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EDITORIAL

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Gastric emptying in the critically ill – the way forward?

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Critical illness can adversely effect gastrointestinal function [1]. One manifestation of this is abnormal gut motility and, in particular, impaired gastric emptying [2]. Several gastric motor abnormalities have been described in mechanically ventilated patients including antral hypokinesis and absence of phase III of the migrating motor complex (the so-called "house-keeper" of the gastrointestinal tract) [3]. The causes of these motor disturbances are poorly understood, but various factors such as medications, hyperglycaemia [4] and brain injury [5] have all been implicated. Perhaps the most obvious practical consequence of gastroparesis is that it leads to intolerance of enteral feeding, despite the presence of a functioning, intact small bowel. This has several important sequelae. Critical illness is associated with gut atrophy and increased mucosal permeability to bacteria and macromolecules such as endotoxin [6]. It has been postulated that the translocation of these products, or at least relative ischaemia and subsequent reperfusion of the splanchnic organs, are somehow implicated in the development of single or multiple organ failure [7]. Food in the lumen of the gut is an important stimulus for maintaining splanchnic blood flow [8] and hence mucosal integrity, enteral nutrients thereby exerting a cytoprotective effect throughout the gastrointestinal tract, which prevents both atrophy and ulceration [9].

Moreover, the failure to establish enteral feeding in the critically ill very often results in the introduction of total parenteral nutrition [TPN] with its greater risk of septic morbidity, mortality and increased expense [10]. Aside from preventing the establishment of nasogastric feeding, impaired gastric emptying is also associated with gastro-oesophageal and duodenogastric reflux, both of which have been implicated in the development of nosocomial pneumonia [11].

Given these adverse effects of gastroparesis, it is not surprising that there is increasing interest in techniques to measure gastric emptying in the critically ill. These techniques have been reviewed elsewhere [12], but briefly they include: radio nucleotide scintigraphy, ultrasonography, gastric impedance monitoring, measurement of the gastric aspirate residual volume, a paracetamol uptake assay and gastric fluid challenge. Of these, the paracetamol absorption test is becoming increasingly popular, presumably because it is relatively easy to perform in the ICU at the bedside. The test relies on the fact that, in healthy individuals, paracetamol is predominantly absorbed in the small intestine and that its absorption depends on the rate of gastric emptying [13]. A standard dose of paracetamol is administered nasogastrically and then serial measurements of its plasma concentration are obtained. From these a concentration: time curve over 60 min can be constructed and, by using the trapezoid rule, the area under the curve calculated (AUC_{60}). This is presented as a measure of gastric emptying. Given that the paracetamol plasma concentration depends not only on absorption but also on the distribution and metabolism of the drug, the test becomes limited if the latter two are abnormal, for example when hepatic function is deranged by sepsis or there is an increase in its volume of distribution.

In this issue of *Intensive Care Medicine,* Tarling et al. report the use of the paracetamol absorption test to describe the range and factors which affect gastric emptying in a group of ICU patients. They investigated 27 patients and looked for some correlation of the gastric emptying time with the presence or absence of bowel

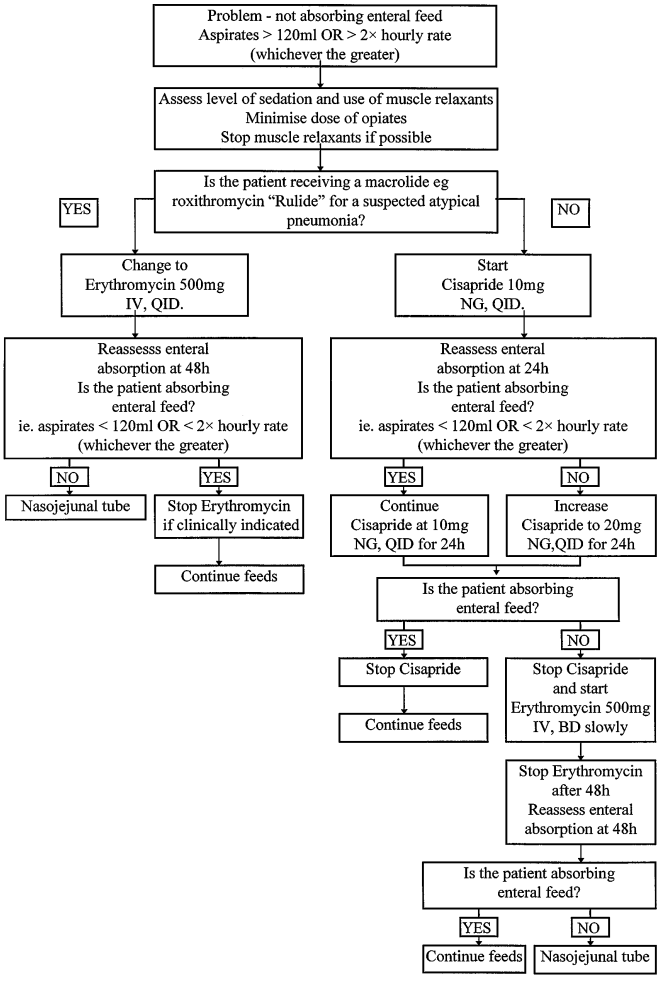

Fig. 1 Feeding via the nasogastric rate incorporating the use of erythromycin and cisapride

sounds, the volume of gastric aspirate, the APACHE II score and its associated estimated risk of death, measurements of the gastric intramucosal pH (pHi) and the use of various medicaments, including dopamine and opiates. Surprisingly, of these, they demonstrate a statistically significant positive correlation between the APACHE II risk of death and increased gastric emptying; that is, as the risk of death increased in this patient cohort, gastric emptying appeared to be more rapid! This is difficult to explain given the usual clinical association of a high volume nasogastric aspirate and a failure to tolerate enteral nutrition with increasing severity of illness. Possible explanations for this anomaly include the APACHE II risk being a poor predictor of outcome in this small group of patients or that the pharmacokinetic profile of paracetamol was significantly deranged in the sicker patients, for example, some gastric absorption of paracetamol occurred in those with an ischaemic and leaky gastric mucosa.

Whatever the explanation, Tarling et al. conclude that predicting gastric emptying in the ICU patient is difficult and recommend further investigation to understand the process. Such understanding would also allow the more rational use of prokinetic agents, but it is not clear that the way forward is via the paracetamol absorption test. After all, "the proof of the pudding is in the eating" or at least, in the absorbing, and since the authors fail to provide any evidence that the paracetamol absorption test can identify those patients who can be fed successfully via the nasogastric route, its relevance remains suspect. Physicians and nurses in the ICU should not be distracted from the critical issue – that is, how can we establish early enteral nutrition in the maximum number of patients requiring nutritional support admitted to our ICUs? This is especially the case since more and more studies are appearing demonstrating survival advantages and reductions in morbidity [14] in patients who achieve early enteral feeding.

Historically, pharmacotherapy for gastroparesis has been somewhat limited but the position is changing with the development of a new class of prokinetic agents called the motilides. This term was introduced by Itoh and Omura [15] to describe all macrolides that had a direct contractile effect in vitro on rabbit duodenal segments and the capacity to induce in vivo phase III activity in dogs. Erythromycin is a widely available, clinically useful motilide interacting directly with the motilin receptor [16]. This agent has been shown to have dramatic effects in the treatment of diabetic gastroparesis, essentially normalising the prolonged gastric emptying times in these patients [17]. Investigation of the effects of erythromycin on gastric motility in intensive care patients, however, is more limited. Dive et al., in a crossover, double-blind, randomised, placebo-controlled study of 10 ventilated patients, were able to demonstrate that intravenous erythromycin increased indices of antral motility and accelerated gastric emptying as assessed by the paracetamol absorption test (with all its caveats) [18]. Concerns regarding the use of an important antimicrobial agent in another role, with the risks of generating bacterial resistance, may make erythromycin an unpopular choice of prokinetic. However, derivatives of the drug, which remain potent motilides but which lack antibacterial activity, are being developed.

An alternative to erythromycin is the substituted benzamide, cisapride, which appears to be a very effective prokinetic. This drug has a unique mechanism of action in that it increases the physiological release of acetylcholine from postganglionic nerve endings of the myenteric plexus without any associated dopamine antagonism. Cisapride has been shown to improve gastric emptying by various favourable effects on antropyloroduodenal motility, including increasing the temporal relationship between duodenal and antral contractions as

well as increasing the number of antral contractions greater than 6 cm in extent [19]. Oral cisapride is usually associated with few and trivial side effects, but a recent report from the FDA in the *New England Journal of Medicine* described 57 patients who either developed torsades de pointes or a prolonged QT interval whilst taking this drug [20]. Interestingly, 32 of these patients were also taking medications of the imidazole class or macrolide antibiotics, some interaction through the inhibition of hepatic cytochrome p450 enzyme system metabolism of cisapride resulting in high blood levels being the most likely explanation. It is now policy in our unit not to prescribe cisapride with these agents.

In our view, enteral feeding should be an **obsession** in the ICU! Failure to feed the patient via an intact small bowel is failure to deliver high quality intensive care. Nasogastric feeding is simple, no special techniques of gaining access to the stomach are required but the question of what proportion of critically ill patients can be successfully fed in this way remains uncertain. We have found that we are able to feed the vast majority (> 85 %) of our patients via the nasogastric route by incorporating the use of erythromycin and cisapride into a management algorhythm for those cases with absorption problems (Figure). Only rarely do we have to resort to nasojejunal tube placement or surgical jejunostomy, both extraordinarily useful techniques in selected groups of patients. But, then, after all, we are obsessed by one way forward being through successful early enteral nutrition.

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