Analgesic Overdose

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Faculty

Dana Bartlett, RN, BSN, MSN, MA, CSPI, is a Certified Specialist in Poison Information. He worked at the Poison Control Center in Philadelphia as a hotline operator from 1993 until 2011. From 2011 to the present, he has been working as a hotline operator at the Connecticut Poison Control Center. Mr. Bartlett received his BSN from the University of Massachusetts, Amherst, in 1976; his MSN from Boston University in 1978; and his MA in journalism from Temple University in 1988. His clinical experience includes 6 years as an ICU nurse and 10 years as an ER nurse. He has authored more than 100 continuing education modules for RNs and allied health personnel, and he has been published in Nursing Magazine, OR Nurse, Journal of Emergency Nursing, Legal Nurse Consultant, American Nurse Today, Journal of Emergency Services, and Orthopedics Today. He has also authored textbook chapters and NCLEX material and has edited and reviewed for several major publishers.

Faculty Disclosure

Contributing faculty, Dana Bartlett, RN, BSN, MSN, MA, CSPI, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner

Jane C. Norman, RN, MSN, CNE, PhD

Director of Development and Academic Affairs

Sarah Campbell

Division Planner/Director Disclosure

The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for nurses who will be caring for patients who have taken an overdose of acetaminophen, aspirin, or ibuprofen.

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Course Objective

The purpose of this course is to provide nurses with the information necessary to identify and treat analgesic overdoses in order to prevent unnecessary sequelae.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the pathophysiology of acetaminophen poisoning.
2. Identify the toxic dose of acetaminophen and components of the assessment of patients with suspected overdose.
3. Evaluate approaches available for the treatment of acetaminophen poisoning.
4. Outline the initial assessment and care of a patient who has taken an overdose of aspirin.
5. Discuss antidotal therapies and specific interventions used for the treatment of aspirin poisoning.
6. Cite the toxic dose of ibuprofen and signs and symptoms of ibuprofen overdose.
7. Describe the treatment of a patient who has taken an overdose of ibuprofen.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Over-the-counter analgesics acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen are very popular. Unfortunately, they are also the cause of thousands of intentional and unintentional overdoses each year. Because they are inexpensive and widely available, these agents are often used with the intent to cause self-harm. With the proper treatment, patients who have taken a toxic amount of one of these medications should recover without sequelae, and the treatment of deliberate overdoses of acetaminophen, aspirin, and the other NSAIDs is not complicated. However, poison center experience indicates a knowledge gap in what many nurses know and what they need to know to deliver good care in these situations. These knowledge gaps can and do cause errors in treatment, some minor and some serious.

This course will provide nurses with comprehensive and up-to-date information about acetaminophen, aspirin, and NSAID poisoning. Assessment and treatment will be thoroughly explained, and common management errors (what they are and how to avoid them) will be discussed. This knowledge will allow nurses to provide the best possible care in cases of analgesic overdose, improving patient outcomes and avoiding potentially damaging long-term effects.

ACETAMINOPHEN POISONING

Acetaminophen is a very popular over-the-counter analgesic and is widely used as an antipyretic as well. It is a common choice for people who take an overdose of medication with the intent to cause self-harm, and serious therapeutic errors are also common. In normal doses, acetaminophen is quite safe. However, when a toxic amount of the drug is taken, severe liver damage and death are possible. Acetaminophen is the leading cause of acute liver failure, and unintentional overdose with acetaminophen is the leading cause of acute liver failure in the United States [1; 2].

PHARMACOLOGY OF ACETAMINOPHEN

The mechanisms of action of acetaminophen are not clearly understood, but its analgesic action is thought to be the result of inhibition of prostaglandin synthesis in the central nervous system (CNS) and blocking pain impulse generation from peripheral pain receptors. Acetaminophen also has antipyretic properties caused by inhibition of the heat regulating center of the hypothalamus. Acetaminophen is not an anti-inflammatory.

In therapeutic doses, the drug is rapidly and completely absorbed from the gastrointestinal tract. The peak serum concentration is seen in approximately 10 to 60 minutes, and the therapeutic serum concentration is 10–20 mcg/mL [3]. The onset of action is within approximately one hour of ingestion, and the duration of action is four to six hours.

After absorption, approximately 90% of acetaminophen is metabolized by the liver and conjugated to glucuronide and sulfate. A very small amount of the drug is excreted unchanged in the urine, and approximately 2% or less is metabolized by cytochrome P450 enzymes to a toxic metabolite called *N*-acetyl-benzoquinoneimine (NAPQI). When acetaminophen is taken in therapeutic doses, NAPQI is conjugated with hepatic glutathione (an antioxidant tripeptide synthesized in the liver) and excreted in the urine and bile. This conjugation with glutathione prevents NAPQI from causing hepatic damage.

The adult dose of acetaminophen is 325–650 mg every four to six hours; the total amount for 24 hours should not exceed 4 grams [3; 4]. The pediatric dose for children younger than 12 years of age is 10–15 mg/kg every four to six hours; the 24-hour total should not exceed 2.6 grams. For both adults and children, dosing should be adjusted if the patient has renal impairment.

Clinicians should be aware that in 2011 the manufacturer of Tylenol products voluntarily changed the packaging information for some of their over-the-counter acetaminophen-containing products, decreasing the recommended 24-hour maximum amount of acetaminophen and decreasing dosing

intervals [5]. For example, package inserts now state the 24-hour maximum dose of acetaminophen for adults should be no more than 3,000 mg, unless otherwise instructed by a physician. Although any amount if acetaminophen may be purchased in the United States, other countries have placed limits on how much acetaminophen may be purchased in a single package [5].

Acetaminophen is available in oral tablets, caplets, capsules, and gel-tabs; oral suspensions and solutions; rectal suppositories; and an IV formulation. It is available in hundreds of over-the-counter preparations, typically in cough and cold formulations, and in combination with prescription analgesics like codeine and oxycodone. The range of available doses is from 80 mg/0.8 mL in infant drops to extended-release acetaminophen doses of 650 mg per unit.

Acetaminophen is contraindicated in patients with hypersensitivity to the drug or with severe hepatic impairment or severe active liver disease. It should be used cautiously in patients with G6PD deficiency, alcoholic liver disease, or renal impairment or who consume three or more alcoholic drinks per day [4]. The oral form of acetaminophen is considered safe to use during pregnancy, but intravenous acetaminophen is classified as category C if used during pregnancy. Acetaminophen does enter breast milk; the drug should be used cautiously by nursing mothers, but serious adverse effects have not been reported, and it is typically considered safe for a nursing infant [6; 7].

The side effects of acetaminophen are minimal, most commonly mild gastrointestinal distress and rash (in children). Potential drug interactions between acetaminophen and other commonly used medications include [4]:

- Barbiturates: The metabolism of acetaminophen may be increased, decreasing the effectiveness of acetaminophen and increasing the risk of liver damage. Risk category C.
- Carbamazepine: The metabolism of acetaminophen may be increased, decreasing the effectiveness of acetaminophen and increasing the risk of liver damage. Risk category C.
- Isoniazid: May enhance the adverse/toxic effects of acetaminophen. Risk category C.
- Lamotrigine: Acetaminophen may decrease the serum concentration of lamotrigine. Risk category C.
- Prilocaine: Acetaminophen and prilocaine used together increase the risk of developing methemoglobinemia. Risk category C.
- Probenecid: The serum concentration of acetaminophen may be increased. Probenecid may also increase the formation of NAPQI. Risk category D (consider modifying drug therapy).
- Warfarin: Acetaminophen may enhance the anticoagulant effect of warfarin if the daily dose of acetaminophen is >1.3–2 grams for more than one week. Risk category C.

PATHOPHYSIOLOGY OF ACETAMINOPHEN POISONING

Acetaminophen toxicity represents an imbalance between how much NAPQI is formed and how much glutathione is available. When a toxic amount of acetaminophen is ingested, the glucuronide and sulfate pathways of metabolism become saturated and a larger proportion of the drug is metabolized to NAPQI. Glutathione stores in the liver are quickly diminished, and when the available amount of glutathione has been reduced to approximately 20% to 30% of the pre-exposure levels, liver damage occurs [8; 9]. NAPQI covalently binds to mitochondrial proteins in the hepatocytes, causing oxidative stress that impairs mitochondrial function and causes hepatic cell death [10]. Other organ systems can be damaged by an overdose of acetaminophen, but liver damage is the most common effect.

PATIENT ASSESSMENT

The initial assessment of a patient who has taken an overdose of acetaminophen should include: details of the ingestion; a physical exam and an assessment of the patient's subjective complaints; a serum acetaminophen level; and measurement of serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), blood urea nitrogen (BUN), serum creatinine, and international normalized ratio (INR). Other laboratory tests may be necessary, as will be discussed in detail later in this section.

Toxic Threshold

Unless it is certain that acetaminophen has not been ingested, an acetaminophen level should be measured in all patients who have taken medications with the intent or a suspected intent to cause self-harm. The toxic amount of acetaminophen for adults and children 6 years of age or older is ≥10 grams or ≥200 mg/kg, whichever is less. [11] The amount of acetaminophen that is potentially toxic for children younger than 6 years of age is ≥200 mg/kg [11].

The pediatric criteria appear to be universally accepted and used, but there is less clarity and agreement concerning what constitutes a toxic amount for adults [12]. Early research indicated that the toxic amount of acetaminophen for adults was between 15 and 16 grams [13; 14]. Poison control centers in the United States usually, but not always, use ≥200 mg/kg or ≥10 grams, whichever is less, as the standard toxic amount for adults [11]. In other areas of the world, a dose of at least 12 grams is considered a toxic amount for adults [15; 16].

Every effort should be made to determine the details of the ingestion, including the time, amount, formulation, and pattern of ingestion. It is usually unwise to depend on the patient's account of the overdose. Patients are often emotionally upset and may not remember how much was taken or when or may deliberately provide inaccurate information. It is also possible that the patient may have taken other medications and does not consider acetaminophen dangerous or worth mentioning. Unrecognized and unreported acetaminophen ingestions, some potentially dangerous, are relatively common (up to 18% of all acetaminophen overdose cases), and in the context of a deliberate overdose, a patient's reporting or not reporting of an ingestion of acetaminophen is not considered reliable [16; 17; 18; 19; 20].

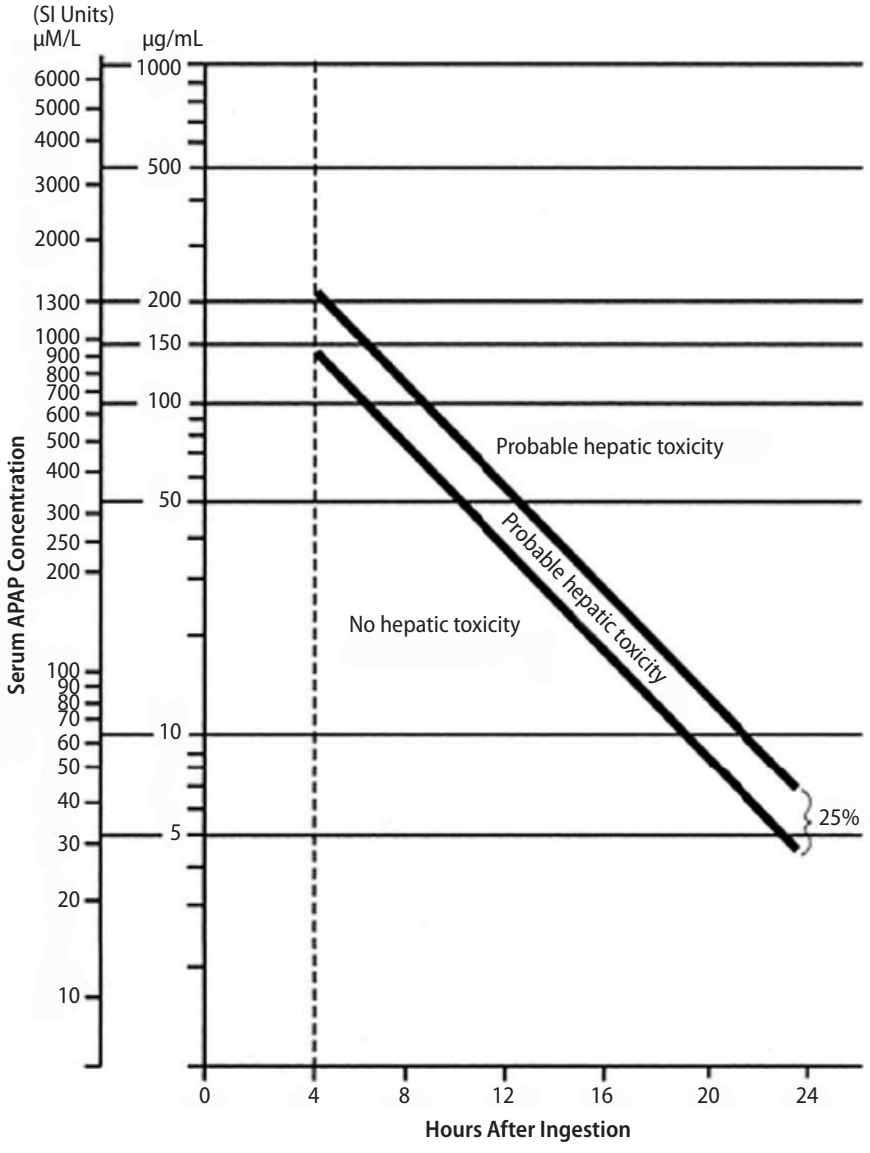
Physical Exam

The initial signs and symptoms of acetaminophen toxicity are gastrointestinal, specifically nausea and vomiting. These are usually mild in severity and will resolve within 12 hours of the ingestion. Many patients are asymptomatic. The exception to this is a massive acetaminophen overdose. Patients who take 75–100 grams of acetaminophen may quickly develop coma, metabolic acidosis, and abnormal vital signs. However, these cases are very uncommon, and unless a massive overdose was taken or a co-ingestant was involved, the patient will have normal temperature, pulse, and blood pressure and will be awake, alert, and oriented. If a patient has taken an overdose of acetaminophen and is clinically unstable, it is prudent to first determine if other medications were taken.

Serum Acetaminophen Level

A serum acetaminophen measurement should be obtained four hours or later from the time of ingestion. The level is plotted on the Rumack-Matthew nomogram (***Figure 1***), and depending on where on the nomogram the level falls, it will be considered toxic or non-toxic. Measuring the serum acetaminophen level and using the nomogram is the most reliable way of determining if a patient has ingested a toxic amount of the drug.

RUMACK-MATTHEW NOMOGRAM



Source: [19] *Figure 1*

The Rumack-Matthew treatment nomogram was developed over a period of years by several investigators, with the goal of establishing an accurate and reliable tool that could predict which patients were likely to develop hepatotoxicity after an acetaminophen overdose [21; 22; 23]. To that end, serum acetaminophen levels were measured in patients who had reportedly ingested a toxic amount of the drug. The levels were obtained at four hours or later post-ingestion, and the patients' clinical course and serum transaminases were followed until a pattern became clear. Patients with a serum acetaminophen level of 300 mg/mL or greater four hours after ingestion are at risk for probable hepatic toxicity, with

the serum threshold lowering over time. Example: Patient A and Patient B each report ingesting 12 grams of acetaminophen. The time of ingestion is certain, and the serum acetaminophen levels are done four hours from that point. Patient A's level is 250 mcg/mL, Patient B's level is 30 mcg/mL. Clinical experience using the Rumack-Matthew nomogram has shown that the first patient is very likely to develop hepatotoxicity, and the second patient clearly did not ingest 12 grams four hours before the level was measured and will not develop hepatotoxicity.

The Rumack-Matthew nomogram has been proven to be highly reliable, but it has limitations and it must be used correctly. The nomogram was developed by examining patients who had an acute overdose. If the patient has ingested acetaminophen over a period of many hours or days and the overdose is chronic in nature, the nomogram cannot be used. (Chronic ingestions will be discussed later in this course.) The nomogram extends to 24 hours post-ingestion. If the patient ingested acetaminophen more than 24 hours from the time of presentation, the nomogram cannot be used.

Hepatotoxicity is defined by the nomogram as an AST level greater than 1,000 IU/L, and the nomogram is designed to predict the likelihood that a patient with a level at a certain point on the nomogram will develop an AST level greater than 1,000 IU/L. The nomogram cannot be used to predict the risk of death, the risk of developing liver failure, or response to treatment. It is highly sensitive but not highly specific, and approximately 40% of patients who have an acetaminophen level greater than the toxic line on the nomogram will not develop hepatotoxicity in the absence of antidotal therapy [23]. However, given the uncertainties surrounding many overdose cases, the potential for serious liver damage, and the success of the nomogram, overtreatment of a certain number of patients is preferable to undertreatment.

The nomogram cannot be used to interpret a level that is measured before four hours post-ingestion [24]. This time constraint is required for two reasons. First, the peak serum level can be delayed when acetaminophen is taken in large amounts. In most cases, the peak serum level will occur within two hours of the ingestion, but it may be delayed for up to four hours. Second, the nomogram begins at four hours post-ingestion, and levels taken before this time cannot be used to determine risk [24; 25; 26].

The acetaminophen level should be interpreted using the nomogram; the level alone is not useful. Very high levels almost certainly indicate a patient is at high risk for untoward effects, but an acetaminophen level can only be determined to be toxic/non-toxic if the time of ingestion is also known.

If a patient has ingested an extended-release preparation, a level should be done at four hours post-ingestion and another level should be taken at eight hours post-ingestion. If either level is toxic, the patient should be treated. If both levels are below the toxicity line, no treatment is needed. If there is a co-ingestant that may delay gut peristalsis, it may be wise to obtain two acetaminophen levels. In these cases, consultation with a toxicologist or the local poison control center is recommended.

***Example**: A physician is caring for a patient who has reportedly ingested a toxic amount of acetaminophen, but the time of the ingestion is not known. The acetaminophen level is 18 mcg/mL. This is within the normal therapeutic range, so the physician discharges the patient. However, the "normal range" of acetaminophen (10–20 mcg/mL) is a based on a therapeutic level measured after a therapeutic dose. If the patient has taken an overdose of acetaminophen, a level of 18 mcg/mL would be considered at-risk if this level was measured 16 hours or later after the ingestion.*

Nomogram "failures" are situations in which the acetaminophen level is below the toxic line, but the patient develops liver damage. These have been reported, but they are very rare and almost certainly involve mistakes in determining the time of ingestion. The original toxic/non-toxic line on the nomogram was 300 mcg/mL. It has since been decreased to 200 mcg/mL to provide a safety factor [13; 20; 27]. As such, the nomogram is quite conservative in nature and failures when used correctly are not possible.

There are situations in which the peak serum acetaminophen level can occur later than four hours after ingestion. Antihistamines and opioids slow gut peristalsis, and there have been case reports documenting a delayed peak acetaminophen level caused by a co-ingestion of diphenhydramine or an opioid [28; 29; 30; 31; 32; 33]. Delayed peak serum levels have also been reported after massive ingestions and after taking extended-release acetaminophen products [34; 35; 36; 37; 38].

Serum Transaminases

The serum transaminases, AST and ALT, are commonly measured on liver function tests (LFTs), and these tests are the most sensitive marker of liver injury caused by acetaminophen poisoning. The AST and ALT levels typically begin to rise 24 hours after ingestion of a toxic amount of acetaminophen, but this elevation can occur as early as eight hours and as late as 36 hours post-ingestion [12; 39; 40]. AST and ALT levels greater than 10,000 IU/L following acetaminophen poisoning are not uncommon.

Therapeutic use of acetaminophen may cause mild and transitory elevations of liver transaminases. However, these doses do not cause liver damage, and when the acetaminophen therapy is stopped, the levels return to normal [41; 42].

Other Laboratory Studies

A serum salicylate level should be measured in persons with confirmed or suspected acetaminophen overdose. Some patients consider all over-the-counter analgesics to be the same and may use the terms Tylenol, aspirin, and ibuprofen interchangeably. In addition, some prescription and over-the-counter products contain both acetaminophen and aspirin.

Every patient who has intentionally taken an overdose of an over-the-counter cough and cold or allergy relief product should be assessed for acetaminophen poisoning unless the product is identified and does not contain acetaminophen.

BUN and creatinine should also be measured, as renal damage can be caused by acetaminophen poisoning. A baseline INR should be measured. Liver damage is reflected by the serum transaminases, but liver damage that causes hepatic dysfunction is reflected by the INR.

THE CLINICAL COURSE OF ACUTE ACETAMINOPHEN POISONING

The clinical presentation of acetaminophen poisoning has four phases [12; 43; 44]. The first phase occurs from 0 to 24 hours post-ingestion. Nausea, vomiting, abdominal pain, and anorexia are commonly observed, but some patients may be asymptomatic. Laboratory evidence of liver damage is possible but is not commonly seen. The patient's vital signs should be normal, and he/she should be awake, alert, and oriented.

Phase II occurs 24 hours to 72 hours post-ingestion. The gastrointestinal signs and symptoms diminish or disappear, while the AST and ALT levels begin to rise. The INR, PT, BUN, and creatinine may become elevated as well.

Phase III, which develops 72 hours to 96 hours post-ingestion, is characterized by recovery or progression to liver failure. Some patients have a mild-to-moderate degree of liver damage, which resolves, and they recover completely. Other patients develop fulminant hepatic failure and either recover or die.

Patients with fulminant hepatic failure may progress to metabolic acidosis, acute respiratory distress syndrome, coagulopathies, coma, hypoglycemia, hypotension, cerebral edema, and possibly renal failure.

From 96 hours post-ingestion to approximately two weeks post-ingestion, phase IV occurs and is characterized by return of liver function. For patients who have survived phase III, hepatic damage is repaired, and function is restored during this period.

Renal Damage

The renal parenchyma can form NAPQI, and acute renal failure occurs in approximately 1% to 10% of all cases of acetaminophen poisoning [45; 46; 47; 48]. In patients who develop severe liver damage, evidence of acute kidney injury has been seen in 53% to 80% of cases [12; 49]. Renal failure following an acetaminophen overdose may occur without evidence of liver damage or fulminant hepatic failure, but this is very unusual [50; 51; 52; 53]. There is no reliable way to predict which patients with acetaminophen overdose will develop renal failure, although children and adolescents appear to be at a higher risk [46].

The onset of renal failure usually 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 [46; 54]. Most patients have a complete recovery of renal function, but approximately 1% will require long-term hemodialysis [46].

Other Organ Damage

There have been rare, sporadic reports of other organ systems being damaged by acetaminophen overdose [55; 56; 57; 58; 59; 60; 61]. Cardiac damage and pancreatitis have been reported, but not as isolated problems directly related to acetaminophen. Some studies suggest that acetaminophen overdose may increase the risk of congestive heart failure, coronary artery disease, and pancreatitis, but further research is needed [62; 63; 64]. Patients with cardiac, pancreatic, or other organ system damage after an acetaminophen overdose are likely either experiencing multi-system organ failure from a massive overdose or an exacerbation of pre-existing medical problems.

Massive Acetaminophen Overdose

Patients who ingest what has been called massive amounts of acetaminophen can rapidly develop profound CNS depression, hypotension, and metabolic acidosis before the onset of hepatic failure, and they may be at greater risk for hepatic injury [65; 66; 67; 68; 69]. This clinical situation typically occurs following ingestion of more than 30–100 grams of acetaminophen or if the serum acetaminophen level is greater than 800 mcg/mL [65; 70; 71; 72].

CHRONIC INGESTIONS

An acute ingestion of acetaminophen is when the total amount of drug is consumed within a four-hour period or less. Chronic overdose ingestions (with the intent to cause self-harm) or long-term therapeutic errors are very common and pose a serious risk.

Assessment of patients with chronic ingestions can be complicated and difficult. The nomogram cannot be used, and clinical signs and symptoms may be absent, equivocal, or caused by a co-ingestant or a pre-existing medical problem. In some cases, serum transaminase levels may not yet have started to rise.

However, an accurate risk assessment of these cases can be done. A patient should be considered at risk for hepatotoxicity after a chronic ingestion (intentional or by therapeutic error) in the following situations [11]:

- In pediatric patients:
  - >200 mg/kg over a single 24-hour period
  - >150 mg/kg per 24-hour period for the preceding 48 hours
  - >100 mg/kg for the preceding 72 hours
- In adult patients:
  - >10 grams or 200 mg/kg (whichever is less) over a 24-hour period
  - >6 grams or 150 mg/kg (whichever is less) over a 48-hour period or longer
  - Referral of adult patients to emergent care should be considered if the patient abuses alcohol, is malnourished, or takes isoniazid and has consumed >4 grams or 100 mg/kg (whichever is less) per day.

- The patient may have taken an excess amount of acetaminophen, the serum transaminases are elevated, and there is no apparent medical reason for abnormal LFTs.
- The patient has a measurable acetaminophen level. If there is a measurable level of acetaminophen after a chronic ingestion, then the total load of NAPQI has not yet been produced and it is not possible to predict the level of risk.
- The patient has any clinical evidence of liver damage.

Misunderstandings about the amount of acetaminophen that is safe to use are very common. One study found that 23.8% of adults would take more than 4 grams in a 24-hour period, and 45.6% would take more than one over-the-counter product containing acetaminophen [73]. A 2015 study found that 72.2% of the people surveyed could not identify acetaminophen as an active ingredient of their prescription, and a 2018 study found that 41.4% of college-aged women surveyed did not know that acetaminophen and Tylenol are the same drug [74; 75]. This lack of knowledge is very significant, as many patients make mistakes with self-administration of acetaminophen, and unintentional acetaminophen overdose is the leading cause of acute liver failure in the United States [76].

INCREASED RISK FOR LIVER DAMAGE

As discussed, acetaminophen poisoning represents an imbalance between NAPQI formation and available glutathione. It makes intuitive sense that anything that may increase the amount of NAPQI and/or decrease the amount of glutathione would increase the risk of developing liver damage from an acetaminophen overdose. Medical conditions that damage the liver and/or compromise liver function increase this risk as well.

Aside from hepatitis C, there is no evidence that specific medical conditions, the patient's health status, or certain medications increase the risk of developing liver damage from an acetaminophen overdose. The Rumack-Matthew nomogram has been in use for more than 40 years, and it has been successfully used to assess many thousands of patients who have these risk factors. Nomogram and treatment failures are rare, and the assessment parameters are very conservative. Therefore, making adjustments and changing treatment protocols for people who have potential risk factors is not necessary.

Enzyme Induction

NAPQI is produced by cytochrome P450 enzymes. The activity of these enzymes may be increased, or induced, by certain drugs, ethanol, and tobacco smoke; however, there is no definitive evidence that people who drink, smoke, or take these enzyme-inducing medications are more susceptible to liver damage from acetaminophen [77]. The concern for increased risk in these situations arose from data from animal experiments and case reports, but it has not been not supported by extensive clinical experience. Susceptibility to liver toxicity in acetaminophen overdose is enhanced by older age, restricted diet, and underlying hepatic or renal disease [77].

Alcohol and Acetaminophen Poisoning

The relationship of alcohol and acetaminophen poisoning is complex. Ethanol is a cytochrome P450 enzyme inducer, but this effect is transitory, and only recently abstinent people who take an overdose of acetaminophen would be at increased risk. Acute ingestion of ethanol together with acetaminophen appears to provide protection against liver damage after an acetaminophen overdose by inhibiting cytochrome P450 enzymes and decreasing the amount of NAPQI that is formed [12; 78]. There is no evidence that people who chronically abuse alcohol have a higher risk for liver damage from acetaminophen poisoning than people who are abstinent [12].

Decreased Glutathione

Malnutrition and starvation decrease hepatic stores of glutathione and decrease the liver's ability to make glutathione. However, the evidence that reduced glutathione stores caused by diet, nutritional status, or chronic alcohol abuse increases the risk of liver damage is equivocal [78; 79].

Hepatitis C

Animal experiments and epidemiologic studies indicate that hepatitis C increases the risk for liver damage after acetaminophen overdose, but there is very little research on the subject [80; 81; 82]. A review of epidemiologic data from 2008 found that patients with hepatitis C infection who were admitted to the hospital for acetaminophen overdose were more likely to progress to severe liver failure and had a higher mortality rate than those without hepatitis [74].

Children and Acetaminophen Overdose

Children appear to be less susceptible to liver damage from acute acetaminophen overdose, even when weight-adjusted doses and serum concentrations are considered [12; 83]. Almost all deaths from acetaminophen in children younger than 6 years of age have been caused by repeated, chronic therapeutic errors. It was previously hypothesized that children had an increased ability to metabolize acetaminophen by conjugation and sulfation or that they had increased glutathione stores compared with adults. These theories have been shown to be untrue. It is now known that children are inherently more resistant to acetaminophen toxicity because of the size of their livers. The liver is proportionately larger in children than it is in adults, so children have greater relative glutathione stores and metabolize acetaminophen faster [77; 79; 84].

INITIAL CARE: ASSESSMENT, DECONTAMINATION, AND LABORATORY STUDIES

The care of a patient with suspected acetaminophen overdose should begin with an assessment of the airway, breathing, and circulation (the ABCs). These should all be normal unless the patient has taken other medications along with acetaminophen or the patient has ingested a massive amount of acetaminophen. If there are significant derangements in the patient's vital signs or level of consciousness, a co-ingestant should be strongly suspected.

A physical exam should be performed, and the details of the ingestion should be ascertained. Special attention should be paid to gastrointestinal signs and symptoms. The patient or any reliable witnesses should be questioned regarding the details of the ingestion, including how much acetaminophen was taken, what dose and form was ingested, when the ingestion happened, and if it was the only ingestion of acetaminophen or if there is a possibility of a chronic exposure.

Activated charcoal can prevent systemic absorption of acetaminophen, and a dose of activated charcoal should be given if the patient has normal, stable ABCs; is awake and alert and has a normal gag reflex; did not take medications that could cause a rapid onset of CNS depression; arrives at the hospital within one hour of the ingestion; and took a toxic dose of acetaminophen. Assess the patient's bowel sounds and ensure there are no medical conditions that would contraindicate the use of activated charcoal. The available evidence has shown that activated charcoal is most effective if it is given within one hour of ingestion, but this is an estimate. It should not be considered inviolable, and if there are no contraindications to the use of activated charcoal and a substantial amount of drug/toxin may still be in the gut, late administration of activated charcoal can be done. Activated charcoal will bind to oral *N*-acetylcysteine (NAC), the antidote for acetaminophen poisoning, but this effect is not considered clinically important [83].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to a Cochrane review, activated charcoal seems the best choice to reduce absorption of acetaminophen following overdose.

(https://www.cochrane.org/CD003328/LIVER_interventions-paracetamol-acetaminophen-overdose. Last accessed June 11, 2021.)

Level of Evidence: Meta-analysis

Gastric lavage should not be used in cases of acetaminophen poisoning. Gastric lavage is invasive, difficult and time-consuming to perform correctly, and unlikely to be effective when treating an acutely poisoned patient [85; 86; 87].

A serum acetaminophen level should be obtained four hours after the time of ingestion. If the time of ingestion is not known, a level should be taken immediately and again after four hours. A level measured earlier than four hours after an ingestion cannot be used to determine the risk for acetaminophen poisoning [83; 88]. Salicylate level, INR, LFTs, BUN, and creatinine should also be assessed. These tests are considered mandatory for every patient who has taken an acetaminophen overdose; other tests may be done as needed.

ANTIDOTAL THERAPY FOR ACETAMINOPHEN POISONING

If a toxic amount of acetaminophen was ingested and the serum level is above the toxic line on the nomogram, the patient should receive antidotal treatment with NAC. When determining whether or not to administer NAC, four variables should be considered: the serum acetaminophen level, the results of the appropriate laboratory studies, the results of the physical exam, and the history of the ingestion. If a patient has reportedly taken an overdose of acetaminophen and any one of those four variables could indicate a risk for acetaminophen poisoning, then the patient should be given NAC. If the next step remains unclear, the local poison control center may be contacted (at 1-800-222-1222) to discuss the case with a poison information specialist or a toxicologist.

N-Acetylcysteine

NAC is the antidote for acetaminophen poisoning. It was first developed and is still used as a mucolytic. The original form of NAC was sterile but not pyrogen-free and was only available in oral formulations. Today, oral and intravenous preparations are used in the treatment of acetaminophen overdose. In 2004, a sterile, pyrogen-free form of NAC (Acetadote) was developed and made available in the United States.

NAC prevents liver damage from acetaminophen overdose by [3; 6; 89]:

- Acting as a substitute for glutathione
- Acting as a precursor to glutathione
- Increasing the amount of acetaminophen that is conjugated to sulfate
- Improving microcirculation in and oxygen delivery to the liver
- Scavenging free radicals

Before the introduction of NAC, the incidence of hepatotoxicity after acetaminophen overdose was approximately 58%; NAC therapy reduced this to 1.6% [89]. In addition, the fatality rate from acetaminophen poisoning dropped from 5% to 0.75% after NAC treatment became the standard of care [89]. When NAC is used soon after an overdose and given correctly, fatalities from acetaminophen overdose are rare [6].

NAC is a highly effective antidote if used correctly. It is most effective if it is given within 8 to 10 hours after the ingestion of acetaminophen, and its effectiveness begins to decline after that point [6; 83]. Glutathione stores are depleted to 20% to 30% of pre-exposure levels at 8 to 10 hours post-ingestion, and this appears to be the critical point at which NAPQI binds to hepatocytes.

EVIDENCE-BASED PRACTICE RECOMMENDATION

A Cochrane review found that *N*-acetylcysteine should be given to people with paracetamol poisoning at risk of liver damage, risk is determined by the dose ingested, time of ingestion, and investigations.

(https://www.cochrane.org/CD003328/LIVER_interventions-paracetamol-acetaminophen-overdose. Last accessed June 11, 2021.)

Level of Evidence: Meta-analysis

Intravenous NAC is usually preferred, but oral NAC is still available and used. If a patient presents within the 8- to 10-hour window, there does not appear to be any difference in effectiveness between oral or intravenous NAC [3; 90; 91; 92]. However, the dosing regimens and the clinical considerations for the two vary.

Case Study

A woman, 44 years of age, presents to the emergency department stating that she took an overdose of acetaminophen "some time yesterday" while also consuming large quantities of alcohol. The patient has a past medical history of alcohol abuse and hypertension. Her vital signs are normal, and except for nausea and abdominal pain, which she describes as mild, the exam is normal. The patient cannot remember how much acetaminophen she took or when she took it, but a family member believes the ingestion occurred between 16 and 24 hours ago. No medical records are available. The laboratory results are:

- AST: 101 IU/L
- ALT: 142 IU/L
- BUN: 9 mg/dL
- Creatinine: 0.8 mg/dL
- INR: 1.0
- Serum acetaminophen level: 19 mcg/mL
- Serum salicylate: Negative
- Serum ethanol: Negative

***Comments and rationale**: Treatment with NAC is warranted in this case. The LFTs are above the upper limit of normal, but given the probable time frame of the ingestion, it is early for this finding. The laboratory test results and the patient's physical complaints are non-specific, and both could be caused by her chronic alcohol abuse or the recent binge, though there is no way to determine if that is so. The only unequivocal data is the acetaminophen level and the patient's stated intent. The serum acetaminophen level confirms ingestion, but it cannot be interpreted because the time of ingestion is not known. NAC treatment should be started.*

Oral Administration

Oral NAC is administered with a loading dose of 140 mg/kg. This is followed four hours later by a 70 mg/kg dose, which is repeated every four hours for the next 68 hours (for a total of 19 doses). The patient's LFTs, BUN, creatinine, and INR should be checked once every 24 hours while receiving oral NAC. Daily acetaminophen levels need not be measured.

Nausea and vomiting are common side effects of oral NAC. If a patient vomits within an hour of receiving a dose, the dose should be repeated. If the patient vomits more than one hour after a dose, absorption is considered complete and repeat dosing is unnecessary.

Oral NAC should be diluted with juice or soda and served cold in a cup with a lid (as the odor is noxious). Patients should be advised to sip it slowly to prevent vomiting. If necessary, NAC can be slowly infused through a nasogastric tube. Antiemetic pre-treatment with ondansetron or metoclopramide is more effective than with prochlorperazine. Contradictions to NAC use include hypersensitivity to acetylcysteine or any component of the formula, an inability or contraindication to using the gut, and persistent vomiting.

Intravenous Administration

When intravenous NAC is used, the dosing regimen is selected based on the patient's weight. If a patient weighs more than 40 kg, a loading dose of 150 mg/kg diluted in 200 mL of diluent (D5W) is infused over 60 minutes [3]. A shorter time for the loading dose infusion was used when IV NAC was first made available, but a 60-minute infusion has been found to decrease the incidence of adverse effects. The second dose of 50 mg/kg in 500 mL of diluent infused over four hours should be given immediately after the first dose is complete. When the second dose is finished, a third dose of 100 mg/kg in 1,000 mL of diluent should be infused over 16 hours; this last dose should be started as soon as the second dose is completed. In patients who weigh more than 100 kg, the maximum doses are 15 g, 5 g, and 10 g; do not use higher doses if the patient weighs more than 100 kg [3; 6].

There has been research suggesting that in case of massive acetaminophen overdose (e.g., >40–50 grams or four-hour post-ingestion acetaminophen level >300 mcg/mL) the standard NAC protocol may not be effective and additional amounts of NAC may be needed [3; 6; 93]. At this time, the 21-hour protocol is still considered to be the standard of care, but if a very large amount of acetaminophen has been ingested and/or the acetaminophen level is >300 mcg/mL, it would be prudent to consult with a medical toxicologist or a poison control center.

Two hours prior to the end of the 16-hour infusion, serum acetaminophen level, AST, ALT, and INR should be obtained. If there is a measurable acetaminophen level or abnormally elevated LFTs or INR, consider administering additional NAC and consult with the local poison control center or a toxicologist to determine whether the therapy should be continued. The decision to stop or to continue NAC therapy with several more doses (the latter being a very common occurrence) is often not clear-cut and each case should be handled individually [4]. Serial measurements of serum acetaminophen level are unnecessary if the patient is receiving intravenous NAC, as declining levels only document metabolism of the drug, not the diminishment of risk. The acetaminophen level and LFTs only need to be remeasured two hours before the third infusion is due to be completed.

Adverse reactions to IV NAC are common, but they are usually minor (e.g., flushed skin, pruritus) and easily managed. Serious reactions (e.g., angioedema, bronchospasm, hypotension) are indicative of an anaphylactoid reaction and typically (but not always) occur when the first dose is being given. Fortunately, serious reactions are uncommon; the incidence of anaphylactoid reactions to IV NAC has been reported to be 8.2%, most of these reactions were dermal (75.4%) and occurred during the first hour of treatment (95.4%) [94]. For patients who experience flushed skin and/or pruritus during infusion, diphenhydramine may be given while continuing the infusion (and perhaps decreasing the infusion rate temporarily) and observing the patient closely. If a patient is having an anaphylactoid reaction, the NAC infusion should be halted and diphenhydramine, beta agonists, corticosteroids, and epinephrine should be given as needed. If the patient is asymptomatic after one hour, the IV NAC should be started at a slower rate [90].

LFTs, INR, and prothrombin time (PT) are measured to determine the presence of liver damage following acetaminophen overdose. It is important to remember that NAC and acetaminophen overdose can cause mild elevations in INR and PT in the absence of hepatotoxicity, but the INR should be <1.5 and the effects should slowly resolve [6; 95; 96]. Patients who develop rhabdomyolysis from a mixed overdose or from the circumstances of the overdose (e.g., opioid-acetaminophen overdose causing prolonged immobility) may have elevated LFTs as well.

NAC in Special Situations

It is not unusual for patients to present more than 8 to 10 hours after taking an overdose of acetaminophen or for the time of ingestion to be unknown. If a patient has taken an overdose of acetaminophen more than 8 to 10 hours before presenting for treatment and needs therapy with NAC, the standard oral or IV treatment regimens should be used. Giving NAC to these patients will significantly decrease the incidence of hepatotoxicity and mortality [89; 97]. If a patient claims to have taken an overdose of acetaminophen but presents to a healthcare facility many hours after the ingestion, the standard diagnostic workup should be done. If it can be reasonably determined that the ingestion happened 12 hours or more before presentation and the serum acetaminophen level is undetectable, the LFTS, coagulation studies, and renal function studies are normal, and the patient has no clinical evidence of liver damage, there would be no need for treatment with NAC [6].

Although the standard oral and IV NAC protocols are sufficient for most patients, some patients will reach the end point of therapy with persistently elevated LFTs and/or a measurable level of serum acetaminophen. Elevated LFTs at the end of NAC therapy indicate liver damage, and it can be difficult to predict if this damage will continue and worsen. A measurable acetaminophen level indicates a potential for more NAPQI to be formed. In either case, extending the NAC protocols beyond the 72-hour or 21-hour limit may be advisable. Making this decision can be difficult, and a toxicologist should be consulted in these cases [4]. It is rare that patients receiving oral NAC would need more than 72 hours of treatment, but it is not uncommon for patients receiving IV NAC to require treatment beyond the standard 21-hour protocol; extended therapy with IV NAC has become an accepted practice. If LFTs remain elevated at the end of the 21 hours of infusion and/or there is a measurable serum acetaminophen level, strong consideration should be given to continuing NAC administered at 100 mg/kg in 1,000 mL diluent over 16 hours [4]. Two hours before this fourth infusion will be finished, recheck the LFTs and the serum acetaminophen level to determine if more NAC is necessary. At times, a fifth or sixth infusion may be necessary.

Acetaminophen can cross the placental barrier and the fetal liver can metabolize acetaminophen, so unborn children can be harmed by excess amounts of acetaminophen. The standard oral or IV NAC protocols may be used during pregnancy [6]. If a pregnant woman has taken an overdose of acetaminophen and is treated with NAC, the fetus should not be harmed and birth defects and/or an abnormal delivery are unlikely [6].

INDICATIONS FOR LIVER TRANSPLANTATION

Some patients do not respond to NAC therapy and develop fulminant hepatic failure, and in these cases, liver transplantation may be needed. It is difficult to determine which patients with acetaminophen-induced hepatic failure are transplant candidates and which ones will recover, and there has been intense interest in identifying the assessment criteria best suited to making this decision. Traditionally, patients were considered candidates for liver transplantation if they had acidosis with a pH less than 7.3 after fluid resuscitation, or a PT >100 seconds, serum creatinine >3.4 mg/dL, and III-IV encephalopathy [88]. This is referred to as the King's College Hospital criteria. The Model for End-Stage Liver Disease (MELD) score, the Acute Physiologic and Chronic Health Evaluation II and III (APACHE) criteria, and other prognostic models have also been used to determine patient selection for transplant and predict transplant success [98; 99; 100]. The commonly used King's College Criteria, slightly modified for acetaminophen-induced liver damage, is a pH of 7.3 (irrespective of the grade of encephalopathy) or grade II or IV encephalopathy and a PT >100 seconds and a serum creatinine >3.4 mg/dL. However, all these prognostic tools have limits to their usefulness and none is universally accepted [98; 99; 100].

ASPIRIN POISONING

Aspirin is the most commonly used oral form of salicylic acid. It has lost some popularity in recent years as other over-the-counter analgesics with fewer side effects have become available. It is also not recommended for use in children because of the association of aspirin with Reye syndrome. Despite this, aspirin and aspirin-containing products are still widely available, and salicylate overdoses are not uncommon. According to data from the AAPCC, there were 16,317 salicylate overdoses and 19 deaths reported to U.S. poison control centers in 2019 [101].

Aspirin poisoning is a complicated toxicity. The assessment and stabilization of ABCs, gastric decontamination, the pathophysiology of aspirin toxicity, and available treatment options all present difficult and complex challenges. Successfully treating aspirin overdose requires an understanding of the pharmacology, pathophysiology, and toxicokinetics of aspirin poisoning, and healthcare professionals require a considerable amount of in-depth knowledge to provide the best care.

PHARMACOLOGY OF ASPIRIN

Aspirin, or salicylic acid, is an NSAID. The therapeutic effects of aspirin and other salicylates are mediated by inhibition of cyclooxygenase 1 and 2 (COX-1 and COX-2). Cyclooxygenase is an enzyme that helps the body to synthesize prostaglandins, hormone-like substances that mediate many physiologic processes, including inflammation, hypersensitivity reactions, platelet aggregation, and vasodilation of specific vascular beds. The inhibition of COX-1 and COX-2 and the resulting inhibition of prostaglandin synthesis are the basis for many of the therapeutic actions of aspirin. The labeled uses for aspirin are [4]:

- Analgesic/antipyretic
- Revascularization after procedures like coronary artery bypass graft
- Treating rheumatic pain in cases of rheumatoid arthritis, osteoarthritis.
- Preventing and treating acute coronary syndromes (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, unstable angina), acute ischemic stroke, and transient ischemic attacks

Dosing and Available Forms

The usual dose of aspirin when used as an oral analgesic or antipyretic is 325–650 mg every four to six hours, with a maximum daily dose of 4 g [4]. When used to treat acute coronary syndromes, the dose is 162–325 mg and the tablet should be chewed. For secondary prevention in most patients with cardiovascular conditions, the daily maintenance dose is 81 mg. Oral preparations of aspirin are available as tablets of 81 mg, 325 mg, and 500 mg, and as enteric-coated tablets in doses of 81 mg, 325 mg, 500 mg, and 650 mg. Enteric-coated aspirin tablets are designed to resist the acidic milieu of the stomach, be absorbed in the small bowel, and avoid the gastrointestinal irritation common with aspirin use. When the tablet reaches the small intestine and a local pH of 6.0, the enteric coating will dissolve and the aspirin can be absorbed. Aspirin is also available as a rectal suppository in doses of 300 mg and 600 mg [4]. In addition, it is included in combination formulations with acetaminophen and other over-the-counter or prescription drugs and in topical preparations that contain methyl salicylate.

There are several other forms of salicylic acid, including homosalate and octyl salicylate, compounds used in sunscreens; trolamine salicylate, a component of topically applied creams used for pain relief; methyl salicylate, used in topical analgesics; and choline magnesium subsalicylate, which is found in antacid preparations (***Table 1***) [102]. One of the more common of these compounds is bismuth salicylate, which is used in over-the-counter antacid preparations such as Pepto Bismol. A dose of 0.5 mg bismuth salicylate is approximately equivalent to 1 mg of aspirin [102]. Toxicity from dermal preparations of aspirin or the less common salicylates (aside from bismuth salicylate and methyl salicylate) is very uncommon.

RELATIONSHIP OF SALICYLATES TO ASPIRIN EQUIVALENT DOSES		
Salicylate	**Conversion Factor[a]**	**Type of Use**
Aspirin	1.0	Oral, suppository
Bismuth subsalicylate	0.5	Oral
Choline magnesium trisalicylate	1.3	Oral
Choline salicylate	0.75	Oral
Magnesium salicylate	1.21	Oral
Methyl salicylate	1.18	Dermal, flavoring agent
Oil of wintergreen	1.4	Dermal, flavoring agent
Salicylic acid	1.3	Dermal
Salsalate	1.4	Oral
Sodium salicylate	1.13	Oral
Trolamine salicylate	0.63	Dermal
[a]Multiply the dose of the non-aspirin salicylate by the conversion factor to get the equivalent dose of aspirin. The conversion factor is calculated by dividing the molecular weight of aspirin by that of the non-aspirin salicylate except for those that dissociate into more than one molecule of salicylate. Magnesium salicylate and salsalate yield two molecules of salicylate; choline magnesium trisalicylate yields three molecules of salicylate. Salsalate may not fully convert to salicylate.		
Source: Chyka PA, Erdman AR, Christianson G, et al. Salicylate poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila). 2007;45(2):95-131.		
Table 1		

Therapeutic Pharmacokinetics

Absorption of aspirin through the stomach and small bowel is rapid. Dermal absorption of salicylate is very limited unless the surface of the skin is compromised. An estimated 50% to 75% of an ingested dose reaches the systemic circulation, with peak serum level reached in approximately one to two hours, and the action of the drug is typically four to six hours. A serum level of 10–30 mg/dL is considered therapeutic. The majority of each dose (80% to 90%) is protein-bound.

Aspirin is primarily metabolized in the liver. In therapeutic doses, it is metabolized by first-order kinetics: the higher the dose, the more active the metabolizing enzymes. The half-life is three hours after a standard dose, but the half-life increases as the dose increases. Aspirin is excreted in the urine, with approximately 10% excreted unchanged as salicylic acid.

PATHOPHYSIOLOGY OF ASPIRIN POISONING

As noted, the pathophysiology of aspirin poisoning is complex. Aspirin is a multi-organ system poison, has many complicated effects on normal physiology, and the pharmacokinetics are changed when it is taken in large amounts.

The harmful effects of aspirin may be organized into two categories. The first category includes the relatively simple, direct toxic effects of the drug, while the second includes the complicated cellular and metabolic effects of aspirin poisoning, specifically aspirin's effects on acid-base balance and energy production. This separation is not clear cut, and the two affect and influence each other. However, it is a useful way of thinking about aspirin poisoning and a helpful approach to conceptualizing how and why the signs and symptoms of aspirin poisoning are produced.

Direct Toxic Effects

Gastrointestinal Effects

Aspirin can be very irritating to the gut, and gastrointestinal bleeding, anorexia, nausea, and vomiting are common effects of aspirin toxicity. Aspirin also directly stimulates the chemoreceptor in the medulla, another cause of nausea and vomiting. These gastrointestinal effects are in part the source of the fluid and electrolyte losses that are common after aspirin poisoning [103].

Otic Effects

Aspirin adversely affects the hair cells of the cochlea. As a result, tinnitus is a well-known and commonly reported direct toxic effect of aspirin use and overdose. Hearing loss can occur, but fortunately this is rarely a permanent effect [103; 104].

Pulmonary Effects

Salicylates stimulate the respiratory center in the medulla and cause hyperventilation and tachypnea, which can result in a respiratory alkalosis [103; 105]. Salicylate poisoning can also cause noncardiogenic pulmonary edema, perhaps by increasing pulmonary capillary permeability [105; 106]. Noncardiogenic pulmonary edema can happen in both acute and chronic aspirin poisoning [103].

Neurologic Effects

Aspirin is directly toxic to the brain and the CNS [95; 98]. It also has more complex effects on the neurologic system, which will be discussed later in this course.

Cellular and Metabolic Effects

An overdose of aspirin disrupts oxidative phosphorylation, and this is perhaps its most important toxic effect [103; 105; 107]. Oxidative phosphorylation is the aerobic mechanism by which mitochondria in the cells make energy in the form of adenosine triphosphate (ATP). In high doses, aspirin interferes with or "uncouples" oxidative phosphorylation and energy must be produced by anaerobic metabolism, and this greater dependence on anaerobic metabolism has several important consequences. Increased amounts of lactate are produced, and the metabolic rate is dramatically increased. Because anaerobic metabolism is relatively inefficient at producing energy, fatty acids are used for fuel, resulting in the creation of ketone bodies. The results of these metabolic derangements are far-reaching and profound. The acid-base disturbances (metabolic acidosis and respiratory alkalosis), fever, changes in glucose and fatty acid metabolism, fluid and electrolyte derangements, and other clinical effects that characterize aspirin poisoning are directly or indirectly caused by the disruption of oxidative phosphorylation. Understanding how aspirin disrupts normal metabolism is vital for understanding aspirin poisoning.

TOXICOKINETICS OF ASPIRIN POISONING

The pharmacokinetics of aspirin are dramatically changed when the drug is taken in a toxic amount, and these changes will influence the clinical course in patients who have taken an overdose. The peak serum levels and clinical effects may be significantly delayed [103; 108]. Serum levels can rise, reach what appears to be a peak, begin to decline, and then rise again to a toxic level [109]. Serum levels may also remain low immediately post-ingestion and for some time after ingestion but then dramatically increase within a period of several hours, and patients who have taken an overdose may initially have a benign clinical presentation [108; 110; 111].

Absorption

When a large amount of aspirin is taken, the absorption of the drug can be significantly delayed for several reasons. Aspirin is known to cause pylorospasm, which can delay the absorption of the drug [103; 110]. Large amounts of aspirin can also form a bezoar, a concretion of foreign material in the gut [103; 112]. This phenomenon is particularly common after an overdose of enteric-coated aspirin or when a patient has a gastric outlet obstruction [112].

Peak Serum Level and Half-Life

When a normal dose of aspirin is taken, the peak serum level occurs within one to two hours. In an overdose, the peak serum level is typically seen after five or more hours post-ingestion, and there are case reports describing peak serum levels of aspirin up to 67 hours after ingestion [103; 108; 111; 113; 114; 115]. The half-life of aspirin after an overdose is increased to as long 30 hours [103].

Volume of Distribution

The volume of distribution of a drug describes the distribution of a drug between plasma and body tissues. When an overdose of aspirin is taken, the volume of distribution is increased, with greater drug levels located in the tissues [104]. This increases the risk of direct and cellular/metabolic poisoning and makes elimination of aspirin more difficult.

Protein Binding

All drugs have some affinity for being bound to proteins in the plasma (e.g., albumin, lipoprotein), and it is the amount of drug that is not bound to plasma proteins that is pharmacologically active. When aspirin is taken in therapeutic doses, 80% to 90% of the drug is protein-bound, but in overdose, the concentration of protein-bound aspirin is decreased to less than 75% [104].

Metabolism

Therapeutic doses of aspirin are metabolized in the liver by first-order kinetics—the higher the concentration of the drug, the greater the activity of the metabolizing enzymes. When an overdose of aspirin is taken, several of the hepatic enzyme systems that metabolize the drug become saturated and aspirin is metabolized by zero-order kinetics. This means that metabolism of aspirin is independent of the amount of drug that is ingested, and elimination of the drug by the renal route becomes more important [104].

Ionized versus Non-Ionized Aspirin

Drugs that are placed in solution (e.g., in the liquid environment of the gut) dissociate and give up protons, thus becoming ionized. Ionization of drugs in solution depends on the pH of the solution and on the acid-dissociation constant, or pKa. When the pKa is relatively low and pH is high, a drug can easily become ionized; this is the case with aspirin. Salicylic acid is a weak acid with a pKa of 3.0, so if the pH is less than 3.0, more aspirin will be non-ionized. As pH rises above 3.0, more aspirin will be ionized.

Aspirin poisoning can cause a metabolic acidosis, and a reduced serum pH results in a greater proportion of aspirin in the non-ionized form. Non-ionized aspirin can cross the blood-brain barrier, so acidosis increases CNS tissue saturation of aspirin.

SIGNS AND SYMPTOMS OF ASPIRIN POISONING

The clinical presentation of aspirin toxicity is highly variable and depends on the amount ingested, when it was ingested, and the health of the patient. Progression to more serious clinical effects can occur quickly or after a relatively long period of time during which the patient may only have mild, non-specific signs and symptoms. Many patients who develop severe, even fatal salicylate poisoning are initially awake, alert, and minimally symptomatic. Aspirin poisoning is an active process, and the clinical status of patients who appear well can deteriorate rapidly. At a certain point, acidosis, dehydration, hypoxia, hypoglycemia, myocardial depression, seizures, and respiratory insufficiency can develop and/or progress to a critical point and result in severe injury or death.

Vital Signs

Tachypnea is a common effect of aspirin overdose [103; 105]. In addition, patients may have an elevated temperature because of the increased metabolic rate and dehydration, but a high fever is not common. Blood pressure should be normal, and the pulse is usually normal or mildly elevated.

Acid-Base Disturbances

Hyperventilation and tachypnea cause many patients to initially present with respiratory alkalosis. As the clinical course progresses and more aspirin is absorbed, the compensatory ability of the kidneys and the lungs become overwhelmed. In addition, the disruption of oxidative phosphorylation and changes in glucose and fatty acid metabolism become more pronounced and metabolic acidosis can occur [103; 105]. This a very serious concern, because it affects aspirin pharmacokinetics and it also adversely affects cardiovascular functioning and neurological status [107; 116]. The low serum pH of metabolic acidosis increases the amount of aspirin that is non-ionized, allowing aspirin to cross the blood-brain barrier and enter the CNS tissues and to be more easily reabsorbed by the kidney tubules. A mixed acid-base disturbance—metabolic acidosis with respiratory compensation—is also commonly seen.

Gastrointestinal Effects

Nausea and vomiting are very common [103; 105]. The resulting fluid losses increase the serum concentration of aspirin and make its renal excretion more difficult.

Fluid and Electrolyte Disturbances

Dehydration is a common result of aspirin poisoning due to the gastrointestinal, pulmonary, and metabolic effects. Patients with aspirin poisoning often have decreased oral intake due to anorexia and loss of fluids from vomiting, and tachypnea causes fluid loss from the lungs. The increased metabolic rate caused by disruption of oxidative phosphorylation increases the production of body heat and causes a low-grade fever, further dehydrating the patient.

Hypokalemia or hyperkalemia may also be seen after an aspirin overdose. Respiratory alkalosis increases renal excretion of bicarbonate and potassium, and metabolic acidosis shifts potassium from the intracellular space to the extracellular space.

Metabolic Effects

The change from aerobic to anaerobic metabolism causes glycogenolysis and gluconeogenesis. Hyperglycemia may be seen early in cases of aspirin poisoning, but in the later stages, hypoglycemia is possible as glucose stores are depleted.

Neurologic Effects

As noted, tinnitus is common as a result of aspirin's effects on the cochlea. Hearing loss can occur but is almost always temporary. CNS depression is an ominous sign, as it indicates the presence of metabolic acidosis, movement of salicylate into the CNS, and/or possible cerebral edema [103]. Seizures may occur, possibly from a direct toxic effect of salicylate on the brain, hypoxia, or a low glucose concentration in the CNS [103]. Seizures can obviously worsen metabolic acidosis and decrease respiratory effectiveness, and seizures are a grim prognostic sign.

Pulmonary Effects

As noted, hyperventilation and tachypnea are common signs of aspirin toxicity. Noncardiogenic pulmonary edema can develop, typically in older patients who have been chronically ingesting large amounts of aspirin, but it can also occur after acute ingestions [103].

Effects in Pregnancy

Aspirin crosses the placenta, and acute or chronic aspirin ingestion can cause birth complications and aspirin poisoning in newborns [94].

TREATMENT OF ASPIRIN OVERDOSE

The ABCs and the Initial Assessment

Specific therapeutic interventions may be used for aspirin poisoning, but there is no antidote. If there are serious derangements in the patient's ABCs, symptomatic and supportive care should be initiated immediately. Most patients with aspirin poisoning are dehydrated, so fluid resuscitation should also be started.

The initial physical assessment should focus on the patient's neurologic and pulmonary status. CNS depression, tachypnea, and low oxygen saturation are specific indications that the patient has a serious poisoning. Intubation and mechanical ventilation may be needed to stabilize the patient, but this is a potentially dangerous procedure when attempted in patients with aspirin overdose. If airway control is necessary, a high tidal volume and rapid respiratory rate are essential to allow the normal compensatory hyperventilation [103; 105; 116]. However, this is difficult to accomplish, and a worsening acidosis is a definite possibility. It is not part of the physical exam, but metabolic acidosis indicates the potential for serious toxicity.

It is also important to determine how much aspirin was consumed and when the ingestion occurred. A toxic amount of aspirin is ≥150 mg/kg, and a fatal dose has been estimated to be 10–30 grams in adults [103; 117]. The patient's medical history and any medications he or she has been prescribed should be determined. The patient or friend/family member should be questioned regarding any co-ingestions; many people who take medications with intent to cause self-harm will take several different drugs.

Gastric Decontamination

Gastric decontamination techniques may be used to remove drugs before they are absorbed. The decontamination technique of choice for aspirin poisoning is activated charcoal.

Activated charcoal binds to aspirin well and can prevent systemic absorption of the drug. A dose of activated charcoal should be given if all the following apply:

- The patient has normal, stable ABCs.
- The patient is awake and alert.
- The patient has a normal gag reflex.
- The patient did not take another medication that could cause a rapid onset of CNS depression.
- The patient arrives at the hospital within one hour of the ingestion.
- The patient has taken a toxic amount of aspirin.

The patient's bowel sounds should be assessed, and any medical conditions that are contraindications for activated charcoal should be noted.

Research has shown that activated charcoal is most effective if it is given within an hour of ingestion of a drug [118]. However, the absorption of aspirin may be delayed following overdose due to the toxicokinetics of the drug and possibly the formation of bezoars. So, strong consideration should be given to extending the one-hour time limit for activated charcoal in patients who have taken an overdose of aspirin [103; 119]. The use of multiple doses of activated charcoal may be helpful, as well; the patient can be given 25 grams every two hours for three doses, or 50 grams every four hours for two doses, after the initial dose of activated charcoal has been administered [103].

Gastric lavage should not be used in cases of aspirin poisoning. This approach is invasive, difficult, and time-consuming to perform correctly, and it is very doubtful that it is effective for treating any acute overdose [120]. Whole bowel irrigation can be used if it is suspected that the patient has a large a number of tablets in her/his gut [105].

Laboratory Tests and Other Diagnostic Procedures

Patients with known or suspected aspirin overdose should have serum aspirin level, arterial blood gas, BUN, creatinine, electrolytes, serum glucose, and serum acetaminophen level measured. Assessment of the salicylate level, electrolytes, and arterial blood gas should be repeated; the timing and frequency should be determined by assessment of the patient's clinical status and the results of previous tests.

An acetaminophen level should be measured in every patient who has taken an overdose. As discussed, patients may confuse the names of over-the-counter analgesics, and unrecognized and unreported acetaminophen ingestions are relatively common [121; 122].

A salicylate level greater than 30–40 mg/dL is often cited as an indicator for specific treatment [103]. A serum level greater than 100 mg/dL following an acute ingestion or greater than 60 mg/dL following chronic ingestion is considered potentially very serious and is typically considered an indication for treatment with hemodialysis [103; 105]. The units of measurement may vary among laboratories. Though most report serum salicylate as mg/dL, some use mg/L, a 10-fold difference, making it important to always confirm the units of measurement.

Salicylate levels should be interpreted carefully, taking into consideration the possibility of significantly delayed peak levels. Serial levels that document a progressive decline may indicate that the aspirin is being excreted or that the patient has developed metabolic acidosis and the aspirin is moving out of the serum and into the CNS. In many cases, a higher serum salicylate level is correlated with a greater risk, though the latter is also accompanied by neurological and pulmonary changes. However, salicylate levels do not consistently correlate with toxicity, and fatalities have been reported in patients with levels of 50–70 mg/dL [123].

Serial salicylate levels should be measured every two hours until at least two successive levels are noted to be within or below the normal range and are decreasing. However, serial measurements of aspirin alone should not be used for determining whether the patient is or is not at risk. The patient's acid-base status should be evaluated, and a physical exam performed every two hours to determine the level of risk and the patient's progress. Salicylate levels should be interpreted in the context of the patient's acid-base and neurologic status. Periodic measurements of serum glucose and potassium should also be done, as hypokalemia and changes in serum glucose are common in aspirin overdose.

An elevated anion gap is common in cases of aspirin overdose, but a normal anion gap in this clinical situation can occur [103]. Aspirin is excreted by the kidneys, and enhanced elimination of aspirin requires normal renal function, so the patients BUN and creatinine should be measured.

Older references may recommend using the Done nomogram, a tool like the Rumack-Matthew nomogram, to predict toxicity. However, the Done nomogram is now considered unreliable and of limited value and should not be used [103; 124].

An abdominal x-ray may detect an aspirin bezoar, but the results are not always conclusive or accurate for this purpose [125; 126]. If there is a suspicion that a patient has developed a bezoar, a radiologist or the local poison control center should be consulted.

Urinary Alkalinization

Urinary alkalinization is the primary therapeutic intervention for treating mild-to-moderate aspirin overdoses [103]. Increasing the serum pH and creating an alkaline environment will ionize aspirin, preventing it from crossing the blood-brain barrier and being re-absorbed by the renal tubules. This effect is called "ion trapping," and it lowers serum aspirin levels, changes concentration gradients, moves aspirin out of the tissues, and increases the renal excretion of the drug. In addition, the urinary excretion of salicylate is dependent on urine pH; increasing the urine pH from 5.0 to 8.0 will dramatically increase renal clearance.

Ion trapping and increasing urine pH have been the traditional explanations for the efficacy of urinary alkalinization in lowering serum salicylate levels, but it is not entirely clear how urinary alkalinization works. There are no randomized trials that have investigated its use—the evidence for its clinical effectiveness comes from case reports and animal studies—and there is no agreed upon definition of mild-to-moderate aspirin poisoning or universally accepted standards on how to achieve urinary alkalinization.

Despite these uncertainties, urinary alkalinization remains a standard of care for treating mild-to-moderate aspirin overdose, and it is indicated for patients who are hemodynamically stable and have [103; 105]:

- Taken a toxic dose of aspirin
- Signs and symptoms of aspirin overdose
- A serum salicylate level > 40 mg/dL
- No significant metabolic and/or neurologic derangements that indicate the need for more aggressive therapy
- Good renal function

The usual formula for urinary alkalinization is to give the patient an IV bolus of 50% sodium bicarbonate, 1–2 mEq per kg, and then begin a continuous infusion with three 50-mL ampules of 50% sodium bicarbonate in 1,000 mL of 5% dextrose in water [103; 105]. Some sources recommend that 40 mEq of potassium chloride be added to the continuous infusion fluid, but alkalinization will not work if the patient is hypokalemic or if she/he is dehydrated. So hypokalemia and volume depletion should be corrected before or during alkalinization [103; 105]. The solution should be infused at 1.5 to 2 times the patient's basic fluid requirement, at least, and the primary goals of this therapy are to attain a urinary pH of ≥ 7.5 and to ensure a good urine output [103; 105; 116]. Done correctly, urinary alkalinization can increase the urinary excretion of aspirin 10-fold [116]. Urine pH should be checked every one to two hours and the infusion rate adjusted as needed. Therapy should be continued until successive serum salicylate levels are less than 30–40 mg/dL and the patient has no clinical or laboratory evidence of salicylate poisoning [127].

The literature conflicts slightly in recommendations for urinary alkalinization. However, these differences could reasonably be considered insignificant, and the basic methods and goals of urinary alkalinization are the same: maintaining a normal serum potassium level and good urine output and creating an alkaline urine pH.

Possible complications of urinary alkalinization include alkalemia, hyperkalemia, and fluid overload. The process should be used cautiously and with close monitoring if the patient is at risk for cerebral or pulmonary edema.

Hemodialysis

Hemodialysis is an effective method of treating severe cases of aspirin overdose. Indications for the use of hemodialysis in these cases are [103; 105; 116]:

- Salicylate level ≥ 90 mg/dL in an acute ingestion in a patient who has normal renal function, or ≥ 80 mg/dL in a patient who has impaired renal function
- A serum level ≥ 60 mg/dL in a chronic overdose
- CNS depression or any other significant changes in sensorium
- Fluid overload or any other condition that prevents the use of urinary alkalinization
- Cerebral edema
- Severe acidosis and/or electrolyte abnormalities
- Acute or chronic renal failure
- Pulmonary edema and/or hypoxia
- Intubation and mechanical ventilation

The serum salicylate level is the least reliable of these criteria for identifying patients who require hemodialysis. A level ≥ 90 mg/dL is used empirically as a criterion, but acid-base status and the clinical condition of the patient are better indicators of the need for hemodialysis, particularly in cases of chronic salicylate poisoning [116].

TOXICITY FROM OTHER FORMS OF ASPIRIN

Toxicity from topical aspirin preparations is unlikely but not impossible. Cases that do occur typically involve overuse, chronic administration, and/or application of topical products to broken skin. Serious harm is unlikely if topical salicylic acid products are used properly, but when applied incorrectly or to areas where skin integrity has been damaged, very high salicylate levels and acid-base and neurologic disturbances have been reported [128].

Oil of wintergreen and methyl salicylate, used as topical analgesics, are potentially dangerous forms of salicylic acid. One teaspoon (approximately 5 mL) of oil of wintergreen contains approximately 7,000 mg of aspirin. Ingestions of these products (particularly by children) can be very dangerous; as little as 4 mL of oil of wintergreen may cause death in a toddler [103].

IBUPROFEN POISONING

Ibuprofen is a popular over-the-counter NSAID and a common drug of choice in intentional overdoses. There were more than 62,000 intentional overdose ingestions of ibuprofen reported by U.S. poison control centers in 2019, resulting in one death [101]. Serious effects after overdose are unusual, and fatalities are rare.

Naproxen is another commonly used over-the-counter NSAID. However, there are far fewer intentional ingestions of naproxen and the clinical effects of naproxen and ibuprofen are the same. So, this section will focus on ibuprofen.

PHARMACOLOGY

Like aspirin, ibuprofen reversibly inhibits COX-1 and COX-2, and this inhibition provides analgesic, antipyretic, and anti-inflammatory effects [4]. The labeled uses of ibuprofen are for the treatment of mild-to-moderate pain, fever, and inflammatory and rheumatoid disorders.

Dosing and Available Forms

The recommended adult dose of ibuprofen is 200–800 mg every four to eight hours, with a maximum 24-hour dose of 3,200 mg. The pediatric dose (up to 11 years of age) depends on body weight and age.

Individuals with chronic kidney disease should use ibuprofen with caution. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that if the patient's estimated glomerular filtration rate is <30 mL/minute/1.73 m^2, ibuprofen should not be used [4].

Over-the-counter ibuprofen tablets are 200 mg, and over-the-counter liquid preparations are available as 1 mL/40 mg, 1.25 mL/50 mg, and 5 mL/100 mg. Prescription tablets are available in doses of 400 mg, 600 mg, and 800 mg. There are two IV preparations of ibuprofen: Neoprofen (1 mL/10 mg) and Caldor (4 mL/400 mg). There is also a topical preparation (EnovaRX-Ibuprofen) that contains 10% ibuprofen [4].

PATHOPHYSIOLOGY

Acute overdose with ibuprofen can cause gastrointestinal, renal, metabolic, and neurologic effects [129]. Ibuprofen inhibits prostaglandin synthesis, and some of the clinical effects of ibuprofen overdose are an extension of this mechanism of action.

COX-1 is found in the gastrointestinal tract and helps maintain the integrity of the wall of the gut [129; 130]. Inhibition of COX-1 by ibuprofen removes the protective effect of prostaglandins in addition to being directly irritating to the gut [131].

Renal blood flow is partially dependent on the activity of prostaglandins, especially if the patient is dehydrated or hemodynamically compromised. Excessive inhibition of prostaglandin synthesis caused by ibuprofen overdose affects the renal afferent arteriole, decreasing capillary perfusion in the glomeruli and potentially resulting in renal failure [131; 132]. Fluid losses from vomiting also contribute.

Ibuprofen and its metabolites are acidic, and very large ingestions of the drug can cause metabolic acidosis. Fluid and electrolyte losses, hypoperfusion, and an acidic metabolite also contribute to the development of acidosis [129; 133; 134].

CNS depression is relatively common in patients who have taken an overdose of ibuprofen. It usually manifests as mild drowsiness, but seizures and coma can occur. The pathogenesis of the neurological effects of ibuprofen are not fully understood, but seizures are likely the result of acidosis, hypoglycemia, hypoxia, or some combination of these.

SIGNS AND SYMPTOMS OF IBUPROFEN POISONING

Most patients who take an overdose of ibuprofen have minor, temporary signs and symptoms; serious toxicity and death are rare [134; 135; 136; 137]. The clinical effects are usually seen within four hours of the ingestion, and most patients experience mild, temporary gastrointestinal distress and CNS depression [129]. Gastrointestinal symptoms include anorexia, epigastric pain, nausea, and vomiting. Significant gastrointestinal bleeding is uncommon. Metabolic acidosis is a well-described but rarely seen effect of ibuprofen overdose, and there have been reports of coma, hypotension, shock, seizures, oliguria, elevations of BUN and creatinine, and other signs of renal damage after ibuprofen overdose [138; 139; 140; 141; 142; 143; 144; 145; 146; 147; 148]. In severe cases, liver damage is possible [136].

Toxic Threshold

Less than 100 mg/kg of ibuprofen is considered nontoxic, and ingestions of more than 400 mg/kg are potentially serious [129; 149; 150; 151]. Reports of serious morbidities like coma, metabolic acidosis, and renal failure have all involved ingestions of more than 20 grams or 400 mg/kg (e.g., 600 mg/kg, 1,200 mg/kg, 72 grams, 100 grams) [135; 152; 153; 154; 155].

TREATMENT

Initial Approach

The initial care of a patient who has taken an overdose of ibuprofen involves the assessment and stabilization of the ABCs. Ibuprofen overdose can cause acidosis, coma, and hypotension, but these effects are rare. If a patient with a reported but unwitnessed and unconfirmed ibuprofen overdose is seriously ill, it is prudent to investigate the possibility that the patient may have either not taken ibuprofen or has taken a co-ingestant.

If the patient is awake, alert, oriented, and hemodynamically stable, a physical examination should be performed. Time should be taken to determine the details of the ingestion and to gather information about the patient's medical history.

Following these steps, a dose of activated charcoal may be considered if the patient is stable and alert, presents within one hour of ingesting a toxic amount of ibuprofen, has an intact gag reflex, and has not ingested any other medications that could induce rapid CNS depression. Before administration of the charcoal, one should be certain that the patient has no contraindications to its use. Gastric lavage and whole bowel irrigation should be avoided.

Blood should be obtained to assess serum acetaminophen level, salicylate level, BUN, creatinine, and serum electrolytes; other laboratory studies can be done as needed. Indications for laboratory studies are situationally dependent (e.g., acetaminophen and salicylate levels would not be needed if the patient is a small child and it was certain that only ibuprofen had been ingested). Ibuprofen levels cannot be obtained in a timely manner, and they are of no value in either predicting risk or making management decisions [149]. Other laboratory tests and diagnostic tests (e.g., electrocardiogram, computed tomography scan) may be obtained if indicated by the patient's condition and medical history.

Continuing Treatment

Patients who have taken a potentially toxic amount of ibuprofen should be observed for at least four to six hours [129; 149]. Treatment is symptomatic and supportive; there is no antidote for ibuprofen poisoning. Depending on the patient's clinical condition, age, and prior medical history, IV hydration may be administered. At the end of the observation period, it may be prudent to measure BUN, creatinine, and serum electrolytes again. Patients who are very young or who have or are at risk for renal disease may require longer periods of observation and more frequent measurements of acid-base status and renal function.

Complete recovery should be expected, even after severe poisoning; death from ibuprofen overdose is very rare. Despite the large number of ibuprofen overdoses, there have been fewer than 10 recorded deaths and many of these involved confounding factors. Most patients who have taken an overdose of ibuprofen have mild and temporary gastrointestinal distress and nothing more. At the end of the observation period, if the patient's clinical status is normal, the laboratory test results are within normal range, and there were no co-ingestants, further care is not required.

CONCLUSION

Over-the-counter analgesics, including acetaminophen, aspirin, and ibuprofen, are the third most common class of drugs taken in overdose with the intent to cause self-harm. In addition, inadvertent overdoses—from both acute and chronic ingestions—are relatively common. Every year, tens of thousands of these cases are reported to poison control centers, and there are doubtless many more that go unreported. With prompt and proper treatment, the great majority of these cases should have a good outcome.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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