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Beyond acid suppressants in gastro-oesophageal reflux disease

The burden of gastro-oesophageal reflux disease becomes apparent when one considers that treatment with acid suppressants accounts for a significant proportion of our national healthcare budget.[1] Oh *et al* present evidence in this issue of *Gut*[2] that a novel antioxidant substance (DA-9601) significantly attenuates the severity of oesophageal inflammation in a rat model of oesophagitis (see page 364). Furthermore, they demonstrated that DA-9601 was more effective in the prevention of oesophagitis than physiological concentrations of ranitidine.[2]

However, before we start prescribing antioxidants for gastro-oesophageal reflux disease, several factors need to be considered. Firstly, it is not clear why the authors chose to compare antioxidants with H_2 antagonists rather than with proton pump inhibitors. Large randomised controlled trials of oesophagitis suggest that whereas after eight weeks of treatment H_2 antagonists achieve complete healing in up to 60% of patients, proton pump inhibitors achieve endoscopically proved healing in approximately 90% of patients.[3–5]

Secondly, DA-9601 acts by scavenging superoxide hydroxyl radicals and reducing lipid peroxidation. The surgical procedure and the 36 hour fast in these animals may themselves have induced oxygen free radicals and affected lipid peroxidation, independent of oesophageal exposure to refluxate.[6 7]

Thirdly, reflux induced in this rat model is non-physiological and may not be directly comparable with human gastro-oesophageal reflux disease. Oh *et al* found that refluxate containing acid alone was not sufficient to cause oesophagitis in rats and hence mixed biliary acidic reflux was induced. This was achieved by inserting a small ring calibre into the duodenum, distal to the ligament of Treitz, as well as performing a longitudinal cardiomyotomy to enhance gastric reflux into the oesophagus. The resultant refluxate would be expected to contain a significant proportion of bile at acidic pH, although the components were not formally quantified. In humans, there is significant variability in the components of refluxate between individuals. Furthermore, it is controversial to what extent bile reflux is involved in the aetiology of gastro-oesophageal reflux disease.[8] It is likely that high concentrations of a mixed bile acid refluxate is important in the pathogenesis of severe oesophagitis and Barrett's oesophagus.[9] Treatment with proton pump inhibitors may decrease the bile acid component due to a reduction in the volume of refluxate and secondary to precipitation of the conjugated bile acids out of solution as the pH is raised. Therefore, it is perhaps not surprising that ranitidine was not sufficient to prevent the severe injury induced by high concentrations of mixed duodenogastric reflux in this rat model.

The role of antioxidants may however be relevant to the small proportion of patients (15–20%) with severe gastro-oesophageal reflux disease who do not achieve complete acid suppression with proton pump inhibitors.[10] This may be particularly important in patients with persistent heartburn or Barrett's oesophagus who are at risk for the development of adenocarcinoma.[11] For these patients one therapeutic option is to combine high doses of proton pump inhibitors with a H_2 antagonist until they are completely acid suppressed. A second option is to abolish the opportunity for gastroduodenal contents to reflux into the oesophagus either endoscopically (for example, stapling or radio-frequency methods) or surgically (Nissen fundoplication). Alternatively, the effect of the components of refluxate on the epithelium might be ameliorated by specific biochemical and molecular strategies. For example, there has been recent interest in cyclooxygenase 2 (COX-2) inhibitors in the oesophagus,[12] and this paper provides evidence to support the concept of reducing oxygen derived free radicals via inhibition of the nuclear factor κB pathway. As bile acids increase COX-2 expression and the production of oxygen free radicals, both these agents may offer a therapeutic approach to the reduction of epithelial damage caused by refluxate with a significant bile acid component.

At a time when adenocarcinoma of the oesophagus is increasing rapidly in the Western world, new therapeutic strategies to reduce carcinogenic oxygen free radicals in

patients with recalcitrant reflux need careful evaluation. The title of this paper suggests that oxidative stress is involved in the pathogenesis of reflux oesophagitis but one needs to be cautious in attributing a causal role for a substance on the basis of the therapeutic effect of a drug—more data are needed. However, further laboratory studies on antioxidants will hopefully pave the way for long term large randomised clinical trials to properly evaluate these novel approaches. In the meantime, acid suppressants are highly effective and will remain the gold standard treatment for the vast majority of patients.

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