Impact of Pharmacist Intervention on Electrocardiogram Monitoring of Pediatric Patients on Multiple QTc Interval–Prolonging Medications

Lisa M. Hutchins, PharmD, BCPPS; Joel D. Temple, MD; and Elora Hilmas, PharmD, BCPS

OBJECTIVES To determine whether dedicated pharmacy services improve the rate of electrocardiogram (ECG) monitoring in patients at risk for medication-induced QTc interval prolongation. In addition, determine how pediatric institutions currently monitor patients at risk for medication-induced QTc interval prolongation.

METHODS A pharmacist-driven monitoring protocol to detect medication-induced QTc interval prolongation was developed using published literature. If patients were prescribed 3 or more medications known to prolong the QTc interval, they were recommended to have a baseline ECG to assess the QTc interval. If 3 or more QTc interval–prolonging medications were administered for 5 or more days, a follow-up ECG was recommended. Patients prescribed medications known to prolong the QTc interval were identified. Prior to pharmacist intervention, electronic medical records were reviewed to determine if baseline and follow-up ECGs were obtained in patients meeting criteria for monitoring. A dedicated pharmacist then prospectively reviewed charts and recommended monitoring. The rate of monitoring during the intervention and baseline period was compared. To determine current practice at pediatric institutions, a survey was distributed to pharmacists.

RESULTS Pharmacist intervention improved the rate of ECG monitoring in patients at risk for medication-induced QTc interval prolongation from 47.8% to 100% ($p = 0.0009$). Of the 55 survey participants, 6 stated their institution had QTc interval monitoring procedures in place, 35 did not have any, and 3 had procedures in process.

CONCLUSIONS Targeted pharmacist intervention improved the rate of ECG monitoring in patients at risk for medication-induced prolonged QTc interval. Our research and survey data reveal that institutions could benefit from targeted pharmacist intervention to monitor patients for medication-induced QTc interval prolongation.

ABBREVIATIONS AHA, American Heart Association; AZCERT, Arizona Centers for Education and Research on Therapeutics; CERT, Centers for Education and Research on Therapeutics; ECG, electrocardiogram; FDA, Food and Drug Administration; ICU, intensive care unit; LQTS, long QT syndrome

KEYWORDS adverse effect; medication interactions; pediatrics; pharmacist intervention; QTc interval; torsade de pointes

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Introduction

Medication-induced QTc interval prolongation is a well-known adverse drug effect. QTc interval prolongation can predispose a patient to the potentially fatal arrhythmia torsade de pointes.^{1,2} A prolonged QTc interval is generally accepted to be a QTc interval above the 99th percentile of population values, or in adults, an interval of over 470 msec for males and over 480 msec for females.³ QTc intervals greater than 500 msec are independently associated with increased risk of torsade de pointes with or without medications on board.^{3,4} The normal QTc interval in pediatric patients changes as they age, with normal values close to those for adults.⁵

A QTc interval increase of 60 msec from baseline is also considered clinically significant, even if the resulting QTc interval is not above the 99th percentile threshold.⁶

In 1999, federal funding enabled the creation of the Centers for Education and Research on Therapeutics (CERT) to perform active surveillance on medication-induced QTc interval prolongation reports. This later became Arizona CERT (AZCERT), an independent non-profit organization based in Arizona.¹ The organization's Web site, CredibleMeds (www.Crediblemeds.org), maintains a continuously updated list of medications known or suspected to contribute to QTc interval prolongation and torsade de pointes.¹ The AZCERT, under contract with the Food and Drug Administration (FDA),

reviews available published literature, drug labels, and reports submitted to the FDA and reports made directly to them and evaluates them to determine a medication's potential to cause QTc interval prolongation and torsade de pointes.¹

CredibleMeds places reviewed medications in categories depending on the risk of inducing torsade de pointes: known, possible, or conditional risk of torsade de pointes and drugs to avoid in patients with known congenital long QT syndrome (LQTS).¹ Medications with known risk are those with substantial evidence that they not only prolong the QTc interval but also contribute to an increased risk of torsade de pointes.^{1,7} “Possible” risk medications are those that are known to prolong the QTc interval but for which evidence is insufficient to conclude that they are associated with torsade de pointes.^{1,7} Medications are considered at conditional risk if the available data supporting their association with torsade de pointes are only in relation to other known risk factors, excessive doses, and/or drug-drug interactions.^{1,7} Patients with congenital LQTS should avoid all the medications in the 3 categories above, and additional drugs are placed in this category if they have a theoretical risk of causing other arrhythmias that could put these patients at increased risk of torsade de pointes.^{1,7} The medication lists have become a reliable tool for health care providers to identify medications that put patients at risk.^{1,7}

The risk of medication-induced QTc interval prolongation in adults is well represented in the literature, but well-controlled studies in pediatric patients are lacking.⁸ Aside from medications, several risk factors for torsade de pointes in adult patients include heart disease, age greater than 65 years, female sex, hypokalemia, hypomagnesemia, hypocalcemia, and bradycardia.^{3,9} Even though the risk of torsade de pointes is rare in adults, it is well-known and dangerous enough that in 2005 the FDA published guidance for the industry requiring medication developers to evaluate the risk of inducing QTc interval prolongation before seeking drug approval.¹⁰ This program does not prevent QTc interval–prolonging medications from entering the market, but it educates health care professionals and patients regarding the risks of these medications. Given that there are medications that have high utility even with this potentially serious side effect, procedures for monitoring would improve the safe use of these medications.

The best way to monitor patients for medication-induced long QTc interval is not well elucidated.³ In 2010, the American Heart Association (AHA) published a scientific statement³ regarding the prevention of torsade de pointes in hospitalized patients, but the recommendations provided are vague and recommend patient-specific and location-specific monitoring protocols be developed. The recommendations do not specifically address hospitalized pediatric patients, who

Figure. Protocol for monitoring QTc interval.

may have different risk factors.^{3,6} Given the lack of clear guidelines for hospitalized patients, hospitals may not attempt to reform outdated practices until a patient experiences medication-induced torsade de pointes or sudden cardiac death.

The primary objective of this study was to determine if practitioners at a freestanding children's institution routinely monitor patients who are ordered multiple QTc interval–prolonging medications. After determining current practice, targeted pharmacist intervention was made to recommend baseline and follow-up electrocardiograms (ECGs) on patients ordered and receiving multiple QTc interval–prolonging medications. The historical practice was compared to the targeted pharmacist intervention period to determine if this intervention improved the rate of cardiac monitoring in these potentially at-risk patients. The last objective was to determine what procedures other institutions had in place to monitor pediatric patients for medication-induced QTc interval prolongation.

Materials and Methods

This was a prospective interventional study with a retrospective cohort. It was completed at a 180-bed tertiary, academic-affiliated, freestanding children's hospital. A protocol for QTc interval monitoring was designed by a pediatric cardiologist and clinical pharmacists after reviewing the AHA scientific statement and published literature (Figure).³ Medications were

Table 1. Medications Known to Cause Torsade de Pointes From CredibleMeds Worldwide*

Alfuzosin	Amantadine	Amiodarone	Amitriptyline	Amoxapine
Anagrelide	Apomorphine	Aripiprazole	Arsenic trioxide	Artenimol/piperaquine
Atazanavir	Azithromycin	Bedaquiline	Bortezomib	Bosutinib
Chloral hydrate	Chloroquine	Chlorpromazine	Ciprofloxacin	Citalopram
Clarithromycin	Clomipramine	Clozapine	Cocaine	Crizotinib
Dabrafenib	Dasatinib	Desipramine	Dexmedetomidine	Diphenhydramine
Disopyramide	Dofetilide	Dolasetron	Doxepin	Dronedarone
Droperidol	Eribulin mesylate	Erythromycin	Escitalopram	Famotidine
Felbamate	Fingolimod	Flecainide	Fluconazole	Fluoxetine
Foscarnet	Fosphenytoin	Furosemide	Galantamine	Gemifloxacin
Granisetron	Halofantrine	Haloperidol	Hydrochlorothiazide	Hydroxychloroquine
Ibutilide	Iloperidone	Imipramine	Indapamide	Isradipine
Itraconazole	Ketoconazole	Lapatinib	Levofloxacin	Lithium
Methadone	Metronidazole	Mifepristone	Mirabegron	Mirtazapine
Moexipril/ hydrochlorothiazide	Moxifloxacin	Nelfinavir	Nicardipine	Nilotinib
Norfloxacin	Nortriptyline	Ofloxacin	Olanzapine	Ondansetron
Oxytocin	Paliperidone	Paroxetine	Pasireotide	Pazopanib
Pentamidine	Perflutren lipid microspheres	Pimozide	Posaconazole	Procainamide
Promethazine	Protriptyline	Quetiapine	Quinidine	Quinine sulfate
Ranolazine	Rilpivirine	Risperidone	Ritonavir	Saquinavir
Sertraline	Sevoflurane	Solifenacin	Sorafenib	Sotalol
Sunitinib	Sulfamethoxazole/ trimethoprim	Tacrolimus	Tamoxifen	Telaprevir
Telavancin	Telithromycin	Tetrabenazine	Thioridazine	Tizanidine
Tolterodine	Toremifene	Trazodone	Trimipramine	Vandetanib
Vardenafil	Vemurafenib	Venlafaxine	Voriconazole	Vorinostat
Ziprasidone				

* Created using available data on September 10, 2014.

determined to put a patient at risk of QTc interval prolongation if they were listed in the conditional, possible, or known torsade de pointes risk categories on CredibleMeds (Table 1) (accessed September 10, 2014).¹ Patients were identified with current active medication orders for these QTc interval–prolonging medications via a report created using the electronic medical record system. Patients met criteria for a baseline ECG when 3 or more of these medications were prescribed together. Patients were not excluded if they were on 1 or 2 QTc interval–prolonging medications prior to the addition of a third medication. Patients were excluded from the study during the intervention period if they had been on 3 or more QTc interval–prolonging medications for more than 7 days prior to study initiation. Patients met criteria for a follow-up ECG when 3 or more of these medications were administered for 5 or more days.

After institutional review board approval was obtained, a retrospective electronic medical record review was conducted on patients admitted from September 4, 2014, through November 14, 2014. The rates of baseline and monitoring ECG obtainment were recorded for the patients who were prescribed and administered 3 or more QTc interval–prolonging medications. From November 17, 2014, through December 5, 2014, a pharmacist prospectively monitored electronic medical records and made recommendations for provision of baseline and monitoring ECG for patients who met criteria. Rates of monitoring were again recorded. Data collected included demographic information (e.g., age, sex), admitting service, and classes of medications prescribed. Statistical analyses were completed using Fisher exact tests. Results were considered statistically significant if the p value was <0.05.

Table 2. Patient Demographics

Characteristic	Control	Intervention	p value
Met criteria for baseline, n	88	42	—
Met criteria for monitoring, n (%)	23 (26)	14 (33)	0.39
Sex			
Male, n (%)	47 (53)	20 (48)	0.54
Age, n (%)			
<1 yr	9 (10)	3 (7)	0.75
1 yr to <5 yr	18 (20)	10 (24)	0.66
5 yr < 10 yr	10 (11)	5 (12)	1.00
5 yr < 10 yr	29 (33)	13 (31)	0.84
15 yr < 18 yr	22 (25)	11 (26)	1.00
Admitting service, n (%)			
Cardiology	6 (7)	2 (5)	1.00
Critical Care	10 (11)	4 (10)	1.00
Hematology/Oncology	33 (38)	25 (59)	0.02
General Pediatrics	39 (44)	11 (26)	0.06
Top classes QTc interval medications prescribed, n (%)			
Antibiotic	71 (21)	34 (19)	0.73
Antiemetic	70 (20)	32 (18)	0.56
Antihistamine	58 (17)	34 (19)	0.54
Antidepressant	32 (9)	13 (7)	0.51
Antifungal	32 (9)	18 (10)	0.88
Diuretic	23 (7)	14 (8)	0.72

To determine institutional practices, an institutional review board–approved 11-question anonymous survey created using REDCap was distributed via a pediatric pharmacy practitioner list serve (survey available from EH). The data collected about the institutions included presence of policies and procedures surrounding QTc interval monitoring in patients at risk for medication-induced QTc interval prolongation, presence and types of warnings issued for at-risk patients, practitioners who received the warnings, and who the responsible party was for monitoring at risk patients.

Results

Patient Characteristics. During the control period, 88 patients were prescribed 3 or more QTc interval–prolonging medications and met criteria for baseline ECG monitoring. Of these patients, 23 actually received at least 3 of the medications and met criteria for a follow-up ECG. Forty-two patients met criteria for a baseline ECG during the 18-day active intervention period. Of these, 14 patients met criteria for a follow-up ECG. Patient demographics are listed in Table 2. The only statistically significant baseline difference between the control and intervention patients is that more patients

were admitted under the Hematology and Oncology Service during the intervention period. Reasons for this difference could not be identified. The top prescribed classes of QTc interval–prolonging medications are also listed in Table 2. There were no statistically significant differences in the classes of medications ordered between the control and intervention periods.

ECG Monitoring. The percentage of patients who were ordered a baseline ECG was not significantly different between the control and intervention groups ($p = 0.14$). There was also no statistically significant difference in the percentage of patients who met criteria for a follow-up ECG between the control and intervention groups ($p = 0.39$). A higher percentage of patients in the intervention group who met criteria for a follow-up ECG had one done than in the control group ($p < 0.001$). The number of pharmacy interventions (i.e., calls made to recommend monitoring) also increased between the control and intervention period ($p < 0.001$). The rate of intervention acceptance by the medical team was not statistically significantly different. Monitoring and pharmacy intervention data are found in Table 3.

Institutional Surveys. Fifty-five completed surveys were submitted. Six respondents stated that their institution had formal policies and procedures for

Table 3. Monitoring Pharmacy Data

Characteristic	Control	Intervention	p value
Baseline ECG			
Met criteria for baseline ECG, n	88	42	—
Baseline ECG obtained, n (%)	70 (79)	38 (90)	0.14
Monitoring ECG			
Met criteria for monitoring ECG, n (%)	23 (26)	14 (33)	0.39
Monitoring ECG obtained, n (% who met criteria)	11 (48)	14 (100)	<0.001
Intervention			
Documented pharmacy interventions, n (%)	9 (10)	20 (48)	<0.001
Accepted pharmacy interventions, n (%)	7 (78)	16 (80)	1.00

ECG, electrocardiogram

medication-induced QTc interval prolongation monitoring in place and 3 stated that policies were in process. A total of 27 locations have electronic alerts that the pharmacist, prescriber, and/or nurse receive (27, 22, and 2, respectively), with one institution also having a daily report that is generated listing patients at risk for medication-induced QTc interval prolongation. The responsible party for follow-up monitoring of QTc intervals was felt to be the pharmacist at 19 of the institutions and the medical staff or prescriber at 7 of them.

Discussion

Without well-controlled studies and evidence-based guidelines describing adequate methods to monitor pediatric patients for medication-induced QTc interval prolongation, hospitals must attempt to create institution-specific procedures that balance provider workload and patient safety. The true incidence of torsade de pointes–induced cardiac death is unknown, since many patients who experience sudden death are not on a cardiac monitor at the time of death,³ but a population estimate of torsade de pointes in one Swedish study was 4 in 100,000 patients.¹¹ A German study estimated the incidence of medication-induced QTc interval prolongation and torsade de pointes together to be 2.5 per million per year for men and 4 per million per year for women.¹² These estimates are drastically higher than the incidence of 0.26 per million figure based on European spontaneous adverse drug reaction reports,¹² implying that the risk of medication-induced prolongation of the QTc interval and torsade de pointes may be much higher than previously believed. Pediatric patients were excluded from these studies; however, there are case reports and reviews^{13–15} describing cardiac arrest and torsade de pointes in pediatric patients due to several medications. The development of monitoring protocols for at-risk hospitalized pediatric patients is important to capture and prevent this potentially fatal side effect.

This study found that dedicated pharmacy services successfully improved the rate of pediatric patient

monitoring when 3 or more QTc interval–prolonging medications were administered. Unfortunately, there was not a significant difference in checking a baseline QTc interval (80% vs 90% control vs intervention, respectively), which puts patients who have an unknown congenital LQTS at higher risk of torsade de pointes secondary to medications. It is currently estimated that 1 in 2,000 people have LQTS.¹⁶ Patients are not routinely screened for this in childhood without a family history or occurrence of an inciting event; there are no data yet to indicate that universal screening is cost effective or that it would improve patient safety. Without formal policies in place, these patients, while rare, can easily be missed and administered medications that could result in significant toxicity. In addition to patient-specific variables, if there are drug interactions or many QTc interval–prolonging medications being administered, an ECG earlier than 5 days would be warranted to ensure a rapidly increasing QTc interval is discovered early.

Survey data revealed that many institutions who treat pediatric patients have not yet implemented formal policies and procedures for identifying medication-induced QTc interval prolongation. Though several identified providers were responsible for monitoring, it would be difficult to manage at-risk patients without policies to guide the practitioner. Most institutions reported the use of electronically generated pop-up alerts to alert the provider at the point of order entry and verification, but this method is known to be flawed. A study¹⁷ examining whether providers monitored adult patients for QTc interval prolongation after an electronic alert found that an ECG was ordered only 33% of the time. Of the patients with ECG monitoring, 31% had clinically relevant QTc interval prolongation on the medications.¹⁷ In this study, there were many patients with the potential for QTc interval prolongation who were not monitored and who may have been at risk for torsade de pointes. Providers may also be experiencing alert fatigue, receiving too many alerts that are of low value, thus increasing the risk that they will override clinically important alerts.¹⁸

This is a known complication with utilizing these notices, and institutions should consider implementing some other form of surveillance to monitor at-risk patients.

The optimal form of monitoring is not well elucidated for adult or pediatric hospitalized patients, and the methods described by the AHA and other sources have drawbacks.^{3,4} Electronic alerts are one of the easiest methods to employ, but in addition to the limitations described above, they are only as accurate as the information entered into the electronic medical record.¹⁷ For example, if a patient had congenital LQTS that was as-yet undiagnosed, the system would not alert the health care team of the patient's enhanced risk. Prescribers often view electronic pop-up alerts as a nuisance and state that alert fatigue is a major issue for them.¹⁸ More prescribers have stated that communication from a pharmacist is more useful than an electronic alert when it comes to medication safety and monitoring.¹⁸ Pharmacist intervention using an algorithm addressing QTc interval–prolonging medications was found to decrease the rate of QTc interval greater than 500 msec and the rate of medication-induced QTc interval prolongation in at-risk adult intensive care unit (ICU) patients.¹⁹ In the algorithm, pharmacists recommended dose adjustments or discontinuation of QTc interval–prolonging medications, discontinuation of medications known to interact with the QTc interval–prolonging medication, electrolyte corrections, laboratory monitoring, and/or ECG monitoring depending on the risk to the patient.¹⁹ The barrier to implementing this protocol in all patients is that the risks in non-ICU patients may not be the same, and pediatric patients in general may have risk factors that differ from those of adult patients. Other methods utilizing pharmacist intervention could be employed since pharmacists are well-respected members of the health care team, as evidenced in this study by the excellent rate of pharmacist intervention acceptance during the control and intervention period and given the pharmacist's role as a medication expert.⁷

After identifying patients who are at risk for medication-induced QTc interval prolongation, the AHA recommends either continuous heart rhythm monitoring or obtaining an ECG every 8 to 12 hours.³ Barriers to continuous monitoring include that not all hospital beds are equipped to implement continuous monitoring and without proper policies practitioners may not be reviewing continuous monitors for QTc interval prolongation. Obtaining an ECG every 8 to 12 hours is inconvenient to practitioners and patients and may increase hospital costs without ensuring increased patient safety. More research needs to be done to determine all risk factors and the most effective method with which to monitor hospitalized patients for medication-induced QTc interval prolongation.

There are several limitations of this study. First, the control patient data were gathered through retrospective review. There are a relatively small number of

patients in each arm of the study gathered during a limited time frame. It is unknown whether improved monitoring would lead to improved patient outcome as the difference between control and intervention QTc interval was not assessed during this study. The threshold of 3 medications was chosen based on anticipated daily workload, but this approach left patients who received only 1 high-risk medication at risk. There were also patients in which the baseline ECG was obtained while the patient was receiving 1 or 2 QTc interval–prolonging medications. These patients could have had significant prolongation with just these medications, and the study could have missed significant changes from true baseline. Recommending an ECG after 5 days of therapy could also allow one to miss a patient who experienced prolonged QTc intervals or torsade de pointes sooner. This time frame was decided upon despite the AHA's recommended every 8- to 12-hour ECG monitoring³ to try to limit the increased workload on non-ICU floors and improve provider acceptance. Since this study was completed, a recommendation to monitor an ECG after 3 to 7 days of therapy with QTc interval–prolonging medication in pediatric patients has been published⁶; therefore, this protocol is in line with this proposal. This protocol is also not conducive to permanent implementation in the hospital setting as the daily time requirements were substantial and would require dedicated pharmacy drug monitoring services just for QTc interval monitoring.

Since it was identified that targeted pharmacist intervention improves monitoring in patients at risk for QTc interval prolongation secondary to medications, a patient care dashboard was developed for clinical pharmacists to easily identify at-risk patients. The dashboard attempts to incorporate all risk factors for QTc interval prolongation, not just medications. Medications are scored according to their risk of causing QTc interval prolongation, according to CredibleMeds, with higher risk medications given a higher score. Points are also assigned for electrolyte abnormalities known to contribute to QTc interval prolongation (hypokalemia, hypocalcemia, hypomagnesemia). The dashboard then assigns points for patients with a prior history or diagnosis of QTc interval prolongation. This resource is now utilized daily by our clinical pharmacists to quickly and easily identify patients who are at risk for QTc interval prolongation and make recommendations for dose adjustments, alternative therapy, or monitoring to decrease the risk of adverse outcomes. Clinical decision-support tools utilizing the electronic medical record, such as this one, have been found to reduce the risk of QTc interval prolongation secondary to medications in adult patients.²⁰ Even though it is not yet validated for pediatric use, this type of patient surveillance system could improve monitoring and patient safety without significantly increasing the burden on the health care team.

Conclusions

Many pediatric institutions do not have policies or procedures in place to identify or monitor patients at risk for medication-induced QTc interval prolongation. Our study showed that a protocol with dedicated pharmacist intervention improves the rate of ECG monitoring in patients who are prescribed multiple QTc interval–prolonging medications. Further research should be done to discover QTc interval–prolonging risk factors specific to pediatric patients and to determine the most efficient procedures with which to identify and monitor these patients while they are hospitalized. Until that occurs, institutions should evaluate their resources and implement their own multidisciplinary protocols to mitigate the risk of torsade de pointes and sudden cardiac death secondary to medications.

ARTICLE INFORMATION

Affiliations Bloomberg Children's Center (LMH), Johns Hopkins Hospital, Baltimore, Maryland, Nemours/Alfred I. duPont Hospital for Children (JDT, EH), Wilmington, Delaware

Correspondence Elora Hilmas, PharmD,
elora.hilmas@nemours.org

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