Acetaminophen

Robert G. Hendrickson

INTRODUCTION

HISTORY AND EPIDEMIOLOGY

By the late 1800s, both phenacetin and acetanilide were used as analgesics and antipyretics, but their acceptance was limited by significant side effects including methemoglobinemia. N-acetyl-p-aminophenol (APAP) is a major metabolite of phenacetin and acetanilide, and is responsible for, both analgesia and antipyresis. APAP was synthesized in 1878 and has a low risk of causing methemoglobinemia. N-acetyl-p-aminophenol is referred to as acetaminophen (N-acetyl-paraaminophenol) in the United States, Canada, Japan, and several other countries and as paracetamol (para-acetylaminocephol) in most other areas of the globe. Both terms are abbreviations of the chemical name. APAP was first used clinically in the United States and the United Kingdom in the mid 1950s, but its widespread acceptance was delayed until the 1970s because of concerns of the toxicities of its precursors. APAP has since proved to be a remarkably safe xenobiotic at appropriate dosage, which has led to its popularity. APAP is available in a myriad of single-agent dose formulations and delivery systems, and in a variety of combinations with opioids, other analgesics, sedatives, decongestants, expectorants, and antihistamines. The diversity and wide availability of APAP products dictate that APAP toxicity be considered not only after identified ingestions but also after exposure to unknown or multiple xenobiotics in settings of intentional overdose, abuse, and therapeutic misadventures.

Despite enormous experience with APAP toxicity, many controversies and challenges remain unresolved. New formulations and new analogs are being introduced, that will require reassessments of the available knowledge. To best understand the continuing evolution in the approach to APAP toxicity, it is critical to start with certain fundamental principles and then to apply these principles to both typical and atypical presentations in which APAP toxicity must be considered.

PHARMACOLOGY

APAP is an analgesic and antipyretic with weak peripheral antiinflammatory and antiplatelet properties. Analgesic activity is reported at a serum [APAP] of 10 μg/mL and antipyretic activity at 4 to 18 μg/mL.

APAP has a unique mechanism of action among the analgesic antipyretics. Most of the nonsteroidal antiinflammatory drugs (NSAIDs) occupy the cyclooxygenase (COX) binding site on the enzyme prostaglandin H_2 synthase (PGH_2) and prevent arachidonic acid from physically entering the site and being converted to prostaglandin H_2. APAP also inhibits prostaglandin H_2 production but does so indirectly by reducing a heme on the peroxidase (POX) portion of the PGH_2, and indirectly inhibiting COX activation. In this way, APAP function is highly dependent on cellular location and intracellular conditions. APAP strongly inhibits prostaglandin synthesis where concentrations of POX and arachidonic acid (“peroxide tone”) are low such as in the brain. In conditions of high peroxide tone, such as inflammatory cells (macrophages) and platelets, prostaglandin synthesis is less affected by APAP, although this is not universal. This dissociation
explains the strong central antipyretic and analgesic effect of APAP but weak peripheral antiinflammatory and antiplatelet effects. Functionally, APAP predominantly acts as a central indirect inhibitor of COX-2 enzymes, with some mild peripheral COX-2 inhibition and minimal COX-1 inhibition (Chap. 37).

Antipyresis and analgesia are predominantly mediated by this central indirect COX-2 inhibition and the resulting decrease in prostaglandin E₂ (PGE₂) synthesis. Additional analgesic effects may be mediated by indirect stimulation by APAP of serotonergic and opioid descending pathways or activation of the cannabinoid system. Stimulation of descending serotonergic pathways is demonstrated in rats and humans, and the analgesic effect of APAP may be inhibited by several serotonin antagonists or serotonin depletion. In rats, the analgesic effect of APAP is attenuated by opioid receptor antagonists. However, APAP binds poorly to opioid receptors and the exact mechanism of opioid stimulation remains unexplained. Finally, activation of the central or peripheral endogenous cannabinoid system, potentially from an APAP metabolite, has been theorized but remains controversial.

PHARMACOKINETICS

After ingestion of a therapeutic dose, immediate-release APAP is rapidly absorbed from the small intestine with a time to peak [APAP] of approximately 30 minutes for liquid formulations and 45 minutes for tablet formulations. Extended-release APAP has a time to peak of 1 to 2 hours but is almost entirely absorbed by 4 hours. The time to peak may be delayed by food and co-ingestion of opioids or anticholinergics. The oral bioavailability is 60% to 98%, and the volume of distribution (Vd) is 1 L/kg. Peak [APAP] after recommended doses typically ranges from 8 to 20 µg/mL. After administration of 20 to 25 mg/kg rectal suppositories, the peak [APAP] ranges from 4.1 to 13.6 µg/mL, the time to peak [APAP] is 2 to 4 hours (range, 0.4–8 hours), and the bioavailability is 30% to 40%. APAP is available in the intravenous form as an APAP solution in the United States, United Kingdom, Australia, New Zealand, and many other countries as well as a prodrug (eg, propacetamol) in the United Kingdom. The time to peak of the intravenous formulations are immediate (< 15 minutes), and peak [APAP] after a 1 g infusion is approximately 30 µg/mL, and after a 2 g infusion is approximately 75 µg/mL with a large range of 31 to 161 µg/mL. The Vd is higher in both pregnant women and neonates, while clearance rates are higher in pregnant women and lower in neonates. APAP has total protein binding of 10% to 30% that does not change in overdose. APAP crosses the placenta, the blood–brain barrier, and in small amounts (< 2% of ingested dose), into breast milk.

After absorption, approximately 90% of APAP normally undergoes hepatic conjugation with glucuronic acid (40%–67%), mostly via UGT1A6, and sulfate (20%–46%), mostly via SULT1A1, to form inactive metabolites, which are eliminated in the urine. A small fraction of unchanged APAP (< 5%) and other minor metabolites reach the urine. The remaining fraction, approximately 5% in therapeutic doses, is oxidized by CYP2E1 (and, to a lesser extent, CYP3A4, CYP2A6, and CYP1A2), resulting in the formation of N-acetyl-p-benzoquinoneimine (NAPQI). Glutathione (GSH) quickly combines with NAPQI, and the resulting complex is converted to nontoxic cysteine or mercapturate conjugates, which are eliminated in the urine (Fig. 35–1). The elimination half-life of APAP is approximately 2 to 3 hours after a nontoxic dose but may become prolonged in patients who develop hepatotoxicity.

**FIGURE 35–1.** Important routes of APAP metabolism in humans and mechanisms of N-acetylcysteine (NAC) hepatoprotection. NAC1 augments sulfation, NAC2 is a glutathione (GSH) precursor, NAC3 is a GSH substitute, and NAC4 improves multorgan function during hepatic failure and possibly limits the extent of hepatocyte injury. APAP = N-acetyl-p-aminophenol = acetaminophen.
TOXICOKINETICS

After most oral overdoses, the majority of APAP absorption occurs within 2 hours and peak plasma concentrations generally occur within 4 hours. Later peaks or double peaks are rarely documented in overdoses and have generally occurred after large ingestions (> 50 g) with or without co-ingested antimuscarinics. Evidence suggests that NAPQI production is largely the result of activity of the CYP2E1 enzyme after both therapeutic and supratherapeutic doses of APAP. Contributions of CYP1A2, CYP3A4, and CYP2A6 to the production of NAPQI in humans are small and insignificant in most cases, but they may be variable, depending on individual host factors and dosage. After clinically significant overdose, nontoxic sulfation metabolism of APAP may become saturated. The amount of NAPQI formed is increased out of proportion to the APAP dose and may account for up to 20% to 50% of metabolism in patients with hepatotoxicity.

The toxicokinetics of intravenous APAP are largely unknown. Doses of 75 mg/kg and 146 mg/kg have produced 4 hour [APAP] of 35 µg/mL and 117 µg/mL, respectively, with half-lives ranging from 2 to 6 hours. One patient who received a 75 mg/kg intravenous APAP dose had a 1 hour [APAP] of 72 µg/mL.

PATHOPHYSIOLOGY

The safety of appropriate APAP dosing results from the availability of electron donors such as reduced GSH and other thiol (S-H)-containing compounds. After therapeutic APAP dosing, GSH supply and turnover far exceed that required to detoxify NAPQI. With ample GSH supply, NAPQI is largely bound by GSH, and no toxicity occurs, although NAPQI-cysteine protein adducts do form within the liver and some are released into the serum. After overdose, the rate and quantity of NAPQI formation outstrip supply and turnover of GSH, resulting in the release of NAPQI within the cell. NAPQI then rapidly binds to hepatocyte constituents, including the cysteine portion of proteins, producing protein adducts within the liver. In animal experiments, hepatotoxicity becomes evident only when hepatic [GSH] decreases to 30% of baseline or below.

When NAPQI formation overwhelms the supply of thiol-containing compounds, it covalently binds and arylates proteins throughout the cell, inducing a series of events that result in cell death. Covalent binding and arylation occur rapidly after GSH depletion. Both covalent binding and GSH deficiency are necessary for hepatotoxicity; however, the selective arylation of specific cellular proteins is more predictive of toxicity than total covalent binding.

Protein binding of NAPQI and the formation of protein adducts does not imply toxicity as adducts are formed at therapeutic [APAP]. However, highly elevated concentrations of protein adducts in the serum may be indicative of cellular necrosis and hepatotoxicity. After covalent protein binding and GSH depletion occur, a cascade of events follows that alters normal cell function and impairs cell defenses against endogenous reactive oxygen species. This cascade can be ameliorated with N-acetylcysteine (NAC) even after covalent binding occurs. These events include mitochondrial dysfunction, an increase in mitochondrial permeability, mitochondrial oxidant stress or peroxynitrite formation, hepatocellular hypoxia, DNA fragmentation, which results from interactions with topoisomerase 2-α, calcium dyshomeostasis, lipid
peroxidation, nitric oxide release, inflammatory cytokine release, and up- or downregulation of protein expression. Which specific events are critical and irreversibly commit the cell to death is not known.

The final pathway of hepatic cell death is predominantly cellular necrosis. Cellular injury leads to release of intracellular molecules, which further activate the immune system. Some of these intracellular components that are released from necrotic cells may be used as biomarkers of hepatic injury and include aspartate aminotransferase (AST), alanine aminotransferase (ALT), microRNA 122 (miRNA-122), high-mobility group box-1 protein (HMGB-1), keratin-18 protein (K-18), and protein adducts. Apoptosis may occur after activation of the immune system in response to this cellular necrosis, although there is evidence that apoptosis may occur early in APAP toxicity as well. Macrophages, neutrophils, and inflammatory cells infiltrate after necrosis followed by a cascade of inflammatory cytokines such as interleukin (IL) 1, IL-6, IL-8, and monocyte chemotactic protein-1 (MCP-1). Hepatocellular destruction caused by secondary inflammation, impairment of microcirculation, and hepatic nitric oxide release are all demonstrated, although none appear to be necessary for hepatic injury.

Hepatotoxicity initially and most profoundly occurs in hepatic zone III (centrilobular) because this zone is the area with the largest concentration of oxidative metabolism (CYP2E1; Fig. 23–1). In more severe hepatotoxicity, necrosis may extend into zones II and I, destroying the entire hepatic parenchyma.

Kidney injury after acute overdose is typically acute tubular necrosis (ATN) that may be caused by local production of NAPQI by renal CYP2E1 enzymes. However, several other nephrotoxic mechanisms have been proposed. Conversion of APAP and heptatically derived APAP–GSH to nephrotoxic π-aminophenol are both demonstrated in selected animal models. NAPQI formation via renal prostaglandin H synthase and prostaglandin-mediated renal medullary ischemia are also suspected of contributing to chronic analgesic nephropathy from APAP alone or in combination with other analgesics. In patients with hepatic failure, volume depletion and hepatorenal syndrome may be the most important contributory cofactors because the rate of acute kidney injury is similar regardless of the cause of hepatic failure. Dose-related renal potassium wasting after acute APAP overdose may be related to APAP-induced renal vasoconstriction due to COX inhibition or a NAC effect, or both.

Direct injury to organs other than the liver and kidney is rarely reported. The mechanism of early central nervous system (CNS) depression after APAP ingestion is undefined, but theoretical mechanisms include serotonin and opioid effects as well as APAP-induced CNS GSH depletion. Metabolic acidosis and elevated lactate early after massive APAP ingestion may be the result of alterations in mitochondrial respiratory function, but the exact mechanism is unknown. Rare cases of metabolic acidosis with 5-oxoprolineuria and 5-oxoprolinemia are reported and appear to be more likely in women with chronic APAP use and chronic kidney disease. In this rare condition, it is theorized that chronic APAP use combined with acute oxidative stress and inflammatory mediators may lead to an alteration of the γ-glutamyl cycle and elevations of γ-glutamylcysteine and 5-oxoproline.

The remaining sequelae of severe toxicity are secondary effects of fulminant hepatic failure rather than direct APAP effects, and the pathophysiology of these complex multisystem problems is well described. For example, myocardial injury and pancreatitis are both reported in patients with APAP-induced fulminant hepatic failure. The ability of NAC to ameliorate secondary multiorgan failure via extrahepatic mechanisms suggests that the oxidation of vital thiols and the loss of normal microvascular function are important components of secondary organ failure.
**CLINICAL MANIFESTATIONS**

Early recognition and treatment of patients with APAP poisoning are essential to minimize morbidity and mortality. This task is made difficult by the lack of early predictive clinical findings. The first symptoms after APAP overdose may be those of hepatic injury, which develop many hours after the ingestion, when antidotal therapy will have diminished efficacy.

The clinical course of acute APAP toxicity can be divided into four stages. During stage I, hepatic injury has not yet occurred, and even patients who ultimately develop severe hepatotoxicity may be asymptomatic. Clinical findings, when present, are nonspecific and may include nausea, vomiting, malaise, pallor, and diaphoresis. Laboratory indices of hepatic function are normal. In rare cases of massive overdose, a decreased level of consciousness, metabolic acidosis and elevated lactate due to inhibition of electron transport by APAP, NAPQI, or both, and even death may occur during this stage in the absence of signs or symptoms of hepatotoxicity. These clinical findings should never be attributed to APAP alone without thorough evaluation of other possible causes.

Stage II represents the onset of hepatic injury, which occurs in fewer than 5% of those who overdose. AST is the most sensitive, widely available measure to detect the onset of hepatotoxicity, and AST abnormalities always precede evidence of actual hepatic dysfunction (prolonged prothrombin time [PT], international normalized ratio [INR], elevated bilirubin concentration, hypoglycemia, encephalopathy, and metabolic acidosis). When stage II occurs, onset of AST elevation is most common within 24 hours after ingestion but is nearly universal by 36 hours. In the most severely poisoned patients, AST concentrations may increase as early as 12 hours after ingestion. Symptoms and signs during stage II vary with the severity of hepatic injury. By convention, acetaminophen-induced hepatotoxicity is defined as a peak ALT concentration above 1000 IU/L. Although lower peak concentrations of AST or ALT represent some injury to hepatic tissue, they rarely have any clinical relevance.

Stage III, defined as the time of maximal hepatotoxicity, most commonly occurs between 72 and 96 hours after ingestion. The clinical manifestations of stage III include fulminant hepatic failure with encephalopathy and coma, and, rarely, hemorrhage. Results of laboratory studies are variable; AST and ALT concentrations above 10,000 IU/L are common, even in patients without other evidence of hepatic failure. Much more important than the degree of aminotransferase concentration elevation, abnormalities of PT and INR, glucose, lactate, creatinine, and pH are essential determinants of prognosis and treatment.

Renal function abnormalities are rare (< 1%) overall, but they can occur in as many as 25% of patients with significant hepatotoxicity and in 50% to 80% of those with hepatic failure. Renal abnormalities may be more common after sustained, repeated excessive dosing and in adolescents and young adults. After acute ingestions, elevations of serum creatinine typically occur between 2 and 5 days after ingestion, peak on days 5 to 7 (range, 3–16 days), and normalize over 1 month. When severe acute kidney injury necessitating hemodialysis occurs, it nearly always occurs in patients with marked hepatic injury. Patients with hepatorenal syndrome are commonly treated with continuous renal replacement therapy, and among those who survive, kidney failure generally resolves within one month. Infrequently, mild acute kidney injury occurs without elevations in aminotransferase concentrations.

Fatalities from fulminant hepatic failure generally occur between 3 and 5 days after an acute overdose. Death results from either single or combined complications of multiorgan failure, including acute respiratory distress syndrome, sepsis, cerebral edema, or, rarely, hemorrhage. Patients who survive this period reach stage IV,
defined as the recovery phase. Survivors have complete hepatic regeneration, and no cases of chronic hepatic dysfunction have ever been reported. The rate of recovery varies; in most cases, AST, pH, PT, and INR, and lactate are normal by 7 days in survivors of acute overdoses. ALT may remain elevated longer than AST, and creatinine may be elevated for more than one month. The recovery time is much longer in severely poisoned patients, and histologic abnormalities may persist for months.\textsuperscript{187, 200-219}

**DIAGNOSTIC TESTING**

Assessing the Risk of Toxicity

Principles Guiding the Diagnostic Approach.

Most APAP exposures result in no toxicity, and the overall mortality rate after acute APAP ingestion is less than 0.5%.\textsuperscript{189} However, APAP is now the leading cause of acute hepatic failure in the United States and much of the developed world.\textsuperscript{18} To maintain the seemingly divergent goals of avoiding the enormous cost of over-treatment while minimizing patient risk, clinicians must understand the basis for and sensitivity of current toxicity screening methods. A discussion of the diagnostic approach follows.

When considering risk determination, it is useful to separate different categories of APAP exposure. There is an extensive body of experience and literature on acute overdose in typical circumstances, permitting a more systematic approach with demonstrated efficacy. For issues related to repeated supratherapeutic APAP dosing, uncertain circumstances, new APAP formulations, and many other permutations, there is an important conceptual framework for decision-making but little in the way of validated strategies. For these challenges, the central concepts and one approach are presented here, with the understanding that the challenges continue to evolve and that more than one approach may have validity.

The ideal model for determining risk after APAP overdose would assess the individual’s metabolic enzyme activity (CYP2E1, UDP-glucuronosyl transferase, and sulfotransferase activity), the amount and rate of NAPQI formation, the availability of hepatic GSH, and the balance of NAPQI formation and hepatic GSH turnover. At present, none of these measures is available to clinicians.

Plasma GSH concentration can be measured or approximated using the plasma γ-glutamyl transferase (GGT) concentration but have an uncertain relationship to hepatic GSH availability.\textsuperscript{283, 302}

Protein adducts indicate intracellular binding of NAPQI to hepatocyte proteins\textsuperscript{78, 147, 247, 339} and can be determined experimentally, but have been inadequately studied to be useful in risk assessment or the assignment of causality of hepatic failure. After over-exposure to APAP, NAPQI is not immediately bound to GSH and is released within the cell to bind with the cysteine components on proteins. One of these protein-APAP adducts is 3-(cysteinyl-S-yl)-APAP, for which there is a research assay. However, hepatic toxicity from APAP requires not only protein binding, and therefore protein adducts, but an inflammatory cascade to produce cell necrosis.\textsuperscript{38} Therefore, protein adducts are signs of NAPQI binding, but not necessarily of toxicity. Animals exposed to APAP overdose develop elevated concentrations of serum protein adducts. However, those who are rescued with NAC have protein adducts within the liver, but little is spilled into the blood because hepatic cellular necrosis does not occur.\textsuperscript{34, 133, 149}

In humans with therapeutic dosing of APAP, protein adducts are usually detected in small quantities in the blood (< 0.5 nmol/mL), likely from intrahepatic protein binding followed by hepatic cellular turnover. However, concentrations of up to 1.0 nmol/mL have also been detected in patients with therapeutic dosing.\textsuperscript{133} In humans after overdose, protein adducts are released into the serum and largely parallel the aminotransferases in their time-course. Peak concentrations are detected in 2 to 3 days and decrease with an elimination half-life of 1.7
days. Protein adducts remain detectable for up to 2 weeks. A protein adduct concentration above 1.0 nmol/mL has been suggested as being consistent with an acute APAP overdose, but this recommendation will require further validation.

Other hepatic cellular components may be detected in serum during APAP toxicity and are being analyzed as biomarkers of hepatotoxicity. miRNA are small, noncoding RNA that regulate cell proteins by repressing mRNA. miRNA-122 is the most abundant hepatic microRNA and is specific to the liver. In human studies, miRNA-122 increases prior to other markers, such as ALT, and may be actively released from hepatocytes prior to cell lysis. [miRNA-122] correlates with peak ALT and peak INR. In patients with acute APAP overdose whose initial ALT is normal and in patients who are treated within 8 hours, [miRNA-122] is higher in those who develop hepatic injury, suggesting that it may be useful in differentiating low risk patients from high risk patients earlier than other markers.

Another biomarker, HMGB-1, is passively released by hepatocytes during necrosis. HMGB-1 is elevated in patients with APAP hepatotoxicity but not in those without hepatotoxicity and correlates with both peak ALT and INR. An acetylated form of HMGB-1 is secreted as an inflammatory mediator by macrophages and monocytes and increases only in patients with APAP toxicity who later either meet transplant criteria (King’s College Criteria), die, or receive a hepatic transplant. This biomarker requires further study, but has promise as an earlier marker for more intensive treatment or for transplant.

Risk Determination Following Acute Overdose.

Determining risk in a patient with acute overdose consists of determining the initial risk based on dosing history and then potentially further risk stratifying with serum [APAP].

Acute overdose usually is considered a single ingestion, although many patients actually overdose incrementally over a brief period of time. For purposes of this discussion, an acute overdose is arbitrarily defined as one in which the entire ingestion occurs within a single 8-hour period. Doses of 7.5 g in an adult or 150 mg/kg in a child are widely disseminated as the lowest acute dose capable of causing toxicity. These standards are likely quite conservative but have stood the test of time as sensitive markers and have been corroborated with some data in humans. However, it is more likely that doses of at least 12 g in an adult or 200 mg/kg in a child are necessary to cause hepatotoxicity in most patients.

The adult standard may be considered less controversial than that for children because massive ingestions, unreliable histories, and factors that might predispose to toxicity occur primarily in adults, justifying continued use of 7.5 g as a screening amount to avoid missing serious toxicity. In patients younger than 6 years of age, with unintentional ingestions, use of a higher 200-mg/kg cutoff has been suggested and is likely appropriate but has been incompletely studied.

The dose history should be used in the assessment of risk only if there is reliable corroboration or direct evidence of validity. Although the amount ingested by history roughly correlates with risk of toxicity and an [APAP] over the treatment line, historic information is not sufficiently reliable in all patients to exclude significant ingestion, particularly in patients with the intent of self-harm or drug abuse. In fact, suicidal patients with ingestions who do not confirm an ingestion of APAP may have a measurable concentration in 1.4% to 8.4% of cases and a concentration over the treatment line in up to 0.2% to 2.2%. Therefore, when the history suggests possible risk, the patient should be further assessed an [APAP].

Interpretation of [APAP] after acute exposures is based on adaptation of the Rumack-Matthew nomogram (Fig. 35–2). The original nomogram was based on the observation that untreated patients who subsequently developed AST or ALT concentrations above 1000 IU/L could be separated from those who did not on the
basis of their initial [APAP]. A nomogram was constructed that plotted the initial concentration versus time since ingestion, and a discriminatory line was drawn to separate patients who developed hepatotoxicity from those who did not. The initial discriminatory line stretched from [APAP] of 300 µg/mL at 4 hours to 50 µg/mL at 12 hours but was lowered to between 200 µg/mL at 4 hours and 50 µg/mL at 12 hours after evaluation of additional patients. The half-life of APAP was not a factor in the development of the nomogram, and the slope of the treatment line is based on empirical clinical data and does not reflect any discriminatory APAP half-life or APAP kinetics. The nomogram is designed and validated using a single value obtained at or greater than 4 hours after ingestion to allow for complete APAP absorption. Although patients who develop hepatotoxicity may have APAP half-lives greater than 4 hours, plotting multiple points on the nomogram or using an APAP half-life to determine risk has not been adequately studied and has significant limitations.

The nomogram was later extrapolated to 24 hours using the same slope of the original nomogram line.

**FIGURE 35–2.**
Rumack-Matthew nomogram (reconstructed) for determining the risk of APAP induced hepatotoxicity after a single acute ingestion. Serum concentrations above the treatment line on the nomogram indicate the need for N-acetylcysteine therapy.

It is important to realize that the line was based on aminotransferase concentration elevation rather than on hepatic failure or death, and it was chosen to be very sensitive, with little regard to specificity. Without antidotal therapy, only 60% of those with an initial [APAP] above this original line will develop hepatotoxicity as defined by aminotransferase concentrations above 1000 IU/L, but the risk of hepatotoxicity is not the same for all such patients. Elevated aminotransferase concentration develops in virtually all untreated patients with [APAP] far above the line, and serious hepatic dysfunction occurs frequently; the incidence of hepatotoxicity among untreated people with [APAP] immediately above the line is very low, and the risk of hepatic failure or death is far less.

The line used in the United States runs parallel to the original but was arbitrarily lowered by 25% to add even greater sensitivity. The lower line, subsequently referred to as the treatment line or 150-line, starts at a concentration of 150 µg/mL at 4 hours following ingestion; declines with a 4 hour half-life, and ends at 4.7 µg/mL 24 hours following the overdose. The treatment line is one of the most sensitive screening tools used in medicine. The incidence of nomogram failures in the United States using this line is only 1% to 3% (depending on time to treatment). These infrequent “failures” may result from inaccurate ingestion histories, or may include patients with currently undefined risk factors for toxicity, including unique GSH handling or CYP enzyme activities.

In September 2012, the United Kingdom adopted a single nomogram line starting at 100 µg/mL at 4 hours (“100-line”) for all acute APAP ingestions. This single 100-line replaced a two-tiered treatment protocol that treated low risk patients if either [APAP] exceeded the “200-line” and high risk patients if their [APAP] exceeded the “100-line”. The change was motivated by concern with regard to a small number of patients with [APAP] between the 100- and 200-lines who developed hepatic toxicity and a desire to simplify the treatment protocol. Why a 100-line was chosen by the UK Medicines and Healthcare Regulatory Agency and not a 150-line is not clear and has been questioned by several authors.

Based on these observations and more than 25 years of use, the 150-line should be considered adequate in nearly all cases and is reliable when rigorously followed. When using the APAP nomogram, it is essential to
precisely define the time window during which APAP exposure occurred and, if the time is unknown, to use the *earliest possible time* as the time of ingestion. Using this approach, patients with [APAP] below the treatment line, even if only slightly so, do not require further evaluation or treatment for acute APAP overdose. This also applies to most patients with factors that may predispose them to APAP-induced hepatotoxicity. There appears to be adequate experience with acute APAP overdose in the settings of potentially predisposing factors such as chronic heavy ethanol use, chronic medication with CYP-inducing xenobiotics, and inadequate nutrition to recommend that no special approach is required in such cases. Further study is needed to determine if rare events, such as acute APAP ingestion in the setting of chronic isoniazid (INH) use, may uniquely predispose patients to toxicity and require alteration of this approach.

The goal should be to determine [APAP] at the earliest point at which it will be meaningful in decision-making. Therefore, measurement of [APAP] 4 hours after ingestion or as soon as possible thereafter is used to confirm the patient's risk of toxicity and, thus, the need to initiate NAC. No established guidelines are available for the use of determinations made less than 4 hours after ingestion, and because of variability in absorption, such values have less predictive value. Although it is optimal to start NAC therapy as soon as possible after confirmation of risk, NAC is nearly 100% effective if started prior to 6 to 8 hours after ingestion. This allows clinicians some leeway to wait for the laboratory results before starting therapy in patients in whom the history of ingestion suggests that the 4h [APAP] will fall below the treatment line. However, it should be noted that delaying NAC therapy longer than 6 to 8 hours after ingestion may increase the patient’s risk. If there is any concern about the availability of an [APAP] before this time, then treatment with NAC should be initiated. In such cases, [APAP] still should be determined as soon as possible. The results, when they become available, should be interpreted according to the treatment line on the APAP nomogram and NAC either continued or discontinued on the basis of this result. In the unusual circumstance in which no determination of [APAP] can ever be obtained, evidence of possible risk by history alone is sufficient to initiate and complete a course of NAC therapy post ingestion.

**Early Measurement of [APAP].**
Measurement of [APAP] between 1 and 4 hours after ingestion may be helpful only to exclude ingestion of APAP. If [APAP] is undetectable in this time frame, significant APAP overdose can likely be excluded. However, an [APAP] that is detectable between 1 and 4 hours cannot be definitively interpreted and, unless undetectable, mandates repeat testing at 4 hours.

**Determination of Risk When the Acetaminophen Nomogram Is Not Applicable**

**Risk Determination When Time of Ingestion Is Unknown.**
With careful questioning of the patient, family, and others, it is almost always possible to establish a time window during which the APAP ingestion must have occurred. The *earliest possible time* of ingestion (“worst-case scenario”) is used for risk-determination purposes. If this time window cannot be established or is so broad that it encompasses a span of more than 24 hours, then the following approach is suggested. Determine both [APAP] and AST concentrations. If the AST concentration is elevated, regardless of [APAP], treat the patient with NAC. If the time of ingestion is completely unknown and [APAP] is detectable, it is prudent to assume that the patient is at risk and to initiate treatment with NAC. If [APAP] is undetectable and the AST concentration is normal, there is little evidence that subsequent consequential hepatic injury is possible and NAC is unnecessary.

**Risk Assessment Following Extended-Release Acetaminophen.**
Extended-release formulations of APAP exist in the United States, Australia, New Zealand, and other countries worldwide. The pills available in the United States consists of a 325 mg immediate-release APAP dose and an
additional 325 mg dose designed for delayed dissolution. The pills found in Australia and New Zealand (all three have identical contents) consist of a 665 mg bilayer tablet with 206 mg in the immediate release form and 459 mg in a sustained-release gel matrix. Both products result in the immediate release of APAP with delayed release of an additional dose. Pharmacokinetic analysis of the US product reveals that the majority of APAP is absorbed within 4 hours; the peak [APAP] is within 4 hours, and a small number of patients may have an initial [APAP] below the treatment line, but then have a subsequent [APAP] above the treatment line ("nomogram crossing"). Nomogram crossing has been described with the Australian and New Zealand products as well. This "nomogram crossing" is not unique to the extended-release products and occurs in up to 10% of acute ingestions of immediate-release APAP. There is little evidence that nomogram crossing affects outcome and no evidence that an alternate approach to extended-release products should be used. In a 9 year review of 2596 extended-release APAP overdoses in the United States, one death was reported from acute overdose and there was no increased risk over immediate-release APAP. In Australia and New Zealand, five cases of overdose have been described. Three patients had an [APAP] over the treatment line at 4 hours or later, were treated with NAC and did not develop hepatotoxicity. One patient ingested 79 g of extended-release APAP, developed a double-hump [APAP] and a peak [APAP] of about 470 µg/mL at 10 to 15 hours, was treated with early NAC and developed mild aminotransferase elevations. The final patient had an [APAP] that was just below the treatment line at 4 hours, just above the line at 6 hours, was treated with NAC, and also did not develop hepatotoxicity. Certainly, a single [APAP] can reliably be plotted on the treatment nomogram after ingestion of the US APAP extended-release ingestion. Whether an alternative approach will be necessary for the Australian and New Zealand products, or any other new formulation, will require additional study.

Acute Overdose of Intravenous Acetaminophen.
Several intravenous APAP and prodrug APAP products exist worldwide and the US Food and Drug Administration (FDA) approved an intravenous APAP product in 2010 (intravenous APAP, 1 g in 100 mL). Experience with intravenous APAP overdoses is limited, but 23 intravenous APAP overdoses have been described, as well as one case of hepatic toxicity with coagulopathy. Errors commonly occur in young children and include 10-fold dosing errors, confusion between mg and mL, and incorrect route (oral product given intravenously). The approach described here is likely conservative and unstudied and is based on limited information including a well-documented case in which a dose of 90 mg/kg intravenously produced a 6h [APAP] of 38 µg/mL with hepatic toxicity and coagulopathy. This approach is reasonable based on current data, but should be modified as more information emerges. If a single dose error occurs that is in excess of 60 mg/kg, then immediate treatment with NAC is recommended. If a single dose is given but the exact dose is unknown, then an [APAP] should be drawn and plotted on the nomogram using a new, lower line starting at 50 µg/mL at 4 hours and decreasing with a 4 hour half-life. If the concentration is above this "50-line," then treatment with NAC is indicated. There are few data on which to base a treatment decision prior to 4 hours if the dose is unknown. However, in this circumstance, there is likely no harm in waiting for a 4 hour [APAP] prior to initiating therapy. Finally, patients receiving multiple supratherapeutic doses of intravenous APAP should be treated with NAC if there is evidence of hepatic toxicity (eg, elevated aminotransferase concentrations or evidence of hepatic failure) or if there is evidence of APAP accumulation (eg, [APAP] is above therapeutic concentrations that are expected for the last dose).

Risk Determination Following Repeated Supratherapeutic Ingestions (or Chronic Overdose).
No well-established guidelines are available for determining risk after chronic exposure to APAP. Conceptually, several factors must be considered before assessing and determining an individual's risk of toxicity. It has been
well established that therapeutic dosing of APAP is safe; however, some risk factors may put individual patients at risk for toxicity at supratherapeutic doses.

The chronic ingestion of “maximal therapeutic” doses (4 g/day) in normal adults without special circumstances appears to be safe. Several randomized, controlled trials have used maximal therapeutic doses of APAP (4 g/day) in thousands of patients over periods from 4 weeks to 2 years with no reported increase in adverse events or hepatic injury. A transient increase in aminotransferases of one to three times normal, but rarely up to 10 times normal is detected in some patients taking therapeutic doses, but these abnormalities resolve spontaneously despite continued use and have not led to hepatic dysfunction. Finally, several studies have evaluated abstaining chronic alcoholics administered APAP 4 g/day for up to 10 days with no evidence of hepatic damage, although elevations in aminotransferases were detected in both APAP and control groups.

In 2009, an FDA advisory committee recommended to the FDA to decrease the daily dose of APAP to 3250 mg/day and in 2011 McNeil Pharmaceuticals limited its recommended daily dose for the 500 mg tablet to 3000 mg/day. This recommendation and the change in dosing was neither evidence based nor based on any safety data. The recommended daily dose for the 325 mg tablet and 650 mg extended-relief tablet remains at 3900 mg/day. The FDA did not mandate this reduction of daily dosing.

Although therapeutic dosing appears to be safe, repeated supratherapeutic ingestions (RSTIs) may lead to toxicity. Given the amount of APAP use, the incidence of serious APAP toxicity after repeated doses is small, and hepatotoxicity appears to occur only after massive dosing or prolonged excessive dosing. The risk of hepatotoxicity is likely proportional to both the total amount of APAP ingested and the duration of the exposure; however, exact cutoffs for safe dosing are difficult to determine and are likely subject to factors related to the individual.

Although short-term prospective studies of supratherapeutic dosing (6–8 g/day) have not identified alterations in APAP kinetics or hepatotoxicity, several series and case reports have identified patients with hepatotoxicity who retrospectively report therapeutic or slightly supratherapeutic doses. Retrospective dosage reporting is prone to significant errors and issues in which those giving the history may be unable or unwilling to report or estimate ingestions accurately. Cases describing hepatic toxicity after in-hospital therapeutic doses exist, but are exceedingly rare, involve unusual risk factors, and demonstrate multifactorial hepatic injury. Furthermore, because APAP is commonly used in patients with chronic heavy ethanol use and viral infections, it is unclear in which cases APAP was causative, contributory, or unrelated to hepatotoxicity.

Conceptually, the groups that are at “high risk” for hepatotoxicity after RSTI of APAP have either potentially increased activity of CYP2E1 and therefore proportionally increased NAPQI formation or have decreased GSH stores and turnover rate. Many reported cases of APAP toxicity from RSTI involve patients who have factor(s) that influence their GSH supply or turnover, NAPQI production, or both, including infants with febrile illness who have received excessive dosing, chronic heavy ethanol users, and patients chronically taking CYP-inducing medications. The interplay of NAPQI and GSH may also be an important factor. For example, malnutrition is theorized to increase the risk of APAP toxicity; however, both CYP2E1 activity and GSH supply are decreased in malnourished patients, and their relative impact on risk is unknown.

When there is concern about risk of toxicity after RSTI dosing, several approaches are suggested. The goal should be to select patients at risk based on dosing history and other risk factors and to then use limited laboratory testing to determine the need for NAC. A logical screening laboratory evaluation consists of determination of [APAP] and AST concentrations, with additional testing as indicated by these results and other
clinical features. The objective is to identify the two conditions that warrant NAC therapy—remaining APAP yet to be metabolized and potentially serious hepatic injury.

**Role of History and Physical Examination in Repeated Supratherapeutic Ingestions.**
The first consideration when evaluating a patient with a history of repeated supratherapeutic APAP dosing is the presence or absence of signs or symptoms of hepatotoxicity. Regardless of risk factors or dosing history, such findings should prompt treatment with NAC and laboratory evaluation. This is particularly important because most reported cases of serious toxicity after repeated dosing are symptomatic for more than 24 hours before diagnosis, and earlier treatment may improve outcome.

In asymptomatic patients, a reasonable approach is to perform laboratory evaluation for those who have ingested more than 200 mg/kg/day (or 10 g/day, whichever is less) in a 24 hours period or more than 150 mg/kg/day (or 6 g/day, whichever is less) in a 48 hours period. In children younger than 6 years of age, laboratory evaluation should be performed if the reported ingestion is more than 100 mg/kg/day during a 72 hours period or longer.

Several factors or characteristics place patients at higher risk for chronic APAP toxicity. High-risk factors that have been theorized include chronic heavy ethanol use; chronic ingestion of INH; febrile illnesses in infants and young children; and malnutrition, AIDS, or anorexia. In some cases, animal or basic science studies show evidence of increased risk, and in most cases, there have been multiple anecdotal reports of toxicity at therapeutic or slightly supratherapeutic doses. Whether these patients require a lower threshold for laboratory screening is unknown.

**Role of Laboratory Evaluation in Repeated Supratherapeutic Ingestions.**
After a patient is determined to be at risk, an [APAP] and [AST] should be determined. These should be interpreted using the concept that a patient may be at risk of hepatotoxicity if there is evidence of hepatic injury (elevation of AST) or there remains enough APAP to produce further hepatic damage.

Using the strategy described here, patients with elevated [AST] are considered at risk, regardless of [APAP]. An [APAP] is useful in patients with normal [AST] as a tool to determine only whether sufficient APAP remains to lead to subsequent NAPQI formation and delayed hepatotoxicity. In many cases, [AST] is normal and [APAP] is below 10 µg/mL, obviating the need for NAC. If the [AST] is normal, then the patient should be considered at risk if [APAP] is 10 µg/mL or above. Higher thresholds for non-treatment, such as APAP below 30 µg/mL or AST twice as high as normal, have been suggested, but have not been studied and their sensitivity is unknown.

Patients who develop highly elevated [AST] after chronic APAP overdose should be treated and further evaluated with laboratory tests to assess hepatotoxicity and prognosis (creatinine, PT, INR, pH, phosphate, and lactate). Initial elevations of INR or creatinine may be markers of poor prognosis in APAP RSTI.

The measurement of APAP protein adducts in urine has been described and theoretically could quantify NAPQI production in the liver. It has been suggested that adduct concentrations may identify APAP-induced hepatotoxicity in undifferentiated patients with elevated [AST]; however, adducts are elevated after both therapeutic and RSTI APAP ingestions and a clear defining value has not been determined. Several other biomarkers, including miRNA-122 and acetylated HMGB-1, have been tested in acute overdoses, but their utility in RSTI is unclear.

Patients who are identified as at risk, with either an elevated [AST] or an elevated [APAP], should be treated with NAC.
Risk Determination Following Acetaminophen Exposure in Children

Serious hepatotoxicity or death after acute APAP overdose is extremely rare in children.\(^{261,315}\) Predominant theories\(^{261,315}\) for resistance to toxicity include a relative hepatoprotection in children because of increased sulfation capacity\(^{207}\) or differences in the characteristics of children poisonings, including smaller ingested doses, overestimation of liquid doses, and unique formulations (pediatric elixirs that contain propylene glycol may result in decreased toxicity due to inhibition of CYP2E1).\(^{261,315}\) This has led some to suggest higher screening values and a higher nomogram line for children.\(^{261,315}\) However, no significant change in NAPQI production has been demonstrated in children, and a more liberal approach to children’s acute APAP ingestions has been inadequately studied and is not recommended. After repeated supratherapeutic APAP dosing, there is no evidence that children are relatively protected. Hepatic injury after therapeutic APAP is likely exceedingly rare in children.\(^{179}\) However, infants and children with acute febrile illnesses comprise one of the few groups in which toxicity after repeated excessive dosing is well described.\(^{246}\) Common sources of dosing errors include substitution of adult for pediatric preparations; overzealous dosing by amount or frequency in attempts to maximize effect, and failure to read the label and dose carefully.\(^{8,246}\) Age younger than 2 years is an independent risk factor for development of toxicity.\(^{156}\) These rare cases of toxicity in febrile children with repeated supratherapeutic dosing may simply reflect that these children constitute the most common setting for pediatric APAP use and that children are at greater relative risk for excessive dosing because of their size. Although logically one can argue that inflammatory oxidant stress and short-term fasting during febrile infectious illnesses affect oxidative drug metabolism and decrease GSH supply, these relationships are complex and not well defined. Of the reported cases of repeated supratherapeutic APAP dosing in children with hepatic injury, the cause was likely an isolated infectious illness in some, APAP in others, and a combination of the two in still others.

Risk Determination Following Acetaminophen Exposure in Pregnancy

The initial risk of toxicity in a pregnant woman is similar to that of a nonpregnant patient with a few exceptions. Little evidence suggests that any alteration of the treatment line is necessary. In fact, there are no reported cases of fetal or maternal toxicity in women with [APAP] below the treatment line or in those treated with NAC within 10 hours of an acute ingestion.\(^{203,255}\) However, there is controversy in assessing the risk of fetal toxicity after the mother has been determined to be at risk. To better understand the issues, a review of maternal–fetal physiology and pharmacokinetics related to APAP and NAC is necessary.

APAP is capable of crossing the human placenta and APAP may be present in concentrations similar to maternal serum concentrations within hours after ingestion.\(^{188,223,256}\) Fetal metabolism of APAP probably is inefficient but is not completely understood. Fetal sulfation and oxidative metabolism of APAP are slower than in adults, and glucuronidation is undetectable until 23 weeks of gestation.\(^{257}\) CYP enzymes that are capable of oxidizing APAP are present in the fetus as early as 18 weeks gestation.\(^{257}\) However, the activity of these enzymes is less than 10% that of adult enzymes at 18 weeks gestation and increases to only 20% activity at 23 weeks.\(^{257}\) How the opposing forces of decreased overall metabolism of APAP and decreased NAPQI formation impact fetal risk is unclear.

The mechanism of fetal risk in women with APAP toxicity remains controversial. The degree of fetal toxicity that is attributable to fetal metabolism of APAP or to maternal illness is unclear. In clinical case series, the majority of pregnant women who overdose on APAP have uneventful pregnancies.\(^{203,255}\) Pregnant women who develop APAP toxicity in the first trimester have an increased risk of spontaneous abortion.\(^{255}\) Fetal demise is described in the second trimester, and those who develop APAP toxicity in the third trimester have a potential risk of fetal hepatotoxicity because of fetal metabolism. However, reports of third-trimester fetal hepatotoxicity are
rare and are only associated with severe maternal toxicity. The factors associated with poor fetal outcome after a large APAP overdose are delayed treatment with NAC and young gestational age.

The decision to treat a pregnant woman with NAC requires consideration of what is known about the efficacy and beneficial effects as well as the adverse events of NAC for both the fetus and the mother. Every indication suggests that NAC is both safe and effective in treating the mother, but there are inadequate data to evaluate efficacy in the fetus, although fetal outcome has generally been excellent after maternal treatment with NAC. Given that NAC has been safely used in many pregnancies and fetal mortality is linked to delays to treatment, NAC should be initiated in pregnant women who meet the same criteria as nonpregnant patients.

The necessary length of NAC therapy is difficult to determine. The 20 hour intravenous protocol probably is the most commonly recommended NAC protocol used for pregnant women worldwide; however, there is a paucity of published experience supporting NAC treatment courses shorter than the oral 72 hour protocol (Chap. 31).

Ethanol and Risk Determination

The effects of ethanol on APAP toxicity are complex and are best described by clearly separating experimental animal data from actual human overdose experience, acute ethanol use from chronic heavy ethanol use or alcoholism, and single from repeated supratherapeutic APAP dosing. Ethanol use itself is difficult to define and many studies used different definitions. For the purpose of this section, the term chronic heavy ethanol use is defined as a person who ingests a mean of greater than two to three standard ethanol-containing drinks per day. Moderate ethanol use is defined as a mean of one to two standard ethanol-containing beverages per day. The term alcoholic will be used to define people whom either self-define as alcoholics or are identified as an alcoholic by the CAGE questionnaire, the Michigan Alcohol Screening Test, or similar screen. Although not entirely consistent, both animal and human data suggest that acute ethanol coingestion with APAP may be hepatoprotective. Ethanol coingestion decreases NAPQI formation presumably by inhibiting CYP2E1 in both humans and animals. In large retrospective evaluations of overdoses, acute ethanol ingestion independently decreases the risk of severe hepatotoxicity in chronic heavy ethanol users and in nonchronic heavy ethanol users, but did not significantly decrease the risk of hepatotoxicity (ALT > 1000 IU/L) in a smaller prospective study.

However, chronic ethanol administration increases the risk of hepatotoxicity from APAP dosing in animals. This may be a consequence of increased NAPQI formation due to induction of CYP2E1 metabolism once the ethanol is metabolized or decreased mitochondrial GSH supply or regeneration.

After acute APAP overdose, chronic heavy alcohol users who have not coingested ethanol may be at a slightly increased risk; however, this elevated risk appears to be of little clinical importance given the sensitivity of the treatment line. There is no credible evidence that chronic heavy alcohol use should alter the approach after an acute APAP overdose using the treatment line. In fact, the treatment line was developed with clinical data that included chronic heavy ethanol users. Given the paucity of data linking chronic heavy ethanol use to nomogram failures, it appears that the treatment line is adequately sensitive for screening after an acute APAP overdose, regardless of the patient’s history of chronic heavy ethanol use.

The relationship between chronic heavy ethanol use and chronic APAP use is complex. Hepatotoxicity has been sporadically reported in patients with chronic heavy ethanol use after repeated supratherapeutic APAP dosing. Complicating these reports are the clinical challenges of obtaining accurate histories in chronic heavy ethanol users, failure to exclude non-APAP causes of hepatotoxicity, and other factors. Alcoholics are at higher risk of both using supratherapeutic doses of APAP and using combinations of multiple APAP-containing
products. In contrast, prospective evidence demonstrates minimal risk of hepatotoxicity in alcoholic patients who ingest therapeutic doses of APAP. However, it should be noted that, in studies involving persons who abuse alcohol, mild AST elevations (< 120 IU/L) were noted in 40% of both study and controls, and more significant increases (> 120 IU/L, or three times normal) were noted in 4% to 6% of participants. In addition, in all studies, a small group of patients developed significant increases in aminotransferases, but most were unchanged. Patients who develop elevated aminotransferases after therapeutic dosing who are then rechallenged with additional APAP develop similar [AST] increases, implying that individual factors are likely more important than the chronic heavy ethanol use itself.

CYP Inducers and Risk Determination
Inducers of the CYP enzymes have long been theorized to increase the risk of toxicity from APAP because of a proportionally increased production of NAPQI. It is now clear that APAP is metabolized to NAPQI largely by CYP2E1 and that only induction of this specific enzyme is likely to increase the risk of hepatotoxicity.

Although ethanol and INH are known inducers of CYP2E1, there is no evidence that the clinical approach to these patients should be altered. Similarly, several other medications, including phenytoin, carbamazepine, and phenobarbital, are theorized to increase APAP toxicity because of nonspecific CYP induction activity. None of these anticonvulsants induces CYP2E1, although there is some evidence that they increase NAPQI formation in cultured human hepatocyte and animal models, possibly through inhibition of glucuronidation. However, clinical experience suggests that there is no need to change the approach to these patients.

Assessing Actual Toxicity: Critical Components of the Diagnostic Approach

Initial Testing.
The [APAP] should be measured in patients with acute APAP overdose and no evident hepatotoxicity, but no other initial laboratory assessment is required. AST concentration should be measured in patients who are considered to be at risk for APAP toxicity according to the nomogram or history (in the case of repeated supratherapeutic dosing) or in those suspected of already having mild hepatotoxicity by history and physical examination.

Unless evidence of serious hepatotoxicity is present, [AST] is a sufficient indication of hepatic conditions, and no additional testing is initially needed. Death of hepatocytes, resulting in release of measurable hepatic enzymes, precedes all cases of serious hepatic dysfunction. Mild renal toxicity may rarely occur without hepatotoxicity; however, at least minimal elevation of [AST] generally precedes evidence of clinically significant nephrotoxicity. Exceptions are rare, and routine screening of renal function in the absence of elevated [AST] is probably unnecessary.

APAP overdose may lead to minor prolongation of PT even without causing hepatotoxicity. This most commonly occurs between 4 and 24 hours following ingestion and may be a result of NAPQI-related inhibition of vitamin K–dependent γ-carboxylation of factors II, VII, IX, and X. These minor prolongations (resulting PT usually is less than twice control) are rarely clinically relevant, are not evidence of hepatotoxicity, and should not be used as prognostic factors or indications for NAC treatment. In fact, treatment with NAC may also prolong PT by interfering with the PT assay, by reversing an APAP/NAPQI effect, or by direct NAC effects.

Ongoing Monitoring and Testing.
If no initial elevation of [AST] is noted, then repeated determination of [AST] alone—without other biochemical testing—is sufficient to exclude the development of hepatotoxicity. [AST] should be determined at the end of the protocol (eg, at 21 hours if using the standard intravenous protocol) or every 24 hours if using a longer protocol. If an elevated [AST] is noted, then PT and INR and creatinine should be measured and repeated every 24 hours or more frequently if clinically indicated. Results of other hepatic tests, such as GGT, alkaline phosphatase, lactate dehydrogenase, and bilirubin, which are useful when determining the cause of hepatic abnormalities, will be abnormal in cases of serious APAP-induced hepatotoxicity but provide little additional useful information if the cause is certain (Chap. 23).

If evidence of hepatic failure is noted, then careful monitoring of blood glucose, pH, PT, INR, creatinine, lactate, and phosphate concentrations are important in assessing extrahepatic organ toxicity and are vital in assessing hepatic function and the patient’s potential need for hepatic transplant (see Assessing Prognosis). In addition, meticulous bedside evaluation is necessary to determine and document vital signs, neurologic status, and evidence of bleeding. Many additional tests may be useful in the setting of hepatic failure based on clinical condition and local protocols. Testing for other rare APAP-associated conditions by electrocardiography, lipase determination, or other studies should be performed on a case-by-case basis only.

**MANAGEMENT**

**Gastrointestinal Decontamination**

In cases of very early presentation or coingestion of xenobiotics that delay gastrointestinal (GI) absorption, gastric emptying may be appropriate for some patients. In general, however, gastric emptying is not appropriate for patients with isolated APAP overdose because of the very rapid GI absorption of APAP and the availability of an effective and safe antidote.

Administration of activated charcoal (AC) shortly following APAP ingestion may decrease the number of patients who have an [APAP] above the treatment line. Although AC is most effective when given within the first 1 to 2 hours following APAP ingestion, it may be reasonable to consider AC at later times provided there are no contraindications.

Interactions between AC and orally administered NAC are likely clinically unimportant. In the majority of cases, there should be no interaction because GI absorption of APAP, and therefore the necessity to give AC, is complete by 4 hours following ingestion, and NAC typically is administered between 4 and 8 hours following ingestion. As a result, there is generally no difficulty separating the doses. If delayed or repeated AC dosing is indicated because of suspected delayed absorption or coingestants, then a strategy using an intravenous NAC protocol should be considered. Alternatively, oral NAC and AC doses may be separated by 1 to 2 hours, with NAC given the priority for the first dose because time to administration of NAC correlates with risk of hepatotoxicity. NAC is absorbed high in the GI tract and is not likely to interact with AC if they are not administered simultaneously.

**Supportive Care**

General supportive care consists primarily of controlling nausea and vomiting and managing the hepatic injury, acute kidney injury, and other manifestations. Treatment of these problems is based on general principles and is not APAP dependent. Discussion of the management of hepatic failure is clearly beyond the scope of this chapter, but certain aspects deserve mention. Monitoring for and treatment of hypoglycemia are critical because hypoglycemia is one of the most readily treatable of the life-threatening effects of hepatic failure. If adequate viable hepatocytes are present, vitamin K may produce some improvement in coagulopathy; thus,
trial dosing is logical as hepatic injury develops and as it resolves. Administration of fresh-frozen plasma (FFP) and prothrombin complex concentrates (PCCs) should be based on specific indications rather than PT and INR alone. Hemorrhage is rare in APAP-induced hepatic failure and correction of coagulopathy should only be necessary for procedures and life-threatening bleeding. Supportive therapy for cerebral edema, including cooling, hypertonic saline, elevation of the head, and support of the cerebral perfusion pressure, are all indicated.

Antidotal Therapy with N-Acetylcysteine.

MECHANISM OF ACTION OF N-ACETYLCYSTEINE.

Conceptually, it is helpful to think of NAC as serving three distinct roles. During the metabolism of APAP to NAPQI, NAC prevents toxicity by limiting the formation of NAPQI. More importantly, it increases the capacity to detoxify NAPQI that is formed (Fig. 35–1). In fulminant hepatic failure, NAC treats toxicity through nonspecific mechanisms that preserve multiorgan function. A complete discussion of NAC can be found in Antidotes in Depth: A3. A brief review follows.

NAC prevents toxicity mostly by serving as a GSH precursor and also as a GSH substitute, combining with NAPQI and being converted to cysteine and mercaptate conjugates. NAC may also lead to increased substrate for nontoxic sulfation, allowing less metabolism by oxidation to NAPQI. Each of these preventive mechanisms must be in place early, and none is of benefit after NAPQI has initiated cell injury. Time is required to saturate nontoxic metabolism, form excessive NAPQI, deplete GSH, and overcome GSH production; thus there is a window of opportunity after exposure to an APAP overdose during which NAC can be initiated before the onset of hepatic injury without any loss of efficacy. Based on large clinical trials, it appears that NAC efficacy is nearly complete as long as it is initiated within 6 to 8 hours of an acute overdose. However, the relationship between the time to administration of NAC and the risk of hepatotoxicity should be considered a continuous variable. The risk of hepatotoxicity begins to increase at 6 hours for patients with very high [APAP] and is closer to 8 hours for patients with [APAP] just over the treatment line. For this reason, NAC therapy should not be unnecessarily delayed past 6 hours if it can be safely administered earlier.

Several observations illustrate the effectiveness of NAC by other mechanisms of action even after NAPQI formation and binding. NAC actually reverses NAPQI oxidation in both a mouse model and an in vitro human hepatocyte model, and even after cell injury is initiated, NAC may diminish hepatocyte injury. Most significantly, a prospective, randomized trial found that even after fulminant hepatic failure was evident, intravenous NAC diminished the need for vasopressors and the incidences of cerebral edema and death. In this study, despite improved organ function and survival in the NAC-treated group, there was no apparent difference in the degree of hepatic injury, implying that much of the benefit of NAC in this setting may not be derived from hepatic effects. Whether based on its nonspecific antioxidant effects, its increase in oxygen delivery and utilization, its ability to enhance GSH supply and mitochondrial ATP production, or its role in mediating microvascular tone, NAC improves function in several organs affected by multisystem failure. In fact, NAC may preserve cerebral blood flow and perfusion in the setting of cerebral edema more effectively than traditional therapies such as mannitol and hyperventilation, which may actually be detrimental.

Although NAC has a defined role in preventing and treating APAP-induced hepatic injury, its role in treating APAP-induced acute kidney injury is less clear. When used early after ingestion in animals, NAC produces a small reduction in kidney injury but does not appear to be harmful. However, few data are available to recommend NAC therapy in treating isolated acute kidney injury or acute kidney injury after resolution of hepatic injury.

N-ACETYLCYSTEINE ADMINISTRATION.
NAC may be administered via the oral or intravenous routes and in protocols that have historically varied in length. The two most common regimens are a 21 hour intravenous infusion and a 72 hour oral dosing protocol. However, the concept of a set-length protocol is obsolete. Conceptually, practitioners should start NAC when the patient is at risk of toxicity, continue NAC while the patient remains at risk or has hepatotoxicity, and stop NAC when that risk or toxicity is gone. Most institutions now use either oral or intravenous NAC in a variable length protocol, using indicators of patient toxicity rather than a set protocol length. These are described at length in Antidotes in Depth: A3.

With the exception of established hepatic failure, for which only the intravenous route has been investigated, the intravenous and oral routes of NAC are equally efficacious in preventing or treating APAP toxicity. The decision to treat with intravenous or oral dosing is complex and is described in Antidotes in Depth: A3. In brief, whereas intravenous NAC has been associated with rare but severe anaphylactoid reactions and medication errors, oral NAC is associated with a greater than 20% risk of vomiting. There are three scenarios in which intravenous NAC is generally recommended: (1) APAP toxicity in pregnant women, (2) APAP-induced hepatic failure, and (3) intractable vomiting preventing oral treatment.

**DURATION OF N-ACETYL-CYSTEINE TREATMENT.**

Known mechanisms of action and the observation that all studied durations of NAC are effective when started within 8 hours suggest that all courses of treatment currently published are effective when NAC is used for its early preventive actions. There is some suggestion that there may be a slightly decreased risk of hepatotoxicity if intravenous NAC, as opposed to oral NAC, is used before 10 hours after the ingestion, but this remains controversial. Results from use of the traditional 21 hour intravenous NAC protocol, the 48 hour and 36 hour intravenous NAC protocols studied in the United States, one 20 hour protocol, and other “short-course” dosing protocols indicate that those therapies are likely safe and effective in these low-risk scenarios.

It is important to realize that even in low-risk patients (those treated within 8 hours), regardless of the protocol length (21, 36, 48, or 72 hours) or route of delivery, NAC therapy should be continued until APAP metabolism is complete (the [APAP] is below detection) and there are no signs of hepatotoxicity. With this concept in mind, it may seem reasonable to shorten a set course of NAC if the patient is low risk and the above criteria are met ([APAP] undetectable, [AST] normal, PT/INR less than twice normal, and no encephalopathy). This approach is conceptually reasonable and is aimed at decreasing unnecessary therapy as there is no evidence that prolonged NAC is helpful and there is one animal study that suggests that prolonged NAC may inhibit hepatic recovery, however, adequate studies have not definitively confirmed its safety.

NAC therapy should be continued beyond the prescribed “protocol length” if there is evidence of hepatic injury ([AST] significantly above normal or PT/INR > twice normal or encephalopathy is present) or APAP metabolism is incomplete ([APAP] detectable). This likely will not be an issue in the vast majority of cases because the aminotransferases of approximately one-half of all NAC-treated patients with [APAP] above the treatment line will remain below 100 IU/L. The intravenous NAC dosing protocol that has proved beneficial in patients with hepatic failure is the same initial dosing as the traditional intravenous protocol but with the third intravenous infusion continued until there is resolution of hepatic failure. These observations suggest that rather than a single duration of therapy for all patients, it is appropriate to extend treatment protocols based on the clinical course of the patient.

After NAC therapy is extended beyond a set-length protocol, the decision to discontinue therapy should be entirely based on the patient’s condition. For patients who develop hepatic failure, intravenous NAC is continued until the PT or INR is below twice the rate of normal and encephalopathy, if present, is
resolved. For patients without hepatic failure but with elevated [AST], NAC is often continued until all hepatic abnormalities resolve (eg, [AST] is decreasing and < 1000 IU/L).

Assessing Risk of Hepatotoxicity.
Most patients who are treated with NAC do not develop hepatotoxicity and have short hospital stays, whereas a small percentage develop hepatotoxicity and an even smaller group develop hepatic failure. It may be helpful to predict the risk of hepatotoxicity based on initial findings to direct the intensity of monitoring and therapy (see Dose Adjustment) and patient disposition.

In general, both the time from ingestion to the initiation of NAC and [APAP] are directly proportional to the patient’s risk of developing hepatotoxicity and hepatic failure. Even in patients treated early after their ingestion, their risk of hepatotoxicity is significant if their [APAP] is highly elevated. Using these principles, a nomogram has been produced that may be used to determine the risk of hepatotoxicity on patient arrival. Unfortunately, this only predicts the risk of a peak aminotransferase concentration above 1000 IU/L and has not been studied to determine the risk of death or need for transplantation. In addition, the multiplicative sum of [AST] (or [ALT]) and [APAP] has also been studied to predict hepatotoxicity, but requires validation. Acetylated HMGB-1 is a promising biomarker for detecting patients who will go on to have severe hepatic failure and may be useful for early prognostication. Initial human studies, [acet-HMGB-1] increased only in patients who later met the King’s College Criteria for hepatic transplant, received a transplant, or died. These results are promising and require validation and further study.

Dose Adjustment.
In rare cases, patients with massive ingestions with or without antimuscarinic co-ingestants may have highly elevated [APAP] for prolonged periods or secondary elevations of the [APAP]. Several of these patients have developed hepatotoxicity despite early (< 6 hours) intravenous NAC therapy, raising the question of whether the traditional intravenous NAC infusion (6.25 mg/kg/h) provides enough NAC for these rare patients with late elevated [APAP] or massive ingestions. Several theoretical solutions have been noted, but none are tested and a consensus opinion on optimal therapy does not exist. In these rare patients, consideration should be given to treating with greater amounts of NAC once prolonged, massive [APAP] are evident. No data exist to determine which, if any, alternative NAC dosing strategy is superior. For a detailed description of increased dosing for massive ingestions, highly elevated [APAP], and prolonged elevations of [APAP], see Antidotes in Depth: A3. A brief synopsis is described below and is based on calculations that use logical inferences, but none of these concepts has been studied and should not be considered standard therapy. The described dosing protocol has little risk, but has unproven benefit, and should be used with caution in extreme clinical cases:

1. If the ingestion is between 16 and 32 g or the initial [APAP] is between the “300-line” and the “500-line,” then consider using 12.5 mg/kg/h as the 16 hour infusion rate.
2. If the ingestion is between 32 and 48 g or the initial [APAP] is above the “500-line,” then consider using 18.75 mg/kg/h as the 16 hour infusion rate.
3. If the ingestion is greater than 48 g, then consider using 25 mg/kg/h as the 16 hour infusion rate.
4. If the [APAP] at 20 hours or later is 25 to 50 µg/mL, then use 12.5 mg/kg/h as the continuous infusion. If the [APAP] at 20 hours or later is > 50 µg/mL, then use 18.75 mg/kg/h as the continuous infusion.
An alternative approach equally logical, but also unstudied, is to combine both the oral NAC protocol with the intravenous NAC protocol. This method provides both an additional bolus dose (290 mg/kg), as well as 23.75 mg/kg/h as the continuous infusion.

**Hepatic Transplantation.**

Hepatic transplantation may increase survival for a select group of severely ill patients who have APAP-induced fulminant hepatic failure. Tremendous improvements in transplantation and supportive hepatic care have increased immediate survival rates after hepatic transplantation to 69% to 78% with 3- to 5-year survival rates of 54% to 66%, respectively, which is similar to transplant survival for other causes of acute hepatic failure. Patients who meet criteria for transplant but do not receive an organ have had survival rates ranging from 5% to 17%, but higher survival rates have recently been reported.

Concerns that patients who receive transplants for APAP-induced fulminant hepatic failure will have lower survival rates and be unable to maintain post-transplant medication regimens have resulted in the majority of patients not being listed for transplant. However, those who meet psychosocial criteria for transplantation have high rates of survival, and 12% later die from intentional rejection or suicide attempts. Techniques that allow subtotal hepatectomy with transplantation and eventual weaning of immunosuppressants are promising and may allow for higher rates of transplantation.

**Assessing Prognosis.**

Determining a patient's prognosis and predicting patients who require transplantation early in the course of the disease is an important area of current research.

The most commonly used indicator of the need for immediate transplantation is the King's College Criteria (KCC; Table 35–1), which was developed and validated on patients with APAP-induced fulminant hepatic failure. The criteria include a serum pH below 7.30 after fluid resuscitation or the combination of creatinine above 3.3 mg/dL, PT above 100 sec (INR > 6.5 is commonly used), and grade III or IV encephalopathy. The survival rate of patients who meet the KCC but do not receive an organ remains below 20% in most centers. Significantly higher survival rates in patients meeting transplant criteria have recently been reported and may be due to the utilization of prolonged NAC therapy and improved supportive care for patients with acute hepatic failure.

<table>
<thead>
<tr>
<th>TABLE 35–1. King’s College Criteria for Predicting Need for Hepatic Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>View Large</td>
</tr>
</tbody>
</table>

When determining the KCC, interpretation of PT and INR must include awareness of concurrent NAC therapy as well as therapy with vitamin K, PCCs, factor VII, and FFP. The use of vitamin K, if effective, implies that transplant may be unnecessary because viable liver remains. If vitamin K is ineffective, then PT and INR can be used, as discussed in the previous paragraph. Transfusion of exogenous clotting factors, such as FFP or PCCs, alters interpretation because improvement in PT and INR may not indicate improvement in hepatic function. The prognostic importance of monitoring PT and INR in this setting suggests that FFP should be given only with evidence of bleeding, with risk of bleeding from known concomitant trauma, or before invasive procedures and not based merely on the PT and INR.

A lactate concentration above 3.5 mmol/L at a median of 55 hours after APAP ingestion or lactate concentration above 3.0 mmol/L after fluid resuscitation is shown to be both sensitive and a specific predictor of...
Additional studies confirmed lactate as an independent predictor of prognosis but suggest that it does not add significantly to the KCC. Others have confirmed a lower specificity than initially reported. Using a higher cutoff (> 4.7 mmol/L) has a high sensitivity (98%) and NPV (95%), but moderate specificity (58%) for determining death or transplant.

Unfortunately, patients often meet the KCC and lactate criteria quite late in their course of disease, so these criteria are not useful as early predictors or as standards for transfer to a facility that performs hepatic transplant. General factors that are associated with increased mortality include unintentional overdose, repeated supratherapeutic dosing, and delays to receiving NAC therapy. Additional predictors of severity of hepatic toxicity in patients treated with NAC include a rapid doubling of [AST] or [ALT] (doubling < 8 hours) and [AST] or [ALT] reaching 1000 IU/L within 20 hours of NAC treatment. Several attempts at determining early predictors of death or the need for transplant have proven to be no more effective than the KCC, including serum phosphate (day 2), Model for Endstage Liver Disease (MELD) score of 32 or above, serum Gc-globulin, factor V concentration, factor VIII:V ratio, worsening day 4 PT and INR, and PT (in seconds) larger than the number of hours since ingestion.

An Acute Physiology and Chronic Health Evaluation (APACHE) II score above 15 in isolated APAP ingestions may be as specific as the above KCC criteria and slightly more sensitive. These criteria may be beneficial in determining whether to transfer a patient to a transplant center because the score is easily calculated, is sensitive, and is available within the first day of admission; however, confounders such as coingestants may decrease its utility. Furthermore, an APACHE III score above 60 may be helpful in identifying additional patients with multiorgan dysfunction who may require transplantation.

Several measurements of organ failure have been postulated as indications for transfer to a regional transplant center from a non-transplant facility. The Sequential Organ Failure Assessment (SOFA) score higher than 7 within the first 96 hours after acute overdose and evidence of the systemic inflammatory response syndrome both predict increased mortality (a 100% sensitivity and a 74% to 77% specificity). Conversely, a patient with a SOFA score of 7 or less during the first 96 hours after acute overdose has a low mortality (< 2%), low risk of requiring renal replacement therapy (< 4%), and low risk of requiring intracranial pressure monitoring (< 2%). Additionally, SOFA score below 6 after repeated supratherapeutic ingestion of APAP predicts survival and a low risk of the need for renal replacement therapy or intracranial pressure monitoring (< 10%).

The KCC, APACHE II, SOFA, and MELD scores, as well as serum lactate 12 hours after admission, have been recently compared and may all be helpful in making patient decisions. The MELD score (> 32) and lactate concentration (> 4.7 mmol/L) are the most sensitive to determine death or transplant in APAP-induced hepatic failure. These scores may be helpful in predicting death or the need for a higher level of care (Table 35–2), whereas, the most specific scores are the KCC, APACHE II (> 11), and SOFA (> 12). These may be most helpful in determining patients who need transplant (Table 35–2).

### Table 35–2. Prediction of Death or Transplant in 125 Patients with APAP Induced Liver Failure

Acetylated HMGB-1 is a biomarker that is released as a proinflammatory mediator from monocytes and macrophages and in one small study was highly correlated with patients that met transplantation criteria or died. These studies are promising, but will require validation before clinical use is postulated.
Additional Elimination Techniques
Several clinical scenarios may benefit from increasing clearance of APAP from the body. Indications early after APAP overdose may include patients with exceedingly high [APAP] who are at high risk of hepatotoxicity despite NAC therapy as well as those with hyperlactatemia and metabolic acidosis. Later in the course of APAP toxicity, elimination techniques may be used to remove elevated [APAP] in patients who are imminently receiving a hepatic transplant or for removal of toxins related to hepatic failure (Table 35–3).

TABLE 35–3. Management of Patients at Risk for APAP Toxicity

| View Large | Favorite Table |

Hemodialysis.
Both intermittent hemodialysis (HD) and continuous venovenous hemodialysis (CVVHD) increase elimination of APAP. HD has been used early after overdose to eliminate highly elevated [APAP], typically above 500 µg/mL,[119,348] and in patients with slow clearance of [APAP] late after overdose.[26] Clearance averages about 150 mL/min[119,123,348] with blood flow of approximately 300 mL/min. In one case, HD removed approximately 2 g of APAP when the initial [APAP] was 103 μg/mL, and the amount that HD removes varies directly with the initial [APAP].[119,348] HD reduces the APAP elimination half-life by approximately 50%[119,229,348] and has an extraction ratio of 50% to 80%.[119,346,348] HD also removes NAC and NAC infusion rates should be increased to 12.5 mg/kg/h (from 6.25 mg/kg/h) during HD.[119]

CVVHD has been described in one case[341] in which the continuous modality was used due to concerns of hypotension on intermittent HD. In 16 hours, CVVHD had an average clearance of 42.1 mL/min and removed about 24 g of APAP; ([APAP] at initiation of CVVHD was 1212 µg/mL).[341]

Plasmapheresis and Plasma Exchange.
Plasmapheresis removes small amounts (5%) of APAP with therapeutic dosing, but few data exist with regard to overdose.[97] Plasmapheresis may be useful in patients with acute liver failure to correct coagulopathy, but it does not reliably correct encephalopathy.[290]

Exchange transfusion was used in one 1.22 kg neonate who had a [APAP] of 75 µg/mL after maternal oral overdose and subsequent delivery.[182] Exchange transfusion eliminated a portion of total APAP as evidenced by reduced [APAP] and rebound [APAP] after transfusion. For example, in one exchange of 210 mL blood (1.22-kg patient), the serum [APAP] decreased from 32 µg/mL to zero, then rebounded to 30 µg/mL.[182]

Liver Dialysis.
Liver dialysis devices include extracorporeal albumin dialysis (eg, molecular adsorbent recirculation system [MARS]), fractionated plasma separation and adsorption and single pass albumin dialysis (SPAD). The MARS system may be used as a bridge to transplantation, for hemodynamic stabilization prior to hepatic transplant, or as a bridge to spontaneous recovery in patients with APAP-induced hepatic failure. Although MARS improves encephalopathy,[120] cerebral blood flow,[120] hemodynamics (increases in SVR, MAP, and decreases in cardiac index [CI] and pulse [HR]),[132] and intracranial pressure,[120] a meta-analysis concluded that MARS has no effect on mortality in multiple cause acute liver failure.[118] One report notes complete removal of APAP from the blood ([APAP] decreased from 40 µg/mL to 0 µg/mL from inflow to outflow) during MARS with rebound [APAP], suggesting that MARS may improve APAP clearance.[120]
Prometheus may also be used as a bridge to transplantation, but is relatively unstudied in APAP induced acute hepatic failure. Prometheus produces higher clearance of ammonia than MARS, but does not improve hemodynamics.\textsuperscript{175}

SPAD is venovenous hemodialysis with a dialysate containing 4.4% albumin. SPAD may more effectively clear ammonia than MARS,\textsuperscript{272} but there were no changes in hemodynamics or encephalopathy after therapy with SPAD in one study of patients with acute hepatic failure.\textsuperscript{155}

**SUMMARY**

- The decision to treat an acute APAP overdose requires plotting a single [APAP] onto the modified Rumack-Matthew nomogram and treating patients with NAC if their [APAP] plots above the treatment line, or the “150-line.”
- Patients should be treated with NAC after RSTIs of APAP if their [AST] is greater than normal or their [APAP] is detectable.
- The King’s College Criteria identifies patients with high mortality and is an indication for evaluation for hepatic transplantation:
  - Arterial pH < 7.3 or lactate > 3.0 mmol/L after fluid resuscitation
    - OR
  - All of the following:
    - Creatinine > 3.3 mg/dL
    - PT > 100 sec (or INR > 6.5)
    - Grade III or IV encephalopathy (somnolence to stupor; responsive to verbal stimuli; confusion; gross disorientation)
- NAC therapy should no longer be given as a set length protocol. Once NAC therapy is started, an informed decision should be made when to stop NAC, which requires an assessment of [AST] and [APAP], that the risk of developing toxicity is low ([APAP] is undetectable and [AST] is normal), and any toxicity that occurred has now resolved ([AST] has decreased and is near normal and there is no evidence of hepatic failure).

**Acknowledgment**

Martin J. Smilkstein, MD, and Kenneth Bizovi, MD, contributed to this chapter in previous editions.

**References**


27.


28.


29.


30.


31.


32.


33.


34.


35.


36.


37.


60. Cholongitas E, Theocharidou E, Vasinopoulou P et al.: Comparison of the Sequential Organ Failure Assessment score with the King’s College Hospital Criteria and the Model for End-Stage Liver Disease Score for the prognosis of acetaminophen-induced acute liver failure. *Liver Transpl.* 2012;18:405–412.


Craig DGN, Reid TW, Martin KG, Davidson JS, Hayes PC, Simpson KJ: The systemic inflammatory response syndrome and sequential organ failure assessment scores are effective triage markers following paracetamol (acetaminophen) overdose. *Aliment Pharmacol Ther.* 2011;34:219–228.


CrossRef [PubMed: 8179480]

85.


CrossRef [PubMed: 8853667]

86.


CrossRef [PubMed: 21719230]

87.


88.


CrossRef [PubMed: 19007345]

89.


90.


CrossRef [PubMed: 8209379]

91.


CrossRef [PubMed: 1987650]

92.


93.


CrossRef [PubMed: 2049229]

94.


CrossRef [PubMed: 2751701]

95.

Esterline RL, Ray SD, Ji S: Reversible and irreversible inhibition of hepatic mitochondrial respiration by acetaminophen and its toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). *Biochem*

CrossRef [PubMed: 2751700]

96.


CrossRef

97.


CrossRef

98.


CrossRef [PubMed: 4568386]

99.


CrossRef [PubMed: 17699243]

100.


101.


CrossRef [PubMed: 4564318]

102.


CrossRef

103.


CrossRef [PubMed: 11752356]

104.


CrossRef

105.

Gelotte CK, Auiler JF, Temple AR et al.: Clinical features of a repeat dose multiple-day pharmacokinetics trial of acetaminophen at 4, 6, and 8 g/day. J Toxicol Clin Toxicol. 2003;41:726.

106.


CrossRef [PubMed: 66465]

107.


CrossRef [PubMed: 17594792]


121.


122.


123.


124.

Haller VL, Cichewicz DL, Welch SP: Non-cannabinoid CB1, non-cannabinoid CB2 antinociceptive effects of several novel compounds in the PPQ stretch test in mice. Eur J Pharm. 2006;546:60–68. CrossRef

125.


126.


127.


128.


130.


131.


132.


Hogestatt ED, Jonsson BAG, Ermund A et al.: Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. *J Biol Chem.* 2006;280:31405–31412. [CrossRef]


170.


171.


172.


173.


[Archives of Internal Medicine Full Text]

174.


175.


176.


177.


178.


179.


180.


181.


182.


220.

CrossRef [PubMed: 2240884]

221.


CrossRef [PubMed: 10422949]

222.


CrossRef [PubMed: 8020810]

223.


224.


225.


CrossRef [PubMed: 3620287]

226.


227.


CrossRef

228.


CrossRef [PubMed: 21652548]

229.


230.


CrossRef

231.


CrossRef [PubMed: 11370851]

232.


233.


250. Raffa RB, Codd EE: Lack of binding of acetaminophen to 5-HT receptor or uptake sites (or eleven other binding/uptake assays). Life Sci. 1996;59:PL37–40. [CrossRef] [PubMed: 8699917]


CrossRef [PubMed: 17522810]

271.


272.


CrossRef [PubMed: 15122770]

273.


CrossRef [PubMed: 8666322]

274.


275.


CrossRef [PubMed: 16184570]

276.


CrossRef [PubMed: 11915034]

277.


CrossRef [PubMed: 12198658]

278.


CrossRef [PubMed: 17326205]

279.


CrossRef [PubMed: 16424712]

280.


CrossRef [PubMed: 11510016]

281.


CrossRef [PubMed: 8967682]

328.


CrossRef [PubMed: 10470790]

329.


330.


CrossRef [PubMed: 9581688]

331.


CrossRef [PubMed: 10401934]

332.


CrossRef [PubMed: 21402629]

333.


334.


CrossRef

335.


CrossRef

336.


CrossRef [PubMed: 18211314]

337.


CrossRef

338.


CrossRef [PubMed: 16820551] [JAMA and JAMA Network Journals Full Text]


