The Treatment of Diabetic Gastroparesis With Botulinum Toxin Injection of the Pylorus

BRIAN E. LACY, PHD, MD[1]
MICHAEL D. CROWELL, PHD[2]
ANN SCHETTLER-DUNCAN, RN[2]
CAROLE MATHIS, PHD[1]
PANKAJ J. PASRICHA, MD[3]

OBJECTIVE — Gastroparesis is a disorder of delayed gastric emptying that is often chronic in nature. Up to 50% of type 1 diabetic subjects have symptoms of gastroparesis, which include nausea, vomiting, and early satiety. Elevated pyloric pressures may be responsible for delayed gastric emptying in diabetic subjects. Botulinum toxin inhibits the release of acetylcholine and produces transient paralysis when injected into smooth muscle. The aim of this study was to determine whether injection of the pylorus with botulinum toxin in patients with diabetic gastroparesis improves symptoms of gastroparesis, alters gastric emptying scan time, and/or changes weight and insulin use.

RESEARCH DESIGN AND METHODS — This was an open-label trial with age- and sex-matched control subjects from a tertiary care referral center for patients with gastroparesis. Eight type 1 diabetic subjects (six women and two men; mean age 41 years; mean years with diabetes 25.3) who had failed standard therapy were enrolled. Intervention consisted of injection of the pylorus with 200 units of botulinum toxin during upper endoscopy. Symptoms, antropyloric manometry, gastric emptying scan times, weight, and insulin use were all recorded before intervention and during a 12-week follow-up period.

RESULTS — Seven of the eight patients completed the full 12-week follow-up period. No complications were noted. Mean symptom scores declined from 27 to 12.1 ($P < 0.01$), whereas the SF-36 physical functioning domain also improved ($P < 0.05$). Four patients noted an increase in insulin use of >5 units/day. Six of the seven patients gained weight ($P = 0.05$). Gastric emptying scan time improved in four patients.

CONCLUSIONS — Botulinum toxin injection of the pylorus is safe and improves symptoms in patients with diabetic gastroparesis. These results warrant further investigation with a large, double-blind, placebo-controlled trial.

Diabetes Care 27:2341–2347, 2004

Gastroparesis is a disorder of gastrointestinal motility defined as a delay in gastric emptying in the absence of mechanical obstruction. Common symptoms include early satiety, nausea, vomiting, anorexia, weight loss, and epigastric pain. Gastroparesis is a common problem in type 1 diabetic subjects (1,2), especially in the presence of hyperglycemia (3). Treatment options include erythromycin (4,5), metoclopramide (6), domperidone (7), and cisapride (8), although all of these medications have limitations. Pylorospasm is thought to be a contributing factor in the development of diabetic gastroparesis (9). Reports of intrapyloric botulinum toxin injection to relieve symptoms of gastroparesis (10–14) prompted us to perform a trial in eight patients with severe diabetic gastroparesis who had failed standard therapy.

The hypothesis was that elevated pyloric pressures delay gastric emptying, and thus transient paralysis of the pylorus should accelerate gastric emptying and improve symptoms of nausea and vomiting. Preliminary data from this study was presented in abstract form at the American College of Gastroenterology meetings in September 2000 (12).

RESEARCH DESIGN AND METHODS

— Pylorospasm was first documented by comparing antropyloric manometry findings between diabetic patients and age- and sex-matched healthy volunteers. Pylorospasm was not present in any of the volunteers. Using a prospective, open-label design, diabetic patients with severe gastroparesis were treated with intrapyloric injections of botulinum toxin. Effectiveness was assessed by comparing symptoms, weight, insulin use, gastric emptying, and antropyloric manometry recordings at baseline and after botulinum toxin injection.

Eight patients with type 1 diabetes (six women and two men) were enrolled in this study. The mean age was 41 years (range 36–46), with a mean duration of diabetes of 25.3 years (range 10–40) and mean insulin use of 24.4 years (range 10–40). All patients had been referred to the Marvin M. Schuster Motility Center for further evaluation due to persistent symptoms of gastroparesis despite the use of standard medications. Mechanical obstruction had been ruled out in all patients by the referring physicians using a number of different tests (upper endoscopy [esophagogastroduodenoscopy], small bowel follow-through, and computed tomography scan of the abdomen

From the [1]Marvin M. Schuster Center for Digestive and Motility Disorders, Johns Hopkins University, School of Medicine, Baltimore, Maryland; [2]Novartis, East Hanover, New Jersey; and the [3]University of Texas at Galveston, Galveston, Texas.

Address correspondence and reprint requests to Brian E. Lacy, PhD, MD, Dartmouth-Hitchcock Medical Center, Section of Gastroenterology, 1 Medical Center Dr., Lebanon, NH 03756. E-mail: brian.lacy@hitchcock.org.

Received for publication 26 March 2004 and accepted in revised form 28 June 2004.

P.J.P. is a paid consultant for Allergan.

Abbreviations: LES, lower esophageal sphincter.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

and pelvis). A solid-phase gastric emptying scan was delayed in all eight patients.

The control group consisted of age- and sex-matched control subjects without diabetes and without any complaints referable to the gastrointestinal system. Exclusion criteria for both groups were as follows: pregnancy; known allergy to eggs, botulinum toxin, or lidocaine; previous surgery to the stomach, pylorus, or small bowel; previous Nissen fundoplication or other antireflux surgery; known pyloric stricture; previous stroke, transient ischemic attack, or chronic diseases involving the central nervous system; concurrent use of opiates or anticholinergics. Women of child-bearing age had both urine and serum human chorionic gonadotropin checked to ensure that they were not pregnant before testing and treatment. Prokinetic and antiemetic agents were continued during the trial; however, new medications were not initiated during the trial. All patients stayed on a gastroparesis diet (small frequent meals low in both fat and fiber). This protocol was approved by the Institutional Review Board of Johns Hopkins Bayview Medical Center.

Gastric emptying scans

Gastric emptying scans were performed in an identical manner both before and 1 week after botulinum toxin injection to objectively measure changes in gastric emptying. After an overnight fast, patients were given a standard meal consisting of two scrambled eggs mixed with one mCi-99 technetium sulfur colloid (15), two slices of white bread, and 300 ml of water (total of 270 kcal; 23% protein, 37% carbohydrate, 40% fat). Images were taken every minute for a minimum of 120 min using a gamma camera (Adak Company, Militas, CA), and the $t_{1/2}$ for gastric emptying was calculated (mean for normal patients in the Nuclear Medicine Department is 90 ± 15 min). Radiologists who read the study were blinded to the study protocol.

Antropyloric manometry

Antral and pyloric intraluminal pressures were recorded using a manometric assembly (optical density 8 mm), which incorporated a 6-cm sleeve sensor and five side holes (Dentsleeve, Wayville, Australia). The 6-cm sleeve sensor was positioned across the pylorus and recorded both pyloric tone and phasic activity. Four side holes located at 0, 3, 6, and 9 cm above the orad end of the sleeve recorded pressure events in the terminal and proximal antrum, respectively. The remaining side hole was located 1 cm distal to the aboral end of the sleeve and recorded duodenal pressure events. The manometry assembly was perfused with distilled water using a low-compliance pneumohydraulic pump (Mui Scientific, Ontario, Canada) with a flow rate of 0.8 ml/min. After preamplification and low pass filtration (PC Polygraf HR; Synectics Medical, Stockholm, Sweden), pressure events were digitized at 16 Hz on a microcomputer (Polygram Upper GI Edition; Synectics Medical).

After topical anesthesia (2% lidocaine HCl; AstraZeneca, Wilmington, DE) to the nose, the catheter assembly was positioned across the pylorus using fluoroscopic guidance. Accommodation time of ~1 h occurred before obtaining 3 h of recordings in a fasting state. The patient was then fed a standard liquid meal (Pulmocare; Ross Products, Columbus, OH) (837 ml; 355 kcal; 16.7% protein, 28.2% fat, 55.1% carbohydrate), and recordings were continued for another 2 h. To minimize exacerbation of gastroparesis (2), blood glucose was monitored during the test, and insulin or glucose was provided to maintain serum glucose between 80 and 150 mg/dl. Antropyloric manometry was performed in an identical manner in the week before and 1 week after injection of the pylorus with botulinum toxin. This portion of the study provided an objective measure of the response to botulinum toxin injection.

Analysis of antropyloric manometry

Pyloric pressure activity was classified into one of three groups, according to the description by Mearin et al. (9). Baseline elevation of the pyloric pressure wave >3 mmHg for >1 min was defined as a tonic pattern; antral-type phasic pressure activity mixed with duodenal phasic activity was categorized as a phasic pattern; and a phasic pattern superimposed on tonic activity was categorized as a combined tonic-phasic pattern. Pylorospasm was defined as prolonged (>3 min) or intense (>10 mmHg) contractions above baseline. Each 15 min of pyloric recording was subjected to area under the curve analysis to assess response to botulinum toxin injection.

Symptom questionnaires and weights

Each patient filled out a symptom questionnaire (see APPENDIX). Each question asked the patient to rate symptoms from none (0 points) to severe (3 points); the maximum score was 36. Patients completed two standardized questionnaires, SF-36 and SCL-90, at the initiation and completion of the study. Questionnaires were included in this study because the U.S. Food and Drug Administration now recommends that subjective measures be included as either primary or secondary end points in studies of gastrointestinal disorders. Patients were asked to record daily insulin use and to monitor the need for additional insulin. Weights were measured at the initiation of the protocol and at routine follow-up after treatment.

Laboratory studies

A complete blood count, blood urea nitrogen, creatinine, fasting glucose, HbA_{1c}, albumin, and urinalysis were checked before enrollment and again at 8 weeks after injection.

Injection of the pylorus

After informed consent, patients underwent esophagogastroduodenoscopy to rule out mechanical obstruction. All procedures were performed by one physician (B.E.L.). Two hundred units of botulinum toxin A (Botox; Allergan, Irvine, CA) were dissolved in 4 ml of sterile normal saline and injected into the pylorus using a standard sclerotherapy 25-gauge, 4-mm needle (Ballard, Draper, UT) (50 units of Botulinum toxin A into each quadrant). The patient was observed for 1–2 h in the recovery area and then discharged home. Telephone follow-up occurred at 24 h to look for immediate side effects or complications. Patients were seen in follow-up at 1, 2, 4, 6, 8, and 12 weeks after the injection therapy.

Statistics

Data were analyzed using the statistical software SPSS. Pre- and postinjection weights, gastric emptying scan times, symptom scores, SF-36, and SCL-90 data were compared using a paired sample Student's *t* test. Pyloric manometry was analyzed by comparing the area under the curve in the pre- and postinjection period using a paired sample Student's *t* test.

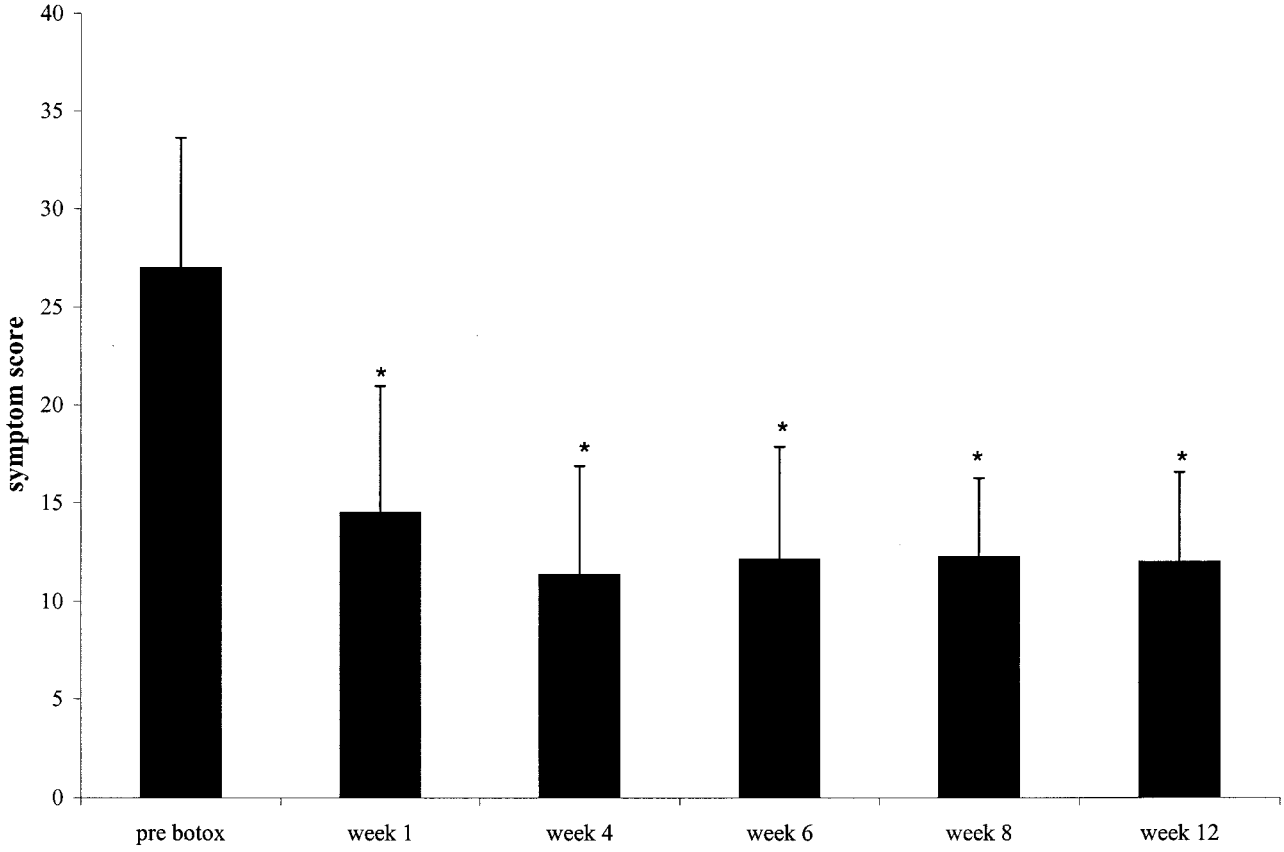

Figure 1—*Symptom scores of patients at baseline (prebotox) and over the 12-week trial period. Symptom scores reflect all eight patients for baseline and 1-, 2-, 4-, and 8-week follow-up visits. Symptom scores for the week 12 follow-up visit reflect seven patients. Maximum symptom score was 36. The x-axis reflects time, and the y-axis reflects symptom score.*

RESULTS

Symptoms

The mean symptom score of all eight patients before treatment was 27.0. Mean symptom scores at weeks 1, 4, 6, and 8 were 14.5, 11.4, 12.1, and 12.2, respectively, for all eight patients (Fig. 1). One patient (C.F.) developed severe nausea and vomiting at week 9 and underwent repeat endoscopy with a second injection (200 units) of botulinum toxin without any complications. Symptoms of nausea and vomiting completely resolved after the second injection. This patient's symptom scores are included for follow-up weeks 1–8 but not week 12. Symptom scores of the seven patients who completed all 12 weeks of follow-up after only one injection of botulinum toxin were not significantly different from the scores listed above for all eight patients and were all significantly reduced compared with baseline ($P < 0.01$ at all visits).

SF-36 scores and SCL-90 scores were measured both before and after botulinum toxin injection of the pylorus. Two patients did not completely fill out both sets of forms and thus were excluded from analysis. In the six patients who completely filled out both pre- and postinjection SF-36 questionnaires, total scores did not change significantly. However, subscores for the physical functioning domain did improve ($P < 0.05$). No significant differences were noted in SCL-90 scores over the 12-week follow-up period.

Gastric emptying scans

Mean solid-phase gastric emptying scan time ($t_{1/2}$) before injection was 339.1 min (range 74–999). Gastric emptying time was reduced by one-third 1 week after injection to a mean of 227.3 min (range 74–906; $P = 0.11$). One patient had a normalization of gastric emptying scan time after injection ($t_{1/2}$ of 142 min compared with 82 min). Three patients had significant improvement in their gastric emptying scan half-times, although they did not normalize (182–108 min; 351–148 min; 800–278 min). Three patients did not have any significant change in their gastric emptying scan half-times, whereas one patient had an increase in gastric emptying scan half-time (78–146 min). These latter four patients all noted an objective improvement in their symptoms on the questionnaire.

Antropyloric manometry

In eight healthy volunteers, there was no evidence of pylorospasm during antropyloric manometry. Pylorospasm was noted in all eight diabetic patients, which confirms the findings of Mearin et al. (9). Data were available for complete analysis from only five patients. Data were excluded from two patients because the catheter migrated during portions of the preinjection period and because of persistent vomiting in one patient. After botulinum toxin injection, area under the curve analysis revealed that pylorospasm was significantly reduced compared with baseline

($P = 0.04$). A reduction in tonic pyloric pressures was also noted, although this was not significantly different compared with the preinjection state ($P = 0.06$) (Fig. 2).

Laboratory tests

Values for the complete blood count, blood urea nitrogen, creatinine, fasting glucose, HbA_{1c}, albumin, and urinalysis obtained at the 8-week follow-up visit were not significantly different from baseline.

Insulin use

No changes were noted in either regular or NPH insulin use in any of the patients at the 1-, 2-, and 4-week follow-up appointments. At the 8-week follow-up visit, four patients noted an increase in NPH insulin requirements of ≥5 units each day, whereas the remaining four patients did not require an increase in NPH insulin use. At the 12-week follow-up visit, three of the four patients still required at least 5 units more of NPH insulin use per day, whereas the other four patients did not have a change in their NPH insulin use compared with baseline. No differences were noted for regular insulin use at either the 8- or 12-week follow-up appointments.

Medication use

Four patients remained on the same dose of domperidone (20 mg p.o. q.i.d.), two patients stopped erythromycin, one patient remained on a stable dose of metoclopramide (20 mg p.o. q.i.d.), and one patient decreased their metoclopramide use (from 20 mg p.o. q.i.d. to 10 mg q.i.d.). Regarding antiemetic use, one patient decreased ondansetron use (from 8 mg b.i.d. to q.d.), whereas one decreased compazine use (from 10 mg p.o. t.i.d. to p.r.n.).

Weight

At the 8-week follow-up visit, one patient's weight remained unchanged, three patients gained 1–4 pounds, one patient gained 5–9 pounds, and two patients gained ≥10 pounds. At the 12-week follow-up visit, one patient's weight was unchanged, two patients had gained 1–4 pounds, one patient had gained 5–9 pounds, and three patients had gained ≥10 pounds ($P = 0.05$).

Complications

Patients were questioned about possible side effects during the telephone interview 24 h after botulinum toxin injection and again at the 1-, 2-, 4-, 8-, and 12-week follow-up appointments. No complications were reported as a result of the upper endoscopy or botulinum toxin injection of the pylorus.

CONCLUSIONS — Several research studies have shown that achalasia, a disorder of esophageal motility characterized by dysphagia and poor emptying of the esophagus, can be effectively treated with botulinum toxin (16–18). Injection of the lower esophageal sphincter (LES) with botulinum toxin relaxes the LES, improves esophageal emptying, and improves complaints of dysphagia with minimal side effects.

Investigations in our laboratory led us to believe that diabetic gastroparesis is similar to achalasia. Both conditions involve smooth muscle sphincters that fail to relax appropriately and have elevated tone. Elevated sphincter tone can prevent normal emptying of either the esophagus or the stomach. Modeling the therapeutic success in achalasia, two patients with severe diabetic gastroparesis had a dramatic improvement in symptoms after botulinum toxin injection of the pylorus (10). These preliminary results led us to initiate the current study involving eight patients with long-standing diabetes and mean insulin use of 24.4 years. All patients had failed standard medical therapy (erythromycin, metoclopramide, cisapride, domperidone) without improvement in symptoms. When asked to objectively measure their symptoms of nausea, vomiting, and abdominal pain, mean pretreatment scores were 27 of a maximum of 36. Subjectively, all eight patients stated that their symptoms greatly reduced their quality of life on a daily basis. Botulinum toxin injection of the pylorus was easily accomplished during routine endoscopy in all eight patients without any immediate or delayed side effects.

Individually, all eight patients noted an improvement in symptom scores over the 12-week study period. Collectively, symptom scores decreased significantly at all follow-up visits when compared with baseline ($P < 0.01$). The greatest decrease occurred in the first week after botulinum toxin injection, with a smaller drop during the second week. Individually, the greatest decline in symptom scores occurred in nausea and vomiting. Total SF-36 scores did not significantly improve in the six patients who completely filled out both pre- and postinjection questionnaires, although the physical functioning score did improve ($P < 0.05$). This may reflect an increased ability to function due to fewer episodes of nausea and vomiting.

Gastric emptying scan times were found to improve or normalize in four of eight subjects. This confirms the findings by Ezzeddine et al. (14). Although the sample size is small, this improvement is remarkable, as these patients had previously failed all other standard therapy. In addition, nearly all previously published studies that evaluated the efficacy of prokinetic agents failed to demonstrate an improvement in gastric emptying scan times. Three patients did not have an improvement in gastric emptying scan time, although all noted an improvement in their symptoms. Interestingly, one patient's gastric emptying scan time increased somewhat, although, subjectively, the patient felt better, and objectively, her symptom scores declined. This discordance might reflect a delayed response to botulinum toxin, transient worsening of pylorospasm, or day-to-day variation in gastric emptying.

Several patients were surprised that, after injection therapy, they were able to gain weight and reverse a gradual trend of weight loss secondary to chronic nausea and vomiting. Three patients gained >10 pounds each, and all three of these patients required at least ≥5 units of NPH insulin each day over the course of the study period. A reduction in early satiety, epigastric pain, nausea, and vomiting in these patients may all have contributed to an increased ability to eat.

This study confirms the previous report by Mearin et al. (9), which showed that patients with diabetic gastroparesis have pylorospasm. In the current study, pylorospasm was reduced in all five patients who completed both antropyloric manometries. This confirms and extends the findings published in a recent case report (13). Symptom scores decreased in all five patients, whereas gastric emptying scan times improved in three patients.

In contrast to current medical therapy, botulinum toxin injection of the pylorus has the unique advantage of treating a specific site within the stomach (the py-

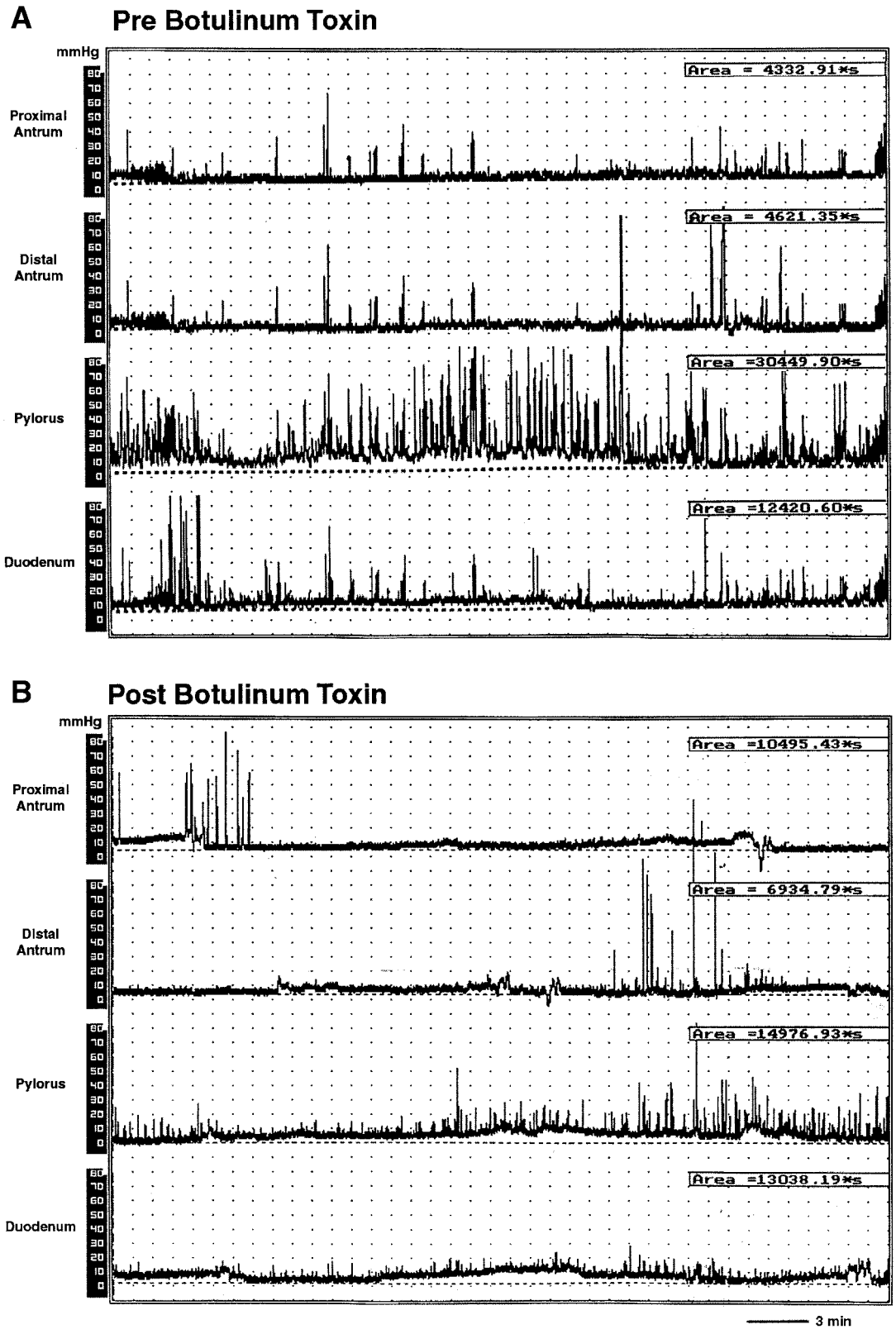

Figure 2—*Antropyloric manometry using a Dentsleeve catheter.* A *and* B*: The first two panels reflect activity in the antrum (proximal and distal), the third panels reflect pyloric activity, and the last panels reflect duodenal activity.* A*: Baseline (preinjection). Area under the curve for the pylorus in this patient is 30,449.90 s.* B*: Postbotulinum toxin injection of the pylorus. In the same patient, a reduction in phasic activity in the pylorus can be visualized. Tonic-phasic activity, as measured by the area under the curve, decreased to 14,976.90 s.*

Table 1—*Symptom questionnaire*

Symptoms	Response			
Upper abdominal discomfort	None	Mild	Moderate	Severe
Regurgitation	None	Mild	Moderate	Severe
Bloating	None	Mild	Moderate	Severe
Heartburn	None	Mild	Moderate	Severe
Loss of appetite	None	Mild	Moderate	Severe
Nausea (# days per week ____)	None	Mild	Moderate	Severe
Vomiting (# times per week ____)	None	Mild	Moderate	Severe
Abdominal pain after eating	None	Mild	Moderate	Severe
Abdominal pain between meals	None	Mild	Moderate	Severe
Abdominal pain after drinking liquids	None	Mild	Moderate	Severe
Early satiety (filling up very quickly)	None	Mild	Moderate	Severe
Burning sensation in chest/upper abdomen	None	Mild	Moderate	Severe

Symptom score = ___.

lorus) that is dysfunctional. Targeted therapy with botulinum toxin injection minimizes the likelihood of systemic side effects, which commonly occurs in patients treated with oral agents. The efficacy of botulinum toxin provides insight into one of the underlying pathophysiological disorders of diabetic gastroparesis—pylorospasm. This may occur due to a relative imbalance between the excitatory neurotransmitter acetylcholine and the inhibitory neurotransmitter nitric oxide. A reduction in nitric oxide–containing neurons could lead to an elevated tonic state in the pylorus and, thus, delay gastric emptying. A study performed by Watkins et al. (19) demonstrated that nitric oxide plays a critical role in pyloric function and that loss of nitric oxide impedes gastric emptying.

As noted previously, our trial was modeled on the therapeutic success of botulinum toxin for the treatment of achalasia, a spastic smooth muscle disorder of the LES. Historically, therapeutic options to treat achalasia were limited to balloon dilation and surgery (myotomy). Botulinum toxin injection of the LES was enthusiastically greeted as a therapeutic option given initial reports describing significant success in relieving symptoms (16,17). Over the last several years, however, an accumulating body of evidence has demonstrated that botulinum toxin injection provides long-term benefits (>12 months) in only a minority of patients (20) and is often ineffective in younger patients (21,22). Balloon dilation of the LES is generally more efficacious at providing long-term relief of symptoms (23) and is more cost-effective (24). Laparoscopic Heller myotomy is preferred by many gastroenterologists and surgeons given its long-term favorable outcome.

Applying these lessons to the clinical scenario of pylorospasm in patients with diabetic gastroparesis is difficult due to a lack of clinical studies. No well-designed studies have been performed to assess the efficacy of balloon dilation of the pylorus in adults with gastroparesis. One study of 19 children demonstrated that balloon dilation of the pylorus led to complete resolution of symptoms in 11 patients and transient improvement in symptoms of up to 8 weeks in 5 patients (25). Pyloromyotomy has been shown to improve symptoms in patients with hypertrophic pyloric stenosis (26), although there are no controlled studies of pyloromyotomy in patients with diabetic gastroparesis. In addition, the underlying pathophysiology of hypertrophic pyloric stenosis is likely quite different quantitatively than diabetic pylorospasm.

Our results point out that botulinum toxin injection of the pylorus can provide significant relief of symptoms over several months. The dose of botulinum toxin used in our study (200 units) was higher than that used to typically treat achalasia (100 units), as the mass of the pylorus is believed to be greater than that of the LES. Botulinum toxin injection of the pylorus may earn a place in our armamentarium of therapeutic agents for patients with mild-to-moderate diabetic gastroparesis who have failed traditional prokinetic agents (metoclopramide, erythromycin, cisapride). This therapy may prove to be most valuable in those diabetic patients with intractable nausea and vomiting who cannot tolerate oral medications and in those with persistent symptoms despite maximal medical therapy. Although our study demonstrated that patients noted an improvement in both nausea and vomiting, it is not likely that this therapy will replace the use of traditional antiemetic agents for gastroparetic patients with only mild nausea, given the expense of botulinum toxin and the need for endoscopy. Future trials will need to evaluate the long-term safety, efficacy, and cost of botulinum toxin therapy compared with balloon dilation of the pylorus, pyloromyotomy, and gastric electrical stimulation.

Summary

In this study, botulinum toxin injection of the pylorus in eight patients with severe diabetic gastroparesis was found to be safe and to improve symptoms of nausea, vomiting, and abdominal pain. Pyloric tone and pressure was reduced after intrasphincteric injection with botulinum toxin. Gastric emptying scan half-times improved in some, but not all, patients, whereas some patients gained weight and required higher doses of daily insulin.

Before botulinum toxin injection of the pylorus is adopted in clinical practice for the routine treatment of diabetic gastroparesis, we recommend that endoscopists interested in using this technique consider pooling both resources and patients to conduct a blinded, placebo-controlled trial to confirm the efficacy of this treatment. Funding agencies such as the National Institutes of Health or the American Diabetes Association should strongly consider support of such research, which has the potential to bring relief to diabetic patients suffering from gastroparesis.

Acknowledgments— This study was funded by donations to the Marvin M. Schuster Center for Digestive and Motility Disorders and by unrestricted educational grants (to B.E.L. [CERT grant from Johns Hopkins and Allergan]).

APPENDIX

Please rate any symptoms that you currently have. If the symptoms were given as numbers, then no symptoms would equal 0, mild symptoms would equal 1,

moderate symptoms would equal 2, and severe symptoms would equal 3 (Table 1).

References

1. Koch K: Gastroparesis: diagnosis and management. *Practical Gastroenterol* 32: 30–43, 1987
2. Horowitz M, Harding PE, Maddox A, Maddern GJ, Collins PJ, Chatterton BE, Wishart J, Shearman DJC: Gastric and oesophageal emptying in insulin-dependent diabetes mellitus. *J Gastroenterol Hepatol* 1:97–113, 1986
3. Rayner CK, Su YC, Doran SM, Jones KL, Malbert CH, Horowitz M: The stimulation of antral motility by erythromycin is attenuated by hyperglycemia. *Am J Gastroenterol* 95:2233–2241, 2000
4. Peeters T, Matthijs G, Depoortere I, Cachet T, Hoogmartens J, Vantrappen G: Erythromycin is a motilin receptor agonist. *Am J Physiol* 257:G470–G474, 1989
5. Anese V, Janssens J, Vantrappen G, Tack J, Peeters TL, Willemse P, Van Cutsem E: Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination. *Gastroenterology* 102:823–828, 1992
6. Albibi R, McCallum RW: Metoclopramide: pharmacology and clinical application. *Ann Int Med* 98:86–95, 1983
7. Soykan I, Sarosiek I, McCallum RW: The effect of chronic oral domperidone therapy on gastrointestinal symptoms, gastric emptying, and quality of life in patients with gastroparesis. *Am J Gastroenterol* 92: 976–980, 1997
8. Kendall BJ, Kendall ET, Soykan I, McCallum RW: Cisapride in the long-term treatment of chronic gastroparesis: a 2-year open-label study. *J Int Med Res* 25:182–189, 1997
9. Mearin F, Camilleri M, Malagelada JR: Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology* 90:1919–1925, 1986
10. Lacy BE, Zayat EN, Crowell MD, Schuster MM: Botulinum toxin for the treatment of gastroparesis (Abstract). *Gastroenterology* 118:A624, 2000
11. Lacy BE, Zayat EN, Crowell MD, Schuster MM: Botulinum toxin for the treatment of gastroparesis: a preliminary report. *Am J Gastroenterol* 97:1548–1552, 2002
12. Lacy BE, Schettler-Duncan VA, Crowell MD: The treatment of diabetic gastroparesis with botulinum toxin (Abstract). *Am J Gastroenterol* 95:2455, 2000
13. Gupta P, Rao SSC: Attenuation of isolated pyloric pressure waves in gastroparesis in response to botulinum toxin injection: a case report. *Gastrointest Endosc* 56:104–107, 2002
14. Ezzeddine D, Jit R, Katz N, Gopalswamy N, Bhutani MS: Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointest Endosc* 55:920–923, 2002
15. Camilleri M, Hasler WL, Parkman HP, Quigley EMM, Soffer E: Measurement of gastrointestinal motility in the GI laboratory. *Gastroenterology* 115:747–762, 1998
16. Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kaloo AN: Intrasphincteric botulinum toxin for the treatment of achalasia. *N Engl J Med* 332:774–778, 1995
17. Fishman VM, Parkman HP, Schiano TD, Hills C, Dabezies MA, Cohen S, Fisher RS, Miller LS: Symptomatic improvement in achalasia after botulinum toxin injection of the lower esophageal sphincter. *Am J Gastroenterol* 91:1724–1730, 1996
18. NIH Consensus Development Conference Statement: Clinical use of botulinum toxin. *Arch Neurol* 48:1294–1298, 1991
19. Watkins CC, Sawa A, Jaffrey S: Insulin restores neuronal nitric oxide synthase expression and function that is lost in diabetic gastropathy. *J Clin Invest* 106:373–384, 2000
20. Martinek J, Siroky M, Plottova Z, Bures J, Hep A, Spicak J: Treatments of patients with achalasia with botulinum toxin: a multicenter prospective cohort study. *Dis Esophagus* 16:204–209, 2003
21. D'Onofrio V, Miletto P, Leandro G, Iaquinto G: Long-term follow-up of achlasia patients treated with botulinum toxin. *Dig Liver Dis* 34:105–110, 2002
22. Neubrand M, Scheurlen C, Schepke M, Sauerbruch T: Long-term results and prognostic factors in the treatment of achalasia with botulinum toxin. *Endoscopy* 34:519–523, 2002
23. Bansal R, Nostrant TT, Scheiman JM, Koshy S, Barnett JL, Elta GH, Chey WD: Intrasphincteric botulinum toxin versus pneumatic balloon dilation for treatment of primary achalasia. *J Clin Gastroenterol* 36:209–214, 2003
24. Richter JE: Comparison and cost analysis of different treatment strategies in achalasia. *Gastrointest Endosc Clin N Am* 11: 359–370, 2001
25. Israel DM, Mahdi G, Hassall E: Pyloric balloon dilation for delayed gastric emptying in children. *Can J Gastroenterol* 15: 723–727, 2001
26. Sun WM, Doran SM, Jones KL, Davidson G, Dent J, Horowitz M: Long-term effects of pyloromyotomy on pyloric motility and gastric emptying in humans. *Am J Gastroenterol* 95:92–100, 2000