CHAPTER SEVEN

The role of gastrointestinal hormones in the treatment of delayed gastric emptying in critically ill patients

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ABSTRACT

Background Delayed gastric emptying limits the administration of enteral nutrition, leading to malnutrition which is associated with higher mortality and morbidity. Currently available prokinetics have limitations in terms of sustained efficacy and side-effects.

Objective To summarize the mechanisms of action and to discuss the possible utility of gastrointestinal hormones to prevent or treat delayed gastric emptying in critically ill patients.

Methods We searched PubMed for articles discussing 'delayed gastric emptying', 'enteral nutrition', 'treatment', 'gastrointestinal hormones', 'prokinetic', 'agonist', 'antagonist', and 'critically ill patients'.

Results: Motilin and ghrelin receptor agonists initiate the migrating motor complex in the stomach which accelerates gastric emptying. Cholecystokinin, glucagon-like peptide-1 and peptide YY have an inhibiting effect on gastric emptying; therefore antagonizing these gastrointestinal hormones may have therapeutic potential. Other gastrointestinal hormones appear less promising.

Conclusions Manipulation of endogenous secretion, physiological replacement and administration of gastrointestinal hormones in pharmacological doses is likely to have therapeutic potential in the treatment of delayed gastric emptying. Future challenges in this field will include the search for candidates with improved selectivity and favourable kinetic properties.

INTRODUCTION

Early enteral feeding is recommended by the European Society for Parenteral and Enteral Nutrition guidelines for perioperative care, but it can only be achieved when patients' conditions allow it (1). Delayed gastric emptying (GE) occurs in approximately 50% of mechanically ventilated critically ill patients and limits the administration of enteral nutrition (EN) (2). The inability to administer EN in critically ill patients is associated with malnutrition, higher rates of infection and mortality, prolonged stay in the intensive care unit, and higher costs (3). EN is also preferred over parenteral nutrition, because it preserves the intestinal integrity and prevents mucosal atrophy and bacterial translocation (4). Therefore, improving GE and tolerance for EN in the critically ill is highly important.

Current guidelines indicate that EN intolerant patients should receive prokinetic drugs to enhance GE (5). Therapeutic interventions to restore the gastrointestinal (GI) function in critically ill patients are motilin receptor agonists (e.g. erythromycin and azithromycin), selective 5-HT_4 receptor agonists (e.g. prucalopride), and dopamine antagonists (e.g. metoclopramide and domperidone) (Table 1) (6). Metoclopramide is the most widely used prokinetic agent in critically ill patients with gastric feeding intolerance. However, this drug has only proven to be effective as a short term therapy, and side-effects, primarily involving the central nervous system, occur in 20% of the patients (5). Erythromycin, acting as a motilin agonist, is a potential substitute, but the prokinetic benefit of erythromycin is restricted by the possibility of producing antibiotic resistance, and concerns also exist about its cardiac toxicity. Domperidone has been frequently prescribed outside of the US, but its use is also limited due to side effects mainly based on its metabolism via CYP3A4. In critically ill patients with feed intolerance, combination therapy with erythromycin and metoclopramide is highly effective in improving the delivery of EN (7).

During the last few years more knowledge on the action of GI hormones has become available and synthetic agonists and antagonists have been developed, in particular in relation to appetite modulation and metabolic diseases. GI hormones are secreted throughout the GI tract; they individually and jointly modulate GE in several ways. The GI hormones, identified and characterised thus far, influence GE via different mechanisms of action. This raises the question whether GI hormones or their analogues might have therapeutic value in the treatment of delayed GE, or whether this is limited by their pleiotropic character. At the same time their mechanisms of action could deliver potential new therapeutic options for intervention, for example by developing more selective agonists or antagonists. The aim of the present review is to summarize the mechanisms of action and to discuss the possible utility of GI hormones to prevent or treat delayed GE in critically ill patients. Treatment of delayed GE may prevent malnutrition, which eventually leads to an improved recovery.

METHODS

A computerized literature search of PubMed was conducted using the following search terms: 'delayed gastric emptying', 'enteral nutrition', 'treatment', 'gastrointestinal hormones', 'prokinetic', 'agonist', 'antagonist', and 'critically ill patients'. Bibliographies of all selected articles and review articles that included information on GI hormones and GE were reviewed

TABLE 1. *Currently available prokinetics for critically ill patients.*

	Type of action	Application	Dose	Indication	Side effects	Other
Erythromycin(8, 9)	Macrolide antibiotic Motilin agonist	IV	3 mg/kg 3x / day	Gastric stasis	GI toxicity Cardiac toxicity Antibiotic resistance	Chronic administration should be avoided Tachyphylaxis
Azithromycin(10, 11)	Macrolide antibiotic Motilin agonist	Oral	500 mg 1x / day	Limited data for the treatment of delayed GE	Antibiotic resistance	Higher costs than erythromycin
Prucalopride(12, 13)	High affinity 5-HT_4 receptor agonist	Oral	2-4 mg 1x / day	Chronic constipation, Delayed gastric emptying	Headache, GI discomfort	Save cardiac profile
Metoclopramide(14-17)	Dopamine antagonist	IV	10-20 mg 3x / day	Gastroparesis not responding to other treatments	Central side effects Extrapyramidal side effects	Less well tolerated than 5HT4 receptor agonists
Domperidone(18-21)	Dopamine antagonist	Oral	10 mg 3-4x / day	Severe gastrointestinal disorders refractory to standard therapy	Cardiac arrhythmias	Not FDA approved in the US

for other relevant articles. This search strategy was done iteratively, until no new potential article citations were found on review of the reference lists of retrieved articles.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF GASTRIC EMPTYING IN CRITCALLY ILL PATIENTS

The process of GE is coordinated and achieved by a delicate interplay between autonomous nervous system (mainly via the vagal nerve), enteric nervous system and the activity of GI and pancreatic hormones. Processes interfering with any of these factors will therefore affect GE (22).

In general, a number of different factors influence the physiology of GE including the position of the body, the size and composition of a meal, its caloric content, viscosity and particle size. One of the most important factors determining GE in critically ill patients is the blood glucose level, which at elevated levels slows down antral action, inhibits motility in the stomach and delays GE (23). Acute changes in blood glucose concentration have a substantial but reversible effect on gastric motility. In critically ill patients, maintaining glucose levels at physiological levels is highly recommended, because normoglycemia reduces morbidity and mortality. Hyperinsulinaemia and insulin resistance are associated with delayed GE and accompanied by GI hormonal disturbance, hereby advocating the importance of normoglycaemia in the ICU (24). Vice versa, the control of GE is of major relevance to postprandial blood glucose concentrations.

In critically ill patients, proximal and distal gastric motility are abnormal, fundal waves are lower in frequency and amplitude and are less frequently followed by antral waves (25). Both the acute illness itself and therapeutic interventions affect GI motility. Chapman *et al.* studied the relationship between motility and GE in critically ill patients. It has been assumed that delayed GE observed in critically ill patients is due to antral hypomotility (26). Abdominal surgery, as well as hemodynamic instability, burns, electrolyte disorders, volume overload, and the need for vasoactive drugs, are major contributors to intestinal motility disturbances. All these factors may lead to an increased epithelial permeability and bacterial translocation. Early enteral feeding improves GI motility, decreases infectious complication, length of hospital stay and intensive care unit mortality (27). Delayed GE may prevent effective delivery of EN. Therefore, it is a major goal for intensive care specialists to treat delayed GE to allow early enteral feeding.

GI HORMONES STIMULATING GASTRIC EMPTYING

Motilin

Motilin was discovered in 1971, and was named after its biological capacity to stimulate the motility of digestive organs. It is synthesized by the endocrine M cells in the upper part of the duodenum in the fasted state (28). Motilin is considered to be an endocrine regulator of the motility pattern of fasting gut, influencing phase III contractions of the migrating motor complex (29).

In the early nineties, it was discovered that motilin and its receptor agonist erythromycin

consistently improved GE in gastroparesis with different etiologies (30). Erythromycin, a macrolide antibiotic, is highly successful in promoting feeding in critically ill patients with high gastric residual volumes (31). A high dose (3 mg/kg intravenously 3 times/day) may be used to 'restart' or 'kick-start' the stomach during acute episodes of gastric stasis in critically ill patients (8). There is also some evidence that lower dosages (1 mg/kg intravenously) might be as effective as high dosage in critically ill patients (32). Administration of erythromycin orally may also improve GE and symptoms for several weeks (33), but over longer periods is often associated with tachiphylaxis due to down regulation of the motilin receptor (34). Tachyphylaxis can be limited by co administration with metoclopramide, probably by the redundancies of these control mechanisms and the multiple actions of combination therapy (35). Prolonged administration (> 3 or 4 days) may also contribute to the spread of antibiotic drug resistance (36). A potential risk is sudden death due to long QT syndrome, particularly when used in patients taking medication that inhibits CYP3A4. Other motilin agonists, such as azithromycin and clarithromycin, have been used but have not been extensively studied. Considerable effort has been devoted to identifying a selective motilin receptor agonist with non-macrolide properties for clinical use. This has led to the discovery of ABT-229, mitemcinal (GM-611), and GSK962040, currently the most advanced options (Table 2) (37, 38). Clinical studies of ABT-229 showed acceleration of GE in healthy volunteers, but failed to demonstrate symptomatic relief in patients with functional dyspepsia and diabetic gastroparesis (39, 40). These disappointing outcomes may be attributed to tachypylaxis and reduction of the gastric fundus compliance and accommodation. The latest study demonstrated mitemcinal to be effective at improving diabetes-related gastroparesis symptoms (41). However, future clinical trials to evaluate their safety and long-term efficacy are required.

Ghrelin

Structurally, ghrelin resembles motilin. Ghrelin was first identified in 1999 and is believed to exert the majority of its actions through the receptor GHSR-1a (42). Gastric ghrelin is released just before food intake from the X/A-like endocrine cells located in the mucosal layer of the gastric fundus and secreted into the bloodstream (43). The main functions of ghrelin are to regulate the secretion of growth hormone, to enhance appetite and food intake, to enhance gastric motility and to accelerate GE (42).

Patients intolerant to gastric feeding generate less acylated ghrelin, which may contribute to gastric hypomotility (44). To date, preclinical and clinical evidence strongly supports the potential of ghrelin receptor agonists as a novel approach to treat delayed GE. Several clinical studies have shown that exogenous administration of ghrelin enhances GE (45-49). The potential therapeutic benefits of ghrelin and ghrelin receptor agonists in patients with delayed GE depend largely on the pharmacological profile of the ghrelin receptor agonist. The use of ghrelin is limited due to its short half-life and low bioavailability. An unfavorable effect of ghrelin receptor agonists is the simultaneous release of growth hormone, which can preclude long-term treatment regimes. Progress has been made through the development of synthetic non-peptide ghrelin receptor agonist like TZP-101, and TZP-102 (Table 2) (50, 51). TZP-101 is a macrocylic peptidomimetic given intravenously with potent binding affinity for the human ghrelin receptor (GHSR-1a). Oral TZP-102 has a substantially longer half-life thereby

TABLE 2. *GI hormone analogues with potential prokinetic properties for the treatment of delayed gastric emptying (dosages used in experimental setting).*

	Type of action	Application	Dose	Subjects/species	Effects	Other
ABT-229(39, 40)	Motilin receptor agonist	Oral	1.25-10 mg 2x / day for 4 weeks	Patients with diabetic gastroparesis	No relief	Tachyphylaxis may have caused lack of therapeutic benefit
Mitemcinal(41)	Motilin receptor agonist	Oral	10 mg 2x / day for 3 months	Patients with diabetic gastroparesis	Adequate relief of gastroparesis symptoms	Specific subgroups should be identified
GSK962040(37)	Motilin receptor agonist	-	-	Healthy dogs	Increases motility of the upper GI tract	Currently being evaluated in healthy volunteers
Ghrelin(45, 46, 48, 49)	Ghrelin	IV	20-40 μg	Patients with dyspepsia and/or gastroparesis	Accelerates GE	Induces growth hormone secretion
TZP-101(51)	Ghrelin receptor agonist	IV	80 μg/kg Single 30-min infusion for 4 days	Patients with diabetic gastroparesis	Improvement in loss of appetite and vomiting	Safety and efficacy study
TZP-102(50)	Ghrelin receptor agonist	Oral	10-40 mg 1x / day for 4 weeks	Patients with diabetic gastroparesis	Reduction of symptoms of gastroparesis	Safety and efficacy study
Dexloxiglumide(57)	Cholecystokinin receptor antagonist	Oral	200 mg 3x / day for 2 weeks	Patients with constipation-predominant IBS	Accelerates GE	Delays transit in the ascending colon
Exendin(9-39)(58)	GLP-1 receptor antagonist	IV	300 pmol/kg · min	Healthy volunteers	Accelerates GE	Interference with glucose metabolism

allowing more sustained action as a potent ghrelin receptor agonist, in a manner analogous to parenteral ghrelin agonist activity (52). These small molecules stimulate GE and food intake without altering growth hormone release in humans.

Glucose-dependent insulinotropic polypeptide

Glucose-dependent insulinotropic polypeptide (GIP), originally termed gastric inhibitory polypeptide, was discovered in the seventies of the last century (53). GIP is secreted by endocrine K-cells, the majority of which are located in the duodenum and proximal jejunum, but with smaller numbers also occurring throughout the entire small intestine. GIP is secreted in response to nutrient ingestion, especially glucose or fat. Glucagon-like peptide-1 and GIP are incretin hormones responsible for the majority of the insulin secreted after a meal (54).

GIP was once believed to slow gastric motility and to delay GE (55). However, results from a study with exogenous administration document that GIP does not inhibit GE, in contrast leading to a modest increase of gastric motility after intravenous infusion (56). Specifically with respect to different parts of the stomach, GIP at a low dose increases the emptying rate of the proximal part, whereas no difference is seen with a high dose. The distal part of the stomach empties slower with GIP at a low dose, while a high dose increases the emptying of the distal part (56). This effect may also be attributed to the incretin effect of GIP, which lowers blood glucose level leading to an enhanced GE. The unfavourable pharmacokinetic profile and the weak biological effects of native GIP limit its effectiveness for the treatment of delayed GE. Taken together, the complex dose-response relationship and the issue of selectivity appear to hamper the development of GIP analogues specifically for use in delayed GE.

HORMONES INHIBITING GASTRIC EMPTYING

Secretin

Secretin was the first intestinal hormone to be identified by Bayliss and Starling in 1902 (59). Secretin primarily acts to regulate the pH of the duodenal contents by controlling gastric acid secretion and buffering with bicarbonate, released from the pancreas after secretin stimulus (59). The major functions of secretin originating from the GI tract are to delay GE, stimulate fluid secretion from pancreas and liver, and optimize the digestion process (60). Exogenous secretin, in both pharmacological and physiological dose ranges, has been shown to inhibit gastric acid output and GE in humans, dogs, and rats (61). Jin *et al*. showed that neutralizing the circulating secretin in dogs significantly increased GE and acid output (62). In humans, pharmacological doses of secretin have been shown to reduce intragastric pressure and to induce contractions of the pylorus, thereby slowing GE (63). Although secretin has shown to play a role in regulating GE, this has not led to the development of successful drug candidates to treat delayed GE so far. Both the patent literature and clinical trials databases do not suggest any recent R&D activity for this indication.

Gastrin

Generally gastrin is not considered one of the main GE regulating hormones. However, there is

some evidence suggesting that gastrin might play a role in gastric relaxation and intragastric pressure (64). Effects of gastrin on human proximal gastric motor function have been proven to be directly related to acid secretion, where duodenal acidification elicits proximal gastric relaxation (65). Furthermore, He *et al*. discovered a relation between elevated gastrin levels and delayed GE in patients with functional dyspepsia (66). Further studies are needed to determine if gastrin plays a role in the pathophysiology of delayed GE, and if an antagonist can be a potential prokinetic.

Cholecystokinin

Cholecystokinin (CCK), a member of the gastrin family, was first identified in 1928 as a gut hormone (67). Intestinal I-cells release CCK in response to dietary carbohydrates, lipids and proteins through mechanisms involving G protein-coupled receptors (68). CCK binds to receptors on vagal afferents and to mucosal receptors in the stomach and small intestine, to potentiate gastric relaxation, stimulate mechanoreceptors sensitive to gastric stretch, and slow GE (69). Interaction with receptors in satiation centers in the hypothalamus and hindbrain also reduces appetite (70, 71).

The main actions of CCK include contraction of the gallbladder, relaxation of the sphincter of Oddi, stimulation of somatostatin release and stimulation of pancreatic growth and enzyme release via the CCK-1 receptor (72). In healthy human subjects, exogenous administration of CCK is associated with relaxation of the proximal stomach, inhibition of antral motor activity, slowing of GE and a reduction in energy intake (73, 74). CCK antagonists have been shown to increase GE and energy intake in humans (75). Currently, dexloxiglumide, a competitive CCK-1 receptor agonist, is being investigated for the treatment of GE disorder (Table 2) (57, 76). In critically ill patients, plasma CCK levels are elevated by approximately two-fold, compared with healthy subject (74). Nutritional deprivation is a possible cause since inadequate nutritional support is common in critically ill patients. Within the intensive care unit population, patients who have feed intolerance have substantially higher plasma CCK levels, than those without intolerance (74). Present observations strengthen the rationale for the potential use of CCK antagonists in the management of feed intolerance in critically ill patients. The purposes of, as well as the mechanisms underlying the elevated CCK levels in critical illness remain to be clarified.

Somatostatin

Somatostatin is produced by paracrine and endocrine-like D-cells and by enteric nerves of the gut and endocrine pancreas (77). Somatostatin's biological actions are mediated through interaction with five somatostatin receptor (SST) subtypes, SST1–5 (78). The function of somatostatin is mainly antisecretory; it inhibits release of gastrin, CCK, secretin, motilin, GIP and OXM (Figure 1). Additionally, somatostatin inhibits release of insulin, glucagon and release of exocrine pancreatic secretions (77). Furthermore, it inhibits gastric acid production, reduces intestinal motility, decreases splanchnic blood flow and prolongs GE (79).

Consistent reports established that somatostatin reduces ghrelin levels as demonstrated in rats as well as in humans (80). Stengel *et al*. showed that a SST2 antagonist prevented

the abdominal surgery-induced decreased circulating ghrelin but not the delayed GE (81). Delayed GE could, however, in experimental settings in mice and rats, be influenced by central administration of $CRF_{1/2}$ receptor antagonists or somatostatin agonist (ODT8-SST) (82). Based on this, it can be concluded that there might be a negative interaction between somatostatin and CRF, more at a central level than a peripheral level. Contradictory, the somatostatin analogue octreotide has been used in clinical condition (eg, intestinal pseudo-obstruction) to promote motility (83). These conflicting findings indicate that too little is known yet about the effects on GE for further lead optimisation.

Oxyntomodulin

Oxyntomodulin (OXM) is, similar to glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2), formed out of preproglucagon in the intestine and central nerve system (CNS) (84). OXM exerts its effect via the GLP-receptor. A separate OXM receptor has not yet been identified (85).

OXM inhibits GE and gastric acid secretion in rodents and humans (84, 86, 87). Schjoldager *et al*. demonstrated this by intravenous infusion of synthetic OXM in healthy human subjects, which significantly decreased GE and postprandial gastroduodenal motility (84). Controversially, Maida *et al*. came with an unexpected finding; they observed that OXM, even at high doses, failed to inhibit GE *in vivo* (88). Taken together, these divergent findings suggest that the actions of OXM are complex and may reflect species-specific interactions with one or more incompletely characterized OXM receptors (88).

Glucagon-like peptide 1

GLP-1 was discovered in the early eighties of the 20st century and together with GIP fulfils the definition of a so-called incretin-hormone (89). GLP-1 is mainly released from the L cells located in the distal ileum in proportion to the calories ingested. GLP-1 reduces fasting and postprandial glycaemia, in part by reducing glucagon secretion (90). Furthermore, GLP-1 inhibits gastric acid secretion and pancreatic enzyme output (91, 92).

Exogenous GLP-1 infusion has been shown to normalize blood glucose concentrations and the overall glycaemic response, in both healthy volunteers and patients with type 2 diabetes (58). This occurs as a result of stimulation of insulin secretion, suppression of glucagon release and slowing GE (93, 94). Exogenous GLP-1 slows GE substantially, and this may be the dominant mechanism by which GLP-1 reduces postprandial glycaemic excursions. The impact of exogenous GLP-1 administration on glycaemic control has also been studied in critically ill patients on small intestinal feeding. Deane *et al.* showed that exogenous GLP-1 infusion markedly attenuates the glycaemic response to EN in critically ill patients (95). This effect cannot be ascribed to the inhibitory effect of GLP-1 on GE, because patients were fed in the small intestine. Additional studies are required to elucidate the mechanism underlying the effect of GLP-1. It is thought that the magnitude of glucose lowering by GLP-1 is likely to be even greater during gastric, rather than during small intestinal feeding.

The powerful inhibitory effect of GLP-1 on GE makes GLP-1 antagonists promising in the treatment of delayed GE. Exendin(9-39) amide, a truncated form of the GLP-1 agonist exendin

4, binds to the GLP-1 receptor without activating this, hereby functioning as a GLP-1 receptor antagonist. Exendin(9-39) accelerated GE and increased the overall glycemic response in healthy volunteers (58). However, antagonizing GLP-1 in critically ill patients may be far from favourable, because it might interfere too much with the glucose metabolism. The development of GLP-1 antagonists specifically stimulating GE is still challenging.

Glucagon-like peptide 2

GLP-2 was first identified in 1996 (96). In intestinal endocrine L cells located in the distal intestine, posttranslational cleavage of the proglucagon precursor molecule liberates the glucagon-like peptides (GLP-2 and GLP-1). Nutrient intake is the primary stimulus for GLP-2 secretion into circulation (97). GLP-2 receptors, members of the G protein-coupled receptor family, have been detected in the GI tract as well as in the hypothalamus, brainstem and lung (98).

GLP-2 administration decreases gastric acid secretion and inhibits antral GE (99-101). In the rat small bowel, GLP-1 and GLP-2 seem to act together to inhibit myoelectric activity, although only in the fasted rat, not when fed (100). Moreover, both GLP-1 and GLP-2 inhibit antral emptying in man, although GLP-1 is a more potent inhibitor (102). A large number of studies have demonstrated that exogenously administered GLP-2 is trophic for the small intestine and, to a lesser extent, the colon (103, 104). Patients with short bowel syndrome who received exogenous GLP-2 subcutaneously exhibited increased nutrient absorption, delayed GE, and increased body weight (105). Reducing GLP-2 may improve GE; nevertheless it is not a preferred target, since this might cause intestinal atrophy.

Pancreatic polypeptide

Pancreatic polypeptide (PP) exerts a variety of regulatory actions, including regulation of food intake, inhibition of pancreatic exocrine secretion, contraction of the gallbladder, stimulation of glucocorticoid secretion, modulation of gastric acid secretion and GE (106, 107).

Peripheral administration of PP in mice and humans reduces food intake and delays GE (108, 109). On the other hand, central administration of PP elicits food intake and GE via neuropeptide Y receptors (109). The latter effect was abolished after vagotomy (110). It is not clear whether reduction in food intake is directly due to elevated PP levels or indirectly due to delaying GE (108, 111).

Peptide YY

In 1982 Peptide tyrosine-tyrosine (PYY) was first isolated from porcine intestine (112). PYY is present throughout the GI tract: in low concentrations in the small intestine, in higher concentrations in the colon, reaching maximal concentrations in the rectum. Additionally, PYY is also present in the central nervous system (113). PYY is released from L cells of the distal gut and binding sites have been identified in numerous brain regions (114).

Most effects of PYY are inhibitory, such as the inhibition of gastric, pancreatic, and intestinal secretion or reduction of GI motility, gallbladder emptying and GE (115, 116). Pharmacological

doses of PYY slow GE and small-intestinal transit (117). In an observational study of seven critically ill patients, Nematy *et al.* reported that fasting PYY concentrations increased approximately threefold in the acute phase of critical illness, when compared with healthy individuals (118). Moreover, fasting plasma PYY concentrations in 39 critically ill patients were increased substantially in those that had delayed GE (119). This suggests that there is a potential role for PYY antagonists in the treatment of delayed GE. However, there appear to be no PYY antagonists available for clinical use.

DISCUSSION

Delayed GE limits the administration of EN, leading to malnutrition which is associated with higher mortality and morbidity. Currently available prokinetic drugs, including metoclopramide, erythromycin, prucalopride and domperidone, carry limitations in terms of sustained efficacy and side-effects (69). The clinical effectiveness of GI hormones is notoriously limited in terms of GE. With this review we aimed to identify possible pharmacological interventions targeting gut hormones receptors in order to improve delayed gastric emptying, a common problem in critically ill patients. We conclude that motilin receptor agonist with non-macrolide properties (ABT-229, and mitemcinal GM-611) are currently the most advanced options. Progress has been made through the development of synthetic non-peptide ghrelin receptor agonist (TZP-101, and TZP-102), competitive CCK-1 receptor agonist (dexloxiglumide), and GLP-1 receptor antagonist (exendin9-39).

One of the difficulties in properly investigating the effect of GI hormonal interference with delayed GE in critically ill patients is the multi-factorial setting. Glucose control has a major impact on GE, thereby determining the influx of EN into the duodenum, which promotes or restricts GI hormonal response. Since decreased insulin sensitivity is related to delayed GE, the authors are of the opinion that an integrated protocol which focuses on the prevention insulin resistance may be effective in the prevention of delayed GE. Enhanced recovery of patients after surgery (ERAS) has become an important focus of perioperative management. The ERAS protocol recommends metabolic control, starting preoperatively with a short period of preoperative fasting and carbohydrate loading up to two hours before surgery. Carbohydrate loading reduces postoperative insulin resistance, and may therefore be effective in the prevention of delayed GE (120).

Overall, it can be concluded that the physiology, pathophysiology and therapeutic potential of GI hormones is still not fully understood, which currently limits their development as drug targets for use in delayed GE. Although drugs derived from GI hormones may not have shown their full potential it is clear that these hormones are modulators of powerful regulatory mechanisms of gastric motility and emptying. Future challenges in this field will include the search for candidates with improved selectivity and favourable kinetic properties.

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