Paracetamol and asthma

The study by Shaheen et al certainly points 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 which is describing 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. 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 wrong impression to patients with asthma which could direct them to self-select the wrong impression to patients with asthma to avoid potential adverse reactions to NSAIDs and litigation problems.

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 wrong impression to patients with asthma which could direct them to self-select the wrong impression to patients with asthma to avoid potential adverse reactions to NSAIDs and litigation problems.

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. 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 attempted to control for confounding factors. We were concerned that one of their definitions of “asthma” was the positive answer to the question “Have you been woken by an attack of shortness of breath over the last 12 months?”. The association they have shown was with people who use paracetamol weekly or daily. We do not believe that there has been an attempt to control for confounding factors, particularly anxiety leading to headaches and symptoms of breathlessness and hyperventilation. We would encourage researchers taking this matter further to consider this in their study designs.

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3 Kuehm SL, Doyle MJ. Medication errors: 3 Kuehm SL, Doyle MJ. Medication errors: 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. 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.

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 use 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.

Shamn has pointed out the marked immune modulating effect of paracetamol leading to less fever, less inflammatory and in turn, 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 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 falsely increase levels of 5-HT metabolites in the urine during evaluation of patients for carcinoid syndrome. 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. 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.

This same agent increases forced desensitisation in a human model of allergic asthma (paracetamol is known to increase desensitisation in allergic rhinitis) and may act in the same way to increase BHR.


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respiratory symptoms with anecdotal success of COX-2 inhibitors at the onset of viral upper respiratory tract infection has been altered in atopic children (77). The prevalence of symptoms of asthma, aspirin intolerance, nasal polyposis and asthma, but one that is iatrogenic. Finally, we wonder about the postulated mechanism of paracetamol ingestion as a precipitant of asthma due to reduction in lung glutathione (GSH). Although the authors quote evidence from animal studies, we are not aware 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 these patients been treated locally by clinicians treating these patients.

In conclusion, we are concerned that the reported association between paracetamol and asthma will be mostly contaminated by the recommendations of the 1993 BTS asthma management guidelines which specifically mentioned avoidance of aspirin. The guidelines were withdrawn 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. This leaves the possibility of selection bias. Also, the diagnostic criteria of asthma based on questionnaires may overestimate the true prevalence of asthma.

Secondly, we ponder the postulated mechanism of paracetamol ingestion as a precipitant of asthma due to reduction in lung glutathione (GSH). Although the authors quote evidence from animal studies, we are not aware 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 these patients been treated locally by clinicians treating these patients.

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In conclusion, we are concerned that the reported association between paracetamol and asthma will be mostly contaminated by the recommendations of the 1993 BTS asthma management guidelines which specifically mentioned avoidance of aspirin. The guidelines were withdrawn 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. This leaves the possibility of selection bias. Also, the diagnostic criteria of asthma based on questionnaires may overestimate the true prevalence of asthma.
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 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 would also disagree that the glutathione (GSH) hypothesis is biologically implausible. Whilst we acknowledge that previous animal experiments may have oversimplified, the predominant indicator 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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(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 if not 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.

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 hypocapnia. 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. We are 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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