PostScript

LETTERS TO THE EDITOR

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Predictors of therapy resistant asthma

We read with interest the report by Heaney *et al*[1] 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 having therapy resistant asthma 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.[2] Pathological gastro-oesophageal reflux, which is often clinically silent, has been found on pH monitoring in 53–65% of asthmatics[3 4] and has been shown in various studies to cause increased capsaicin cough sensitivity,[5] increased airway hyperresponsiveness,[6] increased respiratory resistance,[7] and increased respiratory symptoms.[3 4] Certainly, in the case of chronic cough, gastro-oesophageal reflux has been found to be one of the most frequent underlying causes.[8]

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 alginates 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,[3 9 10] quality of life,[10] and peak flow,[9 10] but extended courses of treatment at doses higher than standard are sometimes required.[9] However, by actually preventing reflux, fundoplication can be used to treat patients who fail on proton pump inhibitors[11] and has been shown in asthmatics also to improve respiratory symptoms,[11–13] decrease use of asthma medications[12 13] and, in one study, to reduce requirement for systemic corticosteroids.[13]

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.[14] 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.[15] Nine of these 11 patients responded to anti-reflux treatment including proton pump inhibitors, alginates, and lifestyle advice.

Since the patients with asthma studied by Heaney *et al* underwent only 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.

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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 does 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] 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 normal we did not proceed to 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

as this would have been impractical given the already high intolerance rate for the initial procedure and the lack of enthusiasm of patients generally to have this invasive procedure repeated. However, all patients in the therapy resistant group with symptomatic reflux did have an improvement in gastro-oesophageal reflux symptoms and yet, despite this, their asthma remained difficult to control. In addition, omeprazole in a dose of 20 mg twice daily (a comparable dose to that used in our study) has been shown to provide successful acid suppression in 22 of 23 patients (96%) with Barrett's oesophagus (a condition associated with excess oesophageal acid exposure) as well as in healthy controls.[4 5] We note that this dose is similar to that used by Morice and colleagues.[1] We therefore believe that failure of adequate acid suppression is unlikely to explain the poor response to asthma therapy.

The authors suggest that reflux of non-acid contents may have been contributory to therapy resistant asthma. In support of non-acid reflux they cite a number of papers (one of which is a review article) examining the role of both fundoplication in asthma and other conditions including chronic cough. The studies are observational and non-controlled and it is notable that the cited review article states that the two controlled studies compared fundoplication with H_2 antagonist therapy yet still concluded that the effects of surgical treatment are similar to what would now be regarded as suboptimal medical acid suppression treatment. We are impressed with the faith the authors place in the addition of alginates to proton pump inhibitors as there is no published evidence that they are an effective additive intervention. We would also point out that Champion *et al*[6] have shown that omeprazole in a dose of 40 mg reduces bile reflux by >80% as well as controlling acid reflux, and would suggest that any improvement in non-acid reflux is more likely to be due to this agent. We feel that suggesting non-acid reflux as a major driver in this subject group is interesting but speculative and remains to be substantiated. We believe there is no current evidence to support adding alginates to proton pump inhibitors in subjects with asthma and co-existing reflux as suggested by the authors.

Finally, the authors suggest that our definition of therapy resistant asthma was symptom based and that these symptoms may have been explained by ongoing reflux. Our definition of therapy resistant disease specifically stated ''… persisting symptoms due to asthma …'' where great attention was paid to ensure that any ongoing respiratory symptoms were repeatedly supported by objective evidence of variable airflow obstruction despite intensive therapy. Given the consistently negative effect of all reflux interventions on lung function, we again suggest that it is improbable that oesophageal reflux is related to the failure to control asthma in this group with severe therapy resistant disease.

The exact association between asthma and oesophageal reflux has been controversial since it was first described by Sir William Osler in 1892. It took a long time for controlled trials to be performed but a recent Cochrane review of 12 randomised placebo controlled trials has shown no consistent benefit of medical anti-reflux therapy on asthma symptoms or lung function when present,[7] a position endorsed by the recent BTS/SIGN guidelines on asthma management.[8] 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 therapy resistant 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.

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FE_{NO} as a diagnostic tool in paediatric asthma

Malmberg and colleagues reported the robust discriminatory properties of exhaled nitric oxide (FE_{NO}) 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.[1] These results are consistent with those reported by Canady and colleagues who noted that 24% of children studied could not perform online NO analysis.[2] 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).[3] 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 identifying children with asthma, use of offline techniques with faster expiratory flow rates may be preferred.

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Author's reply

We appreciate Dr Deykin's comments regarding our recent study comparing the diagnostic power of exhaled nitric oxide (FE_{NO}) and the oscillometric assessment of lung function for asthma in preschool children.[1] We are pleased to learn that our results of the robust discriminatory properties of FE_{NO} are consistent with his findings in healthy and asthmatic adults.[2] Importantly, Dr Deykin also mentions the feasibility problems of standard online FE_{NO} measurements in young children[3] which we and others have found in a series of preschool children. As discussed in our paper,[1] the standard online technique requires considerable cooperation and, according to our experience, is rarely successful in children aged less than 4 years.

Dr Deykin's proposal of using offline measurements has practical advantages over the standard technique which relate to the portability of the samples. However, because of the flow dependence of FE_{NO}, standardisation of the flow rate is necessary even when using this technique, so the measurement may not be significantly easier for the child than the online method. In commercial equipment, dynamic resistors and biofeedback views on the computer screen may increase the feasibility of online measurements in young children, but there is still a need to develop new techniques and recommendations for the measurement of FE_{NO} in children of preschool age and in infants.[3] The findings of Dr Deykin and colleagues that offline measurements, when controlled at low and faster flow rates, maintain good discriminatory properties for asthma are certainly important when such recommendations are to be updated. However, further studies are necessary to see whether these results can be extrapolated and applied to young children.

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