

EDITORIAL

Clinical & Experimental Allergy

Does regular paracetamol ingestion increase the risk of developing asthma?

This editorial discusses the findings in the paper by Evers et al. [13] pp. 482–489.

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Paracetamol has been widely used for the treatment of pain and fever in patients of all ages since its introduction in the mid-1950s. Although it is an extremely well-tolerated drug, there has been an emerging interest in its potential to increase the risk of a number of conditions including asthma. The reason for this line of investigation, initiated in the late 1980s, are manifold and include early evidence, later dismissed, that paracetamol can aggravate asthma in patients with co-existent aspirin and non-steroidal anti-inflammatory sensitivity [1]; an ecological analysis of two major international studies showing that higher paracetamol sales were associated with higher prevalence of both childhood and adult asthma across multiple centres [2]; and evidence for a plausible biological mechanism through paracetamol-induced inhibition of glutathione pathways in respiratory epithelium, resulting in increased airway inflammation [3]. While there is evidence for and against these associations, the debate on whether paracetamol is a cause of asthma, or whether this association is confounded by other factors, remains unresolved.

A number of studies have found an association between regular paracetamol ingestion in early childhood and asthma [4]. The largest study to consider this question was the International Study of Asthma and Allergy in Childhood (ISAAC) phase III, which included 205 487 children aged 6–7 years from 72 countries. This study demonstrated an association between exposure to paracetamol given for fever in the first year of life and current risk of asthma at age 6–7 years [5]. Although the study has many strengths,

including its large size, use of standardized measures and methods and generally consistent results across multiple sites, interpretation is limited by the failure to adjust for the potential confounding factor related to respiratory infections in early life [6]. This is a major methodological weakness, because paracetamol is used to treat fever during episodes of respiratory infections and early life respiratory infections have been repeatedly demonstrated to increase the risk of developing asthma [7]. In addition, the ISAAC findings may have been affected by the recall bias given that exposure data were collected retrospectively.

More recently, a systematic review of paracetamol use and asthma has concluded that paracetamol use is related to an increased risk of asthma in both children and adults [8]. However, the studies included in the review were quite heterogeneous and the authors were unable to stratify the findings by study design quality due to too few studies. Furthermore, three more, recently published longitudinal studies, including our work, have failed to demonstrate any association between the use of paracetamol in infancy or early childhood and subsequent childhood asthma once confounding factors, including indication for use, were accounted for [9–11], although a similar unadjusted association was demonstrated as per previous studies. We also demonstrated that there is no association between paracetamol use for conditions other than respiratory illnesses and the development of subsequent asthma.

Following on from the investigation into postnatal paracetamol exposure and asthma risk, some researchers have now turned to the question as to whether prenatal exposure may instead pose a risk. By assessing prenatal exposure to paracetamol through maternal ingestion, maternal paracetamol use for respiratory illness is unlikely to confound the association because maternal intake is driven by factors related to her own health and not those of the offspring. Interest in prenatal drug exposure and risk of subsequent disease have recently come into focus with increasing

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Cite this as: S. C. Dharmage and K. J. Allen, *Clinical & Experimental Allergy*, 2011 (41) 459–460.

knowledge about *in utero* epigenetic effects and long-term determinants of health and disease in postnatal life. Evolving evidence in the field of epigenetics has demonstrated mechanisms where maternal environmental factors can modify the risk of disease in offspring through *in utero*-mediated mechanisms, including CpG island demethylation and histone deacetylation, resulting in long-term changes to gene expression.

Furthermore, some recent studies support the biological plausibility of an association between prenatal (as opposed to postnatal) paracetamol exposure and asthma risk in the offspring. The main proposed biological mechanism for the association between paracetamol and asthma is the depletion of glutathione in lung tissue leading to impairment of respiratory antioxidant defences [3, 12]. Two recent publications [9, 10] have reported that maternal and child polymorphisms in glutathione S transferase Pi modified the relationship between prenatal paracetamol exposure and childhood asthma. Interestingly, these polymorphisms did not modify the relationship between infant paracetamol use and childhood asthma, and as for previous studies on postnatal exposure, infant paracetamol use and childhood asthma were found to be confounded by pre-existing wheezing.

The paper by Eyers *et al.* published in this issue [13] of *Clinical & Experimental Allergy* is a systematic review of prenatal paracetamol exposure, and using summary estimates of the meta-analysis, concludes that prenatal exposure to paracetamol does increase the risk of childhood asthma. Although the systematic review and analysis were rigorously conducted, the authors used the unadjusted odds ratios as raw data in their meta-analysis. Hence, the

summary estimate generated by meta-analysis is the average of unadjusted odds ratios, and therefore the summary of the findings has not accounted for confounders. The authors attempt to justify the use of unadjusted odds ratios by arguing that potential confounders such as indication for use of maternal ingestion of paracetamol could not possibly confound the association with offspring outcomes. However, residual confounding related to a number of other factors, such as smoking, anxiety score, antibiotic use and alcohol intake [9], may explain the association observed in the study; this is acknowledged by the authors themselves. Hence, this review does not provide conclusive evidence to suggest any change to public health recommendations about the use of paracetamol in pregnancy.

Despite these uncertainties, paracetamol remains a valuable drug in the clinical armamentarium for its analgesic and anti-pyretic effects. Clarification about whether the association with asthma risk is causal and, if so, the population attributable risk of asthma related to this important and widely used drug will be important to minimize community anxiety fuelled by media reporting of contradictory research findings. The alternatives to paracetamol have their own risk profile. Aspirin can cause the rare life-threatening side-effect of Reye's syndrome while ibuprofen can provoke asthma attacks in people with asthma. Although there are insufficient data that postnatal ingestion of paracetamol increases the risk of asthma, the available data on the effects of prenatal exposure justify further rigorous research. For the time being, there is no need to recommend any changes to the current clinical practice.

References

- Settipane RA, Stevenson DD. Cross sensitivity with acetaminophen in aspirin-sensitive subjects with asthma. *J Allergy Clin Immunol* 1989; **84**:26–33.
- Newson RB, Shaheen SO, Chinn S, Burney PG. Paracetamol sales and atopic disease in children and adults: an ecological analysis. *Eur Respir J* 2000; **16**:817–23.
- Kelly FJ, Mudway I, Blomberg A, Frew A, Sandstrom T. Altered lung antioxidant status in patients with mild asthma. *Lancet* 1999; **354**:482–3.
- Eneli I, Sadri K, Camargo C, Jr, Barr RG. Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005; **127**:604–12.
- Beasley R, Clayton T, ISAAC Phase Three Study Group *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.
- Lowe A, Abramson M, Dharmage S, Allen K. Paracetamol as a risk factor for allergic disorders. *Lancet* 2009; **373**:120; author reply 120–1.
- Oddy WH, de Klerk NH, Sly PD, Holt PG. The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J* 2002; **19**:899–905.
- Etminan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, Fitzgerald JM. Acetaminophen use and the risk of asthma in children and adults: a systematic review and meta-analysis. *Chest* 2009; **136**:1316–23.
- Shaheen SO, Newson RB, Ring SM, Rose-Zerilli MJ, Holloway JW, Henderson AJ. Prenatal and infant acetaminophen exposure, antioxidant gene polymorphisms, and childhood asthma. *J Allergy Clin Immunol* 2010; **126**:1141–8.
- Perzanowski M, Miller RL, Tang D *et al.* Prenatal acetaminophen exposure and risk of wheeze at age 5 years in an urban, low-income cohort. *Thorax* 2010; **65**:118–23.
- Lowe AJ, Carlin JB, Bennett CM *et al.* Paracetamol use in early life and asthma: prospective birth cohort study. *BMJ* 2010; **341**:c4616, doi: 10.1136/bmj.c4616.
- Cantin AM, North SL, Hubbard RC, Crystal RG. Normal alveolar epithelial lining fluid contains high levels of glutathione. *J Appl Physiol* 1987; **63**:152–7.
- Eyers S, Weatherall M, Jefferies S, Beasley R. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. *Clin Exp Allergy* 2011; **41**:482–489.