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 peer-reviewed references 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 reduced by a pharmacoepidemiological study. Recent reports in the general press and television about the study could convey the negative impression to patients with asthma which could direct them to self-select paracetamol use. Fatal or near fatal cases associated 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 controlled for potentially confounding factors. We were concerned that one of their definitions for “asthmatic” was the positive association between paracetamol and asthma, which could direct them to self-select paracetamol use. Fatal or near fatal cases associated with aspirin and NSAIDs have been reported.4 5 Finally, I agree with Shaheen et al. that further studies are required.


Shaheen et al. have stated that there is a positive association between paracetamol use and asthma.1 However, they have not really provided compelling evidence for an association, let alone causality, as the odds ratios for the associations between varying levels of paracetamol and asthma were all less than 3.

Case definition, paracetamol consumption, and respiratory symptoms were all based on postal questionnaires and were therefore highly subjective. The reliability of the information from such questionnaires is questionable. No objective measures were used to verify the diagnosis or severity of asthma in this study. Furthermore, the questionnaire response rate was only 50% and Shaheen et al dismiss the other 50% of non-responders in their discussion. The authors argue that it is “unlikely” that paracetamol use 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 kg/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. 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.1 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.

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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. I wish to propose an alternative mechanism to explain the association between paracetamol and asthma.

Sham’s1 has pointed out the marked immune modulating effect of paracetamol leading to less fever, less immune activation 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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I read with interest the report by Shaheen et al.1 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 antagonise ATP, bradykinin and arachidonic acid induced bronchoconstriction in guinea pigs.1

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.


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 study. It is also of interest that a recent case-control study found that irritable bowel syndrome, a disorder also associated with smooth muscle hyperreactivity, is associated with frequent paracetamol use.

We also 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 the most common concern 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 and ibuprofen in asthmatic children. The authors found the odds ratio for asthma was 1.06 in infrequent users, 1.22 in monthly users, and 2.38 in daily users of paracetamol. The strength of the association increased with the severity of the disease. In a review of 92 patients with severe asthma requiring ventilation, Pirro et al found that, in seven patients (8%), the attack was precipitated by an NSAID. Of these, one patient died as a result of anoxia enchepahalopathy. She had asthma for three years requiring chronic bronchodilator and salmeterol treatment and had taken a capsule of herbal medicine which contained 500 mg aspirin. Five of these patients had a history of asthma precipitated by NSAIDs. The other two were first presentations.

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 symptoms with anecdotal success in preventing viral induced asthma exacerbations.

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12 Lesko SM, Mitchell AA. Asthma morbidity following treatment. A dose response effect of paracetamol. Data entered 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 take ibuprofen in preference to aspirin, then this may result in an apparent association between paracetamol and asthma, but one that is iatrogenic.

With regard to the study by Shaheen et al. of the use 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 may well be contaminated by the recommendations of the BTS 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 take ibuprofen in 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 study 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 national sample 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 use increasing the severity of asthma due to reduction in lung gluthione (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 has it been 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 recommendations of the BTS guidelines, and may be affected by selection bias, and of uncertain biological plausibility.

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AUTHORS’ REPLY Dr Wong raises the possibility that avoidance of aspirin or non-steroidal anti-inflammatory drugs (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, 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.

Drs MacDonald and Furness were concerned that the symptom of “waking at night”...
with shortness of breath might represent an 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 responders 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 the issue is rather one of 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 also would 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, this is not supported by 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. 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. 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. 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 these drugs, at least until tested 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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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 hypcapnia. The term “hyperventilation syndrome” has, however, gained widespread acceptance. Van Diahoorn has used the term “dysfunctional breathing” to describe the production of symptoms directly as a result of abnormal breathing patterns. It is argued that existing 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 hypcapnia 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 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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