ACETAMINOPHEN POISONING: A COMPREHENSIVE REVIEW

INTRODUCTION

The American Association of Poison Control Centers publishes annual reports documenting the number and nature of drug overdoses. The data from 2008 (the latest available data) was in similar to the data from almost every previous year: the most common drug taken in an overdose a) with intent to cause self-harm, or b) because of errors in dosing was acetaminophen.\(^1\) Acetaminophen (the drug is called paracetamol in Europe) overdose is now the most common cause of acute liver failure in the United States.\(^2\) The majority of patients who have taken an overdose of acetaminophen will survive: in more than 90% of these cases, the patients will recover completely.\(^3\) However, the mortality rates for patients with acute liver failure caused by acetaminophen overdose can be as high as 28%.\(^4\)

OBJECTIVES

When the student has finished this module, he/she will be able to:

1. Identify the toxic dose of acetaminophen.
2. Identify the toxic effect of acetaminophen overdose.
3. Identify the toxic metabolite of acetaminophen.
4. Identify the basic process by which the toxic metabolite is formed.
5. Identify one organ other than the liver that can affected by an overdose of acetaminophen.
6. Identify the signs and symptoms of Phase I of an acetaminophen overdose.
7. Identify the signs and symptoms of Phase II of an acetaminophen overdose.
8. Identify two laboratory values that may be abnormal after an acetaminophen overdose.
9. Identify the four criteria used to assess a patient who has ingested a toxic amount of acetaminophen.
10. Identify the decontamination technique that can be used for patients who have ingested a toxic amount of acetaminophen.
11. Identify the antidote that is used to treat cases of acetaminophen poisoning.
12. Identify the oral dosing regimen for the antidote.
13. Identify the IV dosing regimen for the antidote.
14. Identify the criteria used to determine which patients are candidates for transplantation.
15. Identify the limitations of using the Rumack-Matthews nomogram.
16. Identify common adverse effects of oral N-acetylcysteine.
17. Identify common adverse effects of IV N-acetylcysteine.
18. Identify the primary mechanism by which N-acetylcysteine prevents liver damage.
19. Identify the proper timing for obtaining acetaminophen levels after ingestion of an extended release acetaminophen product.
20. Identify the time period during which N-acetylcysteine is most effective.
ACETAMINOPHEN: PHARMACOLOGY

Acetaminophen (Note: the name acetaminophen, and the brand name Tylenol®, are both derived from combinations of the letters of the chemical term for acetaminophen, N-acetyl-p-aminophenol) is an over-the-counter analgesic used for mild to moderate pain and as antipyretic: it appears to have minimal anti-inflammatory action. Although it is not completely understood how acetaminophen works, it is thought to produce its analgesic/antipyretic effects by these mechanisms of action:⁵

- It inhibits synthesis of prostaglandins in the central nervous system.
- It blocks pain impulse generation peripherally.
- It acts as an antipyretic by inhibiting the heat-regulating center of the hypothalamus.

Learning Break: Prostaglandins are hormone-like substances that are involved in sensitizing some neurons to pain and mediating many physiological functions, e.g., the inflammatory response.

In therapeutic doses, the drug is rapidly and completely absorbed from the gastrointestinal tract. The serum concentration peaks within two hours, and the therapeutic serum concentration is 10 to 20 µg/ml.⁶ First pass metabolism removes approximately 25% of a therapeutic dose.

After absorption, approximately 90% of acetaminophen undergoes hepatic glucuronide and sulfate conjugation (Note: This is a process by which the acetaminophen is bound to glucuronic acid and sulfate); the acetaminophen/sulfate and acetaminophen/glucuronic acid complexes are harmless and are eliminated in the urine. A very small amount of the drug is excreted unchanged in the urine, and the remainder (approximately 2% or less) is metabolized by several enzymes of the cytochrome P450 enzyme system to N-acetylbenzoquinoneimine (NAPQI). This metabolite is toxic. However, if acetaminophen is ingested in therapeutic doses, NAAPQI is combined with glutathione and the NAPQI-glutathione complex is converted to non-toxic mercaptine or cysteine, both of which are excreted in the urine and bile.⁷

Learning Break: Glutathione (also known as GSH) is a tripeptide synthesized in the liver and in other organs. It acts an antioxidant and it is a very important part of the body’s defense system against free radicals and oxidative stress.

ACETAMINOPHEN TOXICITY

The toxic dose of acetaminophen is generally considered to be = 150 mg/kg or = 7.5 grams, whichever is lower.⁸ These figures are almost certainly very conservative and the toxic dose may be 10 to 12 grams in an adult and > 250 mg/kg in children.⁹,¹⁰ However, = 150 mg/kg or = 7.5 grams have become the accepted norms.

Learning Break: Children under the age of five appear to less at risk for acetaminophen-induced liver damage after an overdose. This may be because the pediatric liver
metabolizes a greater percentage of ingested dose by sulfation, these children have greater glutathione stores, a smaller liver, or more efficient detoxification of the toxic metabolite.

When taken in therapeutic amounts, the pathways of glucuronidation and sulfation effectively metabolize most acetaminophen. Also, there is enough glutathione available in the liver to effectively bind and neutralize the NAPQI. But when acetaminophen is taken in toxic amounts, the conjugation pathways become saturated, and a larger amount of the ingested dose is metabolized to NAPQI. The rate of formation of NAPQI and the amount of NAPQI produced depletes the liver’s glutathione stores and its ability to make more glutathione. When hepatic glutathione stores have been depleted to approximately 70% of pre-exposure levels – which usually takes about 8 hours – NAPQI covalently binds to hepatocytes and causes liver damage. This is the commonly accepted theory for why acetaminophen damages the liver. However, there is some evidence that covalent binding may not completely explain acetaminophen-induced liver damage and other mechanisms of toxicity have been proposed.

**Learning Break:** Acetaminophen poisoning occurs when the rate of formation of NAPQI and the amount of NAPQI formed is greater than the amount of glutathione available and the ability of the liver to produce glutathione. *That is the basis of acetaminophen poisoning.*

**PATHOPHYSIOLOGY**

Acetaminophen when taken in toxic amounts covalently binds to hepatocytes and causes hepatotoxicity (centrilobular necrosis) by these three mechanisms:

- Toxic metabolite: NAPQI is a toxic metabolite. It binds directly to liver cells and by a complicated process that is not completely understood, causes cell damage and death.
- Mitochondrial dysfunction: There is some evidence that NAPQI directly injures mitochondria of hepatocytes.
- Immune system dysfunction: It is possible that the liver damage caused by an acetaminophen overdose alters the immune function of the liver and produce an immune response that may cause harm. Over-activity of activated natural killer cells and natural killer thymus lymphocytes can actually worsen the damage.
- Oxidative stress: In experimental acetaminophen overdose, various species of reactive oxygen species are produced, but it is not clear what role they have in causing liver damage.
SIGNS AND SYMPTOMS OF ACETAMINOPHEN OVERDOSE

Hepatic Damage

The clinical presentation of acetaminophen poisoning has traditionally been described as having four phases. There can be some individual variation in the presentation, but in most cases, these four phases are easily identifiable and follow each other quite predictably.

- **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 will be no laboratory evidence of liver damage.

- **Phase II:** This phase occurs from 24 hours to 72 hours post-ingestion. The gastrointestinal signs and symptoms typically diminish or disappear, but some patients develop pain in right upper quadrant. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) begin to rise above normal levels; levels at or above 10,000 IU/L are not uncommon (together the AST and ALT are commonly called liver function tests or LFTs). The international normalized ratio (INR), and prothrombin time (PT) will also begin to rise above normal levels. Occasionally, serum blood urea nitrogen (BUN) and creatinine will become elevated, as well.

**Learning Break:** AST and ALT are enzymes contained in hepatocytes. If the AST and ALT are elevated, that indicates liver damage. The INR is a measure of the liver’s ability to produce clotting factors; the INR provides information about the liver’s functional ability.

- **Phase III:** This phase develops from 72 hours to 96 hours post-ingestion, and it is characterized by recovery or progression to liver failure. Some patients have a mild to moderate degree of liver damage, but this resolves. Other patients develop fulminant hepatic failure and either recover or succumb. Patients with fulminant hepatic failure may develop metabolic acidosis, ARDS, coagulopathies, coma, hypoglycemia, cerebral edema, and (possibly) renal failure.

- **Phase IV:** This phase is from 96 hours post-ingestion to approximately two weeks post-ingestion, and is characterized by return of liver function. Patients who have survived Phase III, hepatic damage and function are completely healed.

**Learning Break:** If the patient has ingested a massive amount of acetaminophen, he/she may not present with the normal progression through the phases. These patients will rapidly become comatose and acidotic, and survival is unlikely.
Renal Damage

Acute renal failure happens in approximately 1% to 2% of all cases of acetaminophen poisoning. The renal parenchyma may form NAPQI, but it is not clear if this explains renal damage in these cases. Renal failure following an acetaminophen overdose can occur without evidence of fulminant hepatic failure, but this is even more unusual. It does not appear that there is a reliable way to predict which patients with acetaminophen overdose will develop renal failure. The onset of renal failure begins after evidence of liver damage and liver failure; peak serum creatinine levels may not be seen until four to five days after the ingestion.

Other Organ Damage

There have been rare, sporadic instances of other organ systems besides hepatic and renal being damaged by acetaminophen overdose. Cardiac damage and pancreatitis have been reported, but not as isolated problems directly related to acetaminophen. The patient with cardiac or pancreatic damage after an acetaminophen overdose is either suffering from multi-system organ failure or has preexisting medical problems.

RISK FACTORS FOR ACETAMINOPHEN POISONING

Acetaminophen poisoning essentially represents a balance between the amount of NAPQI formed and the rate at which it is formed, and the amount of glutathione available and the ability of the liver to produce more. The major toxic effect of acetaminophen poisoning is liver damage and damage to the liver’s functional capacity. Theoretically, anything that a) increases the amount, or rate of NAPQI formation, b) decreases the amount and rate of glutathione formation, or c) predisposes the liver to injury might increase the risks of liver damage when acetaminophen is taken in a toxic amount. Some researchers have speculated that there are risk factors that do that. Likely suspects include liver disease (e.g. hepatitis C), chronic alcohol abuse or acute alcohol intoxication, concurrent use of certain medication such as antiepileptics or antituberculur drugs (some of these drugs increase the activity of the cytochrome P450 enzyme that produces NAPQI), cigarette smoking, genetic polymorphisms in drug metabolizing enzymes, age, and poor nutrition status (decreased glutathione stores).

However, at this point there is no definitive evidence that most of these purported risk factors would increase an individual’s susceptibility to liver damage after an acetaminophen overdose. The strongest evidence for such an effect is for hepatitis C. The role of alcohol as a risk factor is unclear. Acute ingestion of alcohol may actually have a protective effect; ethanol competes with the cytochrome P450 enzyme that produces NAPQI. Chronic alcohol ingestion decreases glutathione stores and increases the activity of that specific cytochrome P450 enzyme, but people who chronically ingest alcohol do not seem to have an increased risk of liver damage and liver failure after acetaminophen overdose. Yet there is also some evidence that it is the pattern of use that can make alcohol ingestion risky in these situations. People who chronically abuse alcohol may not be more susceptible to liver injury after an acute
overdose of acetaminophen, but may be at a higher risk if they are chronically taking larger than therapeutic doses.

At this time, there is no answer, and the FDA is still examining the issue. And in some ways, the question is moot. If chronic alcohol ingestion or any of these other factors increase the risk of liver damage and liver failure after acetaminophen overdose, this risk can be effectively dealt with by prompt antidotal therapy, and no one has yet developed new criteria for assessing risk in this patient population or new treatment protocols for them.

TREATING THE PATIENT WHO HAS TAKEN AN OVERDOSE OF ACETAMINOPHEN

Deciding Which Patients Are At Risk

Unlike many drugs and toxins, there is an easily available and highly effective antidote that can be used to treat cases of acetaminophen poisoning. Although administering the antidote – N-acetylcysteine – many, many hours after the ingestion may be helpful, N-acetylcysteine (NAC) is most effective if it is given 8 to 10 hours after the ingestion. So, when you are considering whether or not to use the antidote, it is crucial to make the correct decision.

In order to make that decision, you need four pieces of information. You need, a) to know how much acetaminophen was ingested, b) to know the serum acetaminophen level, c) to know if there is laboratory evidence of liver damage, and d) to examine the patient for signs and symptoms of liver damage. This sounds very simple – and it can be – but there are times in which this information is ambiguous or cannot be obtained.

- **Dose**: The toxic dose of acetaminophen is considered to be = 7.5 grams or = 150 mg/kg. If you are considering the ingested dose, making the decision as to whether or not to treat a patient who has taken an excess of acetaminophen should be easy; if the amount ingested was = 7.5 grams or 150 mg/kg, the patient should receive NAC.. Unfortunately, many patients cannot or do not provide accurate information about the amount of drug ingested. The staff treating the patient should try and use all their resources to determine what the ingested dose was, but in many cases involving an attempt at self-harm, this can’t be done.

Learning Break: Chronic acetaminophen ingestions will be discussed, but an acute ingestion is one in which the total amount of acetaminophen is ingested in a four hour (or less) period of time. **If the ingestion occurred over a period of time Greater than four hours it should be considered a chronic exposure.**

- **Signs and Symptoms**: There are signs and symptoms of liver damage caused by acetaminophen that are commonly observed. But these signs and symptoms are to some extent subjective, they are non-specific, and they may be absent or greatly diminished 24 hours or so after the ingestion. Also, although not common, it is possible for the signs and symptoms to be absent and there is no laboratory
evidence of liver damage – yet. Because it is important to treat a patient with an acetaminophen overdoses within 8 to 10 hours after the ingestion, these signs and symptoms are often unreliable or not useful in making a treatment decision.

- **Laboratory:** Elevations of the AST, ALT, and INR certainly can confirm that the patient has taken a toxic dose of acetaminophen. AST and ALT elevations occur first (representing damage) and elevations of INR occur later (representing damage to liver function). However, these elevations occur 24 hours or so after the ingestion, and they indicate that liver damage and damage to the liver’s functional ability have already occurred. It is also possible that laboratory abnormalities could be cause by a medical problem. The goal of treating a patient with an acetaminophen overdose is to prevent harm to the liver. These laboratory studies should be obtained and if they are abnormal, a patient who has taken an overdose of acetaminophen should be treated. But waiting for evidence of damage is not optimal therapy and even if the AST, ALT, and INR are normal, it may simply indicate that liver damage has yet to occur.

**Acetaminophen level:** A serum acetaminophen level should be obtained four hours or later after the ingestion. Although in therapeutic doses absorption and peak serum level are reached within two hours, in the case of an overdose absorption can be delayed, thus the level should obtained four hours or later after ingestion. The level is then plotted on the Rumack-Matthews nomogram. The nomogram is an assessment tool that has been proven to be very effective. It was developed by examining hundreds of acetaminophen levels and AST and ALT results. The developers of the nomogram noted a trend that was very consistent. If the patient had ingested a toxic amount of acetaminophen and the time of ingestion was known with certainty, an acetaminophen level that was obtained at some point four hours or later after that ingestion time could be used to predict which patients would develop liver injury. Example: The patient reports he ingested 10 grams of acetaminophen eight hours prior to arrival; the ingestion time is confirmed by a reliable witness. The acetaminophen level is 160 µg/ml. The level is placed on the nomogram and it is clearly above the line labeled probable hepatotoxicity. The Rumack-Matthews nomogram has been proven to be highly sensitive; if used correctly it will always accurately identify patients at risk. **Only one level is needed to use the nomogram.** Subsequent levels that are lower than previous ones simply document metabolism of the drug; **there is no need to get them and they are of no clinical value.** Also, levels that are within the range of normal values should not be considered non-toxic if the time of ingestion is not known or if the level is toxic according to the nomogram. The level is toxic or non-toxic depending on when, in relation to the ingestion, the level was obtained; **the absolute value in and of itself is of no clinical importance except to confirm that acetaminophen has been ingested.** The nomogram was altered slightly after it was developed. The original line separating patients at risk from those not at risk was lowered 25% as a safety factor (per FDA request) to account for errors in laboratory reporting, etc.; the original line is still used in many other parts of the world. The nomogram will definitely identify
with unerring accuracy which patients will develop liver damage, but it does not predict which patients will develop liver failure or which patients will die.

Learning Break: The acetaminophen level can only be interpreted with the Rumack-Matthews nomogram if the time of ingestion is known with certainty and the level was obtained at a point four hours or later after the ingestion. **If the time of ingestion is not known with certainty or if the level is obtained at less than four hours post-ingestion, the nomogram cannot be used to interpret the level as toxic or non-toxic.**

Learning Break: Children under the age of five may be less susceptible to liver damage if an excess amount of acetaminophen is ingested, but use the same standards outlined above to assess their risk.

Of course, there will be many instances in which the information needed to make a treatment decision will be unobtainable, ambiguous, or can’t be interpreted. Example: The level will be undetectable, but the patient will have nausea and vomiting, the patient reports (but it can’t be confirmed) that she ingested 15 grams of acetaminophen but she cannot remember when she did so, and the AST/ALT are slightly elevated, but there are no medical records available so you can’t determine if these abnormal laboratory values are new or old. Making the decision to administer/not administer NAC can be tricky. The best course of action is to realize that these situations are common, consider the situation as a whole, and err on the side of caution because NAC is highly effective and very safe. The alternative could be liver failure and death. **N-acetylcysteine should be given if:**

- The acetaminophen level is above the treatment line on the Rumack-Matthews nomogram.
- If it has been confirmed that the patient has taken a toxic amount of acetaminophen.
- If it is suspected or reported that the patient has taken a toxic amount of acetaminophen and there is a measurable acetaminophen level.
- If there is a measurable acetaminophen level but the time of ingestion is not known.
- If it is suspected or reported that the patient has taken a toxic amount of acetaminophen and there is laboratory evidence of liver damage.
- If the patient has been chronically ingesting toxic or supratherapeutic amounts of acetaminophen and there is a measurable acetaminophen level and/or laboratory evidence of liver damage.

Learning Break: There are extended release acetaminophen products. If the patient has ingested an extended release acetaminophen product (e.g., Tylenol Extended Relief®), obtain an acetaminophen level at four hours after the ingestion. Obtain another acetaminophen level four to six hours later. If either level is above the treatment line, the patient is at risk and should receive antidotal therapy. If neither level is above the treatment line, the patient doesn’t need antidotal therapy.
Initial Care

Assess the airway, breathing, and circulation (ABCs). If there are significant derangements in the ABCs, it is possible, but not very likely that these changes are due to an acetaminophen overdose. As mentioned previously, a massive amount of acetaminophen can cause coma and metabolic acidosis shortly after the ingestion, but this rarely happens. Look elsewhere if the patient with a reported/alleged acetaminophen overdose is hypotensive, unresponsive, etc., but don’t forget that you could be dealing with an overdose of several medications. You must still assess the patient for the presence of an acetaminophen overdose.

If the patient has normal, stable ABCs, if the patient is awake and alert, if the patient has a normal gag reflex, if there is no co-ingestant that may could a rapid depression in consciousness, and the patient arrives at the hospital within one hour of the ingestion, administer a single dose of activated charcoal. Activated charcoal binds avidly to acetaminophen and if it is given within that one hour time period, it may prevent a toxic amount of acetaminophen from being absorbed and converted to NAPQI. Ipecac should never be given and lavage should not be performed. Acetaminophen can be removed by hemodialysis. Using hemodialysis could be considered if the patient’s acetaminophen level is extremely high. However, such a circumstance would be extremely rare, and as the antidote is safe and easy to administer, extracorporeal removal should not be done.

Learning Break: Activated charcoal will bind to oral NAC. However, it is uncommon to need to give activated charcoal and NAC at the same time, and even if it were required to do so, the binding of NAC to charcoal is not considered important. If there was a need to give activated charcoal and NAC together or in close proximity, there would be no need to increase the dose of NAC.

Perform a physical exam. Pay particular attention to the abdominal area. Ask the patient how much acetaminophen was ingested, what dosage form was ingested (e.g., extra strength, sustained release), when the drug was ingested and over what period of time, and determine if this was the only ingestion or if the patient taken any acetaminophen in the hours and days prior to the current ingestion.

Obtain a serum acetaminophen level. This should be obtained four hours or later from the time of ingestion, but if this time is not known, obtain a level immediately, then another level in four hours. Obtain a serum salicylate level; patients occasionally confuse aspirin and acetaminophen and may use the terms interchangeably. Obtain an INR, LFTS, BUN, and creatinine. Once the acetaminophen level is known, it can be plotted on the nomogram and if the time of ingestion is known, the decision to use/not use NAC can be made.

Antidotal Therapy: N-acetylcysteine

Acetaminophen poisoning results from a balance: a toxic metabolite is formed and the body tries to render this metabolite harmless. At the present time, there are no proven ways to limit absorption of acetaminophen aside from timely administration of activated
charcoal. There are no proven ways to increase the conjugation of acetaminophen to glucuronide or sulfate, and there are no proven ways to decrease the metabolism of acetaminophen to NAPQI. The only proven therapy is NAC, and NAC can prevent liver damage and liver failure caused by an overdose of acetaminophen by increasing the body’s ability to detoxify NAPQI.

There are several ways in which NAC works. Glutathione is synthesized in the liver from the amino acids cysteine, glutamate, and glycine. There is a limited amount of cysteine available in the liver, and NAC provides a source of cysteine so more glutathione can be synthesized. This increased synthesis of glutathione appears to be the primary therapeutic action of NAC. NAC may also work by reversing NAPQI back to acetaminophen, binding directly to NAQI, increasing the amount of ingested acetaminophen that is conjugated to sulfate, changing and ameliorating the course of liver damage once NAPQI binds to hepatocytes (e.g., by increasing hepatic oxygen delivery, acting as an anti-inflammatory and antioxidant agent), and increasing hepatic blood flow.

Learning Break: N-acetylcysteine has two important functions: it prevents liver damage and treats liver damage after the damage has begun.

N-acetylcysteine is very effective. If it is given soon after the ingestion, there is almost no risk that a patient will develop hepatic failure; there may be liver damage, but this will resolve and the patient will recover. Less than 1% of patients who take an overdose of acetaminophen and who are treated promptly with NAC will die. N-acetylcysteine given from 0 to 8 hours post-ingestion of acetaminophen is equally effective. There is evidence that NAC given outside of this time period and even many hours after an ingestion of acetaminophen may be helpful, and it is recommended that NAC be given in these situations.

N-acetylcysteine can be given orally or IV; the IV form is Acetadote. Although there have not been any direct comparisons between oral and IV NAC, it appears that they are equally effective.

- Oral NAC: The patient is given a loading dose of 140 mg/kg. Seventeen doses of 70 mg/kg are then given, one dose every four hours. If the patient vomits within an hour of administration of dose, repeat the dose. The AST, ALT, INR, BUN, and creatinine should be checked every day. Nausea and vomiting are very common side effects. The NAC should be diluted with juice or soda, served cold in a cup with a lid (the odor of NAC is noxious) and sipped slowly. It can also be given through a nasogastric tube. Pre-treatment with an anti-emetic may also be helpful: ondansetron or metoclopramide are more effective than traditional anti-emetics such as prochlorperazine. Contradictions to using NAC include sensitivity to NAC, the inability to use the gut, or persistent vomiting.

- IV NAC: The patient (if he/she is > 40 kg in bodyweight) is given a loading dose of 150 mg/kg of Acetadote® in 200 ml of 5% dextrose; this is given over 60 minutes. This is followed by a dose of 50 mg/kg in 500 ml of 5% dextrose; this is given over four hours. The final dose is 100 mg/kg in 1000 ml of 5% dextrose;
this is given over 16 hours. If the patient’s bodyweight is > 100 kg, the maximum
dose that should be given is 15 grams, 5 grams, and 10 grams, respectively,
regardless of the bodyweight. Adverse reactions to IV NAC are common (66.4% in
one study) but easily managed. These reactions usually occur during the
loading dose and are anaphylactoid; the patients have wheezing, urticaria, rash,
pruritus, flushing, nausea, and vomiting. Serious reactions such as bronchospasm, dyspnea, and hypotension are uncommon. Two hours prior to
the end of the 16 hour infusion, an acetaminophen level, AST, ALT, and INR
should be obtained. If there is a measurable acetaminophen level, or abnormal
LFTs or INR, it may be advisable to administer more IV NAC. (Note: There is a
website sponsored by the company that manufactures Acetadote®,
www.acetadote.net, that has a dosing calculator and a lot of useful information
about the drug.)

Learning Break: You may find older references that recommend infusing the loading
dose of Acetadote® over 15 minutes. This was the original protocol, but it was soon
discovered that the incidence of anaphylactoid reactions was unacceptably high and if the
loading dose was infused within 60 minutes, adverse reactions were far less common.

Learning Break: No one knows what the optimum treatment is for patients who have
received the entire oral or IV course of NAC and have evidence of liver damage or
measurable acetaminophen. It has generally been thought that NAC can be discontinued
when there is evidence that the liver is recovering, but there is no agreed upon definition
of that term.

CHRONIC INGESTIONS OF ACETAMINOPHEN OR LATE PRESENTATIONS

A chronic ingestion of acetaminophen presents problems in assessing risk. The
Rumack-Matthews nomogram can’t be used. There is less information about what is/what
is not a toxic dose. However, if the patient has been chronically ingesting acetaminophen,
the following treatment protocol can be used:

- Assess for risk of toxicity: Check the patients for clinical evidence of liver
damage. Was it is = 7.5 grams or = 150 mg/kg over a 24 hour period?
- Check the acetaminophen level.
- Check AST, ALT, INR, BUN, and creatinine.
- If the patient a) has signs/symptoms of liver damage, b) ingested a toxic amount,
c) has a measurable acetaminophen level, or d) has abnormal laboratory values,
the patient should be considered at risk and treated with NAC.
- Even within those criteria there are sub-groups. If the patient reportedly ingested a
toxic amount of acetaminophen, but the physical exam is unremarkable, the
acetaminophen level is zero, and the laboratory values are normal, the patient would not be considered at risk.

It is not uncommon for patients to present many hours or many days after an acetaminophen ingestion, and/or after the process of liver damage has already begun. The optimal time for administering NAC is 0-8 hours after an ingestion, and NAC is essentially given to prevent liver damage. However there is evidence that NAC can be effective even if it is given many hours or days after an acetaminophen ingestion, and giving NAC in these situations is commonly done.

**LIVER FAILURE AND TRANSPLANTATION**

Acute liver failure leads to sepsis, hypoglycemia, metabolic acidosis, encephalopathy, coagulopathies, and coma. Transplantation can be the only effective therapy in certain cases of acute liver failure. However, some patients will recover and transplantation has many risks, so it is very important to know which patients will and which patients will not, need a transplant.

Currently, the King’s College Hospital Criteria are used to make this decision. These criteria are not perfect. Some authorities have suggested they could be improved, but at they are the standard. According to the criteria, a patient should be considered a candidate for transplantation if:

- Serum pH is < 7.30 despite fluid resuscitation.
- The prothrombin time is > 100 seconds.
- The serum creatinine is > 3.3 mg/dL.

**PREGNANCY AND ACETMINOPHEN OVERDOSE**

Overdose with acetaminophen by pregnant women has been associated with spontaneous abortion and fetal death. Acetaminophen does cross the placenta and reaches the fetus, and there is evidence that the fetal liver can synthesize a toxic metabolite and the fetal liver can be injured. The majority of cases of acetaminophen overdose by pregnant women have had good outcomes, but if it is known or suspected that pregnant woman has taken an overdose of acetaminophen, she should be treated with NAC. If there are signs of fetal distress and the mother has evidence of severe hepatotoxicity, emergency delivery is indicated.

**HOW SAFE IS ACETAMINOPHEN WHEN TAKN IN THERPAEUTIC DOSES?**

In response to concerns about the safety of acetaminophen, the FDA has recently mandated new packaging requirements, and the agency is considering decreasing the 24 hour dosing limit from 4 grams (the current standard) to 3250 mg, and is considering
making changes in other dosing forms and labeling, as well. What prompted these actions and concerns?

One reason is that nearly half of all acetaminophen overdoses are unintentional, and many of these occur because consumers were not aware a product had acetaminophen in it. The FDA is hoping that with better labeling, fewer combination products, and decreasing the maximum available OTC dose, many of these cases can be prevented. Another issue is that the current maximum recommended dose of 4 grams may be far too much for people with liver disease, a history of alcohol abuse, malnutrition, or other risk factors, but this information is not disseminated widely enough or well understood by consumers. Also, because it is impossible to determine the number of people who might fit in one or more of these categories (but the number can be presumed to be fairly large), and because many people with one or more of these risk factors may not be aware that they have them or not be followed by a physician, the FDA feels the potential for large numbers of people to suffer liver damage with the current maximum dose is unacceptable. Whether the dosing limits will be changed is not certain yet, but it does seem as if in many circumstances, the old dosing recommendations should be re-evaluated
REFERENCES


