

Paracetamol as a risk factor for allergic disorders

Richard Beasley and colleagues (Sept 20, p 1039)¹ conclude that use of paracetamol in the first year of life and in later childhood is associated with increased risk of asthma, rhinoconjunctivitis, and eczema at the age 6–7 years. I have some critical observations.

First, there is an issue of recall bias, since parents were asked to recall whether their children received paracetamol 6–7 years ago. Parents whose children were more prone to viral respiratory infections are more likely to recall the use of an antipyretic-analgesic agent.

Second, the question was limited to paracetamol alone, without any attempt to identify the use of alternative antipyretic-analgesic agents such as ibuprofen.

Third, the study did not look for confounding variables. The indication for which the paracetamol was used is likely to be a greater culprit than the paracetamol per se. Viral respiratory infections are known to be an important trigger of bronchospasm in susceptible children.

Fourth, it is not possible to assess reliably the dose–response relation in a retrospective survey.

Fifth, the diagnosis of asthma and eczema was based on the perception of the parents and not confirmed by a physician.

Sixth, the observations contrast with the generally held view that aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) can trigger bronchospasm in susceptible individuals, although there is some risk of cross-reactivity with paracetamol.

Finally, the underlying biological mechanism by which paracetamol potentiates pulmonary damage needs to be assessed.

There is a need to do randomised controlled trials to assess the role of

paracetamol and NSAIDs in the causation of allergic diseases. In the meantime, paracetamol should continue to be used as first-choice medicine for the treatment of fever and pain in children because of its efficacy and safety profile spanning 50 years.

I am a member of the Scientific Advisory Board of GSK Consumer Healthcare.

Meharban Singh
drmbask@gmail.com

Child Care and Dental Health Centre, 625, Sector 37, Noida 201301, India

1 Beasley R, Clayton T, Crane J, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 2008; **372**: 1039–48.

Richard Beasley and colleagues¹ report a strong association between use of paracetamol in the first year of life and asthma at 6–7 years of age, and a dose-dependent association between current paracetamol use and symptoms of severe asthma. We believe Beasley and colleagues might have overstated their conclusions.

With this cross-sectional, retrospective study, Beasley and colleagues contend with the intrinsic difficulties of recall bias, misclassification bias, and confounding by indication.² Paracetamol use has been found to be highly associated with an increased risk of all causes of death,³ highlighting the potential for drawing invalid conclusions about causal relations in observational studies of commonly used drugs.

The categorisation of paracetamol use seems somewhat arbitrary. It is hard to reconcile, for example, the finding that “medium” (at least once per year) use of paracetamol is strongly associated with asthma. We also question the use of “wheeze and whistling in the chest” as a surrogate for the diagnosis of asthma. A physician-based diagnosis would have been preferable. Although Beasley and colleagues state that wheeze and whistling in the chest is a reliable surrogate,⁴ we think it subjective.

We commend Beasley and colleagues for using the population-attributable risk proportion (PAR%) to estimate the fraction of population-level asthma attributable to paracetamol use. However, PAR% is population-specific. Assuming that the association between paracetamol use and asthma is truly causal, regions with a higher frequency of paracetamol use will have a higher proportion of paracetamol-induced asthma in the population (ie, a larger PAR%).⁵ As indicated in Beasley and colleagues’ webtable 1, the prevalence of paracetamol use varies substantially from centre to centre. Thus, we question the appropriateness of calculating a combined PAR% for all 47 centres.

To conclude, we take issue with the statement that “paracetamol use in infancy and frequent use later in childhood strongly increases the risks of asthma”. Findings from this study are suggestive of such an association, but the findings should be interpreted with caution.

We declare that we have no conflict of interest.

**J Lawrence, E Moore, L Port,
M Danchin, *T Connell**
tom.connell@rch.org.au

Department of Paediatrics, University of Melbourne, Royal Children’s Hospital Melbourne, Flemington Road, 3052 Parkville, VIC, Australia

- 1 Beasley R, Clayton T, Crane J, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 2008; **372**: 1039–48.
- 2 Signorello LB, McLaughlin JK, Lipworth L, Friis S, Sorensen HT, Blot WJ. Confounding by indication in epidemiologic studies of commonly used analgesics. *Am J Therapeutics* 2002; **9**: 199–205.
- 3 Lipworth L, Friis S, Mellemkjaer L, et al. A population-based cohort study of mortality among adults prescribed paracetamol in Denmark. *J Clin Epidemiol* 2003; **56**: 796–801.
- 4 Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; **368**: 733–43.
- 5 Koepsell TD, Weiss NS. Epidemiological methods: studying the occurrence of illness. New York: Oxford University Press, 2003.



Science Photo Library

Submissions should be made via our electronic submission system at <http://ees.elsevier.com/thelancet/>