Drug Toxicities of Common Analgesic Medications in the Emergency Department

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KEYWORDS

• Toxicity • Acetaminophen • Opioid • Narcotic • Aspirin • Salicylate
• Emergency department

KEY POINTS

- Acute acetaminophen toxicity is commonly associated with hepatic dysfunction that may not manifest until 24 hours after ingestion; the modified Rumack-Matthews nomogram is used to determine whether treatment with *N*-acetylcysteine is indicated and is based on the serum acetaminophen level beginning at 4 hours after ingestion.
- Acute opioid toxicity is classically characterized by central nervous system depression, respiratory depression, and pupillary constriction; naloxone should be administered to achieve adequate respiration rather than a normal level of consciousness.
- Many opioids have a longer duration of action than naloxone; thus, patients who respond to naloxone should continue to be observed for persistent opioid toxicity.
- Acute aspirin toxicity can present with hyperthermia, altered mental status, coma, pulmonary edema, and shock, which require prompt recognition and initiation of therapy with hydration, sodium bicarbonate administration, electrolyte replacement, and dialysis when indicated.

ACETAMINOPHEN TOXICITY

Background

Acetaminophen was first clinically used in 1955 and since then has become the most commonly used antipyretic and analgesic medication in the United States. Acetaminophen is available as an isolated agent and is a component of prescription and over-the-counter medications used throughout the world. Acetaminophen is safe to administer at standard therapeutic doses, although it has been shown that prolonged use and overdosing of the drug can lead to nonfatal or fatal hepatic injury.[1] In fact,

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acetaminophen toxicity is the most common cause of acute hepatic failure in the United States.[2]

Pathophysiology

Acetaminophen is typically used for its antipyretic and analgesic properties, although it also has mild anti-inflammatory and antiplatelet functions, which are induced by inhibiting prostaglandin synthesis. Contrary to the mechanism of action of nonsteroidal anti-inflammatory drugs, which inhibit peripheral prostaglandin synthesis through the direct inhibition of prostaglandin E_2 (PGE_2) synthase enzymatic activity via the cyclo-oxygenase (COX) binding site, acetaminophen acts on the peroxidase binding site on PGE_2 and indirectly inhibits COX activation.[3,4]

At therapeutic levels, most circulating acetaminophen is metabolized through conjugation with glucuronide or sulfate moieties, converting it into nontoxic products that are renally excreted.[4–6] However, 5% to 15% of acetaminophen is metabolized by cytochrome (CYP) P450 enzymes into *N*-acetyl-*p*-benzoquinone imine (NAPQI), a hepatotoxic highly reactive metabolite. NAPQI has a short half-life and is rapidly conjugated into nontoxic metabolites with glutathione and other moieties before being renally excreted. At therapeutic doses of acetaminophen, there are sufficient glutathione stores to maintain NAPQI metabolism at an adequate rate, and its nontoxic metabolites are renally excreted.

With excessive NAPQI production or with depletion of glutathione stores, such as in acetaminophen overdose or repeated supratherapeutic dosing, the glucuronidation and sulfation metabolizing pathways are saturated. In turn, additional acetaminophen is metabolized by CYP enzymes to NAPQI. It has been demonstrated that when hepatic glutathione stores are reduced by approximately 70% or more, unmetabolized NAPQI causes hepatotoxicity.[7,8] The reactive molecule covalently binds to hepatic cellular proteins, which leads to hepatocyte necrosis within hours of the drug ingestion.[9]

The current US Food and Drug Administration (FDA)-recommended maximum daily dose of acetaminophen is 4 g in individuals 50 kg and greater and 75 mg/kg in individuals less than 50 kg.[10] According to the FDA, exceeding the maximum recommended daily dose of acetaminophen can cause acute hepatotoxicity, particularly in those individuals with underling liver disease, chronic alcohol use, concomitant treatment with medications that induce CYP enzymes, such as phenytoin and isoniazid, malnutrition, and advanced age.[10–13] Such individuals with increased susceptibility can develop hepatotoxicity at lower doses.

Manifestations of Drug Toxicity

Within the first 24 hours of acetaminophen overdose, most patients will be asymptomatic or have mild nonspecific symptoms, such as nausea, vomiting, and malaise.[14] Laboratory studies are usually normal, and elevated anion gap metabolic acidosis (AGMA) is rare at this stage in massive overdoses.[15] Hepatotoxicity usually will not manifest until 24 hours after ingestion, at which point there may be elevations in transaminase levels (**Table 1**), which may be accompanied by other clinical signs of liver injury, including right upper quadrant abdominal pain or tenderness, liver enlargement, and jaundice. There may also be elevations in prothrombin time (PT) and bilirubin as well as signs of renal function abnormalities. Although with severe toxicity, elevations in transaminases may be seen within the first 24 hours.[6,16] The most severe cases of toxicity involve fulminant liver failure, which can manifest as renal injury, coagulopathy leading to hemorrhage, AGMA, cerebral edema, hepatic encephalopathy, sepsis, and multiorgan failure.[14] Patients who survive this phase generally have resolution of hepatic sequelae, although full histologic resolution may take months.[14]

Table 1
Acetaminophen-induced hepatotoxicity without treatment may be conceptualized as occurring in various stages with different manifestations depending on the time since ingestion

Stage	Time After Ingestion (d)	Clinical Signs	Laboratory Markers
1	0–1	Asymptomatic or mild nausea, vomiting, malaise	Normal or increased AST in severe cases
2	1–3	RUQ abdominal pain, nausea, vomiting, lethargy	Increased AST, ALT, PT, bilirubin, and lactic acid
3	3–5	Jaundice, coagulopathy, hypoglycemia, renal dysfunction, hepatic encephalopathy, multiorgan failure	AGMA, increased serum creatinine and ammonia
4	5+	Resolution of hepatotoxicity	Normalization

The first stage may involve mild or no associated symptoms, except in severe toxicity. The fourth stage represents the recovery period and involves the resolution of hepatic injury, which may take months.

Abbreviations: ALT, alanine aminotransferase; RUQ, right upper quadrant.

Data from Defendi GL. Acetaminophen toxicity in children: diagnosis, clinical assessment, and treatment of acute overingestion. Cons Pediat 2013;12(7):301.

Diagnostic Evaluations in Suspected Toxicity

Acetaminophen toxicity risk is most reliably established by correlating the serum concentration level to the time since ingestion. In suspected overdose, a serum concentration level at 4 hours after ingestion should ideally be obtained, although levels drawn before 4 hours may not be representative of peak serum levels due to incomplete absorption and should not be used in the assessment of toxicity. The ingested dose should not be used to predict the risk of hepatotoxicity or need for therapy, because a serum concentration level is a more reliable predictor than ingested dose.[17] Because of its effectiveness and safety profile, the modified Rumack-Matthew nomogram (**Fig. 1**) is the preferred tool to assess the need for treatment with *N*-acetylcysteine (NAC) in those presenting within 24 hours of a single ingestion with a known time of the ingestion.[18] The treatment line indicates serum levels corresponding to hourly time points after ingestion at which NAC should be administered. The initial level is 150 μg/mL at 4 hours, and the final level is 4.7 μg/mL at 24 hours. It is not necessary to treat patients with NAC before the 6-hour mark after ingestion because those treated up to 6 hours afterward, regardless of the initial level or amount ingested, do not have an increased risk of hepatotoxicity.[14] However, even with treatment, the incidence of hepatotoxicity (aspartate aminotransferase [AST] >1000 IU/L) in patients presenting 8 hours after ingestion is approximately 30%.[14] Administering a loading dose of NAC should be considered in cases where a level cannot be obtained before 8 hours after ingestion. Patients with a level below the treatment line can be discharged if otherwise medically cleared. Those with signs of severe toxicity, including AGMA, coagulopathy, hepatic failure, or encephalopathy, should be treated and managed in an intensive care setting.

Management of Toxicity

Appropriate initial care in acute toxicity involves assessment of airway, breathing, and circulatory status as well as assessment of other possible life-threatening coingestions.

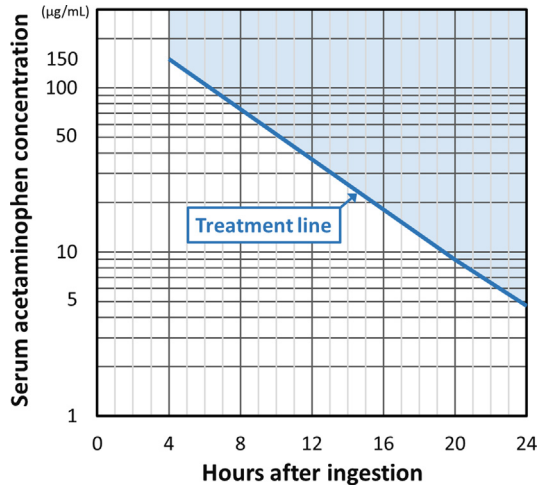

Fig. 1. Modified Matthew-Rumack nomogram demonstrating the treatment line, which indicates the serum acetaminophen level at which NAC should be administered based on the time after ingestion. The 4-hour mark corresponds to 150 μg/mL and the 24-hour mark corresponds to 4.7 μg/mL. (*Adapted from* Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976–1985). N Engl J Med 1988;319(24):1558.)

If a patient presents with stable mental status within 1 hour of ingestion, activated charcoal can be administered, because it effectively adsorbs acetaminophen, although there is ongoing debate regarding its efficacy in improving clinical outcomes.[19,20] It is universally accepted that early administration of NAC is the ideal currently available treatment.[18] NAC acts as a precursor for glutathione synthesis and thus provides more substrate for the conjugation of NAPQI, which leads to detoxification of this reactive metabolite.[21,22] If administered within 8 hours of acetaminophen ingestion, NAC has nearly 100% efficacy in preventing hepatotoxicity, and death is extremely rare regardless of the initial plasma concentration.[18,23] However, there is a significantly higher rate of hepatotoxicity if NAC is administered after 8 hours after ingestion.[14] NAC may be administered via an oral or intravenous route, and both formulations are effective when administered up to 24 hours after ingestion.[14] However, if hepatotoxicity is evident, such as with the onset of coagulopathy or encephalopathy, the intravenous formulation should be administered and is the only formulation that has been studied in such cases.[14] Common side effects of oral NAC include nausea and vomiting in approximately 23% of individuals, which may be attributable to its very unpleasant taste and odor.[24] Severe side effects of the oral formulation such as major anaphylactoid reactions are rare. Side effects of intravenous NAC include mild anaphylactoid reactions, such as rash, pruritus, and vomiting, which are seen in 2% to 6% of individuals.[14] Severe anaphylactoid reactions, such as angioedema, bronchospasm, and hypotension, have been reported with a less than 1% incidence.[14]

Two used NAC administration protocols include a 21-hour intravenous protocol and a 72-hour oral protocol.[25] It remains controversial which treatment protocol is preferable and whether it is essential to complete the full treatment course.[25,26] NAC may be discontinued once the administration protocol is completed, provided that serum acetaminophen has been metabolized (level <10 μg/mL) and there is no sign of ongoing hepatic injury (normal AST level). If acetaminophen metabolism has not

completed (level >10 μg/mL) or there is ongoing liver injury, NAC administration should continue until there are no further signs of liver injury.[14]

OPIOID TOXICITY

Background

Many medications in various drug classes are available for management of acute and chronic pain, with opioids being the most potent and among the most commonly prescribed. The opioid drug class includes natural, synthetic, and semisynthetic drugs, whereas "opiates" specifically include natural agents. Furthermore, the term "narcotic" refers specifically to any substance that blunts the senses, induces coma, or relieves pain and may erroneously be used to refer to any illicit psychotropic substance.

Opioids, which are directly derived from opium, have been used for medicinal and recreational purposes since approximately 3400 BC when opium is known to have first been cultivated.[27] Opium itself is an extract derived from the dried sap of the poppy plant, *Papaver somniferum*. The natural extract contains the opioid alkaloids morphine, codeine, and other nonanalgesic alkaloids.[28] Today opioids and its many derivatives are used predominantly for pain control, although they are frequently abused because of their highly addictive potential.

Pharmacoepidemiology

Opioids are the mainstay treatment of moderate or severe pain and improve quality of life for many individuals despite their potential for misuse and the increase of deaths related to overdose. Opioids, mainly heroin and prescription pain medications, are the drugs most commonly associated with overdose deaths.[29] In 2014, opioid drugs were involved in more than 28,000 deaths, or 61% of all drug overdose deaths.[29] Acute or chronic pain is the chief complaint in more than half of emergency department (ED) visits in the United States, and ED physicians are among the top 5 most prescribing physicians of opioids to patients with chronic noncancer pain.[30,31] As opioid use becomes more common, the risk for dependence and the incidence of overdoses continue to increase. Between 2001 and 2010, the percentage of ED visits during which opioids were prescribed increased from 21% to 31%.[31] The current prevalence of opioid dependence is almost 5 million people in the United States.

Mechanism of Action

Analogous to endogenous opioidlike molecules, including endorphins, dynorphins, and enkephalins, exogenous opioids primarily bind to 3 receptor types to impede neuronal transmission within the central nervous system (CNS) and peripheral nervous system to mediate brain- and spinal-level analgesia, sedation, euphoria, gastrointestinal secretion and motility, respiration, and other functions.[32,33] The 3 primary receptor types, mu (μ), kappa (κ), and delta (δ), are structurally similar transmembrane G protein–coupled receptors that are distributed in various locations, including in sensory neurons, vascular endothelial cells, neurologic respiratory centers, and the gastrointestinal tract.[14,34] Activation of these receptors results in modulating the release of neurotransmitters at the target sites. Opioid receptor antagonists, such as naloxone and naltrexone, competitively inhibit these receptors and reverse the opioid-mediated actions.[14]

Pharmacokinetics

The various types of opioids have different pharmacokinetic properties and varying rates of metabolism. Opioids are generally well absorbed through oral, nasal, and

gastrointestinal mucosal surfaces as well as subcutaneous and intramuscular routes. Synthetic opioids such as fentanyl are also routinely administered through a transdermal patch. Opioids absorbed through the gastrointestinal tract may have reduced bioavailability because of first-pass metabolism in the liver and intestinal wall.[35] Most opioids have relatively large volumes of distribution ranging from 1 to 10 L/kg and consequently are poorly dialyzable.[36] Opioids traverse the placenta, and when administered before delivery, may induce respiratory depression in the infant.[37,38] All opioids are metabolized through hepatic conjugation, and the resultant active or inactive metabolites are renally excreted.[14,39] Thus, opioids have an extended duration of action in the setting of hepatic dysfunction because of decreased hepatic metabolism, which can further potentiate opioid toxicity.[39] Furthermore, renal dysfunction can reduce the excretion of active metabolites, potentiating their effects. Such is the case with morphine, which is conjugated into the active metabolites morphine-3-glucoronide and morphine-6-gluconoride, which are both normally renally excreted.[36,40]

Opioids vary significantly in their serum half-life, which can further be influenced by dose, individual tolerance level, extent of active metabolite presence, and drug distribution (**Table 2**). In opioid-naïve individuals, the serum half-life of a single administered dose varies from approximately 2 to 3 hours with morphine to potentially 150 hours with methadone.[41] Opioids also vary in lipid solubility, which is significant as high lipid solubility promotes more rapid molecule absorption and confers a higher propensity to cross lipid barriers and enter the CNS, providing a more rapid onset and shorter duration of efficacy.[42] Consequently, fentanyl, a highly lipid-soluble opioid, has quick onset and short duration of action when administered intravenously, in contrast to morphine, which is approximately 40 times less lipid soluble and has a longer time of onset and longer duration of action.[42,43]

Table 2
Opioid analgesics vary widely in terms of half-life and duration of action

Opioid	Onset (min)	Duration (h)	Half-Life (h)
Morphine IR	PO 15–60 IM 15–30 IV <5	3–6	2–3
Morphine CR (PO)	20–40	8–12	2–3
Oxycodone IR (PO)	15–30	3–6	2–3.5
Oxycodone CR (PO)	15–30	8–12	2–3
Hydromorphone	PO 15–30 IM 15–30 IV <5	3–6	2–3
Codeine (PO)	30–60	4–6	2.5–3.5
Hydrocodone (PO)	20–30	3–6	2–4.5
Methadone (PO)	30–90	24–48	12–150
Fentanyl (IV)	<1	0.5–1	3.7
Fentanyl (transdermal)	8–12 h	48–72	16–24

Various formulations of routinely used opioid analgesics are shown.

Abbreviations: CR, controlled-release; IM, intramuscular; IR, immediate-release; IV, intravenous; PO, oral.

Data from Smith HS. Current therapy in pain. Philadelphia: Saunders Elsevier; 2009.

Manifestations of Drug Toxicity

Opioid toxicity generally involves, among other symptoms, CNS depression, respiratory depression, pupillary constriction, and decreased gastrointestinal motility. Direct CNS depression is common and can further be complicated by disturbances such as seizures or acute psychosis.[14] Meperidine is known to produce an active metabolite with CNS excitatory function, which has the ability to induce seizures, particularly in individuals with hepatic or renal dysfunction.[44] Parkinsonian symptoms have been identified in intravenous drug users who had injected MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a product in the illicit synthesis of MPP (1-methyl-4-phenylpyridinium), a meperidine analogue, which has been shown to damage dopamine-producing cells in the substantia nigra.[45,46] Serotonin syndrome has been associated with opioids that inhibit serotonin reuptake, including meperidine, dextromethorphan, methadone, and buprenorphine.[14,47]

Respiratory depression, secondary to reduction in respiratory rate or tidal volume, is induced by reducing the sensitivity of chemoreceptors in the medulla to hypercapnia.[48] Acute opioid toxicity has been implicated as a cause of acute lung injury, clinically indistinguishable from acute respiratory distress syndrome. The exact involved mechanisms are unclear but presumably involve increased pulmonary capillary leakage from hypoxemia and histamine release.[49] Opioids induce arterial and venous dilation, causing mild hypotension, which may be advantageous in the setting of acute cardiogenic pulmonary edema by transiently reducing preload in addition to their anxiolytic effects.[50] Common gastrointestinal effects of opioid toxicity include nausea and vomiting, which occur secondary to reduced gastric emptying, increased vestibular sensitivity, and direct stimulation of the medullary chemoreceptor trigger zone.[51] Decreased gastrointestinal motility occurs commonly and in severe cases may progress to intestinal ileus.[52]

Diagnostic Evaluations in Suspected Toxicity

Overdoses of opioids are especially important to identify because of the high morbidity and mortality when left untreated and the ease with which their effects can be reversed. Identifying opioid toxicity is predominantly dependent on elements of the history and physical examination. History should be obtained from Emergency Medical Services providers, family, friends, or bystanders, including any information regarding possible access to medications or drug paraphernalia, and if known, time since ingestion, amount of substance ingested, and presence of other coingested substances. In addition to the aforementioned clinical findings, patients may have needle track marks from repeated intravenous or subcutaneous (“skin-popping”) injections. Patients should be inspected for the presence of transdermal opioid patches. Patients should be screened for hypoglycemia, although other laboratory abnormalities are not seen consistently. Oxygen saturation and capnography may help to identify hypoxia and respiratory depression. A plain abdominal radiograph may be helpful in cases of suspected body packers, also known as “mules,” because ingested packets of paraphernalia such as opioids have a reported detection sensitivity of 85% to 90%.[53] Serum acetaminophen and aspirin concentrations should be obtained in cases where the formulation of the ingested opioid is unknown. Most urine toxicology screening (immunoassays) assays will detect opioids, and the presence and specificity of such analytes can be verified through confirmatory testing modalities, such as gas chromatography-mass spectrometry or liquid chromatography-mass spectrometry. However, routine urine toxicology screens are not recommended, because a false positive

test can result from the detection of nonspecific analytes. Furthermore, a positive screen may not necessarily indicate acute toxicity because a urine test can remain positive for several days after last intake, depending on the half-life of the specific substance.[54] The ingestion of poppy seeds can produce a urine test that is positive for morphine and codeine.[55]

Management of Toxicity

Initial management of patients with opioid toxicity involves aggressive airway control. Emergent intubation may be necessary in patients who are not able to protect their airway despite treatment. Naloxone is a rapid-onset μ-receptor antagonist that should be administered in the presence of severe CNS or respiratory depression. The goal of naloxone administration is adequate respiration rather than a normal level of consciousness. Intravenous administration is preferred due to a faster onset of action of 1 to 2 minutes, although obtaining intravenous access may be time consuming and difficult, particularly in chronic intravenous drug abusers.[56–58] Alternatively, intramuscular, subcutaneous, endotracheal, intraosseous, and intranasal routes may be used. Intranasal delivery of naloxone using an atomizer spray is frequently practiced in the prehospital setting because of the relative ease of administration as well as its rapid onset and effectiveness.[59,60] Regardless of the route, naloxone should be administered judiciously because it may precipitate withdrawal symptoms in some patients, particularly in long-term opioid users. With severe CNS or respiratory depression, an intravenous dose of 0.4 to 2 mg should be administered. With the presence of spontaneous respirations, an initial intravenous dose of 0.04 mg is appropriate and may be titrated up to achieve adequate spontaneous ventilation.[61] Acute withdrawal symptoms may involve nausea, vomiting, and agitation with the potential for aspiration of gastric contents. Additional opioids should not be administered to counter withdrawal symptoms, because intravenous naloxone has a short duration of action of 30 to 60 minutes, and further sedation may occur once its effect dissipates.[56,62]

Because of the short duration of action of naloxone and the long duration of many opioids, it may be necessary to administer additional doses of naloxone, depending on the duration of efficacy of the opioid involved. In this situation, a continuous naloxone infusion may be considered in lieu of repeated bolus administration. A proposed nomogram for naloxone infusion dosing suggests administering at every hour a continuous infusion of two-thirds of the bolus dose that resulted in opioid action reversal.[63] The infusion should be discontinued with the onset of withdrawal symptoms.

Gastrointestinal decontamination using gastric lavage or activated charcoal administration is not appropriate in most cases of opioid toxicity, because there is no available clinical evidence demonstrating benefit. The theoretic benefits of extracting undissolved pill fragments or allowing activated charcoal to bind unabsorbed drugs are outweighed by the risk of aspiration, particularly in patients with CNS depression. Whole-bowel irrigation is occasionally performed in the setting of body stuffing with opioid-containing packets, although there is no convincing evidence from clinical studies that it improves patient outcomes.[64,65]

Opioid withdrawal symptoms that are not precipitated by naloxone administration are not life-threatening and can be managed conservatively. However, administration of naloxone may induce a catecholamine surge with resultant hemodynamic instability and in some cases may cause pulmonary edema.[66,67] Supportive care in the ED is appropriate in the management of most cases of opioid toxicity that required treatment with naloxone. As the effective duration of action of naloxone is 30 to 60 minutes, observing patients for 2 hours to assess symptom resolution and clinical improvement

is appropriate.[68] Overdoses of long-acting opioids such as methadone may require prolonged monitoring and possible hospital admission.

ASPIRIN TOXICITY

Background

Aspirin, also known as acetylsalicylic acid, is a commonly used salicylate drug due to its analgesic, antipyretic, and anti-inflammatory properties through the inhibition of COX isozymes.[69] It is used as an isolated compound in the long-term prevention of cardiovascular diseases or in combination, as seen with drugs such as Fiorital and Excedrin to treat headache.[69–71] Clinicians need to know the signs and symptoms of salicylate toxicity, which can occur in patients who unintentionally take aspirin or cold medication preparations that also contain aspirin.[4] Fortunately, safety packaging and the use of alternatives to aspirin have decreased the incidence of accidental salicylate toxicity.[4,14]

Pathophysiology

Salts of salicylic acid are rapidly absorbed intact from the gastrointestinal tract, and serum concentrations increase within 30 minutes after ingestion; however, large ingestions or ingestions of enteric capsules can prolong absorption.[4,14] Aspirin is hydrolyzed to free salicylic acid in the intestinal wall, liver, and red blood cells.[14] In turn, salicylate is conjugated with glucuronic acid and glycine, whereas a small percentage is oxidized (**Fig. 2**).[4,14] Free salicylate and its conjugates are renally excreted, which follows first-order kinetics at therapeutic concentrations. However, when the concentration is greater than 30 mg/dL, the elimination follows zero-order kinetics.[4,14]

Effects of Aspirin on Aerobic Metabolism

Salicylate stimulates the respiratory center, which causes respiratory alkalosis but depresses the respiratory center at prolonged high serum concentrations.[4,14,69]

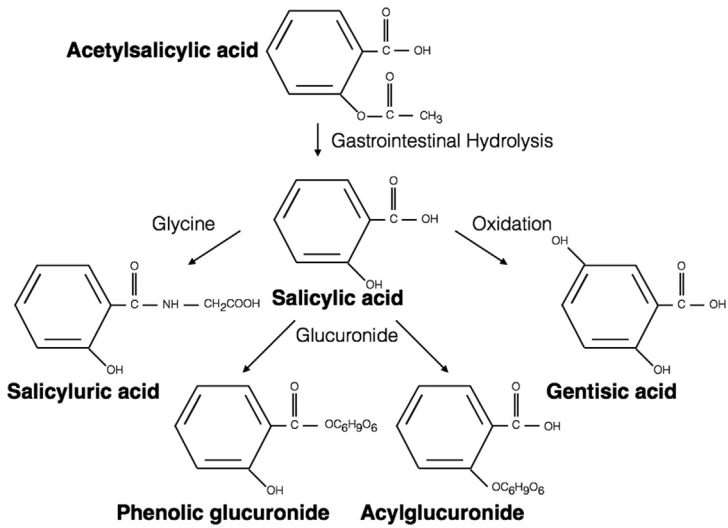

Fig. 2. Metabolism of aspirin, also known as acetylsalicylic acid. The conjugation or oxidation of salicylic acid produces its metabolites, which can be renally excreted. (*Adapted from* Nelson LS, Lewin NA, Howland MA, et al. Goldfrank's toxicologic emergencies. New York: McGraw-Hill; 2011.)

Toxicity of salicylate is caused by its interference with aerobic metabolism.[4] For instance, aspirin inhibits the Krebs cycle and delivery of the metabolites needed by the electron transport chain,[4,14,72] thus reducing the mitochondrial fuel supply and energy flux needed for adenosine triphosphate (ATP) synthesis (**Fig. 3**).[72] On the other hand, salicylate induces the mitochondrial permeability transition, which uncouples mitochondrial oxidative phosphorylation.[72,73] Uncoupling of mitochondrial oxidative phosphorylation and inhibition of the Krebs cycle lead to accumulation of pyruvate and lactic acid. The production of ketone bodies increases due to increased lipid metabolism. Moreover, salicylate toxicity is prone to hypoglycemia due to the increase in tissue glycolysis. The net outcome of these metabolic processes is AGMA.[4,14]

Manifestations of Drug Toxicity

Patients with aspirin toxicity can develop symptoms ranging from vomiting to altered mental status and seizures. These symptoms cause metabolic derangements associated with aspirin toxicity. For example, vomiting due to local gastric irritation at lower doses and stimulation of the medullary chemoreceptor trigger zone at higher doses of aspirin can lead to hypokalemia and metabolic alkalosis. Vomiting and insensible fluid loss from hyperventilation can lead to dehydration, which causes acute kidney insufficiency. The uncoupling of oxidative phosphorylation can lead to decreases in hepatic glycogen storage secondary to increased glycogenolysis and glycolysis. As the salicylate level increases in the CNS, neuronal energy depletion occurs, resulting in cerebral edema. Acute lung injury occurs in the setting of salicylate toxicity due to increased pulmonary capillary permeability and exudation of protein edema fluid into the interstitial or alveolar space.

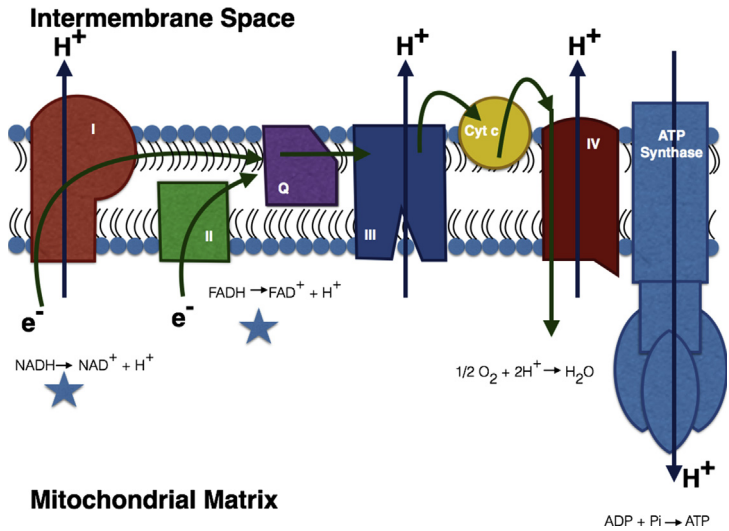

Fig. 3. The production of ATP in the electron transport chain (ETC). Green arrows depict the transfer of electrons from Krebs cycle substrates, whereas the blue arrows depict the movement of protons through the complexes. Blue stars represent the lack of substrates needed for the ETC secondary to inhibition of Krebs cycle by aspirin. (*Adapted from* Fosslien E. Mitochondrial medicine—molecular pathology of defective oxidative phosphorylation. Ann Clin Lab Sci 2001;31(1):46.)

Bleeding can occur secondary to platelet dysfunction from irreversible inhibition of COX-1 and COX-2 isozymes, which prevents the formation of thromboxane A2. However, it is important to realize that the number and morphology of platelets are normal.[4,14]

Diagnostic Evaluations in Suspected Toxicity

The laboratory evaluation in the setting of aspirin toxicity includes a basic metabolic panel, initial serum salicylate level, a repeat serum salicylate level at 2 hours to determine if the concentration is increasing or decreasing, venous or arterial blood pH, and a serum drug screen to evaluate for coingestions, such as acetaminophen and tricyclic antidepressants.[4,14,74] Aspirin uncouples mitochondria and stimulates the respiratory center; this leads to a mixed acid-base disorder with AGMA and respiratory alkalosis (**Table 3**). The bicarbonate is used to neutralize the acid while the body is losing carbon dioxide gas from hyperventilation. The ferric chloride test, Ames Phenistix test, and Trinder spot test have been previously used as bedside salicylate screening tests.[74] However, these tests are not permissible outside of a certified laboratory according to the federal Clinical Laboratory Improvement Amendments in the United States.[4] Spectrophotometry is now used to determine salicylate concentration, which relies on chemical reactions to form a light-absorbing substance. The spectrophotometer takes multiple absorbance measurements in order to determine the rate of change in light absorbance as the reaction proceeds. The rate is constant and proportional to the initial concentration of the analyte at the beginning of the reaction. Unfortunately, spectrophotometry is subjected to interferences by substances that produce light-absorbing products or by substances that consume reagents without producing light-absorbing products. In order to improve the selectivity of the assay, enzymes are often used to catalyze highly selective reactions.[4] The concentration of salicylates in a sample is determined by using salicylate hydroxylase to convert salicylate and NADH to catechol and NAD^+. The change in absorbance at 340 nm is directly proportional to the concentration of salicylate in the sample.[69]

Management of Toxicity

When patients present with clinical findings of salicylate toxicity, it is imperative to initiate treatment as soon as possible (**Box 1**). Activated charcoal has been used

Table 3
The signs and symptoms, laboratory results, and the effects of aspirin toxicity at the cellular level

Symptoms/Signs	Laboratory Results	Cellular Level Effects
Convulsions	AGMA (decreased HCO_3^{2-})	Uncoupling of mitochondrial oxidative phosphorylation
Hyperpnea	Respiratory alkalosis (decreased CO_2)	Increased glycolysis/glycogenolysis
Cerebral edema	Lactic acidosis	Increased ketone production
Pulmonary edema	Hypokalemia	Inefficient ATP production
Dehydration	Elevated creatinine	Inhibition of Krebs cycle

Abbreviations: CO_2, carbon dioxide; HCO_3^{2-}, bicarbonate.

Adapted from Marx JA, Hockberger RS, Walls RM. Rosen's emergency medicine concepts and clinical practice. Philadelphia: Elsevier Saunders; 2014; with permission.

Box 1
Management of patients with aspirin toxicity

Therapy

- Gastrointestinal decontamination with activated charcoal
- Enhance elimination via urine alkalinization
- Hemodialysis
- Fluid replacement
- Correct hypokalemia
- Mechanical ventilation

Adapted from Marx JA, Hockberger RS, Walls RM. Rosen's emergency medicine concepts and clinical practice. Philadelphia: Elsevier Saunders; 2014; with permission.

for treatment of many drug ingestions, including aspirin. Studies have shown that activated charcoal reduces absorption of salicylates by 50% to 80%, and it is recommended that a 10:1 ratio of activated charcoal to ingested salicylate be used in treating salicylate poisoning.[4] Dehydration is a known complication of aspirin toxicity secondary to vomiting, insensible fluid loss, and a hypermetabolic state, which requires careful repletion with intravenous fluid because excessive fluid replacement can worsen cerebral and pulmonary edema.[14] It is recommended that fluid contains dextrose because aspirin toxicity is also associated with hypoglycemia. The administration of intravenous sodium bicarbonate (1–2 mEq/kg) has been recommended as part of the management of salicylate toxicity. Alkalinization of serum reduces the percentage of salicylate in the nonionized form and increases the pH gradient with cerebrospinal fluid, both of which prevent entry and removal of salicylates from the CNS.[4] Furthermore, alkalinization with a target urine pH of 7.5 to 8.0 increases excretion of aspirin from the kidney.[14] It is important to correct hypokalemia to maintain alkaline urine. Hemodialysis should be initiated sooner rather than later in certain patients (**Box 2**).[4,14]

Box 2
Indications to initiate hemodialysis in aspirin toxicity

Indications for hemodialysis

- Renal failure
- Altered mental status
- Hepatic failure
- Pulmonary edema
- Severe acid-based disturbance
- Salicylate concentration greater than 100 mg/dL (acute) or greater than 50 mg/dL (chronic)
- Failure to respond to conservative management

Adapted from Marx JA, Hockberger RS, Walls RM. Rosen's emergency medicine concepts and clinical practice. Philadelphia: Elsevier Saunders; 2014; with permission.

SUMMARY

About 75% of patients present to the ED with a complaint of pain, making it the most common chief complaint[75,76] and leading to the Joint Commission on Accreditation of Hospitals Organization recommending in 2000 that pain be assessed as a fifth vital sign and mandating effective treatment of pain.[76] There are multiple prescribed and over-the-counter medications that are available for the treatment of pain. Aspirin, acetaminophen, and opioids are commonly used agents that are available as single agents or in combination with other medications. However, all of these agents are susceptible to toxic overdose, which requires prompt recognition and initiation of therapy to reduce the risk of morbidity and mortality.

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