Colonic responses to enteral tube feeding

Enteral feeding has become an invaluable treatment in both the hospital and home setting. However, it is not without complications, the commonest of which is diarrhoea. This occurs in up to 25% of patients on general wards\textsuperscript{1–3} and 63% of patients on intensive care units.\textsuperscript{4–6} Diarrhoea not only limits the efficacy of enteral feeding, but also adds to potential complications, distresses both patients and staff, and increases costs.\textsuperscript{6} Until recently, its pathogenesis has remained unknown, although a number of factors have been implicated, including infected diets,\textsuperscript{7} lactose intolerance,\textsuperscript{8} concomitant antibiotic therapy,\textsuperscript{9,10} osmotically active medications,\textsuperscript{11,12} and co-existing hypoalbuminaemia.\textsuperscript{13,14} However, despite attention to these factors, diarrhoea still occurs in up to 15% of patients.\textsuperscript{15} This would imply, therefore, that some other mechanism or mechanisms are involved.

Studies

In an attempt to unravel the pathophysiological mechanisms underlying enteral feeding related diarrhoea, a series of in vivo experiments in humans was undertaken examining the response of the small and large intestine to enteral feeding.\textsuperscript{16–20} In these studies two different strengths of a polymeric diet were infused either intragastrically or intraduodenally: a low load diet infused at 1.4 ml/min (1.4 kcal/min; 8.75 mgN/min) and a high load diet infused at 2.8 ml/min (4.2 kcal/min; 26.1 mgN/min). The low load diet corresponded clinically to the administration of 2 litres (2000 kcal) over 24 hours (equivalent to 2 litres/day), which is what most patients will receive on the wards. Catabolic patients or those being fed cyclically over 12–14 hours per day, a common situation especially in the home setting, require higher dietary loads—the high load diet in our studies corresponded to this type of feeding.

In the small intestinal studies intraduodenal feeding of the low load diet caused a normal postprandial pattern of small intestinal motility and an increase in the volume of fluid entering the colon (colonic in-flow). None of these subjects developed diarrhoea.\textsuperscript{16} However, during the intragastric administration of the same dietary load, both the small intestinal motility and the colonic in-flow remained similar to fasting, but the majority of these subjects developed diarrhoea.\textsuperscript{17} This led to the conclusion that the diarrhoea may be secondary to a disorder of colonic function.

To examine the colonic response to enteral feeding two sets of experiments were carried out—one to look at colonic water and electrolyte transport and the second to look at the motility responses. A new technique of in vivo colonic perfusion was designed to enable simultaneous assessment of water and electrolyte movement in the ascending and distal colon in response to the intragastric and intraduodenal infusion of the same low and high load diets.\textsuperscript{18} Notable secretion of water, sodium and chloride was shown in the ascending colon during the intragastric infusion of the low and high load diet, and during the intraduodenal infusion of the high load diet.\textsuperscript{19} This secretion amounted to approximately 120 ml/h. In the distal colon there was an absorption during fasting and feeding in all the groups.

In a further study the effects of short chain fatty acids (SCFA) on colonic water and electrolyte movement were investigated. These are by-products of carbohydrate fermentation in the colon,\textsuperscript{20,21} and play an important role in salt and water absorption.\textsuperscript{22,24} By infusing them directly into the caecum during enteral feeding, the ascending colonic secretion was reversed.\textsuperscript{25}

When looking at the motility responses, the distal colonic segmental motor activity was unchanged from fasting during the low load diet infusions,\textsuperscript{26} but during the high load infusions there was a significant suppression of activity, occurring immediately the intragastric infusion began, and within three hours of the start of the intraduodenal infusion.\textsuperscript{27}

Findings discussed

These experiments are the first to investigate colonic function during enteral feeding, and we believe that the colonic secretion of water and electrolytes is likely to be of primary importance in the pathogenesis of enteral feeding related diarrhoea. The secretion amounted to an overall colonic load of up to 135 ml/h (in the high load intragastric group) during a perfusion period of six hours. If it is possible to extrapolate this over a 24 hour period, the additional colonic volume would amount to 3.2 litres/day. The normal absorptive capacity of the human colon has been shown to be 5.7 litres/day,\textsuperscript{28} and from this information it may be supposed therefore that the colon ought to be able to absorb this extra fluid. In this study\textsuperscript{29} the caecum of volunteers was intubated and fluid infused at rates sufficient to cause an increase in stool frequency and volume. The figure of 5.7 litres/day was derived from the volume of fluid required to cause diarrhoea (stool weight > 200 g/day) plus the assumed caecal in-flow volumes, and therefore reflected the absorptive capacity of the entire colon. In the tube feeding studies the ascending colon, which in normal circumstances is the site of maximal fluid absorption,\textsuperscript{20} was secreting water and electrolytes, and therefore the absorptive capacity of the colon would have been seriously impaired, such that an increased colonic load of 135 ml/h could cause diarrhoea. To compound matters, the
suppression of segmental colonic motor activity, which will
result in accelerated transit of colonic contents, will
further diminish the absorptive capacity of the colon.

Clinically, diarrhoea occurs more commonly when sub-
jects are fed intragastrically with a high load enteral diet. It
is this group that has the greatest secretion and most
pronounced suppression of motility. In the low load groups,
where motility remains unchanged from the fasting state
and secretion only occurs in those fed intragastrically, di-
arrhoea has not been observed. Therefore, the clinical
observations—that is, the incidence of diarrhoea, are sup-
ported by the experimental results.

The changes in segmental colonic motor activity may be
associated with the alterations in fluid transport. However,
the relation between these two is not clear-cut. In the low
load group no changes in motor activity are observed,
whereas in the high load groups there is a significant sup-
pression of activity. This suppression of motor activity,
however, is unlikely to only occur as a direct result of the
colonic fluid secretion because, firstly, there are no changes
in motor activity in the low load group despite the overall
secretion and, secondly, the suppression of motor activity
in the high load intragastric group starts immediately feed-
ing is started and hence before there is any volume effect
from the secretion. Therefore, the mechanism underlying
the changes in fluid transport and motor activity must be
initiated from the proximal gastrointestinal tract, and are
likely to be either neural, hormonal, or both, in origin.

What mechanisms, therefore, could bring about these
colonic responses, and why do they differ with the site of
feeding and the dietary load? The experiments described
earlier have highlighted the paucity of work on in vivo
human colonic physiology, and the ensuing discussion is
based mainly on animal work, in vitro human studies and
speculation.

Mechanisms speculated

There are three phases to feeding: the first is the cephalic
phase from the vagally mediated response to visual, olfac-
tory and gustatory stimuli. The second is the gastric phase,
in which gastric distension stimulates mechanoreceptors. The third is the intestinal phase, in which chemoreceptors in the duodenum or proximal jejunum are sensitive to specific components of the diet. One
important factor likely to be of considerable relevance is
that the method of enteral feeding is not physiological. The
cephalic phase is abolished altogether; the continuous
infusion of diet into the stomach does not resemble normal
(bolus) eating and it is unlikely to cause sufficient gastric
distension to stimulate the mechanoreceptors; and during
intraduodenal feeding the gastric phase is completely
bypassed. Could it be, therefore, that the abnormal intesti
nal responses that we have observed is because of the
unphysiological nature of enteral feeding?

A recent study has shown that volunteers who swallow a
bolus of enteral feed do not get diarrhoea, whereas those
same volunteers receiving an identical bolus infused intra-
gastrically via a nasogastric tube invariably do. This raises
interesting questions about the cephalic phase. Could it
induce some neurohumoral response that prevents the
secretory effect in the ascending colon or the suppression of
colonic motor activity? Alternatively, could the presence of
a nasogastric tube be of importance? Rogers et al have
demonstrated an increase in distal colonic segmental
motor activity during food discussion, and in the same
study showed a significant increase in pancreatic polypep-
tide, gastrin and motilin concentrations, no change in cholecystokinin and neurotensin and a decrease in peptide YY (PYY) (although only from 31.7 (1.4) to 30.3 (1.1)
pg/ml/1). The same investigators also examined the effects
of the cephalic phase on the small bowel and showed an
increase in small intestinal fluid flow but no change in
motility. Another study has shown an increase in gastric
acid secretion and gastrin in response to food discussion,
sight and smell. These, however, are the only studies to
look specifically at the responses to the cephalic phase of
feeding.

Both the gastric and intestinal phases of feeding are
important in the normal postprandial responses, such as
the absorption of nutrients, fluid flow and the genesis of the
gastrocolic response. There have been a number of studies
identifying a jejunal pro-absorptive response induced by
nutrient osmolality and independent of the cephalic and
gastric phases. In the small intestinal tube feeding studies
motility remained in the fasting state during intragastric
feeding, but was converted appropriately to the normal
postprandial pattern during intraduodenal feeding. In these
same studies colonic in-flow was increased during
intraduodenal feeding and remained unchanged from fast-
ning during intragastric feeding. In other words, intragastric
feeding did not seem to induce any changes in the small
intestine compatible with a fed state. The same dietary load
infused intraduodenally, however, did bring about these
changes. This would imply that the intestinal phase of
feeding is appropriately activated during intraduodenal
feeding and that this is responsible for the normal postprandial responses observed in the small intestine,
whereas during intragastric feeding, because of the gradual
release of gastric contents through the pylorus, the thresh-
hold required to activate these responses is not reached.
This statement would be supported by those studies identifying
the proximal small intestine as the key to initiating the
pro-absorptive response.

In the colonic studies, however, the secretion in the
ascending colon was seen in those fed intragastrically.
Having stated that this site of diet administration probably
does not initiate normal postprandial responses, how can
the secretory effect be explained? One possible explanation
is that both the gastric and intestinal phases of feeding
control the colonic response. It is known that gastric emp-
yting is delayed during intragastric diet infusion via intesti-
nal feedback inhibition. Acid pH, hyperosmolality, diges-
tible fat and carbohydrate in the proximal small intestine
all inhibit gastric emptying. Therefore, during
intragastriac feeding there may be stimulation of neurohu-
moregulatory mechanisms while the diet is retained in
the stomach, and this may explain why a colonic secretion
was seen during the intragastric but not the intraduodenal
infusion of the low load diets. However, it must be stated
that these studies were designed to examine the “end-
organ”—that is, colonic, responses to enteral feeding, and
unfortunately there have been no studies to date looking
for the presence and function of receptors in the proximal
gastrointestinal tract which may initiate such colonic
responses. Presumably the possible stimuli to which these
putative receptors respond include osmolality, nutrients
(for example, fat, amino acids) and volume. Chemorecep-
tors in the duodenum and proximal jejunum respond to
osmolality, fat, glucose, and protein, and distension
has been shown to be an effective stimulus of secretion. Any
of these factors may play an important role in the
colonic responses to enteral feeding.

Colonic motor activity and especially the gastrocolic
response is also likely to be important in responses to
feeding. A 1000 kcal meal can induce the gastrocolic response
while a 350 kcal meal cannot. It has been well established
that the fat component of the diet is a major stimulant of
colonic motility. Oral ingestion of 600 kcal of fat can
induce the same gastrocolic response as a 1000 kcal
meal, and a similar response has been shown with both
Neurohumoral mechanisms

Having discussed the abnormal responses set off by enteral feeding, what are the likely neurohumoral mechanisms that could be responsible? During the various perfusion and motility studies serum was taken for vasoactive intestinal polypeptide (VIP), neuropeptide Y, pancreatic glucagon, and PYY. The concentrations of the first three did not alter at all.

However, PYY increased significantly during intraduodenal feeding but not during intragastric feeding, and the magnitude of this increase was similar to other studies.61 62 PYY is a polypeptide found primarily in mucosal endocrine cells of the ileum, colon and rectum.63 65 66 The gastrointestinal effects of PYY include reduced gastric and pancreatic secretion,66–68 delayed gastric emptying,69 70 slowing of small bowel transit,71 and an increase in small and large intestinal absorption of water and electrolytes.72 73 The pro-absorptive effect of PYY in the intestine is thought to be regulated through c-AMP mediated mechanisms.74 76 There are a group of Y receptors in the intestine which operate to increase intracellular c-AMP in response to the intragastric infusion of whole diets, but we would suggest that the absence of this gastrocolic response is a normal outcome of enteral feeding.

Intragastric feeding, when there is no rise in PYY concentrations—hence a relatively slow rate, there is insufficient stimulus to induce a gastrocolic response. We are unaware of any studies that have specifically looked at the colonic motor response to the intragastric feeding of whole diets, but we would suggest that the absence of this gastrocolic response is a normal outcome of enteral feeding.

Clinical implications

At a clinical level, how might these studies influence clinical practice, especially as intragastric feeding consistently leads to more profound changes in both water and electrolyte secretion, in the suppression of colonic motor activity and, more importantly, to an increased incidence of diarrhoea? Intraduodenal feeding is a physiological method of feeding, in that it provides nutrients to the small intestine in a similar way to the gradual release of gastric contents through the pylorus. Intragastric feeding, however, is unphysiological, and this may be the underlying reason for the abnormal colonic responses that have been observed. Bolus feeding, which is more physiological, has acquired a bad reputation in terms of side effects and complications although there are very few data to actually support this standpoint, and perhaps this method of feeding needs careful evaluation. It would seem logical to suggest that perhaps patients should preferentially be fed postpylorically. Certainly, this could be considered in patients at greater risk of developing diarrhoea, such as those on antibiotics or with hypoalbuminaemia. There are, however, no controlled clinical trials looking at the outcome of pre- and postpylorically fed patients. The experimental findings described above might also imply that if the concentration of caecal SCFA can be increased by diets containing a fibre
source, there may be an improvement in enteral feeding related diarrhoea by reducing, if not reversing, the colonic secretion. It should be remembered, however, that experiments using an in vitro study system have shown that production of SCFA by human colonic polysaccharidase enzyme systems is notably reduced when antibiotics are added to the culture medium. If colonic SCFA are reduced in vivo in patients on antibiotic therapy, this may explain why the incidence of enteral feeding related diarrhoea is so high in patients on concomitant antibiotic therapy, and also why controlled trials have failed to show a beneficial effect of fibre supplemented enteral diets in reducing or reversing the incidence of diarrhoea in enterally fed patients.9 90–92

The future
There is thus still considerable scope for further investigation into this very important clinical problem. More information on basic human in vivo intestinal physiology is the key to clarifying matters. Hormonal analysis during enteral feeding may provide a vital link between proximal nutrient infusion and its distal secretory effect. It would clearly be of great interest to look at the colonic responses to intragastric and intraduodenal bolus feeding, and also to investigate which nutrients in enteral diets are responsible for triggering the distal colonic secretion. The cephalic phase of feeding, or rather its abolition during tube feeding, may play an important role in the physiological responses and this aspect is currently very under-researched. Finally, further work on SCFA is required in terms of their possible therapeutic effects, the role of fibre containing diets and ways of incorporating SCFA into enteral diets, such as micro-encapsulation, so that they arrive in the caecum unaffected by their passage through the small intestine.

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