A Double-Blind Multicenter Comparison of Domperidone and Metoclopramide in the Treatment of Diabetic Patients With Symptoms of Gastroparesis

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OBJECTIVE: A double-blind, multicenter, randomized trial was conducted to compare the side effects and efficacy of domperidone and metoclopramide in symptomatic diabetic gastroparesis.

METHODS: Ninety-three insulin-dependent diabetes patients with a $\geq$ 3-month history of gastroparesis symptoms were recruited; 48 received domperidone 2 $\times$ 10-mg tablets 4 times daily, and 45 received metoclopramide 1 $\times$ 10-mg tablet + 1 placebo tablet 4 times daily. Nausea, vomiting, bloating/distension, and early satiety were evaluated for severity after 2 and 4 wk. Adverse central nervous system (CNS) effects of somnolence, akathisia, asthenia, anxiety, depression, and reduced mental acuity were elicited and graded for severity at 2 and 4 wk.

RESULTS: Domperidone and metoclopramide were equally effective in alleviating symptoms of diabetic gastroparesis. Elicited adverse CNS effects were more severe and more common with metoclopramide. Somnolence was acknowledged by 49% of patients (mean severity score, 1.03) after 4 wk of metoclopramide compared with 29% of patients (mean severity score, 0.49) after 4 wk of domperidone (incidence, $p = 0.02$; severity; $p = 0.03$). A reduction in mental acuity was acknowledged by 33% of patients (mean severity score, 0.62) after 4 wk of metoclopramide, compared with 20% of patients (mean severity score, 0.27) after 4 wk of domperidone (incidence, $p = 0.04$; severity, $p = 0.04$). Akathisia, asthenia, anxiety, and depression were also acknowledged less often, and at a lower severity, after 4 wk of domperidone, although these differences were not statistically significant.

CONCLUSIONS: Domperidone and metoclopramide effectively reduce the symptoms of diabetic gastroparesis; CNS side effects are more pronounced with metoclopramide.

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INTRODUCTION

Gastrointestinal motility disorders are common sequelae of diabetes mellitus, occurring in 10–30%, and occasionally in as many as 75%, of diabetic patients (1–3). Diabetic gastroparesis (DG), a syndrome characterized by symptoms of impaired gastric motility and delayed gastric emptying (4), may occur in both insulin-dependent (5) and non–insulin-dependent (6) diabetic patients. The symptoms of diabetic gastropathy, which may include postprandial nausea, epigastric burning or pain, bloating, vomiting of undigested food, anorexia, and early satiety, reduce the effectiveness of dietary regimens and the absorption of oral medications and, in general, make the underlying diabetes more difficult to control (5). In extreme cases of gastroparesis, nausea, vomiting, and bezoar formation may lead to an increased risk of hospitalization (7).

Although dietary measures, such as reducing the intake of solid foods in favor of liquefied meals, may diminish the risk of major complications in DG, they may significantly impair a patient's quality of life and general nutritional level. Effective drug therapy that allows for a normal diet may therefore offer a clear advantage over dietary measures in controlling DG.

Several prokinetic agents, including the dopamine D_2 antagonists metoclopramide and domperidone, the cholinomimetic cisapride, and macrolide antibiotics such as erythromycin, have been used with varying degrees of success in the treatment of DG (8). However, only metoclopramide has been approved for the treatment of diabetic gastroparesis in the United States. Therapy with metoclopramide has been successful in relieving the symptoms of DG but is associated with prominent central nervous system (CNS) effects (drowsiness, restlessness, lassitude, and fatigue) in 10% of diabetic patients, and extrapyramidal reactions that may preclude its use (8, 9). Among patients with functional

dyspepsia, the incidence of CNS-associated side effects (agitation, insomnia, somnolence, fatigue, and anxiety) was 23% in patients receiving metoclopramide therapy (10).

The efficacy of domperidone in the treatment of DG was demonstrated in a multicenter trial in insulin-dependent diabetic patients maintained on domperidone 20 mg 4 times daily for 4 wk. Patients given domperidone for 4 wk had significant decreases ($p = 0.001$) in all symptoms of DG relative to baseline. Patients were then randomized to receive either domperidone for an additional 4 wk or placebo; those who received domperidone had significantly ($p = 0.05$) better symptom scores than patients switched to placebo. Other studies with domperidone have confirmed that its use results in shorter gastric emptying times and improved symptoms in patients with DG (11–13). Domperidone also produced a sustained improvement in gastric symptoms during long-term treatment of up to 1 yr (14, 15).

The ability of metoclopramide to cross the blood-brain barrier accounts for its CNS-associated adverse effects due to blockade of dopaminergic receptors. Domperidone does not readily cross the blood-brain barrier and would not be expected to interfere with central dopaminergic transmission (16, 17). Therefore, domperidone, a peripheral dopamine antagonist, would be expected to improve DG without inducing the CNS-associated side effects common with metoclopramide therapy.

The aim of the present trial was to compare the CNS tolerability profiles of domperidone and metoclopramide and to assess efficacy in patients with upper gastrointestinal symptoms suggestive of diabetic gastroparesis.

PATIENTS AND METHODS

Ambulatory male or female patients, aged ≥ 18 years, with insulin-dependent diabetes mellitus and at least a 3-month history of symptoms of DG were eligible for inclusion in this multicenter (five centers), double-blind, randomized, parallel group design study. On study entry, patients were required to exhibit at least two of the following gastrointestinal symptoms: nausea, vomiting, bloating/distension, or early satiety. Investigators rated the severity of these four symptoms using a scale of 0 to 3, where 0 = none; 1 = mild (present, but patient able to carry on usual activities); 2 = moderate (interferes with activities); and 3 = severe (disabling). The total symptom score (sum of the four individual gastrointestinal symptom scores) at study entry had to be at least 5 out of a possible score of 12.

Patients with cancer of the gastrointestinal tract or major illnesses (end-stage heart, liver, or lung disease, alcoholism, cancer, or AIDS) were excluded from the study. Also excluded were patients who were receiving dialysis or who had undergone prior gastric surgery, those known or suspected to be using illicit drugs, and those who had received either study drug or an investigational drug within 30 days before study entry. Pregnant women and those likely to become pregnant during the study were also excluded, but

women using adequate contraception were allowed in the trial. Each patient signed a written informed consent statement before entry into the study. Institutional review board approval was obtained before the start of the study.

On study entry, patients provided a medical history and underwent a physical examination, including laboratory determinations, hematology, blood chemistry, and urinalysis. Patients who met entry criteria received either domperidone in the dosage shown to be effective in previous clinical studies of diabetic gastroparesis (11, 14, 15), 20 mg 4 times daily (n = 48), or the recommended dosage of metoclopramide for the treatment of diabetic gastroparesis, 10 mg 4 times daily (n = 47), for 4 wk. Patients received domperidone (two 10-mg tablets) or metoclopramide (one 10-mg tablet and one placebo tablet) 15–30 min before meals (breakfast, lunch, and dinner) and at bedtime.

Medications that could mask the effect of domperidone and metoclopramide (*e.g.*, cisapride or bethanechol) were not permitted during the study. Use of anticholinergics, neuroleptics, opiates, significant analgesics, antiemetics, histamine H_2-receptor antagonists, sucralfate, and omeprazole was discouraged where possible. If antacids or histamine H_2-receptor antagonists were required, they were not to be taken within 30 min of ingestion of the study drug.

Patients were evaluated at Weeks 2 and 4 to evaluate symptoms, note any spontaneously reported adverse experiences, and assess patient compliance (on the basis of unused tablet counts). The patients were also asked specifically if they had experienced any of the CNS-associated side effects that are most common during therapy with metoclopramide (somnolence, akathisia, asthenia, anxiety, depression, or reduced mental acuity), and to grade the severity of these occurrences on the symptom severity scale described above. These elicited CNS-associated adverse effects served as primary indicators of the relative tolerability of the two agents. The primary measures of drug efficacy were the symptom scores for nausea, vomiting, early satiety, and bloating/distention. Repeat physical examination and laboratory tests (hematology, blood chemistry, and urinalysis) were performed on study completion.

Demographic data and baseline vital signs for each treatment group were compared using Student's t test. Noncontinuous variables (sex, race, and global assessments) were compared using the Cochran-Mantel-Haenzel test. Between-treatment comparisons for baseline, 2-wk, and 4-wk means were performed using a two-way ANOVA for the symptom and elicited adverse event severities. Treatment, investigator, and treatment-by-investigator interactions were evaluated. Within-treatment comparisons were performed using a Student's paired t test. For the elicited adverse event data, between-group comparisons of incidences were performed using the Cochran-Mantel-Haenzel test. Symptom and adverse effect severity scores were confirmed nonparametrically using the Wilcoxon signed-rank test for within-group comparisons and two-way ANOVA of the ranked data for between-group comparisons. All com-
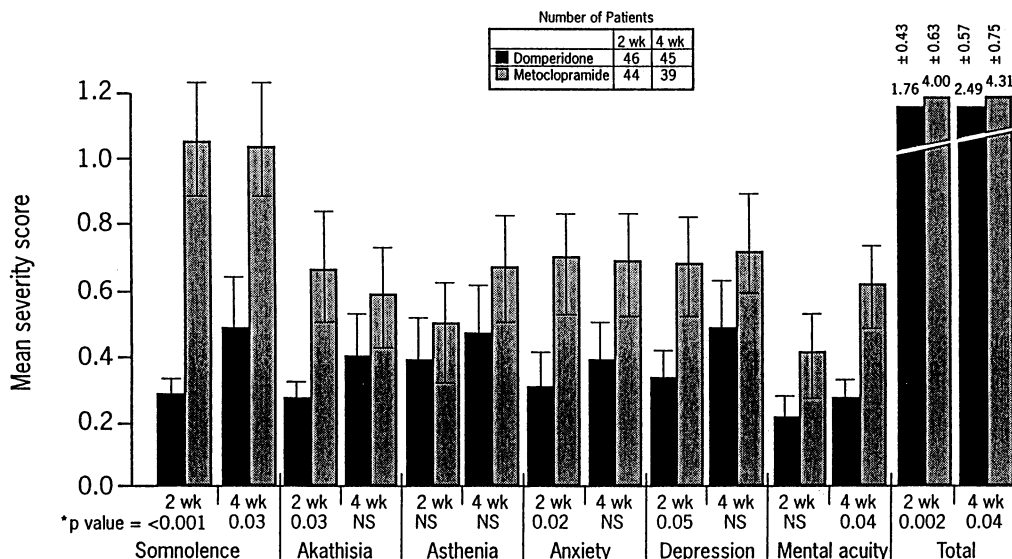
Figure 1. Severity of elicited CNS-associated adverse events in diabetic patients treated with either domperidone or metoclopramide. The total score is the sum of the six individual scores. *Two-sided *p* value, with domperidone having the lower score.

parisons were two-tailed, with a probability value ≤ 0.05 signifying statistical significance.

RESULTS

Patients

Of the 95 patients who entered the study and were randomized to double-blind treatment, 33 were male and 62 were female. The majority of patients were white (80.0%), nonsmokers (76.8%), and nondrinkers (77.9%), and were receiving concomitant insulin therapy (99.0%). Patients ranged in age from 19 to 69 years (median, 39 years), in weight from 41 to 122 kg (median, 68.2 kg), and in height from 1.47 to 1.96 m (median, 1.68 m). The two treatment groups were comparable with respect to demographics,

medical backgrounds, vital signs, and severity of DG symptoms at baseline. Two patients in the metoclopramide group failed to provide efficacy data; therefore, intent-to-treat analysis involved a total of 93 patients (48 domperidone and 45 metoclopramide recipients). Of these, 16 patients (six domperidone and 10 metoclopramide recipients) discontinued treatment prematurely.

Tolerability

Elicited adverse CNS effects were more severe during metoclopramide therapy than during domperidone therapy. At 2 wk, the severities of somnolence, akathisia, anxiety, and depression were significantly greater ($p < 0.001$–0.05; see Fig. 1) with metoclopramide than with domperidone. At 4 wk, the severities of somnolence and reduced mental acuity
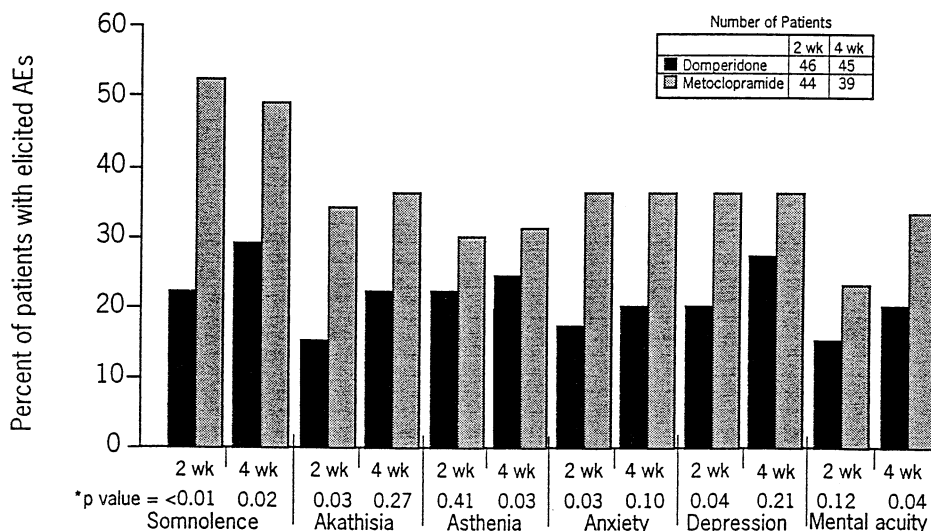
Figure 2. Incidence of elicited CNS-associated adverse events in diabetic patients treated with either domperidone or metoclopramide. *Cochran-Mantel-Haenzel test, with domperidone having the lower incidence. NS = not significant.

Table 1. Incidences of the Most Frequent Spontaneously Reported Adverse Events Occurring With Domperidone and Metoclopramide

Adverse Event	Domperidone (n = 48) (% of Patients)	Metoclopramide (n = 47) (% of Patients)
Vomiting	10.4	4.3
Nausea	10.4	4.3
Headache	6.3	2.1
Insomnia	6.3	0
Diarrhea	6.3	2.1
Prolactin-related	6.3	6.4
Cystitis	6.3	2.1

were significantly greater ($p = 0.03–0.04$; see Fig. 1) with metoclopramide than with domperidone.

Elicited adverse CNS effects occurred more frequently during metoclopramide therapy than during domperidone therapy. At 2 wk, the incidences of somnolence, akathisia, anxiety, and depression were significantly greater ($p < 0.01–0.04$; see Fig. 2) with metoclopramide than with domperidone. At 4 wk, the incidences of somnolence and reduced mental acuity were significantly greater ($p = 0.02–0.04$; see Fig. 2) with metoclopramide than with domperidone.

Of the spontaneously reported adverse effects, nausea, vomiting, headache, insomnia, and diarrhea occurred in 6–10% of domperidone-treated patients and in up to 4% of metoclopramide recipients. The incidence of prolactin-related adverse effects was similar ($\approx 6\%$) in the two treatment groups (Table 1).

A total of nine patients (three domperidone recipients and six metoclopramide recipients) discontinued therapy because of adverse events. Elicited adverse CNS effects were responsible for treatment discontinuation in four metoclopramide-treated patients and in one domperidone-treated patient. No clinically relevant changes in laboratory parameters were evident during treatment with either domperidone or metoclopramide.

Therapeutic Efficacy

Both treatment groups showed significant reductions in the severity of gastroparetic symptoms (Fig. 3). From baseline to endpoint, the total symptom score (sum of four individual symptom scores: nausea, vomiting, early satiety, and bloating/distension) fell from 8.0 ± 0.32 to 4.71 ± 0.46 (41.1% reduction) with domperidone and from 8.33 ± 0.29 to 5.09 ± 0.5 (38.9% reduction) with metoclopramide ($p =$ NS). No significant difference was noted between the effects of the two treatments on any gastrointestinal symptom.

DISCUSSION

In the present study, treatment with domperidone 20 mg 4 times daily or metoclopramide 10 mg 4 times daily for 4 wk were similarly effective in improving gastrointestinal symptoms suggestive of DG in patients with insulin-dependent
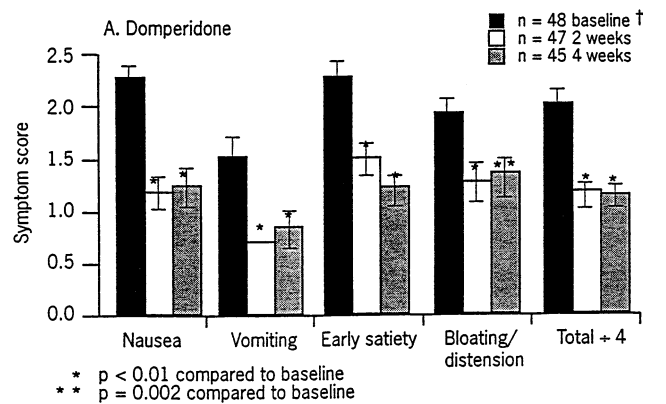

Figure 3. Gastroparetic symptom scores after either domperidone or metoclopramide in patients with insulin-dependent diabetes mellitus. There were no significant differences between treatment groups for any individual or total symptom assessments, or for any timepoint.

diabetes. These results are consistent with the findings of other studies in which domperidone or metoclopramide administered chronically demonstrated significant improvement in symptoms of DG, compared with placebo (11, 12, 18).

When patients were questioned specifically, it was found that both the incidence and severity of CNS adverse events common to metoclopramide were lower in patients receiving domperidone than in patients receiving metoclopramide. These results are consistent with the findings of a previously published double-blind, placebo-controlled crossover study of domperidone and metoclopramide, in which 11 patients receiving metoclopramide reported side effects (including dizziness, depression, and lethargy), as compared with only two patients receiving domperidone and three patients receiving placebo (19). This observed difference is probably due to the ability of metoclopramide to cross the blood-brain barrier and the limited ability of domperidone to cross the blood-brain barrier (16, 17).

In conclusion, domperidone 20 mg 4 times daily and metoclopramide 10 mg 4 times daily appear to have similar efficacy in reducing the gastrointestinal symptoms of DG, although domperidone offers a superior tolerability in terms of unwanted CNS effects.

ACKNOWLEDGMENTS

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