Acetaminophen

ncbi.nlm.nih.gov/books/NBK482369

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Continuing Education Activity

Acetaminophen, also known as *N*-acetyl-para-aminophenol (APAP) or paracetamol in many countries, is a non-opioid analgesic and antipyretic agent utilized for treating pain and fever. Numerous diseases and conditions include pain as a significant component of their presentation. Consequently, effective pain management holds great importance for both clinicians and patients. Clinicians can use acetaminophen for their patients as a single agent for mild-to-moderate pain or in conjunction with an opioid analgesic for severe pain. This activity outlines the utilization, indications, administration, contraindications, and toxicity of acetaminophen, emphasizing the integral role of the interprofessional healthcare team in the care of patients using acetaminophen.

Objectives:

- Identify appropriate scenarios for acetaminophen use by distinguishing between mild-to-moderate and severe pain and assessing the patient's overall health status.
- Assess patients for pain relief effectiveness by monitoring for any signs of adverse effects or toxicity related to acetaminophen.
- Select appropriate acetaminophen formulations and routes of administration based on patient needs, considering factors such as age, weight, and ability to swallow.
- Collaborate with other interprofessional healthcare team members to ensure comprehensive pain management and improve patient outcomes by incorporating acetaminophen appropriately into multimodal treatment plans.

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Indications

Acetaminophen, also known as *N*-acetyl-para-aminophenol (APAP) or paracetamol in many countries, is a non-opioid analgesic and antipyretic agent utilized for treating pain and fever. Numerous diseases and conditions include pain as a significant component of their presentation. Consequently, effective pain management holds great importance for both clinicians and patients. Clinicians can use acetaminophen for their patients as a single agent for mild-to-moderate pain or in conjunction with an opioid analgesic for severe pain.

Mechanism of Action

Acetaminophen is one of the most widely used over-the-counter analgesic and antipyretic medications. Although the exact mechanism of action of the drug remains unclear, it is historically categorized along with nonsteroidal anti-inflammatory drugs (NSAIDs) due to its inhibition of the cyclooxygenase (COX) pathways. Acetaminophen possesses analgesic and antipyretic properties similar to NSAIDs but lacks peripheral anti-inflammatory effects. Acetaminophen may inhibit the COX pathway in the central nervous system (CNS) but not in peripheral tissues. In addition, acetaminophen does not appear to bind to the active site of either the COX-1 or COX-2 enzyme. Instead, it reduces the activity of COX through an alternative mechanism. There is also a theoretical proposition that acetaminophen inhibits a splice variant of COX-1, referred to as COX-3, although this hypothesis has not been verified in humans.

Regardless, the reduction of the COX pathway activity by acetaminophen is thought to inhibit the synthesis of prostaglandins in the CNS, leading to its analgesic and antipyretic effects. The analgesic properties may be due to a stimulating effect on the descending serotonergic pathways in the CNS. Additional research has proposed that acetaminophen or one of its metabolites, AM404, may activate the cannabinoid system. This activation could occur by inhibiting the uptake or degradation of anandamide and 2-arachidonoylglycerol, thereby contributing to its analgesic action. AM404 exerts analgesic effects through dual modulation of glutamatergic synaptic transmission within the spinal cord dorsal horn. This involves facilitating spontaneous transmission and inhibiting C-fiber–evoked transmission, achieved via activation of transient receptor potential vanilloid subtype-1 (TRPV1) receptors.

Pharmacokinetics

Absorption: Oral acetaminophen is rapidly and efficiently absorbed from the gastrointestinal tract, achieving peak plasma concentrations within 30 to 60 minutes. Intravenous (IV) administration of acetaminophen resulted in immediate and higher peak plasma concentrations. The rectal route is preferred for administration to bypass first-pass metabolism, especially in unconscious patients and children. This approach offers an alternative to parenteral administration, thereby mitigating gastric irritation and enabling efficient absorption due to the rich vascular supply in the rectum. Absorption in the upper rectum guides medications into the portal circulation through the superior hemorrhoidal vein, whereas lower rectal absorption results in direct entry into the systemic circulation.

Distribution: Acetaminophen exhibits low plasma protein binding of 10% to 25% and shows extensive distribution throughout the body, excluding fat tissue.

Metabolism: Acetaminophen undergoes primarily hepatic metabolism via first-order kinetics, utilizing 3 distinct pathways—conjugation with glucuronide, conjugation with sulfate, and oxidation facilitated by the cytochrome P450 enzyme system, predominantly CYP2E1. CYP3A4 plays a limited role in acetaminophen metabolism. This process forms a reactive intermediate metabolite

known as *N*-acetyl-p-benzoquinone imine (NAPQI). At therapeutic doses, NAPQI swiftly combines with glutathione, subsequently undergoing further metabolism to generate cysteine and mercapturic acid conjugates.

Elimination: Most acetaminophen metabolites are excreted in the urine, with less than 5% appearing as unconjugated or free acetaminophen. Over 90% of the administered dose is eliminated within 24 hours.

Administration

Available Dosage Forms

Acetaminophen can be administered through oral, rectal, or IV routes.

> Oral: Acetaminophen is available in various formulations, including tablets, capsules, syrup, oral solution, or suspension.
>
> Rectal: Acetaminophen is available as a rectal suppository for adult and pediatric patients.
>
> IV: Acetaminophen is also available as an IV infusion for administration.

Tompkins et al conducted a literature review on the effectiveness of IV acetaminophen in postoperative pain control. The investigators found a lack of evidence supporting the efficacy of IV acetaminophen when compared to oral or rectal acetaminophen, opioid analgesics, NSAIDs, or placebo across various surgical procedures, including abdominal, gynecological, genitourinary, orthopedic, neurosurgical, cardiac, and renal surgeries. The investigators conclude that IV acetaminophen offers limited clinical benefits compared to oral or rectal administration. Establishing the maximum daily allowable dosage of acetaminophen involves considering all modes of administration, including IV, oral, and rectal, as well as all formulations containing acetaminophen.

Dosages for Adults and Adolescents

Adults and adolescents (13 or older) with a body weight of ≥50 kg: The recommended dosage of acetaminophen is 1000 mg every 6 hours or 650 mg every 4 hours. The maximum single dose should not exceed 1000 mg, and the minimum dosing interval is 4 hours. Notably, the maximum daily dosage of acetaminophen should not exceed 4000 mg.

Adults and adolescents (13 or older) with a body weight <50 kg: The recommended dosage of acetaminophen is 12.5 mg/kg every 4 hours or 15 mg/kg every 6 hours. The maximum single dose should not exceed 15 mg/kg, and the minimum dosing interval is 4 hours. In addition, it is essential to adhere to a maximum daily dosage of acetaminophen not exceeding 75 mg/kg, up to a maximum of 3750 mg.

Specific Patient Populations

Hepatic impairment: Acetaminophen is contraindicated in cases of active liver disease or severe hepatic impairment. Caution is advised for patients with mild hepatic impairment, necessitating a reduced total daily dosage of acetaminophen and regular monitoring of liver function.

Renal impairment: In severe renal impairment (creatinine clearance ≤30 mL/min), extending dosing intervals and reducing the total daily dosage of acetaminophen may be advisable.

Pregnancy considerations: Observational studies have associated prenatal acetaminophen exposure with potential reproductive and neurobehavioral effects, including the risks of cryptorchidism, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder with prenatal APAP exposure. However, The American College of Obstetricians and Gynecologists (ACOG) considers acetaminophen safe for pregnant individuals. ACOG emphasizes that current evidence does not conclusively link acetaminophen use to fetal developmental issues. As neurodevelopmental disorders have multifactorial origins and brain development extends beyond birth, allowing for various potential influences, obstetricians must maintain current practices until further research provides more clarity.

Breastfeeding considerations: Acetaminophen is suitable for pain relief and fever reduction in breastfeeding mothers. The levels detected in breast milk are significantly lower than typical infant doses, and there are infrequent reports of adverse effects in breastfed infants.

Pediatric populations: The recommended dosage for children aged 2 to 12 is 12.5 mg/kg every 4 hours or 15 mg/kg every 6 hours. The maximum single dose should not exceed 15 mg/kg, and the maximum daily dosage of acetaminophen is 75 mg/kg.

> Neonates: The recommended dosage for premature children born at ≥32 weeks gestational age or less than 28 days old is 12.5 mg/kg every 6 hours, with a maximum recommended daily dosage of acetaminophen set at 50 mg/kg.
>
> Infants: Infants aged 29 days to 2 years are typically administered a dosage of 15 mg/kg every 6 hours, with a maximum daily dosage of acetaminophen not exceeding 60 mg/kg.

Older patients: As per the American Geriatric Society, the recommended acetaminophen dosage is 325 to 500 mg every 4 hours or 500 to 1000 mg every 6 hours, with a typical maximum daily dosage of 4 g. In individuals with hepatic impairment or a history of alcohol misuse, it is advisable to reduce the maximum dose by 50% to 75%.

Adverse Effects

Common adverse effects associated with oral or rectal administration of acetaminophen may include skin rash, hypersensitivity reactions, nephrotoxicity characterized by elevations in blood urea nitrogen (BUN) and creatinine, and hematological abnormalities such as anemia, leukopenia, neutropenia, and pancytopenia. In addition, it may cause metabolic and electrolyte imbalances,

which may manifest as decreased serum bicarbonate, reduced concentrations of sodium and calcium, hyperammonemia, hyperchloremia, hyperuricemia, increased serum glucose, and elevated levels of bilirubin and alkaline phosphatase.

Additional adverse effects associated with IV administration of acetaminophen include nausea, vomiting, constipation, pruritus, and abdominal pain.

Rare but serious adverse effects include hypersensitivity, anaphylactic reactions, and severe and fatal skin reactions. These include toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and Stevens-Johnson syndrome. In addition, there have been reported instances of a rare pneumonia resulting from drug-induced lung injury due to acetaminophen.

Drug-Drug Interactions

Warfarin: Prolonged oral administration of acetaminophen at 4000 mg/d has been associated with an elevated international normalized ratio (INR) in patients receiving warfarin. Due to the lack of studies evaluating short-term acetaminophen use with oral anticoagulants, increased frequency of INR monitoring may be advisable in these situations.

Alcohol: Chronic alcohol misuse increases the risk of acetaminophen toxicity by inducing CYP2E1, reducing hepatic glutathione (GSH) levels, and impairing NAPQI detoxification. Moreover, it may decrease glucuronidation, enhance oxidation, cause hepatocyte membrane disruptions, and reduce biliary excretion.

Contraindications

Contraindications to using acetaminophen include hypersensitivity to acetaminophen, severe hepatic impairment, or severe active hepatic disease.

Box Warnings

Hepatotoxicity: Acetaminophen use has been associated with liver failure, occasionally resulting in liver transplants or fatalities. The hepatotoxicity observed with acetaminophen use usually corresponds to high doses that surpass the recommended maximum dose. This effect may be associated with the consumption of multiple drug products containing acetaminophen as an ingredient. Liver damage has also been documented in patients with chronic acetaminophen dosing.

Dosing errors: A notable FDA-box warning underscores the importance of preventing dosing errors, especially when administering acetaminophen to pediatric patients. In addition, it underscores the necessity of ensuring that the total daily dose of acetaminophen does not exceed the recommended maximum when accounting for all medications containing acetaminophen.

Although these effects, warnings, and associations have been documented, acetaminophen remains a safe and effective medication when used accurately. The current manufacturer dose recommendation is restricted to between 3 and 3.25 g in 24 hours, depending on the formulation. However, toxicity is rare at doses less than 200 mg/kg for a child or 150 mg/kg for adults.

Monitoring

Patients undergoing acetaminophen treatment should undergo monitoring for desired clinical effects, such as pain or fever relief. Serum concentrations are unnecessary when appropriately dosed. In overdose situations, laboratory evaluation becomes necessary. In acute overdoses where ingestion occurs in less than 8 hours, a serum APAP concentration should be assessed and plotted on the Rumack-Matthew nomogram. The time course should start at the onset of ingestion to determine toxicity and the need for treatment. For nonacute ingestions, assessing acetaminophen concentration and transaminases is required, and treatment should be administered.

Furthermore, caution is warranted for patients with renal or hepatic impairment, alcoholic liver disease, glucose 6-phosphate dehydrogenase deficiency, or severe hypovolemia. However, there is evidence suggesting that acetaminophen may be deemed safe for use in the context of alcoholic liver disease.

Although acetaminophen can traverse the placental barrier, there is no evidence indicating an elevation in teratogenic effects when normal dosages of acetaminophen are used during pregnancy. In addition, acetaminophen is excreted into breast milk, with few observed instances of adverse reactions in nursing infants.

Pregnant women are advised to exercise caution when using acetaminophen early in pregnancy due to emerging evidence suggesting that in-utero exposure to acetaminophen may elevate the risk of neurological, reproductive, and urogenital disorders in the fetus. A study by Alemany et al investigated prenatal and postnatal acetaminophen exposure in relation to Autism Spectrum Conditions (ASC) and ADHD. Acetaminophen exposure was assessed in 73,881 mother-child pairs through questionnaires or interviews. Children aged 4 to 12 exhibiting symptoms of ASC or ADHD were evaluated using well-documented instruments. The study found that children prenatally exposed to acetaminophen had an elevated risk of ASC (19%) or ADHD (21%), manifesting as borderline or clinical symptoms. However, postnatal acetaminophen exposure did not show an association with ASC or ADHD symptoms.

MacIntyre et al conducted a double-blind, placebo-controlled, crossover clinical trial to investigate the effects of oral acetaminophen on daytime systolic blood pressure. One hundred and ten subjects were randomized to receive 1 g of acetaminophen 4 times a day or a placebo for 2 weeks, followed by a 2-week washout period before receiving the alternative treatment. Daytime systolic blood pressure was assessed in subjects who received either acetaminophen or a placebo. The investigators observed a 5-mmHg increase in daytime systolic blood pressure

among those who received a daily dose of 4 g of acetaminophen. As a result, the researchers concluded that the use of high-dose acetaminophen in hypertensive patients could potentially elevate their risk of cardiovascular disease.

Toxicity

Each year, approximately 500 fatalities and 50,000 emergency department admissions in the United States are linked to acetaminophen. In 2021, US poison control centers recorded over 80,000 cases. Acetaminophen is the most prevalent drug-related cause of acute liver failure, with hepatic injury occurring as a consequence of the drug's metabolism properties. After reaching therapeutic concentrations of oral acetaminophen, 60% to 90% of the drug undergoes metabolism in the liver, forming glucuronic acid- and sulfate-conjugate metabolites. A smaller fraction, approximately 5% to 15%, undergoes metabolism via the cytochrome P450 system (CYP450)—metabolism primarily through CYP2E1 results in the formation of the toxic intermediate NAPQI.

Under normal circumstances, NAPQI is neutralized by glutathione to form nontoxic metabolites. However, in the case of excessive doses of acetaminophen, the normal phase II drug metabolism pathways become depleted. The CYP450 pathway metabolizes a more significant portion of the acetaminophen, leading to elevated concentrations of NAPQI formation, and the limited glutathione stores can deplete. When there is a shortage of glutathione, NAPQI concentrations increase, and, as a reactive intermediate, it can react with essential cellular macromolecules such as proteins, lipids, and nucleic acids. This interaction can result in centrilobular (zone 3) hepatic injury and hepatocellular death, along with the potential for nephrotoxicity.

The only approved antidote for acetaminophen overdose and toxicity is *N*-acetylcysteine (NAC). NAC acts as a precursor to glutathione synthesis, aiding in restoring intracellular glutathione stores to neutralize the NAPQI compound, directly inactivating NAPQI. NAC can be administered orally or via the IV route. The IV administration of NAC is typically preferred because vomiting is common with acetaminophen overdose. NAC administration follows a 20-hour IV or 72-hour oral protocol, and clinicians must monitor aspartate aminotransferase/alanine aminotransferase (AST/ALT) levels during treatment.

Notably, the majority of patients do not exhibit symptoms in the initial hours after ingesting toxic doses of acetaminophen. During this early period, symptoms may be limited to abdominal pain and nausea, persisting for the first 12 to 24 hours. Although these symptoms may alleviate between 24 and 72 hours, AST/ALT concentrations may remain abnormal. Patients presenting more than 24 hours after ingesting toxic doses of acetaminophen may manifest symptoms including nausea, vomiting, jaundice, abdominal pain, and hypotension. The management of these patients may involve interventions such as airway management, IV fluids, vasopressors, and addressing symptoms such as cerebral edema as they arise.

A recent consensus statement published by America's Poison Centers, American Academy of Clinical Toxicology, American College of Medical Toxicology, and Canadian Association of Poison Control Centers addresses acetaminophen toxicity. NAC is administered through oral or IV routes, with the initial dose administered promptly upon identifying the need for treatment. The panel recommends a regimen providing a minimum of 300 mg/kg, either orally or IV, within the initial 20 to 24 hours of treatment. Nevertheless, the comparative effectiveness of various regimens still requires evaluation.

The guidelines emphasize the importance of continuous assessment and caution against prematurely discontinuing treatment. Notably, a common clinical error involves administering NAC for 20 or 21 hours and then discontinuing without reassessing the patient. The panel chose to refine the Rumack-Matthew nomogram by retaining only the lines indicating clinical action. In this refined approach, the blood concentration of APAP is directly plotted on the nomogram, and NAC is administered to patients whose concentration exceeds the treatment line. Stopping criteria for NAC include an acetaminophen concentration below 10 µg/dL, an INR level below 2, normal levels of AST/ALT, or a decrease in AST/ALT by 25% to 50%, provided the patient is clinically stable.

High-risk ingestion involves the consumption of at least 30 g of acetaminophen or an acetaminophen concentration surpassing the high-risk line on the nomogram. These cases are managed similarly to other acetaminophen overdoses, with consideration for the extended administration of activated charcoal, especially if the ingestion occurred more than 4 hours prior due to prolonged absorption. In addition, consultation with a clinical toxicologist may be required for an increased NAC dosage. In managing repeated supratherapeutic ingestion in 24 hours, unlike acute ingestion cases, treatment is based on signs and symptoms. If the acetaminophen concentration exceeds 20 µg/mL or AST levels or ALT are abnormal, NAC should be administered until the established stopping criteria are met.

Extended-release acetaminophen products, intended for 8-hour use in the United States or Canada, are managed similarly to other acetaminophen products. Activated charcoal may continue to be effective for longer than 4 hours after ingestion, especially when evidence indicates ongoing absorption, such as an increasing acetaminophen concentration. NAC is required if the acetaminophen concentration from samples drawn 4 to 24 hours after ingestion surpasses the nomogram treatment line. In cases where the concentration from samples drawn 4 to 12 hours after ingestion falls below the treatment line but remains above 10 µg/mL, a follow-up measurement should be taken 4 to 6 hours after the initial assessment.

In simultaneous ingestion with anticholinergic or opioid agonists, the concern is the potential for delays or prolongation of acetaminophen absorption. The management approach aligns with that of other acetaminophen products. If the initial acetaminophen concentration measured 4 to 24 hours after ingestion is 10 µg/mL or lower, further measurements are unnecessary, and N-acetylcysteine (NAC) treatment is not required. Conversely, if any concentration exceeds the treatment line, NAC is indicated.

If the acetaminophen concentration measured within the same time frame falls between 10 µg/mL and the treatment line on the revised nomogram, and clinical signs indicating anticholinergic or opioid toxicity are present, a reevaluation should be scheduled 4 to 6 hours following the initial measurement. Notably, the dosing and duration of NAC treatment strictly follow the established standard protocol for acetaminophen ingestions. The panel recommends hemodialysis with NAC in massive acetaminophen toxicity with a concentration exceeding 900 µg/mL, accompanied by acidosis or altered consciousness.

Enhancing Healthcare Team Outcomes

The prevention of acetaminophen toxicity is of utmost importance, and an interprofessional healthcare team comprising clinicians (MDs, DOs, NPs, and PAs), nurses, and pharmacists plays a critical role. Pharmacists and nurses need to emphasize the daily maximum permitted dose of acetaminophen. Patients should be educated on identifying acetaminophen in various medications and calculating the dosages when combining products.

Pharmacists are responsible for conducting medication reconciliation to assess potential drug interactions and ensuring that the patient's regimen does not include an excessive amount of acetaminophen-containing drugs. Pharmacists should report any concerns to the nurse and prescriber. All healthcare team members must document their findings and inform the entire team regarding the patient's case. With the recent changes in maximum daily dosing for acetaminophen, all interprofessional healthcare team members must be aware of the new guidelines, and they should remain current and stay vigilant for any emerging guidance in the field.

In cases of toxicity or suspicion of toxicity, effective management necessitates the collaboration of an interprofessional team comprising clinicians, nurses, and pharmacists. Specific protocols have been designed to direct the interprofessional healthcare team when patients present to emergency departments with acute acetaminophen toxicity. Developing such protocols involves the input of emergency physicians, nurses, toxicologists, pharmacists, and psychiatrists. Furthermore, dentists can also become involved when the overdose is secondary to dental procedures. As outlined above, patients should receive clear instructions on APAP medication management upon discharge.

Although acetaminophen has been available for many years and is generally considered safe, a coordinated interprofessional team effort is necessary to prevent avoidable toxicity by accounting for all sources of acetaminophen in the patient's medication profile. Based on a recent study, it was found that after the FDA's mandate in 2011, which limited the amount of acetaminophen to 325 mg per tablet when combined with opioids, there was a significant decrease in hospitalizations and the proportion of acute liver failure cases caused by acetaminophen and opioid toxicity. These findings highlight the impact of regulatory interventions on patient safety and medication-related adverse events.

Review Questions

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Disclosure: Valerie Gerriets declares no relevant financial relationships with ineligible companies.

Disclosure: Jackie Anderson declares no relevant financial relationships with ineligible companies.

Disclosure: Preeti Patel declares no relevant financial relationships with ineligible companies.

Disclosure: Thomas Nappe declares no relevant financial relationships with ineligible companies.