Commentary

Prokinetic agents in critical care

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Abstract

Prokinetic agents are commonly used in intensive care, mainly to aid in early enteral feeding. The present commentary reviews some of the recently published papers and highlights the lack of a sizable evidence base, as well as the possible importance of euglycaemia in this important clinical area.

Keywords enteral feeding, erythromycin, hyperglycaemia, intensive care, metolopramide, prokinetic agent

Early enteral feeding is now recognized as one of the fundamentals of critical care practice [1–4]. Enteral nutrition (EN) increases gut blood flow, thereby protecting the gastric mucosa [5,6]. Early feeding results in fewer septic complications, decreased catabolic response to injury, decreased stress ulceration in the ventilated patient, improved gut immune function and improved wound healing [3,4,7,8]. Successful enteral feeding relies on intact gastrointestinal motility, which is frequently impaired in the critically ill.

Prokinetic agents have a valuable role to play in this situation. A recent review by Booth and coworkers [9] with an accompanying editorial [10] in *Critical Care Medicine* systematically reviewed the evidence for the use of gastrointestinal promotility drugs in critical care. The context of the review was that promotility agents may improve tolerance to EN, and reduce gastroesophageal reflux and pulmonary aspiration; they therefore have the potential to improve outcomes of critically ill patients. The authors appear to have conducted a comprehensive search of the available literature over the preceding two decades. The studies were then methodologically assessed for their quality using a previously described scoring system, with attempts made to contact the primary investigators for further information where this was thought necessary.

The review scrutinized 18 studies involving a total of 908 individuals. A significant proportion of the review examined the role of prokinetics in aiding tube placement, whereas the remainder looked at the effects of cisapride, erythromycin and metoclopramide on gut transit/feeding tolerance. (For a summary of the actions of those agents, see Table 1.) Cisapride is currently unavailable in many countries because of cardiac toxicity [11].

A breakdown of the reviewed studies is shown in Table 2. If we exclude the studies on tube placement, those with end-points that involved patient outcomes and those gastrointestinal transit studies that involved cisapride alone, then we are left with only six studies (highlighted in Table 2 with asterisks), involving 80 patients, that examined agents that are available as prokinetics in contemporary practice. The review justified the inclusion of cisapride because there are currently new generation agents undergoing trials; however, it failed to mention that the studies on the new motilin receptor agonists (macrolide derivatives), such as ABT-229, have yielded disappointing results [12,13]. The authors suggested that we should be more cautious with our use of erythromycin, given the increasing incidence of antibiotic resistance, and suggested 20 mg metoclopramide as first-line treatment. This dose appears to have little scientific basis because only one of the tube placement studies [14] used it; the review stated that a dose of 20 mg was used in the gastrointestinal transit study conducted by Jooste and coworkers [15], but it actually employed a 10 mg dose. The value of the review is that it highlights the lack of any large methodolical studies on which to base treatment recommendations.

 EN = enteral nutrition; RGV = residual gastric volume.

Table 1

Summary of features and actions of cisapride, erythromycin and metoclopramide

Drug	Receptor	Class	Action
Metoclopramide	Dopamine antagonist	Motility stimulant	Sensitizes gut to acetylcholine; increases lower oesophageal sphincter tone
Erythromycin	Motilin receptors on enteric nerves and smooth muscle	Macrolide antibiotic	Increased antral activity, which may migrate caudally (depending on dose) ± activation of an intrinsic cholinergic pathway
Cisapride	Activates 5-HT_4 receptors on intrinsic sensory neurones	Motility stimulant	Initiates peristaltic reflex by simultaneously activating ascending excitatory and descending inhibitory neural pathways

5-HT, 5-hydroxytryptamine.

Table 2

Summary of studies of gastrointestinal promotility drugs

Study design	Number of studies	Population (*n*)
Tube placement studies (examining the role of prokinetics in aiding transpyloric intubation)	6	351
Patient outcome studies (examining pneumonia and mortality or gastric and pulmonary colonization)	2	330
Studies that examined the effects of the prokinetic agents on gastrointestinal transit and feeding intolerance		
Cisapride versus placebo	4	147
Erythromycin versus placebo*	2	30
Metoclopramide versus placebo*	2	26
Metoclopramide versus cisapride*	1	14
Metoclopramide versus erythromycin and cisapride*	1	10

*Studies of agents that are available as prokinetics in contemporary practice.

In view of recent critical care trials, it is disappointing that neither the review nor the editorial mentioned the effect of hyperglycaemia on gastric function. It is now recognized that increasing blood glucose in both diabetic patients and normal individuals has a reversible effect on gastrointestinal motor function [16,17]. Also of note is that the gastrokinetic effects of erythromycin were attenuated in healthy individuals when their blood glucose concentrations were increased from approximately 4 to 15 mmol/l [18].

Another study [19], published in June 2002 in *Critical Care Medicine* (too late for inclusion in the review by Booth and coworkers [9]), examined the effects of erythromycin in ventilated patients. It adds considerably to the body of evidence by studying 40 patients randomly assigned to either placebo or erythromycin 250 mg four times daily in 50 ml 5% dextrose. Enteral feeding was commenced at 500 ml/day on the first day, and was increased in 500-ml steps to a maximum of 2000 ml/day. Residual gastric volume (RGV) was measured at 6-hour intervals and feed was discontinued if RGV exceeded 250 ml or the patient vomited. The treatment group exhibited a significant decrease in RGV for the first 3 days of feeding and a significant decrease in the number of patients who were unable to tolerate EN (35% versus 70%).

The ideal dosing of erythromycin still requires clarification; the above regimen produced satisfactory outcomes, but similar results might have been achieved with twice daily dosing [20]. Erythromycin involves two different pathways [21], and its effects are known to vary with dosing. A low dose (40 mg) induces a premature activity front at the antral level, migrating caudally to the small intestine, and is possibly mediated by activation of an intrinsic cholinergic pathway. Higher doses (200–350 mg) induce a prolonged period of strong antral activity that is not followed by phase 1 and does not migrate caudally, and is possibly mediated via a pathway that involves activation of a muscular receptor [22]. The recent cloning of the motilin receptor may help to clarify the correct dose from a molecular level [23].

Metoclopramide may well be more efficacious at a dose of 20 mg, but currently there is no evidence to support this in the absence of an adequately powered and randomized study. On current evidence, the best dose is probably 10 mg intravenously three times daily.

This important everyday area of practise noticeably lacks an evidence base. Perhaps the current move in many units to more aggressive blood sugar control, which requires a more constant source of glucose, will provide the impetus for the much needed further work in patients who are euglycaemic.

Competing interests

None declared.

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