

Acetaminophen Poisoning

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In 2003, the American Association of Poison Control Centers reported more than 127,000 exposures involving acetaminophen (acetyl-para-aminophenol or APAP). Of these exposures, 65,000 patients received treatment in a medical facility, and 16,500 received N-acetylcysteine (NAC). There were 214 deaths involving overdose where an analgesic agent was thought to be primarily responsible. In 62 of these cases, APAP was the single agent involved [1]. APAP toxicity is also a major cause of fulminant hepatic failure (FHF) and is implicated in as many as 39% of cases presenting to tertiary care hospitals [2].

The objective of this current literature review is to enable the clinician to recognize which patients need to be treated for APAP toxicity. In addition, this article discusses NAC treatment protocols and provides clinicians with guidance in the selection of patients who would benefit from transfer to a tertiary care facility capable of liver transplantation.

Diagnosis

Prompt recognition of APAP toxicity is essential to preventing morbidity and mortality. This recognition is made difficult by the nonspecific clinical findings early in the course of APAP toxicity. The first 24 hours are considered the first phase of APAP poisoning and are characterized by

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nonspecific findings, such as nausea, vomiting, anorexia, pallor, and lethargy. In this phase, however, the patient may appear normal. In the second phase of APAP poisoning, the patient begins to develop clinical and laboratory evidence of hepatotoxicity. Classically, it is taught that APAP-induced liver dysfunction occurs only after a latent period of 24 to 48 hours. However, Singer and colleagues [3] demonstrated that liver enzymes often become elevated in the initial 24 hours. In the third phase, the patient progresses to FHF with all its associated complications. Phase four, usually occurring 72 to 96 hours after ingestion, is the resolution of liver function and complete recovery if the patient survives the initial insult.

APAP toxicity should be suspected in all intentional overdoses because of the ubiquitous nature of APAP. The early symptoms of APAP ingestion are often vague or absent, leading to concern that potentially toxic ingestions could be missed owing to the poor histories often encountered in the overdose patient. To address this concern, several studies have attempted to evaluate the role of screening all intentional ingestions with serum APAP levels. Ashbourne and colleagues [4] found that, in patients without history of APAP ingestion, approximately 1 in 70 had detectable APAP levels and approximately 1 in 500 had potentially hepatotoxic APAP levels. A large retrospective study by Sporer and colleagues [5] found similar results: the rate of potentially hepatotoxic APAP levels in patients without history of ingestion was 0.3%.

Based on the wide availability of APAP, the low cost of quantitative APAP levels, and the potentially disastrous consequences of unrecognized APAP ingestion, all intentional overdoses should be screened for APAP toxicity. Since all overdose patients should be screened for APAP, it is equally important that all acute care facilities have the ability to rapidly run an APAP assay.

It should be noted the false positive APAP levels have been seen in patients with hyperbilirubinemia. The actual threshold for bilirubin's interference with the APAP assay is unclear. Because of the treatment and prognostic decisions that could follow a misdiagnosis of APAP induced hepatitis, caution is warranted and the clinician should be aware of this lab phenomenon [6,7].

APAP and histopathology

Predicable histopathologic changes occur following acetaminophen poisoning. From autopsy and liver biopsy specimens, a characteristic pattern is observed in the liver [8–10]. Microscopic examination shows necrosis of the centrilobular hepatocytes. Associated findings include passive congestion, scattered mononucleated and polynucleated leukocytes and no fatty infiltration. Reticulin stain reveals maintenance of the hepatic architecture in areas of hepatocyte necrosis. In one case, a liver biopsy during the acute phase of an acetaminophen poisoning demonstrated the

above changes. A wedge biopsy was obtained 4 years after that showed normal liver architecture and no fibrosis or cirrhosis [8]. However, additional fibrotic changes have been observed months after acute poisoning in association with chronic alcoholism [11]. The kidneys show diffuse acute tubular necrosis with tubular epithelial swelling and fatty vacuolization [9,10]. Autopsies have also demonstrated diffuse acute pancreatitis and diffuse cerebral edema with brainstem herniation [9,10].

Risk factors

Several populations of patients are at increased risk for hepatotoxicity from APAP. An understanding of the pathophysiology is necessary to evaluate the need for treatment in those who may be at increased risk.

With therapeutic dosing, 90% of APAP is conjugated with glucuronide or sulfate to form nontoxic metabolites. Approximately 5% of APAP is metabolized by the hepatic cytochrome p450 mixed-function oxidase enzyme to a toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). In normal dosing, NAPQI is rapidly detoxified by glutathione (GSH) to nontoxic metabolites. Acetaminophen overdoses overwhelm conjugation pathways, resulting in increased use of the cytochrome p450 pathway and increased formation of NAPQI, increased depletion of GSH, and, ultimately, hepatic injury. Because APAP is metabolized to its toxic metabolite, NAPQI, by the p450 system, any agent that induces this system theoretically increases the risk for APAP hepatotoxicity. However, few interactions have been reported or formally studied [12–16]. Ethanol is the best-studied inducer, with chronic alcohol ingestion inducing the p450 enzyme system and in turn making the liver capable of metabolizing more APAP to the toxic metabolite NAPQI. This interaction has been demonstrated in animal models, but its clinical relevance is unknown. Currently, chronic alcoholics who acutely ingest APAP should be treated in the same manner as other patients, by obtaining a 4-hour APAP level and plotting it on the nomogram [16–20].

Chronic alcoholics have been shown to have significantly lower levels of plasma GSH than controls: this may be a risk factor for APAP toxicity [20]. To investigate the influence of acute and chronic alcohol intake on the clinical course and outcome, one study looked at 209 patients who had an acute APAP overdose. This study showed that, after one has corrected for all other factors, chronic alcohol intake is associated with a fivefold increase in the relative risk of developing hepatic encephalopathy. The study was unable, however, to demonstrate a significant change in mortality [21].

Because alcohol and APAP are metabolized by the same enzymes system, some have speculated that they may competitively inhibit each other's metabolism. Acute alcohol intake does not independently influence the clinical course of APAP overdose in humans [21]. By contrast, some animal studies have shown a marginal benefit from acute alcohol ingestion in APAP

overdoses [12,22,23]. The clinical significance of acute alcohol ingestion is probably minimal and should not affect treatment decisions.

Specific drugs metabolized by the p450 system may theoretically play a role in the formation of NAPQI. For example, isoniazid is often implicated as an inducer of the p450 system and thereby may play a role in APAP toxicity [24–28]. APAP is metabolized through a specific subset of enzymes (CYP2E) in the p450 system, and only drugs actually inducing this subset of enzymes affect the formation of NAPQI [16].

GSH is essential for the detoxification of NAPQI. Patients who are at increased risk for APAP hepatotoxicity also include those with decreased GSH stores. The most common reason for decreased GSH stores is malnutrition—for example, anorexia nervosa [29] and chronic alcoholism [19]. Reports also exist of APAP-induced hepatotoxicity associated with fasting from febrile illnesses and chronic disease [30,31]. These risk factors do not appear to play a major role in acute ingestions but may play an important one in nonacute ingestions.

Treatment

The Rumack-Mathew treatment nomogram is the primary tool used to guide treatment after acute ingestion of APAP. A firm understanding of the nomogram's use and its limitations is essential in the management of APAP exposure. The nomogram was first studied retrospectively in 64 cases of acute ingestion of APAP in an attempt to correlate APAP serum levels with hepatotoxicity. Hepatotoxicity was arbitrarily defined as an aspartate aminotransferase (AST) level of 1000 IU/L. Serum APAP levels at or above a line connecting 200 µg/mL at 4 hours postingestion and 6.25 µg/mL at 24 hours postingestion consistently predicted hepatotoxicity [32]. This line is referred to as the probable toxicity line. In Europe, a level above this line is an indication for NAC therapy. When the nomogram was introduced in the United States, the US Food and Drug Administration (FDA) insisted on a 25% reduction of this treatment threshold. A line connecting 150 µg/mL at 4 hours and 4.7 µg/mL at 24 hours, which is considered the possible toxicity line, is used for a treatment threshold [16]. The nomogram was later validated in a large trial using the 72-hour NAC protocol [33].

Acute poisoning, which has not been well defined in the literature, is generally regarded as a single ingestion of APAP over less than a 4-hour time period. The Rumack-Mathew nomogram can only be used to determine the need for NAC treatment after an acute ingestion [16]. All other ingestions are not applicable to the nomogram. Typically, the potentially toxic dose is 150 mg/kg, or 15 g in the healthy adult [34]. These doses would correspond to a potentially toxic level on the nomogram.

After an acute ingestion, the serum APAP levels should be drawn 4 hours after ingestion or at any time thereafter and plotted on the nomogram. Patients with APAP levels falling above the possible toxicity line should be

treated with NAC. The period of 4 hours after ingestion was arbitrarily chosen to assume full absorption and a peak serum APAP level [16].

The time of ingestion is an essential piece of history when plotting levels on the nomogram. However, the exact time of ingestion is not always clear. Patients' histories are frequently unreliable or intentionally misleading. When possible, it is helpful to corroborate a patient's history with a third party. The earliest possible time of ingestion should be used when no reliable history is available. When in doubt, treatment with NAC is always the safest option when the time of ingestion remains uncertain.

Patients who present late after acute APAP ingestion may present some difficulties in determining the need for NAC therapy, because, as the time after ingestion approaches 24 hours, the treatment line on the nomogram approaches the lower limits of detection of some laboratories. In these cases, the need for NAC treatment is determined using a serum APAP, AST, and ALT levels, along with the patient's reported amount of ingestion (usually >7.5 g in an adult or 140 mg/kg in a child [33]) and the patient's risk factors for APAP toxicity. If APAP is detectable, it should be plotted on the nomogram, and treatment should follow if indicated. When APAP is undetectable and AST and ALT are elevated, it should be assumed that the patient is in the second clinical phase of APAP toxicity, and NAC therapy should be initiated. In patients who have undetectable APAP and normal AST and ALT, NAC may probably be safely withheld. Concern exists that impending APAP-induced hepatotoxicity may be preceded by a brief window of time, 24 hours after ingestion but before AST and ALT begin to rise, in which APAP is undetectable and AST and ALT are normal. Such cases are not reported in the literature. However, because of this theoretic concern, some physicians institute NAC therapy in patients who are at increased risk for APAP-induced hepatotoxicity despite normal laboratory values.

Originally, it was believed that NAC therapy was ineffective when started after 15 hours; therefore, it was frequently withheld from late presenters [34–37]. It has since been shown that NAC provides significant benefit to patients presenting with APAP-induced FHF regardless of the time after ingestion [38,39], and it is recommended in any patient with APAP-induced elevations in liver enzymes.

Tylenol Extended Relief

Acute ingestion of Tylenol Extended Relief (TER) is another challenging problem. TER is available in 650-mg caplets intended to provide 325 mg of immediate release and 325 mg more slowly. Because of delayed absorption and possible delayed time to peak serum concentration, the standard 4-hour APAP level plotted on the nomogram may not be a reliable predictor of toxicity.

If an initial 4-hour level falls above the treatment line, NAC therapy should be initiated and further APAP levels are not necessary. If an initial

4-hour APAP serum level falls below the treatment line, obtaining a repeat level at 6 hours should be considered; if a second level falls above the treatment line, NAC therapy should be started [40,41]. Cases have been reported where APAP levels crossed the treatment line as late as 14 hours after ingestion, but their clinical significance is not fully understood [40,42–44]. These case reports suggest the need to check multiple APAP levels in patients who have ingested extended-release formulations; however, other authors have suggested that their pharmacokinetics are so similar to those of regular-release formulations that no change in standard protocol is needed [45].

Nonacute overdoses

Nonacute ingestions of APAP, frequently referred to as subacute or chronic, are ingestions that take place over a period longer than 4 hours. In these cases, the nomogram offers no guidance in treatment, because it is intended only for use with acute ingestions. Furthermore, few studies exist to guide management or determine who warrants screening, making management of nonacute ingestions problematic.

Most cases of nonacute ingestion of APAP that result in hepatotoxicity involve persons taking supratherapeutic doses who are at increased risk for APAP-induced hepatotoxicity [31,46–48]. Based on these observations, a reasonable approach to screening would take into account the overall APAP dosage per day (usually > the manufacturer-recommended 4 g and typically >10 g per day [19,49]) and the existence of risk factors for hepatotoxicity (see previous discussion). In patients where there is concern about possible toxicity from nonacute ingestion of APAP, a serum level along with AST and ALT should be drawn. Patients with detectable APAP or abnormal AST and ALT should be treated with a course of NAC. In patients who have excessive dosing or who have increased risk factors for APAP-induced hepatotoxicity, treatment may be warranted despite normal laboratory testing.

Two small studies provide data to support this approach. In a prospective, observational study of nonacute APAP ingestion, Daly and colleagues [48] found that no patient with chronic APAP ingestion and an AST below 50 IU at presentation went on to develop hepatotoxicity, whereas 15% of those with an AST between 50 and 1000 IU at presentation went on to develop hepatotoxicity. This study has limitations: it reported on a small number of patients, 50% of the normal AST group received NAC therapy, it had no standard treatment protocol, and risk factors were not addressed. A smaller study by Kozer and colleagues [47] found similar results in children but had the same limitations. Despite the studies' limitations, these data support the approach outlined by these authors for chronic APAP ingestions until further prospective studies can be done.

Mechanism of action of N-acetylcysteine

NAC has two roles in the treatment of APAP toxicity. In patients who present <8 hours after ingestion, NAC has preventive mechanisms that rapidly detoxify toxic metabolites or prevent their formation. In patients who already manifest laboratory and clinical evidence of APAP-induced hepatic injury, NAC appears to have secondary mechanisms that improve overall patient outcomes; these are far less effective than its primary effects and are poorly understood.

NAC is an extremely effective antidote when administered within 8 hours after ingestion of a potentially toxic dose of APAP [32–34,37,50,51]. NAC is a precursor of GSH and increases GSH synthesis [52]. Animal models show that significant hepatotoxicity does not occur until total body stores of GSH fall to 30% of baseline [53]. Because it takes a significant time to deplete body stores of GSH, NAC is equally effective whether started immediately after ingestion or within 8 hours.

Ample supplies of GSH, which may be secured by NAC administration, ensure that NAPQI will bind to the thiol groups of GSH instead of binding to hepatocytes. Once the thiol group is bound to NAPQI, it produces cysteine and mercapturic acid conjugates, which are no longer reactive and pose less danger to the liver cells [52,54]. NAC also appears to increase the sulfation of APAP to nontoxic metabolites [55] and may reverse the formation of NAPQI [14].

Clear evidence now exists that NAC is effective no matter how late the therapy is initiated or how profoundly the patient appears to have suffered clinical toxic effects [38]. Improved oxygen delivery by means of increased hepato-splanchnic circulation and increased oxygen extraction have been proposed as mechanisms to explain improved outcomes of late presenters treated with NAC [56–58], but these mechanisms have also been disputed [59]. Improved cerebral blood flow has been demonstrated with NAC therapy [60]. Reversal of the covalent bond between NAPQI and hepatocytes and decreased protein arylation of specific hepatocyte proteins have been reported with NAC administration [61]. A protective antioxidant effect of NAC against oxidative stress has also been reported [62,63], but some evidence suggests that the effect is minimal [64,65], and no human data exist to support a clinical benefit. Another mechanism of NAC's effectiveness may be its limitation of lipid peroxidation, which has been established in mice as another hepatotoxic effect of APAP ingestion [66].

Duration of N-acetylcysteine therapy

Once the decision to treat with NAC is made, the clinician must decide how long to continue therapy. This decision is complicated by the existence of several published protocols, varying in length from 20 to 72 hours.

For more than 20 years in Europe, Australia, and Canada, the standard treatment for potentially toxic APAP ingestions has been 20 hours of

intravenous (IV) NAC. In this 20-hour protocol, NAC is administered as a loading dose of 150 mg/kg over 15 minutes, followed by 50 mg/kg of NAC infused over 4 hours. Over the remaining 16 hours, an additional 100 mg/kg are administered as a constant infusion [34]. Several studies and a long clinical experience validate this protocol as both safe and effective [50]. In 2004, the US FDA approved this same 20-hour protocol for use in the United States [67].

In the United States, before 2004, the standard treatment for APAP toxicity was a 72-hour protocol of oral NAC. Under the FDA approval, the oral dosing protocol of NAC is a 140 mg/kg loading dose followed by a maintenance dose of 70 mg/kg every 4 hours for 17 more doses. Given that nausea and vomiting are reported in 33% of APAP overdoses before NAC and in an estimated 51% during oral NAC therapy [68], vomiting within 1 hour of dosing requires a repeat dose. This protocol has been well studied and found to be both safe and effective, and, until recently, it was the only FDA-approved treatment for APAP toxicity in the United States [16,33,37]. A 48-hour IV protocol [69] and a 36-hour oral protocol [70] have also been described. Both have been found to be safe and effective but are not widely used. Given the recent approval of the 20-hour IV protocol in the United States and the body of evidence to support both 20-hour and 72-hour protocols, it is unlikely that these intermediate protocols will receive much more attention.

The 72-hour oral, 48-hour IV, and 20-hour IV protocols have been compared by retrospective study and through meta-analysis [71]. When started within 8 hours of ingestion, no protocol shows advantage over another. Although there is general consensus that IV administration is preferable in the face of intractable vomiting, no study shows clear evidence that IV therapy is more or less effective than oral NAC therapy [71,72].

In cases of presentation after 8 hours, the 72- and 48-hour protocols appear to have an advantage over the 20-hour IV protocol [71]. Some evidence suggests that longer courses of NAC are more effective in late presenters, especially in the face of FHF [33,39]. In cases with documented elevation in AST and ALT, NAC therapy should be continued indefinitely until significant improvement, liver transplantation, or death [38].

Oral versus intravenous N-acetylcysteine

Until recently, the decision to use IV NAC was complicated by the lack of an FDA-approved preparation for IV administration. Traditionally, the oral NAC solution was diluted in 5% dextrose (D5W) and administered by the IV route through a filter. In 2004, Acetadote became the first NAC solution approved by the FDA for IV use, allowing the United States to join the rest of the industrialized world, which has been using IV NAC since its introduction in 1977. It should be noted that dosing miscalculations occur more frequently with IV dosing and appear to be associated with more serious adverse reactions [73].

Although serious adverse drug reactions (ADR) have been reported with the use of IV NAC, they appear to be rare. Oral NAC has been reported to cause ADR at a lower rate than IV therapy. Most ADR appear to be anaphylactoid in nature and are dose- and rate-related [74,75]. ADR tend to occur during the initial loading dose. The overall rate of ADR from IV NAC ranges from 3% to 25% in most studies; however, one recent small prospective study found the rate of ADR to approach 50% [76]. Children, although less thoroughly studied, appear to have a similar incidence of ADR [77].

Nausea and vomiting are frequently reported ADR with IV NAC therapy [71,72,74–76,78,79]. Antiemetics and IV maintenance fluids are the only treatment required, and the infusion should be continued if no other reactions are observed. Because these symptoms are expected in the natural course of APAP toxicity, it is difficult to separate typical APAP poisoning from ADR associated with antidote therapy. Because most studies include nausea and vomiting as ADR, the true rate of ADR may actually be lower than reported.

The most common reported ADR are cutaneous skin reactions, but more serious ADR, such as bronchospasm, angioedema, and hypotension, have been reported. Treatment of cutaneous reactions by stopping the NAC infusion and administering antihistamines is usually adequate. The NAC infusion may usually be restarted at a slower rate after the reaction has subsided without further incident [79]. More serious, systemic reactions have been reported, including bronchospasm, angioedema, hypotension, and even death, but these are unusual [73,74,80]. A past medical history of asthma does not appear to predict the risk of bronchospasm [78]. Reactive airway disease should be treated in the usual manner with nebulized bronchodilators and systemic corticosteroids after discontinuation of the NAC infusion. The more serious ADR of angioedema and hypotension require the clinician to pay special attention to the patient's airway, breathing, and circulation.

After any adverse reaction, a critical reassessment of the need for NAC therapy is warranted. If treatment is still indicated, evidence shows that restarting the infusion is safe [79]. The infusion is customarily restarted at a slower rate, based on the belief that the ADR are anaphylactoid and rate- and dose-related. Recurrence of ADR is rare but has been reported [79].

Although an FDA-approved NAC preparation now exists, it may not be available in some centers. Because oral NAC is effective and widely available, it will likely continue to be used to treat APAP toxicity. The clinician may be faced with the challenge of treating a patient who cannot tolerate oral NAC and for whom there is no IV NAC immediately available. In this situation, oral NAC may generally be considered safe to administer by way of IV. Dribben and colleagues [81] prospectively evaluated oral NAC suspensions and found them to be safe, sterile, and stable. Moreover, a considerable body of evidence shows that IV use of oral NAC is both safe and effective in clinical practice [78]. However, it is important to note that in all these studies the oral NAC was filtered before use.

Prognosis

Patients who are APAP poisoned have a wide spectrum of clinical presentations. Most present in the first 8 hours and before any signs of hepatotoxicity develop. ICU resources are limited and are not necessary for many APAP-poisoned patients. Close observation for progression of serious toxicity is the most common reason for critical care use. Most patients do not require critical care resources for invasive procedures. Patients who exhibit signs of serious hepatotoxicity, such as coagulopathy, encephalopathy, and metabolic derangements, will likely benefit from the ICU and may need invasive procedures. Patients who have renal failure or other end-organ effects are also candidates for the ICU. Patients who have coingestants with a potential for serious toxic effects may also need close monitoring.

NAC therapy is not an indication for critical care admission. Asymptomatic patients presenting early after ingestion may be cared for on a general ward unless concerns about suicide or self-harm warrant otherwise.

It is important for the clinician to identify patients at increased risk for FHF so as to begin the process of transfer to a specialized center should hepatic transplant become necessary. Although the AST and ALT levels are frequently the first laboratory sign of liver injury in APAP toxicity, the rate of rise and peak level give no indication of prognosis. A collection of clinical parameters and laboratory findings known as the King's College Criteria have been established and well validated to predict poor outcome from APAP toxicity. Patients who have isolated APAP overdoses and develop significant metabolic acidosis (pH < 7.3 after adequate fluid resuscitation), a serum creatinine > 3.3 mg/dL, a prothrombin time > 1.8 times control (> 100 seconds or an international normalized ratio [INR] > 6.5), or grade III or higher encephalopathy have a poorer prognosis [82]. Any patient meeting any one of these criteria should be transferred to a tertiary care center in anticipation of FHF and possible transplantation [82]. These criteria have also been validated by subsequent studies [83–85].

The King's College Criteria (KCC) are well established, but they are not without their limitations. With the exception of fluid resuscitation, therapeutic interventions affecting these criteria may negate their predictive value. However, once criteria are met, further intervention is no longer problematic. For instance, creatinine levels of 3.3 mg/dL or greater already put the patient at higher risk; hence subsequent measurements with or without dialysis are irrelevant.

Monitoring of coagulopathy is also problematic. To establish a rise in prothrombin time, serial levels must be drawn, a process that again may delay identification of patients at risk for FHF. In one series, a prothrombin time > 180 at 4 days was highly suggestive of death [86]. Although this may provide useful information to the liver transplant service, waiting 4 days before transfer to a tertiary center is clearly not beneficial to the patient. The

original KCC were developed before the widespread use of the INR, which makes comparison among prothrombin times difficult.

Reported cases also exist of prolongation of prothrombin time without clinical or laboratory signs of hepatotoxicity [87]. In fact, in both retrospective and small prospective studies, prothrombin time prolongation appeared to correlate with IV NAC use rather than hepatic failure [88–90]. This rise in INR without overt FHF may be due, in part, to decreased factor VII levels [88].

Coagulopathy in the face of FHF, and the associated increase in INR, is due to the reduction of clotting factors. The admission ratio of factor VIII to factor V, and the overall concentration of factor V have both been found to be helpful in predictors of outcome. Factor V levels less than 10 percent were a poor prognostic findings. A factor VIII/V ratio of greater than 30 is also a poor prognostic sign [91]. Because of these observations, some recommend factor monitoring [87]. While this may be useful for the transplant team, it should not be relied upon as a screening tool.

Treatment of coagulopathy can be accomplished with administration of FFP. While many clinicians treat this coagulopathy without signs of bleeding, there is evidence that it is safe to withhold treatment in APAP induced coagulopathy. Gazzard et al compared two groups with APAP induced coagulopathy. The control group was treated with FFP while the experimental group was not unless the INR was over 7. There was no difference in outcome or complications. In the face of bleeding FFP and factor administration is necessary, but with bleeding, it may be possible to withhold blood products [92].

The limitations of the KCC have led to a search for other screening tools. Although many parameters have been suggested and evaluated in small numbers, none are currently as well established or widely used as the KCC.

The acute physiology and chronic health evaluation II (APACHE II) score has shown promise as an early and accurate indicator of impending hepatic failure and the need for transplantation [93]. In a small study, this evaluation was found to be more sensitive and specific than KCC. It was based on patient assessment on the first day of hospital admission, making it possible to determine the need for transplant referral at an earlier time. The disadvantage of the APACHE is that it is cumbersome and difficult to remember. Although this evaluation is intriguing, further study is required.

Changes in serum phosphate levels have been suggested as a prognostic indicator in APAP-induced hepatotoxicity. One prospective study looking at 125 patients who had suspicion of severe APAP-induced hepatotoxicity evaluated the prognostic value of serial serum phosphate measurements [94]. The study revealed that a serum phosphate level >1.2 mmol/L 48 to 96 hours after an APAP overdose specifically and sensitively identifies patients with little chance of survival. The authors hypothesize that the liver

consumes phosphate during hepatic regeneration. Thus, phosphate levels represent a balance of renal failure and liver regeneration. Similar findings in patients who have FHF have been reported [95]; however, other studies show mixed results [96]. Further study is needed to clarify the role of phosphate as a prognostic indicator.

Elevated arterial lactate has been proposed as a prognostic marker for poor outcomes in APAP overdose. A retrospective cohort study revealed that lactate levels >3.5 mmol/L before fluid resuscitation or >3.0 mmol/L after fluid resuscitation were sensitive and specific indicators of survival [97]. A subsequent prospective cohort study was performed for validation [97]. Comparison with the KCC revealed that early lactate levels >3.5 mmol/L identified at-risk patients earlier but had a lower sensitivity and accuracy than the KCC criteria. Postresuscitation lactate concentrations >3.0 mmol/L had equivalent sensitivity and higher specificity and accuracy than the KCC criteria. However, there was no significant difference in time to identification of patients between KCC criteria and postresuscitation lactate [97].

Recently, investigators have shown interest in hyperamylasemia as a possible prognostic indicator in APAP toxicity. A large retrospective study at a Danish referral center found amylase levels >1.5 times normal to correlate with poor outcome and the need for transplantation. Hyperamylasemia did not appear to be due to clinical pancreatitis; however, speciation of the amylase was not performed [98]. Prospective validation of amylase with speciation is needed.

Although it does not directly predict the need for transplantation, a novel approach using easily measurable criteria has been prospectively used to predict encephalopathy in APAP toxicity. Time to NAC therapy, platelet count, and INR are used to determine a prognostic index [99]. Because hepatic encephalopathy requires specialized care, referral based on these criteria may prove useful.

Level of alfa-fetoprotein (AFP) be used to predict favorable outcome in APAP induced FHF. A small increase in AFP one day after peak of ALT was found in survivors compared to non-survivors. Because this increase was small, a highly sensitive assay is required to make reliable predictions [100].

Summary

APAP is likely to remain a common toxic exposure and continue to cause significant morbidity and mortality. To minimize the harm to patients, it is necessary for the clinician to be aware of the current diagnostic and therapeutic management of APAP poisoning. Despite the bulk of literature on APAP, management strategies are likely to continue to change as more studies are conducted to improve our understanding of nonacute ingestions and the role of prognostic markers in defining those most at risk for life-threatening hepatotoxicity.

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