Diarrhoea in the enterally fed patient

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Diarrhoea complicating enteral feeding is very common in all clinical settings. The major risk factor is the use of concomitant antibiotics. The underlying mechanisms for the diarrhoea mainly relate to alterations in the colonic flora and physiological responses to the mode of feed delivery although a clear understanding of what is actually happening in vivo remains elusive. Management of diarrhoea includes rationalising medications, excluding relevant comorbidity and using antidiarrhoeal medications. Altering the method and site of feed delivery—for example, continuous to bolus, gastric to postpyloric—can also be tried in the more difficult cases.

Introduction

Diarrhoea occurring in the enterally fed patient is a common problem, with a reported incidence ranging from 6% to 60%. This large variability is a reflection of the heterogeneity of patients and case mix in the various studies and of the definitions used for diarrhoea. Patients range from critical care to community based elderly, all with varying degrees of comorbidity and polypharmacy. The definitions of diarrhoea are even more variable—33 quoted in a recent paper.[1] Many studies utilise consistency, frequency, stool volume and stool weights either alone or in many different combinations. Some studies have developed diarrhoea scores,[2 3] others just cite 'inconvenient' bowel activity and several have no definition at all.[4] What this all means is that it is difficult to truly determine from the literature how much of a problem there is with diarrhoea in the enterally fed patient.

Causes

Microbiota and antibiotics

The most common association between diarrhoea and enteral feeding remains the concomitant use of antibiotics. The mechanisms that cause the diarrhoea are still disputed but probably involve the colonic flora and short chain fatty acids (SCFA).

The make-up of colonic flora is highly individual and, at least in part, influenced by diet. Studies in both healthy volunteers and patients have demonstrated that enteral feeding influences the flora.[5 6] However, these and other studies demonstrate that the variability in colonic bacterial populations between individuals is enormous, as are any changes that might be observed after intervention, such as antibiotics or enteral feeding. Furthermore, the techniques for analysing colonic bacteria have changed. In the last century, this was primarily done by culturing stool samples, which gives a poor reflection of the bacterial 'situation' within the colon itself. More recently, nucleotide probes targeting specific bacterial groups are being utilised, which marks a substantial improvement in our abilities to understand in vivo activities. These technological changes show up the earlier techniques in a bad light and call into question the scientific robustness of earlier studies and therefore how far their results can be interpreted and utilised.

A recent and very comprehensive meta-analysis has demonstrated a significant reduction in the percentage of patients with diarrhoea when fed with a fibre containing enteral feed (odds ratio of 0.68, with 95% confidence interval of 0.46 to 0.95).[7] Nakao *et al* reported an increase in the ratio of anaerobic to aerobic bacteria with fibre supplemented enteral feeds, which they contended could be protective against diarrhoea on the basis that anaerobic bacteria may suppress the overgrowth of potential pathogens.[8] The benefit of fibre is not necessarily just down to the alteration of this anaerobic:aerobic ratio. SCFAs are almost certainly of some relevance. Their actions, among many, increase salt and water absorption in the ascending colon and are produced primarily by colonic digestion of fibre. In vivo human volunteer studies have demonstrated that enteral feeds with fibre enhance SCFA concentrations and water absorption compared with those without fibre, thereby identifying a possible mechanism for improving diarrhoea.[9] However, clinical studies proving that

SCFA concentrations directly influence the development of diarrhoea are absent.

Antibiotics also affect the colonic flora. Bliss *et al* reported that 93% of patients on enteral tube feeding also receive antibiotics at some point.[10] Antibiotic associated diarrhoea occurs in 5–25% of patients, with *Clostridium difficile* accounting for up to a quarter of these.[11] Diarrhoea is more likely to occur after broad spectrum antibiotics, especially those that target anaerobes, such as the cephalosporins, broad spectrum penicillins and clindamycin. There is no evidence that enteral feeding and antibiotics given concurrently act synergistically to increase the incidence of diarrhoea, and it is probably the case that they are both risk factors acting independently of each other.

Overall, there is little consistent pattern to any changes in bacterial flora either between individuals who develop diarrhoea or between individuals who do not, whether given fibre diets or antibiotics, and whether healthy volunteers or patients. All of this indicates that either we do not understand enough about intestinal bacterial physiology or that there are other mechanisms being brought to bear that have not been considered, or a combination of both—the latter being the most likely. This is illustrated by a recent study which identified that patients developing diarrhoea with enteral feeding had higher *Clostridium* and lower *Bifidobacteria* counts compared with patients without diarrhoea.[12] However, these patients had similar bacterial flora at the beginning of the prospective 14 day study as they did at the end, so it was not a change in bacterial flora that contributed to the genesis of the diarrhoea, and it may just suggest that some patients are more predisposed to developing diarrhoea on the basis of a pre-existing dysbiosis. Clearly much more research is required in this area.

Gut hormones

Intact neurohumoral function plays a fundamental role in controlling intestinal function and disturbance can lead to diarrhoeal states, such as dumping syndrome following vagotomy and neuroendocrine tumours (eg, vipomas, Zollinger–Ellison syndrome). Intestinal neurohumoral physiology is a rapidly expanding and complex field, and a more eloquent exposition of potential mechanisms relevant to bowel function in the enterally fed patient is well beyond the scope of this article.

In brief, enteral feeding is a very unphysiological way of administering nutrients. It entirely bypasses the cephalic phase of feeding—the reaction to anticipation, smell, taste and texture of food—which plays an important role in stimulating postprandial changes. To stimulate normal postprandial physiology requires a fairly substantial caloric load, with evidence suggesting that at least 530 kcal as a bolus being required.[13 14] Intragastric pump feeding delivering 80 ml/h of a 1 kcal/ml feed (a typical rate in clinical practice) comes nowhere near this and in human volunteer studies does not stimulate the normal postprandial neurohumoral responses. The same infusion given postpylorically does, however, stimulate physiology more appropriately,[15] as would presumably an adequate bolus of intragastric feed (not tested in this study), both of these being much more physiological ways of introducing nutrition into the upper gastrointestinal tract. Put in a very simplistic way, a small intestine not primed for food is not able to process it properly. The fasting state leads to fairly rapid delivery of small intestinal content into the colon. The fed state leads to greater motor activity, slower transit to maximise digestion and stimulates the ileal brake, which slows release of small intestinal content into the colon. Therefore, on the basis of some small physiologically orientated studies, standard intragastric pump feeding does not stimulate the gastrointestinal tract out of its fasting state and this could lead to a greater fluid burden being presented to the colon and consequently result in diarrhoea. There are, however, no clinical studies that have evaluated bowel function between gastric and postpyloric feeding or even between continuous and bolus intragastric feeding. Hence, on the back of very limited evidence, but perhaps intuitively, it probably is the case that the manner in which standard enteral feeding is administered must be a contributing factor to the abnormal bowel function that so often ensues.

Other factors

Infected diets, hypoalbuminaemia, hyperosmolar feeds and lactose intolerance have all been proposed as potential causes or risk factors to enteral feeding related diarrhoea. The record needs to be put straight on these.

1. *Infected diets.* A diet infected in the reservoir could lead to diarrhoea. Given that almost all feeds are prepared commercially in sterile conditions, such an infection would have to be acquired retrogradely, either introduced by staff when attaching the giving set or from the lungs/stomach and then ascending into the reservoir and multiplying there before being delivered into the patient. There is plenty of evidence that diets can be infected in this way but no adequate clinical evidence that this leads to diarrhoea 'at the other end'.
2. *Hypoalbuminaemia.* This has been cited as a risk factor for enteral feeding related diarrhoea on the basis that it can lead to intestinal oedema and increased secretions. There is no adequate clinical evidence to support this, and it is much more likely that hypoalbuminaemia is simply a marker of a sick patient who is more predisposed to developing diarrhoea during enteral feeding for other reasons.
3. *Diet osmolality.* Despite much hype that this is a relevant issue—and the rationale for using starter regimens—there has never been any evidence to confirm that hyperosmolar diets cause diarrhoea.[16 17]
4. *Lactose intolerance.* Another mythological cause of enteral feeding diarrhoea. All commercially prepared feeds are lactose free.

Apart from pre- and probiotics, which have excited interest in many different spheres, there has been very little work done on understanding the physiological responses to enteral feeding and the causation of diarrhoea in the past two decades, which reflects the low importance given to such matters by grant giving bodies and also by industry, probably in part because of the lack of potential for commercial gain. Overall, there is no one cause of diarrhoea in enterally fed patients but a number of contributing risk factors. Intuitively, it is logical that diarrhoea occurring in the enterally fed patient is influenced directly by alterations in colonic function and physiological alterations brought about by an unphysiological method of feeding. The few clinical studies undertaken looking specifically at enteral feeding related diarrhoea are small in number and have at best only been able to come up with interesting theories and directions for future research.

Management

As indicated in the introduction, one problem that has blighted clinical studies on enteral feeding related diarrhoea is the lack of consensus on definition. Away from the arena of clinical trials, patient management will be governed by a more pragmatic approach to bowel function, and the definition that many use is that which 'causes inconvenience to patient and/or carer'.

The first step in managing a patient with such a disturbance in bowel function is to consider causes other than enteral feeding. For example:

Medication

(a) *Antibiotics.* For all the reasons discussed above, antibiotic usage must be scrutinised and stopped if possible.
(b) *Osmotically active medications.* This primarily relates to sorbitol which is present in many elixirs. Given that many patients on enteral feeding are, by necessity, on elixir medication as they are unable to swallow tablets or have these introduced by the feeding tube, sorbitol intake is common but often not appreciated.
(c) Other medications which list diarrhoea as a potential side effect. If appropriate these should be stopped.

Comorbidity

(a) Many gastrointestinal diseases may cause diarrhoea, and these need to be considered, investigated for and dealt with where appropriate.
(b) Diabetes.
(c) Thyroid dysfunction.
(d) Any other of the very many causes of diarrhoea.

The comprehensive investigation of diarrhoea is beyond the scope of this article but clearly there will be some situations where more esoteric explanations for diarrhoea may be in play, despite the concurrent use of enteral feeding. Such situations would need to be considered on an individual basis.

Having ruled out any obvious risk factors, simple antidiarrhoeal agents, such as loperamide or codeine phosphate, are often very effective. For patients on short term feeding, in whom the diarrhoea is controlled by such measures, it is probably not necessary to do anything more. These are, however, just symptomatic remedies which do not attempt to manipulate a cause. For patients either on longer term feeding or who are not responding very effectively to antidiarrhoeal measures, the following options can be considered.

Fibre and pre/probiotics

Many would argue—reasonably—that a fibre containing feed should be the default from the beginning. Human physiology and normal diets are designed to contain fibre. It is therefore illogical to subject someone on enteral feeding not only to an unphysiological method of feeding but also to an unphysiological diet. If, however, the feed being used is a standard non-fibre one, then switching to a fibre feed would be worth trying—the rationale being the theoretical effects that this would have on SCFA production by the colonic flora (see above). The evidence that this actually makes a difference is reasonably convincing, as Elia *et al* described in their meta-analysis, despite the heterogeneity of the studies, patient case mix, fibre types and end points studied.[7]

As an extension to the fibre rationale, it does not take a huge leap of understanding to appreciate the potential benefits of prebiotics and probiotics. Several small studies of both probiotics and prebiotics have demonstrated alterations in the colonic flora within individuals but, as described above, the wide variations of 'baseline' flora between individuals makes it impossible to interpret what these changes actually mean (if anything). The use of prebiotics and probiotics is considered to be safe.[18] *Saccharomyces boulardii* has been shown to be of benefit in reducing diarrhoea in an intensive care unit setting.[19] However, although there have been (small) studies on lactobacilli and bifidobacteria (probiotics), and fructo-oligosaccharides and inulin (prebiotics) in the clinical setting, no convincing evidence of benefit has resulted. Therefore, the place for prebiotics and probiotics in the management of diarrhoea in the enterally fed patient should remain in the setting of clinical trials or desperation!

Mode and site of feeding

This relates to continuous or bolus feeding; gastric or postpyloric feeding; and manipulating the volume of feed.

The rationale for the more physiological methods of gastric bolus or postpyloric feeding has been explored earlier. There are no clinical studies to support switching from pump feeding to one or other of these methods, but in a situation where bowel function is causing significant problems and not being resolved by more straightforward means (antidiarrhoeal agents, rationalising other medications, etc) then it is certainly worth trying. Additionally, giving smaller volumes of more calorie dense feeds is also an

approach worth attempting although, again, without any evidence base.

The final sanction for the truly intransigent diarrhoea in those without other aetiology is to resort to parenteral feeding and rest the gut entirely. In a career now spanning 20 years in gastroenterology and specialist nutrition support, this author has had to resort to parenteral feeding in such a situation on only two occasions.

Conclusion

Diarrhoea complicating enteral feeding is common. Colonic flora, SCFA and physiological responses to the mode of enteral feed delivery are probably key to the mechanisms that underlie it. Depressingly, however, understanding the problem has hardly moved forwards in the past decade and there remain very basic questions on gut physiology that are unanswered. There is much scope for further research into this neglected area.

Management of diarrhoea remains a combination of removing risk factors where possible, such as concomitant antibiotics, and treating symptomatically with antidiarrhoeal medications. For the more difficult cases, manipulating feed delivery (eg, bolus, postpyloric) can be of help.

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