Gastric Emptying in the Critically Ill Patient

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ABSTRACT

Objective: To review the pathophysiology of gastroparesis and present a practical approach to the management of this disorder in the critically ill patient.

Data sources: Articles and published abstracts on the mechanisms and management gastroparesis relevant to the critically ill patient.

Summary of review: The importance of early enteral nutrition in the critically ill patient has been recognised for many years. However, while nasogastric tubes are easy to insert, gastric dysmotility is common, and often hinders the introduction of effective enteral nutrition. Small bowel motility problems are uncommon in the intensive care patient, and direct instillation of nutrients into the jejunum will allow enteral nutrition to begin without delay. However compared with gastric tubes, jejunal tubes are often difficult to insert, often requiring endoscopic or surgical techniques.

The cause of gastric dysmotility is multifactorial. Treatment of underlying sepsis, pain, hypotension, dehydration and hyperglycaemia should occur, and opiates and dopamine should be avoided before commencing prokinetic agents. The patient’s head should remain elevated, and oral or nasogastric cisapride (10 mg 6-hourly) administered. If this is not effective then erythromycin (e.g. 250 mg i.v. 8-hourly) may be included.

Conclusions: Gastric dysmotility is common in the critically ill patient. However, treatment of the underlying conditions leading to gastroparesis and the introduction of prokinetic agents will allow the majority of patients to be successfully fed enteraly. (Critical Care and Resuscitation 1999; 1: 39-44)

Key words: Gastroparesis, intensive care, prokinetic agents, enteral feeding

Introduction

Recent research on the physiology, physics and pharmacology of gastric emptying reveals an increasingly complex picture. While much of the advance in knowledge of the basic physiology and pharmacology of gastric emptying can be attributed to the work of Australian researchers, to date there has been little direct application of the monitoring technology used in these studies to evaluate gastric emptying in intensive care patients.

The recognition of the importance of early enteral feeding, together with the availability of advanced monitoring technology may well herald an interesting and productive phase in nutritional care of the intensive care patient.

Physiology of gastric emptying

Ingested food must be stored, mixed with secretions, ground into small particles and delivered at a controlled rate to the duodenum to allow efficient digestion and absorption. Gastric contractions can result in a grinding or mixing of gastric content, and retropulsive movement or forward expulsion of content into the duodenum depending both on the force and co-ordination of a gastric pressure wave.

Pyloric resistance to gastric emptying is controlled by a feedback mechanism from the duodenum and small intestine, and is a component of the normal system which limits the rate at which nutrients leave the stomach. Expulsion of gastric content appears to occur most effectively in the face of vigorous antral contractions, starting high in the antrum, which are associated with late closure of the pylorus. This pattern appears to predominate during fasting when non-digestible residues are expelled from the stomach (so called phase III contractions).
Feedback from small intestinal receptors (stimulated by the luminal contents) predominates in the control of emptying of nutrient. For example, hyperosmotic liquids empty from the stomach more slowly than non-nutrient liquids. Whether such mediation from the small intestine is a significant factor in the pathogenesis of gastroparesis occurring in critically ill patients remains unresolved.

Pathophysiology of gastroparesis

The pathophysiology of gastroparesis remains elusive but appears to be multifactorial. While it is generally assumed that gastric hypomobility is the major cause of delayed gastric emptying, it now appears that abnormally slow stomach emptying may also result from defective sequencing (i.e. co-ordination) of contractions across the antpyloric region. This results in failure of passage of the pressure wave, with the associated failure of movement of gastric content from the stomach into the duodenum. Relaxation of the pylorus at the appropriate time, as the wave passes from the antrum to the duodenum, is also important for successful gastric emptying, and a disturbance in pyloric relaxation might also result in delayed gastric emptying.

Another hypothesis, relating to post-laparotomy gastroparesis, involves an abdominal reflex; the afferent limb of which consists of unmyelinated visceral nerves and the efferent limb involves sympathetic neurones. Strong nociceptive stimuli from the abdominal cavity, in response to bowel manipulation or peritonitis, result in a profound reduction in the vagal excitatory influence on gastric motility. This hypothesis is supported by the observation that capsaiacin (which affects small unmyelinated nerve fibres) applied to the coeliac/mesenteric ganglia reduces post-operative gastric ileus in rats, whereas perivagal capsaiacin has no effect.

Non-adrenergic, non-cholinergic (NANC) intrinsic inhibitory innervation is also considered important in gastroparesis, inhibiting peristalsis and increasing sphincter tone. Agents that are likely to cause chemical mediation of this NANC system include vasoactive intestinal peptide (VIP) and nitric oxide (NO). The calcitonin gene-related peptide (CGRP) antagonist can also reverse, although not entirely, the inhibition of gastric emptying seen after gastric surgery in rats.

Interleukin-1β levels increase in response to inflammation and stress, and have been demonstrated to decrease gastric emptying. For example, in rats, following abdominal surgery, prolongation of gastric emptying is reduced by approximately 30% by treatment with intravenous anti IL-1β.

Finally, functional alterations of the sympathetic and parasympathetic systems have always been important in the pathogenesis of gut hypomobility. Muscarinic receptors are stimulatory, and anti-cholinergic drugs such as atropine delay gastric emptying. Both adrenaline and dopamine have been shown to inhibit the gastric pressure response to physostigmine in isolated guinea pig stomachs. Isoprenaline is significantly less potent, suggesting that dopaminergic and α-adrenergic effects are more important. Infusions of dopamine from 3 to 5 μg/kg/min have been reported to delay gastric emptying in both animals and in man.

Treatment of gastroparesis

Pharmacological manipulation of delayed gastric emptying continues to be hampered by an inadequate understanding of underlying pathophysiology in various clinical conditions occurring in patients in the intensive care unit.

Opiates inhibit gastrointestinal transit primarily as a result of a direct action on gut opiate receptors. Epidural morphine has also been demonstrated to reduce the rate of gastric emptying in healthy fasting volunteers. In contrast, thoracic epidural analgesia with bupivacaine has no influence on gastric emptying.

Cholinomimetic drugs such as a bethanicol have not proved clinically effective, as they result in an increase in gastric contractions without improving the production of a co-ordinated pressure wave.

There is a significant amount of dopamine present in bowel wall, where it has been shown to cause potent inhibitory effects on motility. The dopamine type 1 receptor (DA1 receptor) is located mainly on post-junctional effector cells, while the DA2 receptor is found on both the pre and the post-junctional effector cell. Consequently gut hypomobility may be stimulated through the use of dopamine antagonists. Metoclopramide blocks both DA1 and DA2 receptors while domperidone blocks only the DA2 receptor. However the prokinetic activity of metoclopramide appears to be mainly mediated by stimulation of intrinsic cholinergic nerves by activation of the 5-hydroxytryptamine type 4 receptor (5-HT4 receptor). 5-HT3 antagonism appears to be associated with antiemetic properties rather than prokinetic actions, and drugs with specific 5-HT3 antagonism, such as ondansetron, exhibit minimal prokinetic effect.

Enhanced co-ordination appears a particular feature of cisapride use. Cisapride is a benzamide which accelerates gastric emptying in gastroparesis caused by various mechanisms, an effect which appears to be sustained with repeated dosing. The actions of cisapride include stimulation of the 5-HT3 receptor and direct increase of the release of acetylcholine from post-ganglionic nerve endings of the myenteric plexus. Dopamine antagonism does not appear to be a feature of...
Cisapride activity. Cisapride results in improved temporal association of antro-pyloroduodenal pressure waves which resemble the pattern seen during fasting. Such waves are associated with bulk passage of contents out of the stomach.

Increased acetylcholine release at the gastric neuromuscular junctions appears to be a common final pathway for all of these mechanisms resulting in increased antral contraction and improved co-ordination (Figure 1).

Erythromycin has a motilin-like activity and has been shown to suppress both phasic and tonic pyloric pressure waves while stimulating antral and duodenal pressure waves in human volunteers in whom gastric emptying was suppressed by an intraduodenal lipid infusion. Following erythromycin, antral pressure waves are of unusually high (‘giant’) amplitude. However administration of erythromycin was not found to shorten the period of postoperative ileus in a prospective, double-blind, placebo-controlled study involving seventy-seven patients following laparotomy (250 mg erythromycin given intravenously every 8 h for nine doses upon admission to the recovery room or placebo). The time (in hours) for the first passage of flatus, first liquid meal, first bowel movement, and total length of hospital stay were similar in both groups. Derivatives of erythromycin have now been developed which are devoid of antibiotic activity but have strong prokinetic activity. These have been found to strongly increase the gastric emptying rate in healthy volunteers and may prove to be more effective.

Cholecystokinin results in delay of gastric emptying due to a reduction in intragastric pressure associated with relaxation of the proximal stomach together with increased contraction of the antropyloric region. Cholecystokinin (CCK) antagonists such as devazepide (specific for CCK-A receptors) have been demonstrated to enhance gastric emptying of feeds containing fat and protein (which release endogenous CCK from the duodenum) but have no effect on the emptying of non-nutrient fluids.

Hyperactivity of adrenergic pathways leads to stimulation of α2-adrenoceptors on intrinsic cholinergic neurones, with a reduction in acetylcholine release which in turn contributes to gastrointestinal hypomotility. Experimental post-operative ileus is improved markedly by sympathetic blockade.

The role of nitric oxide (NO) mechanisms in the control of pyloric motility has been evaluated, using the NO donor, glyceryl trinitrate (GTN) sublingually. The tonic pyloric motor response to triglyceride, and both the number and the phasic isolated pyloric pressure waves were reduced by GTN. These observations suggest that NO mechanisms are involved in the regulation of pyloric motor activity in humans.

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The non-steroidal anti-inflammatory drug, ketorolac, has been demonstrated to prevent post-operative ileus in a rodent model but data on the effect of non-steroidal anti-inflammatory drugs (NSAIDs) and gastric emptying in critically ill patients is yet to be published. However, the gastrointestinal and renal complications of NSAIDs may complicate this line of investigation. Posture is also important in the movement of gastrointestinal contents. Gastric emptying of non-nutrient liquid has been shown to be significantly faster in the sitting position than in the left lateral position.

Hyperglycaemia is well recognised to slow gastric emptying in both insulin dependent diabetics and normal subjects. The response to hyperglycaemia includes a reduction in the number of antral pressure waves together with increased pyloric tone, similar to the patterns in response to other stimuli which are associated with reduced gastric emptying. Vagal cholinergic activity is reduced during hyperglycaemia suggesting a central site of action.

Figure 1. The mechanisms of domperidone, metoclopramide and cisapride causing an increase in acetylcholine release and prokinetic effect.
Spinal anaesthesia or adrenergic blockade has been shown to eliminate the gastric inhibitory response to gastric irritation.26

Specific data in intensive care patients

In a prospective study of gastric emptying in 72 mechanically ventilated patients, who were expected to remain in the Intensive Care Unit (ICU) for more than 48 hours; the variables that were associated with delayed gastric emptying included age, sex and use of opioids for analgesia and sedation.27

In twenty-seven ICU patients, reviewed within 3 days of their ICU admission, a statistically significant slowing of gastric emptying was observed in patients who received dopamine (p < 0.005). This study also demonstrated the wide range of gastric emptying rates in critically ill patients.28

The effect of adding oral cisapride to an enteral feeding regime has been investigated in a randomized, controlled study by Spapen et al.29 They studied twenty-one patients, who required prolonged mechanical ventilation and enteral feeding. Patients were randomized to receive either no cisapride or 10 mg of cisapride four times daily. Gastric emptying was evaluated by daily measurements of gastric residue and by bedside scintigraphy (on days 5 - 7). Normal values for gastric clearance were obtained in ten healthy volunteers lying supine. The mean time at which 50% of the technetium m-labeled test meal was eliminated from the stomach (T1/2) in the control group was 31 ± 15 minutes. In the ten critically ill patients (i.e. the enteral nutrition group), gastric emptying was markedly delayed (T1/2) 78 ± 40 minutes (p < 0.002 compared with the control group). In contrast, patients treated with cisapride showed an accelerated gastric emptying (T1/2) 18 ± 7 mins; (p > 0.05 compared with controls; and p < 0.005 compared with enteral nutrition group). The mean gastric residue over a 1-wk period was also significantly lower in the cisapride group than in the enteral nutrition group (17.7 ± 8.9 vs. 94.5 ± 33.4 ml; p < .001). The data strongly supports the use of oral cisapride to enhance gastric emptying in critically ill, sedated, and mechanically ventilated patients.

Rectal cisapride has been evaluated in a separate prospective, randomized, controlled study involving twenty-seven intensive care patients who were not receiving enteral nutrition. These patients received either placebo or rectal cisapride, 60 mg initially followed by two doses of 30 mg at 8-hourly intervals. The large variation in gastric emptying from one day to the next in these patients prevented any statistically significant effect of cisapride being observed.30

Erythromycin (200 mg i.v. over 30 mins) has also been evaluated in a crossover, double-blind, randomized, placebo-controlled study in ten mechanically ventilated, haemodynamically stable patients. Pressure changes in the gastric antrum were recorded by means of a multi-lumen manometric tube (perfused catheter technique) over a period of 300 minutes. Gastric emptying was simultaneously assessed by paracetamol absorption. Compared with placebo, the mean number of contractions (104 + 34 vs. 5 + 8; p = 0.003), the mean amplitude of contractions (52 ± 16 vs. 20 ± 17 mmHg; p = 0.005), and the Motility Index (13.06 ± 0.95 vs. 4.45 ± 3.54; p = 0.004) were significantly increased during the first hour after erythromycin infusion compared with placebo.31

Intolerance to nasogastric feeding is commonly observed after head injury, and gastric emptying has been demonstrated to be delayed twofold (days 3 to 5 following injury) compared with controls (p < .001).32 In 21 brain injured patients requiring sedation, mechanical ventilation and intracranial pressure monitoring, the effect of type of sedative used on gastric emptying has been investigated. Patient’s received either morphine (1-8 mg/h) plus midazolam, or propofol infusions. There were no differences in the measurement of gastric emptying between either infusion. In patients with an intracranial pressure of greater than 20 mmHg the gastric emptying was slower, regardless of sedation.31

Conclusion

Where there is troublesome delay of gastric emptying in the intensive care patient, a number of non-pharmacological and pharmacological approaches may be used, these include:

- Minimizing or avoiding opiates
- Considering epidural local anaesthetic blockade
- Considering discontinuing dopamine infusion
- Sitting the patient up
- Normalizing glucose levels (if hyperglycaemia is present)
- Oral or nasogastric cisapride (e.g. 10 mg 6-hourly)
- Erythromycin (e.g. 250 mg iv 8-hourly)
- Other (e.g. glyceryl trinitrate)

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