Prescriber

Diagnosis and drug treatment of extraoesophageal reflux

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Figure 1. Laryngoscopic views of the larynges to show findings of laryngopharyngeal reflux. Left: normal; centre: near complete ventricular obliteration with mild posterior commisure hypertrophy and moderate vocal fold oedema; right: bilateral pseudosulcus vocalis with mild posterior commisure hypertrophy and vocal fold oedema; the subglottic oedema extends past the vocal process (arrow)

Gastric reflux is not only associated with heartburn and dyspepsia but can also cause a wide range of extraoesophageal conditions. Here the authors describe the recommended management of extraoesophageal reflux.

Gastric reflux not only causes the commonly presenting symptoms of heartburn and dyspepsia but is also an underlying cause of a surprisingly wide range of extraoesophageal symptoms and conditions.

The reflux of gastric contents, which includes acid, pepsin and bile, predominantly manifests as gastro-oesophageal reflux disease (GORD). However, reflux of gastric contents can also pass the upper oesophageal sphincter and enter the larynx, pharynx and upper respiratory system. In this case it can be responsible for a host of symptoms and conditions (see Table 1) that are collectively termed as atypical manifestations of GORD, also known as extraoesophageal reflux (EOR) or laryngopharyngeal reflux (LPR).[1]

The condition of EOR is generally well recognised by primary-care physicians in the USA, and awareness of the condition is increasing among GPs in the UK.

Common symptoms

Some of the more commonly encountered symptoms of EOR include dysphonia, chronic cough and pulmonary conditions such as asthma.

Dysphonia

Dysphonia, or hoarseness, is the most frequent symptom of EOR with a large study finding that 71 per cent of ENT patients with EOR experience hoarseness.[2] Hoarseness is the result of direct irritation to the larynx by the noxious refluxate.[3]

Dysphonia may manifest as intermittent or chronic but may also be exhibited as voice fatigue or the voice breaking during normal use.

Chronic cough

Cough is the most common complaint for which medical attention is sought. Chronic cough is reported by 10-20 per cent of adults and, in the absence of any obvious respiratory conditions, there are three common causes: bronchial asthma, rhinitis (postnasal drip) or reflux.[4]

Cough is a very common symptom in EOR: 51 per cent of ENT patients with EOR have chronic cough.[2] Reflux-induced chronic cough may occur in the absence of classical GORD-type symptoms such as heartburn.

There are three main mechanisms by which reflux of gastric contents can cause cough:[5]

- macroaspiration of refluxed material into the bronchial tree, triggering cough
- microaspiration of refluxed material
- vagally mediated distal oesophageal-tracheobronchial reflex mechanism.

Asthma

The strongest association of pulmonary conditions with reflux

appears to be in asthma. The prevalence of GORD in asthma sufferers has been found to be between 60 and 80 per cent.[6] There is debate as to whether GORD predisposes to asthma or whether asthma, or more particularly asthma medications, promote reflux.

The use of GORD medication in patients with asthma has been successful in improving pulmonary symptoms. A meta-analysis showed symptomatic improvement in 69 per cent, a reduction in asthma medication in 62 per cent and improved lung function in 26 per cent.[7]

Diagnosis and treatment

Primary care

The GP's aim is to control the patient's GORD/EOR symptoms without referral to secondary care (unless alarm symptoms are suspected) and to differentiate these symptoms, which may include non-cardiac chest pain, from more serious disease such as myocardial infarction. An accurate diagnosis is not always easy to make and is often achieved by taking a history and determining the main causes of their symptoms. It is important to determine the probable aetiology of symptoms before initiating treatment.

The type of treatment is dependent on the type and severity of symptoms and is often modified depending on the patient's response. Usually, patients with mild and/or intermittent symptoms can be treated with dietary and lifestyle modifications, alginates and/or acid suppression agents with H_2-antagonists and proton pump inhibitors (PPIs).

Bioavailability studies have demonstrated that alginates – a formulation of sodium alginate and potassium bicarbonate – are compatible with and do not interfere with the activity of acid-suppressing agents such as PPIs,[8,9] and a combination of alginates and PPI has shown benefit in patients presenting with dyspepsia in respect to overall symptom control compared with single treatment.[10]

If the patient's symptoms persist, the GP has the option of stepping up the therapy to higher doses or twice-daily PPIs; if symptoms still remain uncontrolled, patients should be referred for further investigation.

Secondary care

The primary diagnostic tests used by ENT specialists to determine EOR as the cause of symptoms are a combination of reviewing patient symptoms,[11] laryngeal findings by fibreoptic laryngoscopy (see Figure 1)[12] and reflux testing results.[13,14]

Secondary-care specialists have at their disposal a range of diagnostic tests, and for the diagnosis of GORD will often refer patients for ambulatory 24-hour dual-probe oesophageal pH monitoring (pH manometry). For the diagnosis of GORD, an abnormal test is characterised as an oesophageal pH of less than 4 for greater than 4 per cent of a 24-hour period. This technique has also been used in the diagnosis of EOR but the abnormal cut-off parameters may not be sensitive enough as only a small amount of reflux into the larynx is considered pathological.[15]

If pH manometry is to be used, the proximal probe needs to be placed above the upper oesophageal sphincter in order to document EOR.[13]

pH manometry assumes that the pathological component of the refluxate is acid, but it is now established that weakly-acidic and nonacidic components of the refluxate are also important, especially in EOR, and acid alone does not cause tissue damage to either the oesophagus[16] or the larynx.[2]

Symptoms
chronic dysphonia
intermittent dysphonia
vocal fatigue
voice breaks
sore throat
excessive throat mucus
postnasal drip
dysphagia
globus
intermittent airway obstruction
wheezing
Conditions
reflux laryngitis
otitis media
sinusitis
chronic cough
asthma
sleep apnoea
chronic throat clearing
sudden infant death syndrome
globus pharyngeus ('lump in the throat')
contact ulcers and granulomas
subglottic stenosis
laryngeal carcinoma
vocal cord nodules
paroxysmal laryngospasm
dental erosion
lung transplant rejection

Table 1. Symptoms and clinical manifestations of EOR

Pepsin is a substantial aggressor to the mucosa and causes damage similar to that seen in oesophagitis.[16] Bile acids are also an aggressor, especially at a pH of above 4.[17]

To diagnose EOR it is preferable to use the newer technology of multichannel intraluminal impedance (MII). A series of six impedance channels and two pH channels ensures that all reflux events, regardless of pH or composition, can be measured as well as the height that the reflux reaches up the oesophagus.[18]

Where the patient's symptoms of GORD/EOR remain uncontrolled, one reason may be because

the refluxate is weakly acidic and/or nonacidic and contains pepsin and bile acids, which are known to play a role in causing symptoms in patients not responding to treatment with acid-suppression therapy.[19] Alginate reflux suppressants are drugs that can prevent pepsin and bile-acid damage in the oesophagus and laryngeal area during reflux episodes.[20,21]

Role of PPIs

It is believed that aggressive acid-suppression treatment is required to have a benefit in EOR, and a PPI dosing regimen of twice daily, at a high dose and for at least two months is often used as the standard treatment regimen.

Five small, placebo-controlled studies investigating the potential benefit of PPI therapy in EOR have been published covering 140 patients in total.[22-26] These studies predominately showed no benefit of PPI therapy on patient symptoms,[22-24,26] and the only study that showed a significant effect of PPI therapy had an abnormally low placebo response.[25]

A larger prospective, randomised, placebo-controlled trial recruited 145 patients of whom 95 received esomeprazole (Nexium) 40mg twice daily versus placebo (50 patients) for 16 weeks.[27] The patients had extraoesophageal symptoms and reflux laryngitis signs on laryngoscopy. Resolution of the primary symptoms was seen in only 14.7 per cent of patients treated with a PPI and 16 per cent in the placebo group. A meta-analysis has confirmed these findings.[28]

A major confounding factor in PPI use is the rebound acid hypersecretion seen after cessation of treatment, a concept that is well accepted in the gastro-oesophageal reflux arena.[29] Therefore, it can be extrapolated that rebound acid hypersecretion can have clinical importance in the return of symptoms in EOR after cessation of PPI therapy, and indeed there is some evidence for this.[22]

In addition, PPIs have been shown not to reduce the number of reflux episodes that occur, only to change them from acidic to 'weakly acidic' and/or 'nonacidic' reflux.[30]

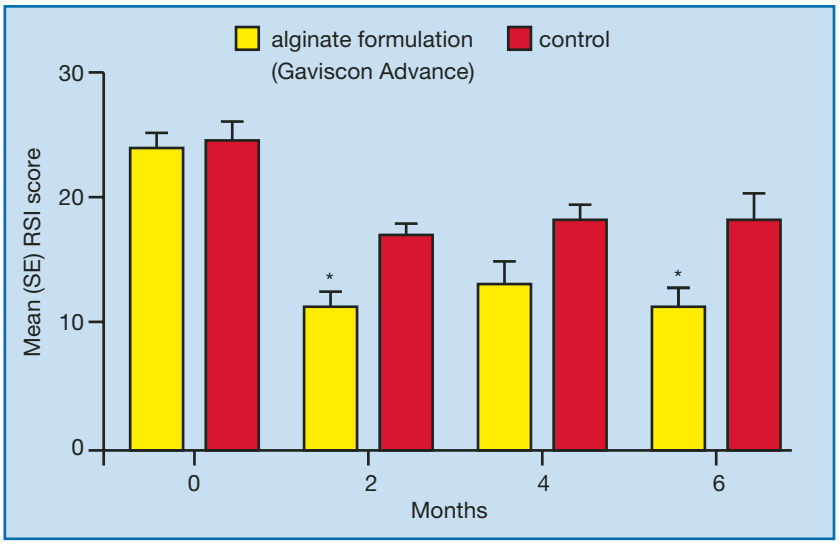

Figure 2. Significant improvement (*) in EOR symptoms (patient-assessed reflux symptom index – RSI) seen after 2 months (p=0.005) and 6 months (p=0.008) with sodium alginate plus potassium bicarbonate treatment (n=22) *vs* control (n=23)

The role of an alginate reflux suppressant

Clinical studies have shown a benefit of using sodium alginate plus potassium bicarbonate (Gaviscon Advance) to manage symptoms in EOR patients.

The alginate formulation was evaluated in the treatment of EOR in a randomised, open, parallel-group study.[31] A total of 49 patients attending an otolaryngology outpatient clinic were randomised to receive vocal hygiene advice with or without 10ml alginate four times daily (after meals and at bedtime) for up to six months. Efficacy was evaluated by scores in the patient-assessed reflux symptom index (RSI)[11] and clinician-assessed reflux finding score (RFS)[12] based on laryngeal fibreoptic examination.

There was a significant fall in RSI following two months' treatment with alginate compared with the control group, and this was maintained at six months (see Figure 2). Assessment of laryngeal findings using the RFS showed that treatment needed to continue for six months before there was a significant improvement compared with the control group (p=0.005). Therefore symptom improvement occurs within two months but six months' treatment is required to normalise laryngeal findings.

An open-label pilot study[32] identified patients with chronic cough associated with reflux and confirmed by 24-hour pH manometry. Daily cough score (0-10) was recorded before and after treatment with 10ml alginate four times daily for four weeks. In the five patients that completed the pilot study, four had a clinically relevant improvement in cough score. Mean baseline cough score was 5.2 falling to 3.8 following four weeks of treatment (see Figure 3).

Conclusion

Reflux of gastric contents above the upper oesophageal sphincter is a frequent occurrence causing a host

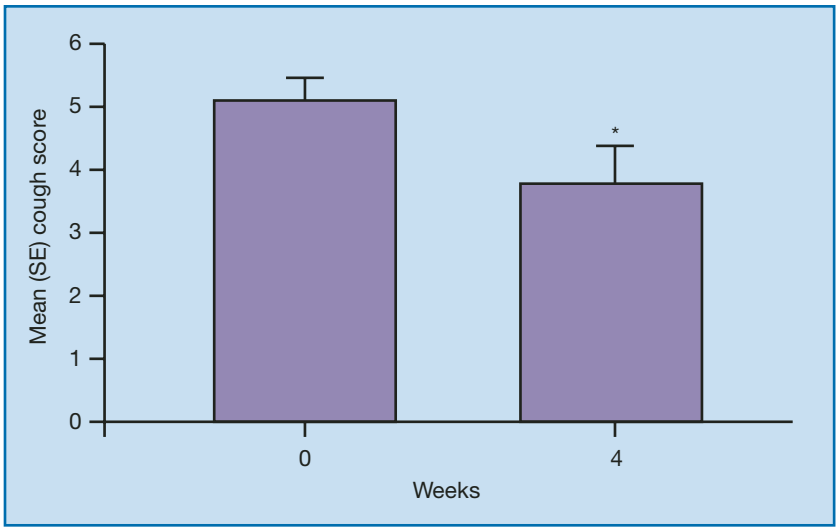

Figure 3. Significant improvement (*) in chronic cough associated with reflux seen after four weeks of treatment with sodium alginate plus potassium bicarbonate (n=5, p=0.03)

of ENT symptoms.

Clinical studies indicate that PPIs are of limited value in these patient groups, even at high dose, as symptoms, which may be caused by weakly acidic or nonacid reflux containing pepsin and bile acids, still persist. A sodium alginate plus potassium bicarbonate reflux suppressant is an alternative option that has shown to be effective in EOR.

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Professor Dettmar has a Special Professorship with the School of Pharmaceutical Sciences, University of Nottingham, and has a special interest in reflux disease and alginate technology, and Vicki Strugala is a research scientist with a particular interest in gastrointestinal physiology and reflux disorders