Risk Factors Predict Acetaminophen Hepatotoxicity

BY MITCHEL L. ZOLER
Philadelphia Bureau

Patients hospitalized for acetaminophen overdose had a 4.5% rate of acetaminophen-induced hepatotoxicity in a population-based study, according to Dr. Robert P. Myers and his associates.

In a multivariate analysis of residents of Calgary and southern Alberta (Canada) during 1995-2004, significant risk factors for acetaminophen hepatotoxicity were alcohol abuse, preexisting liver disease, and unintentional ingestion, the authors said (Clin. Gastroenterol. Hepatol. 2008 August [Epub doi:10.1016/j.cgh.2008.02.053]).

"These findings highlight the necessity of educational initiatives regarding the potential hazards of acetaminophen, particularly in the high-risk groups that we have identified.

In addition, clear labeling of medications with their acetaminophen content must be ensured so as to minimize unintentional overdoses," wrote Dr. Myers, from the liver unit in the department of medicine at the University of Calgary, and his colleagues.

The findings also highlighted the substantial clinical impact that acetaminophen-induced hepatotoxicity can have. At the same time, the findings "reassuringly" showed that acetaminophen hepatotoxicity is uncommon following an overdose, supporting the "relatively benign" nature of most overdoses, the authors said. More than 95% of the overdose episodes did not result in liver damage.

The researchers used administrative databases to track the outcomes of patients hospitalized for acetaminophen overdose in Calgary and southern Alberta during a 10-year period.

The analysis identified 1,543 patients who had 1,680 hospital admissions for acetaminophen overdose during the study period. About 68% were women, and their average age was 26 years, with a range of 0-96 years old. Depression was diagnosed in 55% of the patients, and 34% were diagnosed with alcohol abuse. Underlying liver disease was found in 3% (46 patients), including 11 patients with cirrhosis (0.7%).

The overdoses were deemed intentional in 85%, unintentional in 13%, and other in 2%. The rate of unintentional overdoses rose with age. Among patients younger than 30 years, 9% had unintentional overdoses, which rose to 15% among those aged 30-49 years, and 30% among patients aged 50 years or older (Clin Gastroenterol Hepatol. doi:10.1016/j.cgh.2008.02.053).

Patients with unintentional overdoses had a lower prevalence of depression—18%, compared with 60% among depressed patients—but the prevalence of alcohol abuse was similar among those whose overdoses were unintentional (36%) and intentional (33%). Liver disease was more common among the patients with unintentional overdoses, 14%, than in those with intentional overdoses, 1.3%.

The incidence of hepatotoxicity increased among patients with two or more of the three independent risk factors for developing hepatotoxicity: alcohol abuse, preexisting liver disease, and unintentional overdose. In patients with none of these risk factors, 1.3% developed hepatotoxicity. In those with one risk factor, the hepatotoxicity rate rose to 5%. It was 19% in patients with two risk factors and 52% in those with all three risk factors.

A multivariate analysis of long-term survival among the patients hospitalized for acetaminophen overdose showed that older age, male gender, lower income, greater number of comorbidities, and acetaminophen-triggered hepatotoxicity were all significantly linked with lower survival.

Recent data suggest that the incidence of acetaminophen overdose is on the rise. Data from Calgary and southern Alberta indicated a 24% increase in the rate of unintentional overdoses during 1995-2004. ■

Indeterminate Liver Failure Is Often Due to Acetaminophen

BY ALICIA AULT
Associate Editor, Practice Trends

SAN DIEGO — As many as 18%-20% of cases of indeterminate acute liver failure may be the result of unrecognized acetaminophen toxicity, according to a presentation at the annual Digestive Disease Week.

The etiology is unknown in about 15% of cases of acute liver failure (ALF), said Dr. Niraj Khandelwal of the University of Texas, Dallas.

Using a novel assay that detects acetaminophen (APAP) protein adducts, the Acute Liver Failure Study Group had determined in a previous study that adducts were present in 7 (19%) of 36 cases diagnosed as indeterminate ALF. The APAP adduct levels were comparable with those seen in patients with known acetaminophen overdose (Gastroenterology 2006;130:687).

To further evaluate indeterminate ALF, the authors conducted a larger study using a newer assay—high-performance liquid chromatography with electrochemical detection (HPLC-EC)—that is more efficient and more sensitive, said Dr. Khandelwal.

The assays were conducted on sera from 113 patients in the ALF Study Group registry. The serum samples were taken on the first or second day after admission and were collected from 1998 to 2006.

Of the 113, there were 32 with known APAP overdose, 93 who were adduct negative, and 20 who were adduct positive (defined using a cut point of 1 nmol/mL). Of those 20 patients, 9 (45%) died or received transplants, and 11 (55%) spontaneously survived. Eight patients were given *N*-acetylcysteine (NAC), and six (75%) of those eight patients survived. Only 5 patients of the 11 who spontaneously survived did so without NAC.

The clinical and lab findings of the patients who had adducts equal to or greater than 1 nmol/mL were consistent with findings—including very high aminotransferases, low bilirubin, and favorable outcome—for known APAP overdose patients, most of whom were female. Of the patients in the positive adduct group, 80% were female. The median bilirubin level was 5.05 mg/dL, compared with 24.5 mg/dL for patients with negative adducts (less than or equal to 1 nmol/mL).

The study confirms previous data showing that as many as one in five patients with indeterminate ALF actually has unrecognized acetaminophen toxicity, said Dr. Khandelwal. Given these data and the lack of an adduct assay that can be used at the bedside in real time, NAC should be considered in patients with indeterminate ALF who match the biochemical profile for APAP overdose, he said.

Dr. Khandelwal said he had no disclosures to report. ■