The absence of a drug-disease interaction alert leads to a child’s death

**Problem:** Just this week, we 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 a ZITHROMAX® (azithromycin) Z-Pak. 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 ([www.ismp.org/sc?id=531](http://www.ismp.org/sc?id=531)). After taking the medication for 4 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 (AV) 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 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.

One choice too many... Time to eliminate teaspoonfuls

In an ambulatory pharmacy, a prescription was being refilled for cetirizine 1 mg/mL. When checking the medication, the pharmacist noticed that the directions read, “Take 2.5 mL (1.2 teaspoonfuls) by mouth once daily.” The pharmacist looked at the original prescription and corrected it to read, “Take 2.5 mL (1/2 teaspoonful) by mouth once daily.” The prescription had been filled previously with the incorrect directions. Fortunately, the mother had been giving her child the correct dose, measuring 2.5 mL for each dose and not using the incorrect teaspoonful designation. Typing a decimal point instead of a slash mark (1.2 instead of 1/2) can easily happen when tapping the wrong key on the keyboard because the keys are side-by-side. This longstanding problem wouldn’t happen if teaspoonfuls were no longer used in dosing directions.

Avoid vitamin D products dosed and measured in drops. Breastfeeding is the recommended method of feeding infants in order to provide them with the nutrients and immune factors needed in early life. However, breastfeeding alone does not provide the recommended dose of vitamin D, given low average levels of this vitamin in breast milk. Breastfed infants can synthesize additional vitamin D through routine sunlight exposure, but skin cancer concerns have led parents to protect infants from the sun with clothing, hats, and sunblock.

In 2008, the American Academy of Pediatrics (AAP) doubled the recommended daily dose of vitamin D for infants and children to 400 units a day. Parents may easily be confused given the various vitamin D products on the market with a wide variety of concentrations, such as 400 units in a single drop, 400 units per mL (e.g., ENFAMIL D-VI-SOL), 2,000 units per drop, and between 1,000 units to 10,000 units per mL.

**ISMP plans to publish a list of medication-related measures that can be used as part of a meaningful “dashboard” for senior leadership in healthcare organizations. You can help by taking a quick survey at:** [www.ismp.org/sc?id=512](http://www.ismp.org/sc?id=512) We thank more than 100 practitioners who have already taken the survey, and we hope that many others will join in and provide us with input on how data is currently being used to identify and monitor safe medication use. The survey will remain open for a few more weeks. We really need your input!
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Drugs-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 COPD; 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 package insert, information about the interaction appears in the warnings and precautions sections, 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 all 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 the child 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.

SAFETY Briefs—cont’d from page 1

Recently, a 2-month-old infant was admitted to the hospital with generalized dystonia and cachexia, with prominent skin folds and loose skin reflective of a failure to thrive. The baby was found to have a total serum calcium level of 24.3 mg/dL and an ionized calcium level greater than 3.3 mmol/L, the highest value that could be measured by the laboratory used by the hospital. During the course of the investigation into the cause, it was discovered that the infant’s mother had been giving her baby a vitamin D supplement in a concentration of 400 units per drop. The mother misinterpreted the instructions and gave one dropperful per day for weeks prior to the infant’s hospitalization.

The product was Vitamin D3 Drops for Kids, manufactured by Natural Factors Canada. In addition to the very high concentration of vitamin D, the dropper included with the product could deliver an excessive amount of vitamin D, as happened here. This has been a factor in previous dosing errors and has been addressed as a potentially dangerous practice by multiple organizations, including the US Food and Drug Administration (FDA) (www.ismp.org/sc?id=532). The concentrated drops are problematic if “drop” is confused with “dropperful,” and/or if the prescriber specifies the dose by volume alone. This has happened in other cases, including one in which a mother bought a 2,000 units per drop instead of a 400 units per drop concentration and gave her child 1 mL doses as the doctor recommended instead of one drop (www.ismp.org/sc?id=533). It’s also hard to be sure only 1 drop comes out of a dropper.

Figure 1. The enclosed dropper holds more than the recommended dose of 1 drop. Confusion between drops and dropperful can lead to an overdose.
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. CredibleMeds is one such resource (www.crediblemeds.org). The organization’s website includes a free list of 175 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 US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).

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 from CredibleMeds that should be avoided in patients with a prolonged QT interval, 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, removed, 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, 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 healthcare 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.

Patches and suicide risk. A report describing improper disposal of a fentanyl patch in the trash shed light on another issue with transdermal patches: patients on suicide precautions may remove medication patches or obtain them from disposal bins and ingest large doses of the medication.

Practitioners caring for babies should never assume that parents know which vitamin D product to purchase, how many units to give, or how it should be administered. For infants, errors are less likely if a vitamin D product that contains 400 units per mL is sold, dispensed, or administered, not 400 units per drop. We have notified FDA about the latest infant overdose of vitamin D.
Dr. Ron Jenkins, MD, joined ISMP staff on May 12 as Medica

Director of ISMP. He will lead ISMP in the development and implementation of the ISMP Visual Error Reduction Program (VERP). ISMP is pleased to announce that...
Resources and Services

New Free CE
ISMP is offering two new opportunities for pharmacists and pharmacy technicians to earn CE credits that are free of charge: a downloadable monograph that clarifies misperceptions regarding regulatory requirements and risky practices with IV preparation and administration, and an on-demand webinar that discusses perioperative medication safety issues (which also provides CE for nurses). To access these and other ISMP CE activities, go to:

www.ismp.org/profdevelopment/otherCEOpportunities.asp

Upcoming Webinars
ISMP webinars help healthcare professionals solve current problems and stay ahead of new trends. For more information or to register, go to:

www.ismp.org/educational/webinars.asp

- May 27 – Expanding the Use of Barcode Medication Administration: Making a Difference in the Emergency Department (ED) and Other Outpatient Settings
- June 24 – 2015 Update on the Joint Commission Medication-Related Standards
- July 30 – Missed Safety Opportunities with Subcutaneous Insulin: Addressing the Often Unknown Safety Challenges with Insulin

MSI Workshops
Fast-track your medication safety program and gain the knowledge and the tools to promote successful safety improvements by attending one of ISMP’s Medication Safety Intensive (MSI) workshops. But register soon—there are only two more opportunities to attend the MSI this year.

www.ismp.org/educational/msi/default.asp

- September 17 and 18 Bellevue, WA (near Seattle)
- December 4 and 5 New Orleans, LA (prior to the ASHP Midyear Clinical Meeting)

Annual Fund
Medication safety would be very different today without ISMP’s advocacy efforts, which have led to hundreds of positive product and practice changes. ISMP recently launched its 2015 Annual Fund drive; please consider contributing to support the Institute in its fight against preventable medication errors.

For more information or to make a donation, go to:

www.ismp.org/support

Medication Safety Dashboards
Help develop more meaningful medication safety dashboards — take our quick survey at:

http://surveys.ismp.org/s3/Measurement-Matters-ISMP.