Predictors of therapy resistant asthma

We read with interest the report by Heaney et al. that the use of a systematic protocol for therapy resistant asthma resulted in control of asthma in 53% of patients who were previously poorly controlled. However, we suspect that a significant proportion of the remaining 47% of patients who were classified as therapy resistant actually had underlying gastro-oesophageal reflux disease which was either not adequately investigated (by 24 hour pH monitoring alone) or, once diagnosed, was not adequately treated (with standard dose proton pump inhibitor).

A large northern European study of 2661 subjects found that people with gastro-oesophageal reflux had a significantly higher rate of physician diagnosed current asthma and that those with reflux and asthma had more nocturnal cough, morning phlegm, sleep related symptoms, and more peak flow variability than those with asthma alone.1 Pathological gastro-oesophageal reflux, which is often clinically silent, has been found on pH monitoring in 53–65% of asthmatics2 and has been shown in various studies to cause increased capsaicin cough sensitivity,3 increased airway hyperresponsiveness,4 increased respiratory resistance,5 and increased respiratory symptoms.6 7 Certainly, in the case of chronic cough, gastro-oesophageal reflux should be investigated in all cases.

Heaney et al. state that 17 patients with positive oesophageal pH monitoring were classified as having therapy resistant asthma because their respiratory symptoms did not improve with standard dose proton pump inhibitors. However, proton pump inhibitors have only a minor effect on the reflux of gastric contents; they alter the pH of the refluxate. This mode of action is effective in diseases such as oesophagitis where acid plays a vital role in pathogenesis. However, in airways disease non-acid reflux may be a major problem. It therefore seems surprising that other anti-reflux treatments such as alginites were not tried in this group of patients who had refractory respiratory symptoms and no other identifiable cause.

Treatment of reflux in asthmatics with proton pump inhibitors has been shown to improve respiratory symptoms,1 2 quality of life,8 and peak flow,9 but extended courses of treatment at doses higher than standard are sometimes required.10 However, by actually preventing reflux, fundoplication can be used to treat patients who fail on proton pump inhibitors11 and has been shown in asthmatics also to improve respiratory symptoms,1 2 12 decrease use of asthma medications13 and, in one study, to reduce requirement for systemic corticosteroids.14 In addition, it would appear that patients with reflux related respiratory symptoms are more likely to have ineffective oesophageal motility than those with reflux alone.5 11 In fact, in a series of 34 patients with gastro-oesophageal reflux related chronic cough, 11 (32%) had abnormal oesophageal manometry despite normal pH monitoring.11 Nine of these 11 patients responded to anti-reflux treatment including proton pump inhibitors, alginites, and lifestyle advice.

Since the patients with asthma studied by Heaney et al. did not have oesophageal pH monitoring and no oesophageal manometry, we suggest that patients categorised as having therapy resistant asthma may actually have had undiagnosed gastro-oesophageal disease. In addition, more intensive management of subjects with positive oesophageal function tests would have resulted in improved respiratory symptom control, which was an important factor in defining therapy resistant asthma in this paper.

C F Everett, J A Kastelik, S A Mulrennan, A H Morice

Academic Department of Medicine, University of Hull, Castle Hill Hospital, Cottingham, East Yorkshire, UK

Correspondence to: Professor A H Morice, Academic Department of Medicine, University of Hull, Castle Hill Hospital, Castle Road, Cottingham, East Yorkshire HU16 5JQ, UK; a.h.morice@hull.ac.uk

References

Authors’ reply

In response to the letter from Professor Morice and colleagues, we welcome the growing interest in the role of the oesophageal-lung axis as evidenced by recent publications by both them and us in this journal.1 2 We agree with many of their comments regarding the frequent coinciding of gastro-oesophageal reflux and asthma, but we would suggest that this is not necessarily imply a causal association.

Four issues of substance arise from their letter concerning our paper:

- Were our subjects adequately investigated?
- What is the role of oesophageal dysmotility?
- Were they adequately treated?
- Was our definition of therapy resistant asthma appropriate?

Regarding oesophageal investigation, we would maintain that ambulatory pH monitoring remains the single best test with regard to sensitivity and specificity in the diagnosis of gastro-oesophageal reflux.3 4 We therefore believe it highly unlikely that we failed to diagnose reflux in such a large percentage of patients resistant to therapy (12 of 29 (41%) had pH profiles within normal limits). In addition, our pH probes are placed manometrically and all our subjects undergo a limited manometric study (limited in that, after assessment of the lower oesophageal sphincter, if five water bolus swallows were not made). In other words, the full 10 swallows). In only one subject was an abnormality detected (that patient was in the therapy responsive group and the diagnosis was previously unsuspected achalasia).

We do not believe this supports a prominent role for undiagnosed oesophageal motility disorders in the therapy resistant group.

The authors suggest that inadequate acid suppression may relate to resistance to treatment. We did not repeat oesophageal pH monitoring when patients were treated with standard dose proton pump inhibitors
We believe that the two conditions commonly occur together and this is supported by the high prevalence of gastro-oesophageal reflux in our patients with difficult asthma. However, we did not find any difference in the prevalence of gastro-oesophageal reflux between subjects whose asthma improved with detailed investigation and management and those with persistent asthma. This suggests that, while gastro-oesophageal reflux is common in difficult asthma, its pro-active identification and treatment with proton pump inhibitors does not relate to asthma outcome.

L Heaney, B Johnston
Belfast City Hospital, Belfast, UK

References

FENO as a diagnostic tool in paediatric asthma
Malmberg and colleagues reported the robust discriminatory properties of exhaled nitric oxide (FENO) for asthma in a paediatric population, but also noted that 29% of the subjects studied could not perform the manoeuvres necessary for online NO measurements at a target expiratory flow rate of 50 ml/s. These results are consistent with those reported by Canady and colleagues who noted that 24% of children studied could not perform online NO measurement. We studied healthy and asthmatic adults and found a similarly robust ability of NO to discriminate between those with and without asthma with online technique and flow rate of 50 ml/s (area under ROC curve 0.84). Importantly, we also found that these discriminatory properties were not diminished when simpler offline collection techniques or faster, more tolerable, expiratory flow rates were used (areas under ROC curve 0.79–0.86). If NO measurements are to gain acceptance for identification of children with asthma, use of offline techniques with faster expiratory flow rates may be preferred.

L P Malmberg
Department of Allergy, Helsinki University Central Hospital, Finland

References

A Deykin
Pulmonary Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; adeykin@partners.org