Multiple latent failures align to allow a serious drug interaction to harm a patient

Whenever ISMP assists hospitals with a root cause analysis or conducts its own investigation of an adverse event, we inevitably uncover numerous precipitating latent failures (see definition in box below) that led to the actual event. Similar to dominos that require perfect alignment in order to collapse in a series, latent failures also must align perfectly for an event to occur and go unnoticed. A serious drug interaction between simvastatin and ketoconazole that recently harmed a patient is an example of the perfect alignment of latent failures and its role in adverse events. As you read the details of the event, notice how the drug interaction may have been avoided or captured at numerous points during the patient’s medical care had it not been for the series of latent failures that almost seemed to conspire against the patient and healthcare providers.

**Description of the Drug Interaction**

An elderly patient with numerous medical conditions, including advanced prostate cancer, had been taking oral simvastatin 80 mg daily to reduce his elevated total cholesterol level. After a recent visit to an oncology clinic, the patient’s oncologist added ketoconazole to his drug regimen. (Note: simvastatin 80 mg is a high dose for elderly patients, but apparently this patient was tolerating the dose without adverse effects, at least until ketoconazole was prescribed.)

Ketoconazole is used off-label as an androgen synthesis inhibitor to treat prostate cancer; however, concomitant use of ketoconazole and simvastatin significantly increases levels of simvastatin. This places patients at a higher risk of developing rhabdomyolysis, a condition in which skeletal muscle breaks down, releasing myoglobin and other products into the bloodstream, which can result in acute kidney failure. Ketoconazole inhibits the hepatic CYP450 3A4 enzymes responsible for HMG-CoA reductase inhibitor metabolism of simvastatin.

**Description of Latent Failures**

When the newly prescribed ketoconazole was entered into the patient’s electronic clinic record, a drug interaction alert did not occur. The prescription was then sent to the patient’s community pharmacy. When the pharmacist entered the prescription into the pharmacy computer, a level one (severe) drug interaction warning appeared on the screen. The pharmacist did not call the physician because he had often found with other continued on page 2 — Latent failures
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withdrawn the product, but patients may still have a supply at home. If this product was purchased at your location, please assure that it is removed from inventory.

Lawyers weigh in on consistent use of smart pump libraries. As noted in our April 19, 2007 article, “Smart pumps are not smart on their own” (www.ismp.org/Newsletters/acuteCare/articles/20070419.asp), clinicians should not view the dose-checking feature of smart pumps as an option that can be turned on or off. Nor should the alerts that arise from the system be bypassed without serious consideration. Unfortunately, we still hear about serious medication errors in which users bypassed pump libraries, resulting in patient injuries. A Journal of Nursing Administration article about legal considerations with the use of smart pumps (Harding AD, Connolly MW, Wilkerson TO. Nurses’ risk without using smart pumps. JONA’s Healthcare Law Ethics and Regulation. 2011;13(1):17-20) points out that, when this technology is available but not utilized, litigation could be successful in finding fault with the pharmacy to say his father would take the ketoconazole. A different pharmacist reactivated the prescription and generated a label, but no alert appeared about the severe drug interaction because the prescription was already in the system and the computer was not set up to fire an alert under these conditions. The pharmacist did not recognize the interaction and dispensed the drug.

Three weeks later, the patient was admitted to the hospital with muscle weakness, pain, and extremity edema. The patient’s oncologist was not consulted because the patient was not exhibiting acute oncologic problems. Both ketoconazole and simvastatin appeared on the patient’s medication reconciliation form, and the admitting physician chose to continue both medications. The physician prescribed both drugs using a computerized prescriber order entry system (CPOE), during which a level one (severe) drug interaction alert fired. The admitting physician was able to override the alert without entering an explanation into the CPOE system. The practitioner who reported this event to ISMP felt the attending physician believed that the oncologist and retail pharmacist had already vetted the risks and benefits of concurrent administration and had decided to direct the patient to take both medications.

On the very day that the patient was admitted, the hospital had temporarily suspended the pharmacy computer alert system; thus, a drug interaction warning did not appear on the screen when the pharmacist entered both these drugs into the patient’s profile. The hospital was transitioning to a new electronic medical record system, and on the day of the patient’s admission, a large team of pharmacists were manually re-entering medication orders for all active patients into the new system. Because they believed any alerts for these preexisting medications had already been managed when the orders were first entered, a decision was made to suspend the alert system for 24 hours to eliminate repetitive alerts that would have significantly slowed down the process. Pharmacy staff had agreed to the temporary suspension of alerts and was aware of the risk of overlooking safety problems with new orders during that 1-day window. At the time, the risk appeared to be tolerable if it resulted in less days of disruption to the normal pharmacy dispensing process during transition to the new electronic medical record system.

Despite taking both medications, the patient’s condition appeared to improve enough to be discharged to a long-term care facility just a few days after admission. Again, both simvastatin and ketoconazole were prescribed upon discharge. When the long-term care pharmacy staff entered these orders into the computer, a level one drug interaction warning appeared. The drugs were held until further clarification of the orders could be sought. However, before the prescribing physician could be contacted, the patient was readmitted to the hospital less than 24 hours after discharge.

FDA comments on benzocaine risk of methemoglobinemia.
On April 7, 2011, FDA reported that the agency continues to receive reports of methemoglobinemia, a serious and potentially fatal adverse effect associated with topical benzocaine products. These include sprays used during procedures to numb mucous membranes of the mouth and throat, and over-the-counter benzocaine gels and liquids used to relieve pain from various conditions, such as teething, canker sores, and gum irritation. FDA is not taking regulatory action but has provided recommendations, which can be found at: www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsForHumanMedicalProducts/ucm250264.htm, ISMP first warned about methemoglobinemia in our June 4, 1997 newsletter (Topical anesthetic-induced methemoglobinemia, www.ismp.org/Newsletters/acuteCare/articles/19970604.asp), and we’ve written about it many times since, including a published review of FDA adverse event reports (Moore TJ, Walsh WS, Cohen MR. Reported adverse event cases of benzocaine).
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methylene blue associated with benzocaine products. Arch Intern Med. 2004;164:1192-6). FDA continues to evaluate the safety of benzocaine products and will take appropriate regulatory action if warranted. Meanwhile, see our June 4, 1997, newsletter (link on page 2) for recommendations to lower the risk of methemoglobinemia.

![Image]

**Important national survey on USP <797> compliance.** Please make sure your pharmacy participates in the largest and most comprehensive study ever undertaken of USP <797> compliance. The study is being led by sterile compounding experts Eric Kastango, RPh, MBA, FASHP, and Kate Douglass, MS, RN, APN,C, CRNI. We believe the information gathered in this confidential study will be extremely valuable to the healthcare industry. Only aggregate findings will be reported publicly. By participating in the survey, you will receive a highly detailed Action Plan based on your answers that can be used to implement or continue sterile compounding practice improvements at your facility. ISMP endorses the study, which will take 60–90 minutes to complete (in multiple sittings if desired). Please register for the study today at: www.797study.com, using Survey Code A797C.

**Report drug shortages.** ISMP has partnered with the American Society of Health-System Pharmacists (ASHP) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) to explore and communicate drug shortage issues with FDA’s Drug Shortage Program (DSP). DSP staff have been working hard to address drug shortages and have prevented quite a few. You can assist by providing details regarding severe drug shortages directly to the FDA DSP through contacts and links you’ll find on the DSP website at: www.fda.gov/Drugs/ DrugSafety/DrugShortages/ucm142398.htm.

**Special Announcement…**

On June 29, ISMP will present a webinar, The Overall Impact of Computerized Prescriber Order Entry (CPOE) Implementation on Hospital Medication Systems: Pharmacists Share Their Experiences. Follow the journey as our speakers discuss navigating through transformation of relationships and alterations in workflow and efficiency. The speakers will highlight anticipated benefits and realities before and after the CPOE go-live date. For details, visit: www.ismp.org/educational/webinars.asp.

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The long-term care facility staff had reported that these two drugs were being held until further clarification, which prompted the nurse practitioner who evaluated the patient in the emergency department to order the appropriate lab studies to confirm a suspected diagnosis of rhabdomyolysis. The patient’s creatine kinase (CK) and aspartate aminotransferase (AST) were markedly elevated (CK peaked at 159,000 units/L; AST peaked at 2,310 units/L). This time, the patient was diagnosed with severe rhabdomyolysis and liver dysfunction, and both ketoconazole and simvastatin were discontinued. The patient improved and was discharged back to the long-term care facility after a 1-week hospital stay.

**Lessons Learned**

This event demonstrates that, typically, many things have to go wrong for an error to reach the patient and go unrecognized. In this case, the latent failures set the stage for the event, particularly: the pharmacy practice of not calling prescribers immediately to discuss a severe drug interaction; an order entry system that is not configured to reissue severe drug interaction warnings when inactive prescriptions are activated or refilled; an order entry system that allows easy overrides of severe drug interaction warnings without requiring an acceptable explanation; and the decision to suspend all pharmacy computer decision support alerts during transition to a new electronic medical record system.

This event demonstrates another common factor associated with adverse events: there are typically numerous individuals—not a single individual—involving in making human errors (called active failures) or failing to detect the errors when adverse events occur. In this case, care of the patient was provided by staff at an oncology clinic, where the error originated and was not detected; at a retail pharmacy, where the interaction was initially discovered but not corrected; during an entire hospitalization, where staff did not recognize the interaction despite sophisticated decision support technology (possibly due to alert fatigue); and in a long-term care facility, where the error was finally noticed and communicated to hospital staff during the patient’s second admission.

We encourage practitioners who investigate events to always look for multiple latent system failures and multiple human errors (active failures) that might have occurred along the way. Our natural tendency is to look for simple, singular answers during event investigations. But there are often many hidden twists and turns along the path to an adverse event. By themselves, latent failures are often subtle and may cause no problems. Their consequences are hidden, becoming apparent only when they occur in proper sequence and combine with active failures of individuals to penetrate or bypass the system’s safety nets. This event provides clear evidence that medication errors are almost never caused by the failure of a single system or the fault of a single practitioner. Rather, an adverse event like this is the result of the combined effects of latent failures in the system and active failures by individuals.

**Celebrate Nurses!** On May 6–12, ISMP is joining the American Nurses Association in celebrating Nurses Trusted to Care, as part of National Nurses Week. In honor of the dedication, commitment, and tireless effort of the nearly 3.1 million registered nurses nationwide to promote and maintain the health of this nation, the ANA and ISMP are proud to recognize registered nurses everywhere for the quality work they provide 24 hours a day, 7 days a week, 365 days a year.

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