Leading article

Alkaline reflux oesophagitis

'What is commonly called the heartburn, is not a disease of that organ, but an uneasy sensation of heat, or acrimony, about the pit of the stomach, which is sometimes attended with anxiety, nausea, and vomiting. It may proceed from debility of the stomach, indigestion, bile, the abounding of an acid in the stomach . . .'

William Buchan 1784.¹

Reflux oesophagitis is now a common disease and accounts for as many as 23% of new referrals for endoscopy.^{2,3} It usually causes minor symptoms but can be debilitating, leading to severe heartburn and dysphagia, with stricture formation. The complexity of the condition is confirmed by the poor correlation between the symptoms of reflux, the severity of the disease,^{4–7} and the endoscopic signs.⁸

Historical aspects

The concept of reflux related disease is a relatively modern phenomenon, although lesions of the oesophagus were described as early as 2500 BC.^{9,10} In 1928 Chevalier Jackson¹¹ described a case of peptic ulcer of the oesophagus, and in 1932 Mallory and Weiss¹² described chronic ulcers of the cardia, which they suggested were caused by regurgitation of gastric juice and the corrosive effect of alcohol. A number of obscure causes of oesophagitis have been postulated, including tonsillitis,^{11,13–15} and even allergies. However, it was Winkelstein¹⁶ in 1935 who set the trend for our present concepts of the disease, when he wrote his classic paper on 'peptic oesophagitis', suggesting this was caused by 'the irritant action on the mucosa of free hydrochloric acid and pepsin'.

The notion of refluxing acidic gastric juices 'burning' the oesophagus is now deeply ingrained in most medical minds but the idea that other factors may be involved is not a new one. Helsing¹⁷ in 1958 first pointed out that patients who had undergone gastrectomy could also suffer from severe oesophagitis, studies that were confirmed by several authors.^{18–21} Patients with achlorhydria associated with pernicious anaemia can also suffer from reflux oesophagitis.²²

Constituents of reflux

The two prime factors in the pathogenesis of the condition are acid and pepsin^{23–27} but these are not the only constituents of gastric fluid and oesophageal refluxate. Bile salts are present in the normal human stomach, with mean concentrations varying from 50–500 µmol/l and ranges up to 9 mmol/l,^{28–32} while in patients who have undergone gastric surgery, concentrations may rise to 25 mmol/l.^{33,34} The presence of bile salts in the stomach suggests that concentrations in oesophageal reflux will be similar, and several studies have confirmed this idea.^{35–38} Pancreatic enzymes are also present in the refluxate.³⁹

In this issue of *Gut*, Gotley *et al* have confirmed the presence of pepsin and bile acids, in addition to hydrochloric acid, in refluxate. They have shown a positive correlation between the pepsin concentration and severe reflux disease, particularly at night, confirming the experimental observation that pepsin in an acid medium may be responsible for severe oesophagitis.²⁶

Effects of acid suppression

The H₂ receptor antagonists provide symptomatic relief for patients with oesophagitis but healing is only achieved in 50–70%, even after three months of high dose treatment.^{40–42} The more potent proton pump inhibitor, omeprazole, heals 90% of cases.^{43,44} Other factors may be at work in those whose oesophagitis remains unhealed.

The pH test and alkaline reflux

Measuring acid reflux (pH <4) with a 24 hour oesophageal pH test poses problems in interpretation and reproducibility,^{45,46} with large overlaps between normal and abnormal populations. Pellegrini, using pH metry,⁴⁷ confirmed that alkaline reflux was occurring in man and introduced the concept of mixed acid and alkaline reflux as a separate entity from acid or alkaline reflux. Mixed reflux in an intermediate pH band has since been shown by other workers,^{48–50} and if this is producing toxic effects it may help explain the poor correlation between pH test results, endoscopic findings,^{51,52} and symptoms.^{53,54} At present, using pH testing, it is difficult to prove that reflux is taking place in the intermediate pH range of 4 to 7, as this is too near the normal oesophageal pH of 6. Although pH testing can detect reflux in the alkaline range (above pH 7.5), it does not provide any information about which constituents of the refluxing fluid are causing the damage.

Effects of bile

A specific relation between bile and oesophagitis was first shown in 1957 by Cross and Wangenstein,⁵⁵ who used cat and dog models. They diverted bile from the duodenum directly into the oesophagus, causing severe oesophageal lesions in the absence of acid. Levrat⁵⁶ diverted the duodenal juices of rodents into the oesophagus, producing similar lesions, and also implicated pancreatic enzymes. The work was repeated and confirmed on a number of occasions.^{57–59} Cross⁵⁵ recognised the importance of pancreatic enzymes, and so did Lambert⁶⁰ in 1962. More recently (1983) Lillemo⁶¹ showed that trypsin perfusion at an alkaline pH produced oesophageal mucosal erosions and ulceration in rabbits, without significant changes in hydrogen ion flux – possibly a proteolytic effect. Levrat,⁶² Mud,⁶³ and Salo⁶⁴ have all shown that proteolytic pancreatic enzymes can produce oesophagitis in experimental animals. Lysolecithins have also been implicated.⁶⁵

Extrapolation of the data from these animal studies to humans is difficult, especially as unphysiological concentrations of bile at unphysiological pH, have often been used. The paper from Gotley *et al* in this issue of *Gut* is a careful attempt to document the constituents of refluxate in patients with gastrooesophageal reflux disease, and to correlate constituents of the refluxate with the degree of oesophageal damage. Although pepsin concentrations were high, particularly in patients with severe damage, concentrations of bile acids thought to be pathological in animal studies were found in a few patients only. Furthermore, there was no correlation of bile acid concentrations with the grade of oesophagitis. Trypsin was rarely found. Unfortunately, the small volumes

of refluxate that occurred in most patients necessitated pooling of aspirates into two hourly aliquots, which does not allow detailed analysis of the effects of other potentially toxic components of gastric fluid apart from acid. The possibility remains that brief exposure of the mucosa to high concentrations of toxic bile acids or enzymes at an optimally damaging pH, could occur. There is some evidence for such toxic synergism from experimental studies.

Toxic synergism

It is still not possible to produce a unified theory of the pathogenesis of reflux oesophagitis but the suggestion of a toxic synergism between acid and duodenal secretions is an attractive one.

In 1975 Safai-Shirazi⁶⁶ performed a study in which the ionic permeability of the oesophageal mucosa to hydrogen ions was used as a measure of mucosal damage. He showed, first in dogs then in man, that acid, and to a greater extent bile/acid mixtures, caused massive increases in mucosal permeability to hydrogen ions.

Hopwood in 1981⁶⁷ and Bachir in 1982⁶⁸ showed the cellular disruption caused to the human oesophagus by bile acid solutions, and more recently Salo⁶⁹ has identified the cell membrane and intracellular organelles as the areas primarily damaged by bile.

Toxic synergism between acid and bile has been shown by many workers since then using rabbit or dog models.⁷⁰⁻⁷⁷

Biochemical mechanisms have also been studied. Biancani⁷⁸ showed in 1984 that calcium pathways were disrupted by acid perfusion in the cat, and more recently Manning⁷⁹ showed massive disruption of calcium homeostasis in rabbit oesophagus by bile salt perfusion. He also showed an analogy to the human condition in that the deeper layers of the dermis (stratum germinativum) were damaged first because of their high concentrations of calcium sensitive phospholipases. Kirroff⁷⁷ produced similar findings in the rabbit, showing damage to the deeper layers of the oesophageal mucosa in response to acidified taurocholate solutions.

From this evidence it seems likely, in some cases at least, that acid is not the only aetiological factor in oesophagitis, but the relative importance of other factors is uncertain. It is clear that duodenal secretions are present in the normal and postoperative human stomach, and there seems little doubt that bile salts and pancreatic enzymes are capable of causing oesophageal mucosal damage in the laboratory. The final proof of a direct link between biliary and pancreatic secretions and oesophagitis, however, is still lacking. The answers lie in direct monitoring of duodeno-gastro-oesophageal reflux, with concomitant monitoring of its effect on the oesophageal mucosa.

Human measurements

Bile and enzyme monitors are obvious ways of testing for the presence of 'non-acid' reflux but the technology for this is still in its infancy. There are three ways in which bile salts may be detected. Direct aspiration and assay of oesophageal contents has been attempted but is limited in its potential because of the intermittent nature of reflux. An enzyme probe has been developed to measure variations in redox potentials produced by the 3 α -hydroxy-steroid dehydrogenase enzyme when exposed to bile acid, and this method is sensitive and can detect bile acids at concentrations as low as 100 μ mol/l.⁸⁰ The technique is, however, highly pH sensitive and not suitable for use in the stomach or oesophagus, where pH varies across a wide range.

Bile salts may be radiolabelled for γ monitoring. An intraoesophageal γ probe which can continuously measure ⁹⁹Tc^m labelled bile reflux into the stomach and oesophagus

has been developed. This is a qualitative test only and will not at present measure concentration⁸¹ but such techniques are likely to be important in determining whether the aetiology of reflux oesophagitis is indeed multifactorial and is dependent on 'non-acid' as well as acid reflux. They need to be combined with the development of an effective method for measuring oesophageal mucosal damage in vivo, and the use of potentiometers to detect transmucosal potential difference changes shows promise.⁷⁴

Clinical implications

There are clinical implications if a mixed aetiology for reflux oesophagitis is established. Acid secretion can easily be controlled, while bile salt and pancreatic secretion cannot. However, many of the preparations used to treat oesophagitis may be equally efficacious for acid and alkaline secretions. These include the alginates,⁸² which will act as a raft preparation whatever the underlying gastric contents, and the prokinetic agents, which improve the oesophageal clearance of any noxious agent present. Even the H₂ receptor antagonists and proton pump inhibitors may indirectly reduce mixed reflux by reducing the overall volume of gastric contents. Bile chelating agents may have a place in treatment. Where medical management fails completely the Nissen⁸³ fundoplication will prevent acid or alkaline reflux and rarely, in selected patients in whom non-acid reflux is a proved cause of disease, surgical bile diversion procedures may still have a role.

Summary

Duodenal and gastric contents do reflux into the oesophagus and acid alone certainly causes oesophageal damage which will be worsened by pepsin. In the patient who has undergone gastrectomy duodenal secretions may also be harmful. There is evidence that when the two mix there may be a toxic synergism, leading to mucosal disruption and intracellular damage to oesophageal cells which produces the clinical picture of reflux oesophagitis, with or without symptoms. Clear evidence of the toxicity of duodenal refluxate in humans is lacking, but the ability to measure bile and acid reflux continuously, together with a method of detecting oesophageal damage at a cellular level should help to solve this long debated problem.

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