

A Review of Acetaminophen Poisoning

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KEYWORDS

- Acetaminophen poisoning • Acetaminophen overdose • *N*-acetylcysteine
- Hepatotoxicity • Fulminant hepatic failure • Liver transplant • Paracetamol

KEY POINTS

- Acetaminophen is the leading cause of acute liver failure in the United States. Liver toxicity may result from an acute overdose as well as from chronic excessive ingestion.
- *N*-acetyl cysteine (NAC) is an effective antidote for acetaminophen overdose. Early treatment with NAC prevents the formation of a toxic metabolite that leads to hepatic injury. NAC is also an effective therapy to aid in the recovery of the hepatic injury as a consequence of acetaminophen.
- Obtaining an accurate time of ingestion is essential to interpreting an acetaminophen level in an acute exposure on the Rumack-Matthews Nomogram line. The nomogram line cannot be used to assess the risk of hepatotoxicity in a chronic acetaminophen exposure.
- The King's College Hospital criteria is the most often used to determine which patients are to die from fulminant hepatic failure. Other criteria have been proposed including phosphate, lactate, and a MELD score.

Acetaminophen (APAP) is a safe and effective analgesic and antipyretic.¹ It is widely available as a single-component medication and also as a component of a plethora of combination over-the-counter and prescription medications. More than 28 billion doses of APAP-containing products were dispensed in 2005.² With more than 89 million prescriptions, hydrocodone/APAP was the most commonly dispensed medication in 2003.³ Despite its safety when used properly, APAP is one of the more common overdoses reported to poison centers. Serious toxicity results in hepatic injury, which may progress to fulminant hepatic failure (FHF) and death.⁴ In 2009, the American Association of Poison Control Centers' National Poison Data System reported 401 deaths caused by APAP or an APAP combination product.⁵ APAP is the most common cause of acute liver failure (ALF) in the United States, accounting for nearly half of the cases of

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ALF in the US Acute Liver Failure Study Group.^{6,7} Additionally, a significant number of cases of ALF of unknown cause may be unrecognized APAP toxicity, suggested by the presence of APAP protein adducts.⁸ In children, APAP is much less frequently the cause of acute liver failure.⁹

APAP toxicity may be the consequence of either an acute overdose or from repeated excessive dosing (repeated supratherapeutic ingestion [RSTI]).¹⁰ Unintentional toxicity may also occur from the concurrent use of several different medications that each contains APAP. The Acute Liver Failure Study Group found nearly equal proportions of patients with APAP hepatotoxicity caused by intentional versus unintentional overdose. Unintentional overdoses were often caused by RSTI and tended to present later with signs of hepatic injury apparent on presentation.¹¹ Concerns that combination APAP-opioid products are a risk factor for APAP hepatotoxicity from RSTI led the Food and Drug Administration to recently request that manufacturers of prescription drugs limit the APAP content of each unit dose to 325 mg. They have until early 2014 to comply with this requirement.¹² Earlier this year, in an effort to avoid dosing errors in children receiving liquid formulations of APAP, manufacturers agreed to a uniform strength of 160 mg/5 mL.¹³ Another potential challenge for clinicians is the recent introduction of an intravenous (IV) APAP product, Ofirmev, in the United States and the risk of iatrogenic toxicity.¹⁴

PHARMACOLOGY AND TOXICITY

APAP is rapidly absorbed from the gastrointestinal (GI) tract with peak concentrations achieved within 90 minutes of a therapeutic dose. The presence of food in the stomach may delay the peak but not the extent of absorption.¹⁵ Distribution is rapid with a volume of distribution (V_d) of about 0.9 L/kg and minimal protein binding at therapeutic concentrations.¹⁶ The half-life of APAP is 2.0 to 2.5 hours. With hepatic injury, the half-life is prolonged to more than 4 hours.^{4,16}

APAP undergoes extensive hepatic metabolism. Approximately 85% of a therapeutic dose undergoes phase II conjugation to sulfated and glucuronidated metabolites that are renally eliminated. Of these two pathways, glucuronidation is predominant in adults, whereas sulfation predominates in children up to about 12 years of age.¹⁷ Up to 10% of APAP undergoes phase I oxidation to a reactive intermediate, *N*-acetyl-*para*-benzoquinone imine (NAPQI), which is normally conjugated with glutathione to nontoxic cysteine and mercapturate metabolites.¹⁸ Cytochrome 2E1 is the primary cytochrome p450 (CYP) enzyme responsible for this oxidation. At supratherapeutic doses of APAP (>4 g), sulfation becomes saturated with proportional increases in both glucuronidation and, more significantly, oxidation to NAPQI.^{16,18} Smaller proportions of APAP are eliminated unchanged in the urine and by ring oxidation to a catechol derivative (**Fig. 1**).¹⁸

At toxic doses of APAP, the continued production of NAPQI eventually results in the depletion of glutathione. Once glutathione stores have been depleted by about 70%, NAPQI binds to cellular proteins and leads to cell injury.¹⁹ Glutathione depletion is only one of a cascade of intracellular events that includes mitochondrial oxidative stress, generation of reactive oxygen and nitrogen species, activation of stress proteins and gene transcription mediators, and mobilization of the liver's innate immune system. The balance between these numerous pathways ultimately determines whether there is recovery or cell death.^{20,21} Mitochondrial failure seems to be the terminal event heralding cell death.²¹ Although apoptotic pathways are activated, cell death is typically necrotic because mitochondrial failure precludes ordered cell death. The role of these various pathways in hepatocellular injury remains an area of active research. Zone 3

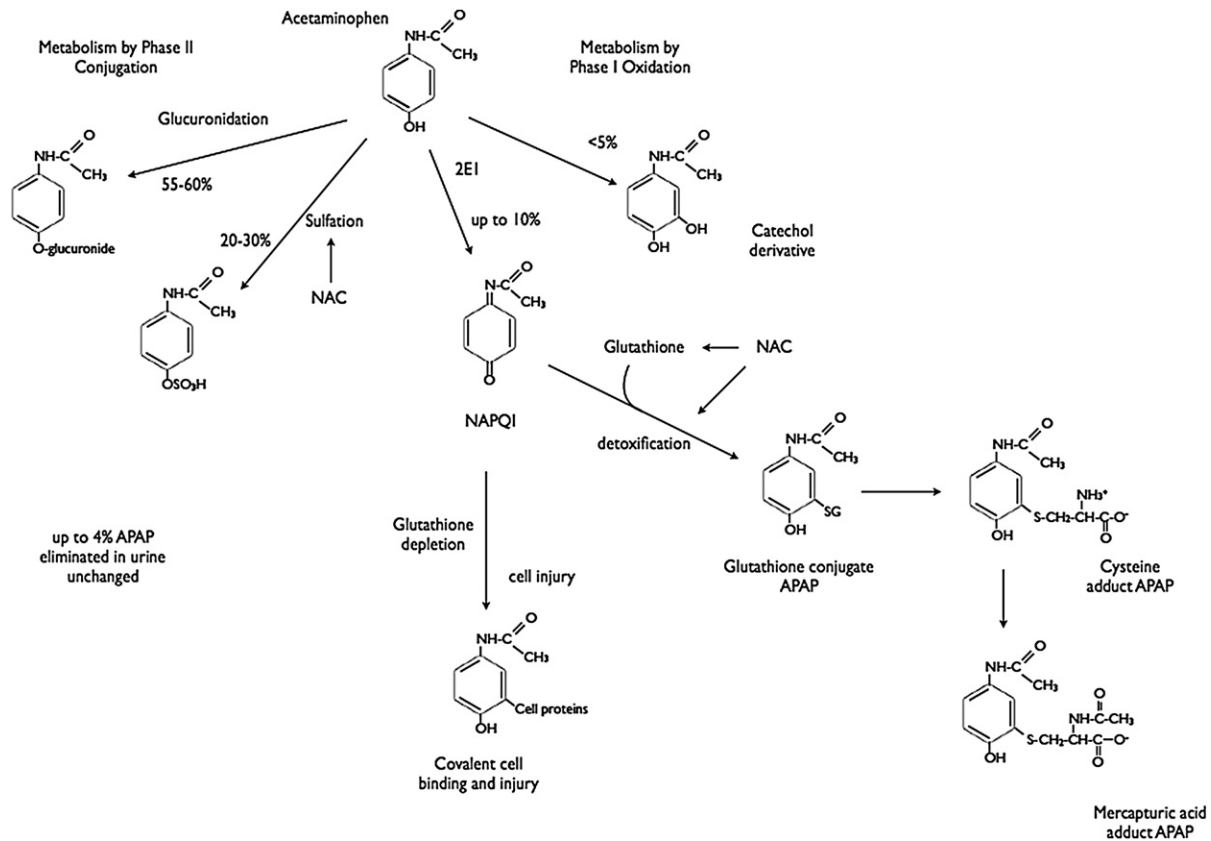


Fig. 1. Metabolism of APAP. NAC, *N*-acetylcysteine.

hepatocytes, rich in CYP 2E1, are most susceptible to injury and this leads to the characteristic centrilobular pattern of hepatic necrosis seen with APAP. Patients on CYP2E1-inducing agents, such as ethanol, isoniazid, or St. John's wort, may be at an increased risk of toxicity because of increased NAPQI production, although there is no compelling data that this occurs at therapeutic dosages of APAP.²²⁻²⁴

Recommended maximum therapeutic dosages of APAP are 4 g daily in an adult and 50 to 75 mg/kg/d in children.¹⁵ A single acute ingestion of greater than 7.5 g in an adult or 150 mg/kg in children has been considered potentially toxic, although these thresholds are probably conservative.²⁵ Single acute ingestions of less than 200 mg/kg in young children (age <6 years) are unlikely to result in toxicity.²⁶⁻²⁸

Asymptomatic elevations of aminotransferases are sometimes seen with chronic use at the maximum recommended daily dose of 4 g. These elevations are typically less than 3 times the upper limit of normal, although occasionally greater.^{29,30} The clinical importance of these elevations during therapeutic use is uncertain.^{29,31} A prospective study in healthy adults consuming up to 8 g/d for 3 days did not find any toxicity.¹

A recent expert panel's guideline to assist poison information specialists in the management of APAP exposures also provides some guidance on doses that should be of concern. Adults and children older than 6 years with an accidental acute ingestion of at least 10 g or 200 mg/kg, whichever is less, within an 8-hour period warrants further evaluation at a health care facility. For children younger than 6 years, the criterion was 200 mg/kg or more within an 8-hour period. The referral recommendations after RSTI in adults and children older than 6 years were at least 10 g or 200 mg/kg, whichever is less, in a single 24-hour period or 6 g or 150 mg/kg, whichever is less, per 24-hour period for 48 hours or longer. For children younger than 6 years, the criteria following RSTI were (1) 200 mg/kg or more over a single 24-hour period, (2) 150 mg/kg or more per 24 hours for the past 48 hours, or (3) 100 mg/kg or more per 24 hours for 72 hours or more.³²

For populations that may be at greater risk of toxicity, a lower threshold for evaluation was recommended. These at-risk groups include pregnancy, prolonged fasting, chronic alcoholism, and chronic use of isoniazid. For these populations, the threshold for referral is ingestion of more than 4 g in 24 hours or greater than 100 mg/kg in 24 hours, whichever is less.³² Immediate evaluation is required for any patient with an intentional overdose, when child abuse or neglect is a concern, and for any patient with symptoms suggesting hepatic injury.

CLINICAL COURSE

There are no specific findings early after an overdose of APAP. Early nonspecific symptoms may include nausea, vomiting, abdominal pain, and malaise. Although these symptoms may improve over the first 24 hours, progressive hepatic injury may manifest as early as day 2 to 3 with right upper quadrant pain and tenderness. Liver enzymes typically start increasing within 24 to 36 hours after an overdose but may increase as early as 12 hours after a massive ingestion.³³ Maximal liver injury typically peaks between 3 to 5 days with jaundice, coagulopathy, and encephalopathy.³⁴ Recovery or progression to FHF occurs over the following several days.

Renal injury, oliguria, and acute renal failure are also seen, although less commonly. The onset is usually after hepatic injury is already apparent. Maximal renal injury lags beyond peak liver injury, and recovery is also more protracted.²⁵ Isolated nephrotoxicity without hepatic injury rarely occurs.^{35,36} Renal failure may also be seen with FHF and hepatorenal syndrome.

The mental status is typically clear after an APAP overdose unless altered by a co-ingested centrally active drug. On rare occasions, however, massive APAP overdoses

may result in coma.^{37,38} Metabolic acidosis is another uncommon finding early in the course of APAP poisoning. This early metabolic acidosis may be a lactic acidosis or very rarely caused by a product of the gamma-glutamyl cycle, 5-oxoproline.^{38,39} Lactic acidosis also occurs late secondary to hepatic failure with an inability to clear lactate.

ASSESSMENT

With acute ingestions of APAP, the Rumack-Matthews nomogram is a valuable tool to assess the risk of hepatotoxicity (Fig. 2). This nomogram was originally constructed in the 1970s as a tool to discriminate those patients likely to suffer hepatotoxicity, defined as an aminotransferase more than 1000 IU/L, from those who would not. A line between 200 $\mu\text{g}/\text{mL}$ at 4 hours after ingestion and 25 $\mu\text{g}/\text{mL}$ at 16 hours, known as the *200 line*, defined this group at risk.^{4,23,40} Fifty-eight percent of patients with an APAP level above this line developed hepatotoxicity and 5% died.^{40,41} A parallel line at 150 $\mu\text{g}/\text{mL}$ at 4 hours, also known as the *treatment line* or *150 line*, was used in the US National Multi-center Open Study of Oral *N*-Acetylcysteine (NAC) for the Treatment of APAP Overdose and is the treatment line most commonly used in the United States.^{23,42}

The nomogram is only useful for acute ingestions when the time of ingestion is known. If there is any uncertainty regarding ingestion time, the worst-case scenario ingestion time should be used. Levels performed before 4 hours will indicate whether APAP has been ingested but cannot be plotted on the nomogram to assess the risk of toxicity. Likewise, the nomogram was constructed with patient data only to about 16 hours and has been validated for use only to 24 hours after acute overdose.^{40,42} The nomogram is not valid for patients who present beyond 24 hours after an acute overdose, patients with an unknown time of ingestion, patients with a history of a staggered overdose, and patients with a history of repeated supratherapeutic ingestion. In one small series, 44% of patients presenting with an APAP overdose could not be assessed using the Rumack-Matthew nomogram.¹⁰

After an acute overdose, a 4-hour APAP level, or as soon thereafter as feasible, should be obtained and plotted on the Rumack-Matthew nomogram to assess risk. Other tests to consider include serum aminotransferase levels, electrolyte and renal function assays, and blood prothrombin time. These tests are especially useful for patients who present more than 8–10 hours after an acute overdose as well as in

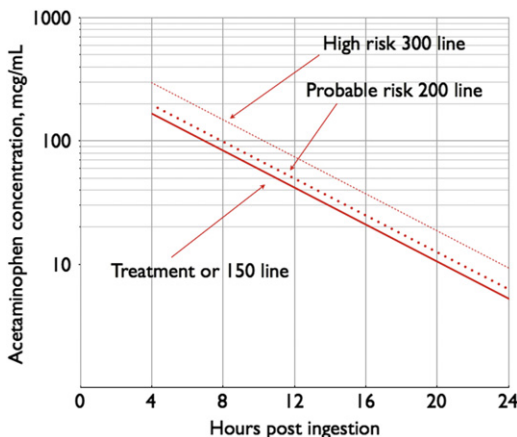


Fig. 2. Rumack-Matthews Nomogram. (Data from Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. *J Toxicol Clin Toxicol* 2002;40(1):3–20.)

any patient with a history of RSTI or staggered overdose. One in 70 patients presenting with drug overdose will have an unanticipated detectable APAP level and, of these, 1 in 500 will have a potentially hepatotoxic level.⁴³ The incidence of an unexpected elevated APAP level is even higher in patients who are unable to provide a history.⁴⁴ Given the consequences of missed APAP poisoning, routine screening in patients who present with known or possible drug overdose seems reasonable.

MANAGEMENT

NAC is an effective antidote for APAP poisoning. When administered early after an acute APAP overdose, NAC provides cysteine for the replenishment and maintenance of hepatic glutathione stores, enhances the sulfation pathway of elimination and may directly reduce NAPQI back to acetaminophen^{45–48} (See **Fig. 1**). NAC dramatically reduces the incidence of hepatotoxicity and progression to FHF when administered within the first 8–10 hours following an acute overdose. In patients who receive NAC within the first 8 hours after an acute overdose, the risk of hepatotoxicity is less than 5% whereas delays beyond 10 hours are associated with an increased risk of hepatic injury.^{40–42,49,50} NAC should ideally be initiated within 8 hours of ingestion if the patient's APAP level plots above the treatment line (the 150 line) on the Rumack-Matthew nomogram. If an APAP level will not be available by 8 hours post ingestion, NAC should empirically be started pending the APAP level.

Patients with hepatic injury also benefit from NAC. This was demonstrated in several seminal papers in the early 1990s that showed improved transplant-free survival in patients with APAP-induced FHF.^{51,52} The mechanism here is not the detoxification of NAPQI but rather enhanced recovery. Several different mechanisms seem to contribute to the efficacy of NAC in this setting. NAC improves hepatic perfusion and oxygen delivery and extraction in patients with APAP-induced FHF.⁵³ Other beneficial effects include scavenging of reactive oxygen and nitrogen species and improved mitochondrial energy production.^{54,55} These beneficial effects of NAC do not seem to be unique to APAP hepatotoxicity.⁵⁶

NAC is available both orally and intravenously. A 20-hour IV infusion of NAC has been widely used worldwide since this schedule was demonstrated effective by Prescott and colleagues⁴⁰ in the 1970s.^{41,49} This regimen includes a loading dose of 150 mg/kg IV over 15 minutes followed by 50 mg/kg over the next 4 hours (rate of 12.5 mg/kg/h) and then 100 mg/kg over the next 16 hours (rate of 6.25 mg/kg/h). For patients weighing more than 100 kg, the US manufacturer of IV NAC recommends dosing equivalent to a 100 kg person (Cumberland Pharmaceuticals Inc. Professional Affairs, Nashville, TN, USA, 2011). The infusion is now more commonly given over 21 hours with the loading dose given over 60 minutes rather than 15 minutes to reduce the incidence of anaphylactoid reactions.

The standard oral course of NAC is a 140 mg/kg loading dose followed by 70 mg/kg orally every 4 hours for a total of 18 doses over 72 hours.⁴² Although the two regimens are very different in duration and total dose, they are both very effective for the treatment of an acute APAP overdose (**Box 1**).^{50,57} Given the disparity between the two regimens, other dosing schedules have been investigated. Shorter courses of oral NAC have been studied and seem to be safe and effective.^{58–61} In the largest of these studies, NAC was discontinued after a minimum of 20 hours of treatment if a repeat APAP level was less than 10 µg/mL, and there was no increase in serum aminotransferases or international normalized ratio (INR) (ie, INR ≤ 1.3).⁶⁰ These abbreviated courses have not been rigorously investigated but suggest that a shorter duration of oral NAC is safe if the previously mentioned criteria are met, that is, no remaining APAP to be metabolized and no evidence of hepatic injury.

Box 1 Dosing of NAC

Oral NAC

140 mg/kg loading dose, then 70 mg/kg orally every 4 hours for 18 total doses

Repeat any dose vomited within 1 hour of administration.

IV NAC (Acetadote)

Adults

Loading dose: 150 mg/kg in 200 mL diluent over 1 hour, then 50 mg/kg in 500 mL diluent over 4 hours (12.5 mg/kg/h), then 100 mg/kg in 1000 mL diluent over 16 hours (6.25 mg/kg/h)

For patient weight more than 100 kg, base the dose on 100 kg weight.

Children

Weight more than 20 kg to 40 kg or less: loading dose of 150 mg/kg into 100 mL diluent over 1 hour, then 50 mg/kg into 250 mL diluent over 4 hours, then 100 mg/kg into 500 mL diluent over 16 hours

Weight less than 20 kg: loading dose of 150 mg/kg into 3 mL/kg diluent over 1 hour, then 50 mg/kg into 7 mL/kg diluent over 4 hours, then 100 mg/kg into 14 mL/kg diluent over 16 hours

Acetadote is compatible with D5W (5% dextrose in water), 0.5NS (0.5% normal saline), and sterile water for injection.

An alternate IV regimen has also been investigated in patients with acute APAP overdose presenting within 24 hours of the overdose. This regimen consisted of 140 mg/kg NAC as a loading dose and then 70 mg/kg every 4 hours for 48 hours. This regimen was equally effective to the standard 72-hour oral and 20.25-hour IV courses.⁶²

Whatever route of administration is selected, there are several very important aspects of management. Following an acute overdose, treatment should not be delayed beyond 8 hours after ingestion because of the dramatic protective effect when given within this time frame (**Box 2**).^{41,42,50} Conversely, because of the benefit of NAC in patients with hepatotoxicity, NAC should be continued beyond the usual course of therapy in any patient with signs of liver injury.⁵² Guidelines on when to

Box 2 Management of acute APAP overdose

1. Plot the APAP concentration onto the Rumack-Matthew nomogram. If the level will not return before 8 hours from the time of ingestion, begin NAC pending the level.
2. If the level plots above the 150 ($\mu\text{g/mL}$) treatment line, begin NAC.^a
3. If NAC is administered IV, repeat the APAP level and measure serum AST and ALT before completion of NAC.
 - a. May discontinue NAC if APAP level is less than 10 $\mu\text{g/mL}$ and serum AST and ALT are not increased more than the reference range and increasing.
 - b. If APAP is more than 10 $\mu\text{g/mL}$ or either the serum AST or ALT are elevated, continue NAC until APAP is less than 10 $\mu\text{g/mL}$ and the AST and ALT have peaked and are improving.

Abbreviations: ALT, alanine aminotransferase activity; AST, aspartate aminotransferase activity.

^a Consider treatment at the 100 $\mu\text{g/mL}$ line (at 4 hours and parallel to the 150 line) if there is chronic alcoholism, prolonged fasting, pregnancy, or chronic isoniazid use.

discontinue NAC in this setting are not well defined but include aminotransferase activities that have peaked and are improving, a normal prothrombin time/INR (≤ 1.3), and no acidosis.

Treatment failures after the standard IV course of NAC have occurred after massive ingestions and after overdoses that included a co-ingestant that may slow GI motility, such as anticholinergic or opioid drugs. In these cases, either APAP was still present (and usually elevated) or signs of hepatic injury were evident at the completion of the 21-hour course of IV NAC.^{63–66} These cases highlight the importance of assessing these same parameters (ie, a repeat APAP level as well as aminotransferase levels and an INR before discontinuing NAC in patients with a history of a large ingestion or one complicated by a co-ingestion). If APAP is still detectable or there are signs of hepatic injury, NAC should be continued until APAP is not detected and, if there were any signs of hepatic injury, these parameters are also improving. In this setting, the usual strategy is to continue NAC at a rate of 6.25 mg/kg/h (ie, the 16-hour bag).

For patients who present after RSTI, assessment should include a serum APAP level and aminotransferase activities, plus a prothrombin time/INR. A conservative definition of RSTI of APAP used by Daley and colleagues⁶⁷ was the ingestion of more than one dose of APAP over a period of more than 8 hours that results in more than 4 g ingested in a 24-hour period in an adult. In the study by Daley and colleagues, patients with a history of RSTI had an APAP level as well as serum transaminase levels measured on presentation. If either the APAP was more than 10 $\mu\text{g/mL}$ or an aminotransferase was increased more than the normal range, NAC was started. NAC was continued until the APAP was less than 10 $\mu\text{g/mL}$ and the transaminases had peaked and were either static or decreasing. With this strategy, the investigators found that no patient with a normal aspartate transaminase on presentation and an APAP less than 10 $\mu\text{g/mL}$ developed hepatotoxicity. Another retrospective review of patients with RSTI found that all patients who progressed to hepatotoxicity, death, or transplant presented with an alanine transaminase of more than 200 IU/L.⁶⁸ The management described by Daley and colleagues is a very reasonable approach to patients seen with a history of repeated excess ingestion (**Box 3**). Clinical decision making in these more complicated cases can be aided by consultation with a regional poison center.

Tylenol ER contains immediate-release and sustained-release APAP. Delayed increases of the APAP concentration have been observed in some cases of Tylenol ER overdose, sometimes with an initial level plotting below and a second above the nomogram treatment line.^{69,70} The clinical significance of line crossing is uncertain, as is the risk of hepatotoxicity in this situation.⁷¹ In several reports, patients who were line crossers had ingested a large quantity of APAP (>35 g in 3 of 4 cases), which may have delayed the time to peak concentration. A reasonable and conservative

Box 3**Management of repeated supratherapeutic ingestion or time-unknown ingestion**

1. Obtain serum APAP level and serum AST and ALT levels.
2. If APAP is less than 10 $\mu\text{g/mL}$ and the AST and ALT are normal, no treatment is necessary.
3. If either the APAP level is detectable more than 10 $\mu\text{g/mL}$ or either the AST or ALT are elevated more than the reference range and not otherwise explained, begin NAC treatment.
4. Continue NAC until APAP is less than 10 $\mu\text{g/mL}$ and the AST and ALT have peaked and are improving and there are no other signs of hepatic dysfunction, including INR of 1.3 or less.

Abbreviations: ALT, alanine aminotransferase activity; AST, aspartate aminotransferase activity.

approach in this group is to obtain an initial APAP level between 4 and 8 hours and repeat this in 4 to 6 hours if the first level plots below the treatment line. If the second line is above the treatment line, NAC should be commenced. If the initial level is below the treatment line but the history suggests ingestion greater than 200 mg/kg, it would be reasonable to start NAC within the first 8 hours after ingestion pending a repeat APAP level. If the subsequent level is also below the treatment line, NAC can be discontinued.

IV APAP was approved for use in the United States in late 2010. It was first approved for use in France in 2001, and experience with overdose by this route is very limited. Most published reports of iatrogenic overdose are in infants. In one case, a 5-month-old child had 6-hour APAP level of 38 $\mu\text{g}/\text{mL}$ after a tenfold dosing error (75 mg/kg). The next day, NAC was started because of increasing aminotransferase activity and an elevated INR. She recovered fully.¹⁴ In several other cases of tenfold plus dosing errors, NAC was started early and no toxicity was reported.^{14,72} Given the limited experience with this route of delivery, current expert opinion recommends the following approach to overdoses of IV APAP. Treatment with NAC should be initiated if either the parenteral dose of APAP exceeds 60 mg/kg or an APAP level plots above a 50 $\mu\text{g}/\text{mL}$ line on the Rumack-Matthew nomogram (a line parallel to treatment line but at 50 $\mu\text{g}/\text{mL}$ at 4 hours).⁷³ NAC should be continued until serum APAP is undetectable and there is no evidence of hepatic injury. This recommendation is very conservative and reflects the limited data available at this time regarding iatrogenic IV overdose.

Adverse effects associated with oral NAC are predominately GI with nausea and vomiting. These effects can be mitigated by pretreatment with an antiemetic.⁷⁴ Anaphylactoid reactions may be seen with IV NAC and are most likely to occur early during the loading dose, with an incidence as high as 15% to 20%. Although a randomized trial conducted in Australia found no difference in the incidence of anaphylactoid reactions when comparing a 15-minute to 1-hour infusion time for the loading dose, other investigators have reported a lower rate of anaphylactoid reactions with a 1-hour infusion.⁷⁵⁻⁷⁷ In 2006, the manufacturer of Acetadote, the parenteral NAC formulation available in the United States, changed the recommended infusion time for the loading dose to 1 hour, increasing the total duration of therapy from 20.25 to 21.0 hours.

Anaphylactoid reactions occur more frequently in patients with lower acetaminophen levels. A study by Waring and colleagues⁷⁸ found a rate of anaphylactoid reactions of more than 20% in patients with an initial APAP level less than 150 $\mu\text{g}/\text{mL}$, whereas the incidence in patients with a level more than 200 $\mu\text{g}/\text{mL}$ was less than 5%. NAC induces the release of histamine from basophils and mast cells, and in an *in vitro* model, higher APAP concentrations reduced the extent of NAC-induced histamine release.⁷⁹ Asthmatics may be at greater risk of adverse events with IV NAC.⁸⁰ Status asthmaticus with cardiac arrest and anoxic brain injury was reported in a patient with steroid-dependent asthma during the loading dose of NAC for APAP overdose.⁸¹

Minor anaphylactoid reactions, such as flushing or rash, can usually be managed with diphenhydramine. With more significant reactions, such as angioedema, hypotension, or wheezing, the infusion should be stopped and standard symptomatic therapy provided. The need for ongoing therapy with NAC should be reassessed and a switch to the oral route considered. If the IV route is considered necessary, the infusion can usually be resumed after about 1 hour at a slower rate.^{78,82}

IV NAC administration to young children has resulted in dilutional hyponatremia and seizure from the free water load associated with the infusion.⁸³ The manufacturer of Acetadote has modified the instructions for the preparation of NAC for administration to young children because of this risk.⁸⁴ Massive overdose of NAC caused by dosing error has resulted in seizures, status epilepticus, intracranial hypertension, and

cerebral edema.^{85,86} The standard administration of NAC involving 3 bags of different concentrations over the 21-hour infusion is complicated and alternatives to this have been proposed.⁸⁷

GI decontamination should also be considered. In volunteer studies, activated charcoal significantly reduced the absorption of APAP when given within 1 hour after ingestion. Although more modest, a reduction was still appreciated with administration at 2 hours after ingestion.⁸⁸ Even more delayed administration of activated charcoal may be beneficial in select cases of very large ingestions. In a group of patients with an APAP level above the 200 risk line and who received activated charcoal between 4 to 16 hours after an acute ingestion, fewer progressed to hepatotoxicity than a group that did not receive activated charcoal.⁸⁹ Contraindications to activated charcoal include a depressed level of consciousness, aspiration, uncontrolled vomiting, or co-ingestion of a corrosive or proconvulsant. Activated charcoal does not significantly interfere with the efficacy of oral NAC.⁹⁰

ALCOHOL AND ACETAMINOPHEN

The interaction between APAP and ethanol is complex. Ethanol is a competitive substrate for CYP 2E1, the primary microsomal enzyme responsible for the metabolism of APAP to NAPQI. In rats, acute ethanol administration is hepatoprotective to a toxic dose of APAP.⁹¹ A protective effect has also been observed in patients presenting within 24 hours of an acute APAP overdose. Hepatotoxicity occurred in 8% of patients who co-ingested ethanol compared with 23% of those who had not in a group of individuals with a presentation APAP level above the 200 line on the nomogram.⁹²

Conversely, chronic ethanol administration to rats increases liver toxicity caused by APAP, with both upregulation of CYP 2E1 and glutathione depletion likely contributing. Both these effects are transient, lasting less than 1 day in rats.^{93,94} Ethanol enhancement of CYP 2E1 is a result of both enzyme stabilization and increased synthesis of a new enzyme.²³ In humans, the maximal increase in NAPQI production after acute enzyme induction with ethanol occurs after 6 to 8 hours of abstinence and is short lived.⁹⁵ This finding suggests that there may be a brief window of increased risk in recently abstinent alcoholic patients who overdoses with APAP.

In a reanalysis of the US National Multicenter Open Study of Oral NAC for the Treatment of APAP Overdose, alcoholic patients in the higher-risk group, those with APAP levels plotting above the 200 line on the nomogram, were at an increased risk of progression to hepatotoxicity. In alcoholic patients with an APAP level plotting below the 200 line or those who received treatment with NAC within 8 hours, no increased risk was observed.⁹⁶ With respect to RSTI, Alhelail and colleagues,⁶⁸ in a retrospective series, found that alcoholic patients are at an increased risk of progression to hepatotoxicity. Makin and colleagues⁹⁷ did not find that alcoholic patients with hepatotoxicity fare any worse than nonalcoholic patients after admission to a liver unit.⁹⁸

Are alcoholic patients at risk with therapeutic doses of APAP? Studies administering APAP at 4 g daily for up to 5 consecutive days in recently abstinent alcoholic patients found no evidence of hepatic injury.^{99,100} Several comprehensive reviews have concluded that it is unlikely that at therapeutic doses of APAP there is any increased risk of hepatic injury in alcoholic patients.^{22,101} Fasting may be a greater risk factor for hepatotoxicity with excessive repeated ingestion (>4 g daily). Fasting was a more common feature in a group of patients with APAP hepatotoxicity from repeated excessive use of 4 to 10 g daily than was chronic alcohol use. In patients who had ingested more than 10 g daily, both fasting and alcoholism were common. No cases of hepatotoxicity were associated with doses less than 4 g daily.²⁴

TRANSPLANTATION

Transplantation can be life saving for those with FHF. The costs of transplantation and subsequent lifelong immunosuppression and the complications thereof are considerable. The challenge is to identify patients who are going to die of FHF from those who will spontaneously recover with supportive care. The most widely used prognostic criteria are those of King's College Hospital (KCH) (**Box 4**). These criteria were derived in the 1980s from a large cohort of patients with APAP hepatotoxicity. The criteria are either arterial pH less than 7.30 after fluid resuscitation or the combination of an INR greater than 6.5 plus serum creatinine greater than 3.4 mg/dL and grade III or IV encephalopathy (ie, marked somnolence, stupor, or coma).¹⁰² These criteria, although not very sensitive, had a high specificity in identifying patients who would do poorly without a transplant. Less than 20% of those who met the KCH criteria survived spontaneously.¹⁰³ A modification to these criteria added blood lactate measured 2 to 3 days after acute overdose. A lactate level on day 2 to 3 greater than 3.5 mmol/L before adequate fluid resuscitation or greater than 3.0 mmol/L after patients have been adequately fluid resuscitated was predictive of death without transplant. This modification improved both the sensitivity and specificity of the KCH criteria.¹⁰⁴ More recently, a much lower specificity of the modified KCH criteria has been reported with increased survival in patients meeting the KCH criteria. This finding may reflect improvements in critical care and the medical management of FHF.¹⁰⁵

Other prognostic criteria have been proposed. A serum phosphate of greater than 1.2 mmol/L at 48 to 96 hours after overdose was predictive of death.¹⁰⁶ Although this marker was very sensitive and specific in the original report, subsequent application of this marker to other series of APAP FHF have not duplicated this finding.^{107,108}

The Model for End-Stage Liver Disease (MELD) score has been investigated with APAP hepatic injury. Components of the MELD score are INR, serum bilirubin, serum creatinine, and cause of liver injury. In a group of patients with APAP hepatotoxicity, a higher MELD score on admission to the intensive care unit (ICU) was associated with progression to encephalopathy, and an increase in the MELD score over the first day after the onset of hepatic encephalopathy was predictive of death. When compared with the KCH criteria, this tool performed no better.¹⁰⁹ The Acute Physiology and Chronic Health Evaluation (APACHE) II score has also been used to predict death from APAP hepatotoxicity. A score of more than 15 on admission to the ICU was a sensitive tool to predict patients likely to progress to FHF and was slightly more sensitive than the KCH criteria on the day of admission.¹¹⁰ A score of more than 20 was associated with a lower transplant-free survival in the US Acute Liver Failure Study Group.¹¹

A critical decision for clinicians is the decision to refer patients to a specialized liver unit. Criteria to consider in this decision include acidosis, renal insufficiency,

Box 4

KCH transplant criteria

Blood lactate concentration greater than 3.5 mmol/L before or greater than 3.0 mmol/L after fluid resuscitation

OR

Arterial blood pH less than 7.30 after fluid resuscitation

OR

Serum creatinine concentration greater than 3.2 mg/dL and INR greater than 6.5 and grade III or IV encephalopathy

a prothrombin time (PT) in seconds greater than the number of hours since the overdose, an INR greater than 5, hypoglycemia, or encephalopathy.¹¹⁰ An increase in the INR from day 3 to 4 after overdose has also been associated with a poorer outcome.¹¹¹ An APACHE II score of more than 15 has also been suggested as a decision aid.¹¹²

LABORATORY

Increases in the INR early after APAP overdose may be seen that are not reflective of hepatocellular injury. An early increase in the INR seen at 12 to 16 hours after overdose seems to be the result of APAP interference in the production of active factor VII and is not reflective of hepatocellular injury. The effect is usually modest, with a mean increase to 1.36 in one series.¹¹³ NAC has also been implicated as a cause of an early increase in the INR. Here too the increase observed was modest, to about 1.3.¹¹⁴ This effect has been observed in patients receiving NAC without APAP present.¹¹⁵ The important point is that a modest elevation in the INR early after an acute overdose and without other signs of liver injury should not be confused with an increasing INR after 24 hours suggestive of hepatic injury.

Colorimetric methods of measuring APAP are subject to interference by bilirubin. Depending on the specific instrument and method, this may occur at bilirubin levels as low as 10 mg/dL.^{116,117} Microdialysis of the serum specimen before assay will correct this false-positive result.¹¹⁷ Compared with other causes of acute liver failure, bilirubin levels more than 10 mg/dL are uncommon with APAP liver injury.⁶

SUMMARY

APAP toxicity is the most common cause of ALF in the United States.⁶ With early recognition and prompt institution of NAC, serious toxicity can usually be mitigated or prevented following an acute overdose. Remember to obtain an appropriately timed APAP level and to start NAC within 8 hours of an acute overdose. With massive ingestions and polypharmacy overdose, there may be prolonged absorption of APAP with measurable levels of APAP still present at the completion of the standard course of IV NAC. NAC should not be discontinued until there is no further APAP to metabolize and any signs of liver injury are improving. In addition to the antidotal properties of early treatment with NAC to prevent the production of the toxic metabolite, NAC also is beneficial in the treatment of acetaminophen induced hepatic injury and should be used in patients with late presentation and signs of hepatic injury. Patients with FHF require expert management and are best served by transfer to a specialized liver unit with transplant capability.

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