DESCRIPTION OF THE NEPHROLOGY—HYPERTENSION TRAINING PROGRAM AT THE UNIVERSITY OF CALIFORNIA, SAN DIEGO, SCHOOL OF MEDICINE

UCSD offers a 2- or 3-yr program in clinical nephrology-hypertension and research training in nephrology-hypertension. This program prepares physicians for careers in both academic and clinical nephrology. There are opportunities for research experience without clinical training for both MDs and PhDs, and approximately 20 fellows are in the current nephrology-hypertension program. These programs are sponsored by a faculty of 21 members, headed by Roland Blantz, MD. The program offers a balance between clinical training in a very active clinical teaching program and a variety of research opportunities and disciplines. Clinical rotations are supervised by faculty members at two UCSD Medical Center hospitals—the San Diego Veterans Affairs Medical Center and the San Diego Naval Regional Medical Center. There are four clinical rotations, which include a rotation on the UCSD Transplant and Pheresis Program. Approximately 120 transplants are performed each year, and several hundred renal transplants are monitored. The Nephrology-Hypertension Consultation Service exposes each fellow to consult experiences in pancreas, liver, lung, and heart transplants as appropriate for these disciplines. There is also an active, vigorous medical intensive care unit exposure during all of the rotations. The fellow has primary responsibility for the care of transplant patients during the acute phase of treatment, and there exists a strong working relationship with the Transplant Surgery Division. More than 100 acute hemodialyses are performed each month at UCSD Medical Center. After clinical training, fellows are exposed to a broad range of laboratory experiences in a unique School of Medicine setting. Within the exception of pharmacology, there are no basic science departments at the UCSD School of Medicine, and there is a vigorous interaction among basic scientists and clinical investigators. Within the division, there are laboratories actively engaged in the study of renal physiology and pathophysiology, biochemistry, cellular physiology and molecular medicine, renal and molecular cellular immunology, research and treatment modalities for acute and chronic renal failure, and programs on the clinical mechanisms of systemic hypertension as well as the genetics of hypertension. The School of Medicine provides extensive training in laboratory methods in research for all research fellows, and there are extensive opportunities for collaboration with Cellular and Molecular Medicine, the Department of Pharmacology Salk Institute, and The Scripps Research Institute. There are also extended research opportunities through two Institutional Physician/Scientist Training Grant Programs. Most of the faculty in the Division of Nephrology-Hypertension are actively involved in clinical and basic research activities that span programs beyond the Division of Nephrology-Hypertension. Each of these laboratories is characterized by a high degree of fellow and faculty interaction. The University of California, San Diego, offers a broad, balanced program directed toward the preparation of individuals for academic careers and the provision of a broad base of scientific techniques that will prepare them for the decades ahead.

Acute Renal Failure due to Acetaminophen Ingestion: A Case Report and Review of the Literature

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ABSTRACT

Acetaminophen is the most commonly reported drug overdose in the United States. Acute renal failure occurs in less than 2% of all acetaminophen poisonings and 10% of severely poisoned patients. At therapeutic dosages, acetaminophen can be toxic to the kidneys in patients who are glutathione depleted (chronic alcohol ingestion, starvation, or fasting) or who take drugs that stimulate the P-450 microsomal oxidase enzymes (anticonvulsants). Acute renal failure due to acetaminophen manifests as acute tubular necrosis (ATN). ATN can occur alone or in combi-
nation with hepatic necrosis. The azotemia of acetaminophen toxicity is typically reversible, although it may worsen over 7 to 10 days before the recovery of renal function occurs. In severe overdoses, renal failure coincides with hepatic encephalopathy and dialysis may be required. Recognition of acetaminophen nephropathy requires the following: (1) a thorough drug history, including over-the-counter medications such as Tylenol® or Nyquil®; (2) knowledge of the risk factors that lessen its margin of safety at therapeutic ingestions, i.e., alcoholism; and (3) consideration of acetaminophen in the differential diagnosis of patients who present with combined hepatic dysfunction and ATN.

Key Words: Acetaminophen, acute renal failure, acute tubular necrosis, drug overdose

Acetaminophen is contained in a wide variety of over-the-counter preparations in the United States (1). Acetaminophen is the most commonly reported drug overdose in the United States (personal communication, San Diego Poison Center), with 80,000 cases in 1992. In toxic amounts, acetaminophen can result in hepatic necrosis and acute tubular necrosis (2-5). At therapeutic dosages, acetaminophen can be toxic in patients who consume alcohol or who take drugs that stimulate the P-450 microsomal oxidase enzymes (6-9). The overall incidence of acute renal failure in patients with acetaminophen poisoning is less than 2%, and renal failure occurs in about 10% of severely poisoned patients (2). Acute renal failure secondary to acetaminophen poisoning occurs alone (10) or in combination with hepatic necrosis (3,4,11,12). The following case provides a forum for discussing acute renal failure after acetaminophen ingestion.

CASE PRESENTATION

A 39-yr-old white woman presented to the emergency room complaining of nausea, vomiting, diarrhea, abdominal pain, and a decrease in urine output. Four days before admission, she developed a sore throat and cough and began medicating herself with Nyquil® (Proctor and Gamble Pharmaceuticals, Inc., Cincinnati, OH; 167 mg of acetaminophen per 5 mL) and Extra-Strength Tylenol® (McNeil Consumer Products Company, Fort Washington, PA; 500 mg of acetaminophen per tablet). She was seen at an outside clinic 2 days later for nausea and vomiting and received amoxicillin, guaifenesin, belladonna and phenobarbital, and pseudoephedrine hydrochloride for a viral syndrome. Worsening symptoms precipitated her emergency room visit.

In the emergency room, she appeared ill with a blood pressure of 150/98 mm Hg, a pulse rate of 107 beats/min, and an oral temperature of 37.4°C (99.4°F). Her examination was remarkable for periorbital edema and ecchymosis, scleral icterus, and an enlarged, tender liver. There was no evidence of hepatic encephalopathy. Routine laboratory tests revealed the following values: sodium, 121 mmol/L; blood urea nitrogen (BUN), 16.4 mmol/L; creatinine, 486 μmol/L; total bilirubin, 94 μmol/L; serum glutamic oxalacetic transaminase (SGOT), 2,216 IU/L; serum glutamic pyruvic transaminase (SGPT), 2,732 IU/L; prothrombin time, 15.7 s; and partial thromboplastin time, 27.4 s (Table 1). A urinalysis had a specific gravity of less than 1.005, 1+ protein, trace blood and positive bilirubin by dipstick. three to four white blood cells per high-power field, and six to eight red blood cells per high-power field. No casts were reported by the laboratory. On admission, the fractional excretion of sodium was 2.9% and her urine sodium was 20 mmol/L. The latter quickly rose to 147 mmol/L by hospital day 3. Urine osmolality and serum osmolality were 146 mOsm/L and 269 mOsm/L, respectively. Serum creatine kinase was normal with a urine negative for myoglobin. Viral hepatitis serologies (A, B, C) were negative. A disseminated intravascular coagulation (DIC) screen was positive (fibrin split products >40; D-dimer >8), and the platelet count

### TABLE 1. Laboratory data for case presentation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
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<td>123</td>
<td>121</td>
<td>120</td>
<td>134</td>
<td>134</td>
<td>131</td>
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<tr>
<td>Potassium (mmol/L)</td>
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<td>3.7</td>
<td>3.5</td>
<td>3.9</td>
<td>4.4</td>
<td>4.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
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<td>84</td>
<td>83</td>
<td>90</td>
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<td>93</td>
<td>90</td>
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<td>CO₂ (mmol/L)</td>
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<td>21</td>
<td>23</td>
<td>21</td>
<td>24</td>
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<td>23</td>
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<tr>
<td>BUN (mmol/L)</td>
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<td>17.5</td>
<td>18.6</td>
<td>20</td>
<td>18.6</td>
<td>16.4</td>
<td>12.9</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>486</td>
<td>537</td>
<td>575</td>
<td>645</td>
<td>557</td>
<td>415</td>
<td>336</td>
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<tr>
<td>Alkaline Phosphatase (IU/L)</td>
<td>105</td>
<td>131</td>
<td>212</td>
<td>276</td>
<td>170</td>
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<tr>
<td>SGOT (IU/L)</td>
<td>2,216</td>
<td>2,060</td>
<td>555</td>
<td>244</td>
<td>149</td>
<td>68</td>
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<tr>
<td>SGPT (IU/L)</td>
<td>2,732</td>
<td>3,226</td>
<td>2,169</td>
<td>1,635</td>
<td>1,044</td>
<td>518</td>
<td></td>
</tr>
<tr>
<td>Total Bilirubin (μmol/L)</td>
<td>94</td>
<td>80</td>
<td>67</td>
<td>38</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Bilirubin (μmol/L)</td>
<td>63</td>
<td>62</td>
<td>43</td>
<td>17</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.6</td>
<td>5.3</td>
<td>5.3</td>
<td>5.8</td>
<td>5.6</td>
<td>5.9</td>
<td></td>
</tr>
</tbody>
</table>
was low at 103,000. A renal ultrasound was normal. No acetaminophen was detected on the serum drawn in the emergency room.

On further questioning, the patient related consuming two oz of Nyquil 4 days before admission and taking one to two tablets of Extra-Strength Tylenol about every 6 h over the 4 days before admission. She drank approximately two glasses of wine a day with occasional heavier intake. She denied intentional overdosing on any medication, illicit drug use, or suicidal ideation. We estimated that she ingested approximately 15 g of acetaminophen over 3.5 days.

The patient's BUN and creatinine continued to rise over the next few days, reaching a peak of 20 mmol/L and 645 μmol/L, respectively, on the fourth hospital day (Table 1). Her transaminases fell gradually, and her DIC parameters normalized. She remained nonoliguric throughout her hospital stay. With conservative management and fluid restriction, her urine output increased. No dialytic support was needed. She was discharged on hospital day 7 with a BUN of 12.9 mmol/L and a creatinine of 336 μmol/L. She did not come to her follow-up clinic appointments.

**OVERVIEW OF ACETAMINOPHEN PHARMACOLOGY**

Acetaminophen is rapidly absorbed from the gastrointestinal tract, with peak drug levels in the plasma within 30 to 60 min of ingestion. The drug is metabolized in the liver in three ways: glucuronide conjugation, sulfate conjugation, and microsomal oxidation (13) (Figure 1). Studies have shown that adults form primarily glucuronide conjugation (major pathway), in contrast to neonates and children (aged 3 to 9 yr), who use sulfate conjugation (14). These metabolites are excreted in the urine. Under normal circumstances, a small fraction of acetaminophen (<5%) is converted by the microsomal P-450 system into an active metabolite that binds glutathione and is then excreted as a mercapturic acid. Approximately 1% of the drug is excreted unchanged (1).

When large doses of acetaminophen are consumed, the limited hepatic stores of glucuronide and sulfate are quickly depleted. This results in increased formation of an active metabolite via the minor pathway, which if not bound by glutathione, binds to cytosol.

![Figure 1. Metabolic pathway of acetaminophen.](image)
proteins in tissue within 1 to 2 h, resulting in cellular necrosis. Increased activity of the mixed-function oxidases leads to a higher proportion of formation of the active metabolite. Drugs that induce the P-450 enzymes (anticonvulsants) or depletion of glutathione (chronic alcohol ingestion, starvation, or fasting) seem to potentiate the hepatic injury in patients with acetaminophen overdose (13). In chronic alcoholics, the toxic dose of acetaminophen may be as low as 4 g.

Like the liver, the kidney is susceptible to acetaminophen toxicity. In humans, the mechanism of acute renal failure after toxic amounts of acetaminophen has not been well defined. Strong evidence for a direct nephrotoxic effect of large doses of acetaminophen has come from animal models. Mitchell et al. using Fischer rats and mice with high microsomal cytochrome P-450 in their kidneys, induced acute necrosis of the proximal convoluted tubules of the inner cortex with a single, nonlethal dose of acetaminophen (15). Pretreatment of these animals with 3-methylcholanthrene, a hepatic selective drug that increases P-450 mixed-function oxidases, resulted in potentiation of hepatic necrosis after the administration of acetaminophen but had no effect on the renal lesion. Furthermore, when a toxic dose of tritium-labeled acetaminophen was given to rats pretreated with 3-methylcholanthrene, the amount of covalent binding of the tritium-labeled drug in the kidney was reduced. On the other hand, cobalt chloride, which inhibits liver and kidney P-450 synthesis, resulted in decreased hepatorenal necrosis. These studies suggest that a renal toxic metabolite of acetaminophen was formed by in situ metabolic activation rather than by a distant effect from hepatic injury.

The depletion of glutathione in the kidney results in the potentiation of renal necrosis, whereas pretreatment with cysteine, a precursor of glutathione, decreased the severity of the acetaminophen-induced kidney lesions. The kidney is thought to form a toxic metabolite only when it is glutathione depleted (15). Thus, the animal studies indicate that when the kidney is overwhelmed with acetaminophen, the oxidation of acetaminophen via the P-450 system results in tubular damage.

REVIEW OF PATHOPHYSIOLOGY

After a toxic dose of acetaminophen, anorexia, nausea, and vomiting appear 12 to 24 h later. Clinical evidence of hepatotoxicity may not become apparent until 4 to 6 days after ingestion, when the level of acetaminophen is no longer detectable. The characteristic lesion in human liver is necrosis around the central vein. This region corresponds to the location of the enzymes responsible for the main metabolism of the drug. The liver becomes enlarged and often tender. There is a rise in the level of transaminases (SGOT and SGPT) that normalizes after 1 to 2 wk. Severe liver damage is associated with transaminases levels over 1,000 IU/L. Despite the hepatocellular damage, the bilirubin levels are usually only moderately elevated (1). Hepatic synthesis of clotting factors is reduced, and prolongation of prothrombin time occurs. DIC in conjunction with hepatic necrosis has been described (16).

ATN associated with acetaminophen poisoning occurs in combination with hepatic necrosis (3,4,11,12) or alone (10). Patients have variable urine output. Urinary findings may help to distinguish ATN from hepatorenal syndrome (HRS) and prerenal azotemia. In ATN (Table 2), the sediment often has granular casts with or without hematuria or pyuria. Urine osmolality tends to be similar to plasma osmolality, whereas urine sodium concentration is >20 mmol/L. HRS and prerenal azotemia differ from ATN in that the urinary sediment is normal, urinary sodium is low (<10 mmol/L), and the urine osmolality is much greater than the plasma osmolality (17). The azotemia of acetaminophen toxicity may increase progressively for 7 to 10 days before the recovery of renal function occurs, as was seen in our case. In severe overdoses, renal failure coincides with hepatic encephalopathy and dialysis may be required.

<table>
<thead>
<tr>
<th>TABLE 2. Renal manifestations of acetaminophen toxicity: an ATN pattern</th>
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<tbody>
<tr>
<td><strong>Urinary Findings</strong></td>
</tr>
<tr>
<td>Urine sediment</td>
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<tr>
<td>Urine osmolality</td>
</tr>
<tr>
<td>Urine sodium concentration</td>
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<tr>
<td>Urinary volume</td>
</tr>
<tr>
<td><strong>Clinical Course</strong></td>
</tr>
<tr>
<td>Light microscopy</td>
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<tr>
<td>Fluorescent microscopy</td>
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<tr>
<td>Electron microscopy</td>
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</table>

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DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute azotemia in a patient with liver disease includes prerenal azotemia, HRS, and acute renal failure due to tubular necrosis. Prerenal azotemia can be secondary to volume contraction or cardiac pump failure. Fluid challenges or correction of the cardiac dysfunction will reverse the azotemia. HRS is renal failure that occurs in patients with liver disease who are not volume depleted and is recognized by avid tubular reabsorption of sodium and water, oliguria, and normal renal pathology. ATN occurs in patients with liver disease, and its causes are multifactorial but include the categories of drugs, toxins, infectious agents, and shock (18) (Table 3).

DIAGNOSIS

A thorough drug history must be obtained. This must include commonly purchased over-the-counter medications that contain acetaminophen and other medications that induce the P-450 system and may potentiate acetaminophen's toxicity (Table 4). Other risk factors include starvation, fasting, and chronic alcohol abuse. A single toxic dose of acetaminophen that will result in adverse effects usually exceeds 15 g in 80% of cases, although much less can be enough to poison some (13). Alcoholics have a predisposition to both the hepatotoxic and nephrotoxic effects of acetaminophen. Ingestions within the manufacturer's recommendation of 4 g/day can result in toxicity in patients using alcohol regularly.

An acetaminophen level should be determined 4 to 12 h after ingestion. Levels obtained before 4 h may not represent peak levels in plasma, and those drawn days after the poisoning may not detect acetaminophen. Acetaminophen levels in plasma can be plotted on Prescott's nomogram to determine the probability of potential hepatotoxic reactions. Severe hepatic injury occurs in patients with drug levels of 200 μg/mL

4 h after ingestion, whereas it usually does not occur in those with values lower than 150 μg/mL. Liver function tests, routine urine and serum electrolytes, and a test for myoglobin and creatine kinase, along with hematology and coagulation parameters, should be obtained.

A renal biopsy may be indicated in patients with an unobtainable history or atypical presentation. Histopathological examination of acetaminophen nephropathy has some characteristic features (Table 2). Light microscopic sections show normal glomeruli and vessels but severe necrosis involving the proximal convoluted tubules as well as the distal tubules (5, 11). Breaks in the tubular basement membrane occur. Casts can be seen in the tubular lumens. Fluorescent microscopy is negative for the deposition of immunoglobulins or complement components. Electron microscopy is remarkable for the loss of luminal brush borders, mitochondrial disarray, multiplication of intramitochondrial vesicles, and disruption of tubular basement membrane (5).

REVIEW OF THERAPEUTIC APPROACH

The treatment of acetaminophen poisoning has emerged over time (Table 5). Gastric aspiration and lavage are effective when performed within the first few hours after the acetaminophen overdose. Activated charcoal reduced acetaminophen absorption,
but only when given within 30 min after ingestion. The administration of sulphydryl compounds (e.g., N-acetylcysteine, cysteamine, or methionine) reduces the extent of liver necrosis after acetaminophen overdose. These drugs are proposed to protect the liver by maintaining or restoring the glutathione levels or by acting as an alternate substrate for conjugation with the reactive metabolite (19). Oral N-acetylcysteine is the current recommended treatment when hepatotoxic levels are present (20). If initial acetaminophen levels are in the toxic range (>200 μg/mL at 4 h or 30 μg/mL at 15 h), the patient should receive an oral loading dose of acetylcysteine (140 mg/kg), followed by 17 doses of 70 mg/kg every 4 h. If therapy is initiated before knowing the acetaminophen level and it is found to be low, N-acetylcysteine can be discontinued. The initiation of treatment 24 h after ingestion is controversial (20). Cysteamine and methionine have also been used as alternative treatments, but N-acetylcysteine is considered to be more effective and has fewer side effects (20,21).

N-Acetylcysteine has not been shown to ameliorate renal tubular damage secondary to acetaminophen and is not recommended for isolated suspected nephrotoxicity. These observations suggest there are additional unidentified factors that contribute to acetaminophen injury to the kidney.

PROGNOSIS

Patients are considered at risk for hepatic failure if their acetaminophen level in plasma after ingestion is 200 μg/mL at 4 h or 30 μg/mL at 15 h (2). Treatment with N-acetylcysteine ameliorates damage in these cases. In general, ATN is reversible, with only a small number requiring temporary dialytic support. There is no known effective treatment to interrupt renal tubular damage at this time.

CONCLUSION

Acute renal failure secondary to acetaminophen poisoning occurs alone or in combination with hepatic necrosis. The renal manifestations of acetaminophen toxicity are those of ATN. The margin of safety of acetaminophen is less in patients with such risk factors as starvation, chronic ingestion of alcohol, or medications that activate the P-450 system. Recognition of acetaminophen nephropathy requires the physician to have knowledge of these risk factors and to obtain an adequate drug history, including over-the-counter medications.

ACKNOWLEDGMENTS

This was supported by NIH Program Physician Scientist Award DK01408 (P.B.).

REFERENCES