Acetaminophen-Induced Nephrotoxicity: Pathophysiology, Clinical Manifestations, and Management

Maryann Mazer, MD, PharmD, and Jeanmarie Perrone, MD

Department of Emergency Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

ABSTRACT

Acetaminophen-induced liver necrosis has been studied extensively, but the extrahepatic manifestations of acetaminophen toxicity are currently not described well in the literature. Renal insufficiency occurs in approximately 1–2% of patients with acetaminophen overdose. The pathophysiology of renal toxicity in acetaminophen poisoning has been attributed to cytochrome P-450 mixed function oxidase isoenzymes present in the kidney, although other mechanisms have been elucidated, including the role of prostaglandin synthetase and N-deacetylase enzymes. Paradoxically, glutathione is considered an important element in the detoxification of acetaminophen and its metabolites; however, its conjugates have been implicated in the formation of nephrotoxic compounds. Acetaminophen-induced renal failure becomes evident after hepatotoxicity in most cases, but can be differentiated from the hepatorenal syndrome, which may complicate fulminant hepatic failure. The role of N-acetylcysteine therapy in the setting of acetaminophen-induced renal failure is unclear. This review will focus on the pathophysiology, clinical features, and management of renal insufficiency in the setting of acute acetaminophen toxicity.

Case: A 47-year-old female was found lethargic at home and brought by ambulance to an emergency department. History from family members suggested an inadvertent acetaminophen overdose, and she had last been seen a few hours earlier. She reportedly ingested 18 tablets of 500 mg acetaminophen (APAP) over the previous two days because she had run out of her prescription pain medication. Her past medical history was significant for fibromyalgia, arthritis, and a prior gastric bypass procedure. She had no history of alcohol abuse or renal insufficiency. She was lethargic. Vital signs: BP 128/96 mmHg, pulse 112/min, respirations 32/min; pulse oximetry 98% on 2L nasal cannula oxygen. Laboratory studies: BUN 9 mg/dL, creatinine 0.9 mg/dl, acetaminophen 12 mcg/mL, AST 5409 u/L and ALT 1085 u/L. A urinalysis was negative for blood with trace protein and ketones. A urine drug screen was positive for marijuana and opioid metabolites. At the initial hospital, she was treated with N-acetylcysteine (NAC) orally. Subsequently, she developed fulminant hepatic failure with elevated transaminases, hypoglycemia, and coagulopathy (Tables 1A and 1B). She was transferred

Table 1A: Trends of Liver Function

Liver Markers	Day 3 Post-Ingestion (Admission)	Day 5	Day 7	Day 12	Day 17	Day 22	Day 27 (Discharge)
T. Bili. (mg/dL)	3.3	4.0	9.3	4.6	2.8	1.8	1.7
A. Phos. (units/L)	134	79	83	269	382	273	200
ALT (units/L)	4620	1715	389	100	77	57	67
AST (units/L)	11,840	5024	248	60	54	40	35
INR	5.1	2.0	1.5	1.2	1.1	1.0	1.1

Key: T. Bili = total bilirubin, A. Phos. = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = international normalized ratio.

Keywords: acetaminophen, nephrotoxicity, N-acetylcysteine, renal failure, hepatotoxicity

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Corresponding Author: Jeanmarie Perrone, MD, Hospital of the University of Pennsylvania, Department of Emergency Medicine, 3400 Spruce Street, Philadelphia, PA 19107. Email: Jeanmarie.Perrone@uphs.upenn.edu

Table 1B: Trends of Renal Function

Lab	Day 3 Post-Ingestion (Admission)	Day 6	Day 9	Day 12	Day 15	Day 18	Day 22	Day 27 (Discharge)
BUN mg/dL	10	27	78	106	56	39	23	28
Creat. mg/dL	2.3	3.8	6.9	8.1	3.6	2.3	1.1	1.3

Key: BUN = blood urea nitrogen, Creat. = serum creatinine.

to our facility two days after initial presentation for liver transplant evaluation. At that time, her APAP level was 2.0 mg/L. Oral NAC therapy was continued after transfer. The patient's liver function subsequently improved and she ultimately did not require transplantation. She did develop acute renal failure during the course of her hospitalization, with a creatinine of 2.3 mg/dL on transfer, which increased to 8.1 mg/dL nine days later (approximately 11–13 days post-ingestion). Medical toxicology was consulted by the intensive care unit team to address whether this was acetaminophen-induced renal failure and if there was a role for NAC in this setting.

INTRODUCTION

Acetaminophen (APAP) is the most commonly reported toxic ingestion in the United States. In 2005, there were over 165,000 exposures reported. Approximately 67,000 of these were acetaminophen only ingestions, and 37% occurred in children. The other 98,000 were combination ingestions, most commonly with opioids, and were more common in adults [1]. APAP is a known toxin to both the liver and extrahepatic tissues. Acetaminophen-induced liver necrosis has been studied extensively, but the extrahepatic manifestations are not described comprehensively in the literature. Overall, renal insufficiency occurs in approximately 1–2% of patients with APAP overdose [2]. Limited data in a retrospective case series of pediatric patients with acetaminophen poisoning suggests that associated nephrotoxicity may be more common in children and adolescents [3]. When significant acetaminophen-induced hepatotoxicity occurs, renal injury is commonly seen. A creatinine elevation >2.0 mg/dL was noted in 43–57% of a prospective study of 275 patients with encephalopathy and coagulopathy secondary to acetaminophen-induced fulminant hepatic failure [4]. This review will focus on the mechanisms, clinical features, and management of renal insufficiency in the setting of acetaminophen poisoning.

PHARMACOLOGY/PATHOPHYSIOLOGY

The primary toxicity of acetaminophen is the result of drug metabolism in both the liver and extrahepatic tissues [5]. Only 1% of the drug is excreted unchanged in the urine. With therapeutic dosing in adults, approximately 63% of acetaminophen is metabolized via glucuronidation and 34% by sulfation. These phase II reactions occur primarily in the liver and result in water-soluble metabolites that are excreted via the kidney. At therapeutic doses, <5% percent of APAP is oxidized by the microsomal P-450 enzyme system to a reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI). In therapeutic dosing, this electrophilic metabolite is then reduced by glutathione and subsequently excreted as mercapturic acid, a relatively benign compound. In the setting of excess APAP, stores of sulfate and glutathione are depleted. This shunts more of the acetaminophen to the CYP-450 mixed function oxidase system, generating more NAPQI reactive intermediates. When large doses of drug are ingested, there is more severe glutathione depletion as well as massive production of metabolites, which compounds the toxicity, leaving large amounts of reactive species unbound. These electrophilic intermediates then form adducts with sulfhydryl and glutathione moieties on cellular proteins [6]. This process disrupts homeostasis, with subsequent activation of caspases and lysosomal enzymes that initiate apoptosis, or programmed cell death. This has been demonstrated in both liver and kidney tissue in animal models. The resultant cell death leads to tissue necrosis and ultimately organ dysfunction [7,8]. The mechanism of acetaminophen toxicity is well described in the liver, but is less clearly understood in the kidney. There are several potential mechanisms of renal toxicity based on both animal and human data. Possible mechanisms include the cytochrome P-450 pathway, as well as prostaglandin synthetase, and N-deacetylase enzymes [6].

The CYP-450 microsomal enzymes involved in this process are found in both the liver and kidney, although they differ somewhat in each organ. The severity of renal damage and the quantity of reactive adducts in tissues can be significantly reduced when the CYP-450 inhibitor piperonyl butoxide is administered [6]. In addition, it has been noted that conditions that are associated with increased activity of the CYP-450 system enhance acetaminophen toxicity. Examples include chronic alcohol use and ingestion of drugs that induce these enzymes, such as anticonvulsants [9].

The CYP-450 isoenzyme that is primarily involved in the biotransformation in the kidney is CYP 2E1, which is inducible by testosterone. This finding accounts for significant gender

differences in the metabolism and toxicity of acetaminophen in the kidneys of animal models [10]. It has been observed that male mice and female mice pretreated with testosterone were more likely to form toxic metabolites and demonstrate nephrotoxicity than untreated female mice. A definitive link between gender and nephrotoxicity has not been noted in humans. It has been suggested that this process is independent of that in the liver, as renal toxicity has been demonstrated in isolated mouse kidney slices [11] and in some cases, renal disease has occurred in the absence of significant hepatotoxicity [12, 13].

Although glutathione has traditionally been considered an important element in the detoxification of acetaminophen and its metabolites, its conjugates have been implicated in the formation of nephrotoxic compounds. Animal models have demonstrated that APAP-induced nephrotoxicity can be mitigated by inhibition of the metabolism or transport of these conjugates. It is uncertain whether the renal injury is due directly to the acetaminophen-glutathione conjugate or one of its metabolites. Another possibility is that the formation of these conjugates may contribute to glutathione depletion, which may inhibit the detoxification of reactive metabolites. These results have not been reproduced in the liver, suggesting a discrete, selective mechanism for glutathione conjugates and glutathione depletion in acetaminophen-induced renal disease [14].

Another potential mechanism of acetaminophen toxicity is related to prostaglandin endoperoxidase synthetase (PGES), although its effect may be more substantial in the chronic rather than the acute setting. PGES is an enzyme found in the kidney that activates APAP into toxic metabolites, most likely NAPQI. This process is more pronounced in the medulla of the kidney, whereas the cytochrome P450 plays a more important role in the cortex. Despite these subtle differences, the endpoint of the two pathways is the same—formation of toxic metabolites, covalent binding to cellular proteins, followed by cell death and tissue necrosis. This process has been demonstrated in both human and animal models. The association with chronic APAP toxicity is suggested in the fact that PGES binds APAP with such high affinity that reactive metabolites are formed even at therapeutic doses. The clinical implications of this finding have yet to be elucidated. The enzyme N-deacetylase has also been implicated in acetaminophen-induced nephrotoxicity, although its role is still uncertain. It is known that the enzyme acts on APAP or NAPQI, deacetylating its substrate to p-aminophenol, which is then converted to a free radical that can bind cellular proteins. This process may occur in combination with the actions of the CYP-450 enzyme system and has been demonstrated in animal models [15].

HISTOPATHOLOGY

Rarely is renal biopsy performed for diagnostic purposes in the setting of APAP-induced nephropathy, however, the histopathology reflects an ATN-type pattern. At the tissue level, these toxins affect the proximal tubule most commonly, although disease may be more diffuse. Light microscopy of renal biopsies in patients with acetaminophen toxicity and renal insufficiency demonstrate tubular epithelial cell necrosis in both proximal and distal parts of the tubules [16]. In some cases, light microscopy demonstrates normal glomeruli and vessels, but with debris and damage to the basement membrane. There is no deposition of immunoglobulins or complement on fluorescent microscopy. Electron microscopy is significant for the loss of the tubular brush border with tubular swelling and distortion of mitochondrial organization [16,17].

Acetaminophen-induced renal insufficiency is consistent with acute tubular necrosis (ATN) [18–20]. Urinalysis can be used to differentiate this from other causes of renal insufficiency, such as hepatorenal syndrome (HRS) or prerenal azotemia. In the setting of ATN, urine sediment will have granular casts with variable hematuria or pyuria. Other causes of renal toxicity have less active urinary sediment. Urine sodium and osmolality may provide additional information. In ATN, urine sodium tends to be $>$20 mmol/L, with an osmolality similar to that of plasma. In HRS and prerenal etiologies, the urine sodium is $<$10 mmol/L and the osmolality is greater than that of plasma (Table 2).

MANIFESTATIONS AND CLINICAL COURSE

Several case reports have attempted to define patients at increased risk of acetaminophen-induced nephrotoxicity. Although the data is limited, it is reasonable to assume that patients at risk may

Table 2: Urinalysis Findings in Acute Renal Failure

Parameter	ATN	Prerenal Azotemia	HRS
Sediment	Granular casts +/− cells	None	None
Osmolality	Same as plasma	Greater than plasma	Greater than plasma
Urine sodium	⩾20 mmol/L	⩽10 mmol/ L	⩽10 mmol/L
Urine output	Variable	Fluid responsive	Non-fluid responsive
Prognosis	Recovery	Recovery	Poor

Key: ATN = acute tubular necrosis, HRS = hepatorenal syndrome.
Reference [19]

be similar to those at risk for hepatotoxicity: patients with depleted glutathione due to causes such as starvation, fasting, or alcoholism. In addition, medications that induce the CYP-450 enzyme system may worsen toxicity and outcomes by increasing the formation of these intermediates [9]. Adolescents and young adults may be more prone to renal insufficiency in the setting of APAP overdose; however, the reason for this finding is unclear [3].

These case reports have also provided valuable information regarding the clinical course of APAP-induced nephropathy. The onset of renal insufficiency tends to range between 1 and 8 days, although most cases were reported between 2 and 5 days post-ingestion. Trends of serum creatinine demonstrated peak levels to occur at an average of 7 days post-ingestion, with a range of 3–16 days. The majority of patients had a return to baseline renal function within 1 month. Approximately 1% of patients went on to require dialysis as a temporizing measure. This was more common in patients with multisystem organ failure and other medical comorbidities, and less likely in patients with isolated renal dysfunction.

In characterizing these trends, one must also consider confounding factors that occurred in many case reports, such as coingestion of other nephrotoxic drugs, dehydration, preexisting liver or renal dysfunction, multiple organ failure, chronic APAP ingestions, and advanced age [21].

RELATIONSHIP TO DOSE AND HEPATOXICITY

The relationship between dose and nephrotoxicity is not as clearly delineated as with that of APAP-induced hepatotoxicity. APAP-induced nephropathy may occur at lower doses than that seen with hepatotoxicity. In 1 of 2 limited poison center retrospective series, almost one third of patients developed renal insufficiency in the absence of significant hepatotoxicity [21]. The mechanism of this phenomenon is hypothesized to be independent production of toxins by both organs, but is poorly understood. It is not surprising that patients with multisystem organ failure tend to have a more complicated clinical course [13].

MANAGEMENT AND THE ROLE OF NAC

As with any exposure, patients who present with acute acetaminophen ingestion should have a thorough history obtained regarding details of the ingestion. This should include all over-the-counter and prescription products, dosages, quantity ingested, illicit substances used, and the time course of the overdose. History of concomitant medical comorbidities as well as risk factors for nephrotoxicity, including malnutrition or chronic alcohol use, should be identified. Laboratory data, including an acetaminophen level, liver function tests, creatinine, and blood urea nitrogen should be obtained and followed. Patient's blood pressure and urine output should be trended as well. If renal insufficiency develops, a urinalysis may help to delineate ATN from prerenal azotemia or hepatorenal syndrome [19].

The administration of N-acetylcysteine (NAC) has been shown to reduce the incidence of hepatic necrosis in the setting of acetaminophen toxicity. Patients may be given NAC via the oral or intravenous route. NAC is a glutathione precursor that helps to replete glutathione stores and detoxify reactive intermediates. NAC has a clear role in preventing acetaminophen-induced liver necrosis, but it has not demonstrated a benefit in preventing nephropathy. This further reinforces the concept that discrete mechanisms of toxicity exist between the liver and the kidney. The role of NAC in acetaminophen-induced nephropathy is derived primarily from retrospective studies and case reports. There have not been any large-scale randomized clinical trials. Analysis of existing case reports yielded no difference in peak creatinine levels between patients treated with NAC and those who were not treated [12,19]. It was suggested that NAC may paradoxically augment acetaminophen-induced nephrotoxicity [22], however, treatment with NAC did not worsen nephropathy in a small series of patients [13]. Although NAC has not proven to be harmful to the kidney, its role in patients without hepatoxicity and only isolated renal function is uncertain. NAC administered either intraperitoneally or orally to APAP-poisoned mice did not protect against nephrotoxicity [23]. Oral NAC is a very safe therapy, but its utility in these patients is unknown. Current data suggests treating with NAC based on the risk of liver necrosis, not on that of renal dysfunction.

CASE DISCUSSION

When the patient presented to our institution, she was obtunded and intubated. Her liver function began to improve; however, her creatinine began to rise. The urine sodium level was 38 mMol/L. A urinalysis on admission to our hospital was significant for pyuria, hematuria, and granular casts, all findings consistent with acute tubular necrosis. Urine output decreased and hypertension occurred. The patient was placed on hemodialysis, which was discontinued after several days with improved renal function. Her course was also complicated by aspiration pneumonia, delirium, and a urinary tract infection. She ultimately improved and was extubated. She was discharged on day 25 after her admission to a rehabilitation facility with a creatinine of 1.4 mg/dL. Her episode of renal failure was consistent with APAP-induced nephrotoxicity including the onset, duration, clinical course and urinary findings. NAC was discontinued when her liver function began to improve.

SUMMARY AND CONCLUSIONS

Acetaminophen-induced nephropathy occasionally occurs in patients with acetaminophen ingestion, though is not as well characterized as hepatoxicity. The mechanisms of necrosis in both organs are similar, yet there are some subtle differences that remain unclear. Patients may present with isolated renal toxicity or in the setting of multisystem organ failure. The clinical course is generally one of recovery, but hemodialysis may be required as

a temporizing measure. NAC has not shown any proven benefit in the setting of renal toxicity to date. A thorough history and physical examination with identification of risk factors, NAC therapy based on potential for hepatotoxicity, supportive care, and serial monitoring of urine output, blood pressure, and markers of glomerular filtration are essential to treatment. Future research should aim to better understand and manage this phenomenon.

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