Gastro-oesophageal reflux and asthma in children – comorbidity or coincidence?

Sharon Kling, MB ChB, DCH (SA), FCPaed (SA), MMEd (Paed), M Phil (Applied Ethics)
Department of Paediatrics and Child Health, Tygerberg Children’s Hospital and Stellenbosch University, Tygerberg, Cape Town, South Africa

ABSTRACT
Gastro-oesophageal reflux (GOR) is commonly associated with asthma and is cited as an aggravating factor for poorly controlled asthma in adults and children. Children with GOR may present with respiratory symptoms such as cough rather than with heartburn. Studies estimate the prevalence of GOR in asthmatic children to be between 19.3% and 80%. Acid suppression does not usually improve asthma control, a result borne out by a study of lansoprazole in which lung function, quality of life and poor asthma control did not improve. Adverse events, notably respiratory infections and activity-related bone fractures, were more common in the proton pump inhibitor (PPI) treated group. Severe asthmatics with poor control or with symptoms of GOR may warrant a trial of PPI therapy, but this therapy should be used with caution.

INTRODUCTION
Gastro-oesophageal reflux (GOR) is ‘the passage of gastric contents into the oesophagus with or without regurgitation and vomiting’.1 It has been implicated both as an alternative diagnosis and as an aggravating factor for poorly controlled asthma in adults and children.1-5 The relationship between GOR and airways disease is complex, and has been the subject of numerous studies and systematic reviews. In this article I discuss the relationship between GOR and asthma, and consider options for diagnosis and treatment of GOR in asthmatic children.

CASE
A 10-year-old asthmatic patient attending the allergy clinic presented with poorly controlled asthma. Attention to medication adherence and technique, adding a long-acting beta-2-agonist to her inhaled corticosteroid therapy and addressing environmental control did not result in improvement, and I decided to request an upper gastrointestinal tract (GIT) contrast study to look for GOR, despite the limitations of this study. Figure 1 is an example of GOR as demonstrated on a contrast swallow. The patient had no symptoms suggestive of GOR. The contrast swallow revealed an indentation in the posterior oesophagus, suggestive of an aberrant right subclavian artery (Fig. 2) and a colleague then requested radionuclide scintigraphy to look for hold-up during swallowing. This study revealed no hold-up but GOR was noticed, and the resultant dilemma was whether to perform an oesophageal pH study or to institute a trial of therapy for the GOR. The advice was to treat for 3 months with a proton pump inhibitor (PPI) and to re-assess. She was commenced on omeprazole, but thus far this has not resulted in a significant improvement in her asthma control.

THE PREVALENCE OF GOR IN CHILDREN WITH ASTHMA
GOR is a relatively common problem in the general population, although few epidemiological studies have been done at population level. Studies in children have suggested that they may not present with the typical symptoms of heartburn with which adults present, but with respiratory symptoms such as cough, especially in young children.6,7 A study of children presenting to a paediatric practice group in the USA showed the prevalence of GOR symptoms to be less than 10%,8 but the prevalence is higher in children with neurological disorders, chronic lung disease, obesity and prematurity.1 A systematic review investigating the relationship between GOR and asthma in adults concluded that almost 60% of adults with asthma exhibit symptoms of GOR, but the causal relationship is not clear.9 The same group performed a systematic review on published studies of

Correspondence: Dr Sharon Kling, e-mail sk@sun.ac.za
asthma and GOR in children. The estimated prevalence of GOR in asthmatic children varied between 19.3% and 80%. In the five studies where controls were included, the prevalence of GOR in asthmatics was 22% compared with 4.8% in controls (pooled odds ratio 5.6 (95% confidence interval 4.3-6.9)). Deeb et al. studied 75 children with refractory asthma prospectively, and found that the relationship between GOR symptoms, and asthma severity was not statistically significant. Macroscopic oesophagitis diagnosed by endoscopy was as high as 71% overall, and was more prevalent in the severe asthma group (76.6%).

**GOR: PATHOPHYSIOLOGY AND MECHANISMS**

GOR occurs when gastric contents move from the stomach into the lower oesophagus through the lower oesophageal sphincter (LES). The first area involved in the prevention of GOR is the gastro-oesophageal junction, comprising the LES, crural diaphragm and the gastric sling. The majority of reflux events occur during transient LES relaxations (tLESRs), which are associated with acid reflux. Pepsin, probably the main cause of GOR symptoms such as heartburn, requires the presence of acid in the refluxate for its activity. Physiological failings in the LES are associated with GOR, as are conditions such as obesity and hiatus hernia. It is thought that tLESRs are neurally mediated via the vagus nerve, as a result of stretch receptors in the stomach being stimulated. The implication is that pharmacotherapy may be directed at the neurotransmitters involved in the neural pathway.

The oesophageal defence mechanisms against GOR include rapid clearance of material by oesophageal peristalsis, and defence mechanisms inherent in the oesophageal mucosa itself. The role played by gastric emptying in the prevention or pathogenesis of GOR is uncertain, and studies have been inconclusive.

**DIAGNOSIS OF GOR**

The diagnosis of GOR involves a combination of symptoms, signs and special investigations. The symptoms may be as a result of GOR or its complications. Oesophagitis as a result of GOR is best diagnosed by means of upper GIT endoscopy. GOR may also be confirmed via oesophageal pH monitoring over 24 hours, oesophageal manometry, intraluminal impedance measurements, or a combination of a pH study and impedance monitoring. Barium contrast studies are useful to rule out anatomical abnormalities that may mimic GOR, and radionuclide scintigraphy is not recommended for routine diagnosis of GOR in children.

**THE RELATIONSHIP BETWEEN GOR AND ASTHMA**

The two theories employed in explaining the effect of GOR on asthma are the ‘reflux’ and the ‘reflex’ theories (Fig. 3). The reflux theory postulates that aspiration of gastric contents may stimulate airway inflammation or microaspiration of acid into the lower airway may lead to airway hyperreactivity. The reflex theory holds that the refluxate stimulates receptors in the distal oesophagus, with resultant vagal stimulation and bronchoconstriction.

The following mechanisms have been proposed to explain the effect of asthma on GOR: increased intra-abdominal pressure affecting the pressure gradient across the LES; changed relationship between the crural diaphragm and gastro-oesophageal junction as a result of hyperinflation; increased negative intrathoracic pressure resulting from airway obstruction; and asthma therapy that affects the LES pressure.

**DOES TREATMENT OF GOR IMPROVE ASTHMA CONTROL IN CHILDREN?**

Generally, studies in children have shown no improvement in asthma or wheezing symptoms with acid suppression. Khoshoo and colleagues published an uncontrolled study in which 27 children aged 5-10.5 years with asthma and GOR disease as established by oesophageal pH monitoring underwent either medical or surgical treatment for GOR. They were able to reduce asthma treatment by at least 50% after a 1-year period in all these children following either medical or surgical treatment for GOR. Only 2 out of 8 children in the study who received medical treatment for GOR despite normal pH studies were able to reduce their asthma treatment. Of interest, children in their study were excluded if they had a family history of asthma or a personal or family history of atopic disease, so the children in this study may have had a specific phenotype of asthma.

A recently published randomised controlled trial of the proton pump inhibitor (PPI) lansoprazole in children aged 6-17 years with poorly controlled asthma but without symptoms of GOR showed no statistically significant improvement in lung function, quality of life or episodes of poor asthma control when compared with placebo after a follow-up period of 24 weeks. Even in children with an oesophageal pH study positive for GOR, there was no evidence that lansoprazole made any difference to any of the asthma outcomes. Worryingly, adverse events were more common in the PPI group, notably respiratory infections and...
activity-related bone fractures (6/149 vs 1/157, PPI vs placebo), although these did not achieve significance. A Cochrane review concluded that treatment for GOR did not lead to improved asthma symptoms, although subgroups of patients may show some benefit. A recent systematic review concluded that PPIs are not useful in reducing symptoms of GOR disease in infants and that other treatments such as ranitidine and alginate are as effective as PPIs in older children.

**APPROACH TO THE CHILD WITH ASTHMA AND SUSPECTED GOR**

According to the paediatric GOR clinical practice guidelines it is possible that subgroups of asthmatics, such as those with heartburn, nocturnal symptoms or steroid-dependent difficult asthma, may benefit from treatment for GOR. The guidelines committee suggests that, if the patient has symptoms such as heartburn or regurgitation, a trial of PPI is warranted. If the asthma is difficult to control or presents with frequent night symptoms, other causes should be sought, and pH monitoring, with or without impedance studies, should be performed. If the pH study is abnormal, a trial of PPI is instituted. The value of medical versus surgical therapy for GOR in children with asthma has not been evaluated.

**CONCLUSION**

The exact relationship between GOR and asthma remains undefined. Certain subgroups of asthmatics appear to be more susceptible to the effects of GOR, should be investigated and may warrant a trial of therapy. In this respect, the most appropriate investigation appears to be 24-hour pH monitoring, possibly with impedance measurement, and therapy implies a trial of PPIs. For the patient in the case scenario above, a trial of a PPI is possibly warranted, but it should be discontinued if no improvement in symptoms or asthma control results.

Caution must be exercised in using PPIs long-term without a clear indication. As Martinez states, ‘an empirical trial of GERD therapy in patients with poorly controlled asthma ... is unjustified. ... The substantial increase in use of PPIs in children during the last decade is worrisome and unwarranted.’ He terms the overuse of PPIs in paediatric practice ‘therapeutic creep’ and points out that it increases the risk of possible side-effects without translating into any benefit for patients. We should take his advice seriously.

**Declaration of conflict of interest**

SK has given talks for MSD and was sponsored to the 2010 ALLSA congress by Cipla Medpro.

**REFERENCES**