Symptomatic Management for Gastroparesis

Antiemetics, Analgesics, and Symptom Modulators

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KEYWORDS

• Antiemetic medications • Opiates • Tricyclic antidepressants
• Neuropathic pain modulators • Fundus relaxants

KEY POINTS

- A recent series reported reduced nausea and vomiting caused by open-label transdermal granisetron, a 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist, in patients with gastroparesis.
- Opiate analgesics are often taken for pain control; however, caution should be exercised because these agents worsen nausea and vomiting and further delay gastric emptying.
- As with antiemetics, support for use of neuromodulatory agents was restricted to individual cases; however, the largely negative findings from a multicenter, randomized, placebo-controlled trial of the tricyclic antidepressant nortriptyline in patients with idiopathic gastroparesis raise doubts about the effectiveness of neuromodulators in this condition.
- Postulated benefits of antiemetic and neuromodulatory therapies must be weighed against adverse outcomes during gastroparesis treatment, which recently have stressed neurologic and cardiac toxicities of these drugs.
- Placebo-controlled trials must be conducted to characterize the usefulness of these drug classes in managing gastroparesis symptoms.

INTRODUCTION

Gastroparesis presents with a range of symptoms referable to the upper gut including nausea, vomiting, early satiety, postprandial fullness, bloating, distention, and upper abdominal pain or discomfort. Although increased gastric retention is mandated for diagnosis, gastroparesis symptom severity correlates poorly with the degree of gastric

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emptying delay. In a large gastroparesis cohort comprising both diabetic and idiopathic patients from the multicenter National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Consortium, gastric retention measured at 2 and 4 hours showed no relation to overall or individual symptom intensities among 319 patients with delayed emptying and 106 with normal emptying.[1] Likewise in functional dyspepsia, emptying parameters show no correlation or are only weakly associated with fullness but not nausea, pain, or bloating. One investigation calculated that only 10% of the variance in dyspeptic symptoms relates to gastric emptying rates.[2] Other physiologic defects are proposed to contribute to symptom development. In studies in which combined gastric emptying and barostat testing was performed in dyspeptic patients, delayed gastric emptying correlated with nausea, vomiting, and postprandial fullness, whereas impaired gastric fundic accommodation associated with epigastric pain, early satiety, and weight loss.[3] In a different report, the prevalence of hypersensitivity to gastric distention was greatest (44%) among patients who rated abdominal pain as their predominant symptom.[4]

Because of the importance of delayed emptying in diagnosing gastroparesis, the main focus of treating this condition has been on prokinetic agents that promote gastric evacuation. However, in gastroparesis and functional dyspepsia, metoclopramide and domperidone reduce symptoms over the long term even when there is diminution of initial prokinetic effects with time.[5] Many benefits of these agents may therefore stem from antiemetic effects in the central nervous system. Furthermore, agents with only prokinetic treatments without central antiemetic effects (erythromycin, pyloric botulinum toxin) may be less effective than therapies with combined prokinetic and antiemetic action. One systematic review calculated benefits in only 43% of patients with gastroparesis receiving erythromycin.[6]

These investigations raise the possibility that pharmaceuticals with actions unrelated to gastrokinesis may be beneficial for some gastroparesis manifestations. Medications with only antiemetic mechanisms of action would theoretically be effective with prominent vomiting (and nausea). In contrast, central analgesics or drugs targeting other sensorimotor defects, such as enhanced sensitivity or impaired accommodation, might be useful for discomfort or pain.

MANAGEMENT GOALS

Given the disconnect between symptoms and gastric emptying, it is reasonable to propose that the primary goal of treating gastroparesis should focus on symptom reductions rather than stimulation of gastric emptying. Pharmacologic agents in diverse drug classes are available that decrease nausea, vomiting, and abdominal pain by acting as antiemetics, analgesics, or modulators of enteric neuronal function. These medications represent the sole forms of treatment of some individuals or may complement gastric prokinetic drugs in others. Little controlled investigation has been performed to define benefits of these agents in gastroparesis. Thus, use of these medications is based on pathophysiologic plausibility and expert opinion.

PHARMACOLOGIC STRATEGIES

The benefits of antiemetic, analgesic, and neuromodulatory medications in gastroparesis are unproved and may be modest in scope. Because of these limitations, decisions on any gastroparesis therapies rely on defining and assessing the severity of symptoms that represent the target of treatment. Introduction of validated surveys to measure numerical symptom intensity represents an advance in quantifying gastroparesis severity. The Gastroparesis Cardinal Symptom Index (GCSI) comprises