Prescribed Drugs, Supplements Tied to Liver Injury

Antimicrobials are the most frequent offenders, with some CNS and immunomodulatory agents following.

BY MARY ANN MOON
Contributing Writer

A wide variety of prescription and nonprescription medications and nutritional supplements are at the root of drug-induced liver injury in the United States.

Moreover, combinations of potentially hepatotoxic agents, rather than single agents, account for at least 20% of cases reported to the Drug-Induced Liver Injury Network (DILIN), a registry of clinically significant cases and a repository of biological specimens established in 2003. The registry is run cooperatively by the National Institutes of Health and five academic clinical centers.

That percentage is much higher than was reported in a recent European study, and it may reflect greater use of medications in the U.S. population, Dr. Naga Chalasani and his colleagues reported (J. Gastro. 2008 December [Epub doi:10.1053/j.gastro.2008.09.011]).

Dr. Chalsani, professor of medicine at Indiana University, Indianapolis, and his associates described the cases and short-term outcomes of the first 300 subjects reported to this registry and enrolled in an ongoing prospective study. The researchers hope the registry and study will furnish data for further research on the etiology and prevention of drug-induced liver injury.

The 300 subjects were enrolled in 2004-2007. Of the group, 93% were adults, including 18% who were older than 65 years. The severity of liver damage was judged to be mild in 27%, moderate in 19%, moderate requiring hospitalization in 33%, severe in 15%, and severe requiring transplant or precipitating death in 6%.

Single prescription medication was the likely cause of the liver injury in 73% of the cases. Multiple prescription medications or a combination of prescription medicine and dietary supplements were the cause in 18%. Single or multiple dietary supplements were the cause in the remaining 9%.

Dietary supplements that caused liver injury included those taken to build muscle, lose weight, cure insomnia, prevent colds, boost energy, and control menopausal symptoms. Many patients were using multiple dietary supplements and, even when a single dietary supplement caused the liver damage, it often contained multiple herbal or nutritional components.

Among prescription medicines, antimicrobials (including antibacterials, antivirals, and antifungals) were the most frequent offenders, causing liver damage in over 45% of cases. This finding is in accord with the results of previous studies.

The reason why antimicrobials have such a propensity to cause liver damage is not yet known. It may be related to the generally high usage of antimicrobials in the U.S. population, or it may be that patients' underlying infection and inflammation confer increased susceptibility to liver injury, Dr. Chalsani and his associates said.

CNS agents such as antiepileptics, antidepressants, and antipsychotics were the likely cause of liver damage in 15% of cases, immunomodulatory agents were the likely cause in 5%, analgesics in 5%, antineoplastic drugs in 4%, antihypertensives in 5%, and lipid-lowering agents in 3%.

The most common single prescription drugs that caused liver injury in registry patients were amoxicillin/clavulanate (23 cases), nitrofurantoin (13 cases), isoniazid (13 cases), and trimethoprim-sulfamethoxazole (13 cases).

This observational study did provide information "of practical relevance in monitoring and counseling patients with drug-induced liver injury," the investigators noted.

First, serum bilirubin reached its peak an average of 1 week after diagnosis, regardless of the patient's age, the pattern of liver injury, or the causative agent. In patients who developed jaundice, the condition took nearly a month on average to resolve; jaundice took even longer to resolve in elderly patients and in those whose liver injury was caused by dietary supplements rather than by medications.

Second, diabetes was a strong independent risk factor for severe drug-induced liver injury. Diabetes has not been considered as a possible confounding factor in previous studies of drug-induced liver injury, Dr. Chalsani and his associates said.

Third, acute hepatitis C infection should be thoroughly ruled out before attributing a case of acute liver injury to acute drug exposure. Several patients in this series had liver damage thought to be unrelated to acute hepatitis C because they initially tested negative for the virus and reported no risk factors. However, they later seroconverted.

"As better diagnostic tests become available for specific causes of acute liver injury, more cases of suspected drug-induced liver injury may be found to have other etiologies," the investigators noted.

The DILIN and this study were supported by the National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Chalsani is a paid consultant to Takeda Pharmaceuticals, AtheroGenics Inc., Advanced Life Sciences, Kari Bio, Metabasis, Pfizer Inc., and Eli Lilly & Co. He received grant support from Debiovision Inc. and Sanofi-Aventis. On his behalf, Indiana University has initiated contract negotiations with Gilead Sciences Inc. and Pfizer for conducting clinical trials unrelated to drug-induced liver injury. In addition, Dr. Chalsani has served as a defendant's expert witness for a product liability litigation involving suspected drug-induced liver injury. ■

Family History Is Key After a Serious Gastroesophageal Event

BY BETSY BATES
Los Angeles Bureau

DENVER, COLO. — A careful physical examination and history, with special attention to the family history, will detect most infants with gastroesophageal reflux who need an intensive work-up following an apparent life-threatening event, according to a review of 313 cases.

Apparent life-threatening events (ALTEs), which include observation of a color change, apnea, alteration in muscle tone, choking, and/or gagging, can have benign or pathologic etiologies, explained Dr. Ami Doshi at a meeting on pediatric hospital medicine, sponsored by the Academic Pediatric Association, American Academy of Pediatrics, and Society of Hospital Medicine.

"The overwhelming majority of patients look great by the time they present for medical attention," said Dr. Doshi, of the Rady Children's Hospital and Health Center in San Diego.

Nonetheless, diagnostic uncertainty leads to expensive testing and sometimes lengthy hospitalization.

"This is not just an unclear entity, but also an incredibly common one," she said. "These patients account for 2%-3% of pediatric inpatient visits in children under 1 year old."

There is no standardized work-up, although a number of studies have attempted to elucidate which tests and predictive factors might distinguish healthy infants who could be safely discharged after an initial hospital evaluation, and which require more intensive investigation.

'This is not just an unclear entity, but also an incredibly common one. These patients account for 2%-3% of pediatric inpatient visits in children under 1 year old.'

One study of 59 previously healthy infants, for example, found that 14% of hospitalizations were ultimately proven necessary, and that a history of multiple ALTEs in 24 hours and age of 1 month or younger had a combined negative predictive value of 100% (Pediatrics 2007;119:679-83).

Dr. Doshi and her associates were particularly interested in the 26%-54% of children with ALTEs whose working or final diagnosis was gastroesophageal reflux (GERD).

They conducted a retrospective chart review of cases in children up to 1 year old who were admitted with such events over a 3-year period at the tertiary children's hospital, which sees 800,000 patients a year. The hospital had developed a specific billing code for ALTEs that simplified the collection of cases. Only cases with at least a 6-month follow-up were included. The average age of babies included in the analysis was 2.1 months. Nearly half were Hispanic, reflecting the hospital's catchment area. Their length of stay was 2.5 days, ranging from 1 day to 66 days. In nearly 40%, a choking episode was the reported ALTE.

Roughly one-third were transported by emergency medical professionals, and 13% required rescue breaths.

An unusual family history was present in 15%.

The discharge diagnosis was GERD or upper respiratory illness in 80% of patients—a 96.6% concordance with the working diagnosis at admission. The "overwhelming majority" of GERD patients appeared well at the time of presentation, Dr. Doshi said.

Ten patients, however, suffered an event in the hospital, including central apnea, choking, oxygen desaturation, or cyanosis. One patient had a seizure and another, viral sepsis. All of these high-risk patients were less than 2.5 months old and 6 were born prematurely. Four had a concomitant diagnosis of bronchiolitis or upper respiratory infection.

"All 10 of these patients' events were directly attributable either to their prematurity or an intercurrent illness, rather than any new, unexpected, undetected diagnosis which we simply did not pick up at the time of admission," she said during her oral presentation at the meeting. "Also, reassuringly, none of these 10 patients came back with a recurrent apparently life-threatening event or repeat admission."

A 6-month follow-up found that 13 of the original 313 patients did suffer a recurrent ALTE, in most cases again due to GERD. These events occurred between 2 weeks and 5 months following discharge.

Other diagnoses in children with a recurrent ALTE included pertussis in one child, seizures in three, and cardiovascular abnormalities in two.

Clues to these later diagnoses were present in the records from the earlier admission, she said, either through noted symptoms such as noisy breathing (in the cardiac patients) or family history.

The family history repeatedly emerged as an important risk factor in the study. It was predictive of both a pathological diagnosis other than GERD and a recurrent ALTE in children with a final GERD diagnosis.

An abnormal family history was considered one that included seizures, genetic disease, congenital heart disease, failure to thrive, developmental delay, sudden infant death syndrome, or infant death(s). ■