A case of severe, refractory diabetic gastroparesis managed by prolonged use of aprepitant

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Background. A 31-year-old woman with an 11-year history of poorly controlled type 1 diabetes mellitus was admitted with severe vomiting and ketoacidosis. The patient had been admitted to hospital on 14 occasions in the past 3 years for diabetic ketoacidosis precipitated by intractable vomiting, and she had been diagnosed with gastroparesis 2 years previously.

Investigations. Assessment of the patient's response to standard treatments for diabetic gastroparesis. These approaches involved tight glycemic control that included subcutaneous insulin infusion via a pump, correction of electrolyte disturbances, use of standard antiemetic and promotility agents, somatostatin-analog treatment, intrapyloric injection of botulinum toxin, and insertion of a percutaneous jejunal feeding tube.

Diagnosis. Severe diabetic gastroparesis refractory to standard treatments.

Management. The neurokinin-receptor antagonist aprepitant was started and her vomiting stopped within 24 h. This treatment was successfully continued for 4 months until a gastric electrical stimulation device was inserted, which enabled aprepitant treatment to be withdrawn and the percutaneous jejunostomy feeding tube to be removed. This successful treatment led to a substantial improvement in the patient's quality of life and overall glycemic control.

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The case

A 31-year-old woman was admitted to hospital with severe vomiting and ketoacidosis. The patient had an 11-year history of poorly controlled type 1 diabetes mellitus, as illustrated by her HbA_{1c} measurements for that period (Table 1). She had stable diabetic retinopathy, but had previously required laser treatment. Her renal function was normal.

In the 3 years before admission, the patient had been admitted to hospital 14 times with diabetic ketoacidosis secondary to intractable vomiting, and had spent a total of over 1 year in hospital during this period. Gastroparesis had been diagnosed 2 years previously while the patient was in hospital, by the use of gastric emptying scintigraphy and endoluminal manometry studies. Autonomic studies carried out at around the same time also showed abnormal findings: no variation in the interval between R waves of electrocardiographic QRS complexes with deep inspiration, no pupillary reaction to light (pseudo-Argyll-Robertson pupils), and postural hypotension.

The patient was transferred to the diabetes unit of a hospital where her glucose control was optimized; however, she continued to vomit. Intravenous or oral suspensions of the promotility agents metoclopramide and low-dose erythromycin did not improve her vomiting. She was treated with various combinations of intravenous, oral or subcutaneous antiemetic drugs, including dopamine agonists (haloperidol and domperidone), a serotonin-receptor antagonist (ondansetron) and antihistamines (cyclizine). Various combinations of agents in escalating doses were used until her symptoms were brought under control.

The patient's vomiting eventually stopped when a combination of cyclizine and haloperidol was given via continuous subcutaneous infusion (150 mg cyclizine and 5 mg haloperidol every 24 h), and suspensions of metoclopramide (10–20 mg three times daily) and low-dose erythromycin (5 mg/kg every 8 h) were given. On this regime the patient was well enough to stay out of hospital for almost 1 year; however, after this time she was readmitted to the diabetes unit of the hospital with ketoacidosis due to intractable vomiting.

The patient was started on a subcutaneous insulin infusion via a pump and percutaneous jejunal feeding was initiated. Despite these measures, and the continuation of the intravenous antiemetic and oral promotility agents, her vomiting continued. Octreotide, a subcutaneous somatostatin analog, was tried in an attempt to reduce the patient's gastric secretions; however, its usefulness was limited by the fact that at therapeutic doses it increased her nausea. The patient was given an intrapyloric injection of botulinum toxin to reduce muscular tone and thus improve her gastric emptying. Unfortunately, this treatment also failed to improve the patient's vomiting.

Competing interests
The authors declared no competing interests.

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Table 1 | The case patient's HbA_{1c} levels over a decade

Month (intervention)	HbA_{1c} (%)
–105	12.4
–102	13.4
–96	14.3
–82	13.7
–79	13.6
–75	14.7
–67	12.8
–63	13.6
–59	12.5
–55	10.8
–51	10.5
–46	11.0
–43	11.4
–30	8.5
–21 (Moved to the diabetes unit)	7.0
–14	8.0
–12	7.0
–9	8.5
–3	8.3
0 (Aprepitant started)	6.5
2	5.9
3	6.7
4 (Gastric electrical stimulation device fitted)	6.7
7	6.9
10	6.2

At 1 month after readmission to the diabetes unit, the patient was assessed for suitability for a gastric electrical stimulation device, and put on the waiting list to have the device fitted. In the interim, owing to her ongoing symptoms, the local Drugs, Therapeutics and Medicines Management Committee gave approval for unlicensed, prolonged use of the neurokinin-receptor antagonist aprepitant. The drug was started at 80 mg daily. The patient stopped vomiting within 24 h of the first dose. She remained free of nausea and vomiting on this drug for several months, which meant that she was able to tolerate oral intake of food and drink for the first time in 2 months. However, percutaneous jejunal feeding was continued overnight to provide supplemental nutrition.

The patient's gastric electrical stimulation device was fitted 4 months after she started taking aprepitant. She did not experience nausea and vomiting for the whole 4-month period, and remained well after the gastric electrical stimulation device was fitted. As is standard procedure, the electrical stimulus of the device was increased 2 months after the device was fitted. The patient was slowly weaned off aprepitant over a few weeks, and the drug was stopped approximately 1 month after the device was fitted. In addition, within 2 months of the device being fitted, overnight supplemental feeding was stopped and the patient's percutaneous jejunal feeding tube was removed. The patient attends the outpatient clinic for check-ups every 3 months, and she had not vomited for a period of 6 months after jejunal feeding was stopped when she was last seen. Her self-reported quality of life and glycemic control (Table 1) have improved substantially since she was successfully treated.

Discussion of diagnosis

Normal gastric emptying is dependent on the coordinated contraction and relaxation of muscles within the stomach and duodenum. When contraction of the stomach and relaxation of the pylorus and duodenum become uncoordinated, gastric emptying times change. If these changes happen too quickly, dumping syndrome is the result; however, a delay in gastric emptying, known as gastroparesis, is much more common.

Gastroparesis is a chronic motility disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction.[1] The most common cause of gastroparesis is diabetes mellitus, which accounts for up to one-third of cases.[2] Other endocrine and metabolic causes of gastroparesis include thyroid dysfunction, parathyroid dysfunction and chronic renal insufficiency.[17]

Up to 12% of people with diabetes mellitus have symptoms suggestive of diabetic gastroparesis.[1] The disorder occurs as a result of autonomic neuropathy, and gastroparesis is often associated with other microvascular complication of diabetes mellitus, namely retinopathy, nephropathy and peripheral neuropathy.[3] In common with these conditions, gastroparesis occurs when the patient has experienced an extended period of suboptimal glycemic control, which suggests a common underlying mechanism. Most people who have gastroparesis have had poorly controlled diabetes for over 10 years.[1] The symptoms of the disorder are listed in Box 1. However, the symptoms of gastroparesis are nonspecific, nondiagnostic, and may overlap with those of functional dyspepsia.[4]

Treatment and management

The aims of the management of gastroparesis are to improve nutritional status, achieve tight glycemic control, correct electrolyte disturbances, and provide symptomatic relief. These aims are achieved by intensification of the insulin regime, dietary modification, and the use of prokinetic and antiemetic agents. However, despite these measures, some patients' gastroparesis remains refractory to treatment. In addition to the standard treatments, several different strategies have been tried to control the symptoms of severe gastroparesis. These approaches include the use of botulinum toxin to reduce muscular tone and thus allow the pylorus to open, or the use of somatostatin analogs such as octreotide to reduce the quantity of gastric secretions.[5,6]

Established antiemetic agents include corticosteroids, antihistamines, serotonin and dopamine-receptor antagonists. These agents have a twofold effect; they interrupt vagal afferent input into the centers in the brain that control vomiting, as well as antagonizing neurotransmitter receptors in the brainstem. Aprepitant belongs to a new class of antiemetics. The drug is licensed for only 3 days of use, to control chemotherapy-induced nausea and vomiting, for which indication it is highly effective and widely recommended.[7,8] Aprepitant is a neurokinin-receptor antagonist that works by blocking the G-protein-coupled neurokinin 1 receptor that is largely responsible for chemotherapy-induced vomiting. The predominant ligand for this receptor is substance P, a tachykinin found in the highest concentrations in those areas of the brain responsible for vomiting (that is, the area postrema and the nucleus tractus solitarius). Substance P is also involved in activating neurokinin 1 receptors in the small bowel, where it mediates blood flow, motility, and secretions.[9]

To our knowledge, no published study has assessed the use of aprepitant in the treatment of severe vomiting and ketoacidosis secondary to diabetic gastroparesis; however, this drug has no demonstrated effect on gut motility in healthy adults.[9] While the patient described did eventually have a gastric electrical stimulation device fitted, she had remained free of nausea and vomiting for 4 months on aprepitant before this procedure. Placebo responses are prominent in patients with symptomatic gastroparesis; nevertheless, as this patient had already failed to respond to numerous other treatments, a placebo response to aprepitant was considered an unlikely explanation for the relief of her symptoms.[10] Unfortunately, the patient did not have repeat gastric motility studies either while on aprepitant or after the gastric electrical stimulation device was fitted.

Data that indicate how long aprepitant can be used safely are lacking, as the phase II and phase III trials that assessed the efficacy of aprepitant as postchemotherapy antiemesis ran for a maximum of 5 days.[11,12] An unsuccessful trial that assessed the use of aprepitant in the treatment of major depression has, however, shown that the drug can be safely used for up to 8 weeks.[13] When used to prevent postchemotherapy vomiting, aprepitant has been reported to be associated with minor adverse effects including hiccups, fatigue, a rise in liver transaminase levels, constipation, headache and anorexia.

Box 1 | Symptoms of gastroparesis

Common

- Nausea
- Vomiting
- Early satiety
- Postprandial fullness

Less common

- Abdominal distention and pain
- Dyspepsia
- Weight loss
- Malnutrition
- Dehydration

The patient described was fitted with an electrical stimulation device, which enabled aprepitant to be stopped. The patient attends follow-up visits every 3 months at the outpatient clinic and continues to enjoy a good quality of life, with HbA_{1c} values less than 7% and no vomiting. Previous studies have shown the benefits of gastric electrical stimulation for gastroparesis caused by a variety of conditions, including diabetes mellitus.[14–16] These studies have shown substantial improvements in patients' symptoms and quality of life, associated with reductions in the use of antiemetic and promotility agents; hospital admission rates have also been reduced.[15]

Conclusions

This article describes the use of aprepitant for the treatment of severe vomiting and ketoacidosis secondary to diabetic gastroparesis. To our knowledge, this case represents the first report of the use of aprepitant for this indication and the first report of the drug being used for a prolonged period of time (4 months). Despite the caution necessary with conclusions based on a case study of one patient, we suggest that this agent may be a useful addition to the armamentarium currently available to treat diabetic gastroparesis, and that further work needs to be carried out to assess the efficacy and safety of aprepitant for this indication.

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