The Evaluation of the Patient with Gastroparesis Secondary to Insulin-Dependent Diabetes Mellitus

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CASE PRESENTATION

A 28-yr-old woman with a 15-yr history of insulin-dependent diabetes mellitus complicated by proliferative retinopathy and peripheral and autonomic neuropathy noted the onset of nausea and abdominal bloating one year ago. She had a 12-lb weight loss that she attributed to anorexia and early satiety. Over the past few months, she had increasing difficulty in controlling her blood glucose levels within a normal range.

Upper endoscopy demonstrated a normal appearing esophagus, stomach and duodenum. However, there was approximately 300 cc of bilious fluid mixed with undigested food in the stomach despite an overnight fast and a nonobstructed pylorus. No gastric peristaltic contractions were noted during the procedure.

To quantify the severity of gastroparesis, a gastric emptying scan was performed using a solid meal labeled with 300 μCi of ^{99m}Tc-sulfur colloid. The meal combined 300 calories, including 40% protein, 40% carbohydrate, and 20% fat, and consisted of a scrambled egg white (*1*). Images of the stomach in the anterior and posterior projections were obtained every 15 min for 2 hr. There was a significant delay in emptying compared to previously established normals in our department (Fig. 1). The gastric emptying rate at 60 min was 31% and at 120 min was 39% compared to a normal rate of 40% and 75%, respectively.

The patient was subsequently given a trial of Metoclopramide without improvement. She was then started on Cisapride, a novel prokinetic agent, which offered her complete relief of her symptoms with subsequent normalization of her weight. Her serum glucoses and HbA1c normalized. A repeat gastric emptying scan demonstrated near normal values for gastric emptying.

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DISCUSSION

Gastroparesis, or delayed gastric emptying, is a frequent gastrointestinal complication of diabetes, which may result in significant morbidity and could potentially result in death. Typical symptoms of gastroparesis are postprandial nausea and vomiting, early satiety, bloating, weight loss and/or abdominal pain. Vomitus often contains undigested food. Wide swings of serum glucose levels with hypoglycemia, hyperglycemia or ketoacidosis may occur due to the unpredictable delay in gastric emptying.

The causes for delayed gastric emptying in diabetes mellitus are complex and multifactorial. Initially, there may be a delay only in the emptying of undigestible solids. In a study of 26 insulin-dependent diabetic patients, 16 patients had retention of undigestible solid markers 6 hr after ingestion despite normal emptying of digestible solids and liquids (*2*). This abnormality in emptying nondigestible foods has been attributed to the loss of phase 3 of the interdigestive migrating motor complex (IMMC) (*3,4*). Antral phase 3 activity corresponds to caudally migrating intense contractions during the fasting phase that sweeps undigestible solids from the stomach to the duodenum.

Patients with longstanding diabetes may have reduced antral contractile activity during the postprandial phase (*5,6*). These patients have delayed emptying of digestible solids and eventually liquids (*7*). Pylorospasm or prolonged, high amplitude contractions of the pylorus also occur in diabetes mellitus and cause a delay in gastric emptying (*8*).

Abnormalities in nerve function appear to play a role since gastroparesis is more common in diabetic patients with neuropathy, especially autonomic dysfunction (*9,10*). Vagal neuropathy is not uncommon in patients with diabetes mellitus, as suggested by reduced acid production to sham feeding and elevated serum gastrin levels (*11*). In addition, antral contractions may be absent in the patient with diabetes mellitus, which may be due to vagal neuropathy because antral contractions in the normal subject can be abolished by atropine, a vagal antagonist.

Hormonal factors also play a role in the control of gastric emptying. Higher levels of motilin, a hormone that stimulates a phase 3 pattern, have been measured in diabetic patients (*12*). However, as previously noted, phase 3

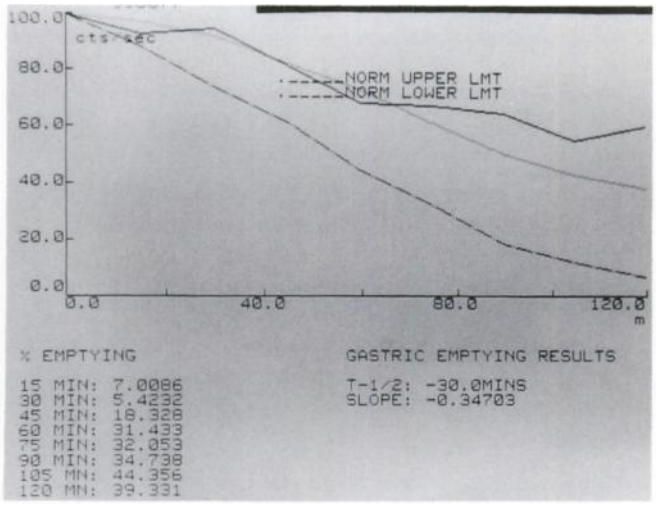

FIGURE 1. Comparison of gastric emptying results.

patterns may be absent in patients with diabetes mellitus. This paradoxical effect may be secondary to altered receptor affinity for motilin. Other factors that affect gastric emptying include acute hyperglycemia, acidosis and hypokalemia (*13*).

Various methods have been utilized to measure gastric emptying, including intubation techniques and barium radiography. Radiologic liquid barium studies to evaluate gastric emptying are insensitive and nonquantitative. Patients with mild or moderate delayed gastric emptying may have normal appearing barium transit on an upper gastrointestinal study. In addition, since barium is not a physiologic meal, it may not accurately represent gastric emptying. The more useful and preferred technique to evaluate emptying of the stomach is external imaging after ingestion of radionuclide tagged foods, which is physiological and noninvasive. Chromium-51 tagged to oatmeal was the first radionuclide used to measure liquid gastric emptying (*14*). Meyer et al. successfully labeled chicken liver by intravenous injection of ^{99m}Tc-sulfur colloid and then cooked the liver into a stew for consumption (*15*). Evaluation of solid phase gastric emptying is more often helpful than liquid emptying because the latter function is often normal until the later stages of diabetes mellitus and after patients have became symptomatic.

Egg whites labeled with 300 μCi of ^{99m}Tc-sulfur colloid cooked in butter and served with bread is the meal used in our laboratory. Technetium-99m-sulfur colloid binds firmly to cooked egg white (*16*). It is advantageous because it is physiologic in content (300 calories, 40% carbohydrate, 40% protein, 20% fat) and has been shown to give reproducible results. In a study examining the effect of meal energy content on gastric emptying, the 300-calorie meal had greater reproducibility than the 150-calorie meal and was not as large as the 600-calorie meal (*1*). Patients are positioned erect in front of a scintillation camera and anterior and posterior images over 1–2 min are obtained every 15 min for a least 2 hr after meal ingestion. Data are stored on an on-line computer for subsequent analysis.

The area of the stomach is outlined as a region of interest on each scan. Decay-corrected counts for the area of interest are determined and corrected for attenuation by calculating the geometric mean of the anterior and posterior counts. The data are expressed as the percentage of radioactivity remaining in the stomach and plotted over time. Gastroparesis is defined as retention of activity greater than the mean ±2 standard deviations from control subjects.

Treatment of symptomatic gastroparesis in the insulin-dependent diabetic patient may be fraught with difficulty due in part to the limitation of effective treatment options. Metoclopramide, possibly via cholinergic pathways, stimulates antral phase 3 activity and reduces the elevated level of motilin found in patients with insulin-dependent diabetes mellitus and gastroparesis (*17,18*). Metoclopramide facilitates gastric emptying in these patients in comparison to placebo (*19*). Chronic administration of metoclopramide, however, has not been demonstrated to be as effective as acute usage (*20*). In addition, a number of patients are not able to tolerate metoclopramide, partially due to central nervous system effects (*21*).

Domperidone, similar to metoclopramide, antagonizes peripheral dopamine receptors, prevents dopamine-induced gastric relaxation, and improves antroduodenal coordination (*22,23*). It appears that domperidone stimulates gastric muscle contractions mediated via postganglionic cholinergic neurons (*24*). Because it does not cross the blood-brain barrier, domperidone has fewer central nervous side effects than metoclopramide.

Cisapride, which is believed to increase acetylcholine release from the myenteric plexus of the gastrointestinal tract, has been shown to facilitate gastric emptying of indigestible solids in patients with diabetes and gastroparesis (*25*). In addition, cisapride increases gastric emptying of solids and liquids both initially and after 4 wk of continuous administration (*26*).

A new class of prokinetic agents are a well established group of antibiotics, including erythromycin. The latter has been shown to increase the duration, amplitude, and frequency of gastric contractions (*27*). Erythromycin may accelerate gastric emptying via its action as a motilin agonist (*28*). Another new class of medications, include the serotonin antagonists, including 5-hydroxytryptamine-3 antagonist which has been useful in controlling symptoms of nausea in patients receiving chemotherapeutic agents. However, patients with delayed gastric emptying did not have any improvement in their gastric stasis with 5-hydroxytryptamine-3 antagonist in comparison to placebo (*29*). Further studies are needed to evaluate the efficacy of this group of medications.

Radionuclide gastric emptying studies are instrumental in the evaluation of the diabetic patient with symptoms of gastroparesis. Confirmation and quantification of the se-

verity of delayed gastric emptying is important because symptoms of gastroparesis are often nonspecific and may be related to other abnormalities. Other indications for using gastric scintigraphy includes the assessment of non-diabetic patients with possible gastric motor dysfunction. Nausea, vomiting, bloating, fullness, weight loss, anorexia, early satiety, abdominal pain, and dyspepsia are nonspecific symptoms that may represent altered gastric motility and are indications for study by a radionuclide emptying scan.

Upper endoscopy and barium upper gastrointestinal studies are used to eliminate a structural cause for the delay in gastric emptying and often complement the nuclear scan. However, radionuclide measurement is far superior to other methods for examining gastric emptying, including barium studies, intubation techniques, and endoscopy because it is reliable, quantitative, noninvasive, and sensitive. It permits a physiologic evaluation of gastric emptying that cannot be assessed by other techniques. Therefore, if there is a concern about a gastric motor abnormality, the radionuclide emptying study is the preferred method of study. In our patient, the radionuclide study provided quantification of the severity of the gastric delay. The effect of pharmacologic intervention can therefore be easily assessed with a repeat study.

Although minor inter- and intra-individual variability exists, these differences do not appear to be significant, either in short- or long-term reproducibility (*30,31*). However, every effort should be made to perform these studies as precisely as possible so that these variabilities are kept to a minimum. Medications that effect gastric emptying, including opiates, anticholinergics, and prokinetic agents, should be routinely discontinued prior to examination. In addition, conditions that may effect emptying, including hypokalemia, should be corrected prior to testing. Furthermore, standardization of the technique among various laboratories is also essential for comparison of results reported by various centers and should be a criterion for accurate interpretation.

We therefore employ nuclear scintigraphy as a safe, noninvasive, reliable method for the assessment of gastric emptying.

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