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Preventable Death Highlights the Need for Improved Management of Known Drug Interactions

Medication regimens are becoming increasingly complex, with many patients taking several medications concurrently to treat multiple conditions. With this increase in the number of medications taken by individual patients has come an increase in the potential for drug–drug interactions. Drug–drug interactions can result in preventable adverse drug events due to changes in the pharmacologic or clinical response to one or both of the drugs involved (e.g., a reduction in efficacy or an increase in toxicity), relative to the anticipated effect of each drug when administered alone.¹

Although the clinical effects of some drug–drug interactions may not be perceptible, and can occasionally be beneficial, they can be a significant source of harm.¹ One study found that more than one-half of all drug–drug interactions that led to an emergency room visit resulted in a hospital admission due to the seriousness of the adverse event.²

Given the sheer number of medications available on the market and the continual influx of newly developed drugs, it is not surprising that new drug–drug interactions are continuously being discovered. It is also clearly impossible for individual prescribers and practitioners to keep track of them all.³ Computerized systems for identifying drug interactions at the time of prescriber or pharmacy order entry can reduce overreliance on human memory to detect dangerous drug combinations. However, these systems do have limitations,

including less-than-timely assimilation of new information into the software and inability to consistently identify clinically significant drug interactions.⁴ These limitations create challenges for healthcare professionals making decisions at the point of care.

One particular drug–drug interaction with potentially dangerous effects involves 2 frequently prescribed medications: citalopram, an antidepressant, and azithromycin, an antibiotic.

This bulletin shares findings from a review of a case in which a drug interaction between these 2 medications caused a heart arrhythmia that was deemed to have contributed to a patient’s death. This review was one of the outcomes of a collaborative project between ISMP Canada and 4 provincial Offices of the Chief Coroner or Chief Medical Examiner. The findings and recommendations from this case are shared with the hope that similar events can be prevented.

Medication Incident

An elderly woman presented to hospital with mild fever and a 3- to 4-day history of feeling unwell. She was taking several medications including, citalopram 40 mg daily, an antihypertensive, an anticoagulant, and nonprescription supplements. Pneumonia was presumed, and she was initially treated with ampicillin and gentamicin. However, because of a

marked increase in cough and fever and worsening results on chest radiography, her antibiotic regimen was changed several days later to azithromycin and ceftriaxone. The next day, the patient experienced a temporary deterioration in clinical status thought to be a transient ischemic attack. An electrocardiogram (ECG) at that time showed atrial fibrillation and prolonged QT interval. A health record notation questioned the possibility of a drug effect; however no changes in the medication regimen were instituted.

In the subsequent days, the patient experienced a series of syncopal episodes, ultimately followed by cardiac arrest. Investigations at the time of the arrest revealed a markedly prolonged QT interval. Laboratory values at that time also revealed a low potassium level, a known risk factor for dangerous heart arrhythmias. Azithromycin and citalopram were discontinued.

The patient died the next day. Prolonged QT syndrome secondary to azithromycin and citalopram was deemed to have contributed to the death.

Background Information about the QT Interval, Arrhythmias and Medication Effects

The QT interval is a measure of the duration between 2 phases of the cardiac electrical cycle, as revealed by electrocardiography (see Figure 1). As the QT interval becomes longer, the risk of a dangerous deterioration in the heart's rhythm rises. An increasing number of medications from many drug classes, including citalopram and macrolide antibiotics such as azithromycin,^{5,6} are known to prolong the QT interval.⁷ Each QT-prolonging medication can have this effect on its own, but the effects can also be additive, whereby patients taking more than one of these drugs have an even higher risk for QT prolongation and subsequent cardiac arrhythmia or sudden cardiac death.⁸ This risk factor is modifiable (i.e., action could be taken to discontinue one or more medications), which makes these adverse events potentially preventable.

In 2012, Health Canada warned about the risk of fatal adverse effects with citalopram.⁵ This drug is now contraindicated for patients with known prolonged QT interval, with 20 mg daily being the maximum

recommended citalopram dose for patients older than 65 years of age.⁹ The US Food and Drug Administration (FDA) released a similar warning in 2011, recommending that adult citalopram doses not exceed 40 mg per day.¹⁰

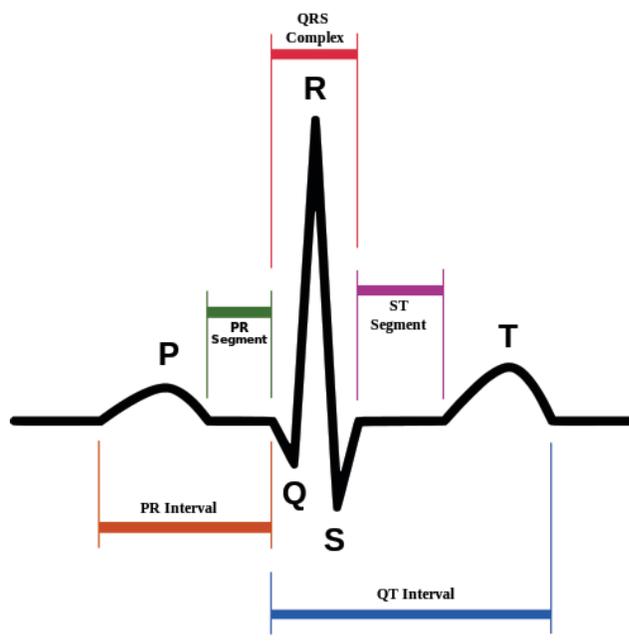


Figure 1. Phases of normal sinus rhythm of the heart as seen on an electrocardiogram. The QT interval is affected by many different medications, and changes in the QT interval can lead to life-threatening cardiac arrhythmias. Source: <http://en.wikipedia.org/wiki/File:SinusRhythmLabels.svg>

Coinciding with publication of a large cohort study linking azithromycin to cardiovascular death,¹¹ the FDA issued a safety alert regarding the risk for prolongation of the QT interval with this drug in 2012.¹² Health Canada followed suit a year later, warning about potentially fatal cardiac arrhythmias associated with the use of azithromycin, including an elevated risk in patients with certain predisposing conditions, such as electrolyte disturbance and pre-existing cardiac arrhythmia.⁶ Health Canada also noted that elderly patients might be more susceptible to drug-associated effects on the QT interval.

Review of Medication Incident Databases

This incident prompted a review of the ISMP Canada medication incident databases and the National System for Incident Reporting (NSIR)

database^{13*} from August 1, 2000, to February 24, 2014,† to identify any incidents submitted as a “Monitoring problem — drug–drug interaction” (for ISMP Canada databases only), with notation of QT prolongation or arrhythmia, and involving citalopram or azithromycin (or both). Eighteen incidents meeting these criteria were identified. Of these, 3 cases involved a drug interaction between citalopram and azithromycin and a concern about QT prolongation. In each of these 3 cases, the interaction had been identified at the time of dispensing and the prescriptions were changed proactively to prevent the interaction. The remaining 15 reports involved a drug interaction with either azithromycin or citalopram.

Of interest were 2 additional incident reports involving QT prolongation attributed to drug interactions with escitalopram, a drug related to citalopram. In both of the escitalopram incidents, the pharmacy computer software did not pick up the potential drug interaction; instead, potential harm was prevented because the pharmacist confirmed suspicions of an interaction by consulting an alternate reference. In all of the incidents identified in the ISMP Canada and NSIR databases, the pharmacist intervened and harm was prevented.

Incident Findings

There are numerous nonmodifiable and modifiable risk factors for QT prolongation listed in Table 1.

The patient in the example case described in this bulletin had both nonmodifiable and modifiable risk factors for QT prolongation. Most of these were noted in the 2011 FDA warning about citalopram¹⁰ which was released about 1 year before the incident. The nonmodifiable risk factors were female sex, age, and pre-existing cardiovascular disease. The modifiable risk factors were a high dose (for age) of citalopram, presence of a second QT-prolonging drug (azithromycin) in the patient’s medication regimen, and hypokalemia.¹⁴ Efforts to reduce the patient’s modifiable risk factors might have reduced the risk for QT prolongation and possibly altered the outcome of this case.

The case review revealed 2 potential points of intervention: during processing of the azithromycin order by pharmacy and at the point when QT prolongation was first identified. Action could have been taken at either of these points to limit the risks of a drug–drug interaction. Additional monitoring to address other modifiable risk factors, such as low potassium level, could also have been instituted.

It remains unknown whether the patient’s medication regimen was assessed to identify this and other potential drug–drug interactions. It is also unknown whether the pharmacy computer system had the capacity to detect the potential interaction between azithromycin and citalopram. Most pharmacy information systems include electronic drug

Table 1. Selected risk factors for prolongation of the QT interval^{10,14}

Disease States or Nonmodifiable Risk Factors	Modifiable Risk Factors
Cardiovascular disease (including previous left ventricular hypertrophy, heart failure, coronary artery disease and bradyarrhythmias)	Electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia)
Eating disorders (which may predispose a person to having electrolyte disturbances)	Use of more than one QT-prolonging medication (e.g., antiarrhythmics, some antipsychotics, gastric motility agents, and certain macrolide and quinolone antibiotics)
Female sex	Use of a medication that increases the blood concentration of a QT-prolonging medication (e.g., omeprazole reducing the metabolism of citalopram) or causes an electrolyte disturbance
Increasing age	
Liver or kidney impairment (which may reduce the metabolism of a QT-prolonging medications)	

* The National System for Incident Reporting (NSIR), provided by the Canadian Institute for Health Information, is a component of the Canadian Medication Incident Reporting and Prevention System (CMIRPS) program. More information about the NSIR is available from: <http://www.cmirps-scdpim.ca/?p=12>

† Each one of the databases searched has a different date of origin. The date of origin shown here is the earliest of these dates.

interaction screening programs that will alert pharmacy staff, at the time new medication orders are processed, to any combinations that may be harmful. Computer programs can be invaluable in flagging potentially serious or fatal drug–drug interactions such as those that prolong the QT interval. However, as mentioned above, these programs have limitations (e.g., poor specificity leading to “alert fatigue”)¹ and the lag between identification of a new serious interaction and its incorporation into the software is variable.

In addition to the ability to identify an interaction, an effective process must be in place to notify prescribers of potentially serious drug interactions. In the case described above, early identification of the drug interaction and notification to the prescriber might have prompted an alternate course of treatment or additional interventions, such as optimization of electrolytes.

Although there may have been clinical reasons for continuing the prescribed treatment, the rationale for continuing both azithromycin and citalopram after the patient’s QT prolongation was first identified was not documented and could not be determined retrospectively.

Recommendations

This case review and analysis generated several recommendations directed toward proactive screening for and identification of potential drug–drug interactions and effective and timely notification of prescribers to manage potential risks.

For Hospital and Community Pharmacists and/or Pharmacy Administrators

1. Ensure that pharmacy information systems have programming to detect dangerous drug–drug interactions and that the system is updated regularly according to the recommended schedule (usually quarterly).
2. Where functionality exists to detect dangerous drug–disease interactions, enter the patient data needed to allow appropriate screening.
3. Ensure that a standardized system is in place to notify prescribers and to follow up on potentially

dangerous drug interactions. Ideally, the notification would include therapeutic alternatives or appropriate courses of action.

4. Become familiar with the upgrade schedules for the drug interaction detection software being utilized and determine the lag time from recognition of new serious interactions to their addition to the software.^{15,16}
5. To address the potential delay in incorporating new information in drug interaction detection software, consider ways to include information about high-risk drug–drug interactions from Health Canada’s MedEffect program in manual warnings until the software is updated.
6. As part of a continuous quality improvement program, periodically test software alert systems to ensure that expected alerts appear when medications known to interact are entered into a patient’s medication profile.
7. Review severity levels for drug–drug interaction alerts in pharmacy information systems to balance information needs and to manage “alert fatigue”.

For Hospitals and Long-Term Care Homes

1. Develop processes to support timely review of all medication orders by a pharmacist, ideally before administration of the first dose. As of January 2014, this is an Accreditation Canada standard for hospitals.
2. In developing electronic prescribing systems, ensure that the systems include clinical decision support for identifying dangerous drug interactions, with consideration of recommendations 1 and 2 for hospital and community pharmacists listed above.

For Prescribers

1. When a dangerous drug combination or potential interaction is identified:
 - reduce the modifiable risk factors, where possible
 - include or increase periodic monitoring of relevant parameters (e.g., ECGs when starting multiple high-risk QT-prolonging drugs)
 - document the clinical rationale for maintaining or altering the patient’s drug therapy

Conclusion

This case illustrates the importance of computerized drug interaction software systems in screening for and avoiding significant drug–drug interactions. Having up-to-date drug interaction detection and decision-support software, as well as processes to communicate significant interactions and adjust care plans accordingly, are critical in preventing adverse effects from these interactions. Timely integration of new information about significant drug interactions and proactive testing of systems will also help to ensure that alerts are functioning as expected.

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Get Involved in a Drug-Drug Interactions Pharmaceutical Opinion Program

Drug-drug interactions can lead to harmful outcomes for patients, including hospitalization and death.¹ Two population-based studies conducted by the Institute of Clinical Evaluative Sciences (ICES) revealed a significant association between specific drug-drug interaction pairs and hospitalizations for adverse events.^{2,3} Front-line community pharmacists rely on tertiary drug information resources and systems to identify and prevent these interactions; however these resources have limitations which may result in patients being exposed to preventable harm.¹

The *Safety Alerts as Drivers for Pharmaceutical Opinion Program* is a community pharmacy-based pilot research project conducted by ISMP Canada, with support from the Canadian Foundation for Pharmacy (CFP) Innovation Fund Grant (<https://www.cfpnet.ca/index.php>). Participants of this pilot research project will be equipped with the knowledge from ISMP Canada Safety Bulletins, which offer awareness of medication incidents and recommendations aimed to prevent such events, and support to prevent potential patient harm related to specific drug-drug interactions while utilizing the Pharmaceutical Opinion Program⁴ (<http://www.health.gov.on.ca/en/pro/programs/drugs/pharmaopinion/>) implemented by the Ontario Ministry of Health and Long-Term Care.

This pilot study is the first of its kind and offers pharmacy practitioners an educational opportunity to further develop their knowledge of drug-drug interactions, as well as facilitating the integration of pharmacists' interventions through the Pharmaceutical Opinion Program. Most importantly, this pilot aims to ultimately reduce the occurrence of specific drug-drug interactions that have been associated with potential hospitalizations by utilizing the specialized knowledge and skills of pharmacy practitioners.

For more information about this project and how to become a participant, visit www.ismp-canada.org/DDI_pharmaopinion/ or email ISMP Canada at ddi@ismp-canada.org.

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The Canadian Medication Incident Reporting and Prevention System (CMIRPS) is a collaborative pan-Canadian program of Health Canada, the Canadian Institute for Health Information (CIHI), the Institute for Safe Medication Practices Canada (ISMP Canada) and the Canadian Patient Safety Institute (CPSI). The goal of CMIRPS is to reduce and prevent harmful medication incidents in Canada.



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