

Risk Factors Predict Acetaminophen Hepatotoxicity

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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 al-

cohol 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. ■

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1%); Libido Decreased (3% and 1%); **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%); **Urogenital:** Ejaculation Disorder* (9% and <1%); Impotence (3% and <1%); Anorgasmia (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. *Primarily ejaculatory delay. -Denominator used was for males only (N=225 Lexapro; N=188 placebo). -Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were: nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). **TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Percentage of Patients Reporting Event) Body System/Adverse Event (Lexapro (N=429) and Placebo (N=427)).** **Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder* (14% and 2%); Anorgasmia* (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. *Primarily ejaculatory delay. -Denominator used was for males only (N=182 Lexapro; N=195 placebo). -Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of \geq 1% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4. Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125); Insomnia (4%, 7%, 14%); Diarrhea (5%, 6%, 14%); Dry Mouth (3%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating Increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 6%); Indigestion (1%, 2%, 6%).** *Adverse events with an incidence rate of at least 5% in either the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Adverse Event: Lexapro (N=407) and Placebo (N=383)); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=737) and Placebo (N=636)); Libido Decreased (3% and 1%); Anorgasmia (3% and <1%).** There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priligis has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes:** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes:** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes:** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes:** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1426 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. **Cardiovascular - Frequent:** palpitation, hypertension. **Infrequent:** bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. **Central and Peripheral Nervous System Disorders - Frequent:** light-headed feeling, migraine. **Infrequent:** tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tic, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. **Gastrointestinal Disorders - Frequent:** heartburn, abdominal cramp, gastroenteritis. **Infrequent:** gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. **General - Frequent:** allergy, pain in limb, fever, hot flushes, chest pain. **Infrequent:** edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. **Hemic and Lymphatic Disorders - Frequent:** bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. **Metabolic and Nutritional Disorders - Frequent:** increased weight. **Infrequent:** decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. **Musculoskeletal System Disorders - Frequent:** arthralgia, myalgia. **Infrequent:** jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. **Psychiatric Disorders - Frequent:** appetite increased, lethargy, irritability, concentration impaired. **Infrequent:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruising, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. **Reproductive Disorders/Female* - Frequent:** menstrual cramps, menstrual disorder. **Infrequent:** menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. **N-905 Respiratory System Disorders - Frequent:** bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. **Infrequent:** asthma, breath shortness, laryngitis, pneumonia, tracheitis. **Skin and Appendages Disorders - Frequent:** rash. **Infrequent:** pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. **Special Senses - Frequent:** vision blurred, tinnitus. **Infrequent:** taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. **Urinary System Disorders - Frequent:** urinary frequency, urinary tract infection. **Infrequent:** urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing spontaneous and clinical trial experience and were not observed during the premarketing evaluation of escitalopram: Blood and Lymphatic System Disorders: hemolytic anemia, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, cardiac failure, myocardial infarction, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma. Gastrointestinal Disorders: gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait. Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction. Investigations: electrocardiogram QT prolongation, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hypoglycemia, hypokalemia. Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis. Nervous System Disorders: akathisia, choreoathetosis, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoesthesia, myoclonus, neuroleptic malignant syndrome, nystagmus, seizures, serotonin syndrome, tardive dyskinesia. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, anger, delirium, delusion, nightmare, paranoia, visual hallucinations. Renal and Urinary Disorders: acute renal failure. Reproductive System and Breast Disorders: priapism. Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism. Skin and Subcutaneous Tissue Disorders: angioedema, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, hypotension, orthostatic hypotension, phlebitis thrombosis. Forest Pharmaceuticals, Inc. Subsidiary of Forest Laboratories, Inc. 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Indeterminate Liver Failure Is Often Due to Acetaminophen

BY ALICIA AULT
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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. ■