Duodenal ulcer pain – the role of acid and inflammation

Over the past 25 years major advances have been made in our understanding of the pathogenesis of duodenal ulcer disease and in our ability to diagnose and treat it. In contrast, there has been a marked lack of progress in explaining the mechanism of the epigastric pain which is the major and usually only symptom of the disorder.

The most widely recognised characteristic of duodenal ulcer pain is that it is worse when the stomach is empty – that is, before eating and during the night – and thus corresponds with the times when intragastric acidity is highest. In addition, ulcer pain is relieved by eating or by taking antacids or ant-secretory drugs, all of which lower intragastric acidity. Because of this correlation of duodenal ulcer pain with high intragastric acidity it is tempting to assume that the pain must be triggered by gastric acid coming in contact with the ulcerated duodenal mucosa. Unfortunately, things are not as simple as they might seem.

The first problem is that duodenal ulcers are in the duodenum and not in the stomach. If exposure of the ulcer to acid is the cause of the pain, then the correlation should be with intraduodenal acidity rather than intragastric acidity. Though intragastric acidity is highest during fasting and falls with the buffering effect of food, this may not be the case for intraduodenal acidity. The pH of the duodenum is determined not only by the pH of gastric juice entering it but also by the rate of emptying of the stomach and duodenum and by the rate of secretion of alkaline juices into the duodenum.

McLoy et al.1 studied duodenal pH and gastric pH with miniature intraluminal electrodes in 11 duodenal ulcer patients. They observed that whereas intragastric pH rose with eating, the pH of the duodenum fell. In a more recent study by Kerrigen et al.2 in patients with active and healed duodenal ulcers, it was noted that the percentage of time that the duodenal pH was below 4 was greater in the first hour after eating than in the fasted state. In contrast to these studies, Bendsten et al.3 reported that the duodenal pH rose with eating. The latter study used a more complex and wider diameter electrode recording probe and it is possible that this influenced the intraduodenal pH by affecting the patency of the pylorus. The data available, though in some ways conflicting, do indicate that duodenal pH does not correspond directly with intragastric pH in duodenal ulcer patients. Though the typical symptom pattern in duodenal ulcer patients corresponds with intragastric acidity, it is not clear whether it corresponds with the acidity in the location of the duodenal ulcer.

In an attempt to clarify this, we examined recently the correlation between epigastric pain and both intragastric pH and intraduodenal pH in patients with active duodenal ulcers.4 Miniature combined glass electrodes were secured endoscopically in the antrum of the stomach and duodenal bulb by means of a clip-fixing device.5 The electrodes were connected to an ambulatory recording system which records the pH every four seconds. During the 24 hour recording period, patients were free to move around and ate normal meals. The presence and severity of pain were recorded every five minutes using a visual analogue scale.

The above study in patients with active duodenal ulceration showed a significant correlation of epigastric pain with low intraduodenal pH (Figure A). However, it also showed a significant correlation of epigastric pain with low intragastric pH (Figure B). We wondered whether the correlation of epigastric pain with low intragastric pH was merely the result of a correlation between low intragastric pH and low intraduodenal pH. Further analysis, however, showed no correlation between intragastric and intraduodenal pH. Consequently, we had to conclude that epigastric pain in patients with active duodenal ulceration was independently related to low intragastric pH and low intraduodenal pH. This observation that the pain of duodenal ulcer correlates with low intragastric pH is consistent with the typical clinical description. But it raises the question as to how a high acid concentration in the gastric antrum, where the gastric electrode was sited, causes pain in patients whose ulcer is in the duodenum.

Is pain in duodenal ulcer disease gastric in origin?

It has been appreciated recently that nearly every patient with an ulcer in the duodenum also has inflammation of the antral mucosa as a result of *Helicobacter pylori* infection.6 Could the pain in duodenal ulcer patients which correlates with a low antral pH be triggered by the effects of acid on the inflamed antral mucosa? If this were a mechanism of pain in patients with duodenal ulcers then we have to explain why the high proportion of the non-ulcer population who have *H pylori* associated antral gastritis do not all experience epigastric pain. The answer may be gastric acid. Patients with duodenal ulcers secrete more acid and have a higher intragastric acidity than non-ulcer control subjects7 and it may be that it is the exposure of the inflamed antral mucosa to their very high fasting intragastric acidity that causes the pain. Support for this comes from the study by George et al.8 in which it was noted that 67% of their patients with non-ulcer dyspepsia and *H pylori* related antral gastritis experienced epigastric pain during the intragastric infusion of concentrated HCL. During a control infusion of normal saline only 40% experienced pain.
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Probably the two factors most constantly present in patients with duodenal ulcers are hypersecretion of acid and H. pylori related antral gastritis. It is worth considering that the pain associated with duodenal ulcer disease may be caused by the interaction of those two factors predisposing to ulceration rather than the ulcer itself.

There have been conflicting data published recently on an association between dyspepsia and H. pylori related antral gastritis. It is possible that including intragastric acidity as well as antral gastritis in the equation may clarify the situation.

Is pain in duodenal ulcer disease duodenal in origin?

Our study also showed an independent association between low intraduodenal pH and pain in patients with active duodenal ulceration. This acid related pain originating from the duodenum may result from the effect of acid on the ulcer itself. Alternatively, or additionally, it might be due to the effect of acid on the duodenitis which usually accompanies duodenal ulceration, and is thus similar to the mechanism proposed for the pain originating in the stomach.

Detailed histological studies of resected ulcers by Kinsella showed that there were very few nerve endings in the ulcer base and any identified were too deep to be accessible to luminal acid. Though nerves were present at the sides of the ulcers, these were generally drawn away from the ulcer edge by the retracting muscular coat under cover of the intact but thickened submucosa. These observations suggest that the acid related duodenal ulcer pain is unlikely to be triggered by a direct effect of acid on the ulcer. It seems more likely that the pain is due to the effect of the acid on the inflamed mucosa. Support for this comes from a multicentre study of 180 duodenal ulcer patients analysed by Wylie. It was noted that relief of pain correlated more closely with improvement in endoscopic duodenitis than with ulcer healing. Further evidence that exposure of an inflamed duodenal mucosa to acid causes pain comes from the study by Joffe and Primrose. In their study acid and normal saline were instilled into the duodenum of patients with active duodenal ulceration, patients with duodenitis but no ulcer, and control subjects. It was found that both the duodenal ulcer and duodenitis patients experienced pain during the acid instillation.

If pain can arise from the effect of acid on the inflamed duodenal mucosa, patients with duodenitis but no ulcer would be expected to have a higher prevalence of dyspepsia than completely healthy control subjects. A recent study was conducted in which 620 subjects in the municipality of Sorreisa in Norway agreed to undergo upper gastrointestinal endoscopy. The finding which most clearly distinguished those with and without dyspepsia was endoscopic duodenitis. Once again, however, it is important to emphasise that if pain can arise from the effect of acid on an inflamed duodenal mucosa then the correlation between pain and duodenitis will depend upon the amount of acid produced.

Weak correlation between duodenal ulcer pain and active duodenal ulcer

Explaining duodenal ulcer pain by the effect of high intraluminal acid concentrations on inflamed mucosa rather than an effect on the ulcer itself would be consistent with the weak correlation between symptoms in duodenal ulcer patients and the presence of an active ulcer. In a study in duodenal ulcer patients, McDonald et al. observed that 25% of those with active ulceration at endoscopy had no dyspepsia and that 24% with dyspeptic symptoms had no active ulcer. This observation was confirmed in a multicentre study comparing cimetidine with placebo for preventing duodenal ulcer relapse. Of the 90 patients in the placebo group who had endoscopies when asymptomatic, 27% were found to have an active ulcer. In another multicentre study reported by Wylie et al. there was discordance between the pain of active and ulcer in 39% of the duodenal ulcer patients studied. Another example of the poor correlation between active duodenal ulceration and pain is seen in patients presenting with complications. In a multicentre study reported by Gilbert et al., it was noted that 57% of patients presenting with a bleeding duodenal ulcer had no history of ulcer pain. There is evidence that duodenal ulcers not associated with dyspepsia are also common in the population at large. Johnsen et al. found that 3-7% of healthy volunteers without a history of dyspepsia had endoscopic evidence of peptic ulceration.

All these studies highlight the weak correlation between the presence of active duodenal ulceration and epigastric pain and suggest that the pain is not directly related to the ulcer.

Clinical implications

The mechanism of pain in duodenal ulcer disease has important clinical implications. If a patient presents with dyspepsia and is found to have a duodenal ulcer at endoscopy then they are told that their pain is caused by the ulcer and appropriate treatment is prescribed. If a patient presents with identical symptoms but endoscopy shows only mild duodenitis or histological gastritis, however, the response is very different. The latter patient is often reassured that he does not have an ulcer, but is given little explanation for his pain or how to treat it. If the characteristic pain of duodenal ulcer disease is an effect of high acid concentrations on gastrogastrodudodenal mucosa these two patients may not have the identical pain but also the identical cause for their pain. Most importantly, both patients would respond to the same treatment—i.e. the combination of hypersecretion of acid and mucosal inflammation which causes pain in duodenal ulcer disease it would be more useful to look for this rather than just for the presence or absence of an ulcer.

The way ahead

The early history of research on duodenal ulcer disease concentrated on the role of hypersecretion of acid. With the recent recognition of H. pylori infection, the interest in acid secretion has waned and all attention has turned to the role of mucosal inflammation. It is now time to focus simultaneously on acid hypersecretion and mucosal inflammation, and study their interaction as a cause of symptoms in patients with and without duodenal ulcers.

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