Identifying drug-drug interactions

New tech helps prevent adverse drug events.

By Jennifer Uscher

Adverse events caused by drug-drug interactions are a growing problem in hospital medicine. Such interactions harm anywhere from 1.9 to 5 million inpatients per year, according to data from the CDC. The problem is likely to grow in the future as the population ages and more people take multiple medications.

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Experts say that the conventional methods of detecting drug-drug interactions, such as adverse drug event reports from clinicians and patients and preclinical toxicity studies, can't uncover all the potentially clinically relevant interactions. As a result, dangerous interactions sometimes aren't identified until a drug has been on the market for many years.

“There may be many potentially important DDIs [drug-drug interactions] that we've not yet identified,” said Sean Hennessy, PharmD, PhD, professor of epidemiology and systems pharmacology and translational therapeutics at the

Perelman School of Medicine at the University of Pennsylvania in Philadelphia. “We need to increase the amount of reliable research on DDIs and improve the translation of that research.”

Researchers are making some progress in developing new ways to detect potentially harmful drug-drug interactions and alert prescribers about them. For example, a study published in the Oct. 18, 2016, *Journal of the American College of Cardiology* highlighted a promising new approach that combined data mining and laboratory experiments.

Using an algorithm known as latent signal detection, researchers scanned 1.8 million adverse event reports from the FDA's Adverse Event Reporting System and 1.6 million electrocardiograms from New York-Presbyterian/Columbia University Medical Center and identified eight pairs of drugs that may be associated with a greater risk of acquired long QT syndrome. Next, they evaluated the effect of two of the drugs—the antibiotic ceftriaxone and the proton-pump inhibitor lansoprazole—alone and in combination, using electrophysiological experiments on individual cells in the lab.

They focused on this combination because lansoprazole is such a commonly prescribed drug and an interaction could have a profound impact on patient safety, as well as because the effects were among the most statistically significant of all those identified. This interaction is also most likely to occur in hospitalized patients, since many could already be taking lansoprazole and then could be prescribed ceftriaxone when they're admitted for surgery, noted study author Nicholas Tatonetti, PhD, assistant professor of biomedical informatics at Columbia University Medical Center.

Results showed that patients taking ceftriaxone and lansoprazole together were 40% more likely to have a QT interval above 500 ms, which is the FDA-stated threshold of clinical concern. When taken together, these widely prescribed drugs block an electrical pathway in the cell called the hERG channel, which helps coordinate the beating of the heart.

“Our method allows us to identify adverse reactions that result from combination therapy no one would have suspected otherwise,” Dr. Tatonetti said. “We can identify a novel hypothesis, corroborate it with an additional data set, and then validate it with experiments.”

His team is currently testing more of the potentially QT-prolonging drug combinations they identified on cells in the lab and using their approach to investigate potential interactions involving beta-blockers and other classes of drugs.

Follow-up confirmation studies are needed before physicians are advised to avoid prescribing ceftriaxone and lansoprazole together, according to the authors of the study and other drug safety researchers.

“While these results are very important, I wouldn't want someone to overextrapolate from these data. For example, we don't yet know if the same interaction will be found with other proton-pump inhibitors and ceftriaxone,” said Raymond L. Woosley, MD, PhD, FACP, professor of biomedical informatics and medicine at the University of Arizona College of Medicine-Phoenix; president of AZCERT, a nonprofit focused on drug safety; and a coauthor of the study.

Dr. Tatonetti and colleagues are currently studying the effects of the drugs individually and in combination on the QT interval in patients already undergoing inpatient electrophysiology studies.

Over the past several years, a number of other research teams around the world have started to leverage data from electronic health records (EHRs), adverse event reporting systems such as the FDA database and the World Health Organization's VigiBase, insurance claim databases, and published literature to identify possible interactions.

“The hope is that with new data-mining techniques and the increasing availability of large clinical databases such as EHRs, we can pick up DDIs much more quickly than in the past and prioritize the ones that are important for further study, in particular, to measure their medical impact and means of prevention,” said Dr. Woosley.

Predicting DDIs in individuals

Another promising investigative approach focuses on predicting potential drug-drug interactions in individual patients. Joseph C. Wu, MD, PhD, director of the Stanford Cardiovascular Institute in California, is developing a method of using induced pluripotent stem cells to determine whether a specific drug or drug-drug interaction is likely to cause damage to an individual patient's heart.

The technique involves taking a patient's blood sample, converting the blood cells to the pluripotent stem cells, and then converting those to heart muscle cells (cardiomyocytes).

These beating heart cells are genetically identical to those of the patient. The researchers then expose the cells to one or more medications and measure the effects on the heart, for instance, whether the medications cause the heart cells to die or to beat irregularly.

This type of testing can help determine which potentially beneficial medication would be safest for a patient. It might also help confirm if a drug-drug interaction is currently taking place in a patient. For example, if a patient with an arrhythmia is on five medications and an interaction is suspected, the testing could be used to find out which of the drugs is causing the problem.

“This platform allows us to test drug-drug interactions in patient-specific and disease-specific human heart cells. The patient doesn't have to be the guinea pig,” said Dr. Wu, who is also a professor of medicine and radiology at Stanford University School of Medicine.

Other scientists are generating kidney, brain, liver, and endothelial cells from induced pluripotent stem cells for drug screening applications. Dr. Wu predicts that within the next five years, a version of this technology will be available for commercial use.

Improving tools for prescribers

For hospitalists and other physicians who are trying to prevent drug-drug interactions in everyday practice, the biggest immediate challenge may be that the existing clinical decision support tools aren't useful enough.

Currently, most computerized provider order entry (CPOE) systems include interruptive alerts that notify prescribers of potential drug-drug and drug-allergy interactions. Since the drug information databases that power these alerts are created and sold by a variety of different companies, there is limited agreement between them.

Physicians and pharmacists typically override about 90% of the alerts, according to numerous studies, since they don't find them to be relevant enough to specific patients and because the alerts interrupt workflow.

“Physicians should be able to rely on the DDI information systems, and right now those systems are failing them,” said Dr. Hennessy. “It's almost certainly true that many of the potential DDIs that we currently send prescribers alerts for aren't clinically important in most patients.”

Many in the drug safety community believe that CPOE systems should ideally provide more specific information about whether an interaction could occur in the patient for which the prescription is being ordered. “What doctors and pharmacists want to know is: Is the DDI likely to cause harm to this specific patient because of their risk profile?” said Dr. Woosley.

Along with collaborators at Banner Health and the University of Arizona College of Medicine-Phoenix and support from the FDA's Safe Use Initiative, he is developing a clinical decision support tool that helps physicians evaluate the risk for torsade de pointes from commonly used antibiotics such as levofloxacin, erythromycin, clarithromycin, and azithromycin.

Running in the background as part of the EHR, the program takes data from the patient's records and calculates a score to estimate risk, looking at such factors as whether the patient is already taking potentially QT-prolonging medications or has sepsis or bradycardia.

When a physician prescribes an antibiotic with a known risk of prolonging the QT interval to a patient with a high risk score, the program issues an advisory and suggests alternative medications or other strategies, such as monitoring the patient's electrocardiogram for excessive QT prolongation or correcting the patient's potassium level if it's low.

The 20 ICUs in the Banner Health system recently adopted this clinical decision support tool, which is based on similar ones that were developed by investigators at Indiana University in Indianapolis and at Mayo Clinic in Rochester, Minn. Dr. Woosley and his colleagues plan to evaluate its effectiveness and continually update it to address changes in medical practice, such as the release of new drugs or the identification of new risk factors.

“This model is the future,” said Dr. Woosley. “Just as airlines use autopilot systems to assist pilots in managing data and making decisions, CPOE systems could provide physicians with the information they need to make optimal decisions about DDIs for individual patients and not make mistakes.”

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