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Acetaminophen May Be a Leading Cause of Acute Liver Failure **CME**

News Author: Laurie Barclay, MD

CME Author: Penny Murata, MD

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Dec. 5, 2005 — In the United States, 42% of acute liver failure (ALF) is caused by acetaminophen, according to the results of a multicenter, prospective cohort study reported in the December issue of *Hepatology*. Accidental overdose is the leading cause, but suicidal ingestion is also important.

“Acetaminophen, the most widely used analgesic in the United States, causes severe hepatic necrosis leading to ALF after suicidal overdoses,” write Anne M. Larson, MD, and the Acute Liver Failure Study Group from the University of Washington Medical Center in Seattle, and colleagues. “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 toxicity, but this remains controversial.”

At 22 U.S. tertiary care centers, the investigators gathered detailed prospective data for a 6-year period on 662 consecutive patients who fulfilled standard criteria for ALF with coagulopathy and encephalopathy. Of these 662 cases, 275 (42%) were determined to result from acetaminophen-induced liver injury.

During the study, the annual percentage of acetaminophen-related ALF rose from 28% in 1998 to 51% in 2003. The median dose ingested was 24 g, equivalent to 48 extra-strength tablets. Of these 275 cases of acetaminophen-induced ALF, 131 (48%) were unintentional overdoses, 122 (44%) were suicide attempts, and 22 (8%) were of unknown intent.

In the unintentional group, 81% reported taking acetaminophen and/or other analgesics for acute or chronic pain syndromes; 38% took 2 or more acetaminophen preparations simultaneously; and 63% used narcotic-containing compounds.

Of the 275 patients with acetaminophen-induced ALF, 178 (65%) survived; 74 (27%) died without transplantation; and 23 patients (8%) underwent liver transplantation, of whom 71% were alive at 3 weeks. The intentional and unintentional groups had similar rates of transplant-free survival and liver transplantation.

“Acetaminophen hepatotoxicity far exceeds other causes of acute liver failure in the United States,” the authors write.

“Susceptible patients have concomitant depression, chronic pain, alcohol or narcotic use, and/or take several preparations simultaneously. Education of patients, physicians, and pharmacies to limit high-risk use settings is recommended.”

Study limitations include restriction to severely ill subjects who meet criteria for ALF, difficulty in determining the true incidence of ALF in the population at large, and difficulty with accurate history-taking in patients with altered mentation.

“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,” the authors conclude. “However, precise information on dosing is often difficult to acquire in some of these patients. We are planning to look at this issue in more detail in a future study.”

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In an accompanying editorial, John G. O’Grady, MD, from King’s College Hospital in London, United Kingdom, notes the potential for unnecessary transplants, as 59% of patients listed for transplantation but who were not allocated an organ survived. Another conundrum is whether the patient who had unintentional hepatotoxicity should be salvaged at all costs, while liver transplantation is selectively offered to patients with intentional liver injury.

“Measures to minimize acetaminophen hepatotoxicity are important but need to be considered in the context that the apparent scale of the problem is a reflection of the huge number of patients taking acetaminophen with good effects and in the absence of any adverse event,” Dr. O’Grady writes. “Educational initiatives to highlight the range of preparations containing acetaminophen, together with reiteration of advice on maximum daily dosing, have potential benefits, especially with respect to unintentional overdosing. Restriction of access to acetaminophen is an alternative, and this approach was taken in the United Kingdom in 1998, when over-the-counter sales of acetaminophen were restricted to 16 g.”

Although this resulted in a 30% reduction in patients with severe acetaminophen-induced ALF admitted to specialist liver units and liver transplant centers for the next 4 years. Dr. O’Grady writes that “The required judgment from society, the medical profession, and other interested parties, is whether that level of restriction is too high a price to pay.”

Hepatology. 2005;42:1252-1254, 1364-1372

Learning Objectives for This Educational Activity

Upon completion of this activity, participants will be able to:

- Describe the incidence and risk factors of patients with acetaminophen-induced ALF.
- Describe outcomes of patients with ALF following unintentional vs intentional ingestion of acetaminophen.

Clinical Context

Hepatotoxicity from intentional or unintentional acetaminophen ingestion can lead to ALF. Unintentional acetaminophen ingestion might occur from self-medication in doses exceeding package recommendations of 4 g/day and is generally identified when the patient becomes symptomatic. Hence, many of these patients would not receive *N*-acetylcysteine within the treatment window needed to prevent hepatic injury. Alcohol use could play a role in the toxic effects of acetaminophen.

In the July 1999 issue of *Liver Transplantation Surgery*, Schiodt and colleagues reported a 20% incidence of acetaminophen toxicity, resulting in ALF. The authors of the current study, Larson and colleagues, participated with the Acute Liver Failure Study Group to investigate the epidemiology and outcomes of ALF in the United States. The authors hypothesized that patients with unintentional acetaminophen overdose would present with more severe disease, higher rate of alcohol abuse, and poorer rate of spontaneous transplant-free survival compared with intentional overdose patients.

This is a prospective study to evaluate the incidence, risk factors, and outcomes of a cohort of patients with acetaminophen-related ALF enrolled in the Acute Liver Failure Study Group registry.

Study Highlights

- Of 662 patients with ALF (international normalized ratio of at least 1.5, hepatic encephalopathy, and presentation within 26 weeks of onset of illness) enrolled for more than 6 years, 275 (42%) had acetaminophen-related hepatotoxicity based on ingestion of more than 4 g/day of acetaminophen within 7 days of presentation, serum acetaminophen detected, or serum alanine aminotransferase levels more than 1,000 IU/L with history of acetaminophen ingestion. Exclusion criteria

included acute hepatitis A and B and other causes of ALF.

- Acetaminophen was the most common cause of ALF, increasing to 51% in year 6; overall, 74% were female, and 88% were white. The median ingestion dose was 24 g (range, 1.2 - 180 g).
- 44% (122/275 patients) reported intentional ingestion (single ingestion, suicidal intent); 48% (131 patients) reported unintentional ingestion (multiple ingestions to relieve symptoms, no suicidal intent); and 8% (22 patients) had unclear reason. The 2 groups were similar in past substance abuse and educational level.
- Unintentional group was older (median, 38 years [range, 18 - 76]) vs intentional group (median, 32 years [range, 17 - 68]; $P = .002$) and had higher rate of multiple acetaminophen-containing preparation use (38% vs 5%; $P = .0001$). Prescription narcotic/acetaminophen compound use was reported by 44% overall (120/275) and more common in the unintentional group than intentional group (63% vs 18%; $P < .0001$).
- Although unintentional group had lower rate of depression (24% vs 45%; $P = .001$) than the intentional group, antidepressant use was similar (37% vs 38%).
- 35% (68/196) met criteria for alcohol abuse (daily consumption at least 40 g of alcohol in men and 20 g in women); 55% (151/273) reported alcohol use. Alcohol abusers had lower acetaminophen levels, lower rates of antidepressant and compound narcotic use, and lower rates of severe hepatic encephalopathy than nonabusers.
- 7% (19/275) of patients were in a low-dose group that took no more than 4 g/day of acetaminophen. The low-dose group was older and reported more unintentional overdose (74% vs 40%; $P < .002$), alcohol use (79% vs 59%; $P = .09$), and alcohol abuse (65% vs 37%; $P = .02$) than the higher-dose group.
- More unintentional patients had hepatic encephalopathy initially (55% vs 39%; $P = .002$), but the 2 groups had similar peak hepatic encephalopathy grade and number of patients listed for transplantation. Unintentional and intentional groups had similar transplant-free survival (64% vs 66%) and liver transplantation (9% vs 7%) rates.
- 71% (196/275) of patients were alive at 3-week outcome period. 65% (178/275) survived without liver transplantation; 27% (74) died; and 8% (23) underwent transplantation.
- On admission, 40 patients met King's criteria for liver transplantation; 19 died without transplant. Of 235 patients who did not meet King's criteria, 163 patients survived without transplant, 55 died without transplant, and 17 patients underwent transplant.
- The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was described for 216 patients; patients with score of at least 20 had lower transplant-free survival (43% vs 92%; $P < .0001$) and higher transplant rate (13% vs 1%; $P = .002$) than patients with a score higher than 20. APACHE II score use had a higher sensitivity (68% vs 26%) and lower specificity (87% vs 92%) than King's criteria on admission.
- Study limitations include patients' mental status affecting accuracy of history, and many cases were not enrolled due to lack of data or consent. Authors speculate there is a narrow therapeutic margin and patients might be unaware of hazards of multiple acetaminophen-containing products.

Pearls for Practice

- Acetaminophen-induced hepatotoxicity is the leading cause of ALF in the United States; susceptible patients include those with chronic pain, depression, substance abuse, alcohol or narcotic use, and multiple acetaminophen-containing product use.
- Patients with ALF following unintentional or intentional acetaminophen overdose have similar rates of transplant-free survival and liver transplantation.

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News Author

Laurie Barclay, MD

is a freelance writer for Medscape.

Disclosure: Laurie Barclay, MD, has disclosed no relevant financial relationships.

Clinical Reviewer

Gary Vogin, MD

Senior Medical Editor, Medscape

Disclosure: Gary Vogin, MD, has disclosed no relevant financial relationships.

CME Author

Penny Murata, MD

is a freelancer for Medscape.

Disclosure: Penny Murata, MD, has disclosed no relevant financial relationships.

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