

Acetaminophen: Most common cause of acute liver failure in US

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Seattle, WA- Acetaminophen/ paracetamol, the most widely used analgesic in the US, has become the most common cause of acute liver failure (ALF), US researchers report in the December 2005 issue of *Hepatology* [[1](#)].

"We were surprised that the incidence of acetaminophen ALF has risen in the US over the years," says lead researcher **Dr Anne Larson** (University of Washington Medical Center, Seattle). "This was rather alarming, particularly since half the cases were accidental (unintentional)," she tells *rheumawire* .

The researchers belong to the **Acute Liver Failure Study Group**, set up in 1997 by **Dr William Lee** (University of Texas Southwestern Medical Center, Dallas), the senior author on the current paper. "The percentage of all ALF cases in our registry that were due to acetaminophen has nearly doubled in six years," they report.

Before the 1980s, there was no mention of acetaminophen as a cause of ALF, they comment. A US retrospective study from 1994 to 1996 found a 20% incidence of acetaminophen toxicity leading to ALF. Now, their own study found an increase in the annual percentage of acetaminophen-related ALF from 28% in 1998 to 51% in 2003.

Half of cases were accidental overdose

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"One of the most alarming findings in our study was that unintentional acetaminophen overdose accounted for half of the cases," the researchers comment. This is a much higher rate than has been reported from other countries: the rate of unintentional overdose has been estimated at 31% in Australia, and nonsuicidal overdoses are only rarely reported in the UK and

in Europe, they note.

The team found that of 275 cases of ALF resulting from acetaminophen liver injury, unintentional overdoses accounted for 131 cases (48%), intentional overdose (ie, suicide attempts) for 122 cases (42%), and the remaining 22 cases (8%) were of unknown intent. The clinical picture and outcomes were similar for the intentional and unintentional overdoses, with a mortality rate of 29% and liver transplantation in 7% and 9% of cases, respectively. Although the serum levels of acetaminophen were lower in the cases due to unintentional overdose, these patients were more likely to have severe hepatic encephalopathy on admission, perhaps because they had waited longer before seeking medical care (median of four days after symptom onset vs one day for the intentional group).

In many of the cases of unintentional overdose with acetaminophen, there appeared to be multiple factors at play, the researchers comment. This group was more likely to be taking several different products containing acetaminophen (38%), and they were more likely to be using prescription products containing a combination of acetaminophen with narcotics (63%). The most popular of these was Vicodin (acetaminophen with hydrocodone, Abbott Laboratories). Another issue was that individuals were taking more tablets than the maximum of 4 g daily recommended on product package inserts; the mean daily dose in this group was 7.5 g (1.0-7.8 g).

"Patients with chronic pain appear to be particularly susceptible to this problem," Larson et al comment. Most of the cases in the unintentional-overdose group reported taking the products specifically for pain (79%). The most common causes of chronic pain that were mentioned were chronic back pain and headache, but fibromyalgia, rheumatologic pain, and orthopedic pain all featured as reasons that individuals were using acetaminophen products.

"Many claimed to have ingested modest amounts of acetaminophen over weeks or months," the researchers comment "Why, then, the sudden onset of severe liver injury? Our data suggest that there is a narrow therapeutic margin and that consistent use of as little as 7.5 mg/day may be hazardous." The researchers also note that some of the cases resulted after less than seven days of ingestion, which suggests "that there is no chronic form of injury, but rather a threshold of safety that may be breached

with devastating results."

More than half used OTC products

Our data suggest that there is a narrow therapeutic margin and that consistent use of as little as 7.5 mg/day may be hazardous.

More than half of all the ALF cases in this study (147 subjects, 53%) were using over-the-counter acetaminophen products. The researchers note that a third of patients who were using narcotics also took an OTC acetaminophen product, which points to a lack of awareness of the hazards of using OTC products in combination with prescription drugs.

Unintentional overdose is now the leading form of acetaminophen hepatotoxicity in US ALF subjects, the researchers point out, although they add that suicidal ingestion remains important as well. "Efforts to limit OTC package size and to restrict the prescription of narcotic-acetaminophen combinations (or to separate the narcotic from acetaminophen) may be necessary to reduce the incidence of this increasingly recognized but preventable cause of ALF in the US."

Restrictions on OTC package sizes of acetaminophen are already in place in the UK, and they have reduced the problem, comments **Dr John O'Grady** (Institute of Liver Studies, King's College Hospital, London, UK) in an accompanying editorial [[2](#)]. The UK introduced a maximum 16-g pack size for OTC acetaminophen in 1998, and in the four years following that change in legislation, there was a 30% reduction in the number of patients with severe acetaminophen-induced acute liver failure admitted to specialist liver units and liver transplant centers [[3](#)]. Even more severe restrictions operate in France (where the maximum packet size is 8 g), and this measure is highly effective in minimizing severe acetaminophen hepatotoxicity, he adds.

In contrast, OTC acetaminophen products are freely available in the US and are sold in large packs in supermarkets and other stores. "People can buy megabottles of it," says Larson, adding that "it's advertised as completely safe." In addition, acetaminophen is contained in many different products, such as cold remedies, flu remedies, headache tablets, etc. "As a group, the Acute Liver Failure Study Group believes that there should be some restrictions on acetaminophen in the US similar to what has been

done in the UK." In addition to restrictions on pack sizes in the UK, there is also widespread use of blister packs.

"The most alarming part of our findings was the unintentional poisoning," Larson tells **rheumawire** . "This is a completely preventable problem with proper education (of physicians, pharmacists, and consumers) and medication packaging."

"The most important message we have is EDUCATION!" she says. Patients should always be informed what is in the preparations they're being given (eg, told that Vicodin contains acetaminophen), and they should be strongly counseled against polypharmacy. Patients must be taught to read labels and not to combine products, she adds.

Sources

1. Larson A, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology* 2005; 42:1364-1372. [Abstract](#)
2. O'Grady JG. Broadening the view of acetaminophen hepatotoxicity. *Hepatology* 2005; 42:1252-1254. [Abstract](#)
3. Hawton K, Simkin S, Deeks J, et al. UK legislation on analgesic packs: before and after study of long-term effect on poisonings. *BMJ* 2004; 329:1076. [Abstract](#)

