Published in final edited form as:

Curr Opin Allergy Clin Immunol. 2014 February ; 14(1): 25–28. doi:10.1097/ACI.0000000000000026.

The association between acetaminophen and asthma - is there anything to learn from the upper airways?

Haejin Kim, MD¹ and Christine Cole Johnson, PhD²

¹Division of Allergy and Clinical Immunology, Henry Ford Health System, Detroit, MI

²Department of Public Health Sciences, Henry Ford Health System, Detroit, MI

Abstract

Purpose of review—to examine literature evidence for the association between acetaminophen (paracetamol) use and development of rhinitis

Recent findings—Increased use of acetaminophen (paracetamol) as the favored antipyretic during pregnancy and infancy has been hypothesized to be a risk factor for the development of asthma. There is a paucity of well-designed birth cohort studies to examine paracetamol as a risk factor in the development of rhinitis. Confounding by antibiotic use, viral infections, and recall bias are problematic for many of the studies that are published.

Summary—Prospective birth cohorts need to dedicate adequate time and research personnel to adequately assess paracetamol exposure as a primary variable of interest rather than as an incidental exposure variable collected during routine questionnaires administration.

Keywords

Rhinitis; acetaminophen; paracetamol

Introduction

When Reye's syndrome was initially described, epidemiologic evidence indicated that aspirin ingestion was present during the viral illness that preceded encephalopathy and fatty liver degeneration in children [1]. After warning labels became mandatory in the 1980s warning consumers of the risk of Reye's syndrome for all aspirin-containing products, there was a marked decline in the number of reported cases [1]. Because of the danger of Reye's syndrome, alternative antipyretics such as acetaminophen (paracetamol) have become standard of care when treating fever in infants and young children. The increased use of paracetamol starting in the 1980s and the parallel increase in atopic disorders seen over the same time period, especially in Westernized countries, led to the hypothesis of a causal

Author of correspondence: Haejin Kim, 1 Ford Place, Suite 4B, Detroit, MI 48202, Phone (313) 876-2662, Fax (313) 876-2094, hkim3@hfhs.org.

Conflicts of Interest:

HK declares no conflicts of interest relevant to this review.

CCJ declares a one-time honorarium from McNeil paid to HFHS for a one-day meeting of experts.

relationship. Multiple studies have subsequently suggested associations between its use the development of atopic diseases; however results have generally been equivocal.

Mechanistically, paracetamol is thought to interfere with the natural antioxidant glutathione. Glutathione acts as a free radical scavenger, mitigating damage caused by reactive oxygen species and serves as the major endogenous antioxidant in all human cells, including endothelial cells [2]. The concentration of glutathione in lung endothelial fluid is equivalent to the intracellular concentration [3]. In healthy human volunteers, maximum therapeutic doses of paracetamol reduce total serum antioxidant capacity in as little as two weeks [4]. This perturbation in natural antioxidant activity can result in endothelial damage especially if it were to occur during viral respiratory infections, as the host may be unable to repair oxidative damage caused by viral inflammation [5]. A similar process likely occurs in the nasal epithelium, as *in situ* glutathione levels and cytotoxic damage fluctuates in response to ozone and particulate matter [6].

Existing evidence that supports paracetamol as a risk factor for asthma is modest with odds ratios around 2, but must be interpreted with caution as specific studies do not always adjust for confounders such as respiratory infections [7,8]. Administration of questionnaires and exposure timing also vary greatly among studies, focusing on the prenatal and/or the early childhood periods. Participants are often required to recall exposures over a long period of time at a single encounter [9]. Because acetaminophen is often given as an anti-pyretic in pregnancy and infancy during viral infections, it would seem obvious that upper respiratory infections, which are also related to atopic outcomes, are significant confounders that need to be addressed in statistical models. Multiple studies have been published that do not account for viral infections or only examine them in univariate modeling. Even large national drug and birth registries were not able to adjust for upper respiratory infections or antibiotic usage despite data being reported in univariate models. Others were not able to account for over the counter use of paracetamol [10,11].

Although the current literature focuses heavily on asthma as an outcome, there is a paucity of epidemiologic studies examining the effect on rhinitis. The same confounders need to be examined since the upper airways represent the gateway to the lower airways and are likely to be affected by the same processes.

Methods

A PubMed search was performed using the terms “acetaminophen” and “rhinitis”, as well as with the terms “acetaminophen” and “asthma”. Both searches were limited to articles in English, yielding a total of 311 articles. Individual abstracts were reviewed for relevance to this review, and were included only if one of the examined outcomes included rhinitis. Review articles were excluded, as well as articles that included rhinitis only as an effect modifier or as a predictor.

Results

A large ecological study of acetaminophen sales in the UK was performed between 1994 and 1995, examining atopic diseases and sales of acetaminophen in 1994 and 1995 [12]. 12-

month prevalence of allergic rhinitis was determined using ISAAC questionnaires in children aged 6–7 (parental assessment) and ages 13–14 (self-assessed). This same study examined rhinitis (hay fever or nasal allergies) in adults (20–44 years old) using standardized questionnaires from the European Community Respiratory Health Survey. Paracetamol sales were obtained from hospitals, pharmacies and retailers and used to calculate grams of paracetamol/person/year, adjusted for GDP. In children and adolescents, prevalence of rhinoconjunctivitis increased about 12% for every gram increase in per capita paracetamol sales, adjusted for GDP. The relationship was greater in adults (35%). Interestingly the authors performed a post hoc analysis controlling for the “anglophone effect” in English speaking countries (UK, Eire, USA, Australia, and New Zealand) and noted that all of the significant associations seen between paracetamol sales and atopic outcomes either became non-significant or were greatly attenuated. The authors speculate that there is likely a confounder strongly associated with English-speaking countries that is responsible for the effect. It is well known that ecological studies suffer from the fact that exposure data is not linked to individuals, and thus this study design is considered to be weak and solely hypothesis generating [13].

In New Zealand data from the general population showed that in 6–7 year old children, paracetamol use in the past year (directly antecedent to the outcome assessment) at least once per month was associated with current allergic rhinoconjunctivitis (OR 1.77 [95% CI 1.43–2.18]) [14]. Paracetamol use in the first year of life, however, was not associated with this outcome. Antibiotic usage during the first year of life was also associated with current allergic rhinitis (OR 2.04 [95% CI 1.60–2.61]) but there was no adjustment for upper respiratory infections during the first year of life. Although it is possible that both paracetamol use and antibiotic use in the first year of life could be surrogates for upper respiratory infections, the study does not adequately address this concern. Because this was not a prospective cohort study, parents were asked to recall details about paracetamol exposure dating back at least 6 years, perhaps contributing to the lack of association seen between exposure during the first year of life and current allergic rhinoconjunctivitis symptoms.

There are multiple papers published examining rhinitis in phase 3 of the International Study of Asthma and Allergies in Children (ISAAC). Adolescents (age 13–14) from 36 countries were interviewed regarding their paracetamol use and is impressive due to the number of participants (over 300,000) and use of a standardized questionnaire [15]. The exposure to paracetamol (none, once, or more than once per month in the past 12 months) was measured in the year directly antecedent to the outcome of rhinoconjunctivitis, showing a modest risk (OR between 1.3 and 2.3) Although the authors did adjust for socioeconomic status, maternal smoking, and number of siblings, other early exposures such as viral infections and antibiotic exposure were not included in the models. Similarly, a Canadian phase 3 ISAAC study also showed a small increased risk of rhinitis (OR 1.83 [95% CI 1.61–2.08]) in adolescents without adjustment for viral infections [16], and a Mexican study showed increased risk of rhinitis in both 6–7 year olds (OR 1.51 [95% CI 1.31–1.75]) and in 13–14 year olds (OR 1.31 [95% CI 1.20–1.43]) [17]. In these last two studies, because acetaminophen use was ascertained only in the year prior to the assessment of outcome and was asked of adolescents for the entire 12 months antecedent to questionnaire

administration, confounding due to viral infections cannot be ruled out, and recall bias is a substantial concern.

A 10 year follow up study of the Environment and Childhood Asthma (ECA) cohort in Oslo cohort found that maternal use of paracetamol during the first 6 months of pregnancy was associated with allergic rhinitis (doctor's diagnosis or nasal allergic symptoms in the past 12 months) at age 10 (OR 2.30 [95% CI 1.06–4.97]). Although this was a prospective birth cohort, questions regarding paracetamol exposure were administered *at the time of delivery* and mothers were asked to recall their use up to 9 months prior. No prospective study has perfect methodology, but the timing of these questionnaires surrounding delivery may not be the most conducive towards gaining an accurate history, as opposed to cohorts where mothers were recruited earlier during pregnancy [18].

Taiwan recently switched to a large single payer health insurance program in 1995. From this, over 200,000 children were analyzed with respect to prescription antibiotics and paracetamol use during the first year of life. The authors found an association between paracetamol use during the first year of life and allergic rhinitis for two birth cohorts (HR 1.93 [95% CI 1.85–2.02] and HR 1.42 [95% CI 1.25–1.61]) between ages 2–6 years [19]. Outcomes were based on insurance claims for outpatient visits. The authors note that over the counter use of paracetamol was not captured in their study. They justify that most parents will not administer paracetamol in Taiwan without a prescription, but do not provide any evidence for this supporting.

Taken together, literature evidence supporting the association between paracetamol exposure and rhinitis is inconsistent as methodology differs among various studies. The main difficulty that seems common is the ability to obtain valid information regarding paracetamol dosage and timing during pregnancy or during the first year of life. Thus, the majority of studies must rely on paracetamol use in the year directly antecedent to the outcome assessment as most participants cannot be expected to accurately recall paracetamol use several years, or perhaps several weeks, in retrospect. Moreover the drug is used in many combination over the counter combination drugs. Second, viral infections as confounders are not routinely considered in several statistical models.

We would like to conclude by reviewing two studies that examine atopy and asthma as examples of better-conducted cohort studies. Wickens et al. demonstrated that both dose and timing of the exposure of paracetamol may determine associations with disease outcomes. First, paracetamol use before 15 months of age was associated with atopy at age 6 (a positive skin test to a food or aeroallergen) even after adjustment for bronchial infections (OR 3.61 [95% CI 1.33–9.77]). When examining doses of paracetamol in the 12 months year prior to the outcomes at age 6, increasing doses of paracetamol use appeared to increase risk for wheeze, current asthma, and atopy (also adjusted for bronchial infections). This suggests that paracetamol exposure early in life may be more important for the development of atopy and exposure later in life may be more important for development of asthma [20]. Finally, in a prospective cohort study of pregnant women, participants were recruited and interviewed before 24 weeks of gestation. Mothers were asked specifically about paracetamol use during the first three trimesters early in their confinement to minimize recall bias, and were also

querified specifically about quantity of paracetamol use (none, 1–7 days per month, 8–14 days per month, more than 14 days per month, and every day) in detail. Dosages were calculated in mg and the authors developed 6 classes of “per month” dosages as well as 4 classes of “per day” dosages. The same questions were asked 1 month post-partum. Confounders were assessed and outcome measures were collected at a 6 year follow up. Unexpectedly this study showed that frequent paracetamol during the first and third trimesters of pregnancy was associated with a decreased risk of asthma (OR 0.76, 95% CI [0.53–1.10]). Cumulative (but not current) rhinitis symptoms at age 6 were also assessed in the multivariate model and was found to be significant (OR 3.23 [95% CI 2.28–4.60]). This study is notable for the amount of detail dedicated to recording paracetamol use [21].

Conclusion

It is apparent that carefully designed, hypothesis targeted prospective birth cohort studies are required to better understand the relationship between paracetamol use and rhinitis. Some existing studies do suggest increased risk with paracetamol use, but conclusions are flawed due to lack of adjustment for confounders such as viral infections, or due to recall bias. Studies need to be designed with paracetamol as a primary predictor in mind rather than as an additional variable that happens to be collected during administration of a questionnaire. Several contact points with participants should be planned in order to maximize validity of exposure data and obtain detailed information on indications for medication use. Although the obvious “best” study would be a double blind placebo controlled trial using paracetamol, it would be difficult to include a placebo arm as use of another medication complicates interpretation.

References

1. Belay ED, Bresee JS, Holman RC, et al. Reye's syndrome in the United States from 1981 through 1997. *N Engl J Med*. 1999 May 6; 340(18):1377–1382. [PubMed: 10228187]
2. Shaheen SO, Sterne JA, Songhurst CE, et al. Frequent paracetamol use and asthma in adults. *Thorax*. 2000 Apr; 55(4):266–270. [PubMed: 10722764]
3. Lauterburg BH. Analgesics and glutathione. *Am J Ther*. 2002 May-Jun;9(3):225–233. [PubMed: 11941382]
4. Nuttall SL, Khan JN, Thorpe GH, et al. The impact of therapeutic doses of paracetamol on serum total antioxidant capacity. *J Clin Pharm Ther*. 2003 Aug; 28(4):289–294. [PubMed: 12911681]
5. Johnson CC, Ownby DR. Have the efforts to prevent aspirin-related Reye's syndrome fuelled an increase in asthma? *Clin Exp Allergy*. 2011 Mar; 41(3):296–298. [PubMed: 21294782]
6. Hernandez-Escobar SA, Avila-Casado MC, Soto-Abraham V, et al. Cytological damage of nasal epithelium associated with decreased glutathione peroxidase in residents from a heavily polluted city. *Int Arch Occup Environ Health*. 2009 Apr; 82(5):603–612. [PubMed: 19034489]
7. Eyers S, Weatherall M, Jefferies S, et al. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. *Clin Exp Allergy*. 2011 Apr; 41(4):482–489. [PubMed: 21338428] This is a meta-analysis of cohort studies examining the role of paracetamol and its association with asthma.
8. Kreiner-Moller E, Sevelsted A, Vissing NH, et al. Infant acetaminophen use associates with early asthmatic symptoms independently of respiratory tract infections: the Copenhagen Prospective Study on Asthma in Childhood 2000 (COPSAC(2000)) cohort. *J Allergy Clin Immunol*. 2012 Dec; 130(6):1434–1436. [PubMed: 23102919]

9. Perzanowski MS, 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 Feb; 65(2):118–123. [PubMed: 19850963]
10. Kallen B, Finnstrom O, Nygren KG, et al. Maternal drug use during pregnancy and asthma risk among children. *Pediatr Allergy Immunol*. 2013 Feb; 24(1):28–32. [PubMed: 23331527]
11. Kelkar M, Cleves MA, Foster HR, et al. Prescription-acquired acetaminophen use and the risk of asthma in adults: a case-control study. *Ann Pharmacother*. 2012 Dec; 46(12):1598–1608. [PubMed: 23170033]
12. Newson RB, Shaheen SO, Chinn S, et al. Paracetamol sales and atopic disease in children and adults: an ecological analysis. *Eur Respir J*. 2000 Nov; 16(5):817–823. [PubMed: 11153577]
13. DiPietro NA. Methods in epidemiology: observational study designs. *Pharmacotherapy*. 2010 Oct; 30(10):973–984. [PubMed: 20874034]
14. Cohet C, Cheng S, MacDonald C, et al. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. *J Epidemiol Community Health*. 2004 Oct; 58(10):852–857. [PubMed: 15365112]
15. Beasley RW, Clayton TO, Crane J, et al. Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: International Study of Asthma and Allergies in Childhood Phase Three. *Am J Respir Crit Care Med*. 2011 Jan 15; 183(2):171–178. [PubMed: 20709817] ISAAC study examining paracetamol and rhinitis, notable to large number of adolescents.
16. Wang HY, Pizzichini MM, Becker AB, et al. Disparate geographic prevalences of asthma, allergic rhinoconjunctivitis and atopic eczema among adolescents in five Canadian cities. *Pediatr Allergy Immunol*. 2010 Aug; 21(5):867–877. [PubMed: 20492543]
17. Del-Rio-Navarro BE, Luna-Pech JA, Berber A, et al. Factors associated with allergic rhinitis in children from northern Mexico City. *J Investig Allergol Clin Immunol*. 2007; 17(2):77–84.
18. Bakkeheim E, Mowinckel P, Carlsen KH, et al. Paracetamol in early infancy: the risk of childhood allergy and asthma. *Acta Paediatr*. 2011 Jan; 100(1):90–96. [PubMed: 21143295] Study examining paracetamol use during pregnancy and risk of rhinitis at age 10.
19. Wang JY, Liu LF, Chen CY, et al. Acetaminophen and/or antibiotic use in early life and the development of childhood allergic diseases. *Int J Epidemiol*. 2013 Aug; 42(4):1087–1099. [PubMed: 24062298] Study from Taiwan examining paracetamol use and the development of rhinitis. This study only examined prescription-based claims for paracetamol and did not account for over the counter paracetamol
20. Wickens K, Beasley R, Town I, et al. The effects of early and late paracetamol exposure on asthma and atopy: a birth cohort. *Clin Exp Allergy*. 2011 Mar; 41(3):399–406. [PubMed: 20880297] This study suggests that exposure to paracetamol early in life may be a risk factor for atopy but not necessarily asthma, whereas exposure later in life may be a risk factor for asthma
21. Kang EM, Lundsberg LS, Illuzzi JL, et al. Prenatal exposure to acetaminophen and asthma in children. *Obstet Gynecol*. 2009 Dec; 114(6):1295–1306. [PubMed: 19935033]

Key points

- Prospective birth cohort studies and cross sectional studies examining the role of paracetamol and its association with rhinitis are prone to the same epidemiologic pitfalls as those examining paracetamol and its association with asthma
- Evidence in the literature is modest at best, with varying degrees of exposure data
- Prospective birth cohorts specifically to address paracetamol exposure need to be designed with multiple contact points in order to maximize data on exposure and to minimize recall bias