Current issues on safety of prokinetics in critically ill patients with feed intolerance

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***Abstract*:** Feed intolerance in the setting of critical illness should be treated promptly given its adverse impact on morbidity and mortality. The technical difficulty of postpyloric feeding tube placement and the morbidities associated with parenteral nutrition prevent these approaches being considered as first-line nutrition. Prokinetic agents are currently the mainstay of therapy for feed intolerance in the critically ill. Current information is limited but suggests that erythromycin or metoclopramide (alone or in combination) are effective in the management of feed intolerance in the critically ill and not associated with significant cardiac, haemodynamic or neurological adverse effects. However, diarrhoea is a very common gastrointestinal side effect, and can occur in up to 49% of patients who receive both erythromycin and metoclopramide. Fortunately, the diarrhoea associated with prokinetic treatments has not been linked to *Clostridium difficile* infection and settles soon after the drugs are ceased. Therefore, prolonged or prophylactic use of prokinetics should be avoided. If diarrhoea occurs, the drugs should be stopped immediately. To minimize avoidable adverse effects the ongoing need for prokinetic drugs in these patient should be reviewed daily.

***Keywords*:** adverse effects, critical illness, enteral feeding, feed intolerance, prokinetic therapy, safety

Introduction

For many years, it has been well recognized that critical illness is associated with hypercatabolism, resulting in loss of muscle mass, impaired organ function, and reduced reparative and immune function [Barton, 1994]. In critically ill patients, the addition of nutritional deprivation or malnutrition is associated with further impairment of immunological function, increased risk of infection, prolongation of mechanical ventilation, increased length of intensive care unit (ICU) and hospital stay and ultimately higher mortality [Harrington, 2004; Slone, 2004; Chandra, 1999; Giner *et al.* 1996]. In order to minimize the complications associated with malnutrition during critical illness, the practice of nutritional support (by either enteral or parenteral routes) has become a standard treatment in these patients.

Enteral nutritional support is preferred in critical illness as it is cheaper, has fewer infective complications and is associated with preservation of gut mucosal barrier function, compared to the parenteral route. Disturbances in gastrointestinal motility, however, are common and subsequent intolerance of nasogastric (NG) feeding occurs in up to 50% of critically ill patients [De Beaux *et al.* 2001; Multu *et al.* 2001; Dive *et al.* 1994]. This compromises their nutritional status and increases their risk of gastroesophageal reflux and aspiration [Multu *et al.* 2001; Heyland *et al.* 1995; Mullen *et al.* 1980] adversely affecting both morbidity and mortality [Heyland *et al.* 1995; Dempsey *et al.* 1988; Mullen *et al.* 1980].

Prokinetic therapy is generally regarded as first-line therapy for feed intolerance during critical illness [Stroud *et al.* 2003; Tisherman *et al.* 2002; MacLaren, 2000]. Of the available prokinetic agents, treatment of feed intolerance during critical illness is limited to metoclopramide (a dopamine agonist) and erythromycin (a motilin agonist) in terms of evidence-based practice. Despite its similarity to metoclopramide, the role of domperidone (a peripherally acting dopamine antagonist with theoretically no extrapyramidal side effects) in the management of gastroparesis and feed intolerance in critically ill patients has not been evaluated. Although cisapride accelerates gastric emptying in both

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diabetic and critically ill patients [MacLaren *et al.* 2001, 2000; Reddy *et al.* 2000; Goldhill *et al.* 1997; Heyland *et al.* 1996; Spapen *et al.* 1995], this agent has been withdrawn due to its associated lethal cardiac toxicity [Walker *et al.* 1999].

Metoclopramide has been reported to improve gastric emptying in critically ill patients [Stroud *et al.* 2003; Tisherman *et al.* 2002; MacLaren, 2000], but its efficacy on the success of feeding in feed-intolerant patients remains controversial [Stroud *et al.* 2003; Tisherman *et al.* 2002; MacLaren, 2000]. In small studies, a single dose of enterally administered metoclopramide had no effect on the gastric residual volume (GRV) and only modest reductions in volume were observed after three doses [Stroud *et al.* 2003; Tisherman *et al.* 2002; MacLaren, 2000]. In contrast, low-dose (3–7 mg/kg/day) erythromycin has been shown to increase both gastric emptying and the success of feeding in critically ill patients with feed intolerance [Stroud *et al.* 2003; Tisherman *et al.* 2002; MacLaren, 2000]. Comparative data amongst prokinetic agents have shown that enterally administered metoclopramide and cisapride may have a quicker onset of action than erythromycin, but the impact of these agents on GRV in the critically ill is similar [Stroud *et al.* 2003; Tisherman *et al.* 2002; MacLaren, 2000]. A recent double-blind randomized trial showed that low-dose (200 mg) intravenous (IV) erythromycin is more effective than metoclopramide in the management of feed intolerance, however tachyphylaxis developed rapidly over 7 days in the case of both agents [Nguyen *et al.* 2007b]. In the group of patients who failed to respond to either agent, *rescue* combination therapy with erythromycin and metoclopramide was highly effective and tachyphylaxis was less prominent [Nguyen *et al.* 2007b]. The role of combination prokinetic therapy in the treatment of feed intolerance during critical illness was subsequently evaluated in a formal randomized trial [Nguyen *et al.* 2007a]. In comparison to erythromycin alone, combination therapy was significantly more effective in improving the success of feeding with a significantly greater percentage of prescribed feed delivered to the patients during treatment and a lesser degree of tachyphylaxis noted [Nguyen *et al.* 2007a]. In both trials, neither treatment arms were associated with major adverse effects [Nguyen *et al.* 2007a, 2007b].

The problems associated with slow gastric emptying are often assumed to be bypassed by placement of a feeding tube beyond the pylorus. The benefit of postpyloric feeding in patients with no evidence of impaired gastric emptying, however, is uncertain and postpyloric feeding is not currently recommended [Ho *et al.* 2006; Heyland *et al.* 2002; Marik and Zaloga, 2001]. In particular, both randomized trials [Davies *et al.* 2002; Montecalvo *et al.* 1992] as well as meta-analyses [Ho *et al.* 2006; Heyland *et al.* 2003; Marik and Zaloga, 2003; McClave *et al.* 2002] have not shown an advantage in mortality for small bowel over gastric feeding in these patients. Although a meta-analysis by Heyland and colleagues [Heyland *et al*. 2002] suggested that postpyloric feeding increased nutrient delivery couple with a shorter time to achieve nutritional goals, a reduction in gastroesophageal reflux and a lower rate of ventilator-associated pneumonia [Heyland *et al.* 2002], subsequent meta-analyses have not confirmed these findings [Ho *et al.* 2006; Marik and Zaloga, 2003]. The benefits demonstrated by Heyland and colleagues [Heyland *et al.* 2002] appear to depend largely on a study that compared early aggressive enteral feeding with standard feeding [Taylor *et al.* 1999]. In fact, only 34% of patients in the aggressive feeding group had a postpyloric tube inserted [Taylor *et al.* 1999]. In addition, postpyloric feeding without concurrent gastric decompression results in significant undrained GRVs potentially increasing the risk of aspiration [Metheny *et al.* 2005]. More recently, a randomized trial has indicated that early postpyloric feeding offers no advantage over early gastric feeding in terms of overall nutrition received and complications [White *et al.* 2009]. Whilst gastric feeding with erythromycin as a prokinetic is equivalent to transpyloric feeding in meeting the nutritional goals of unselected critically ill patients, a similar study has not been performed in critically ill patients with feed intolerance. Although direct small intestinal feeding has been recommended for patients with feed intolerance refractory to prokinetic therapy [Davies and Bellomo, 2004], evidence to support this practice is lacking. Furthermore, placement of postpyloric feeding tube often requires endoscopy and, therefore, is invasive, technically demanding, costly and requires support from gastroenterological services. Similarly, non-endoscopic-assisted techniques to insert postpyloric feeding tube, such as the use of a Cath-locator or Cortrak device, require specialized equipment,

training and experience; and currently are not used routinely in most ICU centres.

Alternatively, for patients who are at risk of malnutrition and in whom enteral nutrition cannot be initiated due to gastrointestinal dysfunction, total parenteral nutrition can be used with meticulous care and management of line sepsis and hyperglycaemia.

Whilst these findings strongly support the use of low-dose erythromycin, particularly in combination with metoclopramide, their efficacy must be balanced against the potential adverse effects of these agents, prior to the implementation of clinical guidelines that recommend their routine use in the management of feed intolerance during critical illness. In particular, the risk of the development of bacterial resistance related to widespread use of erythromycin has been a major concern amongst intensive care physicians [Hawkyard and Koerner, 2007; Singh, 2007]. The aim of this review is to discuss the adverse effects as well as the issues of safety related to the use of these prokinetic agents in the treatment of feed intolerance during critical illness.

Cardiovascular adverse effects

Both metoclopramide and erythromycin have been reported to cause cardiac arrhythmias through prolongation of the QT interval, including the potentially fatal ventricular arrhythmia, *torsades de pointes* (torsades) [Tonini *et al.* 1999]. These agents cause delayed repolarization, leading to QT prolongation and, potentially, torsades is thought to relate to the blockade of the rapid component of the cardiac delayed rectifier K(+) current (I(Kr)), encoded by the human ether-a-go-go-related gene (HERG) [Gallacher *et al.* 2007; Lu *et al.* 2007]. *In vitro* studies have shown that cisapride and domperidone are the most potent blockers of HERG currents and are approximately 100 times more potent than that of metoclopramide and erythromycin [Gallacher *et al.* 2007; Lu *et al.* 2007]. This explains the significantly less frequent occurrence of fatal cardiac adverse events from metoclopramide and erythromycin, in comparison to cisapride. In addition, a number of patient-related risk factors are known to increase the risk of torsades. These include increased age, female gender, hypokalemia, history of previous QT prolongation or cardiac arrhythmia, structural heart disease and poor left ventricular function [Roden, 2004].

In the setting of critical illness, patients generally receive many different drugs as part of their treatment and a number of important drug interactions can occur, particularly in the case of erythromycin, which is a CYP3A4 isoenzyme inhibitor. It is reported to be associated with an increase risk of adverse cardiac events with the concurrent administration of antifungal drugs (ketoconazole, itraconazole, fluconazole, astemizole and terfenadine), antiarrhythmic drugs (including disopyramide, procainamide, amiodarone, sotalol and quinidine), calcium channel blockers (diltiazem and verapamil), haloperidol and pimozide [Roden, 2004].

The magnitude of cardiac adverse effects related to these prokinetics, however, is not known in critically ill patients. The concerns are extrapolated from reports or studies performed patients who were not critically ill in which these agents were often given for a longer period and in a higher dosage. The duration of prokinetic therapy for feed intolerance in critically ill patients is often shorter (less than 1 week) and the agents are often ceased soon after enteral feed is tolerated. Thus far, no cardiac toxicities or arrhythmias related to the use of either metoclopramide or erythromycin have been reported in clinical trials that examined the impacts of these prokinetic therapies for feed intolerance in critically ill adults or preterm infants [Ng and Shah, 2008; Nguyen *et al.* 2008, 2007a, 2007b, 2007c]. In a small study ($n = 90$), cardiac arrhythmia was not observed even when metoclopramide and erythromycin were given in combination (with 95% confidence interval: 0–3.3%) [Nguyen *et al.* 2007c]. It is important to realize that cardiac arrhythmias are relatively common during critical illness and up to one fifth of patients who are admitted to ICU experience significant arrhythmias, with ventricular tachycardia and atrial fibrillation the most frequent [Reinelt *et al.* 2001]. In this report, only 3.7% of the arrhythmias were torsades and were not related to the use of either metoclopramide or erythromycin [Reinelt *et al.* 2001].

Given the adverse effect profile of prokinetic agents and the dose-dependent effect on the HERG current, the use of a minimum dosage to achieve clinical prokinetic effects has been suggested. Whilst a single dose of 70 mg erythromycin resulted in a similar effect on gastric emptying as compared with a 200 mg dose in a small group of critically ill patients [Ritz *et al.* 2005], data on

the effectiveness of low-dosage erythromycin over a period of time on the success of feeds in these patients is lacking. Furthermore, there is no evidence to guide the minimum effective dosage of metoclopramide.

Haemodynamic adverse effects

In addition to its cardiac toxicity, low-dose erythromycin has recently been shown to induce hypotension in healthy volunteers, with a 10 mmHg reduction in systolic blood pressure [Mangoni *et al.* 2004]. The hypotensive effect was thought to be mediated by motilin-induced endothelial relaxation with a transient reduction in blood pressure. Although this may be of minor concern in the context of good health, such a reduction in systolic blood pressure may be clinically relevant in critically ill patients whose cardiovascular function is already compromised. The acute effects of erythromycin (200 mg intravenously [IV]) on blood pressure and heart rate were evaluated in 19 mechanically ventilated critically ill patients, who were intolerant of NG feeds and not requiring inotropic support. In this small study [Nguyen *et al.* 2007c], there were no significant differences in systolic or diastolic blood pressure and heart rate after erythromycin or placebo, providing reassurance that treatment with this agent is safe in stable patients. The safety of erythromycin in patients with haemodynamic instability or those who require inotropic support, however, requires further evaluation.

Neurological adverse effects

Neurological adverse effects, such as somnolence, nervousness, dystonic reactions and tardive dyskinesia, are often of concern with the use of metoclopramide, observed in up to 20% of patients who are not critically ill [Ganzini *et al.* 1993]. Elderly females are more prone to these adverse effects. Although metoclopramide commonly increases pituitary prolactin release, it infrequently leads to clinical problem of galactorrhea and menstrual disorders [Garcea *et al.* 1983]. In patients with traumatic head injury, metoclopramide should be used with caution having been shown to be associated with an increased intracranial pressure [Deehan and Dobb, 2002], albeit its prokinetic effect was poor in these patients [Marino *et al.* 2003]. Although erythromycin has been reported to cause seizures and weakness [Grondahl and Langmoen, 1993], these side effects are rare. The use of erythromycin, however, should be avoided in patients with myasthenia gravis as it can precipitate myasthenia crisis [Absher and Bale, 1991].

As mechanically ventilated critically ill patients are often deeply sedated and occasionally paralyzed, these neurological adverse effects are often difficult to recognize and data regarding their prevalence during critical illness are lacking. Although the occurrence of these side effects have only been reported in case reports [Deehan and Dobb, 2002; Henderson and Longdon, 1991], it should be suspected in patients who are difficult to ventilate or do not tolerate weaning of ventilation or sedation without other obvious medical causes.

Gastrointestinal adverse effects

Erythromycin, particularly when given at antimicrobial dosage, is well known to cause abdominal pain, nausea, vomiting and diarrhoea [Tonini *et al.* 1999]. Of these, watery diarrhoea is the most readily recognized adverse effect in sedated critically ill patients and can occur in up to 25% of enterally fed patients [Ringel *et al.* 1995; Kelly *et al.* 1983]. The cause of diarrhoea in these patients is thought to be multifactorial and the majority of cases are not related to infection. In addition to increased gastrointestinal transit [Landry *et al.* 1995], osmotic diarrhoea is likely to occur in these patients [Ringel *et al.* 1995; Kelly *et al.* 1983] due to reduced intestinal absorption [Hernandez *et al.* 1999], disturbed carbohydrate fermentation from altered bowel flora [Ringel *et al.* 1995], and the hyperosmolar effects of enteral feeds [Ringel *et al.* 1995; Kelly *et al.* 1983]. Diarrhoea has been shown to be more frequent when the enteral feeding rate is >50 ml/h [Smith *et al.* 1990] and improves when the feeding rate is reduced [Ringel *et al.* 1995; Kelly *et al.* 1983].

The direct impact of prokinetic therapy on the occurrence of diarrhoea was recently evaluated in 180 enterally fed critically ill patients who did not tolerate NG feeds. Overall, diarrhoea occurred in 40% of patients approximately 10 days after commencement of therapy with a mean duration of 3.6 ± 1.2 days [Nguyen *et al.* 2008]. Diarrhoea was most prevalent in patients that received combination therapy with erythromycin and metoclopramide (49%) and was significantly more common in comparison with those who received erythromycin alone (30%; $p = 0.02$) and metoclopramide alone (32%; $p = 0.08$) [Nguyen *et al.* 2008]. The occurrence

of diarrhoea was also positively correlated with the amount of feeds delivered [Nguyen *et al.* 2008]. In all cases, the diarrhoea was not related to *Clostridium difficile* (CD) infection and settled shortly after the prokinetic therapy was ceased [Nguyen *et al.* 2008].

Clostridium difficile infection and pseudomembranous colitis

Whilst less than 10% of critically ill patients who have diarrhoea are related to CD infection, the presence of pseudomembranous colitis is associated with higher morbidity and mortality [Ringel *et al.* 1995; Kelly *et al.* 1983]. Given antibiotic use is the main risk factor for CD infection and such antimicrobial therapy is frequently required in the setting of critical illness [Garey *et al.* 2008], CD-related diarrhoea has always been a major concern amongst intensive care physicians [Riddle and Dubberke, 2009; Singh, 2007]. This concern extends to the widespread use of low-dose erythromycin as a prokinetic agent because of its antibiotic property, even though supporting data for this concern is lacking. In a recent study, CD infection did not develop in 143 enterally fed critically ill patients who received erythromycin prokinetic therapy for more than 1 week duration [Nguyen *et al.* 2008]. It has been postulated that the lack of CD infection seen in this study may be attributed to the prokinetic effects of increased gastrointestinal transit [Landry *et al.* 1995], preventing colonization and growth of the significant pathogens in the gastrointestinal tract [Riddle and Dubberke, 2009; Smith *et al.* 1990]. Although these preliminary findings suggest prokinetic therapy with erythromycin is not associated with CD infection in critically ill patients, larger studies are required to confirm the results.

Potential development of bacterial resistance

This hypothetical but important concern arises from observational studies that showed that 'sublethal' concentrations of antibiotics exert selective pressure on bacteria and can lead to the development of bacterial resistance [Burgess, 1999]. The antibiotic properties of erythromycin raise ongoing concern with regards to its clinical application as a prokinetic agent with the possible development of bacterial resistance [Hawkyard and Koerner, 2007; Singh, 2007], particularly in the setting of critical illness. This risk remains theoretical, however, with no data in the current literature to support this hypothesis regarding the use of a short course of low-dose erythromycin [DiBaise and Quigley, 1999]. Although a number of motilin derivatives have been specifically developed to avoid bacterial resistance, their prokinetic effects and durability are poor due to rapid development of tachyphylaxis [Netzer *et al.* 2002; Talley *et al.* 2001, 2000].

Conclusions

Treatment of feed intolerance in the setting of critical illness should be instituted promptly given its adverse impact on morbidity and mortality. The technical difficulty of postpyloric placement and the morbidities associated with parenteral nutrition do not allow these approaches to be considered as first-line therapy. Instead, the use of prokinetic agents are the mainstay of therapy for feed intolerance in the critically ill. In view of the relatively poor efficacy of metoclopramide, and the paucity of available newer safe and effective prokinetic agents, avoiding the use of erythromycin may compromise patients' outcomes from the complications of feed intolerance. Based on the current evidence evaluating the adverse effects of prokinetic agents in critical illness and the lack of prokinetic agents with a safer adverse effect profile, short-term use of low-dose erythromycin and metoclopramide (alone or in combination) is a reasonable approach for feed intolerance, whereby the benefits appear to outweigh the risks.

Although the studies are relatively small, the current literature suggests that erythromycin or metoclopramide, alone or in combination for management of feed intolerance during critical illness, is not associated with significant cardiac, haemodynamic or neurological adverse effects. This is provided that patients do not have risk factors such as ventricular arrhythmias, prolonged QT interval, structural heart disease, hypokalemia or the concurrent administration of drugs with potential interactions. Furthermore, erythromycin should be avoided in the case of myasthenia gravis and metoclopramide in patients with traumatic head injury and raised intracranial pressure.

Diarrhoea, however, is a very common gastrointestinal side effect, which occurs in up to half of those who receive combination therapy with erythromycin and metoclopramide. Fortunately, the diarrhoea related to prokinetic treatment is not been associated with CD infection and settled soon after the cessation of the drugs. Hence, prolonged prokinetic therapy should be avoided

and in the event of diarrhoea the drug(s) should be stopped immediately. Furthermore, the need to continue the prokinetic drug should be reviewed on a daily basis to avoid unnecessary adverse effects. The impact of combining smaller doses of erythromycin (70 mg instead of 200 mg) with metoclopramide on the success of feeds and the development of diarrhoea needs to be further evaluated. In view of the theoretical risk of bacterial resistance development and the common side of effect of diarrhoea, prophylactic use of prokinetic therapy to prevent feed intolerance must be avoided.

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Conflict of interest statement

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