

Liver Failure and Liver Disease

Acetaminophen-induced acute liver failure Results of a United States multicenter, prospective study

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[NOTE: Acetaminophen is the primary ingredient in Tylenol, and is also found in dozens of other drug products.]

FROM ABSTRACT

Severe acetaminophen hepatotoxicity frequently leads to acute liver failure.

We determined the incidence, risk factors, and outcomes of acetaminophen-induced acute liver failure at 22 tertiary care centers in the United States.

Detailed prospective data were gathered on 662 consecutive patients over a 6-year period fulfilling standard criteria for acute liver failure, from which 275 (42%) were determined to result from acetaminophen liver injury.

The annual percentage of acetaminophen-related acute liver failure rose during the study from 28% in 1998 to 51% in 2003.

Median dose ingested was 24 g (equivalent to 48 extra-strength tablets).

Unintentional overdoses accounted for 131 (48%) cases, intentional (suicide attempts) 122 (44%), and 22 (8%) were of unknown intent.

In the unintentional group, 38% took two or more acetaminophen preparations simultaneously, and 63% used narcotic-containing compounds.

81% of unintentional patients reported taking acetaminophen and/or other analgesics for acute or chronic pain syndromes.

Overall, 178 subjects (65%) survived, 74 (27%) died without transplantation, and 23 subjects (8%) underwent liver transplantation.

In conclusion, acetaminophen hepatotoxicity far exceeds other causes of acute liver failure in the United States.

Susceptible patients have concomitant depression, chronic pain, alcohol or narcotic use, and/or take several preparations simultaneously.

THESE AUTHORS ALSO NOTE:

“Acetaminophen, the most widely used analgesic in the United States, causes severe hepatic necrosis leading to acute liver failure after suicidal overdoses.”

“Unintentional liver injury from self-medication for pain or fever that leads to daily doses exceeding the 4 g/day package recommendations is also well-recognized.”

Fasting and alcohol use may enhance acetaminophen toxicity.

“N-acetylcysteine (NAC) can prevent hepatic injury if given within 12 hours of a single ingestion.” **[Important]**

“Extended acetaminophen dosing, delay in seeking medical attention, and/or failure to institute NAC therapy are associated with greater morbidity and mortality.”

RESULTS

In this study, 42% of acute liver failures were attributed to acetaminophen toxicity.

“Over the study period, the percentage of acute liver failures cases attributed to acetaminophen increased from 28% in 1998 to 51% in 2003.” **[Important]**

The median ingested dose of acetaminophen prior to acute liver failure was 24 g, but importantly, some suffered acute liver failure with ingesting as little as 1.2 g of acetaminophen. **[Very Important]**

Most of the acetaminophen overdoses and consequent acute liver failure were unintentional (48%), with an additional 8% that were labeled as “unknown.”

Most of the acetaminophen used (53%) prior to acute liver failure were from over-the-counter drugs.

44% of the subjects used a “prescription acetaminophen/narcotic compound (e.g., Vicodin).” **[Important]**

The unintentional overdose acute liver failure group listed the reasons for taking acetaminophen as:

Chronic generalized pain	31%
Chronic back pain	22%
Headache	13%
Chronic abdominal pain	8%
Migraine	8%
Viral URI	7%
Toothache	6%
Orthopedic pain	5%
Rheumatologic pain	5%
Fibromyalgia	4%
Chronic pancreatitis	2%
Postsurgical pain	2%
Hangover	1%
Earache	1%
Fever	1%
Menstrual pain	1%
Insomnia	1%
Leg pain	1%

15% of the unintentional overdose acute liver failure group reported that they had used acetaminophen for more than 7 days.

The most commonly used prescription acetaminophen/narcotic compound used to cause acute liver failure was Vicodin. **[Important]**

Those who chronically used or abused alcohol required lower amounts acetaminophen to cause acute liver failure. **[Important]**

7% of subjects achieved acute liver failure from taking 4 g acetaminophen per day before presentation.

[Important, because this is within labeling guidelines]

DISCUSSION

“Acetaminophen poisoning has become the most common cause of acute liver failure in both the United States and the United Kingdom.” **[Important]**

“Current data suggest a dramatic increase in acetaminophen toxicity recently; the percentage of all acute liver failure cases in our registry that were due to acetaminophen has nearly doubled in 6 years.”

“Patients with chronic pain appear to be particularly susceptible” to acetaminophen overdose and acute liver failure. **[Important]**

The numbers of acute liver failure reported in this study are conservative/low because:

- 1) Only the most severely ill subjects with acute liver failure were assessed.
- 2) Some with acute liver failure are not properly diagnosed.
- 3) Some with acetaminophen overdose only had mild liver disease and were not therefore assessed.
- 4) Some patients die prior to diagnosis of etiology and therefore are not counted.
- 5) Sick patients often give poor histories as to acetaminophen ingestion.

36% of Americans ingest an acetaminophen-containing compound at least once a month, adding up to millions of tablets consumed on a daily basis.

“One of the most alarming findings in our study was that unintentional acetaminophen overdose accounted for 50% of our cases.”

Early ingestion of NAC (N-acetylcysteine) is effective treatment, preventing hepatotoxicity and death.

“Amongst unintentional overdose patients, most (79%) reported that they were taking the medication(s) specifically for pain or constitutional symptoms (8%).” **[Important]**

“Many claimed to have ingested modest amounts of acetaminophen over weeks or months, with 63% reporting use of narcotic combinations [Vicodin].”

“Our data suggest that there is a narrow therapeutic margin and that consistent use of as little as 7.5 g/day may be hazardous.” **[Very Important]**

Factors that deplete glutathione (illegal and legal narcotic use, other drug use [metal toxicities, etc.]) increase chances of acute liver failure from acetaminophen ingestion. **[Very Important]**

Some will suffer from acetaminophen poisoning at lower doses because of genetic reasons [reduced ability to produce glutathione].

38% of the unintentional overdose acute liver failure group were consuming acetaminophen in 2 or more different preparations, including taking over-the-counter acetaminophen with Vicodin, suggesting the patients' lack of awareness of the hazards of doing this.

A third of the subjects with acetaminophen acute liver failure also abused alcohol, and ingested lower doses of acetaminophen before achieving liver failure.

“In conclusion, acetaminophen poisoning now accounts for at least 42% of U.S. acute liver failure cases and one third of the deaths.”

“Unintentional overdose is the leading form of acetaminophen hepatotoxicity in United States.”

“Efforts to limit over-the-counter package size and to restrict the prescription of narcotic-acetaminophen combinations [like Vicodin] (or to separate the narcotic from the acetaminophen) may be necessary to reduce the incidence of this increasingly recognized but preventable cause of acute liver failure in the United States.”

KEY POINTS FROM DAN MURPHY

- 1) [Acetaminophen is the primary ingredient in Tylenol, and is also found in dozens of other drug products.]
- 2) 42% of US acute liver failures are caused by acetaminophen, and in the final year of this study the number rose to 51%.
- 3) Unintentional overdoses of acetaminophen leading to acute liver failure account for half of the failures.
- 4) In the unintentional group, 38% took two or more acetaminophen preparations simultaneously, and 63% used narcotic-containing compounds, primarily Vicodin.
- 5) 81% of unintentional patients reported taking acetaminophen for acute or chronic pain syndromes.
- 6) “Acetaminophen hepatotoxicity far exceeds other causes of acute liver failure in the United States.”
- 7) Acetaminophen is the most widely used analgesic in the United States, and can cause severe hepatic necrosis leading to acute liver failure.
- 8) Fasting and alcohol use enhances acetaminophen toxicity to liver failure.
- 9) Early ingestion of NAC (N-acetylcysteine) is effective treatment, preventing hepatotoxicity and death. “N-acetylcysteine (NAC) can prevent hepatic injury if given within 12 hours of a single ingestion.” **[Important]** [I purchase N-acetylcysteine (NAC) in the product **Complete Glutathione From Nutri-West: 800-443-3333. NAC** works because it elevates the body’s production of the antioxidant detoxifier **glutathione. Undenatured Whey Protein** will also elevate glutathione levels and help protect the liver. I use **Complete Whey-G, also from Nutri-West.**]

- 10) Factors that deplete glutathione (illegal and legal narcotic use, other drug use [metal toxicities, etc.]) increase chances of acute liver failure from acetaminophen ingestion. **[Very Important]**
- 11) Some patients suffered acute liver failure with ingesting as little as 1.2 mg of acetaminophen.
[Very Important, as that is less than 3 Extra Strength Tylenol tablets.]
- 12) 7% of subjects achieved acute liver failure from taking 4 g acetaminophen per day. **[Important, because this is within labeling guidelines]**
- 13) 53% achieved acute liver failure from ingesting over-the-counter acetaminophen products.
- 14) 44% of the subjects used a "prescription acetaminophen/narcotic compound (e.g., Vicodin)." **[Important]**
- 15) "Acetaminophen poisoning has become the most common cause of acute liver failure in both the United States and the United Kingdom." **[Important]**
- 16) The percentage of all acute liver failure cases due to acetaminophen has nearly doubled in 6 years.
- 17) "Patients with chronic pain appear to be particularly susceptible" to acetaminophen overdose and acute liver failure. **[Important]**
- 18) The numbers of acute liver failure reported in this study are conservative/low.
- 19) 36% of Americans ingest an acetaminophen-containing compound at least once a month, adding up to millions of tablets consumed on a daily basis.
- 20) Consistent use of as little as 7.5 g/day of acetaminophen is hazardous.
- 21) Efforts to limit over-the-counter acetaminophen package size and to restrict the prescription of narcotic-acetaminophen combinations [like Vicodin] may be necessary to reduce the incidence of acute liver failure in the United States.