LETTERS TO THE EDITOR

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 textbook or prescribing reference states that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) could potentially worsen asthma.1 Health professionals will therefore certainly choose paracetamol for patients with asthma to avoid potential adverse reactions to NSAIDs and litigation problems.2 It is unlikely that this bias could be resolved in a pharmacopoeiological 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 ibuprofen. Fatal or near fatal cases would encourage researchers taking this matrix into the association of paracetamol and asthma. In our view the association between varying levels of paracetamol and asthma were all less than 0.3. 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 hypothesis, the patients who had to exceed the LD50 of paracetamol; the glutathione hypothesis is really provided compelling evidence for an association of paracetamol and asthma. In our view the 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.

Shann3 has pointed out the marked immune modulating effect of paracetamol leading to less fever, less immunosuppression 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 provokeation 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).

We were interested to read of the association between paracetamol use and asthma in adults reported by Shaheen et al.4 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 of “asthmatic” 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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Shaheen et al. have observed an important association between asthma and paracetamol intake in children. 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.

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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 control study7 that found that irritable bowel syndrome, a disorder also associated with smooth muscle hyperreactivity, is associated with frequent paracetamol use.

The prevalence of sensitivity to aspirin and other non-steroidal anti-inflammatory agents (NSAIDs) is quite low. In a population survey of a population based sample of 4300 adults in Southern Finland, Hedman and colleagues1 found the prevalence of symptomatic aspirin intolerance was 1.2%. This was higher (8.8%, 95% confidence interval 6.4 to 11.2%) in patients and those with allergic rhinitis (2.6%). Recent media attention to the paper by Shaheen et al highlights the public concern regarding the use of anaphylaxis drugs in patients with asthma.22 Modulation of airway hyperresponsiveness and paracetamol use. 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 1879 children with asthma and rhinitis.23

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 no apparent effect in preventing viral induced asthma exacerbations.”

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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 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.

Drs MacDonald and Furness were concerned that the symptom of “waning at night
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.

(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 them until formally 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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Letters

Hyperventilation syndrome

In his comprehensive review of the hyperventilation syndrome1 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 wide currency both in research studies and in clinical practice, often without precise diagnostic criteria being specified or hypocapnia 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 hypocapnia, 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 hypocapnia, 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 faced with 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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References


