

Acetaminophen use and asthma in children

Teeranai Sakulchit MD Ran D. Goldman MD FRCPC

Abstract

Question A child with a history of asthma came to my clinic with acute fever. I have heard that acetaminophen might be associated with exacerbation of asthma. Is it safe if I recommend acetaminophen for this child?

Answer Most studies suggest an association between acetaminophen use in children and development of asthma later in childhood. However, several confounding factors in study design might contribute to this positive correlation, and without a prospective controlled trial, confirming this finding is challenging. If children have a known history of asthma, it is likely safe to administer a single dose of acetaminophen without concern of precipitating adverse respiratory symptoms. Regular use of acetaminophen to relieve fever or pain does not seem to exacerbate asthma in children more than ibuprofen does.



This article is eligible for Mainpro+ certified Self-Learning credits. To earn credits, go to www.cfp.ca and click on the Mainpro+ link.

La traduction en français de cet article se trouve à www.cfp.ca dans la table des matières du numéro de mars 2017 à la page e166.

Acetaminophen is the most widely used over-the-counter antipyretic and analgesic drug in children.¹ Its mode of action is unclear, but it is generally accepted that it is similar to nonsteroidal anti-inflammatory drugs in that it inhibits cyclooxygenase activity, with predominant cyclooxygenase-2 inhibition.^{2,3} This in turn reduces the concentration of prostaglandin E₂, which lowers the hypothalamic set-point to reduce fever and activation of descending inhibitory serotonergic pathways to produce analgesia.³ Although acetaminophen is considered a weaker analgesic than nonsteroidal anti-inflammatory drugs,³ it is often preferred owing to better tolerance and a better safety profile (no adverse effects such as bleeding associated with antiplatelet activity and gastrointestinal upset).^{2,3}

However, several epidemiologic observations suggest that acetaminophen use might be a risk factor for asthma development, as well as asthma exacerbation.³ It is believed that the metabolite of acetaminophen depletes glutathione levels in the respiratory tract and thus leads to vulnerability to oxidative stress. This process might cause airway inflammation, bronchoconstriction, and subsequent symptoms of asthma.⁴

Use of acetaminophen and asthma development

Early acetaminophen use. Several studies report conflicting findings on whether there is an association between acetaminophen use in the first year of life and childhood development of asthma. Beasley et al⁵ conducted a cross-sectional study as part of a worldwide research program, the International Study of Asthma and Allergies in Childhood, obtaining questionnaires from

parents of 205487 children aged 6 and 7 years old from 73 centres in 31 countries, asking about symptoms of asthma, rhinoconjunctivitis, and eczema. They also asked about the use of acetaminophen in the first year of life and frequency of acetaminophen use within 12 months before the survey. Use of acetaminophen for fever in the first year of life was associated with the risk of developing asthma (odds ratio [OR]=1.46, 95% CI 1.36 to 1.56). The study was included in a systematic review and meta-analysis containing 13 cross-sectional studies, 4 cohort studies, and 2 case-control studies.⁶ The risk of asthma in children using acetaminophen within the first year of life was statistically significantly higher than for those not using acetaminophen (OR=1.47, 95% CI 1.36 to 1.56).

The same direct association was reported in 4 other studies. A cross-sectional study of 16933 children aged 6 and 7 years old in Italy reported that acetaminophen administration in the first year of life was associated with early wheezing (symptom within the first 2 years of life) (OR=2.27, 95% CI 1.98 to 2.62) and with persistent wheezing (symptom within the first 2 years of life and 12 months before the study) (OR=1.77, 95% CI 1.49 to 2.10), whereas the association with late-onset wheezing (symptom within the last 12 months before the study) was weak (OR=1.12, 95% CI 0.97 to 1.31).⁷ Gonzalez-Barcala et al⁸ reported that after adjusting for sex, body mass index, having pets in the house, maternal education, parental asthma, and parental smoking, the consumption of acetaminophen during the first year of life was associated with asthma (OR=2.04, 95% CI 1.79 to 2.31 for wheezing at some time) in more than 20000 Spanish children aged 6 and 7. Similar findings

were reported in 1037 children aged between 5 and 9 in Portugal.⁹ Early acetaminophen use was associated with a risk of having at least one episode of asthma attack in life (OR=2.9, 95% CI 1.8 to 4.5), at least one episode of asthma attack in the past 12 months before the study (OR=2.4, 95% CI 1.5 to 3.6), and at least one episode of wheezing (OR=2.5, 95% CI 1.8 to 2.4). Furthermore, among 263620 Taiwanese children who were born in 1998 and followed until 6 years of age, a positive relationship was documented between acetaminophen or antibiotics exposure during the first year of life and the development of allergic diseases (atopic dermatitis, asthma, and allergic rhinitis).¹⁰ The adjusted hazard ratios of asthma development were 1.66 (95% CI 1.58 to 1.74) for children who were exposed only to acetaminophen and 1.73 (95% CI 1.66 to 1.81) for those who were exposed to both acetaminophen and antibiotics.¹⁰

On the contrary, 4 studies established no association between the use of acetaminophen in the first year of life and development of asthma. Lowe et al¹¹ concluded that acetaminophen use in early life among 620 Australian children, followed from birth to 7 years of age, with a family history of allergic disease, was weakly associated with an increased risk of childhood asthma (crude OR=1.18, 95% CI 1.00 to 1.39, per doubling of days of use). Furthermore, after adjustment for frequency of respiratory infections, this association further diminished (OR=1.08, 95% CI 0.91 to 1.29).

A birth cohort study from New Zealand included questionnaires about acetaminophen exposure between birth and 15 months of age (n=505) and outcome data at 6 years of age.¹² The adjusted OR for the effect of acetaminophen exposure in early life on asthma was 1.78; however, the 95% CI and *P* value suggested that this result was not significant (95% CI 0.75 to 4.21; *P*=.19). Similar findings among 9910 Taiwanese children born in 2003 were not statistically significant, with an adjusted hazard ratio of 1.1 (95% CI 0.95 to 1.29).¹⁰

In a case-control survey among families with Iranian children between the ages of 2 and 8, acetaminophen use during the first year of life was reported by 172 (97%) and 390 (99%) guardians in the case and control groups, respectively. Acetaminophen use during this period of life did not have an association with the risk of asthma (*P*=.19).¹³

Recent acetaminophen use. Several studies suggested an association between acetaminophen use within 12 months before the studies and the development of asthma. In a systematic review and meta-analysis,⁶ risk of asthma in children using acetaminophen in the year before asthma diagnosis was elevated (OR=1.60, 95% CI 1.48 to 1.74). A study from Spain also reported that acetaminophen use in the year before the study increased probability of wheezing at some time in young children (OR=3.32, 95% CI 2.51 to 4.41). Risk of asthma

development with recent acetaminophen use was also reported in adolescents aged 13 and 14 years old (OR=2.12, 95% CI 1.68 to 2.67).⁸

Evidence seems to remain conflicting, with most retrospective studies suggesting some association between the use of acetaminophen in early life and developing asthma later in childhood.

Dose dependency

A dose-dependent association has been suggested with frequent childhood exposure to acetaminophen. Using questionnaire data on 1006 Ethiopian children, Amberbir et al¹⁴ reported that by the age of 3, risk of wheezing was increased if children were given 1 to 3 acetaminophen tablets (no dosage reported) in the month before the study compared with never using the medication (adjusted OR=1.88, 95% CI 1.03 to 3.44). When 4 or more tablets were used, the risk was statistically significantly higher (adjusted OR=7.25, 95% CI 2.02 to 25.95). Subsequently, these children were followed until the age of 5, and high exposure (use of acetaminophen in the previous month at ages 1 and 3) was associated with a risk of new-onset wheezing (adjusted OR=3.64, 95% CI 1.34 to 9.90) compared with nonusers.¹⁵

Exposure to acetaminophen later in childhood was also associated with asthma development. Among 914 children from New Zealand,¹² the OR for developing asthma in children with 3 to 10 exposures to acetaminophen (no dosage given) between 5 and 6 years of age was 1.63 (95% CI 0.92 to 2.89), while the OR for those who were exposed more than 10 times was 2.16 (95% CI 1.19 to 3.92) compared with those who were exposed only 0 to 2 times, after adjustment for potential confounders, such as number of chest infections and antibiotic use. A similar result was seen in the study from Iran.¹³ An association between acetaminophen use during the year before the study and asthma in children aged 2 to 8 was reported in a dose-dependent manner, with higher odds of asthma development when using acetaminophen once every 2 to 3 months (OR=3.35, 95% CI 1.82 to 6.17) and using it monthly (OR=4.22, 95% CI 2.36 to 7.55) when compared with once or less use (*P*<.001 for both).

Beasley et al¹⁵ also reported that if the children used acetaminophen at least once a year ("medium use"), the risk of asthma development was higher (OR=1.61, 95% CI 1.46 to 1.77) compared with no use. The OR rose to 3.23 (95% CI 2.91 to 3.60) when the frequency of acetaminophen use increased to at least once a month ("high use"). This association was also reported in another large study by the same authors among 322959 adolescents aged 13 and 14 from 113 centres in 50 countries.¹⁶ If participants had "medium use" within the past year, the OR was 1.43 (95% CI 1.33 to 1.53); however, if they had "high use," the OR increased to 2.51 (95% CI 2.33 to 2.70) compared with no use.

We conclude that there is consensus for a dose-dependent association between acetaminophen use and the development of asthma.

Acetaminophen and asthma exacerbation

Asthma exacerbation, rather than disease development, was also looked at by investigators worldwide. In a recent multicentre randomized controlled trial,¹⁷ 300 children aged 12 to 59 months with mild persistent asthma were prescribed either acetaminophen or ibuprofen for fever or pain management. Over a 46-week follow-up period, the number of exacerbations were similar (0.81 and 0.87 per participant in the acetaminophen and ibuprofen groups, respectively [relative rate of 0.94, 95% CI 0.69 to 1.28; $P=.67$]). Other outcomes such as percentage of asthma-controlled days, use of albuterol rescue inhaler, and unscheduled health care use for asthma were also not significantly different.


Another randomized controlled trial from Israel¹⁸ reported no significant changes in physical examination findings, spirometry results, and fractional exhaled nitric oxide levels before and 60 minutes after ingestion of a single dose of acetaminophen (15 mg/kg [160 mg/mL]) or volume-matched placebo among 42 children with asthma and 21 healthy age-matched controls.

Hence, a single dose of acetaminophen in children with underlying history of asthma does not significantly precipitate an attack, and long-term use of acetaminophen results in exacerbations of asthma to the same extent as ibuprofen.

Research limitations

The evidence for association between acetaminophen use and development of asthma in children needs to be reviewed with several limitations in mind. Using surveys might have resulted in recall bias by parents. Furthermore, one of the most confounding issues is the indication to give the medication. Because respiratory tract infections commonly lead to asthma, those children who demonstrated asthma symptomatology might have received more acetaminophen for their fever, discomfort, and respiratory symptoms. Without a controlled (randomized, blinded) study, it is impossible to conclude that the acetaminophen is the cause for (or even clearly associated with) asthma.

Conclusion

Based on questionnaire, cross-sectional, cohort, and case-control studies, there is some association between acetaminophen use and the development of asthma in children. However, with limitations in methodology, acetaminophen should not be withheld from children at this time until large controlled trials are conducted to confirm this effect. Using acetaminophen does not precipitate exacerbation of asthma. 

Competing interests

None declared

Correspondence

Dr Ran D. Goldman; e-mail rgoldman@cw.bc.ca

References

- Goldman RD. Acetaminophen in children. An old drug with new warnings. *Can Fam Physician* 2013;59:1065-6 (Eng), e449-50 (Fr).
- Anderson BJ. Paracetamol (acetaminophen): mechanisms of action. *Paediatr Anaesth* 2008;18(10):915-21.
- Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* 2013;21(3):201-32. Epub 2013 May 30.
- Dimova S, Hoet PH, Dinsdale D, Nemery B. Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *Int J Biochem Cell Biol* 2005;37(8):1727-37. Epub 2005 Apr 26.
- Beasley R, Clayton T, Crane J, von Mutius E, Lai CK, Montefort S, 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(9643):1039-48.
- Ettman 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 metaanalysis. *Chest* 2009;136(5):1316-23. Epub 2009 Aug 20.
- Rusconi F, Gagliardi L, Galassi C, Forastiere F, Brunetti L, La Grutta S, et al. Paracetamol and antibiotics in childhood and subsequent development of wheezing/asthma: association or causation? *Int J Epidemiol* 2011;40(3):662-7. Epub 2011 Jan 23.
- Gonzalez-Barcala FJ, Pertega S, Perez Castro T, Sampedro M, Sanchez Lastres J, San Jose Gonzalez MA, et al. Exposure to paracetamol and asthma symptoms. *Eur J Public Health* 2013;23(4):706-10. Epub 2012 May 29.
- Muc M, Padez C, Pinto AM. Exposure to paracetamol and antibiotics in early life and elevated risk of asthma in childhood. *Adv Exp Med Biol* 2013;788:393-400.
- Wang JY, Liu LF, Chen CY, Huang YW, Hsiung CA, Tsai HJ. Acetaminophen and/or antibiotic use in early life and the development of childhood allergic diseases. *Int J Epidemiol* 2013;42(4):1087-99.
- Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Allen KJ, Robertson CF, et al. Paracetamol use in early life and asthma: prospective birth cohort study. *BMJ* 2010;341:c4616.
- Wickens K, Beasley R, Town I, Epton M, Pattermore P, Ingham T, et al. The effects of early and late paracetamol exposure on asthma and atopy: a birth cohort. *Clin Exp Allergy* 2011;41(3):399-406. Epub 2010 Sep 29.
- Oshnouei S, Salarilak S, Khalkhali A, Karamyar M, Rahimi Rad M, Delpishe A. Effects of acetaminophen consumption in asthmatic children. *Iran Red Crescent Med J* 2012;14(10):641-6. Epub 2012 Oct 30.
- Amberbir A, Medhin G, Alem A, Britton J, Davey G, Venn A. The role of acetaminophen and geohelminth infection on the incidence of wheeze and eczema: a longitudinal birth-cohort study. *Am J Respir Crit Care Med* 2011;183(2):165-70. Epub 2010 Oct 8.
- Amberbir A, Medhin G, Hanlon C, Britton J, Davey G, Venn A. Effects of early life paracetamol use on the incidence of allergic disease and sensitization: 5 year follow-up of an Ethiopian birth cohort. *PLoS One* 2014;9(4):e93869.
- Beasley RW, Clayton TO, Crane J, Lai CK, Montefort SR, Mutius Ev, 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;183(2):171-8. Epub 2010 Aug 13.
- Sheehan WJ, Mauger DT, Paul IM, Moy JN, Boehmer SJ, Szeffler SJ, et al. Acetaminophen versus ibuprofen in young children with mild persistent asthma. *N Engl J Med* 2016;375(7):619-30.
- Soferman R, Tsivion A, Farber M, Sivan Y. The effect of a single dose of acetaminophen on airways response in children with asthma. *Clin Pediatr (Phila)* 2013;52(1):42-8. Epub 2012 Oct 9.



Child Health Update is produced by the Pediatric Research in Emergency Therapeutics (PRETx) program (www.pretx.org) at the BC Children's

Hospital in Vancouver, BC. Dr Sakulchit is a member and Dr Goldman is Director of the PRETx program. The mission of the PRETx program is to promote child health through evidence-based research in therapeutics in pediatric emergency medicine.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in children? We invite you to submit them to the PRETx program by fax at 604 875-2414; they will be addressed in future Child Health Updates. Published Child Health Updates are available on the *Canadian Family Physician* website (www.cfp.ca).