Future Directions in the Treatment of Gastroparesis

Pankaj Jay Pasricha, MD

KEYWORDS

• Gastroparesis • Gastric emptying • Prokinetics • Future treatment
• Functional dyspepsia

KEY POINTS

- The pathophysiology of gastroparesis is complex and requires more sophisticated approaches than current being used.
- Treatments aimed at symptomatic relief have to go beyond simply improving gastric emptying.
- Disease modifying therapies that address the root cause of inflammation and ICC loss are needed.

INTRODUCTION

Effective and rational drug therapy is based on the identification of key molecules or processes involved in the pathogenesis of the disorder being treated. This basis clearly does not apply in gastroparesis, in which neither the biological basis of the condition nor the pathophysiologic basis of its cardinal symptoms where is fully understood. At this point it is therefore important to acknowledge that all current therapy for gastroparesis is palliative as well as empirical. Many of these treatments have been covered elsewhere in this edition. Nevertheless, it is a useful exercise to briefly review the knowledge of existing targets before considering what the future might hold (**Box 1**). These targets can be classified into the following categories, recognizing that they are not mutually exclusive and pathophysiologic contributions from both may exist in different proportions in individual patients.

APPROACHES TO IMPROVE MOTILITY

The intramural structures responsible for motility that are potentially affected in gastroparesis are diverse and in close proximity to each other, representing an environment

Dr P.J. Pasricha is supported by a grant from the NIH (NIDDK 073983).
Department of Medicine, Johns Hopkins Center for Neurogastroenterology, Johns Hopkins School of Medicine, 720 Rutland Street, Ross 958, Baltimore, MD 21205, USA
E-mail address: ppasric1@jhmi.edu

Gastroenterol Clin N Am 44 (2015) 185–189
http://dx.doi.org/10.1016/j.gtc.2014.11.014 **gastro.theclinics.com**
0889-8553/15/$ – see front matter

Box 1
Potential therapeutic targets: pathophysiologic changes in patients with gastroparesis

- Impaired relaxation
- Fundic hypocontractility
- Antral hypomotility
- Pylorospasm
- Antropyloroduodenal incoordination
- Gastric arrhythmia
- Autonomic neuropathy
  - Vagal motor
  - Vagal sensory
  - Sympathetic
- Spinal sensory neuropathy

that is unlike any other in the body in its complexity. These structures include the enteric nervous system (neurons, glia, and interstitial cells of Cajal [ICC]), associated extrinsic nerves (vagal and spinal), and smooth muscle. The state of knowledge does not yet permit clinicians to identify which of these elements, if any, represents the primary or predominant site of disease. However, much of the current evidence points to a pivotal role for the ICC, which seem to be most consistently affected in both animal models and humans with gastroparesis.[1] Further, diabetic gastroparesis is associated with hypofunctional variations in anoctamin-1, a chloride channel that contributes to slow wave generation and proliferation of ICC.[2] In addition, loss of ICC correlates with delay in gastric emptying.[3] Thus, specific drugs that address ICC loss, dysfunction, or channelopathies/arrhythmias could potentially be useful in treating gastroparesis. In this context, perhaps gastroenterologists can learn from cardiologists about antiarrhythmics. In contrast with ICC, little attention has been paid to smooth muscle dysfunction in gastroparesis as a therapeutic target. Restoring impaired contractility and responsiveness to neurotransmitters in gastroparesis remains a desirable but unexplored objective.[4]

On the neural side, much attention has been paid to the role of loss of nitric oxide in the pathogenesis of gastroparesis, as reviewed by Farrugia elsewhere in this issue. Although pathologic studies in humans have revealed mixed evidence of loss of nitrinergic neurons,[1] loss of nitric oxide can occur even without loss of protein expression.[5] The enzyme neuronal nitric oxide synthase is a complex molecule and requires other cofactors, such as tetrahydrobiopterin (BH4), to maintain a functional dimeric state. BH4 deficiency, seen in diabetes, can therefore result in loss of nitric oxide production; conversely, BH4 supplementation in animal models can reverse gastroparesis.[6,7] In this regard, a pilot study of BH4 treatment in a small group of patients with diabetic gastroparesis has shown promising results.[8]

Similar concepts can be extended to augmenting cholinergic neural activity. Inhibition of acetylcholinesterase can be achieved by classic agents such as pyridostigmine as well as by several other drugs, such as the H2-receptor antagonist, nizatidine, and the dopaminergic antagonist, itopride. The efficacy of these drugs in gastroparesis remains unproved. Acotiamide is a newer acetylcholinesterase inhibitor that can accelerate gastric emptying and has been shown to be of benefit in patients with functional dyspepsia. Other drugs that can enhance cholinergic activity or act via other