



Review

Management of acetaminophen toxicity, a review

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ABSTRACT

Acetaminophen (APAP) is a widely used drug in our environment with few adverse effects. Because of this, several patients affected by APAP hepatotoxicity unknown that the APAP dose-intake was excessive. This damage is mainly produced via one of APAP metabolites: N-acetyl-para-benzo-quinone imine (NAPQI), which is very toxic. The drug's ingested doses as well as the length of time from APAP ingestion to N-acetylcysteine (NAC) therapy are the most essential determining factors in both the development and severity of APAP hepatotoxicity. However, there are other factors related, including alcohol intake, herbs and medications, age and genetic factors, nutritional status, and chronic liver disease. The ingestion of a toxic dose of APAP causes different clinical manifestations that depend fundamentally on the time elapsed since the intake. The diagnosis process depends on the intake (acute single overdose or after repeated overdoses). The Rumack-Matthew nomogram is acceptable after an acute single overdose, being the "possible hepatic toxicity" point 200 µg/mL at 4 hours and 25 µg/mL at 16 hours). This nomogram is not applicable in after repeated overdoses. NAC is the antidote for APAP intoxication, and could be administered orally or intravenous. Finally, a multidisciplinary approach with the support of Psychiatry, Intensive Care Unit as well as Gastroenterology and Digestive Department will be necessary, especially in the case of attempted autolysis and severe liver failure.

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1. INTRODUCTION

Acetaminophen (APAP), a drug included in the list of

essential medicines of the World Health Organization, is a widely used drug in our environment. It is considered a high effective and safety analgesic and antipyretic drug due to the few adverse effects administered in a correct manner [1,2]. The mechanism of action is not entirely clear. It has a

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mechanism of action in common with non-steroidal anti-inflammatory drugs (NSAIDs), which is based on the inhibition of cyclooxygenase (COX), although in a weaker and selective way for the system central nervous than NSAIDs. For this reason it has no peripheral anti-inflammatory properties and is not gastrolesive [3]. In addition, part of the APAP analgesic activity could be due to other central actions, such as the inhibition of spinal hyperalgesia caused by the activation of NMDA receptors, the activation of the descending serotonergic pathways that inhibit pain transmission in the posterior horn of the spinal cord, or the activation of hypoalgesic mechanisms mediated by nitric oxide [3].

The antipyretic action of APAP is based on the inhibition of prostaglandin E2 (PGE2) synthesis, dependent on COX activity, at the hypothalamic temperature regulating center. Its effect causes a reduction in the body's thermostatic value, which activates the phenomena of heat dissipation through cutaneous vasodilation and increased sweating [3]. The United States Food and Drug Administration (FDA) advertised that APAP is safe in doses up to 4,000 mg every 24 hours, concluding that consumption at this dose generally does not yield any toxic effects [2,4]. Because of it is easily accessible in various formulations, it may be difficult to recognize APAP toxicity due to intentional and non-intentional overdose [2].

Since the mid-1980s, where the first reported cases of APAP-induced hepatotoxicity emerged in the United States, its incidence has grown [5]. It has been reported that this is one of the most common pharmaceutical products to cause drug-induced liver injury [5,6]. Mortality rates have been approximated at 0.4% in overdose patients [1]. Although hepatic failure is usually observed in toxic ingestions over 150 mg/kg, several reports suggested that lower doses of APAP may confer acute liver injury and liver failure [1-4]. This phenomenon is called "therapeutic misadventure", and it was described by Zimmerman et al. in patients with acute liver failure despite consumption of "safe" doses of APAP [7]. This rare entity has been suggested to be produced by some specific risk factors, including nuances in APAP metabolism at the mitochondrial and molecular level, which are currently under investigation.

The purpose of this review is to summarize the key points of physiopathology, diagnosis and treatment of APAP toxicity, especially in the Emergency Department (ED).

2. EPIDEMIOLOGY

APAP is one of the most commonly used analgesics in the United States and reportedly the most common cause of acute liver failure in this country [2,3]. Every year are admitted to hospital around 30,000 patients in the United States because of APAP hepatotoxicity [8]. Because of the wide use of this drug due to their few adverse effects, near the 48% of reported cases of APAP toxicity unknown that the APAP dose-intake was excessive [8]. While the majority of patients experience mild adverse reactions,

including hepatitis, cholestasis or asymptomatic liver enzyme elevation, APAP hepatotoxicity is generally estimated to account for approximately 48% of acute liver failure diagnoses [1,2,4]. Moreover, some studies observed that 29% of patients with acute liver failure secondary to APAP toxicity undergo liver transplant, with mortality rate of 28% [1].

All this data has been increased with the advent of APAP/opioid combination analgesics. In the last decade, 63% of unintentional overdoses of APAP occur due to this combination, with an additional 17% of adults suffering liver injury [6,8].

According to this data, APAP toxicity is a real concern, especially if we observed studies where has been demonstrated that at least 6% of filled prescriptions for either acetaminophen alone or acetaminophen in combination with opioids exceeded the safe daily dose (4000 mg per day of acetaminophen) [4,6,8].

3. PHYSIOPATHOLOGY AND METABOLISM

APAP absorption occurs mainly in the duodenum due to its property as a weak acid [9]. A delay in the time, but not in the extent of drug absorption, is observed if APAP is consumed with food. This is especially important in patient affected by chronic liver disease because they are at risk of prolonged drug serum half-life (by an average of 2.0 to 2.5 hours, and up to more than 4 hours) [9]. While the safe intake of APAP achieves peak concentrations within 1.5 hours, with a half-life of 1.5-3 hours, overdose of APAP yields peak serum concentrations (10-20 mg/mL) within 4 hours [9].

APAP circulates together with plasma proteins by up to 50% and is metabolized mainly at the liver level, in the microsomes. The main route of metabolism is carried out by glucuronization or sulphation processes, which result in non-toxic metabolites, which are eliminated in the urine. On the other hand, 5-10% of the drug is metabolized by the cytochrome P450 2E1 route, producing N-acetyl-para-benzo-quinone imine (NAPQI) which, unlike the products of the other route, NAPQI is very toxic [10-12]. Under normal conditions, this molecule is associated with glutathione, being neutralized, so that it forms cysteine and other compounds that are not toxic to the body [9].

When therapeutic doses are exceeded, the main glucuronization and sulphation pathways become saturated, so that the cytochrome P450 pathway (oxidative pathway) increases, increasing the production of NAPQI, which cannot be completely neutralized by glutathione (GSH), occurring oxidative stress and mitochondrial dysfunction leading to depletion in adenosine triphosphate (ATP) stores, which ultimately causes hepatocellular necrosis and cell death [4,10,12].

Other mechanisms of hepatotoxicity include the formation of toxic free radicals, such as peroxynitrite (ONOO-), from the reaction of superoxide (O₂⁻) and nitric oxide (NO·) [10,12]. Reactive oxygen species as well as ONOO- are neutralized by GSH, which is reduced during APAP

toxicity, increasing by this manner the oxidative damage. ROS as well as reactive nitrogen species (RNS) leads to mitochondrial membrane dysfunction via disruption of the mitochondrial membrane permeability transition pore. It produces organelle swelling, which leads to cellular necrosis [10-12].

In non-toxic ingestion of APAP, the processing of NAPQI occurs with rapid conjugation by hepatic GSH to form nontoxic mercaptate and cysteine compounds that are excreted in urine [9]. As we described previously, the main route of metabolism is carried out by glucuronization or sulphation processes. However, when this via is overwhelmed at hepatotoxic doses of APAP, the majority of APAP is metabolized via the CYP2E1 pathway to NAPQI resulting in GSH depletion [10,11].

Myeloperoxidase and cyclooxygenase-1 are enzymes involved in the CYP2E1 pathway processing NAPQI into non-reactive metabolites. In addition, the innate immune system also prevents liver toxicity mediated by the natural killer (NK) and natural killer T cells (NKT). Both are abundant in hepatocytes and cause the release of pro-inflammatory cytokines and chemokines that enhance hepatocellular cytotoxicity [5,13].

4. RELATED FACTORS WITH APAP INDUCED HEPATOTOXICITY

The drug’s ingested dose as well as the length of time from APAP ingestion to N-acetylcysteine (NAC) therapy are the most essential determining factors in both the development and severity of APAP hepatotoxicity [14,15]. However, there are other factors summarized in Table 1 that influent in the development and severity of liver injury after APAP over-ingestion.

Clinical implications	Factors
↑ APAP toxicity	Dose and pattern of use Chronic EtOH intake Herbs and medications Age and genetic factors Nutritional status Chronic liver disease
↓ APAP toxicity	Acute EtOH intake

Table 1: Factors influencing APAP-related hepatotoxicity. APAP: Acetaminophen; EtOH: Ethyl alcohol.

Alcohol intake may be observed I patients with the intent of self-harm. However, its regular or acute intake may generate different effects through a non well know mechanism related with their competitive effect in CYP 2E1 metabolism [16-18]. A study revealed that the concurrent acute ingestion of alcohol and APAP resulted in hepatotoxicity (ALT>1000 U/L or an international normalized ratio (INR) of >1.3), in 5.1% of patients versus 15.2% of patients who did not consume alcohol [19]. The mechanism is unclear, but it is suggested to be related with the ethanol’s competitive utilization of the CYP 2E1 substrate, which diminishes the NAPQI production [17,19].

Another suggested hypothesis is that ethanol may directly enhance the activity of NAD(P)H:quinone reductase, serving to limitate the toxic metabolites through reconverting quinone metabolites back to native APAP [19]. On the other hand, chronic alcohol ingestion promote APAP hepatotoxicity by up-regulating, enhancing and increasing the synthesis and activity of CYP 2E1 and decreasing GSH stores and synthesis, which leads to liver necrosis [9,19]. Chronic alcoholism and APAP overdose may potentiate liver failure, but there is no indication that the combination of alcoholism and taking therapeutic amounts of APAP will necessarily cause hepatotoxicity [5,19].

Medications that stimulate the CYP system can predispose patients to APAP hepatotoxicity by causing enhanced production of NAPQI via the oxidative pathway [20]. Anti-epileptic drugs, such as phenobarbital, phenytoin and carbamazepine, as well as anti-tuberculosis drugs, such as isoniazid and rifampin, may increase APAP toxicity. Herbs and dietary supplements, including as St. John’s wort, garlic and germander, may mechanistically enhance the CYP system [1].

Malnutrition is associated with conditions consistent with GSH depletion. In addition, poor nutritional status is often associated with chronic alcoholism, decreasing GSH stores as well as enhancement of the CYP enzymatic activity [21].

Attending to the age, younger patients are better able to overcome acute liver failure as a result of APAP hepatotoxicity, probably due to the larger hepatic cell mass that as well as the better capacity of those cells for non-toxic metabolism and their increased capacity for regeneration [16]. On the other hand, patients over 40 years have a increased risk of APAP hepatotoxicity [22]. Due to that, it is suggested that APAP metabolism is age-dependent [23]. The enzymes UGT (glucouronidation), SULT, CYP 450, GST, N-deacetylase (deacetylation), NAT2 (deacetylation), and fatty acid amide hydrolase are involved in APAP metabolism and have been observed to be related to both hepatic and nephrotoxic effects of the analgesic medication [24]. It is suggested that genotypic changes of these enzymes leads to potentially different risk/benefit ratios when APAP is ingested.

Finally, APAP metabolism is reduced in patients with chronic liver disease, including cirrhosis. However, chronic liver disease patients with an infrequent alcohol intake do not appear to be at an elevated risk of developing APAP Hepatotoxicity [17,19]. Due to that, reduced dose limits are recommended in these patients (2000mg per day), especially in patients with hepatic decompensation or active alcohol abuse [19].

5. CLINICAL MANIFESTATIONS

The ingestion of a toxic dose of APAP causes different clinical manifestations that depend fundamentally on the time elapsed since the intake. Most of the patients have only minimal and non-specific symptoms that are

comparable to viral prodrome (i.e. malaise, nausea with or without vomiting, and abdominal pains). There are four established sequential stages of APAP hepatotoxicity [5]:

- **Stage I (0-24 hours post-intake):** Patients may be asymptomatic or may experience pain in the right hypochondrium, nausea, vomiting and general malaise. The severity and impact on the patient depends on the dose ingested.
- **Stage II (24-72 hours post-intake):** Patients may be asymptomatic or may have pain in the right hypochondrium and moderate involvement of the general condition, some degree of acute renal failure and rarely cause acute pancreatitis. Analytically they show an increase in transaminases, a decrease in prothrombin time and antithrombin III (ATIII). The evolution can be towards healing or towards the next phase.
- **Stage III (72-96 hours post-intake):** In this phase the hepatocellular failure is completely established, producing hepatic encephalopathy, pancreatitis, coma, renal failure and metabolic acidosis. Analytically, maximum elevation of transaminases, coagulation disorders, hypoglycemia and hypophosphatemia appears. The evolution may be favorable if treated, but the patient may die from fulminant hepatitis with cerebral edema, shock and multiorgan failure.
- **Stage IV (4-14 days post-intake):** There is recovery and improvement or progression of general deterioration, multiorgan failure and death. Resolution occurs in about 2-3 months after intoxication. While clinical manifestations may be observed 2-3 months after the intoxication, the histologic recovery period may take several months longer than the clinical recovery. Chronic hepatitis has not been reported as a complication of APAP overdose-associated acute liver failure [1].

APAP hepatotoxicity is one of few bona fide causes of liver injury that can raise serum aminotransferases >10,000 IU/L. The most worrisome time for maximal organ damage occurs between 3 and 5 days following the acute ingestion, straddling stage III and stage IV hepatotoxicity. Due to that, prompt recognition of APAP toxic ingestion with an early initiation of treatment is extremely important to prevent acute liver failure.

6. DIAGNOSIS OF APAP OVERDOSE

Patient history as well as physical examination is extremely important, especially in delineating the time course and formulation of APAP ingested. APAP level measurements are commonly realized when a patient is admitted in the ED with a toxic ingestion of unknown substance, altered mental status and/or suspicion of intent of self-harm. It is critical to obtain a 4-hour APAP level to guides the therapy and impacts patient outcome. Additional laboratory studies

are necessary to obtain other important clinical parameters, including arterial blood gas (to investigate acid/base status), coagulation profile, basic metabolic panel, hepatic function tests, and urine drug screen (to determine possible co-ingestions) [25].

The diagnosis process depends on the intake (acute single overdose or after repeated overdoses).

The Rumack-Matthew nomogram is acceptable after an acute single overdose (less than 24 hours of the intake) [25]. The nomogram plots the independent time in hours versus APAP concentration. The most important point is the “possible hepatic toxicity” (APAP level of 200 µg/mL at 4 hours and 25 µg/mL at 16 hours after acute ingestion). Patients with these serum levels of APAP are at risk of severe hepatotoxicity (defined as AST>1000 IU/L) [26-29]. NAC therapy is recommended in such clinical scenarios, to overcome the reported incidence rates of 60% for severe hepatotoxicity and 5% for mortality [30]. A “high toxicity line” is parallel to the “probable toxicity line”, and this begins at 300 µg/mL at 4 hours, equating to a 90% incidence of severe hepatotoxicity and 24% mortality [30]. In the United States, Australia and New Zealand, the treatment line is established a more at a 4-hour APAP concentration of 150 mg/mL [25]. This line sits 25% below the “probable toxicity line.” Studies have already shown that the “treatment line” (also known as the “150 line”) serves well to identify and help protect high-risk patients who may already have diminishing APAP levels [25]. Table 2 summarizes the “150 line”. In general, due to the less adverse effects of NAC therapy, if there is any doubt about the concentration of serum APAP or the timing of ingestion, NAC treatment must be initiated [25].

Time after APAP intake	APAP serum concentration
4 hours	>150 µg/ml
6 hours	>100 µg/ml
8 hours	>80 µg/ml
10 hours	>50 µg/ml
12 hours	>30 µg/ml
14 hours	>20 µg/ml
16 hours	>10 µg/ml
18 hours	>7 µg/ml
20 hours	>6 µg/ml
22 hours	>5 µg/ml
24 hours	>4 µg/ml

Table 2: APAP serum concentration depending the time after APAP intake. APAP: Acetaminophen.

Patients with unintentional APAP overdoses have usually ingested APAP often over many days as an analgesic or antipyretic therapy. Symptoms of hepatotoxicity may have already begun by presentation. Jaundice, right-upper quadrant pain, nausea, vomiting, hepatomegaly and encephalopathy indicate high levels of APAP ingestion [31]. The Rumack-Matthew nomogram is not applicable in these cases, and treatment with NAC would be appropriate for a finding of APAP levels>20 µg/mL, with or without ALT elevation [26,27].

7. TREATMENT OF APAP OVERDOSE

APAP poisoning does not usually cause cardio-respiratory failure, except for advanced stages with fulminant liver failure [5]. Level of consciousness is also not decreases. If we find a patient with a low level of consciousness we should suspect a concomitant intake of other toxins that are often benzodiazepines [25].

General treatment includes:

- Gastric lavage: it should always be done in the first 2 hours post-intake. If it is not known exactly the time of taking or other toxic substances are involved, it should be also performed [32].
- Activated charcoal (dose of 1 gr/Kg): It is useful in the first 4-6 hours or when the time of intake is not known. It can be administered together with NAC. In cases where the patient has a low level of consciousness (Glasgow <9), we must first ensure the airway by orotracheal intubation and then administer the activated carbon by nasogastric tube [32].
- Metoclopramide (20mg up to 1 mg/Kg IV): If nausea or vomiting occurs.
- Ondansetron (0.15 mg/kg): In case metoclopramide does not take effect and vomiting persists.
- Hemodialysis: In case of severe renal insufficiency, coma, acidosis and plasma concentrations of Acetaminophen greater than 1000 µg/ml [33].

7.1. NAC

NAC is a cysteine prodrug and hepatic GSH precursor, and should be administered immediately as an antidote in patients with established APAP hepatotoxicity or those with high risk of developing this condition. NAC replenishes and maintains hepatic GSH stores by providing cysteine, which detoxifies reactive metabolites of APAP [18,26,34]. In addition, it may reduce NAPQI back to APAP by increasing the sulfonation pathway of APAP metabolism [26,34]. The administration of NAC may reduce mortality from 5% to 0.7% of patients [35]. Due to that, its early administration is critical. Table 3 summarizes the current accepted indications for treatment with NAC in the setting of acute over-ingestion.

NAC effects are suggested to be produced due to its capacity to improve hepatic perfusion and oxygen delivery, to refine mitochondrial energy metabolism, and to facilitate scavenging of ROS and RNS [26,27]. NAC administration attending to its via (oral or intravenous) are represented in table 4 [26].

- Initiation of NAC within 24 hours of ingestion
- Serum APAP levels from 140 mg/L at 4 hours to 50 mg/L at 10 hours
- Acute poisoning (ingested in 1 hour) with no other products containing acetaminophen in the past 24 hours
- Acute poisoning with no ingestion of sustained release formulations
- Baseline normal ALT, AST and INR
- Used ideally within the first 8-10 hours with risk of hepatotoxicity being < 5%, especially if APAP level is above the treatment line on the Rumack-Matthew nomogram
- Empirical use when APAP levels cannot be obtained within 8 hours of ingestion

Table 3: Clinical indications for NAC use. APAP: acetaminophen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; NAC: N-acetylcysteine.

Oral NAC treatment

Initial dose: 140 mg/kg diluted to 5% in a liquid (usually fruit juice)

Posterior doses: 70 mg/kg in the same concentration every 4h for 17 times

Total administered dose: 1330 mg/kg

Duration of treatment: 72 hours

Intravenous NAC treatment

Initial dose: 150 mg/kg in 250 ml of 5% glucose serum in 1 hour

Posterior doses: 50 mg/kg in 500 ml of glucose 5% serum in 4 hours. 100 mg/kg in 500 ml of 5% glucose serum in 16 hours

Total administered dose: 300 mg/kg

Duration of treatment: 21 hours

After the treatment, it must be prolonged (150 mg/kg/24h) if there has been an important cytolysis or signs of liver failure. This perfusion of NAC should be prolonged for the necessary time until the improvement of liver function is achieved or until the transplant or death.

Table 4: NAC treatment attending to its via (oral or intravenous). NAC: N-acetylcysteine.

There is currently a shorter schedule, which consists of initially administering 100 mg/Kg of NAC, diluted in 150ml of 5% glucose serum and perfused in 2 hours, and then 200 mg/Kg diluted in 1000 ml of 5% glucose serum and perfused in 10 hours. This guideline has proved to be of the same utility as the previous ones and allows shortening the infusion time, and therefore, the stay in the ED [36].

While there are two treatment options, the clinical scenario should determine the route of NAC administration. The efficacy between the two preparations appears the same, although no head-to-head trial currently exists [5,27,37].

8. CONCLUSIONS

APAP poisoning is an increasingly common occurrence in our environment, although it has a very wide therapeutic range.

As we have commented, it is one of the medications whose use is most widespread, and patients may dispose of it with ease, acquiring it at any pharmacy. Therefore, accidental

overdoses or related to suicide attempts are not uncommon. In any case, APAP poisoning can have lethal consequences in a short period of time, and therefore it is important to know the clinical characteristics and how we should handle it in the ED.

If an APAP poisoning is suspected, a correct medical history is essential to find out the dose taken, the time elapsed and the patient's risk factors.

Attending to NAC treatment, if normal transaminases levels are observed in the blood test, the physician may wait for APAP levels to begin the treatment. However, when they are increased or there are doubts, NAC will be administered immediately, according to the safety of the treatment and the risk of serious toxic hepatitis if it is not administered.

A multidisciplinary approach with the support of Psychiatry, Intensive Care Unit as well as Gastroenterology and Digestive Department will be necessary, especially in the case of attempted autolysis and severe liver failure.

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