ACETAMINOPHEN POISONING AND TREATMENT

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Topic Overview

Acetaminophen poisoning is the most common cause of acute liver failure in the United States and other countries. Liver damage often occurs after an acetaminophen overdose, but liver failure and death are rare. N-acetylcysteine (NAC) is a highly effective antidote for an acetaminophen overdose. If a patient with acetaminophen poisoning is treated with the NAC protocol promptly, the patient is almost sure to recover and survive the event. Pharmacists and pharmacy technicians should be aware of the potential risks associated with this commonly used over-the-counter medication. They should also learn what they can do to minimize acetaminophen overdoses and implement these strategies in their daily practices.

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How to Earn Credit: From September 22, 2022, through September 22, 2025, participants must:

1) Read the "learning objectives" and "author and planning team disclosures;"
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Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Describe** the pharmacology of acetaminophen
2. **Identify** the prevalence and circumstances that give rise to acetaminophen poisoning
3. **Describe** the criteria for diagnosing acetaminophen poisoning
4. **Describe** treatment guidelines for acetaminophen overdose

Disclosures

The following individuals were involved in the development of this activity: Susan DePasquale, MSN, PMHNP-BC, Amanda Mayer, PharmD, and Jeff Goldberg, PharmD, BCPP. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

Introduction

The leading cause of acute liver failure in the United States and other developed countries is the intentional or accidental overdose of the common over-the-counter medication acetaminophen. An overdose of acetaminophen not only causes liver damage but, in rare instances, can cause renal and other organ system damage as well. Healthcare teams that are prepared with the appropriate knowledge and skill to recognize acetaminophen poisoning and provide the appropriate diagnostic and treatment steps can help to save a person from significant physical harm. After a chronic overdose, the toxic dose of acetaminophen depends on how long the patient has been taking the drug and the presence of risk factors. The use of the Rumack-Matthew nomogram helps to determine whether acute acetaminophen ingestion can be expected to be toxic or non-toxic. In chronic acetaminophen use, a serum level should be measured to determine the need for treatment. The standard treatment for acetaminophen overdose is N-acetylcysteine, and if patients are treated appropriately and promptly, the prognosis is typically good. Hemodialysis may be used as a treatment option and in severe cases liver transplantation may be needed.

Acetaminophen Use and Incidence of Overdose

Acetaminophen (APAP), also known as paracetamol in Europe and many other countries, is an over-the-counter analgesic used for mild to moderate pain and an antipyretic.[1,2] It is sold globally as an over-the-counter drug and it is the "most widely used [OTC], non-narcotic analgesic agent for the treatment of mild to moderate pain and fever."[1]

At therapeutic doses, acetaminophen is regarded as a safe drug, especially when compared to aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) used for mild to moderate pain and fever.[1] However, acetaminophen overdose is a well-known cause of liver injury.[3,4] This has led to some clinicians calling for reduced dosing or even replacement of this drug.[2,3]

Acetaminophen overdose is the leading cause of acute liver failure in the United States, Europe, and Australia.[3] Reports from the United Kingdom reveal that 82,000–90,000 patients are hospitalized each year due to acetaminophen toxicity.[4] In the United States, approximately 30,000 patients are hospitalized for acetaminophen toxicity. Up to one-half of acetaminophen overdoses are unintentional, largely related to opioid-acetaminophen combinations and attempts to achieve better symptom relief.

Liver injury occurs in 17% of adults with unintentional acetaminophen overdose.[5] Acetaminophen toxicity has been reported as the second most common cause of liver transplantation worldwide and the most common in the U.S.[5] When diagnosed and treated promptly, acetaminophen toxicity mortality is less than 2%.[4]

In the United States, annual deaths from acetaminophen overdose are estimated to be 0.4% of overall overdose patients. This means that about 300 patients die each year from acetaminophen poisoning.[6] Lee (2004) reported 458 annual deaths from acetaminophen poisoning. Deaths were the result of acute liver failure.[7]

The American Association of Poison Control Centers (AAPCC) publishes annual reports documenting the number and nature of drug overdoses, including acetaminophen, that may be accessed at the AAPCC website and on PubMed.[8,9]

Acetaminophen Pharmacology

Acetaminophen appears to have minimal anti-inflammatory activity.[1] It is not completely understood how acetaminophen works, but it is thought to produce its analgesic and antipyretic effects by inhibiting the synthesis of prostaglandins in the central nervous system, blocking pain impulse generation peripherally, and by inhibiting the heat-regulating center of the hypothalamus.[10] In therapeutic doses, acetaminophen is rapidly and completely absorbed from the gastrointestinal tract. The serum concentration of an oral dose reaches peak levels within 10 to 60 minutes. The onset of

action is within one hour and the therapeutic concentration is generally 10 to 20 mcg/ml.[10] First-pass metabolism removes approximately 25 percent of a therapeutic dose.[10]

After absorption, approximately 88% of acetaminophen undergoes hepatic glucuronidation and sulfate conjugation. The acetaminophen/sulfate and acetaminophen/glucuronic acid complexes are harmless and are eliminated in the urine.[11] Part of the remainder of the acetaminophen undergoes oxidative metabolism via CYP2E1 producing the hepatotoxic metabolite *N*-acetyl**-**benzoquinone imine (NAPQI), and less than 5% of the drug is excreted unchanged in the urine.[11] If acetaminophen is ingested in therapeutic doses, NAPQI is combined with glutathione (GSH), and the NAPQI-glutathione complex is converted to non-toxic mercapturic acid or cysteine, both of which are excreted in the urine and bile.[11,12] Increased concentrations of NAPQI and hepatotoxicity can be attributed to supratherapeutic or repeated therapeutic doses of acetaminophen, fasting, and alcoholism, which may deplete glutathione stores.[12]

Acetaminophen Dosing and Available Forms

Acetaminophen is available in several different dosages and formulations. Dosing has been controversial and has changed over the past several years because of the risk of liver injury.

Acetaminophen Dosing

The usual adult oral dose of acetaminophen is 325-650 mg every four to six hours (or 1000 mg every six hours), and the total amount ingested for 24 hours should not exceed 4000 mg.[12] The dose for children and adolescents > 12 years of age is the same as the adult dose. For children < 12 years of age, the usual acetaminophen dose is 10-15 mg/kg every four to six hours (max 75 mg/kg/day or 4000 mg per 24 hours, whichever is less). The max dose for all patients is 1000 mg in any six-hour interval and 4000 mg in 24 hours.[12]

There has been long-term concern that the 4000 mg maximum recommended daily dose of acetaminophen may be too high and potentially harmful.[2-4,7] In 2011, the Food and Drug Administration (FDA) asked manufacturers to limit the amount of acetaminophen to a maximum of 325 mg in prescription combination products by January 2014, but no request was made to lower the 4000 mg per day limit.[13] In April 2014, the FDA recommended that a pharmacist who receives a prescription for a combination product with more than 325 mg acetaminophen per dosage unit should contact the prescriber to determine if a product with a lower dose of acetaminophen would be acceptable.[14] There are currently no combination prescription medications available in the United States that have more than 325 mg of acetaminophen per dose; however, there are over-the-counter formulations of acetaminophen that contain up to 500 mg per tablet/capsule.[14]

Available Forms of Acetaminophen

Acetaminophen is available in oral tablets, caplets, capsules, gel tablets, oral suspensions, oral solutions, rectal suppositories, and in intravenous (IV) formulations. Acetaminophen is frequently added to over-the-counter cold and cough medications, allergy relief medications, sleep medications, and analgesics. Prescription-strength opioid analgesics and acetaminophen are frequently combined as well.[12]

Contraindications

Acetaminophen is contraindicated in patients who have hypersensitivity to the drug or if the patient has severe hepatic impairment or severe active liver disease. It should be used cautiously if the patient has glucose-6-phosphate dehydrogenase (G6PD) deficiency (a genetic condition associated with hemolytic anemia that may be exacerbated by acetaminophen use), consumes ≥ three alcoholic drinks per day, or has renal impairment. Oral formulations of acetaminophen are considered safe to use during pregnancy. Acetaminophen does enter the breast milk, and the drug should be used cautiously by nursing mothers.[12]

Adverse Effects

The adverse effects of acetaminophen are generally minimal if taken appropriately. Common side effects are mild and temporary gastrointestinal distress and rash. A rash is more common in children, so close monitoring is recommended.[12]

Drug-Drug/Drug-Disease Interactions

Some drug interactions between acetaminophen and commonly used medications include the following:[12]

- Barbiturates: The metabolism of acetaminophen may be increased (along with increased levels of the toxic metabolite NAPQI), decreasing the effectiveness of acetaminophen and increasing the risk of liver damage.
- Carbamazepine: The metabolism of acetaminophen may be increased, decreasing the effectiveness of acetaminophen, and potentially increasing the percentage of NAPQI generated.
- Isoniazid: Induces CYP2E1, which may enhance the hepatotoxic effects of acetaminophen.
- Prilocaine: Taking acetaminophen and prilocaine together can increase the risk of developing methemoglobinemia.
- Warfarin: Acetaminophen may enhance the anticoagulant effect of warfarin and cause an increase in the patient's international normalized ratio (INR). Frequent assessment of INR may be appropriate in patients initiating, adjusting, or terminating therapy with acetaminophen while on warfarin.

Certain disease states, such as infectious hepatitis, alcoholism, malnourishment, starvation, and liver injury from other causes, may increase the risk of acetaminophen overdose.[4,15]

Acetaminophen Toxicity

The Rumack-Matthew nomogram was developed to ascertain whether a patient who ingested acetaminophen would be likely to develop liver toxicity. Serum concentration levels of acetaminophen are plotted on a graph against the time that has elapsed since the drug was ingested. In recent years, concern has been raised that the maximum 24-hour therapeutic amount of acetaminophen and the amount considered to be potentially toxic are both too low.[12,17]

Therapeutic Dose and Potential Toxicity

As mentioned above, there has long been concern that the 4000 mg maximum recommended daily dose of acetaminophen may be too high and potentially harmful in certain patients.[2-4,7] Yoon, *et al.* (2016) describe what is referred to as a "therapeutic misadventure."[6] These are instances when a patient who received a safe or recommended dose presents with acute liver injury.[6]

McNeil Pharmaceuticals, the manufacturer of the Tylenol® brand, has decreased the 24-hour maximum recommended dose of its acetaminophen-containing products to 3000 mg of the 500 mg preparations and 3250 mg of the 325 mg preparations.[20] However, other manufacturers of acetaminophen products continue to use 4000 mg per day as the limit, and this is the maximum dose that will be found in pharmaceutical references.

Clinical Presentation of Acetaminophen Poisoning

The clinical presentation of acetaminophen poisoning has traditionally been described as having four phases or stages.[6,16,23] Individual variations in the presentation exist, but in most cases, these four phases are easily identifiable and follow each other predictably.[6,16,23]

Phase I

This phase occurs from 0 to 24 hours post-ingestion. Nausea, vomiting, abdominal pain, and anorexia are commonly observed, but occasionally, the patient may be asymptomatic. There is usually no laboratory evidence of liver damage. However, the serum transaminases can begin to rise as early as eight hours and as late as 36 hours after ingestion.[6,16,23]

Phase II

This phase occurs from 24 hours to 72 hours post-ingestion. Gastrointestinal signs and symptoms typically diminish or disappear, but some patients develop right upper quadrant pain. The patient's liver function tests (LFTs), specifically serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), may begin to rise above normal levels. AST levels at or above 1,000 IU/L are not uncommon following an severe acetaminophen overdose.[6,16,23]

A very high AST level soon after overdose indicates a potential for serious poisoning.[16] The international normalized ratio (INR) and prothrombin time (PT) may also begin to rise above normal levels. Occasionally, serum blood urea nitrogen (BUN) and creatinine will also become elevated, indicating potential kidney damage.[6,16,23]

Phase III

This phase develops from 72 hours to 96 hours after ingestion and it is characterized by recovery or progression to liver failure.[6,16] Most patients, even those who do not receive treatment, will have a mild to moderate degree of liver damage, but this often resolves. Other patients develop fulminant hepatic failure and either recover or succumb. Patients with fulminant hepatic failure may develop metabolic acidosis, acute respiratory distress syndrome (ARDS), coagulopathies, coma, hypoglycemia, cerebral edema, and renal failure.[6,16,23]

Phase IV

Phase IV is the recovery phase. It is from 96 hours after ingestion to approximately two weeks after ingestion, and it is characterized by a return of liver function.[6,16,23] For patients who have survived Phase III, hepatic damage and function are generally stable at this point. It is important for clinicians to be aware that if the patient has ingested a massive amount of acetaminophen, the patient may not present with a normal progression through the phases. These patients will rapidly become comatose and acidotic and may require liver transplantation.[6,16,23]

Acetaminophen Overdose and Organ Damage

As mentioned previously, acetaminophen is a major cause of medication overdose-related liver failure and death in the U.S., as well as in other countries. Identifying overdose is key to preventing the development of acute liver failure. The dose ingested and the time from ingestion to treatment appear to be the most important factors for the presentation of severe liver failure and the possible need for liver transplantation.[6] About 29% of patients who present with acute liver failure from acetaminophen poisoning will have a liver transplant. The mortality rate for these liver transplant patients is approximately 28%.[6,10] As mentioned above, co-ingestion of alcohol, chronic alcoholism, malnutrition, and drug interactions could place a patient at an increased risk of hepatotoxicity following an acetaminophen overdose.[4,15] In addition to liver damage, renal and other organ damage may result from acetaminophen poisoning as well.[24]

Liver Damage

As mentioned above in the section on acetaminophen pharmacology, when acetaminophen is taken in therapeutic amounts, the pathways of glucuronidation and sulfate conjugation effectively metabolize 90% of the drug, and there are generally sufficient stores of glutathione available in the liver to bind and neutralize the toxic NAPQI effectively.[10] However, when acetaminophen is taken in toxic amounts, the conjugation pathways become

saturated, and a larger proportion of the ingested dose is metabolized into NAPQI. The rate of formation of NAPQI and the amount of NAPQI produced deplete the liver's glutathione stores and surpass the liver's ability to make more glutathione.[10-12] When hepatic glutathione stores have been depleted to approximately 70% of pre-exposure levels, NAPQI levels increase, and it beings to covalently bind to hepatocytes, causing oxidative injury and subsequent liver damage.[25]

Renal Damage

Acute renal failure occurs in <2% of all cases of acetaminophen poisoning.[28] Most cases of renal impairment caused by acetaminophen poisoning occur along with acute hepatic injury.[28] The onset of renal failure caused by acetaminophen overdose typically begins after liver damage and liver failure. It does not appear that there is a reliable way to predict which patients with an acetaminophen overdose will develop renal failure, and the peak serum creatinine levels may not be seen until two to seven days after the ingestion.[28]

Other Organ Damage

Cardiotoxicity and acute pancreatitis have been reported after acetaminophen overdose.[18] Elevated serum amylase is also common after acetaminophen overdose. Cardiac damage and dysrhythmias, and acute pancreatitis are rare, and these conditions are unlikely to be directly caused by acetaminophen. They are likely sequelae of hepatic failure, an idiosyncratic response, unrelated to the overdose, or due to an exacerbation of pre-existing medical problems from acetaminophen-induced hepatic failure.[18]

Acute Acetaminophen Overdose

Acetaminophen poisoning and acute liver injury are seen when a patient ingests the drug in amounts over this maximum dose; however, they can occur with ingestion of a therapeutic, recommended daily maximum dose.[23]

This has caused some drug developers to lower the recommended thresholds on their products voluntarily to make the product safer for patients.[23]

The healthcare team members work together to identify patients who may have been poisoned from ingesting acetaminophen and those who require antidotal treatment. The healthcare team tries to determine the dose that was ingested, when it was ingested, and the serum acetaminophen level. They also evaluate the results of the pertinent laboratory tests and examine all the signs and symptoms the patient may be exhibiting.[29] For example, elevated blood lactate concentrations may be an indication of acetaminophen poisoning.[30]

Acetaminophen Toxic Dose and Time of Ingestion

Acute acetaminophen overdose is defined as ingesting a toxic amount within 8 hours or less. A chronic overdose, or repeated supratherapeutic ingestion (RSTI), is the ingestion of a toxic amount over a period greater than 8 hours.[31] It is important to inquire with the patient about the dose and time of ingestion to aid with treatment.[23]

Measuring Acetaminophen Serum Levels

In patients with suspected acetaminophen poisoning, a serum acetaminophen level should be obtained four hours after ingestion or as soon as possible if the four hours has potentially been exceeded after ingestion.[6,26,33]

The Rumack-Matthew Nomogram

The Rumack-Matthew nomogram uses serum acetaminophen levels at specific points in time post-ingestion to predict the risk of hepatotoxicity and guide treatment. If serum acetaminophen levels are above the "treatment line" which typically starts at 150 mcg/mL at 4 hours and extends to 4.7 mcg/mL at 24 hours, then treatment is indicated. When the time of ingestion is unknown but falls within the last 24 hours, the earliest possible time of

ingestion should be estimated and plotted on the nomogram. Use of the nomogram should be avoided until 4 or more hours post-ingestion as levels may be misleading during that time frame.[23] Nomogram failures are rare and probably represent incorrect use of the nomogram, inaccurate ingestion histories, or outliers in terms of unidentified risk factors.[16]

Toxic Levels of Acetaminophen

A level below 150 mcg/mL at 4 hours post-ingestion or below 37.5 mcg/mL at 12 hours post-ingestion predicts minimal hepatic damage. In the U.S., toxicity from acetaminophen in adults is defined as serum acetaminophen concentration levels above 150 mcg/ml at 4 hours. Most other countries define toxicity from acetaminophen as concentrations above 200 mcg/ml at 4 hours.[18,26,32]

Acetaminophen Poisoning and Potential Co-ingestion of Other Drugs

A salicylate level should also be measured as patients occasionally confuse aspirin and acetaminophen and may use the terms interchangeably.[34] If a patient has co-ingested opioids or anticholinergic medications, a post-ingestion level should be checked at 4 hours post-ingestion and repeated at 6 hours post-ingestion due to decreased GI tract motility.[23] Hendrickson (2015) notes that if the acetaminophen level is measured between one and three hours post-ingestion and the level is undetectable, "... significant APAP overdose can likely be excluded."[16] However, research has shown that acetaminophen levels measured before the four-hour mark cannot be used to determine risk and will miss potentially toxic exposures. The level is then plotted on the Rumack-Matthew nomogram.[16]

Laboratory Tests

Initial laboratory testing in acute liver failure may reveal a prolonged prothrombin time, INR greater than 1.5, elevated AST, ALT, and bilirubin levels, thrombocytopenia, electrolyte abnormalities, elevated ammonia levels, and acid-base disturbances.[23] Normal laboratory values may indicate that

toxic ingestion has not occurred, but may also reflect ingestion that recently happened.[16] If the AST, ALT, or INR are above the normal range, if the patient has (or may have taken) an overdose of acetaminophen, and there is no other reason for the laboratory abnormalities, this is a strong indication of a need for treatment.[6,16,35]

Signs and Symptoms of Acetaminophen Toxicity

Abdominal pain, nausea, and vomiting are common signs and symptoms of an acetaminophen overdose. These gastrointestinal complaints are nonspecific and may be absent or greatly diminished around 24 hours after the ingestion, but their presence or absence could be a factor in determining who has acetaminophen toxicity.[36]

Initial Treatment for Acetaminophen Overdose

During the initial care for individuals with acetaminophen overdose, pre-hospital and hospital healthcare teams should assess the patient's airway, breathing, and circulation (ABCs). If there are significant derangements in the ABCs, it is possible that the patient is experiencing an acetaminophen overdose. Large amounts of acetaminophen can cause coma and metabolic acidosis shortly after ingestion.[6,16]

Gastric Decontamination

Activated charcoal is the preferred method of gastric decontamination and is believed to be most beneficial if administered within the first 4 hours post-ingestion.[23] Activated charcoal binds to acetaminophen in the GI tract and prompt administration of activated charcoal can prevent acetaminophen from being absorbed and converted to NAPQI and reduce the need for antidotal therapy.[6,16] A single dose of activated charcoal should be administered for the following reasons.[16]

- A toxic amount of acetaminophen has been ingested.
- The ABCs are normal.

- The patient is awake, alert, and has a normal gag reflex.
- The patient has co-ingested a substance that may rapidly cause depressed consciousness.
- The patient has a functioning gastrointestinal tract.

Antidotal Therapy: N-Acetylcysteine

N-acetylcysteine (NAC) is a highly effective antidotal treatment for acetaminophen poisoning. Administering this treatment is safe and straightforward. Acetylcysteine is the official term designated by United States Adopted Names for N-acetylcysteine, or NAC.[37]

N-acetylcysteine acts by being hydrolyzed to cysteine, which in turn, restores glutathione levels as well as provides thiol groups that react directly with NAPQI. This allows NAPQI to be removed from the body.[23] The standard recommendation is that NAC, distributed under the brand name Acetadote®, is most effective when given intravenously within eight hours of an acetaminophen overdose.[6,16] However, the prescribing information notes that NAC should be given 8-10 hours after an overdose, and Hendrickson (2015) recommends that NAC therapy should not be unnecessarily delayed past 6 hours if it can be safely administered earlier.[16] Overall, NAC should be administered as soon as possible after a patient has been diagnosed with acetaminophen overdose.[6,16]

Although administering NAC many hours or even days after an acetaminophen overdose may be helpful, NAC is most effective if it is given ≤ 8-10 hours after ingestion.[29] After 8-10 hours have passed from the time of ingestion, the effectiveness of NAC begins to decline, so prompt identification of patients at risk is important.

When the serum acetaminophen level and the laboratory test results are known, and the history and physical examination are completed, a decision regarding treatment can be made. A patient is at risk and should receive antidotal therapy for the following findings:[36,38]

- The acetaminophen level is above the treatment line on the Rumack-Matthew nomogram.
- It has been confirmed that the patient has taken a toxic amount of acetaminophen.
- It is suspected or possible that the patient has taken a toxic amount of acetaminophen and there is a measurable acetaminophen level.
- There is a measurable acetaminophen level, but the time of ingestion is not known.
- There is a measurable level of acetaminophen, but no one witnessed the person ingesting the drug. There is no other report of acetaminophen ingestion.
- It is suspected or possible that the patient has taken a toxic amount of acetaminophen and there is laboratory or clinical evidence of liver damage.

Modes of Administration

N-acetylcysteine can be given orally or intravenously and both routes are acceptable options for preventing and treating liver damage from acetaminophen overdose.[26] The oral formulation has been used in the U.S. for many years; however, the IV route has become the most common route of NAC administration.[26]

Oral NAC

When using NAC orally, the patient is given a loading dose of 140 mg/kg followed by 17 doses of 70 mg/kg at 4-hour intervals. If the patient vomits within an hour of administration of the dose, the dose should be repeated or the patient should be switched to the IV formulation.[39] Monitoring of the patient during treatment includes daily laboratory testing of the AST, ALT, INR, BUN, serum creatinine, and serum acetaminophen level.

Adverse effects of oral NAC are primarily nausea and vomiting. Oral NAC smells like rotten eggs and has an unpleasant taste, so nausea and vomiting are very common (reported in at least 20% of patients).[16,18] These side effects can be prevented by diluting oral NAC with juice or soda, serving it cold in a

cup with a lid, and instructing the patient to sip it slowly. If needed, oral NAC can be given through a nasogastric tube.[40]

Contraindications to using oral NAC include sensitivity to NAC, the inability to use the GI tract, or persistent vomiting.[39,40] Oral NAC cannot be given to patients who do not have a functioning GI tract and it cannot easily (or at times safely) be given to patients who have an altered mental status. Disruption of treatment because of nausea and vomiting is common and patients may refuse to drink oral NAC because it is noxious.[39,40]

Intravenous NAC

Intravenous NAC can be used for any patient who has acetaminophen poisoning. NAC given intravenously is preferentially used if the patient is pregnant, has hepatic failure, or the oral form cannot be used (for example, in the case of intractable vomiting or a non-functioning gastrointestinal tract).[16,18] The standard "three-bag" protocol dosing for intravenous (IV) NAC is as follows:[16,18]

- Patients > 40 kg are given three doses:
    - 150 mg/kg of NAC in 200 mL of 5% dextrose in water (D5W), infused over 60 minutes, and followed immediately by
    - 50 mg/kg of NAC diluted in 500 mL of D5W, infused over four hours, and followed immediately by
    - 100 mg/kg of NAC, diluted in 1000 mL of D5W, infused over 16 hours.
- The maximum doses of IV NAC are 15,000 mg, 5,000 mg, 10,000 mg for the three respective infusions and these correspond to a patient who weighs 100 kg. There are no clinical studies that have investigated higher doses, but as liver size does not differ significantly between obese and non-obese patients, no dosage adjustments are necessary for patients weighing >100 kg.
- Dosing is adjusted in patients less than 40 kg, in which case the package insert should be referenced. In these patients, the above dosing regimen provides too much free fluid and can cause hyponatremia and seizures.[39]

Monitoring of patients receiving intravenous NAC generally involves:[16,18,39]

- ALT or AST should be measured at 18-20 hours after the start of NAC infusion and repeated every 12 to 24 hours until the patient recovers.
- If no acetaminophen is detected and AST, ALT, and INR are normal, the infusion can be finished, and treatment is complete.
- If there is measurable acetaminophen (indicating the possibility of further formation of NAPQI), or AST, ALT, or INR is elevated (evidence of hepatotoxicity), the infusion should be continued.

Allergic reactions (including anaphylaxis) have been identified to occur in up to 18% of patients who are given intravenous NAC.[41] These reactions are mostly mild to moderate, with the patients having flushing, itching, and rash. Severe reactions characterized by angioedema, bronchospasm, and hypotension can occur, but they are rare. Anaphylactoid reactions are more likely to happen with the initial one-hour infusion, if a patient has a lower acetaminophen level (<300 mcg/mL), in women, if the patient has previously been given NAC, and if a patient has asthma.[16,41]

The two bag method of IV NAC administration (off-label dosing) consists of two doses totaling 300 mg/kg. The first dose is 200 mg/kg, infused over 4 hours, and the second dose is 100 mg/kg, infused over 16 hours. The two-bag method has been correlated with a lower incidence of milder, nonallergic anaphylactic reactions in comparison to the manufacturer's recommended dose.[42]

Patients observed to have a minor allergic reaction (with erythema and flushing) can continue the intravenous NAC infusion and should be closely monitored.[43,44] If the patient has urticaria, diphenhydramine may be administered (intravenously for faster onset). If a patient is experiencing a severe allergic reaction, the NAC infusion should be stopped, and emergency measures should be initiated as needed. Intravenous NAC can be restarted if symptoms resolve; however, if they do not resolve, the patient should be switched to oral NAC.[43,44]

Duration of Therapy

If, at the end of the 24-hour IV NAC treatment, there is measurable acetaminophen, elevations of AST, ALT, or INR, or clinical evidence of hepatic encephalopathy, the patient will require more IV NAC. In this scenario, begin the fourth bag, 100 mg/kg in 1000 mL of D5W, and infuse at a rate of 6.25 mg/kg/hr. Intravenous NAC should then be continued until there is no measurable acetaminophen and the patient's clinical status and laboratory test values are improving.[16] The need for IV NAC beyond the standard three-bag protocol is not uncommon, and this approach is universally agreed upon.

The endpoint of extended IV NAC therapy is less clear, and there are no consensus protocols for this situation. Many clinicians feel that if the patient's clinical condition is normal, the AST has been steadily declining and is below 1000 IU/L, and the INR is <2.0, it is safe to discontinue the NAC.[16] Each case should be considered and treated individually, and a clinical toxicologist consulted if needed.

The IV NAC protocol has been in place for over 40 years, and it has been highly successful. The protocol is generally applied to every patient, without consideration of the acetaminophen level or the amount of drug ingested. Hendrickson, Howland, and Heard, *et al*., note that if the patient has taken a massive overdose, increasing the IV NAC dose can be considered.[16]

Hemodialysis

Hemodialysis can remove acetaminophen from the blood. Hemodialysis is an extracorporeal treatment that may be used if a patient's acetaminophen level is extremely high. Hemodialysis is rarely needed since, in most cases, NAC is effective and sufficient.[6,16]

The Roles of Pharmacists and Pharmacy Technicians in Preventing Acetaminophen Overdose

Pharmacists and pharmacy technicians, especially in an outpatient setting, can play a major role in the prevention of acetaminophen overdose.[46,47] Over-the-counter medications, such as acetaminophen, can be dangerous because many individuals assume that since they can obtain it without a prescription, it is always safe or poses minimal danger. When an individual is purchasing acetaminophen, it is important to ask if they have any questions regarding the medication or dosing, and the pharmacist should screen for potential drug interactions and therapeutic duplications. A barrier for many pharmacists is that patients often do not have a complete medication list, and they are able to purchase acetaminophen over the counter anywhere, not just at the pharmacy where they fill prescriptions. It is imperative that pharmacists and technicians, upon dispensing any medication, encourage the patient to call with questions or for interaction checks upon initiation of any new OTC or prescription medication. Gilson, *et al.* (2020) found a potential benefit when providing over-the-counter drugs, such as acetaminophen, when a pharmacy used a "Senior Section" that provided specific help and information to older patients.[47]

Proper dose dispensing tools (such as oral syringes) should also be distributed to the patient to aid in the administration of liquid formulations of medications. Some caregivers find it helpful if the pharmacist marks a dose on the syringe for products they will be using. If a dose mark is made, the product name should also be written on the oral syringe, as well as the dose intended to be given. Phone calls about acetaminophen dosing are commonly made to outpatient pharmacies and should be given the proper attention.

All pharmacies should have the Poison Control phone number for their state readily available as a resource. The national phone number is 1-800-222-1222, and is available 24/7; however, the Poison Control Centers website provides more detailed contact information.[45] Poison control phones are staffed by pharmacists, physicians, nurses, and poison information providers, who are toxicology specialists.[45]

Summary

Acetaminophen is one of the most commonly taken drugs when a person intends to cause self-harm. Therapeutic errors with acetaminophen are very common as well, and intentional or accidental acetaminophen overdose is the most common cause of acute liver failure. If acetaminophen is ingested in massive amounts, the onset of acidosis, coma, and organ damage (particularly hepatotoxicity) is possible.

In order to determine if a patient has taken a toxic dose of acetaminophen, the healthcare team needs to know how much acetaminophen has been ingested, the time taken, and the patient will need to receive a complete physical assessment and laboratory tests, that include a serum acetaminophen level. It is helpful to know how long the patient has been taking acetaminophen, the dose of acetaminophen taken, and of any existing risk factors. The use of the Rumack-Matthew nomogram is useful to clinicians in determining whether acetaminophen ingestion is likely to be toxic or non-toxic and whether NAC will need to be used.

The mainstay treatment for acetaminophen overdose is N-acetylcysteine, which is highly effective when given within 8-10 hours of ingestion. If given after that time, its efficacy is reduced. N-acetylcysteine can be given orally or intravenously. If patients are treated promptly and correctly, survival is virtually assured, and permanent liver damage will likely be avoided. Patients who present late or have taken a massive ingestion lead to poor outcomes, liver failure, and death. Antidotal therapy should still be used in these situations, but liver transplantation may be necessary.

Acetaminophen toxicity continues to be the most common cause of acute hepatic failure and is the second most common cause of liver failure requiring transplantation. Prompt physical assessment and standard treatment need to be initiated in order for clinicians to effectively identify patients at risk for liver damage from acute acetaminophen overdose.

Course Test

1. **Acetaminophen is metabolized and converted to a toxic metabolite by**

    a. conjugation.
    b. CYP2E1.
    c. inhibiting the synthesis of prostaglandins.
    d. absorption.

2. **The maximum recommended daily dose of acetaminophen for adults is**

    a. 4000 mg
    b. 6000 mg
    c. 7500 mg
    d. 10,000 mg

3. **When acetaminophen is taken in toxic doses, the amount of N-acetyl-benzoquinone imine (NAPQI) the toxic dose produces will deplete the liver's production and storage of**

    a. cytochrome P-450 enzymes.
    b. eicosanoids.
    c. glutathione.
    d. arachidonic acid.

4. **A massive overdose of acetaminophen can cause a rapid onset of**

    a. metabolic acidosis and coma.
    b. splenitis.
    c. hypertension.
    d. glutathione production and hepatic encephalopathy.

5. **In patients with suspected acetaminophen poisoning, a serum acetaminophen level must be measured**

    a. immediately after ingestion.
    b. ≥ 4 hours after ingestion.
    c. 2 hours after ingestion.
    d. one hour after ingestion.

6. The antidotal therapy for acetaminophen poisoning is

a. glucagon.
b. methylene blue.
c. sodium thiosulfate.
d. N-acetylcysteine (NAC).

7. N-acetylcysteine (NAC) treatment for a patient with acetaminophen poisoning should be continued

a. until there is no measurable acetaminophen and the patient's clinical status and laboratory test values are improving.
b. until the three-bag NAC protocol has been reached.
c. only if it is effective, otherwise, alternative treatments, such as activated charcoal, should be used.
d. until the maximum, combined dose of 5,000 mg is reached.

8. Drug interaction between acetaminophen and carbamazepine may result in _____ metabolism of acetaminophen.

a. an increased
b. blocking the
c. delayed
d. a decreased

9. Acetaminophen is contraindicated if a patient

a. consumes any amount of alcohol.
b. is pregnant.
c. has severe hepatic impairment.
d. All of the above

10. A patient who has been prescribed emergency administration of N-acetylcysteine (NAC) but who does not have a functioning gastrointestinal tract would benefit most from

a. a liquid form of NAC.
b. intravenous NAC.
c. oral NAC, crushed.
d. sublingual NAC.

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