Prokinetic drugs in the intensive care unit: reviewing the evidence

K Grant, R Thomas

Delay in gastric emptying is common in the critically ill, and can lead to abdominal distension, diarrhoea or constipation, and vomiting, and may contribute to increased incidence of reflux and nosocomial infection. Prokinetic agents increase the rate of luminal transit as well as the force of contraction, and are commonly used in the intensive care unit. This article summarises the current state of knowledge about the use of prokinetics and explores potential agents which might be used in the future in this group of patients.

Keywords: *gastrointestinal motility; prokinetics; intensive care; erythromycin; metoclopramide*

Introduction

Malnutrition on the intensive care unit is associated with difficulty weaning, longer in-patient stays and increased mortality. Critically ill patients require nutritional support to improve their clinical outcome, and early enteral feeding has shown beneficial effects.[1] Enteral nutrition causes increased blood flow to the mucosa, which decreases stress ulceration and enhances gut immune function.[2] It is less costly and is associated with fewer septic complications than parenteral nutrition.[3]

Problems commonly associated with enteral nutrition are related to high gastric residual volumes, which lead to abdominal distension, diarrhoea or constipation, and vomiting.[4] Reflux is recognised as a common cause of nosocomial infection.

In addition, delay in gastric emptying is common in the critically ill for a variety of reasons,[5] and around half of intensive care patients are affected.[6] Prokinetic agents increase the rate of luminal transit as well as the force of contraction, and are used commonly in the intensive care unit.

In a 2002 review of the literature, Booth *et al* examined the existing evidence base for the use of prokinetics in the critically ill.[6] There have been several studies published since that review, and this article aims to summarise both Booth's findings and more recent research.

Methods

A computerised bibliographic search of MEDLINE was performed, similar to that described by Booth *et al*. 'Critical care', 'intensive care' or 'critically ill' was combined with 'prokinetic', 'gastric motility', and 'metoclopramide', 'erythromycin', or 'cisapride,' for the period 1980 to 2008. Studies were selected if they involved critically ill adult patients and investigated the effect of prokinetic agents on gastrointestinal motility; studies involving nasogastric tube placement were excluded. Any other papers fulfilling the selection criteria featured in review article references, but not identified on computerised search, were also included.

Cisapride

Cisapride is a 5-HT_4 agonist which was previously a popular choice for prokinesis in the intensive care unit. However, it was withdrawn in the UK in 2000 due to concerns about associated cardiac dysrhythmias.[5]

Metoclopramide

Metoclopramide is a dopaminergic D2 receptor antagonist with mixed 5-HT_3 antagonist and 5-HT_4 agonist effects. It is a centrally acting antiemetic, which increases gastric motility via muscarinic receptors. This agent is contraindicated in those with head injuries due to concerns about increasing intracranial pressure.[7]

Booth *et al* examined five studies involving metoclopramide in their meta-analysis. The majority of studies used surrogate markers such as gastric residual volume or paracetamol absorption to assess gastric motility. However, Yavagal *et al* studied a more clinically related topic, the development of nosocomial pneumonias. The authors noted that the use of metoclopramide, 10 mg three times daily via a nasogastric tube, delayed the onset of pneumonia, but had no significant effect on mortality or frequency of infection.[8]

Metoclopramide *vs* placebo

Booth *et al* described two studies that examined the effects of intravenous metoclopramide versus saline on gastric emptying as measured by paracetamol absorption and residual gastric volumes.[9,10] In the first study, ten critically ill patients received 20 mg metoclopramide intravenously. In the second study, researchers examined the effect of 10 mg doses given intravenously to 16 intensive care patients. Both studies concluded that metoclopramide administration resulted in a significant increase in paracetamol absorption, and hence gastric emptying.

Metoclopramide *vs* cisapride

Maclaren *et al* compared the efficacy of metoclopramide and cisapride.[11] In this study, 14 intensive care patients were randomly allocated to receive either enteral cisapride 10 mg or metoclopramide 10 mg every six hours for a total of seven doses. There were statistically significant improvements in gastric motility, resulting in improved tolerance to intragastric enteral nutrition. Gastric residual volume was lower in those given metoclopramide.

Erythromycin

Erythromycin is a macrolide antibiotic derived from *Streptomyces*. In addition to its antimicrobial activity, erythromycin is a motilin receptor agonist that stimulates contractions in the gallbladder and gut, and triggers a phase of migrating myoelectric complexes.[5] This prokinetic quality has resulted in its use in a variety of situations, including post-vagotomy, gastroparesis, chronic intestinal pseudo-obstruction and in insulin-dependent diabetes mellitus.[12] There are some reports of cardiac dysrhythmias associated with the use of intravenous erythromycin.[6]

Erythromycin *vs* placebo

Booth *et al* appraised two studies that investigated the effect of erythromycin compared to a placebo on gastric motility. The first study[13] used antral manometry and acetaminophen (paracetamol) absorption to examine the effect of 200 mg of intravenous erythromycin in 10 ventilated intensive care patients. They concluded that significant increases in both antral contractions and drug absorption were seen with this drug compared with placebo. The second study[14] involved 20 intensive care patients. The results of this study also showed a statistically significant increase in gastric emptying as measured by gastric residual volume, with 200 mg intravenous erythromycin compared to placebo. After an hour, 90% of erythromycin-treated patients were tolerant to nasogastric feeding, compared with 50% of those given the placebo.

Since the publication of the meta-analysis, there have been a number of studies investigating the role of erythromycin as a prokinetic. One of the larger studies involved 40 critically ill patients and investigated the usefulness of erythromycin in early enteral feeding.[15] The authors found that addition of 250 mg intravenous erythromycin four times daily, when compared with placebo, resulted in lower gastric residual volumes up to three days after the instigation of nasogastric feeding. The number of patients that tolerated enteral nutrition was significantly higher with prokinetic treatment than with placebo (14/20 and 7/20, respectively).

The effects of erythromycin versus those of placebo were examined in 68 critically injured patients.[16] Those who had failed feeding within the first 48 hours, with gastric residual volume more than 150 mL, were randomly allocated to receive either placebo or erythromycin. Although erythromycin was shown to significantly improve the proportion of amount of successful feeds (58% with erythromycin compared with 44% with placebo, p=0.001), there was no statistically significant improvement in the actual number of patients who became successful feeders.

Metoclopramide *vs* erythromycin *vs* cisapride

The effects of sequential single doses of prokinetics on gastric residual volume and paracetamol absorption were studied in 10 intensive care patients who were intolerant of enteral nutrition.[17] The researchers compared twice-daily nasogastric doses of 200 mg erythromycin, 10 mg metoclopramide, and 10 mg cisapride. Their results suggested that metoclopramide and cisapride were more effective than erythromycin in improving impaired gastric motility when used in twice-daily single doses over 48 hours.

Erythromycin dosing

A paucity of studies with adequately sized study populations means that there is little firm evidence to inform the optimal dosing regimes of erythromycin. A study in 2005[18] used ^{13}C octanoic acid breath testing to assess the effect of either 70 mg or 200 mg erythromycin intravenously versus placebo on gastric emptying in 35 critically ill patients. The researchers found that both doses of erythromycin significantly increased gastric emptying, with no significant difference between the two doses given. This suggests that doses lower than those traditionally used in the intensive care units may be equally efficacious. More research on dosing regimes for prokinesis is required. There is a suggestion that the prokinetic effect of erythromycin may only occur within a narrow dose range.[19]

Combination therapy

Prokinetics are often used in combination if feeding intolerance does not improve with a single agent. Nguyen and colleagues studied 75 mechanically ventilated patients intolerant of enteral nutrition with gastric residual volumes greater than 250 mL.[20] Twice-daily intravenous erythromycin 250 mg was compared with combination therapy comprising erythromycin and metoclopramide 10 mg intravenously. They found that gastric residual volume was significantly decreased after combination therapy, compared with metoclopramide alone. The use of both agents did cause diarrhoea more frequently, but this was not infective. Tachyphylaxis was seen in both groups of patients, but was less marked in those receiving the combination of drugs.[20]

A novel method for assessing gastric motility was used to compare the effects of erythromycin and metoclopramide in 31 critically ill patients. Hersch *et al* used expiratory $^{13}CO_2$ recording after intragastric administration of $^{13}CO_2$ sodium acetate in Osmolite. They compared metoclopramide alone intravenously 10 mg four times daily with metoclopramide and continuous erythromycin, 10 mg/hour. They also used erythromycin alone, 200 mg twice daily and in combination with the continuous erythromycin infusion. They found that the least effective prokinetic was metoclopramide alone, with best results from bolus metoclopramide with continuous erythromycin.[21]

A recent randomised controlled trial by Nyugen and colleagues[22] studied 90 patients to compare intravenous metoclopramide 10 mg four times daily and intravenous erythromycin 200 mg twice daily. Both agents significantly improved gastric residual volume and produced successful

feeders with residual volumes less than 250 mL in 62% and 87% of critically ill subjects respectively. Perhaps more importantly, they also showed that combinations of erythromycin and metoclopramide provided effective 'rescue' therapy in those patients intolerant of enteral nutrition using one agent, with 92% of those initially intolerant becoming successful feeders. Interestingly, the study showed tachyphylaxis developed very quickly with both agents, but more so with metoclopramide.

Controversies

The use of an antimicrobial for an alternative effect is not seen as prudent prescribing by some researchers. Dall'Antonia *et al*[23] have expressed concern about the use of sub-inhibitory doses of erythromycin in the intensive care unit, believing that it could contribute to the spread of antibiotic resistance and also increase the risk of *Clostridium difficile* infection. Hawkyard and Koerner echo these concerns in their 2007 article.[5] They argue that the use of erythromycin not only increases the resistance to that specific agent, but that cross selection can cause spread of clones resistant to other bacteria. They suggest that unless the patient has failed other prokinetic treatment and is intolerant to metoclopramide, erythromycin should not be used as a prokinetic.

In their recent study, Nguyen *et al* demonstrated no associated increased risk of *C. difficile* diarrhoea with the use of erythromycin for prokinesis.[24] Highest rates of non-*C. difficile* diarrhoea were associated with use of combination treatment (erythromycin and metoclopramide) in 49% patients. Around 30% of patients had diarrhoea when given either drug alone.

Other agents

$5HT_4$ receptor agonists

Tegaserod is a selective partial $5HT_4$ receptor agonist.[25] In an Australian trial,[26] 40 patients were given 6 mg tegaserod three times daily down a nasogastric tube after failing to respond to two previous doses of metoclopramide. Statistically significant differences were seen in median daily gastric aspirate volumes. The authors state that tegaserod was an effective prokinetic in 85% of patients, and they believe it warrants further investigation.

Cholecystokinin-1 antagonists

Dexloxiglumide is a cholecystokinin-1 blocking agent which has been trialled in patients with constipation-predominant irritable bowel syndrome.[27] The authors showed a statistically significant increase in gastric emptying with this agent, and suggest that further work on critically unwell patients should be undertaken.

Ghrelin analogues

Animal studies have shown that an analogue of ghrelin (an appetite-stimulating hormone) RC-1139 acts as a potent gastrokinetic.[28] It was also shown to treat post-operative ileus effectively even with addition of opioids. Although much more work is required, its potential in humans should be explored.

Motilin agonists

ABT-229 is one of the motilides (motilin receptor agonists) designed to provide prokinetic effects similar to those seen with erythromycin.[29] Studies on this drug in patients with functional dyspepsia and gastroparesis have been disappointing. Tachyphylaxis is a major problem, thought to be associated with motilin receptor down-regulation.

Opioid antagonists

Alvimopan is a peripherally acting μ-receptor opioid antagonist, which has been investigated in the treatment of opioid-induced constipation and post-operative ileus.[30, 31] It has been found to restore bowel function and reduce hospital stay in postoperative patients. Its role in critically ill patients has not yet been investigated.[32]

Discussion

The effects of various factors on gastric emptying, including recumbent posture, are well recognised.[6] Illness severity correlates with poor gastrointestinal motility[24] and may be linked to specific diagnoses, with slower gastric emptying in severe sepsis, burns, and multiple trauma. Also, a wide range of medications, including inotropes, opioids, calcium-channel blockers, anticholinergics and proton-pump inhibitors, impair gastric motility.[7] However, neuromuscular-blocking compounds have not been shown to affect this.[33] Hyperglycaemia is known to slow gastric emptying in diabetic and healthy patients,[7] but its role in the critically ill needs to be further investigated. In their randomised controlled trial,[22] Nyugen *et al* found that those patients with higher pre-treatment gastric residual volumes responded worse to therapy than others. Future studies need to carefully match participants to controls for these variables, and further work is required to assess the impact of these parameters on gastric motility and enteral feeding success.

Recommending prokinetic agents is difficult as the collection of studies have tended to involve small numbers of patients. The majority of studies do not use clinically important endpoints, but instead consider variables such as gastric residual volume and 'area under the curve' as surrogate markers. Asai[19] suggests that studies examining more relevant outcomes such as mortality, nutrition, length of hospital stay and incidence of nosocomial pneumonias are needed.

Intensive care unit feeding recommendations[34] published in the *Journal of Parenteral and Enteral Nutrition* acknowledge the clinical usefulness of prokinetic agents, but recognise that the evidence base is limited, as the majority of studies involve small numbers of patients, and use only surrogate endpoints (except for Yavagal's study).[8] They conclude that, although there is no clear body of evidence, prokinetics are relatively cheap and, in general, safe. Prokinetics should be considered as an adjunct to improve nutrition on the intensive care unit. The use of erythromycin is controversial, and there are concerns surrounding both its cardiac effects and the possible development of antibiotic resistance. The authors recommend that metoclopramide is used as a first-line agent. In contrast, Nyugen *et al* believe that erythromycin is more efficacious than metoclopramide and should be used first line.[20] A combination

of erythromycin and metoclopramide is an effective treatment option in those not responding to a single agent.

There is evidence for the development of tachyphylaxis with both metoclopramide and erythromycin,[22] and this merits more in-depth research. Combination therapy seems promising in problem feeders, but again more evidence is needed in terms of the efficacy and safety of using multiple agents. The addition of several prokinetics to the medication regime of ICU patients could potentially add to the risk of serious drug interactions.[19]

In conclusion, more large-scale randomised controlled trials are required before one can make wholly evidence-based recommendations on the use of prokinetics in the critically ill. Our understanding of the mechanisms that cause poor gastric motility is increasing,[35-37] and may provide new therapeutic angles to treat feed intolerance. New therapies under investigation could potentially provide effective prokinetic activity without the clinical concerns associated with current agents.

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Katherine Grant Trainee Doctor in Anaesthetics, North Hampshire Hospital, Basingstoke
kgiles@doctors.org.uk

Richard Thomas Consultant in Anaesthesia and Intensive Care, Royal Hampshire County Hospital, Winchester