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Educating the healthcare community about safe medication practices

A federally certified Patient Safety Organization

ISMP Medication Safety Alert!® Acute Care

January 12, 2012 ■ Volume 17 Issue 1

SafetyBriefs

HIGH-ALERT **Study provides evidence base for ISMP's ambulatory care high-alert drug list.** More than two-thirds of the drugs tied to hospitalization after emergency department (ED) visits for adverse drug events in older adults appear on our **List of High-Alert Medications in Community/Ambulatory Healthcare** (www.ismp.org/communityRx/tools/ambulatoryhighalert.asp). Furthermore, nearly two-thirds of the hospitalizations and half of the ED visits not requiring admission were due to unintentional drug overdoses in this population. These findings, from a study published in November 2011 by Budnitz et al. in the *New England Journal of Medicine* (www.nejm.org/doi/full/10.1056/NEJMsa1103053?query=featured_home), were derived from adverse event data in the Centers for Disease Control and Prevention's National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2007-2009). The study estimated that nearly 100,000 elderly patients are hospitalized for adverse drug events each year! Among the specific drugs accounting for more than two-thirds of all such admissions are warfarin, insulins, oral antiplatelet agents, and oral hypoglycemic agents. The study results are of great importance since they support a focused effort to educate patients about the proper use of high-alert drugs. ISMP is in the midst of an Agency for Healthcare Research and Quality (AHRQ)-funded project to design patient education materials to support mandatory patient education by community pharmacists for selected high-alert drugs. Please check out the Budnitz and colleagues study and the ISMP list of ambulatory care high-alert drugs (links above), and be sure to target patients for specific medication error prevention education if they are discharged on a high-alert medication. The AHRQ-funded patient education materials designed by ISMP for about a dozen high-alert medications will be freely available for use in both inpatient and outpatient settings this summer.

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QuarterWatch™ (First Quarter 2011)

Signals for dabigatran and metoclopramide

QuarterWatch™ is an ISMP surveillance program that monitors all serious, disabling, and fatal adverse drug events (ADEs) reported to the US Food and Drug Administration (FDA) by drug manufacturers and by the public through its MedWatch reporting program. The goal of QuarterWatch™ is to improve patient safety through the identification of signals that may represent important drug safety issues. The term *signal* means evidence we judge to be substantial enough to warrant publication but which usually requires further investigation to determine its frequency of occurrence and establish a causal relationship to the suspect drug.

Reporting totals and trends

Based on recently released FDA data, the agency received 40,151 domestic reports of serious, disabling, or fatal injuries associated with drug therapy in the first quarter of 2011. The total represents a 3% increase over the previous calendar quarter, and a 19.5% increase over the first quarter of 2010. The greatest increase was in the number of reports originating from consumers and submitted to FDA through drug manufacturers. According to the IMS Health National Prescription Audit, the number of dispensed prescriptions also increased by 1% compared to the previous quarter and by 3% compared to the same quarter of 2010.

ADE signals for selected medications

Dabigatran (PRADAXA). This drug, which was launched in October 2010 to reduce the risk of stroke in patients with atrial fibrillation, generated hundreds of adverse event reports during the first quarter of 2011. Overall, 932 serious adverse events were linked to this drug, including 120 deaths, 25 cases of permanent disability, and 543 cases requiring hospitalization. Of the 932 events, 505 cases involved hemorrhage, **more than any other monitored drug including warfarin**, which ranked second with 176 cases of hemorrhage. The total included 120 cases that described the event with terms indicating hemorrhagic stroke, which is particularly problematic given that the drug's primary indication is to prevent ischemic strokes.

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HazardAlert

Do not use an insulin pen for multiple patients!

PROBLEM: A single pen device is never suitable for use with multiple patients due to the risk of cross-contamination and transmission of blood-borne diseases. In our 2008 newsletters (March 27, May 8), we reported that at least two studies demonstrated that biological contamination of insulin occurred in up to half of all reused insulin pens. Air bubbles and pathogenic contaminants can enter the cartridge after injection while the needle is still attached to the pen, even for short periods of time. In 2009, ISMP cooperated with the US Food and Drug Administration (FDA) on a **Patient Safety News** video (www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=86#9) that discusses how contamination can happen. The video was prompted by a 2009 incident at two US Army hospitals in which 2,114 insulin-dependent diabetic patients were placed at risk because insulin pens were used for multiple patients. Just last year, an incident in Wisconsin required notification of more than 2,000 potentially exposed patients due to inappropriate sharing of insulin demonstration pens used during patient training. Repeated event reports suggest that an alarming and widespread misunderstanding that sterility can be maintained between patients by affixing a fresh needle on a pen device continues even today, despite fervent warnings from ISMP, the Centers for Disease Control and Prevention (CDC), FDA, and pen device manufacturers.

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HIGH-ALERT **Chemotherapy mix-up between eribulin and epirubicin.** An order for the antimicrotubular antineoplastic agent "eribulin" (eribulin mesylate, **HALAVEN**) was misinterpreted by a pharmacist and entered into the computer system as epirubicin, an anthracycline antineoplastic agent. Fortunately, the error was detected by a nurse when comparing the pharmacy label to the original order, and the patient did not receive the wrong drug. Both drugs are associated with breast cancer treatment. Eribulin mesylate injection was approved in November 2010 for treatment of metastatic breast cancer in patients who have received at least two prior chemotherapy regimens including an anthracycline and a taxane. Eribulin may be new to healthcare professionals, and the names above are similar enough to warrant proactive measures to prevent look-alike or sound-alike mix-ups. The hospital is now applying tall man lettering and adding the salt "mesylate" to the eribulin listing in their computer systems to prevent similar errors. The drugs are now listed as eri**BUL**in mesylate injection and epi**RUBICIN** injection (although, ISMP would recommend **EPI**rubicin to prevent confusion with other anthracycline antineoplastics). A pharmacist should verify and independently recalculate the dose of any antineoplastic agent before dispensing it. In this case, the typical dosing is very different and should have prompted a call to the prescriber for verification. The dosing for epirubicin is 60-120 mg/m^2 depending on the type of therapy the patient is receiving. The recommended dose for eribulin is 1.4 mg/m^2. Incidentally, the person who reported this event mentioned that similar close calls had occurred previously in the pharmacy but were never reported through the hospital's internal error reporting process and, therefore, no steps were taken to prevent future mix-ups. Perhaps if previous episodes had been reported and addressed, the recent changes would have occurred earlier, thus preventing this latest incident. If both drugs are available in your organization, we hope you will consider this hospital's experience and take proactive steps, such as utilizing tall man lettering, to prevent a similar occurrence.

Pharmacy student discovers overdose in product labeling. Thanks go out to **Sal Rivas**, a 3rd year pharmacy student at Roseman University of Health Sciences College of Pharmacy in Henderson,

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The adverse events related to hemorrhage occurred in elderly patients with a median age of 80 (compared to 56 years of age for all other drugs). A quarter of these patients were 84 years or older, raising a question regarding safe dosing and monitoring in older patients. Unlike warfarin, dabigatran was approved in a "one size fits all" dose of 150 mg twice a day (except for patients with severe renal impairment). The FDA rejected a lower dose regimen of 110 mg twice daily, which had been sought by Boehringer Ingelheim, the drug's manufacturer, and approved in Canada, Japan, and European countries.

Impaired renal function, which often occurs in older patients, is a related safety issue. In studies of dabigatran, patients with mild renal impairment had dabigatran blood levels that were 50% higher than patients with normal kidney function, and moderately impaired kidney function could result in dabigatran blood levels three times higher. Dabigatran prescribing information does not recommend dosage adjustment except in cases of "severe" renal impairment, where a dose of 75 mg twice daily is recommended (www.fda.gov/Drugs/DrugSafety/ucm282724.htm). We believe FDA and the manufacturer should reevaluate dosing in the elderly or those with moderate renal impairment to determine optimal dosing and monitoring requirements.

These concerns and recommendations were shared with Boehringer Ingelheim, the manufacturer. While the company had also observed a large volume of serious adverse event reports, a representative noted that the prescribing information already warned about an increased risk of significant and sometimes fatal bleeding. The company attributed the volume of reports to the drug's rapid acceptance and active sales force with extensive physician contact. The company reported it is working with FDA to provide better guidance to physicians on treating elderly patients, especially those with transient (e.g., contrast media use) or chronic impaired renal function. The company declined to comment on whether it would again seek FDA approval for the lower 110 mg dose.

Metoclopramide (REGLAN). Metoclopramide, a widely prescribed drug used to treat nausea, gastric reflux, and gastroparesis has a troubling side effect known as dyskinesia—involuntary, abnormal movements including lip smacking, eye rolling, drooling or protruding tongue, and sometimes repetitive movements of limbs. If the dyskinesia becomes irreversible, it is called tardive dyskinesia. In the first quarter of 2011, 63 new cases of dyskinesia were identified along with 1,180 cases arising from lawsuits against the drug's manufacturer for adverse events that occurred over a longer period of time. This side effect challenges the core concept that a drug's benefits (control nausea and reflux, improve emptying of the stomach) must outweigh its risks (irreversible neurological damage).

The drug blocks dopamine receptors in the brain, which help control muscle movement, mood, behavior, sexual devel-

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Table 1. Reported serious ADEs for the most widely dispensed prescription drugs (2011, Q1)

Drug	Medical Use	Millions of Rx*	Serious ADEs	Median Age	Reported Adverse Effect
HYDROcodone-acetaminophen	Pain	32.4	390	43	Overdose/Suicide
levothyroxine	Hormone replacement	23.8	69	52	Overdose/Suicide
simvastatin	Lipid-lowering	22.4	132	63	Rhabdomyolysis
lisinopril	Hypertension	20	168	60	Hypersensitivity ACE Inhibitor Cough
azithromycin	Infection	18.2	18	51	Severe Cutaneous Reactions (including Stevens-Johnson Syndrome)
Total		116.8	777		

** IMS Health National Prescription Audit*

Please encourage your patients and staff to visit www.consumermedsafety.org often. **It may save a life!**

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NV, who contacted us about a website dosing error for **LITTLE NOSES DECONGESTANT NOSE DROPS**, which contains phenylephrine HCl 0.125%. During a website redesign project, the company, Little Remedies, inadvertently listed the product dose as 1 **mL** for 2- to 6-year-old children. The correct dose should have been listed as 2 to 3 **drops** in each nostril. If a parent followed the website dosing instructions using an oral syringe, their child would have received up to 10 times more phenylephrine than recommended. ISMP immediately contacted the manufacturer and the website was fixed the same day. Note to Roseman's professors: We think Sal deserves some extra credit!

ISMP errata. In our December 1, 2011 newsletter, in an article regarding ISMP's stance on use of metric measurements, we mentioned errors associated with weighing a patient in pounds but entering the value as kilograms in the medical record. The sentence that stated "One pound equals 2.2 kg, which can cause a greater than two-fold overdose," has caused confusion, as we all know 1 kilogram equals 2.2 pounds, not the other way around. Our intention was to state that, if a patient is weighed in pounds but the value is entered as kilograms, each pound would represent 2.2 kilograms, and a two-fold overdose could result. We apologize for the confusion.

Special Announcements ...

ISMP Fellowships

ISMP is now accepting applications for its **2012-2013** ***ISMP Safe Medication Management Fellowship*** and the ***FDA/ISMP Safe Medication Management Fellowship***. These 1-year learning opportunities offer practitioners interested in patient safety a challenging and rewarding experience that will enhance their career growth. The application deadline is **March 30**. For more information and a copy of the application, visit: www.ismp.org/profdevelopment/default.asp).

For the first time, ISMP is also offering a 1-year physician fellowship in patient and medication safety for an eligible PGY4 medical resident. This ***Stephen R. Lewis, MD Fellowship*** is a unique program that will be operated jointly by ISMP and Abington Memorial Hospital in nearby Abington, PA, under the direction of the physician Chief of Patient Safety. The applica-

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opment, and weight regulation. The drug also blocks serotonin receptors, which affect mood and regulate the digestive system. Its mechanism of action is similar to the most powerful drugs used to treat psychosis and schizophrenia—thus it shares some of the same risks. Antipsychotic drugs are believed to cause tardive dyskinesia in 5-10% of patients during the course of a year.[1-2] Data are less clear for metoclopramide, but there are published estimates of tardive dyskinesia in 1-10% of patients, depending upon the length of exposure.[3] One may argue that tardive dyskinesia may be an unavoidable risk with drugs used to treat the most severe mental disorders, particularly when other drugs are ineffective. However, for less severe disorders, and with safer alternatives available, the risk may outweigh the benefits of using metoclopramide.

The FDA's Office of Surveillance and Epidemiology conducted a study in 2007 and discovered that doctors were frequently disregarding an important safety measure—limiting use of the drug to 12 weeks or less; 20% of prescriptions were for longer durations.[4] Two years later, FDA required a prominent *Boxed Warning* regarding tardive dyskinesia and a *Medication Guide* to warn patients about the dangers of prolonged use. The warning may have contributed to a slow decline in the volume of prescriptions, but still, more than 986,000 outpatient metoclopramide prescriptions for oral tablets were dispensed in the first quarter of 2011.

Patients have been exposed to this poorly controlled drug risk since the drug's approval in 1980. Safer alternatives exist for the treatment of nausea and gastric reflux, but apparently, metoclopramide is the only drug FDA-approved for gastroparesis. However, recent review of metoclopramide for this indication found no benefit after 1 month of therapy.[3] Given that gastroparesis is a chronic disorder, this short-term benefit may not justify the risk.

FDA and manufacturers should consider substantial action to reduce tardive dyskinesia caused by this widely used drug, such as highly restricted availability limited to a few weeks of use and repeal of all its first-line indications. Its use in injectable form for nausea from surgery and chemotherapy should also be reassessed, given the presence of numerous safer alternatives.

High-volume prescription drugs. For the first quarter of 2011, we looked at the serious adverse events associated with the five most widely dispensed prescription drugs: **HYDRO**codone with acetaminophen, levothyroxine, simvastatin, lisinopril, and azithromycin. One would hope that the most time-proven (all were on the market for 20 years or longer) and widely used drugs rank among the safest. We found 708 reports of serious injuries and death reported among the 116.7 million dispensed prescriptions for these drugs. The predominant adverse events identified in these reports are relatively well known risks. However, the adverse events with these older drugs may infrequently be reported to FDA given familiarity with their safety profiles.

QuarterWatch

Even when reporting rates are low, a single quarter of adverse event data still reveal important information about the reported risks of these prescription drugs (listed in Table 1 on page 2). For levothyroxine, we noted an unexpected signal of suicidal and self-injurious behavior, with 20 completed suicides in the quarter. In a problem we have noted before, three companies reported the same suicides that were listed in a poison control annual report even though levothyroxine was not the suspect drug but just one of many drugs found in the blood of the overdose victims who had also taken drugs with an established suicide risk.

References

1) American Psychiatric Association Task Force on late neurological effects of antipsychotic drugs. Washington, DC: American Psychiatric Association. 1980:17.

2) Schooler N, Rabinowitz J, Davidson M, Emsley R, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry*. 2005;162:947–53.

3) Lee A, Kuo B. Metoclopramide in the treatment of diabetic gastroparesis. *Expert Rev Endocrinol Metab*. 2010;5:653–62.

4) Kaplan S, Staffa JA, Dal Pan GJ. Duration of therapy with metoclopramide: a prescription claims data study. *Pharmacoepidemiol Drug Saf*. 2007; 16: 878–81.

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tion deadline for the physician fellowship is also **March 30.** For more information please email ismpinfo@ismp.org and express your desire to learn more about the program.

The unSUMMIT

Want to refine your strategies for bedside barcoding? Attend this year's **unSUMMIT for Bedside Barcoding** in Anaheim, CA, on **May 2-4, 2012**. ISMP newsletter subscribers will receive a $50 discount applied to the registration fee by entering the code ISM12 at: www.unsummit.com/.

1-week "rotation" at ISMP

We have room for just a few more participants in our weeklong **ISMP Practitioner in Residence Program** on **February 13-17, 2012**, at ISMP's office in suburban Philadelphia, PA. The program provides healthcare professionals with medication safety oversight in their organization with a unique opportunity to work closely with ISMP staff. For details, visit: www.ismp.org/consult/practitioner.asp.

ISMP webinar

Join ISMP on **February 15** for our webinar on ***Challenges in Oncology Medication Safety: Identifying Risk and Opportunity***. Risks are often present when providing oncology services due to the complexity of chemotherapy regimens, variability in dosing, the toxic nature of the drugs, and the specialty staff required. Join interdisciplinary speakers as they address these unique challenges and discuss the release of the *free* ***2012 International ISMP Medication Safety Self Assessment for Oncology***. For details, visit: www.ismp.org/educational/webinars.asp.

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Last month, we received two reports in which nurses knowingly used the same insulin pen for multiple patients. Both nurses thought the practice was acceptable because they changed the needle between patients. In one case, it was later determined that the original patient had human immunodeficiency virus (HIV)! Follow-up exposure treatment and testing are being conducted on the affected patient. The nurse involved in the event reported that sharing insulin pens after changing the needle was routine practice at another hospital where she had worked. In the other case, two pens were used to administer insulin to three patients, even though each pen had a patient-specific label. One of the pens was borrowed from another patient while the nurse was waiting for pharmacy to dispense an insulin pen for her new patient. Insulin pen cartons state that the pens are intended for "Single patient use only;" however, labels on the pens do not include this warning (Figure 1), and the cartons are rarely dispensed to patient care units.

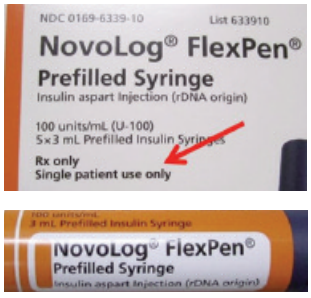

Figure 1. Pen carton includes warning for single patient use in small print. The pen itself carries no warning.

According to the CDC, evidence continues to mount that this dangerous practice is still affecting thousands of patients (www.cdc.gov/injectionsafety/blood-glucose-monitoring.html). **This concern led the CDC to again issue a clinical reminder just last week** (www.cdc.gov/injectionsafety/clinical-reminders/insulin-pens.html), stating that the agency has increasingly become aware of reports of improper use of insulin pens, which places individuals at risk of infection.

Insulin pens are convenient and offer the possibility of improving safety when viewed from the perspective of reducing dosing errors, particularly errors that occur when drawing the correct volume into a syringe and the addition of several extra steps in administration. The dose preparation step is simpler and involves just turning a dial to the prescribed dose and affixing a special needle to the device before injection. However, keep in mind that insulin pens were originally designed for home use by diabetic patients, and less so for inpatient use.

Safe Practice Recommendations: To reduce the risk of cross contamination, insulin pens used in inpatient settings should be assigned to individual patients and labeled accordingly. Unfortunately, space is lacking on the pen for application of a patient label, so pharmacists must affix a "flag" label, taking care to attach the label to the body of the pen, not the cap, without covering the drug name. If the label is on the cap, once the cap is removed, the pen is no longer labeled.

Please also heed the advice we provided in our February 12, 2009, **HazardAlert!** in which we noted that safety could only be assured through timely education and ongoing monitoring. Unfortunately, hospitals may find education and monitoring difficult to accomplish due to staff turnover and time constraints. If ongoing education and continuous monitoring cannot be accomplished, hazardous conditions may persist, and hospitals may need to take a long, hard look to determine if patients would be safer by dispensing vials of insulin or prefilled syringes. Another option is allowing patients to bring their own pens to the hospital for use, but only if the hospital has effective procedures in place to verify, label, and securely store the pens.

We are interested in learning about other safety efforts hospitals have instituted to prevent sharing of pen devices. Please send us your ideas (ismpinfo@ismp.org) so we can share them with others! Here are some other safety efforts already reported to us by hospitals that use insulin pens: 1) develop staff orientation and continuing education programs on the proper use of pen devices, 2) include warnings about proper pen use on computer-generated and electronic medication administration records, and 3) create screen savers and posters about the risk of sharing pens that can be displayed in medication areas. ISMP also recommends conducting a failure mode and effects analysis on pen device use to determine the scope of risk, plan an effective risk-reduction action plan, implement the plan, and measure its effectiveness.

Pen manufacturers also need to step up their efforts. Manufacturers should prominently label the pens with a bold statement such as, "Warning! For Single Patient Use ONLY." Space must also be devoted on the pen body for a patient label so that a patient's name can be specified on each pen. FDA oversight is needed to ensure that pen manufacturers communicate with hospitals, outpatient pharmacies, physician offices, and ambulatory centers about the risks associated with pen sharing.