mg t.i.d.	80
8	F	67	13	Stable	Mild	Carbidopa–levodopa 25/100 (5 × ½)	Carbidopa–levodopa 25/100 b.i.d. Selegiline 5 mg/day Ranitidine 150 mg (at bedtime)	80
9	F	79	15	Stable	Mild	Carbidopa–levodopa 25/100 (5 × ½) Selegiline 5 mg b.i.d. Bromocriptine 5 mg at breakfast, 7.5 mg at lunch	Carbidopa–levodopa 25/100 (5 × ½) Selegiline 5 mg b.i.d.	80–120
10	F	81	10	Gained	Mild	Carbidopa–levodopa 25/250 3 × ½ Selegiline 5 mg b.i.d.	Carbidopa–levodopa 25/100 6 × ½ Carbidopa–levodopa CR 25/100 5 × ½	80–120
11	M	48	3	Stable	Mild	Carbidopa–levodopa CR 50/200 t.i.d. Carbidopa–levodopa 25/250 1 tab/day Selegiline 5 mg b.i.d.	Carbidopa–levodopa 50/200 b.i.d. Selegiline 5 mg b.i.d. Mineral oil 1–2 oz/day	80

PD, Parkinson's disease; tab, tablets.

Assessment of Gastrointestinal Symptoms

Patients completed a standard questionnaire regarding GI symptoms that was administered by one of the investigators (R.W.M.) at baseline and at each visit. This GI symptom questionnaire was modified from that previously used by Horowitz et al. (16). Specifically, eight GI symptoms were assessed: nausea, vomiting, anorexia, abdominal bloating, heartburn, dysphagia, regurgitation, and constipation were scored as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. These assessments were completed at baseline, at 2-week intervals for the first 2 months, and then at 3-month intervals. Delayed gastric emptying because of organic obstruction and other upper GI pathology was excluded by upper GI endoscopy or barium studies. A global assessment of PD symptoms by using the Unified Parkinson's Disease Rating Scale was performed by one of the investigators (G.F.W.) (17). Patients were not taking medications for GI complaints at baseline and made no changes in medicines during the study except for those listed in Table 1. None of the patients were taking anticholinergic medications for their PD during the study.

Measurement of Gastric Emptying

Baseline gastric emptying was evaluated. The standard gastric emptying meal at the University of Virginia consists of 7½ oz (0.2 kg) commercial beef stew (single serving can) mixed with 30 g chicken liver. The chicken liver was microwaved to a firm consistency and cut into 1-cm cubes. A total of 500 μCi of [^{99m}T]sulfur colloid was injected evenly throughout the cubes. The liver cubes were mixed into beef stew that was heated in a microwave oven. The meal was served to the patient with two saltine crackers and 8 oz (0.24 L) water and was consumed within 15 min. The entire meal consisted of 274 kcal, 12 g fat, 16 g protein, and 26 g carbohydrates. For this project, two gamma cameras were used, a Raytheon DS-150T and a General Electric starcam. After consuming the meal, the patient was asked to lie supine under the camera for 2 h, during which time anterior abdominal images were acquired continuously. All images were stored in a computer for subsequent analysis. Stomach regions of interest were drawn and stomach counts were obtained from each image. The counts were decay corrected and normalized to give percent solid food retained in the stomach over time.

Assessment of the Effects of Domperidone on Gastrointestinal Symptoms and Gastric Emptying

Following a baseline gastric emptying test, patients were treated with a starting dose of domperidone 20 mg p.o. q.i.d. (30 min before each meal and at bedtime). Symptoms were assessed and side effects of treatment were evaluated in the outpatient clinic every 2 weeks during the first 2 months and subsequently every 3 months. A follow-up gastric emptying test was repeated at least 4 months after domperidone therapy was started. The average interval for the follow-up gastric emptying test was 6.6 months. Blood for determining standard chemical profiles and a fasting serum prolactin concentration was obtained initially and at each follow-up visit.

Statistical Methods

Continuous variables were evaluated for normality by the Wilk–Shapiro test and then appropriate parametric or nonparametric tests were applied. Student's *t* test was used for parametric data, and the Wilcoxon rank sum test was used for nonparametric data. All data were expressed as mean ± SD, unless indicated. Statistical significance was assigned with a $p < 0.05$.

RESULTS

The entire study spanned 6 years. The mean follow up was 3 years, ranging from 2 to 6 years.

Symptoms

Beginning after week 2 of domperidone therapy, patients experienced significant improvement in all symptoms compared to baseline ($p < 0.05$), except for dysphagia and constipation (Fig. 1). Although the daily domperidone doses varied from 50 to 120 mg, most patients improved with 80 mg daily. Nausea and vomiting resolved in all patients taking domperidone and did not reappear during the study. Dysphagia was not severe enough in any of the patients to threaten nutrition or the ability to take medications. One patient had occasional oral regurgitation because of dysphagia, but experienced no aspiration. During the follow-up period, 7 of 11 patients remained at the same weight, two lost weight, and two gained weight.

Of 11 patients, nine had mild PD; one, moderate; and one, severe. The patients' global assessment of PD remained stable (Fig. 1). Only one patient's cumulative PD symptom scores improved compared to baseline scores.

Gastric Emptying

At baseline, patients retained 60.2 ± 6.4% (mean ± SEM) of isotope in the stomach 2 h after the meal, compared with 37 ± 2.2% retention during domperidone therapy ($p < 0.05$) (Fig. 2).

Adverse Events

One patient experienced transient nipple tenderness. Serum prolactin levels in all patients were elevated after week 2 of domperidone therapy; a mean serum prolactin

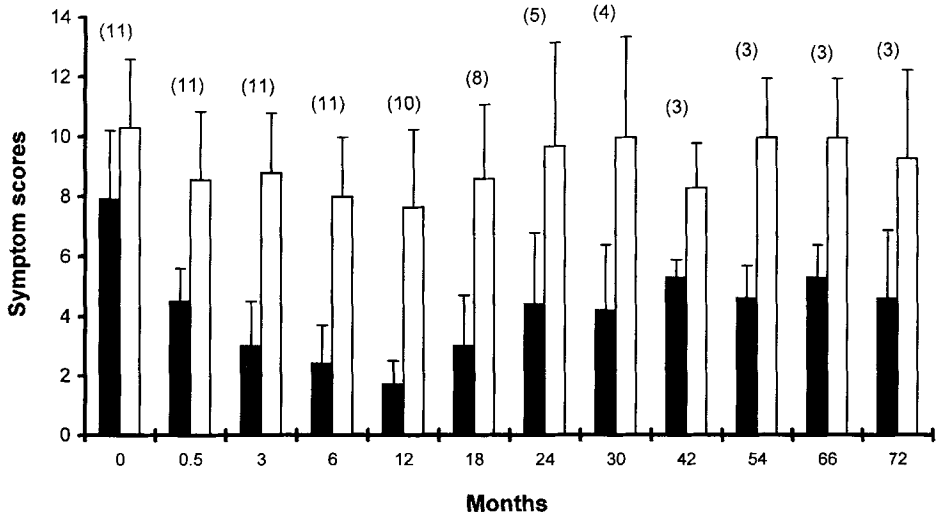

FIG. 1. Gastrointestinal symptom scores (■) of patients during domperidone treatment improved significantly ($p < 0.05$) compared with baseline; Parkinson's disease (□) symptom scores remained stable (*numbers on the bars* represent the number of subjects followed at each visit).

level of 26.74 ± 9.64 ng/ml predomperidone treatment, compared to 38.36 ± 9.39 ng/ml (which is an average of all follow-up visits) during domperidone therapy ($p < 0.05$), was noted. No other side effects were reported.

DISCUSSION

These results demonstrate that, in individuals with PD, chronic oral domperidone therapy will (a) significantly reduce upper GI symptoms and accelerate gastric emptying of a solid meal without interfering with the response to PD treatment, (b) not improve either dysphagia or constipation, and (c) elevate the serum prolactin level, which can reflect both compliance and absorption.

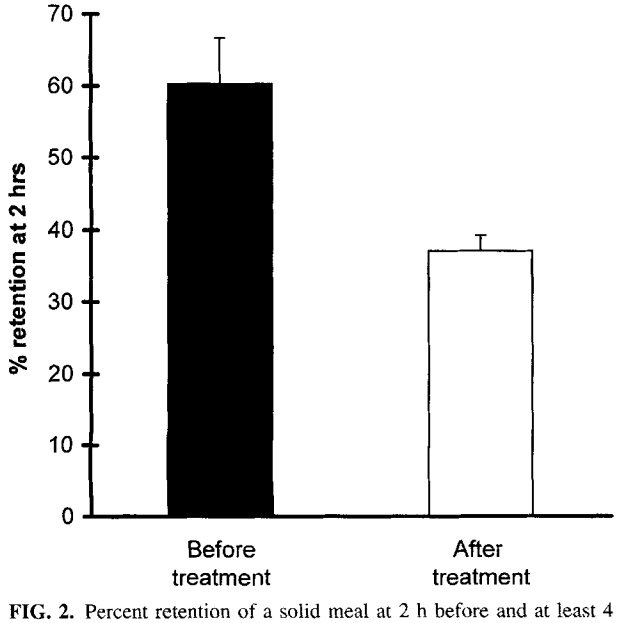

FIG. 2. Percent retention of a solid meal at 2 h before and at least 4 months after domperidone therapy. The baseline retention of 60.2 ± 6.4% at 2 h decreased to 37.0 ± 2.2% ($p < 0.05$).

Of the various manifestations of PD, a disproportionately small amount of attention has been given to those affecting the autonomic nervous system. This is unfortunate, because these symptoms are common and frequently amenable to therapy. Patients with PD often complain of GI symptoms of two particular types: those originating from the disease itself and those related to drug therapy. Previous studies by Lieberman et al. (18) and Bushmann et al. (19) have demonstrated an association between dysphagia and PD. The finding of Lewy bodies in the esophageal myenteric plexus of PD patients with dysphagia and in patients with achalasia suggests that neuronal degeneration may be responsible for esophageal dysfunction in such cases (20). Constipation is another problem in PD and has been attributed to different factors, including decreased physical activity, decreased forcefulness of abdominal muscle contraction, and decreased intake of food and water. Both anticholinergic drugs and dopaminergic agents may further interfere with lower bowel motility and increase constipation (2). However, using modern techniques for the detailed study of defecation, Mathers et al. (21) have suggested that abnormal control of the pelvic floor musculature caused by PD itself may play a significant role in the constipation of these patients. Kupsky et al. (22) found cytoplasmic inclusions identical to Lewy bodies in ganglion cells of the colonic myenteric plexus of a patient with PD and acquired megacolon, suggesting primary involvement of the enteric nervous system in PD. This is consistent with

the observation that constipation typically precedes the clinical diagnosis of PD and is not related to levodopa therapy. Singaram et al. (23), who investigated the presence and distribution of dopamine-containing neurons in the colons of 11 patients with PD, found that nine of their patients had substantially fewer dopaminergic myenteric neurons than did controls.

Other frequent GI complaints include anorexia, nausea, vomiting, heartburn, and abdominal bloating. Several lines of evidence suggest that these complications may be attributable to peripheral, pharmacokinetic mechanisms; mainly, to delayed gastric emptying as a side effect of levodopa. Delayed gastric emptying has been reported in PD, but most patients studied were already receiving levodopa therapy (1–4). There is evidence that dopamine mediates physiologic gastric relaxation and inhibits gastric motility (24). Levodopa therapy could prolong gastric emptying time, and patients experience epigastric discomfort or fullness, early satiety, and postprandial distress during therapy with levodopa (1,6, 25). In terms of effect of age on gastric emptying in men, Moore et al. (26) found no significant differences in solid-food-emptying rates between the young and aged men. Likewise, Evans et al. (27) compared the gastric emptying rate of elderly parkinsonian, elderly nonparkinsonian, and young healthy volunteers. Mean gastric emptying rate was slower in both of the elderly patient groups than in the young subjects, but the mean gastric emptying rate of the two elderly subject groups did not differ significantly. Robertson et al. (28) showed that levodopa affects gastric emptying to a similar extent in both elderly and young volunteers. Delayed gastric emptying is significant for more than just the gastroenteric discomfort that it produces. Since levodopa is absorbed primarily from the proximal small intestine and not from the stomach, delayed levodopa egress from the stomach may result in delayed intestinal absorption and consequent motor deterioration (29,30). Dopaminergic agents also activate the medullary vomiting center via the chemoreceptor trigger zone, resulting in nausea, abdominal bloating, and vomiting (2).

Domperidone is a benzimidazole derivative with a molecular weight of 426, which acts primarily at the chemoreceptor trigger zone that is on the blood side of the blood–brain barrier on the floor of the fourth ventricle, and on dopamine receptors in the gut. It has gastrokinetic and antiemetic properties, but does not readily cross the blood–brain barrier and rarely causes extrapyramidal side effects. The high molecular weight and low lipid solubility of domperidone may explain its inability to cross the blood–brain barrier. This selective peripheral effect and lack of central effect have been used effectively to block the undesirable peripheral side effects of dopaminergic agents used in the treatment of PD (5,8). Domperidone has a high affinity for GI tissue, and high concentrations of the drug are found in the esophagus, stomach, and small intestine. Current evidence indicates that the entire effect of domperidone on GI smooth muscle is due to its antagonism of dopamine receptors. This commences with an impairment of partial inhibition of receptive relaxation in the stomach, and continues with improved antroduodenal coordination of peristaltic waves and acceleration of small intestinal transit (8).

In our study, chronic domperidone use in PD significantly improved GI symptoms as well as the gastric emptying rate for a solid meal compared to baseline measurement. The efficacy of domperidone in relieving GI symptoms was similar to that in a double-blind trial of domperidone in patients with dyspepsia in which domperidone reduced the level of the symptoms of dyspepsia by 76% compared to a 16% reduction with placebo (31). In the present study, patients experienced a significant improvement in anorexia, nausea, vomiting, abdominal bloating, and regurgitation, but not in dysphagia and constipation. The major sites of action of domperidone are in the upper gut; hence, it was not surprising that constipation did not change. The efficacy of domperidone may diminish slightly with long-term chronic administration (Fig. 1); however, our recent data on domperidone suggest that it is useful beyond a year in gastroparesis patients (32).

The effects of orally and intravenously administered domperidone on gastric emptying have been described, but most studies have examined only the short-term effects (6,33,34). Horowitz et al. (16) compared the short-term and long-term effects of domperidone on delayed gastric emptying in patients with diabetes mellitus and showed that acute administration of domperidone increased the rate of both solid and liquid emptying. After chronic administration, however, domperidone had no significant effect on solid emptying, but was still effective in increasing liquid emptying. Day and Pruitt (35) reported a gastroparetic patient with diabetes mellitus and PD who was treated with domperidone with a good response. In our study, gastric emptying of a solid meal in PD patients after long-term therapy (2–6 years) with domperidone remained significantly accelerated.

Domperidone is particularly well tolerated and seldom causes serious side effects. It has a potent effect on prolactin secretion, however, which can result in side effects that are more inconvenient than disabling. Breast enlargement, nipple tenderness, and galactorrhea occur, particularly in women (8). One of our male patients ex-

perienced transient nipple tenderness. Hyperprolactinemia occurs with domperidone therapy and is caused by blockade of endogenous dopamine in the pituitary. Dopamine appears to be a physiologic inhibitor of prolactin release from the pituitary (5). Hyperprolactinemia, which was observed in all of our patients after domperidone therapy, can reflect both compliance and absorption.

Importantly, our patients' global assessment of PD remained stable throughout study and actually improved in one instance. Delayed gastric emptying induced by levodopa therapy can be prevented by domperidone. Domperidone can affect the plasma pharmacokinetics of levodopa, providing enhanced gastric emptying and earlier delivery of levodopa to the upper small intestine, its principal site of absorption (13).

In conclusion, in patients with PD, oral domperidone therapy may significantly reduce GI symptoms without interfering with antiparkinsonism therapy. Its actions on gastric emptying as well as on the chemoreceptor trigger zone explain its efficacy in resolving nausea and vomiting. Cotherapy with domperidone in PD is efficacious and safe and represents an exciting pharmacologic innovation.

REFERENCES

1. Edwards L, Quigley EMM, Hofman R, Pfeiffer RF. Gastrointestinal symptoms in Parkinson's disease: 18-month follow-up study. *Mov Disord* 1993;8:83–86.
2. Tanner CM, Goetz CG, Klawans HL. Autonomic nervous system disorders in Parkinson's disease. In: Koller WC, ed. *Handbook of Parkinson's disease.* New York: Marcel Dekker, 1992:185–215.
3. Edwards LL, Pfeiffer RF, Quigley EMM, Hofman R, Balluff M. Gastrointestinal symptoms in Parkinson's disease. *Mov Disord* 1991;6:151–156.
4. Byrne KG, Pfeiffer R, Quigley EMM. Gastrointestinal dysfunction in Parkinson's disease: a report of clinical experience at a single center. *J Clin Gastroenterol* 1994;19:11–16.
5. Champion MC, Hartnett MH, Yen M. Domperidone, a new dopamine antagonist. *Can Med Assoc J* 1986;135:457–462.
6. Broekaert A. Effect of domperidone on gastric emptying and secretion. *Postgrad Med J* 1979;55(suppl 1):11–14.
7. Bianchine JR, Calimlim LR, Morgan JP, Dujuvne CA, Lasagna L. Metabolism and absorption of L-3,4 dihydroxyphenylalanine in patients with Parkinson's disease. *Ann NY Acad Sci* 1971;179:126–140.
8. McCallum RW. Review of the current status of prokinetic agents in gastroenterology. *Am J Gastroenterol* 1985;80:1008–1016.
9. Sol P, Pelet B, Guignard J-P. Extrapyramidal reactions due to domperidone. *Lancet* 1980;2:802.
10. Debontridder O. Extrapyramidal reactions due to domperidone. *Lancet* 1980;2:802.
11. Spirt MJ, Chan W, Thieberg M, Sachar DB. Neuroleptic malignant syndrome induced by domperidone. *Dig Dis Sci* 1992;37:946–948.
12. Leeser J, Bateman DN. Domperidone. *BMJ* 1985;290:241–244.
13. Shindler JS, Finnerty GT, Towlson K, Dolan AL, Davies CL, Parkes JD. Domperidone and levodopa in Parkinson's disease. *Br J Clin Pharmacol* 1984;18:959–962.
14. Langdon N, Malcolm PN, Parkes JD. Comparison of levodopa with carbidopa, and levodopa with domperidone in Parkinson's disease. *Clin Neuropharmacol* 1986;9:440–447.
15. Bogaerts M, Braems M, Martens C. Domperidone in the prevention of L-dopa induced nausea. *Postgrad Med J* 1979;55(suppl 1):51–52.
16. Horowitz M, Harding PE, Chatterton BE, Collins PJ, Shearman DJC. Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. *Dig Dis Sci* 1985;30:1–9.
17. Koller WC. Unified rating scale for parkinsonism version 2.0—December 1985 [Appendix]. In: Koller WC, ed. *Handbook of Parkinson's disease.* New York: Marcel Dekker, 1987:475–492.
18. Lieberman AN, Horowitz L, Redmond P, Pachter L, Lieberman I, Leibowitz M. Dysphagia in Parkinson's disease. *Am J Gastroenterol* 1980;74:157–160.
19. Bushmann M, Dobmeyer SM, Leeker L, Perlmutter JS. Swallowing abnormalities and their response to treatment in Parkinson's disease. *Neurology* 1989;39:1309–1314.
20. Qualman SJ, Haupt HM, Yang P, Hamilton SR. Esophageal Lewy bodies associated with ganglion cell loss in achalasia: similarity to Parkinson's disease. *Gastroenterology* 1984;87:848–856.
21. Mathers SE, Kempster PA, Law PJ, et al. Anal sphincter dysfunction in Parkinson's disease. *Arch Neurol* 1989;46:1061–1064.
22. Kupsky WJ, Grimes MM, Sweeting J, Bertsch R, Cote LJ. Parkinson's disease and megacolon: concentric hyaline inclusions (Lewy bodies) in enteric ganglion cells. *Neurology* 1987;37:1253–1255.
23. Singaram C, Ashraf W, Gaumnitz EA, Tarbey C, Sengupta A, Pfeiffer R. Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. *Lancet* 1995; 346:861–864.
24. Valenzuela JE. Dopamine as a possible neurotransmitter in gastric relaxation. *Gastroenterology* 1976;17:1019–1022.
25. Bramble MG, Cunliffe J, Dellipiani AW. Evidence for a change in neurotransmitter affecting esophageal motility in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1978;41:709–712.
26. Moore JG, Tweedy C, Christian PE, Datz FL. Effect of age on gastric emptying of liquid–solid meals in man. *Dig Dis Sci* 1983; 38:340–344.
27. Evans MA, Broe GA, Triggs EJ, Cheung M, Creasey H, Paull PD. Gastric emptying rate and the systemic availability of levodopa in the elderly parkinsonian patient. *Neurology* 1981;31:1288–1294.
28. Robertson DRC, Renwick AG, Macklin B, et al. The influence of levodopa on gastric emptying in healthy elderly volunteers. *Eur J Clin Pharmacol* 1992;42:409–412.
29. Kurlan R, Rothfield KP, Woodward WR, et al. Erratic gastric emptying of levodopa may cause "random" fluctuations of parkinsonian mobility. *Neurology* 1988;38:419—421.
30. Kurlan R, Nutt JG, Woodward WR, et al. Duodenal and gastric delivery of levodopa in parkinsonism. *Ann Neurol* 1988;23:589—595.
31. Arts E, Anthoni H, de Roy G, D'Holander J. Domperidone in the treatment of dyspepsia: a double-blind placebo-controlled study. *J Int Med Res* 1979;7:158–161.
32. Soykan I, Sarosiek I, McCallum RW. The effect of oral domperidone therapy on gastrointestinal symptoms, gastric emptying and quality of life in patients with gastroparesis. *Am J Gastroenterol* 1997;92:976–980.
33. Corinaldesi R, Stanghellini V, Zarabini GE, et al. The effect of domperidone on the gastric emptying of solid and liquid phases of a mixed meal in patients with dyspepsia. *Curr Ther Res* 1983;34: 982–986.
34. McCallum RW, Ricci D, DuBovik S. Effect of domperidone on gastric emptying and symptoms of patients with idiopathic gastric stasis [Abstract]. *Gastroenterology* 1984;86:1179.
35. Day JP, Pruitt RE. Diabetic gastroparesis in a patient with Parkinson's disease: effective treatment with domperidone. *Am J Gastroenterol* 1989;84:837–838.