Acute and Chronic Effects of Domperidone on Gastric Emptying in Diabetic Autonomic Neuropathy

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Gastric emptying was studied with a double radioisotopic method in 12 patients with insulin-dependent diabetes mellitus complicated by autonomic neuropathy and in 22 control subjects. In the diabetics, the acute and chronic effects of oral domperidone on gastric emptying, symptoms of gastroparesis, and glycemic control were assessed. Gastric emptying of solid and liquid was slower in diabetics than controls (P < 0.001). Acute administration of domperidone increased the rate of both solid and liquid emptying (P < 0.005). Domperidone was most effective in those patients with the greatest delay in gastric emptying. After chronic administration (35–51 days), domperidone had no significant effect on solid emptying (P > 0.05), but was still effective in increasing liquid emptying (P < 0.025). Symptoms of gastroparesis were less after domperidone (P < 0.001).

Complications involving the gastrointestinal tract are common in diabetes mellitus (1). Diabetic gastroparesis is most often found in long-standing insulin-dependent diabetes and is frequently associated with evidence of autonomic nerve dysfunction, including impairment of cardiovascular reflexes, bladder and sexual function (2, 3), and complications of peripheral neuropathy, nephropathy, and retinopathy (1). Delayed gastric emptying is usually attributed to vagal damage, occurring as part of a generalized autonomic neuropathy (4, 5), although other contributory factors such as hyperglycemia (6) and hormonal changes (7) have been suggested.

There is little data regarding the proportion of diabetics who have abnormal gastric emptying, partly because of the previous lack of sensitive and simple tests to investigate these patients (4, 5, 8, 9) and the fact that asymptomatic patients may have abnormalities (1, 10). Asymptomatic gastroparesis may contribute to poor glycemic control (10).

Scintigraphic techniques, using food labeled with radioisotopes, have recently been used to measure gastric emptying in various disorders of upper gastrointestinal motility, including diabetes mellitus (2, 11–17). These methods are more sensitive than barium radiographic techniques, are relatively simple to perform, unlike intubation techniques, and permit the measurement of the emptying of both solid and liquid meal components (2, 12, 18).

The treatment of diabetic gastroparesis is unsatisfactory. Drugs such as metoclopramide and bethanechol have been shown to stimulate gastric motor activity (4, 5), probably through a cholinergic-mediated action on gastric smooth muscle (19), but while the stimulatory effects of these drugs on gastric...
motility are well established, their efficacy in the long term is uncertain and mainly based on the results of uncontrolled trials (20, 21). Metoclopramide, which has been the most extensively studied of these drugs, also has a central antiemetic effect which may be responsible for improvement in symptoms (19). In many studies (20–22) measurement of gastric emptying before and after a treatment period has not been performed, and consequently a relationship between improvement in symptoms and alterations in motility has not been established.

Up to 10% of patients given metoclopramide develop significant neurological side effects (19). Domperidone is a new gastrokinetic drug which is a potent peripheral dopamine antagonist like metoclopramide, but lacks cholinergic activity and does not cross the blood brain barrier in significant amounts; consequently neurological side effects are rare (23). Reports have indicated that domperidone is effective in the treatment of a variety of gastrointestinal disorders such as nausea and vomiting (23), esophageal reflux (24), and dyspepsia (25).

We have studied gastric emptying in diabetics with autonomic neuropathy, using a sophisticated scintigraphic technique (11, 13) and assessed the acute and chronic effects of oral domperidone on gastric emptying, symptoms of gastroparesis, and glycemic control.

**MATERIALS AND METHODS**

Twelve patients (six male, six female), mean age 43 years (range 21–61), who were ambulant outpatients, had insulin-dependent diabetes for at least 10 years and were subsequently demonstrated to have autonomic neuropathy, participated in the study. All had other complications of diabetes mellitus including nephropathy, retinopathy, and peripheral neuropathy. All were nonsmokers and were not taking medication known to affect gastrointestinal motility. Informed consent was obtained in all cases, and the study was approved by the Research Review Committee of the Royal Adelaide Hospital. After entering the study, patients were seen at least at monthly intervals and standard adjustments were made to diabetic therapy if there had been any deterioration in glycemic control.

All diabetic patients underwent: (1) a subjective assessment of gastrointestinal symptoms and symptoms of autonomic neuropathy unrelated to the gastrointestinal tract, (2) an objective assessment of autonomic nerve function by standard noninvasive physiological methods, (3) an assessment of glycemic control, (4) measurement of gastric emptying of a mixed solid and liquid meal, and (5) assessment of the acute and chronic effects of domperidone on gastric emptying and symptoms of gastroparesis.

Gastric emptying tests were also performed in 22 normal volunteers (14 male, 8 female), mean age 34 years (range 21–62) who were nonsmokers, on no medication, and with no evidence of gastrointestinal disease.

**Assessment of Gastrointestinal Symptoms and Symptoms of Autonomic Neuropathy**

Patients were evaluated by a standard questionnaire for symptoms of delayed gastric emptying. Each of the following four symptoms: anorexia/nausea, early satiety, epigastric fullness/upper abdominal discomfort, and postprandial vomiting was scored as 0 = none, 1 = mild (symptom could be ignored if the patient did not think about it), 2 = moderate (symptom could not be ignored, but did not influence daily activities), 3 = severe (symptom influenced daily activities). Symptoms of dysphagia and heartburn were scored similarly. Delayed gastric emptying due to organic obstruction was excluded by upper gastrointestinal endoscopy.

**Objective Assessment of Autonomic Nerve Function**

Parasympathetic function was evaluated by the heart rate variation (R-R interval) during deep breathing and the immediate heart rate response to standing (30:15 ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. All patients were required to have abnormal results on both tests of parasympathetic function, according to criteria outlined by Ewing and Clarke (3).

**Assessment of Glycemic Control**

All patients kept a record of their urinalysis results for glucose, their insulin doses, and hypoglycemic episodes. Plasma glucose was measured at the completion of each gastric emptying study (3 hr postprandially). Plasma glucose was not measured before the test because of possible effects of venepuncture on gastrointestinal motility (18). Hemoglobin A1c (HbA1c) levels were measured by ion-exchange chromatography and the concentration determined by spectrophotometry (26) on two occasions (day 0 and between 35 and 51 days).

**Measurement of Gastric Emptying**

**Preparation of Solid and Liquid Markers.** Twenty-seven millicuries of $^{99m}$Tc-sulfur colloid were injected into a wing vein of a live chicken as described by Meyer et al (27). After 20 min, the chicken was killed and the liver removed. The amount of liver containing 1–1.5 mCi of $^{99m}$Tc-sulfur colloid was mixed into 100 g of ground beef and the resulting "hamburger" cooked on a grill. The total calorie content of the solid meal (25 g protein, 21 g fat) was approximately 270 kcal. The liquid marker was 0.75–1 mCi of $^{131}$In-DTPA mixed in 150 ml of 10%