An older adult patient with numerous medical conditions, including advanced prostate cancer, had been taking oral simvastatin 80 mg daily to reduce his elevated total cholesterol level. Simvastatin 80 mg is a high dose for older patients, but apparently this patient was tolerating the dose without adverse effects. After a recent visit to an oncology clinic, his oncologist added ketoconazole to his drug regimen.

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

**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 1 (severe) drug interaction warning appeared on the screen. The pharmacist did not call the physician because he had often found with other patients that the prescriber had discontinued the pre-existing medication involved in the potential interaction with the newly prescribed medication. Instead, he filled the prescription and placed a note on the prescription bag to remind himself to ask the patient if the prescriber had instructed the patient to stop taking simvastatin.

Before the ketoconazole prescription was picked up, the patient’s son called 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 1 (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 said he felt the attending physician believed the oncologist and community pharmacist had already vetted the risks and benefits of concurrent administration and had decided to direct the patient to take both medications.

**Lessons learned**

This event demonstrates that, typically, many things have to go wrong for an error to reach the patient without being recognized. In this case, the latent failures set the stage for the event, in particular: 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, and an order entry system that allows easy overrides of severe drug interaction warnings without requiring an acceptable explanation.

This event demonstrates another common factor associated with adverse events: numerous individuals—not a single individual—are usually involved in making human errors (called active failures) or in 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; and at a community pharmacy, where the interaction was initially discovered but not corrected.

This event provides clear evidence that medication errors are almost never caused by the failure of a single system or the mistake of a single practitioner. Rather, an adverse event like this one is the result of the combined effects of latent failures in the system and active failures by individuals.

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Have you experienced a medication error or close call? Report such incidents in confidence to ISMP’s National Medication Errors Reporting Program (MERP) at www.ismp.org, ismpinfo@ismp.org, or 800-324-5723 to activate an alert system that reaches manufacturers, the medical community, and FDA. Your information may also be published anonymously to alert your professional colleagues.

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