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REVIEW ARTICLE

Acetaminophen hepatotoxicity: an updated review

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Abstract As the most common cause of acute liver failure (ALF) in the USA and UK, acetaminophen-induced hepatotoxicity remains a significant public health concern and common indication for emergent liver transplantation. This problem is largely attributable to acetaminophen combination products frequently prescribed by physicians and other healthcare professionals, with unintentional and chronic overdose accounting for over 50 % of cases of acetaminophen-related ALF. Treatment with *N*-acetylcysteine can effectively reduce progression to ALF if given early after an acute overdose; however, liver transplantation is the only routinely used life-saving therapy once ALF has developed. With the rapid course of acetaminophen-related ALF and limited supply of donor livers, early and accurate diagnosis of patients that will require transplantation for survival is crucial. Efforts in developing novel treatments for acetaminophen-induced ALF are directed toward bridging patients to recovery. These include auxiliary, artificial, and bioartificial support systems. This review outlines the most recent developments in diagnosis and management of acetaminophen-induced ALF.

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Introduction

Acetaminophen, also known as paracetamol, *N*-acetyl-*p*-aminophenol, and APAP, is one of the most commonly used medications for its analgesic and antipyretic properties. It is available over the counter both as a single-entity formulation and in combination with other medications, as well as by prescription when combined in various quantities with opioids. While acetaminophen is a safe and effective drug at recommended doses, it has the potential for causing hepatotoxicity and acute liver failure (ALF) with overdose (Chun et al. 2009; Bunchorntavakul and Reddy 2013; Michaut et al. 2014).

The recommended dosing of acetaminophen in adults is 325–650 mg by mouth every 4–6 h with a daily maximum of 4 g/day (recommended 2 g maximum per day in patients with an elevated risk of hepatotoxicity). In children, the recommended dose is 10–15 mg/kg every 4–6 h with a maximum daily dose of 50–75 mg/kg (Schilling et al. 2010).

Epidemiology

Acetaminophen hepatotoxicity remains the leading cause of ALF in the USA and Europe, with over 300,000 hospitalizations annually in the USA and up to 42 % of all cases of ALF attributable to acetaminophen overdose (Larson et al. 2005; Blieden et al. 2014). Additionally, the incidence of acetaminophen-related ALF has been rising since the 1990s (Larson et al. 2005). In 2012, the National Poison

Data System annual report listed acetaminophen alone and acetaminophen combination products as the fourth and sixth highest causes of fatalities related to substance poisoning (Mowry et al. 2013).

With approximately half of all acetaminophen-related hepatotoxicity caused by unintentional overdose and 63 % of these cases involving opioid combination products, there is growing concern over unintentional overdose with acetaminophen combination medications (Michna et al. 2010). A recent report cited that 6 % of adults in the USA are currently being prescribed over 4 g/day of acetaminophen, largely due to combination medications (Blieden et al. 2014). Due to this growing concern, the US Food and Drug Administration (FDA) voted in 2009 to recommend elimination of prescription acetaminophen combination products. However, they subsequently revised this recommendation in 2011 to no more than 325 mg of acetaminophen in each combination tablet (Michna et al. 2010; Blieden et al. 2014). As of January 2014, over half of pharmaceutical manufacturers have complied with this recommendation and the FDA has urged physicians to avoid prescribing combination medications with >325 mg of acetaminophen per tablet (Blieden et al. 2014).

Pathophysiology

It is not acetaminophen itself that causes hepatotoxicity, but rather a reactive metabolite (Fig. 1). When taken at recommended doses, 85–90 % of acetaminophen is metabolized by glucuronidation or sulfation and then excreted into the urine, 2 % is excreted into the urine unchanged, and <10 % is metabolized by the cytochrome p450 system (mainly CYP2E1) into the reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). Under normal circumstances, NAPQI is rapidly converted to nontoxic metabolites by glutathione (GSH). However, in situations of GSH depletion

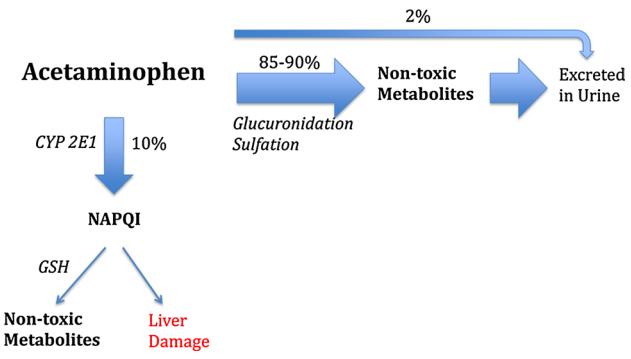

Fig. 1 Metabolism of acetaminophen. NAPQI, *N*-acetyl-*p*-benzoquinone imine; GSH, glutathione [adapted from (Bunchorntavakul and Reddy 2013)]

such as acetaminophen overdose, chronic alcohol ingestion, and malnutrition, NAPQI persists and leads to liver damage (Jaeschke et al. 2012; Bunchorntavakul and Reddy 2013). The main mechanisms by which NAPQI is thought to cause hepatic injury include forming protein adducts by reacting with sulfhydryl groups leading to mitochondrial dysfunction and cell death, as well as modulation of the innate immune system of the liver (Jaeschke et al. 2012).

The mitochondrial dysfunction seen in acetaminophen hepatotoxicity is due to the disruption of the mitochondrial membrane and cessation of ATP production. Mitochondrial protein adduct formation with NAPQI causes oxidant stress and creation of reactive oxygen species within the mitochondria. This leads to mitochondrial DNA damage, opening of the mitochondrial permeability transition pore (MPT), and cessation of ATP production. Additionally, through mechanisms that are incompletely understood, there is early translocation of the membrane protein BAX, which combines with Bak within the outer mitochondrial membrane to form pores and allow the release of intermembrane proteins such as cytochrome c. A recent study in murine models suggests that NAPQI causes selective inhibition of mitochondrial complex II and that administration of methylene blue can protect against mitochondrial damage by acting as an alternative electron carrier, transferring electrons from the injured complex II to cytochrome c, and restoring ATP production (Lee et al. 2014). Ultimately, the release of mitochondrial proteins and cessation of ATP production together leads to cell death (Jaeschke et al. 2012).

Alteration of innate immunity and sterile inflammation within the liver plays a significant role in the progression of hepatic failure after acetaminophen overdose. Early cell death due to mitochondrial damage causes the release of multiple damage-associated molecular patterns (DAMPS) including DNA fragments, heat shock proteins (HSPs), and high-mobility group box 1 protein (HMGB1) which subsequently activate toll-like receptors (TLRs) on Kupffer cells. Activated Kupffer cells release cytokines and chemokines that recruit neutrophils and monocytes and cause cellular injury. The direct action of cytokines and chemokines, rather than inflammatory cells, is thought to cause cellular injury by altering intracellular events within hepatocytes. These intracellular actions include induction of nitric oxide (NO) synthase and expression of acute-phase proteins such as HSPs and heme oxygenase-1. Current evidence supports the hypothesis that sterile inflammation within the liver plays a beneficial role by removing debris and promoting hepatocyte proliferation and repair (Jaeschke et al. 2012).

The primary mechanism of cell death in acetaminophen-induced liver failure, apoptosis versus necrosis, is under debate. Animal studies had previously suggested necrotic death due to depletion of intracellular ATP to be the primary mechanism, but a more recent study demonstrated

increased serum markers of apoptosis (caspase cleaved CK-18, also referred to as M30) in patients with acetaminophen-induced ALF, compared to matched controls. Additionally, M30 levels on admission predicted progression to liver transplantation or death with a sensitivity of 89 % and a specificity of 69 %, suggesting a critical role of apoptosis in the progression of ALF in acetaminophen overdose (Possamai et al. 2013).

Risk factors

As not all individuals with acetaminophen overdose progress to ALF, a significant area of study is identifying risk factors for hepatotoxicity in these patients (Table 1). Malnutrition, fasting, and chronic liver disease all increase risk of hepatotoxicity through decreased glutathione stores. Additionally, drugs that induce the CYP 450 system or modulate liver injury and repair can also place a patient at increased risk of hepatotoxicity and fulminant hepatic failure. Commonly used CYP 450-inducing drugs include isoniazid, rifampin, and phenobarbital. Chronic alcohol use also induces the CYP 450 system leading to increased production of NAPQI. In a study of over 6,000 patients with acetaminophen-associated liver injury, fibrates, nonsteroidal anti-inflammatory drugs (NSAIDs), and alcohol were associated with a higher incidence of death. Statins were associated with a decreased incidence of death in men, but increased mortality in women (Suzuki et al. 2009). Unintentional overdose of acetaminophen has also been found to be a risk factor for hepatotoxicity, compared to intentional overdose (Myers et al. 2008).

With the growing incidence of nonalcoholic fatty liver disease (NAFLD) in the USA and the known association between underlying liver disease and acetaminophen hepatotoxicity, recent studies have focused on determining the role of obesity and NAFLD in acetaminophen-associated liver injury. Rates of NAFLD in the USA have exceeded 20 % in adults and 10 % in children and adolescents, with progression to nonalcoholic steatohepatitis in 10–20 % of cases. While both obesity and NAFLD are associated with increased CYP2E1 activity, clinical studies have shown a 4–7 times increased risk of acetaminophen-induced hepatotoxicity in patients with NAFLD, but no increased risk in patients with obesity alone (Michaut et al. 2014).

Pharmacogenomics is a promising area of investigation into characterizing a patient's risk for development of hepatic failure following acetaminophen overdose. While certain alleles have been identified that may modulate this risk, particularly those affecting the CYP 450 system, clinical trials to support these small studies are lacking (Zhao and Pickering 2011; Court et al. 2014). In addition to identifying genetic variation within the CYP 450 system, recent evidence suggests that NAD(P)H:quinone oxidoreductase 1 (NQO1) plays a protective role by metabolizing NAPQI into a nontoxic hydroquinone. Studies with NQO1 knockout mice show more severe mitochondrial dysfunction and larger areas of hepatic necrosis with acetaminophen overdose compared to controls (Hwang et al. 2014). Variation in intestinal microbiota may also play a role in susceptibility to hepatotoxicity as germ-free mice show a milder form of ALF with acetaminophen overdose, possibly due to reduced TLR4 and LPS signaling (Possamai et al. 2014).

Table 1 Risk factors for hepatotoxicity with acetaminophen overdose

Decreased glutathione stores
Malnutrition
Fasting
Chronic liver disease
Upregulation of CYP 450
Isoniazid
Rifampin
Phenobarbitol
Chronic alcohol use
Unclear mechanism
Statins (in women)
Fibrates
Nonsteroidal anti-inflammatory drugs

Adapted from (Myers et al. 2008; Suzuki et al. 2009)

Acute liver failure clinical presentation and diagnosis

Acute liver failure is defined as the sudden loss of hepatic function in patients without a prior history of liver disease that progresses to coagulopathy, jaundice, and encephalopathy (Craig et al. 2010b). Early symptoms of ALF are generally nonspecific and include abdominal pain, fatigue, anorexia, and fever. Acetaminophen-related ALF most often progresses in a hyperacute timeframe with hepatic encephalopathy developing within 0–7 days after the onset of jaundice. Encephalopathy can be divided into four grades, with higher grades strongly correlating with poor clinical outcomes (Table 2). The mildest Grade I encephalopathy is characterized by minor changes in mental status with a normal Glasgow coma score (GCS) and no EEG changes, with increasing levels of altered mental status and asterixis up to Grade IV, defined as coma with decerebrate posturing and marked EEG abnormalities. Patients with Grades III and IV encephalopathy are at particularly high risk of developing cerebral edema due to hyperammonemia, inflammation, loss of cerebral blood flow autoregulation, and hyponatremia. Additional sequelae of ALF

Table 2 Classification of encephalopathy

Grade I	Minor changes in mental status and level of consciousness, normal GCS and EEG
Grade II	Lethargy and disorientation, asterixis, GCS 12–15, EEG showing generalized slowing
Grade III	Somnolent and difficult to arouse, GCS 8–11, markedly abnormal EEG
Grade IV	Comatose, decerebrate posturing, GCS <8 with markedly abnormal EEG

GCS Glasgow coma score, *EEG* electroencephalogram [adapted from (Craig et al. 2010b)]

include vasodilatory shock, pulmonary edema, and acute renal failure (Craig et al. 2010b).

Clinical management

Early presentation and diagnosis are crucial to the treatment of acetaminophen overdose, as early interventions can significantly decrease the risk of ALF. Activated charcoal limits gastrointestinal absorption of acetaminophen if administered within 4 h of an acute overdose; after 4 h, there is no demonstrated benefit. If there is any question of airway compromise or gastrointestinal tract injury, activated charcoal should not be given (Bunchorntavakul and Reddy 2013).

N-acetylcysteine (NAC) can prevent hepatotoxicity following acetaminophen overdose by replenishing hepatic glutathione stores. NAC has also been shown to improve hemodynamic instability, hepatic clearance, and cerebral edema possibly through actions as a free radical scavenger (Heard 2008). While it has been established that NAC can improve outcomes in acetaminophen overdose, indications and dosage are debated. The Rumack–Matthew nomogram (Fig. 2), developed in 1970 to determine the risk of hepatotoxicity after a single acute ingestion, is a plot of serum acetaminophen level against time from ingestion. Traditionally, the "200 line," representing a serum level of 200 μg/ml at 4 h post-ingestion, has been used as a threshold for initiating treatment, as this was determined to be the level above which there is significant risk for development of ALF (Rumack et al. 1981; Bunchorntavakul and Reddy 2013). Because of a case in which a patient who was not treated with NAC per the "200 line" guidelines died of ALF, the UK's Commission on Human Medicines further investigated the nomogram and decided to institute a decreased treatment threshold in September of 2012. The UK's standard is now to treat any patient with a serum acetaminophen level equivalent to 100 μg/ml at 4 h post-ingestion or any patient with staggered overdose or unknown time of ingestion. Recent studies of these changes in treatment guidelines have shown an increase in admissions related to acetaminophen overdose by 7.1 % and an increase in treatment by 13.2 % with an estimation of one life saved every 2 years and a cost of 17.3 million euros for each life saved (Bateman et al. 2014a, b). A staggered overdose pattern in which patients are exposed to repeated supratherapeutic doses is associated with high risk of adverse outcomes including multi-organ failure and does not fit the Rumack–Matthew nomogram for treatment criteria. These patients should be considered for NAC treatment regardless of serum acetaminophen levels on admission (Craig et al. 2012).

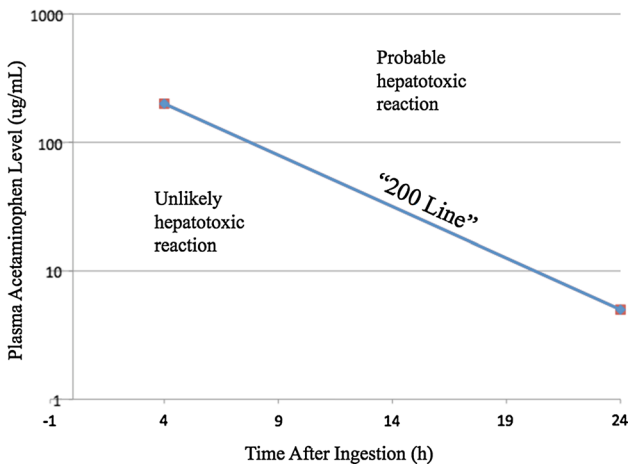

Fig. 2 Rumack–Matthew nomogram [adapted from (Rumack et al. 1981; Bunchorntavakul and Reddy 2013)]

N-acetylcysteine can be given intravenously or by mouth depending on the patient's mental status and ability to tolerate oral medications. Intravenously, it is given as a loading dose of 150 mg/kg over 1 h then 50 mg/kg over the next 4 h and 100 mg/kg given over 16 h. When dosed orally, a loading dose of 140 mg/kg is given initially followed 4 h later by 70 mg/kg every 4 h for 18 doses in total (Bunchorntavakul and Reddy 2013). Adverse effects of NAC are generally not life threatening and include nausea, vomiting, and anaphylactoid reactions with initial infusion. Because of these reactions, recent studies have investigated modified protocols that extend the loading dose. While these studies show decreased side effects requiring interruption of treatment, they have not been adequately powered to ensure efficacy at the suggested modified dosing (Bateman et al. 2014c).

Liver support systems

Artificial and bioartificial support systems have been developed with the goal of bridging ALF patients to

Table 3 Summary of validated prognostic tools for transplantation

King's College Criteria	pH < 7.3 (regardless of encephalopathy grade) or PTT > 100 s and Cr > 3.4 mg/dL with Grade III or IV hepatic encephalopathy
Lactate modification	KCC met, plus early lactate >3.5 mmol/L or post-resuscitation lactate >3.0 mmol/L

PTT prothrombin time, *KCC* King's College Criteria [adapted from (Craig et al. 2010a)]

transplantation or recovery by filtering toxins, replenishing hepatic products, and reducing inflammation. Artificial support systems employ hemodialysis with adsorption to charcoal or albumin to remove toxins, while bioartificial systems use human or porcine hepatocytes for plasma filtration. These systems are currently used only in investigative trials, but meta-analyses have shown reduced bridging to transplantation in patients with acute-on-chronic liver failure with artificial systems and improved mortality in ALF with bioartificial systems (Craig et al. 2010a; Bateman et al. 2014c).

Liver transplantation

Liver transplantation is the ultimate treatment for patients with acetaminophen overdose who progress to ALF despite NAC treatment. Without liver transplantation, survival is as low as 20 % for all causes of ALF and 36 % for acetaminophen-related ALF (Craig et al. 2010b).

The most important and challenging aspect is to determine which patients will require and benefit from transplantation (Table 3). The King's College Criteria, developed by O'Grady and colleagues in 1989, has a high specificity for identifying patients that will require transplantation, but a poor negative predictive value with up to 26 % of patients unfit for surgery by the time they fulfill the criteria of either arterial pH < 7.3 or PT > 100 s (INR > 6.5) and Cr > 300 μmol/L (3.4 mg/dL) with Grade III or IV hepatic encephalopathy (Craig et al. 2010a). The lactate modification, proposing that patients should be considered for transplantation with an early lactate >3.5 mmol/L or a post-resuscitation lactate >3 mmol/L, showed improved prognostic accuracy initially, but this finding was not reliably reproduced in subsequent studies (Craig et al. 2010a). Small studies suggest promise with further modifications such as AFP, APACHE II scores, and serum IL-6, although further investigation is still needed (Craig et al. 2010a). The Clichy criteria (Bernuau et al. 1986) originally derived in patients with fulminant hepatitis B were subsequently found to be inferior to King's College in acetaminophen-induced disease (Izumi et al. 1996). In 2012, a small retrospective study found that the Sequential Organ Failure Assessment (SOFA), evaluating multisystem dysfunction, is a better predictor than the King's College Criteria for identifying patients that will ultimately require transplantation, but again, further investigation is needed (Cholongitas et al. 2012). Additional areas of promise for determining prognosis in acetaminophen-related ALF include individual bile acids such as glycodeoxycholic acid, markers of apoptosis such as M30, and indocyanine green (ICG) clearance (Milesi-Halle et al. 2011; Rutherford et al. 2012; Woolbright et al. 2014). ICG clearance is a measure of the functional capacity of the liver and has shown positive correlation with extent of hepatic necrosis in murine models of acetaminophen hepatotoxicity (Milesi-Halle et al. 2011). In humans, ICG clearance combined with MELD scores showed superior results in predicting 3-month mortality compared to MELD alone or the King's College Criteria. This study, however, was performed in patients with hepatitis B as the most common cause of ALF (Feng et al. 2014).

In select patients, auxiliary liver transplantation provides a bridge to survival without the need for lifelong immunosuppression. In auxiliary liver transplantation, most commonly a right lobe graft is transplanted orthotopically after a recipient right hepatectomy. This leaves the left lobe in situ with the goals of regeneration of the native liver and weaning of immunosuppressive medications after 1–3 years. The success of auxiliary transplantation depends on the ability of the native liver to regenerate. This procedure is best suited for patients with hyperacute liver failure due to acetaminophen toxicity without any prior liver disease (O'Grady 2007, 2012). Additional criteria used in a 2014 study evaluating outcomes of 24 patients with whole graft auxiliary transplant for acetaminophen overdose included meeting the King's College Criteria, age <50 years, no prolonged circulatory arrest, and a cerebral perfusion pressure >40 mmHg (Lodge et al. 2008). In this study, there was a 63 % survival in the patients receiving auxiliary transplantation, with all survivors successfully weaned from immunosuppressive medications by 5 years post-transplantation (Rajput et al. 2014).

Hepatocyte transplantation, in which donor hepatocytes are infused through the portal vein or ectopic sites with the native liver left in place, has shown promising results in patients with inborn errors of metabolism but has yet to be proven effective in cases of ALF. The lack of efficacy of hepatocyte transplantation in ALF might be explained by the need for more cells than can be safely transplanted. A 1999 case series of 18 patients showed no effects of hepatocyte transplantation on clinical outcome in ALF. More

clinical trials are currently in progress, and murine studies with human hepatocyte transplantation are promising (Dhawan et al. 2010; Herrera et al. 2013; Struecker et al. 2014).

Outcomes

Overall mortality of patients hospitalized for acetaminophen overdose is reported at 1 %, with risk factors for in-hospital mortality including older age, unintentional overdose, alcohol abuse, and chronic liver disease (Myers et al. 2008). Patients receiving liver transplantation for acetaminophen-related ALF have a 73 % rate of survival to discharge. With the higher incidence of psychiatric illness and prior suicide attempts in these patients, long-term survival can be affected by repeated suicide attempts, substance abuse, and nonadherence to medications (Cooper et al. 2009; Karvellas et al. 2010). A review of the Acute Liver Failure Study Group data showed better long-term survival following acetaminophen overdose with transplantation than with spontaneous recovery, possibly due to the need for closer follow up with healthcare professionals after transplantation (Fontana et al. 2014).

Summary

As the most common cause of ALF in the USA and UK, acetaminophen hepatotoxicity remains a significant issue. With approximately half of all cases of acetaminophen-related ALF due to unintentional overdose, patient education and further attention to acetaminophen combination products will likely have a positive effect in reducing the problem. There are many promising areas of study with regard to improved prognostication and novel treatments and bridging mechanisms for acetaminophen-related ALF.

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