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EDITORIAL

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Have the efforts to prevent aspirin-related Reye's syndrome fuelled an increase in asthma?

This editorial discusses the findings of the paper in this issue by Wickens et al. [1] pp. 399–406.

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The analyses based on a New Zealand birth cohort reported by Wickens et al. [1] add further evidence to prior publications suggesting a relationship between the use of paracetamol (acetaminophen) and an increased prevalence of asthma in children [2]. Wickens et al. [1] focus on exposure to the drug in the first 15 months of life and between the ages of 5 and 6 years with outcomes assessed at age 6 years. Their analysis adds to the literature a distinction between atopic and non-atopic asthma in relationship with paracetamol. Early drug exposure was associated with both atopy and atopic asthma, but later exposure was associated with asthma regardless of atopic status [1].

The paper further demonstrates, as have others, the pervasive use of this drug. In the Wickens et al. [1] birth cohort, 90% of the children had been given the drug in the first 15 months of life, and 95% were dosed between 5 and 6 years. Indeed, only 51 of the 505 children with early life data were not exposed to paracetamol. In a recent large study of pregnant women in the northeastern United States, 68.8% had used this medication during their pregnancy [3]. With this high prevalence of use, even a small paracetamol-related increase in the risk of asthma in children or adults would imply a substantial public health burden. Using data from Table 3 in the published report, the calculated attributable risk percent in the population is 36.8%, meaning that this percentage of the disease incidence would be potentially removed if the early childhood use of paracetamol were eliminated.

As scientists and physicians search for reasons for the asthma epidemic, a hypothesis associated with paracetamol is attractive. From the ecologic perspective, the dramatic increase in the use of paracetamol when aspirin use was associated with Reye's syndrome parallels the rise in asthma prevalence, although many other potential factors also parallel this rise in developed countries, such as a decrease in physical activity, an increase in obesity, the amount of time spent indoors and the use of group day care [4, 5]. There are three commonly proposed mechanistic theories to explain how ingestion of paracetamol could induce asthma. The first proposed mechanism is from the depletion of glutathione, which is a major antioxidant in the body. The depletion of glutathione increases the risk of oxidative damage to the lungs [6]. The increased risk of oxidative damage might be especially important if paracetamol was given to a child during the course of a viral respiratory infection as a lower ability to suppress inflammation-related oxidative damage might result in greater damage to lung tissues. The second frequently mentioned theory is that paracetamol does not produce suppression of COX-2 when given during infections that can result in higher production of prostaglandin E_2, which favours a T-helper type-2 (Th2) over a Th1 immune response [7]. The third theory is that the paracetamol molecule is homologous to many low-molecular-weight chemicals known to cause asthma from occupational exposures [8]. These chemicals share the common property of having two basic functional groups such as hydroxyl, carboxyl, sulphonyl, or isocyanate or similar groups. Paracetamol has an acetamide group on one side of the central benzene ring with a hydroxyl group on the other side fitting the structural pattern of many other asthmogenic low-molecular-weight compounds. It is also possible that these proposed mechanisms could act together in varying proportions.

However, epidemiological studies of drug use, that is, observational studies associating medications with disease outcomes, are especially methodologically challenging, and particularly problematic when using data that

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were not collected with the specific medication hypothesis in mind. Even with over-the-counter drugs, the use of medications is inherently intertwined with other characteristics that may be associated with other risk factors as well as disease outcomes and therefore confound exposure–disease associations. Consumption of medications may be highly correlated with other risk factors for disease, such as viral illnesses. Medication use in children is associated with parents who are attuned to symptoms of discomfort in their children, and also associated with parental belief that medications are effective. Such parents may be more likely to take their children to the doctor, therefore increasing the probability that the child will receive a diagnosis of a disease such as asthma. Parents taking their children to the doctor more frequently are likely to be given more advice regarding the taking of medications when a child becomes ill. They may also be more likely to report both respiratory symptoms and the use of a drug. In other words, the association of a drug and disease can be explained by a general higher level of 'medicalization' among the cases.

Other biases are of concern. 'Reverse causation' or 'confounding by indication' bias suggests that a drug might be given for early symptoms of the disease or for the disease and related comorbidities post-diagnosis. Recall bias is always a consideration when asking parents with and without a diseased child about the child's exposures, including the use of previous medications. Misclassification of exposure is highly likely, given that paracetamol is contained in many different drug combinations marketed under multiple trade names; for example 64 names were reported in the Kang et al. [3] study of adult women. Without a carefully collected medication usage history that includes indication for and the frequency and dose of all medications, the probability of invalid exposure classification is high. Many of the dose or the frequency of use categories have been very broad; in the paper by Wickens et al. [1] for example, a child who took paracetamol only once in 15 months was classified the same as a child who took the drug for multiple episodes of illness during that same time period. Misclassification bias only drives associations towards the null if it is not differential between levels of exposure and diseased and non-diseased subjects, which may not be the case in these largely cross-sectional and case–control studies [9]. Genetic variants, such as those related to drug metabolism, may also be important [10].

Although many observational studies consistently indicate associations between pre-natal and post-natal exposure to paracetamol and asthma in children (one of Hill's criteria for causality) [11], there are indications that some of these biases may be operating. Considering previous publications in total, there is a lack of specificity in the exposure–disease relationships in terms of disease, which is an argument against causality [11–13]. In the paper by Wickens et al. [1], early exposure is related to atopy, but later exposure is not. While the focus and biological plausibility has been on asthma, other reports have found paracetamol to be associated with each of the diseases under study, including atopic dermatitis and allergic rhinitis, and chronic obstructive pulmonary disease in adults [14]. Some investigators have found associations to be stronger with severe asthma, suggesting a bias in that a more debilitated asthmatic might take more medications for discomfort relief [15]. The results of Kang et al. [3] from a large cohort of pregnant women, avoiding many of the limitations of previous studies and adjusting for multiple variables, suggest, in contrast to other studies [16], that pre-natal exposure to paracetamol, if anything, may be protective for asthma in offspring at age 6 years. These authors also found that paracetamol use was associated with asthma diagnosis and asthma symptoms among the mothers. An association between asthma and paracetamol use is likely as many physicians advise asthmatics to avoid aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) because of the risk of inducing severe asthma. Tapiainen et al. [17] evaluated cohort data from a large prospective study that carefully documented early occurrences of fever, antipyretic use and reason for use, and found that the number of febrile days associated with respiratory infections, but not use of antipyretic medications, was associated with both asthma and atopic dermatitis in adolescence, suggesting that children developing these conditions had more respiratory tract infections in early childhood, which led to more febrile days and the use of antipyretic medications. There was no difference with respect to febrile days due to gastrointestinal infections. Wickens et al. [1] also found that paracetamol use at age 5–6 years of age was associated with chest infections and systemic antibiotic use, and antibiotic use was associated with paracetomol use in early infancy, although of borderline significance ($P = 0.09$).

We agree with the conclusions of these authors and several other editorials: a drug that is so commonly used from childhood throughout adulthood, including in pregnancy, and that has been associated in multiple studies with a common childhood disease causing a high social and financial burden, demands more definitive studies [18, 19]. While pharmaco-epidemiology studies of previously collected data provide important clues, it is time for (1) large prospective epidemiological studies focused specifically on paracetamol exposure and designed to overcome the limitations of previous work and/or (2) randomized clinical trials. As non-aspirin NSAIDs have not been shown to be associated with increased childhood asthma, the ideal trial would compare the risks of paracetamol, ibuprofen and placebo for asthma and other outcomes of interest. A placebo is valuable to be sure that ibuprofen is not associated, directly or inversely, with

asthma risk. Practically, the use of a placebo would likely be problematic for many parents and physicians, making a three-way study difficult. However, a recent meta-analysis [20] concluding that ibuprofen is at least as if not more effective in reducing pain and fever in children than paracetamol and equally safe suggests that, in the meantime, ibuprofen should be the drug of choice for small children.

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