Gastro-oesophageal refluxate: does it always have to be acid to be noxious?

No-one doubts that acid and pepsin are the major factors responsible for symptoms and oesophageal mucosal damage which comprise the clinical spectrum of gastro-oesophageal reflux disease. Clinical and in vitro studies overwhelmingly support this view. However, the relations between both symptoms and increasing oesophageal injury on the one hand and increasing duration of acid reflux (assessed by oesophageal pH monitoring) on the other have not always been shown to be as close as one might expect. Symptom occurrence reflects changes in oesophageal mucosal sensitivity which do not always vary as expected with increases in oesophageal acid exposure. The production of mucosal damage is influenced by the ability to clear or neutralise the refluxate (primary and secondary peristalsis, saliva and possibly oesophageal bicarbonate production). Another factor which has been studied in this latter regard has been the role of refluxed duodenal contents, in particular bile acids and trypsin. The impetus for study came from clinical observations of both symptoms and oesophagitis in patients with achlorhydria (for example, pernicious anaemia) and following total gastrectomy. Animal models using surgical diversion of bile or duodenal contents into the oesophagus have clearly shown their ability to cause oesophagitis. During oesophageal perfusion experiments, bile salts cause little or no oesophagitis on their own, but conjugated bile salts act synergistically with acid at pH 1–2 to disrupt the oesophageal mucosal barrier. However, at the same concentrations, bile salts will also inactivate pepsin. Unconjugated bile salts and trypsin act synergistically to cause oesophagitis at neutral pH, but trypsin is completely inactivated at pH <4.

Do these observations have clinical relevance? There has long been controversy about whether duodenogastric reflux occurs in excess in patients with oesophagitis: at the very least, it occurs as a normal event in healthy individuals so the potential for the duodenal contents to reflux into the oesophagus certainly exists. For a long time it was assumed that “alkaline” periods (pH >7) during oesophageal pH monitoring represented duodenogastro-oesophageal reflux (DGOR), and some investigators reported such periods to be (curiously) increased in patients with more acid reflux. It is now clear from studies using two or more pH electrodes to monitor proximal and distal oesophagus, or oesophagus and stomach simultaneously that most such episodes are due to swallowed saliva and only rarely to true DGOR.

Direct measurement of bile or trypsin in oesophageal refluxate has proved difficult to achieve. Direct monitoring of bile acids using an electrode device has been described but not so far reported for long term monitoring. Other techniques include continuous aspiration using a sump tube, a sodium sensitive electrode (based on differences in sodium concentration between gastric and duodenal juice) and a device measuring bilirubin concentrations spectrophotometrically (the Bilitec probe) as a proxy for bile acids. Oesophageal aspiration studies in patients with an intact stomach have detected conjugated bile acids but rarely trypsin in oesophageal contents, with the highest concentrations occurring at night perhaps due to the diluting effects of saliva during the day; bile acids were generally detected in samples also containing refluxed acid. However, the concentration of bile acids rarely reached those found (>1 mmol/l) in experimental models to be the minimal necessary to cause oesophageal damage. Furthermore, no clear relation between bile acid concentration and severity of oesophagitis has been found.

Vaeezi and Richter, in this issue (see page 297), report their observations using the Bilitec probe in conjunction with continuous pH measurement in a group of patients who had had gastric surgery and presented with upper gastrointestinal symptoms. Their results are of interest for both the information they provide about the aetiology of symptoms in post-gastrectomy patients and more widely for the insight provided into the role of DGOR in the production of oesophageal symptoms and oesophagitis. How reliable is the Bilitec probe? Validation studies indicate a good correlation of bilirubin measurement with bile acid concentration. At low pH (<3.5), bilirubin (and therefore bile) concentrations are underestimated by about 30%, and the device has to be used with a liquid diet free of substances absorbing light of the same wavelength as bilirubin (470 nm). The technique is, however, simpler and more easily applicable than aspiration.

Vaeezi and Richter found that oesophagitis only occurred in patients in whom bilirubin and acid reflux occurred together, supporting the findings of the animal perfusion studies alluded to earlier. In previous studies, the group had shown a clear gradient of both increasing acid and bile reflux with worsening severity of oesophagitis, including differences in patients with complicated and uncomplicated Barrett’s oesophagus; again, bile reflux was invariably associated with acid reflux. With regard to symptom production, heartburn and acid regurgitation were almost exclusively associated with reflux episodes containing both acid and bile. As the group have previously shown that bile reflux is drastically reduced in patients with Barrett’s oesophagus if acid reflux is suppressed with a proton pump inhibitor, they suggest that the first line of attack in post-gastrectomy patients with predominant heartburn should be similar. This may initially seem surprising as gastric acid output should be drastically reduced following a partial gastrectomy, though it is well known that after vagotomy for duodenal ulcer the incidence of reflux disease is of the order of 30–40%. There are patients after partial gastrectomy with oesophagitis refractory to medical treatment who can be shown to have genuine DGOR with high concentration of trypsin and bile salts. These are likely to respond to surgical Roux-en-Y conversion. Nevertheless, the suggestion to treat medically with acid suppression in the first instance is both entirely reasonable and probably what most clinicians do in practice.
The work of Richter’s group presented in this issue and their meticulous studies in other groups of patients with reflux disease give a clear picture of the role of bile reflux in this condition. They have been the most productive researchers using the Bilitec probe: in view of the controversies over the years regarding DGOR it would be good to see data from other groups using the Bilitec probe, appearing perhaps also with alternative technologies such as the sodium electrode.

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