Acetaminophen in children
An old drug with new warnings

Ran D. Goldman MD FRCPC

Abstract

Question I frequently suggest to parents to use acetaminophen to treat their children’s fever and pain. Recently, I had a child in my office who presented with a target-lesion skin rash a day after receiving acetaminophen. The rash resolved after 3 days and after stopping administration of acetaminophen. Does acetaminophen carry a risk of adverse events such as this?

Answer Like any other medication or active substance, acetaminophen preparations might carry a risk of adverse events. In recent years a potential association between acetaminophen and asthma was investigated, and the US Food and Drug Administration recently published a warning about potential severe but rare skin reactions associated with acetaminophen. Although acetaminophen is mostly a safe medication, health care providers should be alert and advise parents about the possibility of rare but severe adverse events.

Acetaminophen is the over-the-counter (OTC) antipyretic and analgesic medication most commonly used in children. While a large number of parents underdose the medication for fever and are also unaware of the availability of the medication in a form for rectal administration (eg, for children who are vomiting), acetaminophen is being used commonly worldwide.

Despite its frequent use and years of research, the exact mechanism of action of acetaminophen is unknown. Reduction of pain through suppression of inflammatory-related prostaglandins has been offered as a possible mechanism, and reduction of fever via a central effect on the temperature centre in the brain has also been shown. It is metabolized by the liver.

Since the approval of acetaminophen by the US Food and Drug Administration (FDA) in 1951, a tremendous amount of research has been conducted on the drug, and thousands of reports have been published documenting its potential adverse effects.

Side effects of a common drug

Acetaminophen monographs might surprise clinicians and parents alike, as many consider the drug safe to use and provide parents with the “feeling of mastery.” Numerous potential adverse effects are mentioned in guidelines for its labeling. However, most severe adverse effects are generally rare. In one large study from Boston, Mass, children younger than 2 years of age with fever were randomized to receive acetaminophen (12 mg/kg) or ibuprofen and were found to have a low rate of adverse effects. Among the more than 9000 children who received acetaminophen, the absolute risk of hospitalization for asthma or bronchiolitis was 260 children per 100 000, and the risk of hospitalization for vomiting or gastritis was 24 children per 100 000.

For several decades, investigators forewarned clinicians about the potential association between acetaminophen and the development of asthma, but the evidence that is currently available is somewhat controversial. The largest study to date, among a group of 6- to 7-year-old children from Phase Three of the International Study of Asthma and Allergies in Childhood program, investigated previous use of acetaminophen and the risk of asthma. This study, which included more than 200 000 children from 31 countries, found that use of acetaminophen for fever in the first year of life was associated with an increased risk of asthma symptoms (odds ratio [OR] 1.46, 95% CI 1.36 to 1.56). Use of acetaminophen at the time of the study was also associated with a dose-dependent risk of asthma symptoms for medium (OR 1.61, 95% CI 1.46 to 1.77) and high (OR 3.23, 95% CI 2.91 to 3.60) use versus no use. However, in a more recent prospective birth cohort study from Australia, among 620 children with family history of allergic disease, with acetaminophen use prospectively documented on 18 occasions from birth to 2 years of age, children 7 years of age were not found to have a higher risk of subsequent allergic disease after adjustment for respiratory infections or when acetaminophen use was

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restricted to infections other than those in the respiratory tract.\textsuperscript{12}

Earlier in 2013, after a review of the FDA Adverse Event Reporting System database of severe skin reactions associated with products containing acetaminophen, the FDA published a warning about potential severe but rare skin reactions associated with acetaminophen.\textsuperscript{13} Several reports of cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis prompted action by the FDA.

Considerations when recommending acetaminophen

Other considerations that health care providers need to address when recommending the use of acetaminophen for children include the following:

- the multitude of dosages available,
- the fact that many pediatric products on the market contain acetaminophen, and
- the potential side effects associated with interaction.

The approval of acetaminophen for all ages resulted in the availability of the drug in a multitude of concentrations and various packaging. After several reports in 2009 of drug administration errors in infants, when parents mistakenly administered large dosages of acetaminophen formulation, some manufacturers decided to voluntarily change their liquid acetaminophen products marketed for infants to the same concentration (160 mg/5 mL) as liquid acetaminophen products labeled for children.\textsuperscript{14}

Furthermore, many OTC preparations, such as cough and cold medications, might contain acetaminophen as an active component\textsuperscript{15} and inadvertently parents might administer acetaminophen and these products together, resulting in a higher-than-recommended dose of the antipyretic drug.

Finally, the metabolism of acetaminophen through the liver is a source for potential interaction with other prescribed or OTC medications, as well as complementary and alternative preparations,\textsuperscript{16} that are not always reported to health care providers. Medications with the potential for interactions include antiepileptic medications\textsuperscript{17} and warfarin;\textsuperscript{18} therefore, repeated measurements of international normalized ratio in children receiving these medications is needed.

Competing interests

None declared

Correspondence

Dr Ran D. Goldman, BC Children’s Hospital, Department of Pediatrics, Room K4-226, Ambulatory Care Bldg, 4440 Oak St, Vancouver, BC V6H 3V4, telephone 604 875 2345, extension 7333, fax 604 875 2414, e-mail rgoldman@cw.bc.ca

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