**Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs**

**Summary**

Measurements of luminal pH in the normal gastrointestinal tract have shown a progressive increase in pH from the duodenum to the terminal ileum, a decrease in the caecum, and then a slow rise along the colon to the rectum. Some data in patients with ulcerative colitis suggest a substantial reduction below normal values in the right colon, while limited results in Crohn’s disease have been contradictory. Determinants of luminal pH in the colon include mucosal bicarbonate and lactate production, bacterial fermentation of carbohydrates and mucosal absorption of short chain fatty acids, and possibly intestinal transit. Alterations in these factors, as a result of mucosal disease and changes in diet, are likely to explain abnormal pH measurements in inflammatory bowel disease (IBD). It is conceivable that reduced intracolonic pH in active ulcerative colitis impairs bioavailability of 5-aminosalicylic acid from pH dependent release formulations (Asacol, Salofalk) and those requiring cleavage by bacterial azo reductase (sulphasalazine, olsalazine, balsalazide), but further pharmacokinetic studies are needed to confirm this possibility. Reports that balsalazide and olsalazine may be more efficacious in active and quiescent ulcerative colitis, respectively, than Asacol suggest that low pH may be a more critical factor in patients taking directly pH dependent release than azo bonded preparations. Reduced intracolonic pH also needs to be considered in the development of pH dependent colonic release formulations of budesonide and azathioprine for use in ulcerative and Crohn’s colitis. This paper reviews methods for measuring gut pH, its changes in IBD, and how these may influence current and future therapies.

**Introduction**

Over the past 15 years, the development of radiotelemetric technology has made possible the measurement in vivo of the luminal pH of the entire human gastrointestinal tract using orally ingested free fall pH sensitive capsules. In this review, we compare methods available for investigating gut pH distal to the stomach, describe the pH profiles obtained in normal controls and in patients with inflammatory bowel disease (IBD), and discuss the mucosal and luminal factors likely to account for differences in health and disease. Lastly, we consider the therapeutic implications of altered gut pH in IBD and, in particular, the potential influence of reduced colonic pH on the bioavailability of drugs such as 5-aminosalicylic acid (5-ASA), which are formulated in a pH dependent release system.

**Measurement of intestinal luminal pH**

Luminal gut pH can be measured directly in vivo using either radiotelemetric capsules (RTC) or tube mounted pH sensitive electrodes passed orally. Peri-mucosal colonic pH can be recorded in vivo by electrodes inserted endoscopically as well as applied directly in vitro to biopsies or operative specimens.

**Radiotelemetric measurement of intraluminal gut pH**

RTC consist of a reference and pH sensitive electrode which samples and transmits the pH of the gut lumen. They are battery powered, approximately 20×7 mm in size, and contain a radiofrequency transmitter. Signals can be transmitted at frequencies of 6–60/second and are received by an aerial and stored on a data logger. The orally ingested RTC take 1–5 days to pass through the gastrointestinal tract by free fall.

The approximate location of the capsule in relation to surface abdominal landmarks can be determined either by fluoroscopy or by identification of the maximal radio signal with the help of a radio receiving probe. Although this method of identifying the site of the capsule does not allow its precise location in relation to sphincters and other intestinal anatomical sites, the pH changes themselves indicate the location of the electrode. For example, a sudden fall in pH when the probe is in the right iliac fossa indicates its arrival in the caecum.

**Another problem with radiotelemetry pH recording is poor signal quality. Effective data transmission and retrieval is necessary to construct a pH profile for all segments of the gut. Low signal strength occurs when the capsule in the gut lumen and the aerial are not optimally aligned or when the capsule exceeds the optimal distance to the aerial for maximum reception of the transmitted signal, a frequent problem in the colon. Some studies have reported up to 75% data loss in individual patients.

**Measurement of intraluminal gut pH using per oral tube mounted electrodes**

Per oral tube mounted pH electrodes measure small bowel and right colonic luminal pH accurately and continuously. The pH catheter is passed into the stomach and the tip of the tube manoeuvred across the pylorus under fluoroscopy; a small balloon inflated at the tip assists passage through the small intestine into the colon. Luminal pH measurements are recorded and stored by a digitrapper from several electrodes positioned at specific intervals along the axis of the tube; their anatomical location can be identified fluoroscopically. This method avoids a potential hazard of the radiotelemetric capsule, namely impaction at the site of small bowel strictures in patients with Crohn’s disease with consequent intestinal obstruction.

**MEASUREMENT OF PERI-MUCOSAL COLONIC pH**

Peri-mucosal pH can be measured by endoscopic placement of pH sensitive electrodes on to the luminal surface of the colonic mucosa. A surface layer of mucus approximately 100–800 µm thick covers the mucosa. Beneath this layer and adjacent to the apical membrane lies an area apparently protected from the contents of the lumen and relatively unaffected by changes in the colonic lumen. The...
In vitro, a mean perimucosal surface pH of 6.6 was recorded in rat colonic mucosa and human rectal biopsy specimens. However, the in vivo surface pH of human colonic mucosa ranged between 7.1 and 7.5 and was consistently higher at all anatomical segments than luminal pH. The fall in luminal pH is in part attributable to the action of colonic bacteria which ferment carbohydrates entering the caecum from the ileum generating the short chain fatty acids (SCFA) acetic, propionic, and butyric acid, and hydrogen ions. The SCFAs are weak acids, pKa 4.8, and are present as organic anions in the normal colonic lumen. The faecal concentration of these organic anions is negatively correlated with faecal pH. SCFAs, especially butyrate, are absorbed and metabolised by the colonic epithelium for which they are a principal energy source.

A falling intraluminal concentration of SCFAs may contribute, in common with colonic mucosal bicarbonate secretion, to a pH rise along the distal colon. A slight drop in pH may occur in the rectum due to faecal stasis and the subsequent action of colonic bacteria fermenting any remaining carbohydrates.

Ammonia is formed in the colonic lumen from the bacterial metabolism of proteins, amino acids, and particularly urea. While, theoretically, a high protein diet may therefore raise colonic pH, the influence of ammonia on colonic pH is thought to be smaller than that of bicarbonate and organic acids.

Dietary intake can influence intracolonic pH through its effects on SCFA production. Thus increased dietary fibre, as well as non-absorbable sugars such as lactulose, increase caecal acidity by providing a carbohydrate meal to colonic flora.

The effects of lactulose on gut pH may also be modified by its effects on intestinal transit. However, the effects of changes in colonic transit time on intraluminal pH are difficult to predict. Theoretically, a shortened transit time could either increase pH by reducing the time available for bacterial fermentation of carbohydrates to SCFAs or decrease it by causing carbohydrate starved bacteria to produce more lactate. In fact, a mixture of magnesium sulphate and carbonate given to healthy volunteers in sufficient doses to increase stool weight threefold produced no change in pH in the colon itself, and a small rise in the rectum. Conversely, in a study of gall stone patients with slow transit constipation, there was a higher proximal colonic pH (6.8) than in controls (pH 6.4).

The almost neutral small bowel contents then empty into the caecum where the luminal pH (6.4) is relatively acidic. This fall in luminal pH is in part attributable to the action of colonic bacteria which ferment carbohydrates entering the caecum from the ileum generating the short chain fatty acids (SCFA) acetic, propionic, and butyric acid, and hydrogen ions. The SCFAs are weak acids, pKa 4.8, and are present as organic anions in the normal colonic lumen. The faecal concentration of these organic anions is negatively correlated with faecal pH. SCFAs, especially butyrate, are absorbed and metabolised by the colonic epithelium for which they are a principal energy source.

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controls. Colonic luminal pH; pH was again higher than in normal
mild-moderately active ulcerative colitis had no decrease in

Table 3 Intestinal luminal pH, measured using radiotelemetry capsules, in patients with ulcerative colitis (UC)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with UC</th>
<th>Proximal</th>
<th>Distal</th>
<th>Caecum/right colon pH</th>
<th>Left colon/rectal pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raimundo, 1992a</td>
<td>7 active</td>
<td>6.1</td>
<td>7.2</td>
<td>4.7</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>6 inactive</td>
<td>5.9–6.6</td>
<td>6.9–7.4</td>
<td>4.9–5.5</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>3 very active</td>
<td>Normal range</td>
<td>Normal range</td>
<td>Normal range</td>
<td>N/A</td>
</tr>
<tr>
<td>Press, 1998bc</td>
<td>7 active</td>
<td>6.8</td>
<td>8.2</td>
<td>7.2</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>4 inactive</td>
<td>6.5</td>
<td>7.9</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Ewe, 1999d</td>
<td>4 active</td>
<td>6.5</td>
<td>6.8</td>
<td>5.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Nugent, 2000f</td>
<td>6 active</td>
<td>7.3</td>
<td>8.3</td>
<td>6.7</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(5.8–7.3)</td>
<td>(4.8–7.3)</td>
</tr>
</tbody>
</table>

N/A, data not available.

Table 4 Intestinal luminal pH, measured using radiotelemetry capsules, in patients with Crohn’s disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with CD</th>
<th>Proximal</th>
<th>Distal</th>
<th>Caecum/right colon pH</th>
<th>Left colon/rectal pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fallingborg, 1998g</td>
<td>9 with ileocaecal resections</td>
<td>6.3</td>
<td>7.3</td>
<td>6.7</td>
<td>N/A</td>
</tr>
<tr>
<td>Sasaki, 1997h</td>
<td>3 active+1 inactive</td>
<td>7.2</td>
<td>7.8</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Press, 1998i</td>
<td>5 active</td>
<td>6.5</td>
<td>7.9</td>
<td>7.2</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>7 inactive</td>
<td>6.8</td>
<td>8.2</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Ewe, 1999j</td>
<td>12 active</td>
<td>6.5</td>
<td>7.5</td>
<td>6.2</td>
<td>6.5</td>
</tr>
</tbody>
</table>

N/A, data not available.

In one study, a low colonic luminal pH, similar to that reported in patients with active ulcerative colitis, was found in patients with Crohn’s disease. Four patients with Crohn’s colitis, three active, had lower right (pH 5.3) and left (pH 5.3) colonic luminal pH values than normal controls (pH 6.8). The reported tendency for pH to rise from the right to the left colon was lost in two of the four patients but there was no obvious relation between gut luminal pH and mucosal disease activity or site. Press et al and Ewe et al failed to confirm these findings. In a total of 24 patients with Crohn’s disease, small bowel and colonic luminal pH was similar to that recorded in healthy control subjects, irrespective of disease activity or site. In a fourth report, right colonic pH (mean 6.7) was higher in nine patients with an ileocaecal resection for Crohn’s disease than in 13 normal controls (mean pH 5.7) but was still within the normal range; neo-terminal ileal pH (7.3) was normal.

Determinants of colonic luminal pH in IBD

Reduced mucosal bicarbonate secretion, increased mucosal and bacterial lactate production, and impaired SCFA absorption and metabolism may each contribute to a reduction in colonic luminal pH in patients with inflamed colonic mucosa. Changes in intestinal transit and dietary fibre intake during an acute flare up may also influence colonic pH.

Decreased faecal bicarbonate concentration and reduced rectal mucosal bicarbonate secretion are found in patients with active ulcerative colitis and could account for the acidic colonic lumen. However, bicarbonate secretion appears to be unaltered in Crohn’s disease.

Elevated colonic luminal concentrations of SCFAs have been found in active ulcerative colitis, decreasing colonic pH, and this could be explained by impaired SCFA absorption and utilisation reported in some but not all studies.

In contrast, it has been suggested that a reduced intake of dietary fibre in patients with active colitis could limit the amount of carbohydrate available for utilisation as an energy source by colonic bacteria, resulting in the preferential production of lactate instead of SCFAs. Indeed, elevated concentrations of luminal lactic acid have been reported in active colitis.

The effects of increased SCFAs or lactate concentrations on colonic luminal pH are likely to be buffered in active colitis by the presence of blood and mucus, although the quantitative importance of these mechanisms is uncertain. Furthermore, bacterial generation of ammonia from urea and other nitrogenous blood constituents may also...
antagonise any tendency of colonic pH to fall in patients with active colitis.21

Contrary to widespread assumption, mouth to anus intestinal transit times in ulcerative colitis are not reduced; indeed, small bowel transit time is prolonged.33–35 Furthermore, transit time through the whole colon is similar to that of healthy controls.33 Several studies, however, show regional differences in transit within the colon in ulcerative colitis.36–38 Passage of luminal contents through the proximal colon is delayed while that through the left colon is accelerated.33 These changes tend to be more marked in, but are not restricted to, patients with distal disease, but their effects on intracolonic pH, as indicated earlier, are difficult to interpret.

Therapeutic implications of low colonic luminal pH in IBD

Several drugs used for the treatment of ileal and colonic IBD have been formulated so as to deliver the active agent directly to the site of inflammation, thereby reducing their absorption in the proximal gastrointestinal tract and reducing systemic side effects. Some of these agents utilise pH dependent release systems (for example, Asacol, Salofalk, and budesonide) while others depend on bacterial enzymatic metabolism (sulphasalazine, olsalazine, balsalazide) which may also be affected by changes in colonic luminal pH.

5-ASA drug delivery to the colon

Sulphasalazine was the first 5-ASA containing drug to show therapeutic benefit in ulcerative colitis. The active component, 5-ASA, is bound to an inert carrier, sulphapyridine,33 and is released in the colon by the action of colonic bacterial azo reductase. Newer preparations depend on bacterial azo reduction are olsalazine (two 5-ASA molecules azo bonded together), and balsalazide (5-ASA azo bonded to an inert carrier, 4-amino-benzoyl-alanine).

The pH dependent delayed release formulations of 5-ASA release the active moiety when their Eudragit coating dissolves as luminal pH rises above a critical value (for 5-ASA release the active moiety when their Eudragit coat is bonded to an inert carrier, 4-amino-benzoyl-alanine). This ensures that the drug reaches the target site of inflammation in the colonic lumen with its subsequent mucosal absorption, rather than being released into the distal small bowel, where it is metabolised to an inactive metabolite, 43 44 and is excreted in the faeces and urine (table 1).

How might changes in intraluminal gut pH and transit time in IBD mitigate against optimal bioavailability of 5-ASA from its presently available formulations?

Potential effects of altered colonic pH and transit on bioavailability of 5-ASA in IBD

Theoretically, it is possible that reduced right colonic pH in ulcerative colitis could reduce bioavailability of 5-ASA from both Eudragit coated pH dependent and azo reductase dependent formulations, without affecting bioavailability of 5-ASA from the slow release preparation Pentasa.

Thus intraluminal pH could inhibit release of 5-ASA from Asacol and Salofalk if it failed to exceed 7.0 and 6.0, respectively, for long enough to ensure complete coat dissolution. Direct evidence on pH dependent release in ulcerative colitis is not yet available but preliminary data...
suggest that in most patients small bowel pH, measured with a radiotelemetry capsule, is high enough for sufficient time to allow capsule dissolution.\(^7\) In vitro studies have shown that a low pH inhibits colonic bacterial metabolism of carbohydrate, urea, and other nitrogenous compounds\(^8\): it is possible that increased colonic acidity could also reduce azo reductase activity and release of 5-ASA from sulphasalazine, olsalazine, and balsalazide.\(^9\)

Rapid transit of luminal contents reduces the duration of contact of released 5-ASA with the mucosa as well as the time for this release to occur and for exposure of azo bonded 5-ASA formulations to bacterial azo reductase. In normal subjects, intestinal transit accelerated by Bisacodyl decreases systemic absorption, as indicated by reduced urinary excretion, and increases faecal excretion of 5-ASA from all formulations (table 5).\(^6\) This effect is most pronounced with azo bound 5-ASA formulations as much of the 5-ASA remains bound to its carrier. Under conditions of accelerated intestinal transit the proportion of N-acetyl-5-ASA in faeces is reduced,\(^10\) indicating that although luminal 5-ASA concentrations are increased, 5-ASA is released more distally in the colon.

The relevance of these points to what actually occurs in patients with IBD in relation to the bioavailability of 5-ASA is uncertain. As indicated above, low colonic pH has not been found universally and transit appears to be delayed in the small intestine and right colon, and accelerated only distally in patients with ulcerative colitis.

**Bioavailability of 5-ASA in IBD**

The effect of ulcerative colitis on the distribution of 5-ASA derived from a representative of each of the main types of 5-ASA formulations is summarised in tables 5 and 6.

Rijk et al compared five different formulations in 20 IBD patients with and without diarrhoea. The azo formulations sulphasalazine and olsalazine were less completely split in patients with diarrhoea than in those without diarrhoea.\(^6\) Release of 5-ASA from Asacol in patients with diarrhoea was characterised by a high proportion of 5-ASA in stools but little in the acetylated form, indicating release primarily in the distal colon.\(^10\) In patients with diarrhoea, release of 5-ASA from Salofalk and Pentasa was also impaired but the changes were less substantial and their bioavailability more favourable. However, in the absence of diarrhoea, faecal 5-ASA concentrations were highest with olsalazine and Asacol, consistent with predominantly colonic release of 5-ASA from these formulations.\(^10\)

In another study of Asacol bioavailability in ulcerative colitis, greater faecal excretion of 5-ASA was confirmed in patients with active compared with inactive disease,\(^11\) Lastly, a comparative study of four 5-ASA formulations in quiescent ulcerative colitis showed urinary and faecal N-acetyl-5-ASA excretion to be greatest after ingestion of Pentasa and Salofalk.\(^12\) These studies indicate that bioavailability of 5-ASA from all its formulations is reduced in patients with active IBD with results being least untoward for Pentasa and Salofalk. However, further comparative studies of the various 5-ASA formulations in patients with IBD are needed to clarify the effect of disease severity and extent on the bioavailability of 5-ASA and in particular its relation to changes in intraluminal pH as well as transit time.

**Clinical efficacy of 5-ASA formulations in IBD**

Although the pharmacokinetic data described above suggest that pH dependent or azo bonded formulations of 5-ASA could be less effective in active ulcerative colitis than slow release preparations, there are no direct comparative clinical trials of Pentasa with other 5-ASA formulations to confirm or refute this possibility.

**New formulations of other drugs in IBD: budesonide and azathioprine**

Changes in intraluminal intestinal and colonic pH in affected patients also require consideration in the assessment and design of other existing and novel drugs for the treatment of IBD.

Controlled ileal release budesonide approaches prednisolone in efficacy for the treatment of active ileocaecal Crohn’s disease.\(^13\) Two different pH dependent preparations of budesonide are now available: Budesonide CR (Entocort CR) gelatin capsules contain acid stable microgranules of budesonide suspended in ethylcellulose with an inert sugar core. The microgranules are coated with a layer of methacrylic copolymer which dissolves at a pH above 5.5 so that 50–80% of an oral dose is absorbed in the ileum or proximal colon in healthy volunteers.\(^14\) Budesonide is released from a Eudragit coating in the more recently launched Budenofalk\(^15\) when the pH exceeds 6.4. In this context, it is of interest that Budenofalk appeared relatively ineffective in patients with active Crohn’s disease confined to the left colon and rectum,\(^16\) in whom colonic pH may be low.

Budesonide-beta-D-glucuronide is a colon targeted potential oral prodrug for the treatment of colonic IBD. The rate of hydrolysis of budesonide-beta-D-glucuronide
in human faecal samples from patients with ulcerative colitis and normal volunteers is similar but it is unclear if a reduction in pH in the colon in patients with IBD may inhibit bacterial deconjugation of the prodrug. Clinical trials of buidxesone-beta-glucuronide in active colitis are awaited.

Azathioprine is an effective immunomodulating treatment for IBD, the use of which is restricted, by its toxicity, to patients with refractory disease. A new pH dependent release formulation effectively delivers the drug to the terminal ileum and colon with minimal systemic absorption in healthy volunteers. The formulation has a polymer coating which starts releasing the drug in the distal ileum at luminal pH > 7.0. Again, the low colonic luminal pH found in some patients with active colitis could reduce azathioprine bioavailability and limit its therapeutic efficacy.

Conclusions

Some data point to colonic pH being reduced in patients with ulcerative colitis, particularly when active; no definite conclusion can be drawn about gut pH in Crohn’s disease. The efficacy of pH dependent and azo-bonded S-ASA preparations in active ulcerative colitis, and in Crohn’s disease, is at best moderate, and further studies are required to assess whether this is due to an adverse effect of reduced gut luminal pH on their bioavailability. Pharmacokinetic studies of new pH dependent formulations of other drugs targeted at the distal ileum and colon, including budeso- nide and azathioprine, must be undertaken in patients with IBD as well as in healthy volunteers if maximal bioavailability is to be ensured in affected patients. In the final analysis, however, the efficacy of novel drugs whose bioavailability may be altered by changes in gut pH in IBD requires confirmation in controlled clinical trials.

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