Paracetamol and asthma

The study by Shaheen et al 1 rightly pointed out that some patients with asthma deliberately avoid aspirin and are more likely to use paracetamol, hence a “consumer selection bias.” However, they failed to mention the “professional’s selection bias.” Any standard text would prescribe references stating that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) could potentially worsen asthma. 2 Health professionals will therefore certainly choose paracetamol for patients with asthma to avoid potential adverse reactions to NSAIDs and litigation problems. 3

It is unlikely that this bias could be resolved in a pharmacoepidemiological study. Recent reports in the general press and television about the study could convey the impression wrong to patients with asthma which could direct them to self-select aspirin or ibuprofen. Fatal or near fatal cases of breathlessness and hyperventilation. We were concerned that one of their case-control studies, the authors argue that it is “unlikely” that paracetamol was strongly negatively associated with asthma in the non-responders. Shaheen et al have not excluded concurrent illnesses such as influenza or respiratory tract infections, or non-steroidal anti-inflammatory drug use which may have increased asthma symptoms. This could give a false impression that increased paracetamol use led to more asthma symptoms.

The authors point to animal studies of glutathione depletion in the lung to help explain the association of paracetamol and asthma. In one of the studies paracetamol was administered to rats in doses of 3 g/kg. In an average 70 kg human this would be equivalent to a dose of 210 or 420 × 500 mg tablets. Other studies in mice have shown pulmonary toxicity with doses of more than 800 mg/kg. This indicates that, in order to support the glutathione depletion hypothesis, the patients would have had to exceed the LD₅₀ of paracetamol; the glutathione hypothesis is therefore biologically implausible. Other studies have shown that paracetamol antagonises ATP, bradykinin and arachidonic acid induced bronchoconstriction in guinea pigs. 4 We would agree with Shaheen and coworkers when they say that their findings “should be interpreted with caution.” The data presented do not support an association between paracetamol and asthma. They certainly do not fulfil Bradford Hill’s criteria for causality and our view is that asthmatic patients should not be advised to avoid paracetamol on the basis of this paper.

2. Shaheen et al have observed an important association between asthma and paracetamol intake in adults. They have drawn attention to the reduction in glutathione (GSH) caused by paracetamol and propose that this may be the underlying mechanism of the observed association. We wish to propose an alternative mechanism to explain the association between paracetamol and asthma. Shanm has pointed out the marked immune modulating effect of paracetamol leading to less fever, less inflammation and in turn, to increased viral load and prolonged viral shedding. If we accept that viruses can provoke asthma then there is a prima facie connection.

expiratory volume in one second (FEV₁) in subjects with asthma and reduces methacholine hyperresponsiveness. Increased levels of serotonin in plasma have also been demonstrated in patients with symptomatic asthma. Thus, frequent use of paracetamol may affect BHR more than actual airway inflammation; this would account for the lack of correlation of paracetamol use with rhinitis in subjects with asthma in Shaheen’s paper. It is also of interest that in a recent case report study found that irritable bowel syndrome, a disorder also associated with smooth muscle hyperreactivity, is associated with frequent paracetamol use.

We found some evidence that aspirin use was protective, although the data were inconsistent. The authors also dismiss my hypothesis regarding the protective effect of aspirin in preventing childhood asthma as asthma was not more common before the introduction of aspirin. I would suggest, however, that all allergic diseases are new to this century. According to the widely quoted National Health Interview Survey on chronic diseases in the United States, the prevalence of hay fever among children has remained steady over the last 17 years while asthma has increased by 80%. As atopy is the best known risk factor for asthma in children, and viral infections are the most common trigger of asthma exacerbations in children, I would propose that the immune response to viral infection has been altered in atopic children due to the removal of COX-2 inhibition and/or an adverse effect of paracetamol. Data to support this hypothesis are provided by a recent report by Lesko and Mitchell in a double-blind, controlled study on the safety of ibuprofen in children with asthma and fever. Compared with paracetamol, ibuprofen was associated with a significant reduction in surgery visits for asthma in the 30 days following treatment. A dose response effect was observed with ibuprofen (3 mg/kg versus 5 mg/kg) on this beneficial effect, suggesting a protective effect of COX-2 inhibition.

In our laboratory we are currently investigating the effect of paracetamol on non-specific BHR. We are also treating children with ibuprofen and adults with specific COX-2 inhibitors at the onset of viral upper respiratory infections with symptomatic success in preventing viral induced asthma exacerbations.

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Letters

With regard to the study by Shaheen et al of the role of paracetamol in adults with asthma, there are several issues we would like to raise concerning the findings of this study and the authors’ conclusions.

Firstly, we question whether the association between paracetamol use and asthma could be explained by the influence of the 1993 BTS asthma management guidelines which specifically mentioned avoidance of aspirin. The guidelines were disseminated before the initial 1996 Greenwich asthma study, from which this current study is based, and were used by nurse specialists to educate patients in that study. If patients with asthma were advised to use paracetamol then preference to aspirin, then this may result in an apparent association between paracetamol and asthma, but one that is iatrogenic.

Secondly, the response rates in the original guidelines were low at only approximately 50% (12 238 respondents of 24 400 surveyed). The response rates in this study were also only approximately 50%, potentially resulting in a highly selected subset of the population. There is also the possibility of selection bias. Also, the diagnostic criteria of asthma based on questionnaires may overestimate the true prevalence of asthma.

Thirdly, we wonder about the postulated mechanism of paracetamol use and asthma which specifically mentioned avoidance of aspirin. As decreased GSH due to paracetamol ingestion worsens asthma, why is this not a problem in, for example, paracetamol overdose? We have not found this mentioned in the literature, nor has it been noted locally by clinicians treating these patients.

In conclusion, we are concerned that the reported association between paracetamol and asthma may well be contaminated by the recommendations of the BTS guidelines, affected by selection bias, and of uncertain biological plausibility.

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with shortness of breath" might represent anxiety induced hyperventilation rather than asthma. However, this symptom has been validated as a strong predictor of bronchial hyperresponsiveness in adults. Furthermore, in our study the majority of cases of asthma were not defined on the basis of this symptom alone (most were defined by reported asthma (treatment or attacks) with or without this symptom). Nevertheless, we agree that anxiety and depression should be considered as potential confounders in future studies as these conditions may be associated with increased use of analgesics and with asthma symptoms.

Questionnaire data on analgesic use without blood levels may be inadequate in clinical toxicology, but they have proved highly informative in previous epidemiological studies.

Shin et al are wrong to say that our data do not support an association between paracetamol use and asthma. An association is clearly informative in previous epidemiological studies. The terms "automatically withheld". Like Wong, our wording was modified in the revised paper to clarify our meaning.

For the diagnosis of hyperventilation syndrome, we believe that the term "disproportionate breathlessness", "air hunger", and "behavioural breathlessness" are more useful. We also consider that the bias implied by the term "hyperventilation syndrome" itself is a potential confounder in future studies. We would also disagree that a causal link between frequent paracetamol use and asthma should not be considered. We were careful to emphasise that the questionnaire on respiratory symptoms has been extensively tested and used, and that the unbiased error implied by Shin et al would have reduced, rather than increased, the estimate of any association.

We do not support the view that a causal link between paracetamol and asthma is only possible for daily users who are able to reduce their usage. Apart from a possible improvement in their asthma, this might be beneficial in other ways—for example, the predominant indication for frequent paracetamol use in our study was headache, and it is well recognised that excessive analgesic use can make headache worse.

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Hyperventilation syndrome

In his comprehensive review of the hyperventilation syndrome Gardner points out the difficulties in terminology and definition that have dogged this complicated and confused area. As he states, it is physiologically inappropriate to use the term "hyperventilation" in the absence of demonstrated hypoxia. The term "hyperventilation syndrome" has, however, gained wide currency both in research studies and in clinical practice, often without precise diagnostic criteria being specified or hypoxia rigorously demonstrated. This situation may have arisen from the perception of many clinicians that there is a real but poorly defined clinical entity causing morbidity in real world practice resulting from breathing abnormalities. Abnormal breathing patterns may, indeed, result in hyperventilation and hypoxia, but rapid, irregular and shallow breathing may not necessarily result in increased ventilation yet may still cause significant symptoms. Isocapnic hyperventilation studies have shown that many of these symptoms are independent of hypocapnia, and other mechanisms have been suggested. Other descriptive labels have been applied to patients with characteristic symptoms associated with breathing abnormalities, with or without hypoxia, such as "disproportionate breathlessness", "air hunger", and "behavioural breathlessness" but these terms have not gained widespread acceptance. Van Diahoom has used the term "dysfunctional breathing" to describe the production of symptoms directly as a result of abnormal breathing patterns. We are well aware of considering functional problems in other physiological systems but have not applied this concept to breathing until recently. The diagnosis of dysfunctional breathing may be suggested by characteristic symptom patterns and clinical pictures but, as Gardner points out, these symptoms are all non-specific. Ultimately the verification of the label must lie in the response to breathing retraining interventions in these patients. This umbrella term allows inclusion of patients with and without hyperventilation, and moves the focus of attention from physiological hypocapnia to pragmatic clinical responses.

Gardner points out that the "hyperventilation syndrome" has been associated with other conditions, including psychiatric syndromes and asthma. The association of dysfunctional breathing with asthma may explain the anecdotal success of interventions which rely on breathing retraining, such as the Butenko method, to improve patients' well being. Studies are needed to clarify the presence of abnormal breathing in common and important clinical situations and to objectify anecdotal reports of responses to breathing retraining interventions.

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