Acetaminophen Toxicity (Paracetamol Toxicity) in Children — Diagnosis and Treatment

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Acetaminophen toxicity in children is very common because of the over-the-counter availability of the drug and the ease of accessibility to the analgesic by children and their caregivers. Intentional acute single ingestion overdose of acetaminophen can cause hepatotoxicity and fulminant hepatic failure. The risk of hepatotoxicity is dependent on the amount of ingested acetaminophen, the blood concentration of acetaminophen, and the time of initiation of n-acetylcysteine. Late presentation is associated with a significantly higher risk of fulminant hepatic failure and death.

Overview

Acetaminophen use in children is very common with some scientific sources claiming that it is the most commonly used analgesic medication by children in the United States. Acetaminophen toxicity is defined as the single acute ingestion of oral formulations of acetaminophen. Acetaminophen toxicity can also happen after the administration of
the intravenous formulation but this is not within the scope of this article.

Classifications of Acetaminophen Dosage in Children

The most common cause of acetaminophen toxicity in children is overdose due to a miscalculation by the parent or caregiver or due to intentional overdose intake, i.e. suicidal attempt. To define what is an acetaminophen overdose in pediatrics, we first have to define the different dosages of acetaminophen in children.

The maximum acetaminophen dosage in children older than 12 years of age who weigh 50 kg or more is 4 grams per day, the same as the maximum allowed dosage for adults. This dosage should be divided into 1 gram every 6 hours.

The maximum dosage of acetaminophen in children younger than 12 years of age or those who weigh less than 50 kg is 80 mg/kg or a cumulative dose of 2.6 g per day. This dosage should be split upon several daily doses of 10 to 15 mg/kg per dose.

The minimum toxic dosage of acetaminophen is defined as the minimum dose to start causing significant liver damage. The minimum toxic dosage of acetaminophen is approximately 150 to 200 mg/kg for acute ingestion.

Absolute toxic dosage of acetaminophen is a dose of more than 250 mg/kg for an acute ingestion. Children who ingest more than 350 mg/kg of acetaminophen are at risk of developing severe hepatotoxicity.

Epidemiology of Acetaminophen Toxicity in Children

Separate epidemiological estimates of acetaminophen toxicity in children are scarce but most cases of fatal acetaminophen toxicity are due to intentional overdose and not accidental overdose.

Acetaminophen toxicity alone was reported in approximately 50,000 cases in 2014 in the United States which resulted in 65 deaths that year. A clear distinction between the number of cases of acetaminophen toxicity in children and adults in that year was not readily available.

The prognosis of single dose acute ingestion of acetaminophen has improved after the introduction of the antidote N-acetylcysteine (NAC). NAC decreased the mortality and morbidity of acetaminophen toxicity in children and adults.

Acute exposures in children younger than 6 years of age are usually less severe compared to adolescents and adults which explains the lower mortality in this age group. The most common cause of mortality in children with acetaminophen toxicity is acute hepatic failure due to hepatotoxicity.

Pathophysiology of Acetaminophen Toxicity

The peak plasma concentration after acute ingestion of an acetaminophen overdose is usually observed after 4 hours. When acetaminophen is combined with opiates or anticholinergic drugs, the peak plasma concentration is further delayed.
Acetaminophen is primarily metabolized by the liver. The intermediate metabolites produced by hepatic metabolism of acetaminophen are secreted by the kidneys. Sulfate and glucuronide conjugates are of acetaminophen metabolites are usually produced and are eliminated in the urine.

Approximately, 4% of the ingested dose will be biotransformed into a highly toxic metabolite known as N-acetyl-p-benzoquinoneimine (NAPQI) which is believed to be responsible for hepatotoxicity and hepatic cell damage.

When acetaminophen is taken in a therapeutic dose, glutathione usually binds to NAPQI rendering it a non-toxic metabolite that can be readily excreted in the urine. In case of overdose, glutathione stores become depleted and the toxic metabolite NAPQI starts accumulating. This is believed to be the main pathologic mechanism involved in the pathogenesis of hepatotoxicity in case of acetaminophen overdose.

Clinical Presentation of Acetaminophen Toxicity in Children

Adequate history taking is essential to identify what the child ingested, whether it was intentional or accidental and whether acetaminophen was ingested alone or in combination with other drugs. The ingested dose of acetaminophen should also be estimated and the caregivers of the child should be asked to bring the empty tablet boxes with them to confirm the ingested dosage.

During physical examination of the child, the level of hepatotoxicity should be determined. The level of hepatotoxicity is dependent on the stage of acetaminophen toxicity.

Stage 1: Presentation of hepatotoxicity after acetaminophen overdose (0 to 1 day post-ingestion)

At this stage, children usually present with anorexia, nausea, vomiting and diaphoresis. At this stage, cardiovascular and central nervous system changes are rare. When the child has impaired level of consciousness at this stage, the possibility of co-ingestion of acetaminophen with salicylates or other compounds such as opiates should be excluded.

During this stage, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) start going up but remain below the normal uppercut.

Stage 2: Presentation of hepatotoxicity after acetaminophen overdose (1 to 3 days post-ingestion)

At this stage, the symptoms and signs start to become more specific to hepatic involvement as pain and tenderness become localized to the right upper quadrant. Elevated ALT and AST levels are usually evident at this stage. Children can also have impaired synthetic hepatic function at this stage which manifests as an increased prothrombin time.
Stage 3: Presentation of hepatotoxicity after acetaminophen overdose (3 to 5 days post-ingestion)

This stage is characterized by the reappearance of the stage 1 symptoms in addition to jaundice and hypoglycemia. Encephalopathy is usually evident at this stage and children might develop sepsis. Renal failure and heart failure can happen at this stage. ALT and AST levels become markedly elevated at this stage. Most fatalities occur during stage 3.

Stage 4: Recovery after acetaminophen overdose (5 to 21 days post-ingestion)

During this stage, liver enzymes and hepatic healing start to occur. Children can undergo either complete resolution or they might develop fulminant hepatic failure and die during this stage.

Diagnostic Workup for Acetaminophen Toxicity in Children

Before we discuss the Rumack-Matthew Nomogram test that is used to confirm acetaminophen toxicity, we will first discuss the different laboratory and radiographic tests that can support the diagnosis of acetaminophen toxicity.

Serum levels of AST and ALT should be assessed in children with acetaminophen overdose. Additionally, serum levels of ammonia which correlate with the severity of encephalopathy should be measured. Prothrombin time, and bilirubin might be elevated in children with hepatic toxicity due to acetaminophen overdose especially in stage 2 and 3 disease.

Children with altered level of consciousness should undergo a head computed tomography scan to exclude cerebral edema which is commonly seen in children who are in stage 3.

The diagnosis of acetaminophen toxicity and the risk of hepatotoxicity are usually determined by tracking the levels of acetaminophen in the blood in the first 24 hours after acute ingestion. The modified Rumack-Matthew nomogram, also known as the acetaminophen toxicity nomogram, is the method of choice to track the serum concentration of acetaminophen in children after acute single dose ingestion.

For the nomogram to be used, a child must present within the first 24 hours after the acute ingestion of acetaminophen. Acetaminophen blood levels within the 4 to 18 hours time-window after ingestion are most reliable in the prediction of the risk of hepatotoxicity. The nomogram can help us answer the question of whether the child might develop hepatotoxicity or not but is not a prognostic test and does not predict the risk of fulminant hepatic failure.

Serum acetaminophen levels that are above 150 µg/mL or 993 µmol/L at 4 hours post-ingestion are predictable of a high risk of developing hepatotoxicity. The patients usually undergo repeated measurements and the results are plotted on the nomogram. The nomogram has a probable line and if one of the values obtained from the serum acetaminophen concentration is above this probable line then the risk of hepatotoxicity is
Treatment of Acetaminophen Toxicity in Children

Any child who presents to the emergency department within the first 24 hours after the acute ingestion of acetaminophen toxicity who has hepatotoxicity or an increased risk of hepatotoxicity due to the result of a nomogram should receive NAC. Additionally, children with hepatotoxicity but no signs of hepatic failure due to confirmed acetaminophen toxicity who present at stage 2 or 3 should also receive NAC.

Once NAC is initiated, it should be continued until the normalization of prothrombin time, ALT and AST levels. Children who present in stage 2 or 3 disease should undergo a single acetaminophen concentration test in addition to the assessment of hepatic function but the Rumack-Matthew nomogram should not be used in late presentation of acetaminophen toxicity.

Children who develop metabolic acidosis, renal failure, coagulopathy and encephalopathy due to hepatotoxicity should be evaluated for possible liver transplantation. Without liver transplantation, the possibility of developing fulminant hepatic failure and death is very high.

Children who present within 1 hour of ingestion should undergo gastric lavage. Children who present within 4 hours of ingestion should receive activated charcoal which can be lifesaving and can prevent hepatotoxicity.

NAC is usually started at a loading dose of 140 mg/kg followed by 17 divided doses of 70 mg/kg each every 4 hours for 72 hours.

Children in stage 1 can have severe vomiting which can limit oral intake. In that case, antiemetics should be used to suppress vomiting. If this fails, then intravenous NAC should be used which has been approved for use in children in 2006. Additionally, children with altered level of consciousness should also receive intravenous NAC.

Allergic reactions to intravenous NAC have been previously described and include skin rash, and flushing. If this happens, intravenous NAC should be stopped and antihistamines should be started followed by the re-administration of intravenous NAC at a slower infusion rate. It is important to stop intravenous NAC temporarily because of the possible risk of developing severe bronchospasm and hypotension in allergic children.

References


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