Multiple Latent Failures Align to Allow a Serious Drug Interaction to Harm a Patient

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Whenever the Institute for Safe Medication Practices (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 sidebar) that led to the actual event. Similar to dominos that require perfect alignment to collapse in a series, latent failures also must align perfectly for an event to occur 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 this alignment’s role in adverse events. As you read the details of the event, notice how the drug interaction might have been avoided or detected 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 health care providers.

Description of Latent Failures

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. 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 for 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 CYP 450 3A4 enzymes responsible for HMG-CoA reductase inhibitor metabolism of simvastatin.

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Latent Failures

Latent failures refer to less-apparent failures in the design of organizational systems, the environment, or equipment that are often hidden until they contribute to the occurrence of errors or allow errors to go unrecognized until they harm patients. Whereas an active failure (human error), such as incorrectly programming an infusion pump, may be an obvious cause in the aftermath of an event, a latent failure, such as the organization providing several types of infusion pumps for staff to use, is a less-obvious condition that makes errors more likely. Thus, latent failures are “accidents waiting to happen.”

Adverse events often occur when multiple latent failures align perfectly, like the holes of several stacked slices of Swiss cheese, to allow errors to reach patients. The Swiss cheese model, proposed by patient safety expert James Reason, suggests that a system is analogous to a pile of Swiss cheese slices; each slice represents a part of the system that defends against errors. A hole in one slice of cheese, or system, may allow an error to get through a single layer, but in the subsequent layers, if the holes are not aligned correctly, the error may be stopped. For an adverse event to occur, the holes need to align perfectly for the error to get through the many layers of the system.
iting acute oncological 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 (CPOE) system, 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 was manually re-entering medication orders for all active patients into the new system. Because they believed any alerts for these pre-existing 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 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 one-day window. At the time, the risk appeared to be tolerable if it resulted in fewer days of disruption to the normal pharmacy dispensing process during transition to the new electronic medical record system.

Despite taking both medications, the patient 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.

The long-term care facility staff had reported that these two drugs were being held for 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 one-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 was not configured to reissue severe drug-interaction warnings when inactive prescriptions were activated or refilled; an order-entry system that allowed 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—involved 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.