Gut

Leading article

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[1–3] and 63% of patients on intensive care units.[4 5] Diarrhoea not only limits the efficacy of enteral feeding, but also adds to potential complications, distresses both patients and staff, and increases costs.[6] Until recently, its pathogenesis has remained unknown, although a number of factors have been implicated, including infected diets,[7] lactose intolerance,[8] concomitant antibiotic therapy,[9 10] osmotically active medications,[11 12] and co-existing hypoalbuminaemia.[13 14] However, despite attention to these factors, diarrhoea still occurs in up to 15% of patients.[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.[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.[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.[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.[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.[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,[20 21] and play an important role in salt and water absorption.[22–24] By infusing them directly into the caecum during enteral feeding, the ascending colonic secretion was reversed.[25]

When looking at the motility responses, the distal colonic segmental motor activity was unchanged from fasting during the low load diet infusions,[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.[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,[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[28] 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,[29] 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,[30] will further diminish the absorptive capacity of the colon.

Clinically, diarrhoea occurs more commonly when subjects are fed intragastrically with a high load enteral diet.[27] It is this group that has the greatest secretion and most profound suppression of motility. In the low load groups, where motility remains unchanged from the fasting state and secretion only occurs in those fed intragastrically, diarrhoea has not been observed. Therefore, the clinical observations—that is, the incidence of diarrhoea, are supported 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 groups no changes in motor activity are observed, whereas in the high load groups there is a significant suppression 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 feeding 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, olfactory and gustatory stimuli.[31] The second is the gastric phase, in which gastric distension stimulates mechanoreceptors.[32] The third is the intestinal phase, in which chemoreceptors in the duodenum or proximal jejunum are sensitive to specific components of the diet.[32] 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 intestinal 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 intragastrically via a nasogastric tube invariably do.[33] 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,[34] and in the same study showed a significant increase in pancreatic polypeptide, 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) pmol/1).[35] 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.[36] Another study has shown an increase in gastric acid secretion and gastrin in response to food discussion, sight and smell.[31] 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.[37–43] 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.[16 17] In these same studies colonic in-flow was increased during intraduodenal feeding and remained unchanged from fasting 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 threshold 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.[37–43]

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 emptying is delayed during intragastric diet infusion via intestinal feedback inhibition.[44] Acid pH,[45] hyperosmolality,[46] digestible fat and carbohydrate[45 47] in the proximal small intestine all inhibit gastric emptying. Therefore, during intragastric feeding there may be stimulation of neurohumoral 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. Chemoreceptors in the duodenum and proximal jejunum respond to osmolality,[41] fat,[48 49] glucose,[50] and protein,[51] and distension has been shown to be an effective stimulus of secretion.[52 53] 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.[54] It has been well established that the fat component of the diet is a major stimulant of colonic motility.[55] Oral ingestion of 600 kcal of fat can induce the same gastrocolic response as a 1000 kcal meal,[55 56] and a similar response has been shown with both

a 500 kcal fat meal[57] and the duodenal infusion of 178 kcal of lipid over 30 minutes.[32 58] Neither oral ingestion of amino acids[55 59] nor intraduodenal infusions of saline, glucose and amino acids separately[32] induce a gastrocolic response. In our studies the low load diets only provided 1.39 kcal/min or 83 kcal/h, and the high load diets 4.2 kcal/min or 252 kcal/h, providing 47 kcal/h fat, 22 kcal/h protein and 66 kcal/h carbohydrate. As the threshold for a bolus meal inducing a gastrocolic response lies between 350 and 1000 kcal,[18] even with the high load diets it would take 83 minutes to provide 350 kcal. It would seem, therefore, that because nutrients are delivered to the proximal gastrointestinal tract during enteral feeding at such 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 infusion of whole diets, but we would suggest that the absence of this gastrocolic response is a normal outcome of enteral feeding.

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), neurotensin, 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,[60] 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.[61 63–65] 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 concentrations and thereby stimulate intestinal secretion.[77] It is this mechanism by which VIP stimulates a secretory response. PYY has a high affinity especially for the Y4 receptor subtype and it can inhibit the increase in c-AMP concentrations, thereby inhibiting secretion.[76 78]

There are a growing number of stimuli of PYY secretion, including cholecystokinin, gastric inhibitory peptide, bombesin, cholinergic and adrenergic agonists, bile acids, SCFA, and fibre.[79 80] PYY concentrations also increase after ingestion of a meal, but there is a calorie threshold of at least 530 kcal below which there is no rise in PYY.[61] As discussed earlier, this will not be exceeded during intragastric feeding, but clearly there is sufficient stimulus during intraduodenal feeding to induce PYY secretion, a finding shown in several studies.[41 43 60]

We can hypothesise from our studies that a secretatogogue is released during enteral feeding, which is inhibited by PYY during intraduodenal feeding but not during intragastric feeding, when there is no rise in PYY concentrations—in other words there is a loss of a negative feedback loop. The nature of this secretatogogue, however, is not clear. Although a lot is known about the small intestinal responses to feeding and the neurohumoral influences on water and electrolyte movement, very little is known about the colonic responses, either in vitro or in vivo. The only hormone known to cause colonic secretion of water and electrolytes is VIP.[77 81–83] Although VIP concentrations remained unchanged throughout our studies, there are several other peptides in the VIP "family" which can bind to VIP receptors and have a similar effect on intestinal secretion, but yet are not detected by the specific VIP assay. One such peptide is pituitary adenylate cyclase-activating polypeptide (PACAP).[84] However, little is known about its biological characteristics, and specifically whether it is released postprandially. In a recent study Schubert *et al* demonstrated that different grades of gastric distension led to differing hormonal responses, with lower grades of distension to only 10% of normal feeding capacity leading to activation of VIP neurones, while higher grades of distension do not.[85] It is possible that a VIP-like peptide could act as a secretatogogue released during the continuous intragastric infusion of a polymeric diet and consequent low grade gastric distension, and without the pro-absorptive effect of PYY (owing to insufficient nutrienuyt stimulation) to counteract the effect of the VIP-like peptide, a colonic secretion ensues.

Other than VIP little is known about the possible effects of other hormones on the human colon. Pancreatic peptide, neuropeptide Y, PYY[72 76] vasopressin, and somatostatin[86] have all been shown to stimulate colonic absorption of water and electrolytes in in vitro animal studies. There have been only a few studies examining the influence of hormones on colonic motility. Motilin, cholecystokinin,[87] neuropeptide Y, pancreatic polypeptide, and PYY[87 88] have all been shown to increase colonic motor activity, again all in animal studies. No studies, to our knowledge, have demonstrated a hormonally mediated suppression of colonic motor activity.

The hormonal data we obtained during our studies are very limited and although it is tempting to implicate PYY in the pathogenesis of enteral feeding related diarrhoea, it is clear that this may well be too simplistic. There are very few in vivo human studies looking at colonic function and, prior to the experiments described above, there have been no studies examining the colonic responses to enteral feeding. Therefore, on the basis of current knowledge, it is difficult to hypothesise on the mechanisms underlying the colonic secretion and suppression of motor activity that have been demonstrated during enteral feeding. No one mechanism seems to unify these observed colonic changes, and more information on the human colonic responses to feeding is required before an explanation is likely to be forthcoming.

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 stool culture system have shown that production of SCFA by human colonic polysaccharidase enzyme systems is notably reduced when antibiotics are added to the culture medium.[89] 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,[9 90] 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 also be playing 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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