Editorials

Gastro-oesophageal reflux disease:

illness or illusion?

Gastro-oesophageal reflux disease (GORD) is well entrenched in the clinician's mind. But, is it a spurious or artificial concept and what do we actually know about it? There are just too many things that don't add up.

When communicating with patients most doctors still cite the traditional concepts relating to GORD, that it is related to one or more of the following: 'excessive acid' into the oesophagus; 'failure of the valve' at the gastro-oesophageal junction; 'delayed gastric emptying'; and 'damage' at the lower oesophagus. Regrettably, none of these holds true. And, as clinicians who base our explanatory models on what we construct for our patients we are almost certainly on the wrong track.

> *"... the spectrum of lesions and causes ranges hierarchically from erosive oesophagitis, non-erosive reflux disease, acid sensitive oesophagus to functional heartburn, with the effectiveness of acid suppression reducing in that order."*

GORD IS NOT NORMALLY RELATED TO EXCESSIVE ACID

The 'excessive acid' explanation is clearly flawed as acid-secretion levels are normal in people with GORD (except rarely, in the Zollinger–Ellison syndrome), lower oesophageal sphincter pressures are not different (although periods of relaxation may be more frequent) and there seems to be no consistent evidence about delayed gastric emptying in the majority of sufferers. Worse still, in terms of explanatory models, there is no consistency from symptom association analyses when symptoms are evaluated against pH monitoring.

THE IMPACT OF ACID-SUPPRESSION DRUGS

The increase in the prevalence of GORD coincided with the era of acid suppression drugs. The mid-1980s saw the widespread use of the histamine H_2 receptor antagonists in volumes far greater than were anticipated for ulcer disease alone. The more powerful acid suppressors, the proton-pump inhibitors (PPIs), were also indicated initially for peptic ulcers but have become the mainstay for GORD. Ironically, GPs were criticised for prescribing them in patients without ulcers. The concept of GORD became entrenched in the Montreal Consensus in 2006[1] only after many years of acid-suppression therapy in clinical practice. Here, GORD was defined as:

'... a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.'[1]

A wonderfully handy concept, this covered all situations from someone with an endoscopic lesion (albeit even without symptoms) to one who had symptoms but no other findings. In a near-perfect model of the consensus approach we encompassed both symptoms and findings with reflux as the common factor.

First, symptoms. The cardinal symptoms ascribed to GORD are heartburn and regurgitation. These seem convenient and well encapsulated within our thinking. But, how reliable and consistent are these? In the Diamond study,[2] the authors, many of whom were part of the initial Montreal Consensus, critically assessed the value of symptoms in patients judged as having GORD. The results were startling as well as revealing: that GORD was considered to be present in only 65% of patients so diagnosed initially and that only 49% of patients with GORD selected heartburn or regurgitation as their most troublesome symptom. Therefore the value of these symptoms is questionable.

IS THE PPI TEST WORTHWHILE?

Furthermore, the use of esomeprazole, a PPI, in therapeutic doses proved neither sensitive nor specific for the diagnosis of GORD and a 2-week course of this did not add to diagnostic precision.[2] This clearly challenged the previously-held adage that a PPI response test could help to distinguish patients with GORD from other conditions. In pragmatic terms a positive result merely indicates that the patient has improved, rather than indicating what the problem happens to be, and there is the placebo effect to be considered. This reflects the common experience of GPs who are used to variable responses to PPIs for what they perceive to be GORD. Studies confirm that the majority of patients on long-term PPIs continue to suffer moderate to severe symptoms.[3] The corollary to this is the perverse therapeutic mindset which assumes that either the patient has been non-compliant or that the doses and timing of the acid suppression agents need to be altered.

Against this confusing backdrop, what are we actually treating? Mainie *et al* in a seminal paper on GORD management,[4] reported on patients taking twice-daily PPIs. Of the 200 patients in their study, 86% had continuing symptoms. Using impedance pH measurements they demonstrated that only 8% of them had acid reflux, 35% had non-acid reflux, and that in 57% their symptoms were not related to reflux at all. These findings, since confirmed, shed new light on the origins of so-called GORD symptoms, indicating that at least some patients have an aetiology not related to reflux per se, and also not related to acid.

Meanwhile, the prevalence of GORD as we understand it is rising. The Norwegian HUNT Research Centre reports a 31% increase in the prevalence of gastro-oesophageal symptoms over 10 years to 2009 with a corresponding 47% increase in the frequency of symptoms.[5] Startlingly, the increase is strongly marked in those aged >60 years, a stage at which possible cancer is an issue.

CHALLENGES AND NEW CONCEPTS

A number of new concepts have emerged which challenge our traditional understanding of GORD. Firstly, the discovery of the acid pocket, demonstrated by Beaumont *et al*,[6] whereby acid is noted to accumulate after a meal above the stomach contents, below the gastro-oesophageal junction and, in those with a hiatus hernia, into the hernia sac. These predispose to acid reflux and pH pull-through studies, which measure acid exposure at different parts of the oesophagus, have demonstrated the drop

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in oesophageal pH in such patients.[7] These offer an explanation for postprandial symptoms in some patients and set up alternative therapeutic possibilities: whereas acid suppression therapy may not abolish all the acid, other agents such as alginates may offer the opportunity of mucosal protection. Such treatment could be an adjunct to PPIs or an alternative where acid suppression is not needed to manage endoscopic oesophagitis.

A further concept that may explain the inconsistencies in our construct of GORD is a better understanding of the mucosal integrity of the lower oesophagus. Impaired mucosal integrity may be the result from repeated reflux episodes and studies have shown that slow recovery after acid challenge is associated with increased oesophageal sensitivity.[8] Admittedly while these concepts remain acid related, they may benefit patients not responding to conventional therapies, such as through the development of mucosal protective agents.

OVERLAP OF CAUSES AND LACK OF SPECIFICITY OF SYMPTOMS

The background to abdominal problems, as GPs know, is the overlap of symptoms from different causes, including functional gastrointestinal disorders. The label of functional heartburn has been only sparsely applied to date, with its implications of visceral hypersensitivity and associations with IBS. This may be clarified as the outputs of the Rome Foundation for Functional GI Disorders progress to their next iteration. For now, the spectrum of lesions and causes ranges hierarchically from erosive oesophagitis, non-erosive reflux disease, acid-sensitive oesophagus to functional heartburn, with the effectiveness of acid suppression reducing in that order.[9]

People with 'GORD' symptoms clearly represent a heterogeneous population with complex and differing underlying mechanisms for the problem. A clinical diagnosis and acid suppression alone both have marked limitations, which the clinician needs to recognise. Matching the right approach for the individual patient is more crucial than trying to fit people within a model which, now, is looking less practical than some years ago.

IS GORD A REAL ENTITY?

It is likely that no such entity as GORD actually exists. It is more likely that a common group of symptoms can be ascribed to different causes, even non-gastrointestinal. An effective therapeutic approach in this complex area requires a tailored regimen; diet and weight advice initially, a possible trial of acid-suppression drugs, normally PPIs, postprandial alginates, and a careful evaluation of the level of success. PPIs alone are not the answer for most sufferers and a re-evaluation of the diagnosis and underlying reasons for the symptoms may require a completely different approach: one geared to functional problems or non-GI causes. Some patients with especially troublesome symptoms may need referral for sophisticated testing such as pH monitoring and manometry to try to pin down the cause of the symptoms but the returns are likely to be low.

The truth is that what was thought to be a straightforward condition related to acid reflux has turned out to encompass complex issues, for which there is often no answer. And, don't forget, cardiac and other causes such as cancer, for the symptoms. Old paradigms die hard.

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