LETTERS TO THE EDITOR

Paracetamol and asthma

The study by Shaheen et al. 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 book or reference state that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) could potentially worsen asthma. Health professionals will therefore certainly choose paracetamol for patients with asthma to avoid potential adverse reactions to NSAIDs and litigation problems.1

It is unlikely that this bias could be resolved by a pharmacoepidemiological study. Recent reports in the general press and television about the study could convey the wrong impression to patients with asthma which could direct them to self-select aspirin or other “anti-asthmatic” was the possible association with aspirin and NSAIDs have been reported.2 3 Finally, I agree with Shaheen et al. that further studies are required.

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We were interested to read of the association between paracetamol use and asthma in adults reported by Shaheen et al.1 We recognise that the link is not causal and that further randomised trials are needed to clarify this link.

In their paper they comment that they have shown was with people who use paracetamol. However, they 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 g or 420 × 500 mg tablets. Other studies in mice have shown pulmonary toxicity with doses of more than 800 mg/kg.3 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 asthma patients should not be advised to avoid paracetamol on the basis of this paper.

3. Kuehm SL, Doyle MJ. Medication errors: a professional’s selection bias. Any standard text book or reference state that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) could potentially worsen asthma. Health professionals will therefore certainly choose paracetamol for patients with asthma to avoid potential adverse reactions to NSAIDs and litigation problems.1

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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.

Shann 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.

I therefore propose that paracetamol leads to an increased viral load which, in turn, increases the provocation of asthma, hence explaining the observed association. Another way of putting it is that “asthma is an immune disease, paracetamol affects the immune system, therefore paracetamol may affect asthma” (or, indeed, any other immune disease).

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We read with interest the report by Shaheen et al. of an association between paracetamol (acetaminophen) use and symptoms of asthma which, according to the authors, corresponds with bronchial hyperresponsiveness (BHR). They speculate that, by depleting glutathione in the airway, paracetamol enhances Th2 like inflammation and thus increases BHR.

As the extent of airway inflammation does not necessarily correlate with BHR, I would propose another hypothesis to explain their findings. The mechanism of action of paracetamol is unknown, but it is known to affect serotonin (5-HT), 5-hydroxytryptamine) metabolism and can falsify increase levels of 5-HT metabolites in the urine during evaluation of patients for carcinoid syndrome.1 It also appears that the anti-nociceptive effect of paracetamol involves the central serotonin system by increasing 5-HT and its effect on the 5-HT, receptor.1 In a mouse model of allergic asthma, ketanserin, a 5-HT receptor antagonist, has been found to prevent BHR and airway eosinophilia after allergen challenge.2 This same agent increased forced


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in preventing viral induced asthma exacerbations with anecdotal success. Supporting the evidence of its efficacy, a protective effect of paracetamol in asthma was found that irritate bowel syndrome, a disorder also associated with smooth muscle hyperreactivity, is associated with frequent paracetamol use. Birkett et al. 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, a total of 179 million people 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 infection is the most common trigger of asthma exacerbations in children, I would propose that the immune response to viral infections 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 10 mg/kg) on this beneficial effect, suggesting a protective effect of COX-2 inhibition. In our laboratory we are currently investigating the effects 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 symptoms with anecdotal success in preventing viral induced asthma exacerbations.

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4. De Bie JJ, Hendriks PAJ, Cruikshank WW, et al. Validation of a model for predicting asthma in children with atopy and asthma may well be contaminated by the postulated mechanism of paracetamol causation of asthma due to reduction in lung glutatione (GSH). Although the authors quote evidence from animal studies, we are not sure of the applicability to humans. If 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 have we seen 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 association 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 widely 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 avoid aspirin 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 Greenwich population 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 surveyed in this study, with the possibility of selection bias. Also, the diagnosis of asthma based on questionnaires may overestimate the true prevalence of asthma.

Thirdly, we wonder about the postulated mechanism of paracetamol causation of asthma. If it was identified, we would like to see it associated with selection bias, also of uncertain biological plausibility.

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AUTHORS’ REPLY Dr Wong raises the possibility that avoidance of aspirin or other non-steroidal anti-inflammatory agents (NSAIDs) by asthmatic individuals might explain our findings. While we did not have information on use of NSAIDs, we did address the issue of aspirin avoidance in our discussion and concluded that this could be, at best, only partly explain our findings since the association between frequent paracetamol use and asthma was not restricted to individuals taking paracetamol only, but was also seen in those who reported using aspirin too.

Dr MacDonald and Furness were concerned that the symptom of waking at night

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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.

Questionnaires have their limitations, as pointed out in our paper, these are not likely to have been responsible for the results reported and we do not agree with Shin et al that they should be dismissed as a source of valid information. We would reiterate 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. 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 present, and it makes very little sense to dispute interpretation. We were careful to emphasise that a causal link between paracetamol and asthma was only one of the possible explanations for our findings, but the clear dose-response relation would support such an interpretation. We would also disagree that the glutathione (GSH) hypothesis is biologically implausible. Whilst we acknowledge that previous animal experiments may have used toxic doses to deplete the lung of GSH, recent in vitro studies have suggested that depletion of GSH in pneumocytes and alveolar macrophages can occur with clinically relevant doses of paracetamol.1 Balzer suggests a different mechanism to explain our findings, although Shann’s review of the literature suggested that possible effects on the immune system and viral load were not specific to paracetamol, but were also seen with aspirin.2 Varner’s speculations are interesting and also provide an alternative possible mechanism for the effect.

We agree with Shin et al and with Raghuram and Archer that asthmatic patients should not be advised to avoid paracetamol, and that effective analgesia should not be “automatically withheld”. Like Wong, our biggest concern prior to publication was that press coverage might result in widespread switching from paracetamol to aspirin or NSAIDs. Whilst sensitivity reactions are uncommon, they are potentially life threatening, as illustrated by Picado’s study.3 Hence, we would stand by the advice to adult asthmatic patients that we emphasised in our paper and in our communications with the media, namely:

(1) If patients have taken aspirin or NSAIDs and know that these drugs do not adversely affect their asthma, they should continue to take them.

(2) If they do not know whether aspirin or NSAIDs affect their asthma, they should avoid aspirin until their asthma has been retested for sensitivity (in a clinical setting).

(3) While we have not established a causal link between frequent paracetamol use and asthma, it would nevertheless seem sensible for daily users to see whether they 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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Letters

Hyperventilation syndrome

In his comprehensive review of the hyperventilation syndrome,1 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 hypoxemia, 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 hypoxia,1 and other mechanisms have been suggested.2 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 Diahorn has used the term “dysfunctional breathing” to describe the production of symptoms directly as a result of abnormal breathing patterns.3 We are concerned about the reporting of 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 hypoxia 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 Buteko 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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