The Absence of a Drug–Disease Interaction Alert Leads to a Child’s Death

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PROBLEM: The Institute for Safe Medication Practices (ISMP) learned about the tragic death of a 12-year-old child with congenital long QT syndrome (LQTS) after a physician unknowingly prescribed a medication that prolongs the QT interval and increases the risk of torsades de pointes (torsades), even when taken as directed. The young girl was evaluated in a health-system outpatient clinic and found to have bilateral otitis media and sinusitis. The clinic physician sent an electronic prescription to the health system’s outpatient pharmacy for azithromycin (Zithromax Z-Pak, Pfizer). This antibiotic has been associated with prolongation of the QT interval and may itself increase cardiovascular death, especially in patients with a high baseline risk of cardiovascular disease.1 After taking the medication for four days, the child developed palpitations, dizziness, nausea, and transient fainting spells. The child was taken by ambulance to the health system’s emergency department, where cardiac monitoring showed complete atrioventricular block associated with QT prolongation. The child quickly developed torsades, and her cardiac rhythm deteriorated to ventricular fibrillation. The young girl died despite all efforts to save her.

Although the clinic physician had generated the prescription for azithromycin using the health system’s electronic health record (EHR) prescribing system, it did not alert the physician to the risks associated with prescribing this drug for a patient with congenital LQTS. Likewise, the ambulatory pharmacy computer system, which was also maintained by the health system, did not alert the pharmacist to the risk of further QT prolongation or torsades in patients with congenital LQTS when dispensing this antibiotic. There are several reasons for these failures in an otherwise robust alert system.

Drug–disease alerts disabled. To prevent alarm fatigue, the health system had turned off the drug–disease interaction alerts that were available in the prescriber order-entry and ambulatory pharmacy computer systems. The health system’s drug information vendor allowed the drug–disease interactions to be filtered according to severity level. The most restrictive level included medications that were contraindicated given specific disease states. When restricting the drug–disease alerts to those rated as contraindicated, the health system felt up to 90% of the alerts provided false-positive or clinically insignificant results (e.g., lidocaine with EPINEPHrine and tachyarrhythmia; pseudoephedrine and chronic obstructive pulmonary disease; propafenone and cardiac conduction disturbances).

Absence of system alerts. Even if the drug–disease interaction alerts had been turned on to display contraindicated interactions, the system still would not have alerted the physician and pharmacist to the lethal interaction. In the official azithromycin prescribing information, information about the interaction appears in the “Warnings and Precautions” section, not under “Contraindications.” The warning about prolongation of the QT interval and torsades suggests considering this risk in patients with certain cardiovascular conditions, including known QT prolongation. However, the health system’s drug information database employed with the prescriber order-entry system and pharmacy computer classified the importance of this interaction as “not recommended,” which was below the “contraindicated” and “extreme caution” severity levels. According to the health system, some other medications that prolong the QT interval (e.g., ondansetron) do not cause an alert at any severity level. The health system is following up with its EHR and drug information vendors to determine the cause, which could be related to how disease conditions are coded.

Unlinked comorbid condition. Even if the drug–disease interaction alerts had been turned on and were functional for azithromycin and congenital LQTS in the ambulatory pharmacy system, the pharmacist would not have been alerted to the interaction. This is because the child’s comorbid condition—congenital LQTS—was not documented in the ambulatory pharmacy computer system. The diagnosis had been listed in the child’s EHR, but it was not linked to the pharmacy computer.

In this health system, physicians were required to provide an indication when ordering medications. In this case, the physician complied when prescribing azithromycin for the child (otitis media, sinusitis). Although prescriptions had been filled for the child previously at the ambulatory pharmacy, the child’s congenital LQTS was not one of the diagnoses listed in the computer because she had never taken a specific medication to treat this condition. The pharmacist did not have any reason to seek out additional diagnoses given that the physician had provided an appropriate indication for the azithromycin.

Overreliance on alerts. Given an otherwise robust order-entry alert system for allergies and drug–drug interactions, both the physician and pharmacist had come to rely on the computer alerts to warn them of any safety issues with the prescribed medications. They did not consider the fact that the systems would not necessarily alert them to drug–disease warnings and precautions identified in the prescribing information. From a human factors perspective, given that an alert was not issued, both practitioners believed there was no problem with the order.

SAFE PRACTICE RECOMMENDATIONS

The health system where this event happened is taking steps to ensure that an alert will be provided to both prescribers and pharmacists when a medication
is contraindicated or not recommended for patients with a prolonged QT interval. To facilitate this process in your health system, consider the following recommendations.

**Evaluate your drug information database.** Using a reliable resource, review the parameters of your drug information database and order-entry systems to determine if an alert will appear when a drug that prolongs the QT interval and increases the risk of torsades is entered for a patient with a history of prolonged QT interval or torsades. One such resource is www.CredibleMeds.org. This organization’s website includes a free list of 236 medications that prolong the QT interval, which can be used to help evaluate the effectiveness of your order-entry alert systems. The medications are grouped into one of four risk categories via a stratification process, which includes monitoring and analysis of scientific articles published in the literature, information in the official drug label, reports submitted to its website, and data from the Food and Drug Administration (FDA) Adverse Event Reporting System.

**Build/modify severity of critical alerts.** Work with your drug information vendor to build or modify the severity of alerts necessary to warn practitioners about possible serious or fatal adverse events in certain populations with drugs that prolong the QT interval. The health system where this error happened has downloaded a list of medications that should be avoided in patients with a prolonged QT interval from CredibleMeds and has written the code necessary to ensure a clinically valid alert appears during order entry. CredibleMeds offers a free update service and will notify users whenever a drug is added to, removed from, or changed on the list. Although the time to build custom alerts varies depending on the technology in use, it took this health system about 20 hours to build the medication list and related diagnosis codes for the custom alerts.

**Include comorbid conditions.** Establish a system to gather and document all comorbid conditions in a structured diagnosis/problem list field in the patient’s EHR and to link this information to the prescriber and pharmacy order-entry systems to promote appropriate drug–disease interaction screening when new drugs are prescribed.

**Avoid overreliance.** While technology is often a pathway to improved patient outcomes, remind staff to avoid full reliance on any technology involved in the medication-use process. Also be sure prescribers and pharmacists know the types of alerts not available or turned off in the order-entry systems. Keep in mind that the use of technology should be one part of an otherwise well-integrated process that provides several levels of redundancy to ensure patient safety.

**Reduce insignificant warnings.** Work to reduce the frequency of warnings that are not clinically significant to users. Frontline staff who repeatedly encounter clinical warnings can provide a wealth of information on this topic.

Once insignificant warnings have been reduced, organizations may want to display alerts related to contraindications (highest-level alerts) and warnings and precautions (potentially lower-level alerts) for pharmacists, but display only contraindications for physicians. Displaying different levels of alerts may be a strategy used for drug–disease interactions as well as drug–drug interactions and other drug safety issues.

**Assess other chronic conditions.** As appropriate, expand this alert evaluation process to include other chronic conditions (e.g., myasthenia gravis, glaucoma, Parkinson’s disease) for which certain medications should be avoided to prevent serious harm or death.

**Patient/family education.** While health care providers are ultimately responsible for each patient’s safety when providing care, knowledgeable patients (and families) can provide an additional level of protection if they are active participants in their care and have been educated about the importance of communicating comorbid conditions to all health care providers. They may also find it useful to carry a list of key medications that must be avoided based on existing comorbid conditions to share with health care providers.

**Regulatory/pharmaceutical company/drug information vendor changes.** ISMP encourages the FDA to require label updates for drugs that should be contraindicated in patients with QT prolongation, replacing current warnings or precautions with a decisive contraindication when appropriate. Drug information vendors are encouraged to review the list of drugs that prolong the QT interval at CredibleMeds (which includes links to evidence in the literature) to determine whether the severity of any drug–disease interaction alert needs to be modified.

On a related note, ISMP encourages drug information vendors to evaluate their drug–drug interaction alert settings when more than one drug that prolongs the QT interval is prescribed (e.g., azithromycin and ondansetron) and to modify severity levels as necessary. Taking more than one drug with this adverse effect can lead to a similar tragic outcome.

**REFERENCES**


The reports described in this column were received through the ISMP Medication Errors Reporting Program (MERP). Errors, close calls, or hazardous conditions may be reported on the ISMP website (www.ismp.org) or communicated directly to ISMP by calling 1-800-FAIL-SAFE or via email at ismpinfo@ismp.org.