Austin Journal of Psychiatry and Behavioral Sciences

Open Access

Austin Publishing Group

Review Article

Acetaminophen is not Safe in Childhood

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Received: March 29, 2018; **Accepted:** September 26, 2018; **Published:** October 03, 2018

Abstract

Acetaminophen is recommended as the safest analgesic and antipyretic medicine for children, and it is widely used all over the world. Acetaminophen use in childhood is associated with autism spectrum disorder, asthma, wheezing, rhinitis, community acquired pneumonia, obesity, atopic eczema, allergic diseases, and acute kidney injury. Acetaminophen is not safe than previously thought especially in childhood. We should recognize that acetaminophen is danger in childhood. Fever and pain in childhood themselves are probably associated with adverse childhood outcomes. Acetaminophen should not be withheld from children for fears it might develop adverse effects. Acetaminophen is the safest medicine as analgesics for nociceptive pain and antipyretics in childhood. Acetaminophen should be used at the lowest effective dosage and for the shortest time. In order to protect children, especially newborns, I would like public organizations or academic associations to declare danger (or safety) of acetaminophen in childhood.

Keywords: Acetaminophen; Paracetamol; Adverse effects; Autism; Asthma; Community acquired pneumonia

Introduction

Acetaminophen is recommended as the safest analgesic and antipyretic medicine for children, and it is widely used all over the world. Recent studies suggest that acetaminophen is a hormone disrupter (i.e., it interferes with sex and thyroid hormone function essential for normal brain development) [1] and thus may not be considered a safe drug in childhood. Recently many adverse effects of acetaminophen in childhood have been reported. A narrative review of risks of acetaminophen in childhood is conducted and the situation of the world on the issue is explained.

Autism spectrum disorder

A case-control study showed that acetaminophen use after measles-mumps-rubella vaccination was significantly associated with autistic disorder when considering children 5 years of age or less (odds Ratio [OR] 6.11, 95% Confidence Interval [CI] 1.42-26.3), after limiting cases to children with regression in development (OR 3.97, 95% CI 1.11-14.3), and when considering only children who had post-vaccination sequelae (OR 8.23, 95% CI 1.56-43.3), adjusting for age, gender, mother's ethnicity [1], and the presence of illness concurrent with measles-mumps-rubella vaccination [2]. Ibuprofen use after measles-mumps-rubella vaccination was not associated with autistic disorder [2].

Bauer et al. reported that for studies including boys born after 1995, there was a strong correlation between country-level (n = 9) autism/Autism Spectrum Disorder (ASD) prevalence in males and a country's circumcision rate (r = 0.98) [3]. A very similar pattern was seen among U.S. states and when comparing the 3 main racial/ethnic groups in the U.S [3]. Paracetamol has been widely prescribed for male circumcision since the mid-1990s [3].

Asthma, wheezing, and rhinitis

In a cross-sectional, study design, 9,991 children, aged 13-14 years in 61 primary schools in 32 districts of Istanbul were evaluated [4]. Use of paracetamol in the last 12 months, consumption of fruit and animal fats acted as a protective factor against asthma [4].

In a multicenter, prospective, randomized, double-blind, parallel-group trial, Sheehan et al. enrolled 300 children (age range, 12 to 59 months) with mild persistent asthma and assigned them to receive either acetaminophen or ibuprofen when needed for the alleviation of fever or pain over the course of 48 weeks [5]. Among young children with mild persistent asthma, as-needed use of acetaminophen was not shown to be associated with a higher incidence of asthma exacerbations or worse asthma control than was as-needed use of ibuprofen [5].

Beasley et al. reported as follows: A total of 322,959 adolescent children (13- to 14-year-old) from 113 centers in 50 countries participated [6]. In the multivariate analyses the recent use of acetaminophen was associated with an exposure-dependent increased risk of current asthma symptoms (OR 1.43, 95% CI 1.33-1.53 and 2.51, 95% CI 2.33-2.70 for medium and high versus no use, respectively) [6]. Acetaminophen use was also associated with an exposure-dependent increased risk of current symptoms of rhinoconjunctivitis and eczema [6].

A cross-sectional study included 1,063 children (5-9 years old) from the primary schools in Coimbra, Portugal [7]. Muc et al. found that early paracetamol use significantly increased the risk of asthma ever (at least one episode in life) (OR 2.9, 95% CI 1.8-4.5), current asthma (OR 2.4, 95% CI 1.5-3.6), wheezing ever (OR 2.5, 95% CI 1.8-3.4), rhinitis ever (OR 2.4, 95% CI 1.7-3.3), and current rhinitis (OR 2.8, 95% CI 2.0-3.9) [7]. Muc et al. further found that increased frequency of paracetamol use during the last 12 months preceding the study facilitated the appearance of allergic symptoms, suggesting a dose-dependent associations [7].

A cross-sectional study was performed by applying a standardized written questionnaire from the international study on wheezing in

Citation: Toda K. Acetaminophen is not Safe in Childhood. Austin J Psychiatry Behav Sci. 2018; 5(1): 1068.

infants (Estudio Internacional de Sibilancia en Lactantes - EISL), phase 3 [8]. Factors associated to wheezing were studied using bivariate and multivariate analysis [8]. Paracetamol use for upper respiratory tract infections (OR 2.13, 95% CI 1.54-2.95) was one of risk factors for wheezing [8].

The number of 2,428 elementary school children in Seoul and Jeongeup cities was recruited [9]. Subjects who used acetaminophen with a family history of asthma had an increased risk of both asthma diagnosis ever and current asthma [9]. Family history of asthma and acetaminophen usage were risk factors for bronchial hyperresponsiveness [9].

Sordillo et al. examined the associations of acetaminophen and ibuprofen (per unit increase in exposure category) during pregnancy and infancy with wheeze, asthma, and allergen sensitization in early childhood (3-5 years of age, n = 1,419) and midchildhood (7-10 years of age, n = 1,220) [10]. Unadjusted models showed an increased asthma risk in early childhood for higher infant acetaminophen (OR 1.21, 95% CI 1.04-1.41) and ibuprofen (OR 1.35, 95% CI 1.19-1.52) intake [10]. Controlling for respiratory tract infections attenuated estimates for acetaminophen (OR 1.03, 95% CI 0.88-1.22) and ibuprofen (OR 1.19, 95% CI 1.05-1.36) [10]. Prenatal acetaminophen was associated with increased asthma (OR 1.26, 95% CI 1.02-1.58) in early childhood but not midchildhood [10].

A cross-sectional, multicentre, descriptive epidemiological study was carried out in a representative sample of 958 infants in the first year of life, born in Cantabria, Spain, to determine the prevalence of wheezing during the first year and its associated risk factors [11]. A relationship was found with paracetamol use> 1 a week (OR 2.49, 95% CI 1.31-4.73) [11].

Magnus et al. used information from the Norwegian Mother and Child Cohort Study, including 53,169 children for evaluation of current asthma at 3 years, 25,394 for current asthma at 7 years and 45,607 for dispensed asthma medications at 7 years in the Norwegian Prescription Database [12]. There were independent modest associations between asthma at 3 years with prenatal paracetamol exposure (adjusted Relative Risks [RR] 1.13, 95% CI 1.02-1.25) and use of paracetamol during infancy (adjusted RR 1.29, 95% CI 1.16-1.45) [12]. The results were consistent for asthma at 7 years [12].

Piler et al. used data from 3,329 children born in the 1990s as members of the prospective Czech European Longitudinal Study of Pregnancy and Childhood [13]. Being exposed to paracetamol both in prenatal and postnatal period was associated with asthma development (unadjusted OR 1.98, 95% CI 1.02-3.87) [13]. Being exposed only in the postnatal period was also significantly associated with increased risk of asthma. No association between prenatal exposure only and outcome was found [13].

Etminan et al. sought to quantify the association between acetaminophen use and the risk of asthma in children and adults [14]. In 2009, a systematic review and metaanalysis reported as follows [14]: The pooled OR for asthma among subjects using acetaminophen was 1.63 (95% CI 1.46-1.77). The risk of asthma in children among users of acetaminophen in the year prior to asthma diagnosis and within the first year of life was elevated (OR 1.60, 95% CI 1.48-1.74 and 1.47, 95% CI 1.36-1.56, respectively). Only one study reported the association between high acetaminophen dose and asthma in children (OR 3.23, 95% CI, 2.9-3.6). There was an increase in the risk of asthma and wheezing with prenatal use of acetaminophen (OR 1.28, 95% CI 1.16-41 and 1.50, 95% CI 1.10-2.05, respectively).

In 2013, a systematic review reported as follows [15]: The weight of evidence of the collected studies in the review strongly suggests that the association of antibiotics with childhood asthma reflects various forms of bias, the most prominent of which is confounding by indication. Recent studies and meta-analyses support the same conclusion for paracetamol. There is no sound reason to replace paracetamol as the preferred pain relief and fever medication in this age group.

In 2014, a systematic review of the whole literature relating early life environmental exposures to childhood asthma causation reported that the observational literature is likely to be affected by publication bias, reverse causation and confounders [16].

In 2014, a review published by Kim et al. reported as follows [17]. 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.

In 2015, a review published by Weatherall et al. reported that most of the evidence for the link with asthma was from non-experimental studies of paracetamol exposure in utero, infancy, childhood and adult life; however, it had been difficult to rule out confounding and bias in the associations observed [18].

In 2017, a review published by Sakulchit et al. reported as follows [19]: 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.

Community acquired pneumonia

Demographic, clinical, and laboratory data were prospectively collected and compared in children with noncomplicated and complicated (parapneumonic effusion/pleural empyema, necrotizing pneumonia, and lung abscess)-Community Acquired Pneumonia (CAP) [20]. Two-hundred and three patients aged from 2 months to 17 years were enrolled [20]. Asymmetric chest pain as well as prehospital treatment with ibuprofen and acetaminophen were significantly more common in patients with complicated CAP ($P < 0.001$, $P = 0.02$ and $P = 0.003$, respectively) [20].

Obesity

Paracetamol use in the first 12 months of life (reported by parents/guardians of 6- and 7-year-olds) or in the past 12 months (reported by parents/guardians of 6- and 7-year-olds or self-reported

by adolescents aged 13-14) was examined in relation to Body Mass Index (BMI) in a large multicentre cross-sectional study (2000-2003) [21]. Data were available from 76,216 children (18 countries) and 188,469 adolescents (35 countries) [21]. BMI was +0.07 kg/m^2 higher in children with early life paracetamol exposure, from affluent countries only [21]. Frequent recent paracetamol use was associated with higher BMI (+0.17 kg/m^2, $P < 0.0001$) among adolescents from affluent countries only, but not in children ($P = 0.41$) [21].

Atopic eczema

Suárez-Varela et al. report the rates of isolated Atopic Eczema (AE), AE associated with asthma and AE associated with rhinitis among 13- to 14-year-old 28,717 Spanish adolescents and the level of association of these conditions with the use of acetaminophen [22]. Suárez-Varela et al. observed an association between acetaminophen use and AE among the adolescents who had used acetaminophen in the previous month [22]. Furthermore, the prevalence rate increased with the number of allergic processes: for AE alone, the adjusted Prevalence Ratio (aPR) was 1.81 and for AE associated with rhinitis or with asthma, aPRs were 2.20 and 3.03, respectively [22].

A review reported that focussed pharmacovigilance to explore the potential causal association between paracetamol exposure during perinatal life and infancy and subsequent atopy was warranted [23].

Allergic diseases

The authors conducted a prospective birth cohort study of 263,620 children born in 1998 and 9,910 children born in 2003, separately, from National Health Insurance Research Database [24]. Wang et al. reported that observed a positive relationship between acetaminophen and/or antibiotic exposure during the 1st year of life and the subsequent development of the three examined allergic diseases (atopic dermatitis, asthma and allergic rhinitis) in the 1998 birth cohort, but the observed relationship of drug exposure in the 2003 cohort, especially for atopic dermatitis and asthma, was lower than for those in the 1998 cohort and was not statistically significant [24].

In 2005/6, a birth cohort of 1,006 newborns was established in Butajira, Ethiopia [25]. Paracetamol use in the first 3 years of life was reported in 60% of children and was associated with increased incidence of wheeze, eczema, rhinitis and allergic sensitisation between ages 3 and 5, which was statistically significant for wheeze and eczema [25]. High exposure (reported use in the past month at age 1 and 3) was associated with a more than 3-fold increased risk of new onset wheeze (adjusted OR 3.64, 95% CI 1.34-9.90) compared to never users [25]. Use in the past year at age 3 but not age 1 was associated with ORs at least as large as those for use in first year of life only [25]. Significant positive dose-response effects of early life use were seen in relation to the prevalence of all outcomes at age 5 [25].

A total of 11,483 children aged 6-7 years in 75 primary schools from all districts of İstanbul were surveyed [26]. Frequent paracetamol use in the first year of life was one of independent risk factors for allergic rhinitis [26].

Acute kidney injury

Yue et al. analyzed the association of Acute Kidney Injury (AKI) with ibuprofen, acetaminophen, and the combination of both drugs in children (0-12 years) by using the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) database between January 2004 and June 2012 [27]. In total, 47,803 reports were included in the study [27]. After adjusting for year of reporting, age, and sex, the Reporting Odds Ratios (RORs) for an AKI in children who used only ibuprofen or acetaminophen compared with children who used neither ibuprofen nor acetaminophen was 2.14 (95% CI 1.59-2.88) and 1.53 (95% CI 1.18-1.97), respectively, while the adjusted ROR was 4.01 (95% CI 2.96-5.43) when both drugs were concomitantly used [27].

Discussion

Paracetamol is commonly used to control mild-to-moderate pain or to reduce opioid exposure as part of multimodal analgesia, and is the only compound recommended to treat fever in neonates [23]. Acetaminophen is regarded as the safest analgesics for nociceptive pain and antipyretics in adulthood. Acetaminophen is also regarded as the safest analgesics for nociceptive pain and antipyretics in childhood and in pregnancy. However, many aforementioned articles showed adverse effects of acetaminophen in childhood and one review showed adverse effects of acetaminophen in pregnancy [28]. Acetaminophen is not safe than previously thought especially in childhood and in pregnancy.

At the present moment, any public organizations or academic associations have not declared the danger of acetaminophen in pregnancy or in childhood. In 2013, the Spanish Paediatric Societies subscribing to this paper consider that current evidence is insufficient to discourage the use of paracetamol during gestation or in children with or at risk of asthma [29]. In 2015, the FDA announced it has reviewed possible risks of pain medicine use during pregnancy and stated: "Based on our evaluation of these studies, we believe that the weight of evidence is inconclusive regarding a possible connection between acetaminophen use in pregnancy and Attention Deficit Hyperactivity Disorder in children [30]." The FDA did not subsequently make a statement about safety (or danger) of acetaminophen in pregnancy. In 2017, the Society for Maternal-Fetal Medicine: Publications Committee made a statement about safety of acetaminophen in pregnancy [31]. I am afraid that the cited articles ([32,33], etc.) are only one part of articles which showed risks of acetaminophen in pregnancy. I sent a letter to the editor, however, it was rejected. In 2017, the letter to the editor was published as a review in Scandinavian Journal of Pain [28].

I think that intensity of adverse effects of acetaminophen is, in pregnancy > in childhood > in adulthood and those are more serious in the younger children among children. If this review showing adverse effects of acetaminophen in childhood and a review [28] showing adverse effects of acetaminophen in pregnancy are compared, adverse effects in pregnancy are more serious than those in childhood. Moreover, long-term use and/or a lot of usage probably increases the occurrence of adverse effects. We cannot conduct a meta-analysis of different adverse effects such as ASD, asthma, obesity, and AKI. Each article has poor power to show risks of acetaminophen, however, the integration of the articles that showed adverse effects of acetaminophen may have power to show them.

We should recognize that acetaminophen is danger in childhood.

However, it does not mean the prohibition of the use of acetaminophen. Acetaminophen is the safest medicine as analgesics for nociceptive pain and antipyretics in childhood and pregnancy [28]. There is no alternative medication of acetaminophen. Acetaminophen should not be withheld from children or pregnant women for fears it might develop adverse effects [28]. Fever and pain in childhood themselves are probably associated with adverse childhood outcomes. Evidence of acetaminophen risks is inconclusive. However, the warning is necessary about acetaminophen use in childhood and pregnancy [28]. For example, few pediatricians recognize fibromyalgia and some children with fibromyalgia receive acetaminophen over a long period in Japan. Acetaminophen is not effective for non-nociceptive pain (neuropathic pain) such as fibromyalgia, but effective for nociceptive pain. Acetaminophen should be used at the lowest effective dosage and for the shortest time in case that it is effective. We should recognize risks of acetaminophen. When we know the possible, rare but serious complications, we should use acetaminophen in childhood only when needed and no safer option for pain or fever relief is available. Health care providers should help inform the general lay public about this difficult dilemma.

To my knowledge, few pediatricians do not explain the adverse effects of acetaminophen to parents of patients and some children receive acetaminophen over a long period. In order to protect children, especially newborns, I would like public organizations or academic associations to declare danger (or safety) of acetaminophen in childhood.

Conclusion

Acetaminophen use in childhood is associated with ASD, asthma, wheezing, rhinitis, CAP, obesity, AE, allergic diseases, and AKI. We should recognize that acetaminophen is danger in childhood. Acetaminophen is the safest medicine as analgesics for nociceptive pain and antipyretics in childhood. Acetaminophen should be used at the lowest effective dosage and for the shortest time. In order to protect children, especially newborns, I would like public organizations or academic associations to declare danger (or safety) of acetaminophen in childhood.

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