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## What You Forgot About Acetaminophen

by Amy Schilling, Pharm.D.

**Introduction:** Acetaminophen (APAP) is a common antipyretic and analgesic agent found in many over-the-counter and prescription products currently available from cough and cold remedies to narcotic pain relievers (See Table 1).<sup>1</sup> APAP is generally considered safe, but it can be toxic when total daily doses exceed recommendations. The annual number of accidental and intentional overdoses is concerning. The 2006 Annual Report from the American Association of Poison Control Centers implicates APAP alone or in combination with other products in nearly 140,000 poisoning exposure cases.<sup>2</sup> Over 100 deaths were reported in these patients.<sup>2</sup> According to a position statement from the American Association for the Study of Liver Diseases (AASLD), the rates of APAP-related liver toxicity have been steadily increasing over the past decade to become the most common cause of acute liver failure (ALF).<sup>3</sup>

APAP-related hepatotoxicity can be characterized into two categories: intentional (i.e., suicide attempt) and unintentional (i.e., multiple therapeutic but excessive doses over a period of time, usually >3 days).<sup>4</sup> Up to 50% of APAP-related liver failure cases are unintentional. Unintentional overdoses or “therapeutic misadventures” are most often due to APAP duplication in multiple products, APAP-narcotic combinations, and/or co-ingestion with alcohol.<sup>3</sup> Also, it has been noted that APAP hepatotoxicity may occur even with therapeutic doses in the presence of select

conditions such as age, chronic alcohol use (i.e., >3 drinks per day), malnutrition (e.g., poor nutritional status, anorexia), and concurrent use of enzyme-inducing medications.<sup>5</sup>

The Food and Drug Administration (FDA) Medwatch Database contains information regarding 307 unintentional APAP overdoses between 1998 and 2001, with 25% of these patients taking more than one APAP-containing product.<sup>6</sup> In an Institute for Safe Medication Practices (ISMP) Medication Safety Alert, one hospital reported that an average of one patient per day exceeded the recommended daily APAP limit of four grams.<sup>6</sup> Consumers are often unaware of all the medications that contain APAP; therefore, education about the APAP content in products is needed, as are steps to prevent unintentional overdoses.

**History:** The first use of APAP in medicine was in 1893.<sup>1</sup> The use of APAP became widespread in 1949 when it was found to be the less toxic metabolite of two of its parent compounds, acetanilide and phenacetin.<sup>1</sup> APAP is an effective antipyretic and analgesic agent, but its antiinflammatory properties are minimal, especially in comparison to nonsteroidal antiinflammatory drugs (NSAIDs). A benefit of using APAP over NSAIDs is the lower risk of gastrointestinal (GI) toxicity (e.g., ulceration and bleeding), which may lead to better tolerance.<sup>1</sup>

**Indications and Dose:** APAP is indicated for the treatment of mild-to-moderate pain or fever, including pain due to osteoarthritis. The use of APAP in chronic inflammatory conditions, such as rheumatoid arthritis, is not recommended due to its lack of antiinflammatory properties. The usual dose of APAP for adults and children >12 years of age is 325 to 650 mg orally or rectally every 4 to 6 hours or 1000 mg three to four times daily.<sup>7</sup> Package labeling recommends that the total daily dose of APAP should not exceed four grams per day in most adult patients; however, lower maximum daily doses (e.g., two grams per day) are recommended in patients who may be at higher risk for APAP hepatotoxicity (e.g., alcoholics or chronic alcohol consumption, malnourished patients, or patients taking enzyme-inducing drugs).<sup>7,8</sup> Specifically, it is noted on Tylenol® products, “If you consume three or more alcoholic drinks every day, ask your physician if you should take acetaminophen.” For pediatric patients, the recommended APAP dose is 10 to 15 mg/kg/dose orally or rectally every 4 to 6 hours for children up to 12 years of age. The maximum dose in children up to 12 years of age should not exceed five doses (or 50 to 75 mg/kg) in 24 hours.<sup>7,9</sup> The use of APAP in a child <2 years of age or <11 kg, should be under the direction of a physician.

**Pharmacokinetics:** Typically, APAP has excellent bioavailability (up to 98%), but the exact amount absorbed varies based on dosage form and concomitant administration with other medications.<sup>10</sup> Therapeutic doses yield a half-life of about 2 hours; peak plasma concentrations are achieved 30 to 60 minutes after the dose is administered.<sup>1</sup> Co-ingestion with opioids, anticholinergics, or even food may delay the time to peak concentration by delaying gastric emptying.<sup>10</sup> The major metabolic pathway for APAP in adults is Phase II metabolism via hepatic conjugation with glucuronic acid (40-67%) and sulfuric acid (20-46%).<sup>11</sup> These metabolites, as well as small amounts that have been hydroxylated and deacetylated, are recovered in the urine. Under normal circumstances, a small amount of APAP undergoes oxidative metabolism by cytochrome P450 (CYP450) enzymes (primarily by CYP2E1 and to a lesser extent by CYP1A2, CYP2A6, and CYP3A4) forming a toxic metabolite (*N*-acetyl-p-benzoquinone imine or NAPQI). Then, the sulphydryl groups of glutathione (GSH) convert this reactive intermediate (NAPQI) into harmless metabolites that are excreted in the urine.<sup>1,9</sup>

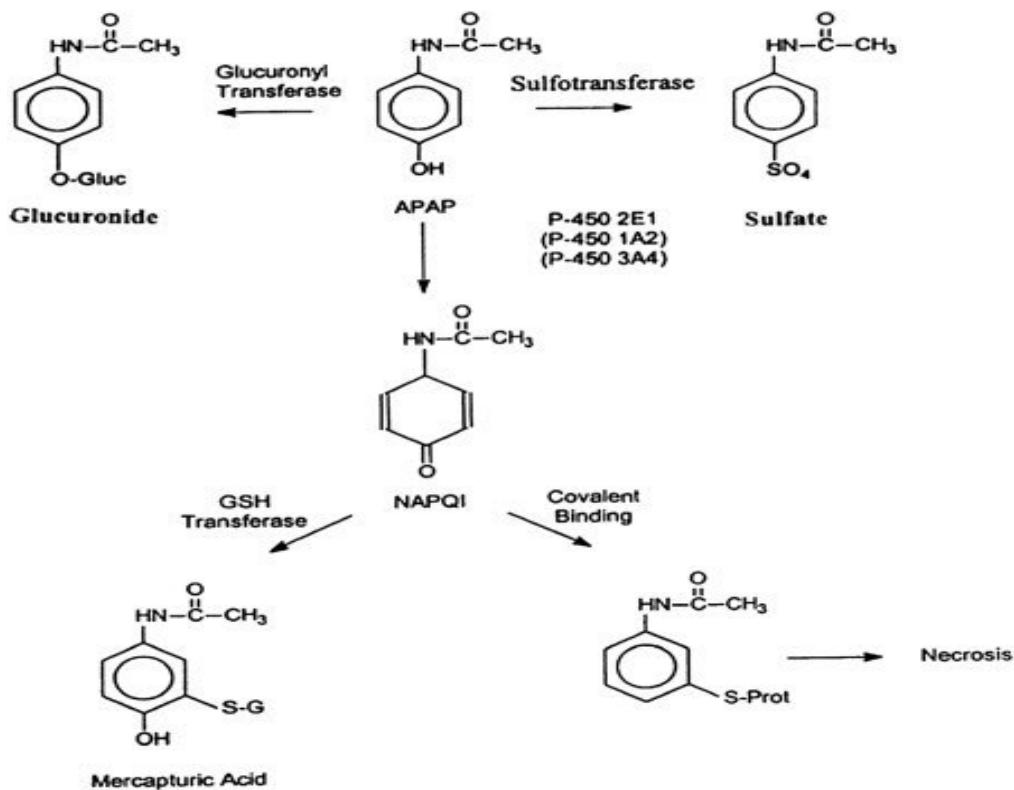
**Adverse Drug Reactions:** At recommended therapeutic doses, APAP is well-tolerated. APAP is considered a relatively safe medication when used according to labeling instructions. Rarely, patients experience an erythematous or urticarial rash or other allergic complications.<sup>1</sup> However, APAP is a dose-dependent hepatotoxin and excessive doses (whether from a suicidal intent or therapeutic use) may lead to ALF. In addition, even when taken in therapeutic doses, APAP may still cause transient liver enzyme elevations and possibly hepatotoxicity in select patients (e.g., malnourished/alcoholic patients or patients taking certain enzyme-inducing medications).<sup>4,5</sup>

**Toxicity:** Glucuronidation and sulfation, the major metabolic pathways, become saturated following APAP overdose.<sup>9</sup> When Phase II metabolism of APAP becomes saturated, more of the highly reactive intermediate, NAPQI, is formed by CYP450 mediated N-hydroxylation. More specifically, this shifts the metabolism of APAP to primarily the CYP2E1 pathway, the minor metabolic pathway, resulting in the formation of increased amounts of NAPQI, the toxic metabolite. When GSH is depleted following large doses of APAP or in malnourished individuals, the toxic metabolite accumulates resulting in liver damage (See Figure 1).<sup>5</sup> APAP-induced hepatotoxicity occurs by two mechanisms. The NAPQI metabolite binds to hepatic cell macromolecules, which causes dysfunction of the enzymatic systems as well as structural and metabolic disarray and eventually necrotic cell death. The hepatocytes are also at risk for oxidative stress due to the depletion of GSH. In pediatric patients, single APAP doses of 120 to 150 mg/kg of body weight have been associated with hepatotoxicity.<sup>12</sup> In adults, single APAP ingestion of >150 mg/kg or a total dose of greater than 7.5 grams have been associated with hepatotoxicity.<sup>5</sup> However, the minimal dose of APAP that has been associated with liver injury has ranged from four to ten grams, and in healthy volunteers even therapeutic doses of one gram orally every 6 hours resulted in mild liver injury.<sup>13</sup>

**Table 1. Selected Acetaminophen-Containing Brand Name Products<sup>7,20-22</sup>**

Over-the-Counter (OTC)	APAP (mg) per dosage form	Prescription	APAP (mg) per dosage form
Tylenol Arthritis® Midol® Pamprin® Tylenol® Extra Strength Benadryl® Severe Allergy and Sinus Headache Sudafed® Sinus and Headache Tylenol® Allergy, Flu, PM Goody's® Fast Pain Relief Excedrin®	650	Vicodin® ES	750
	500	Darvocet-N100®	650
	500	Lorcet® 10/650	650
	500	Lortab®	500
	325	Vicodin®	500
	325	Tylox®	500
	325	Fioricet®	325
	260	Norco®	325
	250	Percocet®	325 to 650
		Ultraceet®	325
		Tylenol® #3	300

**Figure 1. Mechanism of APAP Toxicity<sup>5</sup>**



**Toxicity (continued):** Patients who are malnourished or fasting are thought to be at greater risk for APAP hepatotoxicity due to a deficiency in GSH at baseline. In addition, even at lower than therapeutic doses, induction of CYP450 enzymes, due to drugs or chronic alcohol consumption may lead to an increase in the formation of NAPQI resulting in an increased risk of hepatotoxicity.

**Clinical Presentation:** Establishing the diagnosis of APAP overdose following patient presentation is often determined by a thorough patient history. Some challenges to obtaining the pertinent information include: altered mental status of the patient at presentation, ignorance of any risk involved from the use of over-the-counter APAP preparations, embarrassment on the part of the patient, and an incomplete questioning and medication history.<sup>14</sup>

**Clinical Presentation of Acute Intentional APAP Toxicity:** The symptoms of toxicity may not be apparent immediately following ingestion of an acute overdose of APAP, but early recognition and treatment can prevent more severe damage to the liver, decreasing morbidity and mortality.<sup>11</sup> Phase I of an APAP overdose begins shortly after ingestion and can last for 12 to 24 hours. Although the signs and symptoms of overdose show a consistent pattern, these are not diagnostic. The patient may have signs of GI irritability, nausea, vomiting, anorexia, diaphoresis, and pallor. These symptoms are more pronounced following larger acute overdoses. However, these symptoms are not specific to an APAP overdose. During phase II of acute APAP toxicity (up to 48 hours after ingestion), the patient may begin to feel better, but the hepatic enzymes, prothrombin time (PT)/international normalized ratio (INR) values may continue to rise, and right upper quadrant pain may develop. Additionally, renal insufficiency can develop due to APAP-induced acute tubular necrosis, as well as other lab test abnormalities can occur.<sup>5</sup> Most patients receive the antidote (N-acetylcysteine) before or during this phase and if so, liver function most likely will gradually return to normal. If a patient reaches phase III, there may be severe hepatic necrosis, typically 3 to 5 days following ingestion. Symptoms during this phase may vary from less severe (e.g., nausea and general malaise) to severe (e.g., confusion and stupor). Also, at this time, liver enzymes can be as high as 10,000 IU/L or greater, and lactic acidosis and coagulopathy may worsen. If mortality should occur, it is most likely due to complications associated with fulminant hepatic failure.<sup>9</sup>

**Clinical Presentation of Unintentional APAP Toxicity:** Patients who present with unintentional APAP toxicity are often exposed over several days for which they are taking APAP-containing products to treat an acute or chronic medical condition. These patients often have low or undetectable serum APAP levels following 2 to 3 days of non-specific symptoms.<sup>13</sup>

**Management of APAP Overdose:** As stated previously, an overdose of APAP leads to the formation of a toxic metabolite (NAPQI) resulting in hepatotoxicity. Serum APAP levels may be useful for single, acute overdoses, if the time since ingestion is known. The Rumack-Matthew Nomogram, which is utilized in cases of acute (not unintentional) APAP overdoses, predicts the possibility of hepatotoxicity based on plasma levels in relation to time intervals post-ingestion.<sup>14,15</sup> The Nomogram can be found in the APAP package labeling or on the Cleveland Clinic homepage, under Clinical Resources, then under Formulary by searching for acetaminophen.<sup>9,10</sup> Unintentional overdoses occur over a more prolonged period, therefore, APAP levels cannot be applied to the Nomogram. N-acetylcysteine (NAC) is the antidote for APAP toxicity and should be administered within 8 hours of APAP ingestion for maximal protection against hepatic injury for patients whose serum APAP levels are above the “possible” toxicity line on the Nomogram.<sup>15</sup> If time elapsed since ingestion cannot be determined and APAP overdose is suspected, NAC should be administered immediately regardless of the quantity of APAP ingested.<sup>16</sup> In cases of unintentional overdose, NAC is often administered based on the discretion of the physician.

NAC limits the toxicity of APAP by 1) increasing the capacity to detoxify NAPQI, and 2) treating hepatotoxicity by other nonspecific mechanisms.<sup>10</sup> In addition, NAC may prevent further hepatic damage in any patient thought to have APAP-related liver toxicity even beyond the first 12 hours of an overdose.<sup>1</sup> NAC is available as an oral (Mucomyst<sup>®</sup>) and an intravenous (Acetadote<sup>®</sup>) formulation. Oral and intravenous (IV) NAC have similar efficacy for managing APAP hepatotoxicity. Many patients have difficulty tolerating the unpleasant taste of the oral solution. It is recommended to dilute the oral solution in a 1:3 ratio with cola, orange juice, or other soft drink to mask its unpleasant flavor; this mixture should be used within 1 hour of preparation.<sup>7</sup> Anaphylactoid reactions have been observed in patients receiving IV NAC for APAP overdose and occur soon after initiation of the infusion. The frequency of infusion-related reactions has been reported to be 0.2 to 20.8%, and reactions most commonly occur during the loading dose.<sup>15</sup> The recommended dosing for both oral and IV NAC can be found on the Cleveland Clinic homepage, under Clinical Resources, then under Formulary by searching for acetylcysteine.

The timely use of NAC and supportive care is important to the treatment of APAP toxicity. Activated charcoal can be used if the patient presents within 1 to 2 hours following ingestion (i.e., rapid GI absorption of APAP yields this treatment ineffective in most cases of APAP overdose).<sup>11</sup> In patients with ALF and poor prognosis, early referral to a liver transplant center is essential. King's College Criteria, a widely used prognostic model in patients with ALF, incorporates arterial pH, PT/INR, severity of encephalopathy, and serum creatinine and is used to predict the need for liver transplantation in these patients.<sup>5</sup>

**Patient Outcomes:** Ostapowicz and colleagues, as part of the Acute Liver Failure Study Group, published a study in 2002 to prospectively characterize the short-term outcome following ALF in a large number of patients at 17 tertiary care centers in the United States over approximately 41 months.<sup>17</sup> All centers except one performed liver transplants. Eligible patients had to meet criteria for ALF including an INR  $\geq 1.5$ , evidence of hepatic encephalopathy, and presentation within 26 weeks of illness onset without apparent chronic liver disease. Of the 308 patients with ALF, 39% (n=120) were due to APAP overdose. APAP was found to be the most common cause of ALF, with 37% of patients ingesting APAP with a suicidal intent, and 57% of cases were due to accidental toxicity with the remaining reasons for APAP overdose unknown. The median amount of APAP ingested was 13.2 grams per day (range 2.6- to 75-grams); 99 of 120 patients ingested more than four grams per day. There are differences between the patients with APAP-related acute liver toxicity and those with other causes of ALF (e.g., idiosyncratic drug reactions or indeterminate causes). Those with APAP-related liver toxicity had shorter disease duration, higher serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum creatinine (SCr) levels when compared to ALF due to other causes. The APAP group also had lower bilirubin and arterial pH levels when compared to patients in the remainder of the ALF groups. Liver transplantation rates in the APAP group versus the group with “other” drug-induced liver toxicity were 6% and 53%, respectively, with the rate of transplantation in the remaining groups of 36%. Of the APAP group, 47% met the criteria for transplant, but only 27% were listed for transplant. The group excluded from the transplant list had medical contraindications or were excluded for psychosocial reasons. The short-term transplant-free survival was 87% in the APAP group. Of the patients with APAP-induced liver toxicity, 83% of these patients consumed greater than the maximum daily recommended dose. Overall, 11% of patients enrolled in this study died, including 28% of the APAP group. The authors concluded that most liver injury in the United States is due to medications and may be preventable.

APAP-related liver toxicity, including a subgroup of patients from the Ostapowicz study, was analyzed by Larson and colleagues, as part of the Acute Liver Failure Study Group.<sup>18</sup> They examined the incidence, risk factors, and outcomes of APAP-induced ALF at 22 tertiary care centers in the US over a 6 year period. Of the 662 patients enrolled in the study, 302 had APAP-related toxicity and 275 were enrolled in the final analysis. During the study period, the number of cases of acute liver toxicity related to APAP increased from 28% to 51%. Of those enrolled in the study, 56% of the patients met the criteria for a potentially toxic APAP ingestion. Of those who met the criteria, 77% had detectable APAP levels in their serum, and 91% had ALT  $\geq 1,000$  IU/L. The range for onset of symptoms was 1 to 32 days, and the median dose was 24 grams with a range of 1.2 to 180 grams. APAP use in these patients included 96% who reported using one over-the-counter product,

**Patient Outcomes (continued):** and 44% who reported using an APAP and narcotic combination product. An unintentional overdose was reported in 48% of patients and 44% of patients reported were due to an intentional overdose. The remaining 8% did not have a definable reason for overdose. The unintentional overdose group had lower serum APAP levels compared to the intentional overdose group, but they were more likely to present with severe hepatic encephalopathy. The concern brought forth in this study is the number of patients with an unintentional overdose. A third of the patients, who were ingesting a narcotic and APAP combination product, were also consuming an additional APAP-containing product. The authors concluded that unintentional overdose is the leading cause of APAP-related hepatotoxicity and efforts to limit the over-the-counter package size and to restrict prescriptions of narcotic-APAP combinations may be necessary to decrease the incidence of this preventable cause of ALF.

Finally, a study by Squires and colleagues from the Pediatric Acute Liver Failure Study group, examined the pathogenesis, treatment, and outcome of ALF in children.<sup>19</sup> The patients in this study were any age from birth to 18 years with no previous evidence of chronic liver disease, evidence of acute liver injury, or hepatic-based coagulopathy. From December 1999 to December 2004, 348 patients were enrolled in this study. The median dose of APAP ingested by these patients was 183 mg/kg. Acute liver failure due to APAP ingestion was found to be 14% with a majority of these patients being white females, with 96% of patients older than 3 years of age. Hepatic encephalopathy was more common in the non-APAP groups than the APAP group, although this is often difficult to assess in many infants and children. Children with APAP toxicity had the most significant spontaneous recovery rate of 94% (45/48). Although there are relatively fewer APAP-related cases of ALF in children, the use of APAP is still a concern in this patient population. The authors concluded that in cases where hepatic encephalopathy is absent, children with APAP-induced liver toxicity have an excellent outcome.

**Summary:** An unintentional overdose with APAP is of concern because many patients are not aware of all the products that contain APAP and the dangers of consuming too much. Ostapowicz and colleagues found that APAP overdose was the cause of 39% of ALF in adults. According to the AASLD Position Statement, many times APAP toxicity involves 1) multiple preparations consumed concurrently that contain APAP, 2) use of APAP and narcotic combinations, and 3) impulsive behavior involving a lack of understanding of possible injury in consuming multiple APAP-containing products. Many patients may overlook the active ingredients on the label, may not be aware of the total maximum recommended daily dose, or may not be able to calculate the total daily intake from the information on the label. Larson and colleagues found that one-third of patients that had an unintentional APAP overdose were ingesting a narcotic and APAP combination product in addition to another APAP-containing product. This may be due to the fact that, many prescription medication labels contain abbreviations or inconsistent formatting which make it difficult to determine if APAP is in the product. APAP remains a top seller (both OTC and prescription), yet overdoses are responsible for more emergency room visits than any other medication on the market. The education of patients and healthcare professionals is needed regarding the dangers of consuming greater than four grams of APAP daily, and even less APAP in some patient populations, to prevent these unintentional overdoses.

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