

P & T News

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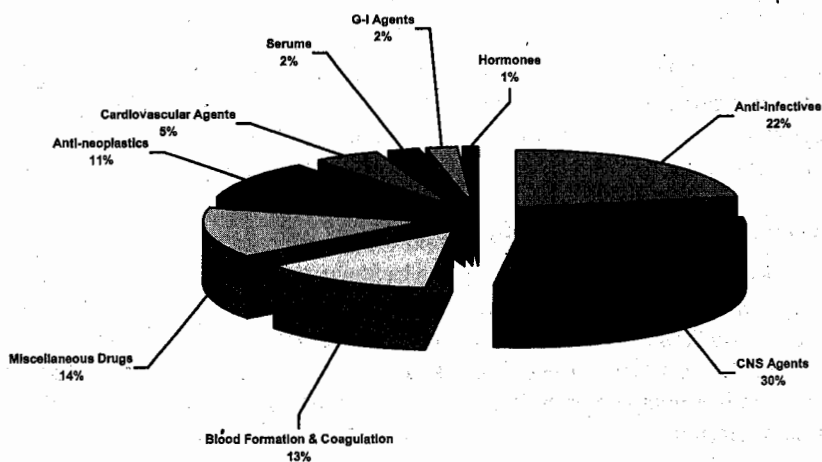
ADVERSE DRUG REACTION (ADR) REPORTING PROGRAM: UPDATE AND RECENT DRUG SAFETY WARNINGS

Kevin Bebout, R.Ph.

During fiscal year 2004-2005, the Pharmacy and Therapeutics (P&T) Subcommittee reviewed 287 direct adverse drug reaction (ADR) reports; an additional 922 ADR notifications were automatically submitted electronically to the UIHC ADR Reporting Program via INFORMM Patient Record (IPR). From all of these reports, 6 were subsequently submitted to the Food and Drug Administration (FDA) via the MedWatch Program because they were identified as severe, unusual, or occurring with a newly marketed drug.

During the year, the ten most frequently reported causative agents at UIHC were: **iohexol, warfarin, morphine, vancomycin, heparin, phenytoin, paclitaxel, nafcillin, oxaliplatin, and parenteral nutrition solutions** (see Figure 1 for a summary of the agents and drug classes associated with ADRs). As in years past, anti-infective agents and drugs that affect the central nervous system were associated with over one half of all ADR reports submitted directly to the UIHC ADR Reporting Program. Within these two therapeutic drug classes, beta-lactam antibiotics (including penicillins and cephalosporins) were identified 36 times, and opioids 29 times. It should also be noted that anticoagulants and blood formation modifying drugs were likewise associated with a substantial number of adverse reactions (41 reports total).

Figure 1: ADRs by Drug Class



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The Important Role of Health Care Professionals

All health care professionals must perform vigilant post-marketing surveillance in order to continue the necessary monitoring after new agents reach the market. New data are used to update the prescribing information of recently approved agents and, in some cases, drug entities that have been marketed for years.

Whenever you become aware of an adverse drug reaction (whether in the inpatient or ambulatory care environments), please complete and submit an adverse drug reaction incident report using IPR. Look for "Adverse Drug Reaction (NOT Med Error)" under IPR's Incident Reporting tab (a blank form as provided by IPR is depicted below). All ADR reports submitted via IPR are automatically forwarded to the UIHC ADR Reporting Program for review and summary report generation for the Pharmacy and Therapeutics Subcommittee; no additional notifications are required. Alternatively, staff who wish to report an adverse drug reaction may telephone the Drug Information Center at 6-2600.

THE UNIVERSITY OF IOWA HOSPITALS AND CLINICS		Patient Adverse Drug Reaction Report				Adverse Drug Reaction Number		
Patient Information								
Name	ID	Gender	Date of Birth	Age				
Adverse Drug Reaction Medication								
Medication	Dozes : Strength/Volume	Route	Occurrence Start Date	Occurrence End Date	Occurred Unit	Dept / Service	Attending Physician	
Reaction(s)								
Severity / Concurrent Medications								
Causality								
Preventability								
Author Comments								
Provider Comments								
Physician Comments								
Pharmacist / FDA / P.E. T. Submitter								

An ADR Form May Be Completed and Submitted via IPR

Recent Drug Safety Warnings

In recent months, the FDA and/or drug manufacturers have distributed new nationwide safety warnings and instituted labeling changes on various prescription drug products prompted by submission of adverse drug event reports to the MedWatch Program and because of findings in post-marketing safety studies. New warnings and revised product labeling, which are summarized below, have been issued for atomoxetine, pimecrolimus ointment, tacrolimus ointment, duloxetine, and telithromycin.

Atomoxetine-Associated Liver Dysfunction

The FDA directed Eli Lilly to revise the labeling for Strattera® (atomoxetine) to include a bolded warning statement regarding the potential for severe liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after atomoxetine is discontinued. Patients should be counseled to seek medical attention if they experience signs and symptoms of liver dysfunction (e.g., pruritus, jaundice, dark urine, upper right-sided abdominal tenderness, or unexplained "flu-like" symptoms). **Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury; therapy should not be restarted.**

Atomoxetine is currently approved in the United States to treat ADHD in children, adolescents, and adults; it has not been studied in children under 6 years of age. This product is currently included on the UIHC Formulary.

Adapted from FDA Talk Paper, December 17, 2004

Pimecrolimus and Tacrolimus Ointment-Associated Malignancies

The FDA, Astellas Pharma (maker of Protopic® Ointment [tacrolimus]), and Novartis Pharmaceuticals (maker of Elidel® Cream [pimecrolimus]) updated labeling for these two topical eczema drugs with a boxed warning about a possible risk of cancer. Rare cases of malignancy (e.g., skin cancer and lymphoma) have been reported in patients treated with topical pimecrolimus and tacrolimus. Therefore, continuous, long-term use in any age group should be avoided and application limited to areas of involvement with atopic dermatitis. The labeling changes include clarification that these drugs are recommended for use as second-line treatments; other prescription topical agents should be tried first. **Use of these drugs in children under 2 years of age is not recommended.** In addition, a Medication Guide (with FDA-approved patient labeling) must be distributed to help ensure that patients using these prescription medicines are aware of this concern. These products are currently included on the UIHC Formulary.

From FDA News, January 19, 2006

Duloxetine-Associated Liver Toxicity

The FDA and Eli Lilly notified healthcare professionals of a revision to the PRECAUTIONS/Hepatotoxicity section of the prescribing information for Cymbalta® (duloxetine), indicated for treatment of major depressive disorder and diabetic peripheral neuropathic pain. Postmarketing reports of hepatic injury (including hepatitis and cholestatic jaundice) suggest that patients with preexisting liver disease who take duloxetine may have an increased risk for further liver damage. The new labeling extends the Precaution against using duloxetine in patients with substantial alcohol use to include those patients with chronic liver disease. It is recommended that duloxetine not be administered to patients with any hepatic insufficiency. Duloxetine is restricted at UIHC to prescribing by the Pain Medicine Service.

PRECAUTIONS

Hepatotoxicity — Cymbalta® increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta®-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In the full cohort of placebo-controlled trials in any indication, 1% (39/3732) of Cymbalta-treated patients had a >3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, **Cymbalta® should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.**

"Dear Healthcare Professional" Letter,
October 5, 2005
Eli Lilly and Company

Telithromycin-Associated Liver Toxicity

During January, 2006, *Annals of Internal Medicine* published on-line an article reporting three patients who experienced **serious liver toxicity, including death**, following administration of telithromycin (Ketek®, manufactured by Aventis Pharmaceuticals). These cases have also been reported to FDA MedWatch. Telithromycin is marketed and used extensively in many other countries, including countries in Europe and Japan. While it is difficult to determine the actual frequency of adverse events from voluntary reporting systems such as the MedWatch program, the FDA is continuing to evaluate the issue of liver problems in association with use of telithromycin in order to determine if labeling changes or other actions are warranted.

Telithromycin is an antibiotic of the ketolide class approved by the FDA for the treatment of respiratory infections in adults caused by several types of susceptible microorganisms including *Streptococcus pneumoniae* and *Haemophilus influenzae*. Telithromycin is not included on the UIHC Formulary.

While FDA is continuing its investigation of this issue, it provided the following recommendations to healthcare providers and patients:

- Healthcare providers should monitor patients taking telithromycin for signs or symptoms of liver problems. **Telithromycin should be stopped in patients who develop signs or symptoms of liver problems.**

- Patients who have been prescribed telithromycin and are not experiencing side effects such as jaundice should continue taking their medicine as prescribed unless otherwise directed by their healthcare provider.
- Patients who notice any yellowing of their eyes or skin or other problems like blurry vision should contact their healthcare provider immediately.
- As with all antibiotics, telithromycin should only be used for infections caused by a susceptible microorganism. Telithromycin is not effective in treating viral infections, so a patient with a viral infection should not receive telithromycin since they would be exposed to the risk of side effects without any benefit.

FDA Public Health Advisory, January 20, 2006

Additional Information

Additional information about recent safety alerts for drugs, biologics, medical devices, and dietary supplements available in the United States may be viewed on the FDA's web site at: <http://www.fda.gov/medwatch/safety.htm>.

Prepared by Kevin Bebout, Administrative Pharmacy Practice Specialist, Department of Pharmaceutical Care. Questions about the UIHC Adverse Drug Reaction Reporting Program may be directed to Mr. Bebout

PHARMACY AND THERAPEUTICS SUBCOMMITTEE ACTIONS

DRUGS ADDED TO STOCK

BROMFENAC

Ophthalmic Solution: 0.09%

Bromfenac (Xibrom[®]) ophthalmic solution is indicated for the treatment of postoperative inflammation following cataract surgery.

ESCITALOPRAM

Tablets: 10 mg and 20 mg and Oral Solution: 1 mg per ml

Escitalopram (Lexapro[®] - Forest) is a selective serotonin reuptake inhibitor indicated for the treatment of major depressive disorder and generalized anxiety disorder.

GALSULFASE

Injection

Galsulfase (Naglazyme[®] - BioMarin) is an enzyme replacement therapy indicated for the treatment of mucopolysaccharidosis VI.

Note: The prescribing of galsulfase is restricted to Pediatric Medical Genetics.

OMEGA-3 FATTY ACIDS

Capsules: 1 gram

Omega-3 fatty acid capsules (Omacor[®] - Reliant) as adjunct therapy to diet to reduce very high triglyceride levels.

PACLITAXEL PROTEIN-BOUND PARTICLES

Injection

Paclitaxel protein-bound particles for injection (Abraxane[®] - Abraxis) is indicated for the treatment of breast cancer after failure of combination for metastatic disease or relapse.

Note: The prescribing of Abraxane[®] is restricted to Pharmacy and Therapeutics Subcommittee approved criteria.

DRUGS DELETED FROM STOCK

ETHINYL ESTRADIOL 0.5 mg WITH LEVONORGESTROL 0.25 mg (Preven[®])

Discontinued by the manufacturer. Plan B[®] is available.

HALOTHANE INHALATION SOLUTION

Discontinued by the manufacturer. Desflurane, isoflurane, and sevoflurane are available.

KETOROLAC (Acular[®]) 0.5% OPHTHALMIC SOLUTION

Discontinued due to low use. Acular[®] LS and Acular[®] PF are still available.

LOPINAVIR 133.3 mg WITH RITONAVIR 33.3 mg (Kaletra[®]) CAPSULES

Discontinued by the manufacturer. Kaletra[®] 200 mg/50 mg tablets are available.

METRONIDAZOLE 0.75% (Metrocream[®]) TOPICAL CREAM

Discontinued by the manufacturer. Metronidazole 1% topical gel (MetroGel[®]) is available.

PANCRELIPASE (Pancrease[®]) CAPSULES

Discontinued by the manufacturer. Crean-10[®], Ultrase MT-12[®], and Pancrease MT-16[®] are available.

PHENYLEPHRINE 10% VISCOUS OPHTHALMIC SOLUTION

Discontinued by all manufacturers. A 10% non-viscous solution is available.

TELITHROMYCIN TABLETS

Discontinued due to reports of liver toxicity. Erythromycin, clarithromycin, and azithromycin are available.

VITAMIN A 25,000 UNIT CAPSULE

Discontinued by all manufacturers. A 10,000 unit capsule is available.