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Title:

Gastro-duodenal motility & nutrition in the critically ill.

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List of contents

Chapter 3
Gastric and small intestinal structure and function in health

3.1 Introduction
3.2 Anatomy of the antro-pyloro-duodenal region
- *3.2.1 Gross anatomy*
- *3.2.2 Muscular anatomy*
  - 3.2.2.1 The pylorus
- *3.2.3 Neural anatomy*
  - 3.2.3.1 Introduction
  - 3.2.3.2 Extrinsic neurological supply
  - 3.2.3.3 Enteric nervous system
  - 3.2.3.4 Interstitial cells of Cahal

3.3. Regulation of gastric and small intestinal motility
- *3.3.1 Interstitial cells of Cahal*
- *3.3.2 Neural Regulation*
  - 3.3.2.1 Extrinsic Neurological Control
  - 3.3.2.2 Intrinsic Neurological Control
- *3.3.3 Humoral*
  - 3.3.3.1 Inhibitory hormones
    - Cholecystokinin
    - Endogenous opioids
    - Glucagon-like peptide-1
    - Nitric oxide
    - Somatostatin
    - PeptideYY
  - 3.3.3.2 Excitatory hormones
    - Motilin
    - Ghrelin
    - Serotonin
- *3.3.4 Small intestinal nutrient feedback*
  - 3.3.4.1 Effect of nutrient type on enterogastric feedback
  - 3.3.4.2 Effect of nutrient blood concentrations on enterogastric feedback
  - 3.3.4.3 Small intestinal feedback

3.4 Motility of the stomach & small intestine in health.
- *3.4.1 Fasting motility*
- *3.4.2 Control of MMC activity*
  - 3.4.2.1 Neural mechanisms
    - Intrinsic
    - Extrinsic
  - 3.4.2.2 Hormonal mechanisms
    - Motilin
    - Other hormones and drugs
  - 3.4.2.3 Intestinal microflora
- *3.4.3 Postprandial motility*
  - 3.4.3.1 Proximal gastric postprandial motility
  - 3.4.3.2 Distal gastric postprandial motility
  - 3.4.3.3 Gastric emptying
  - 3.4.3.4 Small intestinal transit

3.5 Factors affecting gastric emptying in health

Chapter 6
Evaluation of gastric and small intestinal motor and absorptive function in critical illness

Chapter 8
Subjects and methods used in the studies reported in this thesis

Studies

Chapter 9
Measurement of gastric emptying in critical illness

Chapter 10
Feed intolerance and delayed gastric emptying in the critically ill

Chapter 11
Gastric and small intestinal motility in critical illness

Chapter 12
Glucose absorption and gastric emptying in critical illness

Chapter 13
Erythromycin for the treatment of delayed gastric emptying and unsuccessful feeding in critical illness

Chapter 14
The effect of cefazolin on gastric emptying in the critically ill

Chapter 15
A novel technique for postpyloric tube insertion in the critically ill

Chapter 16
Discussion and Conclusion

Appendices

Bibliography

List of figures & tables

Figure 15.3 *Computer screen display, showing tracking of the feeding tube relative to the diaphragm and midline. Position identified at 10 second intervals, represented by arrows.*

Figure 15.4 *Insertion of Cathlocator™ device into a patient in ICU with a tracheostomy.*

List of abbreviations.

3-OMG - 3-O-methyl glucose
5-HT - serotonin
ACCP - American College of Chest Physicians
AD - antro-duodenal
APD – antro-pyloro-duodenal
APACHE II score – acute physiology and chronic health evaluation II score
ATP - adenosine triphosphate
AUC - area under curve
BMI - body mass index
BTt_{50} – breath test gastric half emptying time
cAMP - cyclic adenosine monophosphate
CCK - cholecystokinin
cGMP - cyclic guanosine monophosphate
CI – confidence interval
Cmax - maximal concentration
CO_2 – carbon dioxide
EIT - Electric impedance tomography
EN- enteral nutrition
GE - gastric emptying
GEC – gastric emptying coefficient (breath test)
GLP-1 - glucagon-like peptide-1
GRV(s) – gastric residual volume (s)
h – hour(s)
ICH = intracranial haemorrhage
ICP- intracranial pressure
ICU – intensive care unit
IL-1 - interleukin-1
IPPWs - Isolated pyloric pressure waves
IV – intravenous
L/R - lactulose / L-rhamnose
min – minutes (s)
MMC - migrating motor complex
MRI - Magnetic Resonance Imaging
NGT - nasogastric tube.
NO - nitric oxide
NS - not significant
op - operative
OR- odds ratio
Postop - postoperative
Pts - patients
PYY - Peptide YY
REE - Resting energy expenditure
resp = respiratory failure
s – second(s)
SCI - spinal cord injury
scintigraphic t½ – scintigraphic half emptying time

SEM – standard error of the mean
TBI - traumatic brain injury
Tmax - time to maximal concentration
TMPD - transmucosal potential difference
TNF-α - tumour necrosis factor-α
TPN – total parenteral nutrition

Summary of thesis
Gastro-duodenal motility & nutrition in the critically ill

Inadequate delivery of nutrition to the critically ill is common, and may adversely affect clinical outcomes, including survival. This thesis reports studies designed to characterise the gastrointestinal dysfunction underlying feed intolerance in the critically ill, as well as the pathophysiology of these dysfunctions, and investigate potential therapeutic measures.

While it has been established that enteral nutrition is frequently unsuccessful in the critically ill, assessment of the success of feeding in an Australian intensive care unit (ICU) had not been performed previously. A prospective survey examined the incidence of, and risk factors for, feed intolerance in the ICU at the Royal Adelaide Hospital and demonstrated that, in 40 patients receiving enteral feeding, only about 60% of their nutritional requirements were met at the end of the first week. The main cause for this lack of success was large gastric residual volumes, indicative of delayed gastric emptying (GE). This study, accordingly, quantified the limitations of nutritional delivery in contemporary practice in a local ICU. The results suggest that a better understanding of the pathogenesis underlying this problem is warranted in order to direct research into improved therapies.

Scintigraphy is the most accurate technique to measure GE, but is difficult to perform in the ICU. A simpler, more convenient, test would increase the accessibility of GE measurement for both research and clinical purposes. A study comparing a breath test technique and gastric residual volume measurement to the scintigraphic measurement of GE in 25 mechanically ventilated patients demonstrated that GE measured by a breath test technique closely correlated with that measured by scintigraphy. While the breath test had a specificity of 100% it only had a sensitivity of about 60% in the prediction of delayed GE. Similarly, gastric residual volume measurement correlated with scintigraphic measurement of GE but also lacked sensitivity. The breath test has previously been demonstrated to be highly reproducible and it represents a useful option for repeated measurement of GE in the same patient. It is therefore likely to be useful to determine changes in GE over time or in response to a therapeutic intervention.

There is a lack of information about the prevalence and determinants of delayed GE in the critically ill. Previous studies have substantial limitations and scintigraphic measurement of GE has only rarely been used. A study comparing GE measured by scintigraphy in 25 patients to 14 healthy subjects demonstrated that GE was delayed in approximately 50% of the ICU patients (>10% retention at 4h) and markedly delayed in about 20% (>50% retention at 4h). Patients with trauma and sepsis appeared to have a relatively higher prevalence of delayed GE (80% and 75% respectively). In addition, the longer the patient had been in ICU the more normal the rate of GE. Quantification of delayed GE may prove useful by defining patients who may benefit from preventative or therapeutic options.

The abnormalities in gastrointestinal motility underlying delayed GE in the critically ill are poorly characterised. Simultaneous manometric and gastric emptying measurements were performed in 15 mechanically ventilated patients and 10 healthy subjects. These studies demonstrated that delayed GE was associated with reduced antral activity, increased pyloric activity and increased retrograde duodenal activity in the patients. Persistent fasting motility during feeding was also frequently observed. Furthermore, the feedback response to small intestinal nutrients was enhanced. This latter observation may provide an explanation for the delayed GE and warrants further investigation. Recent studies suggest that the hormone

cholecystokinin may be a mediator of increased small intestinal feedback and, if confirmed, this has clear therapeutic implications.

Nutrient absorption has rarely been measured in the critically ill. GE and glucose absorption (using 3-O-methyl glucose) were measured simultaneously in 19 ICU patients and compared to 19 healthy subjects. Glucose absorption was shown to be markedly reduced in the patients. Slow GE was associated with delayed, and reduced, absorption. However, glucose absorption was also reduced in patients with normal GE suggesting that reduced glucose absorption in critical illness is only partly due to delayed GE. Accordingly, measures to improve the effectiveness of GE and thereby improve overall nutritional status may be compromised by abnormal small intestinal absorption. The mechanisms underlying this warrant further investigation.

A number of therapeutic options directed at improving the delivery of nutrition were examined. In a study involving 20 mechanically ventilated patients, administration of 200mg erythromycin intravenously was shown to be superior to placebo for treating feed intolerance. The optimal dose of erythromycin, however, was unclear. In a subsequent study involving 35 ICU patients, GE was measured using a breath test technique, before and after 2 different doses of erythromycin or placebo and a ‘low’ intravenous dose (70mg) of erythromycin appeared to be as effective as a ‘moderate’ dose (200mg). Both doses were only effective in subjects who had delayed GE at baseline. Based on the outcome of these studies, low doses of erythromycin have subsequently been routinely used to treat feed intolerance in the critically ill patients at the Royal Adelaide Hospital.

Animal and human studies suggested that the antibiotic, cefazolin, may have a prokinetic effect. Cefazolin, however, did not demonstrate similar prokinetic activity at a ‘low’ dose (50mg) in a critically ill cohort. The results of this study do not support the use of this agent, at this dose, as a prokinetic, in this population. If nasogastric administration of nutrition proves unsuccessful an alternative is to infuse nutrient directly into the small intestine. However, the placement of feeding tubes distal to the pylorus is technically difficult. A novel technique for postpyloric tube insertion was examined with promising results.

In summary, the studies described in this thesis have provided a number of insights relevant to the management of the critically ill by quantifying the prevalence of feed intolerance and delayed GE, characterising some of the disturbances in gastrointestinal motility underlying this problem, and evaluating a number of therapeutic interventions.

Declaration

The work reported in this thesis has been submitted to the University of Adelaide for the degree of Doctor of Philosophy. The studies reported herein are entirely original and were preformed by the author between 1999 and 2005. This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis (as listed in Appendix A) resides with the copyright holders of those works.

Signed …….

Marianne Chapman

Date …….

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