

How to Prescribe Drugs With an Identified Proarrhythmic Liability

The Journal of Clinical Pharmacology
2020, 60(3) 284–294
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Clinical Pharmacology
DOI: 10.1002/jcph.1551

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Abstract

This is an article in the *Journal of Clinical Pharmacology's* Core Entrustable Professional Activities in Clinical Pharmacology series that discusses drug-induced proarrhythmia and is offered as a teaching aid for medical students and residents. Drugs from diverse pharmacological classes can lead to multiple types of arrhythmias including the polymorphic ventricular tachycardia torsades de pointes (TdP). Although typically occurring in self-limiting bursts with or without associated symptoms, which can range from mild lightheadedness and palpitations to syncope and seizures, TdP can also occasionally progress to ventricular fibrillation and sudden cardiac death. To provide patients with the optimal therapeutic benefits of potentially proarrhythmic drugs, prescribers are responsible for obtaining a good understanding of the compound's benefit-risk properties and perform a judicious assessment of the patient's clinical characteristics and individual risk factors. Dose adjustments and/or additional monitoring of electrocardiograms and electrolyte balances may be appropriate in some cases. This article explains the pharmacological mechanism of action of drug-induced proarrhythmia associated with compounds that prolong the repolarization period, illustrates how this liability is conveyed in a drug's prescribing information (label), details the clinical characteristics of patients most susceptible to this type of proarrhythmia, and describes interventions that can be made if TdP occurs. Three clinical vignettes are provided at the end of the article to highlight the relevance of the preceding discussions.

Keywords

drug-induced proarrhythmia, QT interval, torsades de pointes, predisposing clinical risk factors, drug-drug interactions, electrocardiogram monitoring, electrolyte monitoring, cardiac safety

The Association of American Medical Colleges has identified critical knowledge and skills that medical students should acquire before graduation in preparation to function independently at the beginning of their residency training: these are known as entrustable professional activities (EPAs).^{1–4} A core component of EPAs in clinical pharmacology/prescribing is the ability to prescribe medications appropriately. Knowledge and understanding of clinical pharmacology are vital in facilitating such prescribing, and, accordingly, the American College of Clinical Pharmacology has created an educational series titled “Pearls for Clinical Practice,” published in the *Journal of Clinical Pharmacology*. The target audience includes medical students and residents, medical educators, and faculty at academic medical centers. These articles also serve as refreshers for practitioners and other medical professions.⁵ Each one focuses on a specific topic within the realm of clinical pharmacology. A succinct analytical review of the topic is provided and then followed by clinical vignettes and associated commentaries that illustrate the practical application of knowledge learned from reading the review.

The topic of this article is drug-induced proarrhythmia, with a focus on one specific arrhythmia that can be elicited by drugs that prolong the cardiac repolarization

period, the rare polymorphic ventricular arrhythmia called torsades de pointes (TdP).⁶ We introduce the preapproval nonclinical investigations and clinical studies employed to assess a new drug's proarrhythmic liability before a licensing application is made to regulatory agencies, explain the pharmacological mechanism of action of this occurrence, illustrate how such liability is conveyed to physicians in a drug's prescribing

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Submitted for publication 5 September 2019; accepted 10 October 2019.

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Figure 1. An ECG strip showing an Episode of TdP.

information (label), discuss the clinical characteristics of patients most susceptible to TdP, and address what interventions can be made if TdP occurs. We also emphasize that drugs with a proarrhythmic liability can be used safely to provide important therapeutic benefit as long as they are prescribed judiciously.

Torsades de Pointes

TdP has 3 defining characteristics that can be seen on a surface electrocardiogram (ECG), as shown in Figure 1:

- The shape of the QRS complex (QRS morphology) twists around an imaginary axis, and there may also be a change in the amplitude of the waveform.
- The QRS complex takes on many shapes (morphologies) when twisting around its axis, leading to the descriptor polymorphic.
- It is associated with prolongation of the QT interval. This interval represents cardiac depolarization and repolarization, and prolongation is indicative of delayed repolarization.

TdP typically occurs in self-limiting bursts, with or without associated symptoms that can range from mild lightheadedness and palpitations to syncope and seizures. However, this arrhythmia also has potentially catastrophic consequences—it can occasionally progress to ventricular fibrillation and sudden cardiac death.⁷

Normal Cardiac Ion Channel Activity, Inherited Long QT Syndrome, and Drug-Induced QT Prolongation

TdP is the characteristic ventricular tachycardia resulting from a constellation of inherited long QT syndromes (LQTS). Of specific interest is long QT syndrome 2 (LQT2),^{8–10} and of immediate relevance is that a similar clinical presentation can be seen because of acquired (drug-induced) prolongation of cardiac repolarization. The mechanism linking delayed cardiac repolarization, expressed on the ECG as long QT, and subsequent incidence of TdP is described next.

Cardiac depolarization and subsequent repolarization are mediated by ionic currents flowing through ion channels expressed in cardiomyocyte cell membranes. Depolarization occurs when the permeability to

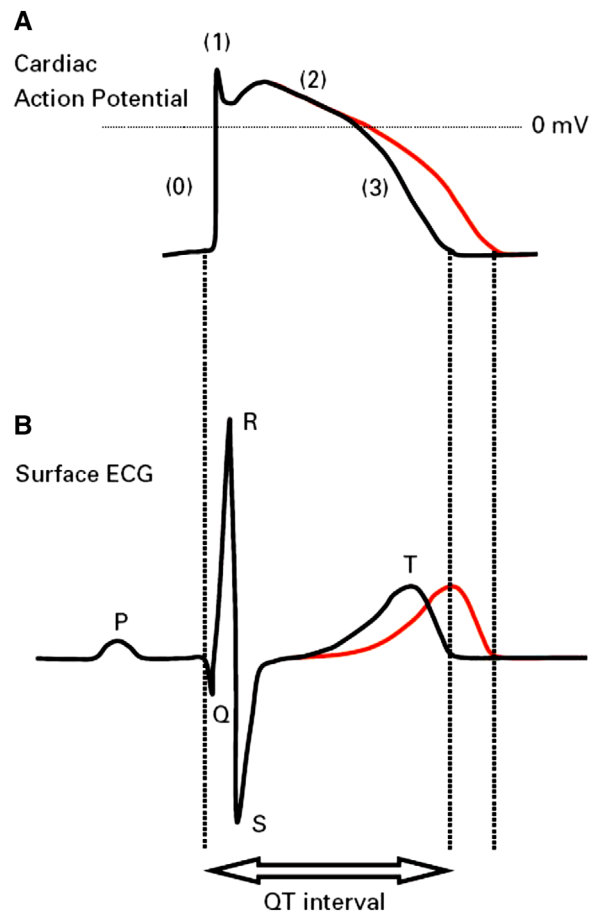


Figure 2. Stylistic representation of the relationship between the cardiac action potential and the surface ECG and of QT interval prolongation. (A) Cardiac action potential and also a drug-induced more gradual decline in phase 3 of the action potential (red). (B) Surface ECG and the QT interval. QT interval prolongation is shown in red. Reprinted with permission from Satin et al.⁵⁵

sodium increases and sodium ions (Na^+) enter the cell (phase 0 of the cardiac action potential: see Figure 2). Repolarization is mediated in large part by the outward movement of potassium (K^+) ions via voltage-gated channels. One such channel is the hERG cardiac potassium channel, so-named because its central pore (the α subunit of the channel) is encoded by *hERG*, the human ether-a-go-go related gene. The potassium ionic current I_{Kr} , the rapid component of the delayed rectifier potassium current responsible for the late phase of cardiac repolarization, flows through the hERG channel and is often referred to as the hERG current.

Under usual circumstances, during every cardiac cycle, hERG current flows normally through the hERG channel from the inside of the cell to the outside. This results in normal phase 3 repolarization, represented on a surface ECG as a QT interval, that is, the time between onset of the QRS complex and the offset of the T wave, of normal length (see Figure 2). In contrast, abnormal cell membrane expression or function of hERG channels leads to delayed repolarization, seen on the ECG as QT prolongation. Patients with an abnormal variant of *hERG* have a defect in the hERG channel's central pore, which leads to loss of function (ie, decreased repolarizing hERG current), a more gradual slope in phase 3 of the action potential (ie, delayed repolarization), and QT prolongation. This genetic syndrome is called LQT2. When phase 3 of repolarization is prolonged, there is a risk of having abnormal depolarization currents before completion of normal repolarization (called early after depolarizations) that could evolve to arrhythmic events such as TdP.

The constellation of inherited LQTS has been highly investigated, but remains largely the domain of cardiologists, cardiac electrophysiologists, and specialized centers.¹¹ For the subset of readers who may wish to pursue this specialty, references are provided.¹²⁻¹⁴

As a result of its relatively large size and the nature of the specific amino acid residues forming the inner wall of the channel's pore, the hERG channel (compared with many other ion channels) is remarkably susceptible to block by a wide range of small-molecule drugs.¹⁵ Drug block leads to reduced hERG current, reduced net repolarizing currents, QT prolongation, and sometimes proarrhythmia. Of direct relevance here is that although the precipitating influences are different in LQT2 and drug block of the hERG channel, the similarity in the consequences in each case makes drug-induced QT prolongation of considerable clinical concern.

In contrast to the medical specialties focusing on LQTS, drug-induced QT prolongation is relevant to a much wider group of health care professionals involved in therapeutic decisions, for example, physicians in family practice and a wide variety of medical specialties, physician assistants, nurses, and pharmacists¹⁶⁻¹⁹ and hence this article's focus on this topic. A wide range of drugs and drug classes²⁰⁻³² for many conditions as diverse as liver³³ and kidney³⁴ disease, chronic obstructive pulmonary disease,³⁵ psychiatric conditions,³⁶ and posttraumatic stress disorder³⁷ have an identified proarrhythmic liability. If prescribed to patients with certain risk factors, they can occasionally precipitate bradyarrhythmias and tachyarrhythmias, including TdP. These risk factors are discussed in due course.

Preapproval Assessments of a New Drug's Proarrhythmic Liability

As Link and colleagues³⁸ observed, "One of the most feared complications in medicine is sudden death caused by drug-induced proarrhythmia. Accordingly, concerted efforts have been made to define a drug's proarrhythmic potential before regulatory approval." These concerted efforts were spurred by increasing scientific, clinical, and regulatory concerns regarding multiple proarrhythmic events that led to drug marketing withdrawals from the late 1980s to the early 2000s.³⁹ The consensus recommendations were formalized in 2005 with the release of 2 guidelines from the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH).⁴⁰ ICH is an organization representing an amalgamation of clinical, scientific, and regulatory expertise from pharmaceutical organizations and regulatory agencies across the world. The intent of these guidelines, which have been adopted by multiple regulatory agencies, is to determine to the greatest degree possible during premarketing nonclinical investigations and clinical assessments whether a new drug has a proarrhythmic liability.

ICH S7B⁴¹ addresses nonclinical investigations and focuses on 2 main components: assessments of any drug-induced reduction in hERG current and the evaluation electrocardiographic parameters, including the QT interval, measured in conscious or anesthetized animals with relevant drug exposures.

ICH E14⁴² includes recommendations to evaluate the effects of new agents on the QT interval as well as the collection of cardiovascular adverse events. It introduced a clinical pharmacology study called the Thorough QT/QTc (TQT) Study, a dedicated study examining a drug's effects on ECG parameters, including propensity to increase the QT interval.^{7,43,44} The term *QTc* in the TQT study's name arises because the QT interval duration varies inversely with heart rate, regardless of any drug effect. Hence, the absolute QT measurement is "corrected" for heart rate to yield QTc. Various correction formulas are employed to enable objective comparison of repolarization times at different heart rates.⁴⁵

Regulators want sponsors to document a drug's effects on cardiac repolarization at therapeutic and suprathreshold exposures. The suprathreshold dose (typically several multiples of the therapeutic dose unless the therapeutic dose is close to the maximum tolerated dose) is intended to reveal what may happen in the "worst-case scenario," that is, the highest exposures that could be attained from a therapeutic dose given to patients because of effect modifiers including pharmacokinetic variability, drug-drug interactions,

alterations in metabolism or elimination, or underlying heart disease.⁷

The regulatory threshold of concern is a population mean QT prolongation of “around 5 msec.”⁴² This is operationalized by calculating the 2-sided 90% confidence intervals (CIs) around the mean difference point estimate of QTc prolongation for each time in the study. If the upper limits of the CIs for all times for the suprathreshold dose are less than 10 milliseconds, this implies that even at suprathreshold exposures, there is a very low likelihood that there will be clinically significant drug-induced QT prolongation and that subsequent phase 3 trials will not require intensive ECG monitoring. In contrast, if any upper limit is 10 milliseconds or higher, more extensive ECG/QTc evaluations may be needed during subsequent phase 3 trials to better characterize potential proarrhythmic events.

In addition to this analysis of the mean changes for all participants in a TQT study, ICH E14 also recommends presentation of categorical data in 2 ways to capture outliers: the number of study participants showing absolute QTc values of greater than 450, 480, and 500 milliseconds, and the number of study participants showing changes from their own baseline values of greater than 30 and 60 msec.⁴² At an individual patient level, changes of less than 60 milliseconds with a QTc less than 500 milliseconds are very seldom associated with proarrhythmia.

How Proarrhythmic Liability Is Conveyed in Drug Labels

The science of proarrhythmic cardiac safety can be considered to have two parts. The first is preapproval identification of a drug’s proarrhythmic liability and the selection of the most appropriate risk management actions including, sometimes, the addition of warning language in its label. The major players in premarketing cardiac safety assessment are drug developers, research clinicians, and regulators. The second part is the employment of this information to guide judicious prescription of the drug during the clinical practice of medicine: this part involves readers of this article.

The results of the early assessments of drug-induced effects in cardiac repolarization, ECG parameters and cardiovascular adverse events play a predominant role in determination of the ECG monitoring needs in additional clinical studies in a drug’s preapproval development program and, of specific interest here, warning language placed in its label when it receives marketing approval if a proarrhythmic liability was identified. As examples, Table 1 provides warning language for 3 oncologic drugs: vandetanib,⁴⁶ nilotinib,⁴⁷ and

Table 1. Selected Examples of Warning Language for Oncologic Drugs Taken From the Respective United States Prescribing Information

Drug	Summary of Warning Language
Vandetanib	<ul style="list-style-type: none"> • Vandetanib can prolong the QT interval. Torsades de pointe and sudden death have occurred in patients receiving vandetanib. • Do not use vandetanib in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. • Correct hypocalcemia, hypokalemia, and/or hypomagnesemia prior to vandetanib administration. • Monitor electrolytes periodically. • Avoid drugs known to prolong the QT interval.
Nilotinib	<p>There is a boxed warning for QT prolongation and sudden deaths. Accordingly:</p> <ul style="list-style-type: none"> • Monitor for hypokalemia and hypomagnesemia prior to nilotinib administration and correct identified deficiencies. • Monitor QTc at baseline, 7 days after initiation of treatment, and periodically thereafter, especially following any dose adjustments. • Do not administer to patients with long QT syndrome. • Avoid the concomitant use of drugs known to prolong the QT interval and strong CYP3A inhibitors. • Avoid food 2 hours before and 1 hour after taking a dose.
Ivosidenib	<ul style="list-style-type: none"> • Patients treated with ivosidenib can develop QTc prolongation and ventricular arrhythmias. • Concomitant use of ivosidenib with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes. • In patients with congenital long QTc syndrome, congestive heart failure, or electrolyte abnormalities or those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary. • Interrupt ivosidenib if QTc increases to greater than 480 milliseconds and less than 500 milliseconds. Interrupt and reduce ivosidenib if QTc increases to greater than 500 milliseconds. Permanently discontinue ivosidenib in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

ivosidenib.⁴⁸ Recommendations are provided concerning individuals who should not be prescribed the drug, monitoring that should take place for individuals who are prescribed the drug, and dose adjustments that should be made when QTc prolongation of a certain magnitude is seen. The basis for these recommendations is discussed in more detail in the next two sections.

Demographic and Clinical Characteristics of Patients Most Susceptible to Drug-Induced Proarrhythmia

Advanced age and female sex are risk factors for drug-induced QTc prolongation. In addition, drug-induced effects can also be amplified by many clinical conditions including the following: cardiac conditions (bradycardia and conduction abnormalities, structural heart disease, heart failure); thyroid, neurological, and metabolic disturbances; electrolyte imbalances (mainly hypokalemia, hypocalcemia, and hypomagnesemia); renal and liver impairment (with associated increases in serum concentration of the drug); and genetic predisposition (LQTS). Drug-drug interactions should also be considered.^{49–51}

Using demographic, medical, and drug data, one research group has developed a score called RISQ-PATH to identify patients at high risk for QTc prolongation and proposed that the RISQ-PATH model can be used in clinical decision support systems to create smart QT alerts.^{52,53}

Risk Management: Judicious Prescribing, Monitoring Strategies, and Interventions

When considering prescribing a drug with an identified proarrhythmic liability, the demographic and clinical risk factors just discussed should be carefully considered. That said, as noted at the beginning of this article, it is important to emphasize that drugs with a proarrhythmic liability can be used safely to provide important therapeutic benefit as long as they are prescribed judiciously. There are many occasions when a physician will consider, after circumspect consideration of the risks and the desired therapeutic benefit, that prescription of a drug with an identified proarrhythmic liability is justified for a specific patient because the benefit-risk balance is favorable.

In such cases, accurate implementation of recommended monitoring strategies and interventions is critical to patient safety. First, consider ECG monitoring.⁵⁴ This immediately raises the question of what QTc interval values are of clinical concern. Three reasonable starting points to answer this question are as follows. One is to determine what is considered a “normal QTc interval.” It is hard to categorize the normal QT interval for any individual precisely, as it changes with every heartbeat. Moreover, it can also change considerably because of normal daily activities that affect heart rate. However, using expert opinion to gain some perspective, we can consider the typical ranges observed in groups of individuals following a period of supine rest. In this context, the QT interval for

adult men and women can be regarded as ranging from 350 to 460 and 360 to 470 milliseconds, respectively (note that the values for women are slightly higher).⁵⁵

The second is to revisit the ICH E14 recommendations for reporting the results of TQT studies as presented earlier in this article. These were absolute QTc values greater than 450, 480, and 500 milliseconds and changes in QTc from baseline greater than 30 and 60 milliseconds. As was noted at that point in this article, at an individual patient level, changes of less than 60 milliseconds with a QTc less than 500 milliseconds are very seldom associated with proarrhythmia. The third is to look at information provided in drug labels and, if necessary, consult with professionals who have expertise in cardiac safety.

Electrolyte monitoring is a key component in the risk management for compounds known to affect cardiac repolarization.⁵⁶ It was noted previously that hypokalemia, hypocalcemia, and hypomagnesemia are risk factors for drug-induced QTc prolongation. Importantly, these are modifiable risk factors (in contrast to advanced age, female sex, and LQTS). Again, this observation pertains to both monitoring and appropriate interventions (see Table 1).

Physician and Patient Education in Cardiac Safety

Having read this article and become aware of the need to gain a knowledge and understanding of medications and drug-drug indications that can affect the QT interval, an additional resource could be the CredibleMeds website.^{57,58} This resource lists several hundred drugs (updates are made regularly) that are broken down into 3 primary categories based on a drug's likelihood to cause QTc prolongation or TdP. List 3 contains those with a conditional risk, list 2 contains those with a possible risk, and list 1 contains drugs with a known risk. Definitions of these categories and selected examples are provided in Table 2.

There is also a fourth category comprising drugs that pose a high risk of TdP for patients with inherited LQTS. Drugs in this category include all those in the conditional, possible, and known categories, plus additional drugs that do not prolong the QT interval per se, but which have a “special risk” because of other associated drug-induced effects that could lead to proarrhythmia not necessarily linked with QT prolongation. Examples of drugs in this category include amphetamine (a central nervous system stimulant indicated for attention deficit and hyperactivity disorder), dobutamine (an inotrope indicated for heart failure with cardiogenic shock), and pseudoephedrine (a decongestant indicated for allergic rhinitis).⁵⁷

Table 2. CredibleMeds Drug Risk Categories for QT Interval Prolongation and Occurrence of TdP and Examples of Drugs and Indications

TdP Risk Category	Category Definitions and Examples
Conditional	<p>Drugs that are associated with TdP <i>but</i> only under certain conditions of their use (eg, excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) or by creating conditions that facilitate or induce TdP (eg, by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP). Some examples are:</p> <ul style="list-style-type: none"> • Amantadine (influenza, Parkinson's disease) • Atazanavir (HIV/AIDS) • Diphenhydramine (allergic rhinitis, insomnia) • Esomeprazole (gastric hyperacidity, GERD) • Telaprevir (hepatitis C) • Ziprasidone (schizophrenia)
Possible	<p>Drugs that can cause QT prolongation <i>but</i> currently lack evidence for a risk of TdP when taken as recommended. Some examples are:</p> <ul style="list-style-type: none"> • Bedaquiline (multidrug-resistant tuberculosis) • Crizotinib (metastatic non-small cell lung cancer) • Felbamate (epilepsy) • Lithium (bipolar disorder) • Nicardipine (hypertension) • Venlafaxine (depression) • Vorinostat (lymphoma)
Known	<p>Drugs that prolong the QT interval <i>and</i> are clearly associated with a known risk of TdP, even when taken as recommended. Some examples are:</p> <ul style="list-style-type: none"> • Arsenic trioxide (leukemia) • Ciprofloxacin (bacterial infection) • Donepezil (Alzheimer's disease) • Fluconazole (fungal infection) • Methadone (narcotic dependence, pain) • Propofol (anesthesia)

It should be acknowledged here that although there is considerable interest in predictive analytics for the identification of patients at risk for drug-induced interval prolongation, the impact of such predictive analytics on overall patient safety outcomes requires further study.⁵⁹

With regard to patient education, patients should be advised to go directly to the emergency room if they experience palpitations, lightheadedness, or syncope.⁶⁰

Interventions When Episodes of TdP Occur

Interventions should be made when episodes of TdP (rather than just QTc prolongation) occur. The first intervention to consider is termination or dose reduction of the drug. If this is not possible or desirable, other interventions are available.

Thirty years ago, Iseri and colleagues⁶¹ noted that multiple tachyarrhythmias including TdP respond

favorably to magnesium therapy. Shortly thereafter, Banai and Tzivoni⁶² endorsed the use of intravenous magnesium sulfate and observed that treatment of TdP is aimed at shortening the QT interval. This can also be achieved by accelerating heart rate (recall earlier discussions that the QT interval is inversely related to heart rate), thus preventing the recurrence of the arrhythmia.

More recently, Thomas and Behr⁶³ presented more detailed discussion. When TdP occurs in recurrent self-terminating bursts, the more common occurrence, treatment has 2 aims: stabilize the myocardium using magnesium sulfate and shorten repolarization time (the QTc interval) by increasing heart rate using either chronotropic drugs such as isoproterenol and atropine or cardiac pacing.

Intravenous magnesium sulfate is recommended as an immediate first-line treatment and is simple and relatively safe to administer. That said, care should be taken not to cause hypermagnesemia: higher doses can lead to nausea, vomiting, drowsiness, and hypotension: substantially high doses can lead to slurred speech, double vision, neuromuscular blockade, respiratory depression, hypophosphatemia, hyperosmolar dehydration, cardiac arrhythmias, coma, and cardiac arrest.⁶³

Prolonged episodes of continuous TdP are likely to be associated with hemodynamic instability or cardiac arrest and should be terminated by prompt defibrillation (note that the oscillating R wave of this polymorphic ventricular arrhythmia prevents synchronization, and therefore delivery of an unsynchronized defibrillation is necessary).⁶⁴

Summary Comments

Before presenting our clinical vignettes, 3 brief quotes provide appropriate “take-home messages” from the material discussed to this point regarding the prescription of drugs with an identified proarrhythmic liability. First, quoting again from Link and colleagues,³⁸ “One of the most feared complications in medicine is sudden death caused by drug-induced proarrhythmia.” It is therefore advisable for physicians to become very familiar with this aspect of drug prescription. Second, quoting from the CredibleMeds website, “Based on ongoing systematic analysis of all available evidence, CredibleMeds® places drugs into broad categories based on whether each can cause QT prolongation or [TdP]. These actions are highly dependent on the circumstances of each drug’s use AND each patient’s clinical characteristics.”⁵⁷ Third, Beach and colleagues³⁸ observed as follows in the context of psychotropic medications, many of which are associated with proarrhythmia: “The most important risk-reducing intervention clinicians can make is undertaking a careful analysis

of other QT risk factors when prescribing psychiatric medications.” This quote can meaningfully be extended to include the prescription of any medication associated with drug-induced proarrhythmia.

Clinical Vignettes and Commentaries

Clinical Vignette 1

A 62-year-old woman presented to the emergency department early in the morning having experienced 3 days of cough that had progressed to right-sided pleuritic pain associated with general malaise, light-headedness, nausea, and vomiting. The patient did not regularly see doctors but did admit to a long-standing history of daily alcohol use. The patient was mildly confused and disoriented when interviewed by the admitting physician, and physical examination revealed a febrile, tachycardic, hypotensive patient with rales auscultated at the posterior right lung base. Laboratory testing was pertinent for leukocytosis, low serum albumin, and thrombocytopenia. The patient was diagnosed with community-acquired pneumonia and was given intravenous fluid resuscitation as well as parenteral ceftriaxone and azithromycin for empiric antimicrobial therapy. Chest x-ray showed features of right middle lobe consolidation consistent with this diagnosis. Over the following 12 hours the patient's blood pressure, heart rate, and fever curve improved. However, the patient remained confused and late in the evening started to become agitated and aggressive toward members of staff. The night-float intern was called and prescribed 1 mg of intravenous haloperidol to treat the patient's agitation in the setting of presumed infectious delirium, an off-label indication but relatively common practice. A second dose was prescribed 3 hours later as the patient's agitation waxed and waned during the night. In the early hours of the morning an alarm was raised from telemetry monitoring as the patient developed polymorphic ventricular tachycardia with QRS morphology typical of TdP. The patient was found to be unresponsive and pulseless when the emergency response team arrived, and chest compressions were initiated. Pads were swiftly applied, and the patient was defibrillated with restoration of sinus rhythm with a palpable pulse. A 12-lead ECG was performed at this time and showed that the patient's corrected QT interval was 612 milliseconds.

Commentary: Concomitant Use of QT-Prolonging Agents

The scenario described is an example of how concurrent administration of medications with proarrhythmic liability, especially in the setting of multiple high-risk comorbidities, can place a patient at significant risk of this life-threatening arrhythmia. The primary mistake that was made by the inexperienced prescriber working this night shift was to prescribe haloperidol, a known

agent with QT-prolongation properties to a patient also receiving azithromycin, another drug known to prolong the QT interval. It is extremely important to learn which commonly prescribed medications have been shown to cause QT prolongation. If prescribing these drugs, a baseline QT interval should be acquired by ECG, and a risk-versus-benefit assessment must be made prior to prescribing. There is a high risk of TdP when multiple QT prolonging agents are comedicated. The CredibleMeds website or an alternative resource should be consulted prior to administration of an agent if its QT-prolonging effect is not known by the prescriber.

Although the most obvious error made here was prescription of concomitant QT-prolonging agents, there are several more subtle risk factors that should be noted and that placed this particular patient at even higher risk. The patient was an elderly woman, a demographic known to be more susceptible to proarrhythmia, and she also admitted to heavy alcohol intake with blood work suggestive of possible synthetic liver dysfunction (low serum albumin and thrombocytopenia), which should raise alarms of possible underlying cirrhosis. That this patient likely had cirrhotic hepatic impairment and that haloperidol is metabolized by the liver may have increased her proarrhythmia risk further and underlines the importance of awareness of drug pharmacokinetics. Impaired metabolism or excretion of any drug can increase the risk of drug toxicity and adverse outcomes. In addition, although not present in this patient, one should have high suspicion of electrolyte derangement, another risk factor for proarrhythmia in a patient with a history of excessive alcohol consumption, as associated nutritional deficiencies are common.

A final point to highlight regarding this case is that proarrhythmia risk is higher when the offending medications are given by intravenous route, as in this case, so if a challenging risk-versus-benefit profile arises in clinical practice, risk can be mitigated by prescribing enteral formulations.

Clinical Vignette 2

A 55-year-old man presented to his cardiologist's office complaining of shortness of breath, weakness, and fatigue. He had a medical history of coronary artery bypass surgery 3 years ago following a myocardial infarction in the setting of triple-vessel coronary disease and resultant ischemic cardiomyopathy with severely reduced left ventricular function. The patient had also developed paroxysmal atrial fibrillation 6 months prior and had unfortunately required multiple hospital admissions because of decompensation of his heart failure since then. His cardiologist had started an antiarrhythmic medication, dofetilide, when the patient was last admitted 2 months prior to attempt to maintain

the patient in sinus rhythm, and since then the patient had felt well until his presentation to the cardiologist. The patient also was taking aspirin, atorvastatin, carvedilol, valsartan/sacubitril, furosemide, and apixaban. The patient was found to have conversational dyspnea and had noticed his legs had again become swollen. His pulse oximetry showed an oxygen saturation of 86% when breathing room air. He had an elevated jugular venous pulsation, an irregularly irregular rhythm by auscultation, bibasal rales, and pitting edema in his lower extremities. The patient was diagnosed with acutely decompensated heart failure in association with recurrence of atrial fibrillation and was admitted to the hospital. ECG revealed atrial fibrillation with heart rate of 110 bpm, and QTc of 445 milliseconds. Chest x-ray showed pulmonary edema, and laboratory studies were significant for mild acute kidney injury, serum potassium of 3.8 mmol/L, serum magnesium of 1.8 mg/dL, and elevated B-type natriuretic peptide. The patient was started on an infusion of loop diuretic and responded to this with 4.5 L of urine output over the following 24 hours, and within this period he spontaneously converted back to sinus rhythm at a heart rate of 55 bpm.

The patient reported that his breathing felt much better, but he had developed occasional muscle cramps and still felt very weak. The following morning the patient was awoken by the nurse at 6 AM doing rounds for daily blood work, inclusive of serum creatinine, potassium, and magnesium. Once this was drawn, the patient got up and walked toward the bathroom, as he needed to urinate, but collapsed suddenly on the way. The nurse heard the thud and ran back in to find the patient on the floor unresponsive and pulseless. Unfortunately, a prolonged resuscitation effort was unsuccessful, and the patient died. The laboratory studies sent just prior to the patient's syncope revealed serum potassium was 2.2 mmol/L, and serum magnesium was 1.1 mg/dL. Retrospective review of the continuous telemetry monitoring revealed a progressive prolongation of the QT interval since admission and TdP initiation correlating with the moment the patient collapsed.

Commentary: Electrolyte Disturbance

This vignette demonstrates the importance of anticipating secondary effects of the treatments given to patients. This particular patient appeared to have profound intravascular volume overload, leading to shortness of breath from pulmonary edema, and the initiation of a loop diuretic was the correct management and was proving to be effective in improving the patient's respiratory symptoms. However, aggressive diuresis, especially via diuretic infusion, can lead to significant derangement in serum electrolytes, as occurred in this case. The acquired prolongation of the QT interval

experienced by this patient was likely multifactorial, although the severe hypokalemia and hypomagnesemia from aggressive diuresis and high volume of urine output was likely the predominant etiology.

Other noteworthy contributors to proarrhythmia risk in this case were that the patient was taking dofetilide (which has QT-prolonging effects), the patient had converted out of atrial fibrillation and was in sinus bradycardia (another known proarrhythmia risk factor), and the patient had substantial underlying structural heart disease (ie, ischemic cardiomyopathy). The important learning curve in this case is to be proactive in anticipating potential adverse effects of the therapies we deliver. This patient had multiple proarrhythmia risk factors, and given that intravenous diuresis is expected to lead to a decrease in serum electrolytes, this patient should have had electrolyte levels checked more frequently to guide electrolyte repletion. As a rule, aggressive therapies require aggressive monitoring.

This case also illustrates the potential for serious consequences when severe QT prolongation is allowed to occur. Although resuscitation attempts can be successful, a patient with significant comorbidities and underlying severe ischemic heart disease is precisely the type of patient who may not respond to resuscitation efforts, as an already sick heart has less reserve to bounce back from an insult. Given his underlying risk factors, this patient would have been better served by receiving a less aggressive management plan (a once-daily dose of intravenous diuretic with prompt correction of resultant electrolyte abnormalities could have been tried prior to starting an infusion), along with more intensive monitoring during implementation.

Clinical Vignette 3

A 32-year-old woman decided to establish care with a family physician, as she had never regularly seen a general practitioner before and decided it would be a good idea. Meeting her for the first time, the family doctor took a full history and elicited that she had no chronic medical conditions and took no medications on a regular basis. She drank alcohol only occasionally and had never smoked cigarettes or used illicit drugs. She was employed as an actuary and was generally very physically active, running on average 20 miles per week and participating in competitive swimming on weekends.

Regarding family history, her mother was also a talented swimmer but tragically passed away in her late thirties from drowning while swimming in a public pool early one morning. The patient had no specific current complaints, but a review of systems revealed that she had a passing-out spell, something she had never experienced before, during a recent bout of viral gastroenteritis. She described that she was having a lot

of diarrhea, and while sitting on the toilet one evening, she lost consciousness without warning and woke up on the floor with blood on her face from a cut to her forehead sustained when she passed out. She felt fine immediately once regaining consciousness and thought she must have had a fainting episode related to having a bowel movement. Her vital signs and physical examination were both unremarkable. The family doctor was concerned by the history of this syncopal event and asked for an ECG. The ECG revealed that this patient had a corrected QT interval of 590 millise.

Commentary: Congenital Long QT Syndrome

A QT interval of this length, found because of the astute decision by this practitioner to check an ECG, is likely a result of this patient having a diagnosis of congenital LQTS. An important concept to highlight in this case is the vital role of taking a careful history in arriving at the correct diagnosis. Syncope is a notoriously hard presentation to evaluate, and that this patient had the event during a bowel movement could lead one to think that it was of benign, vagally mediated etiology. However, several features of the story should raise concern.

First, she describes the absence of a prodrome, which is a characteristic of syncope secondary to cardiac arrhythmia, as is the relatively swift recovery she described. Second, she was sitting at the time of the syncopal event, and although not impossible, it would be unusual to suffer from a vasovagal episode from a seated or supine position. Third, the patient sustained a facial injury that suggests she had sudden complete loss of consciousness and was not anticipating the fall and so was unable to break her fall in any way, another feature typical of syncope because of arrhythmia. One could speculate with reasonably high suspicion that this patient may have had some electrolyte derangement during her bout of gastroenteritis that, in the setting of congenital LQTS, may have precipitated TdP that thankfully was not sustained.

Aside from the nature and mechanism of her syncope, there is also a red flag within her family history. Her mother's death is unusual, and it is important to remember that sudden cardiac death can manifest in many ways, including unexplained drowning. Congenital LQTS is an important diagnosis that has many implications. The majority of the genes implicated are inherited in an autosomal-dominant fashion such that if the mother carried an autosomal-dominant LQTS gene, all her children would have a 50% chance of having this condition and should therefore all be tested. The patient would need to be evaluated and consideration be given to treatment with beta-blocker therapy, limitation of intense physical activity, and prophylactic implantation of an implantable cardioverter

defibrillator, as well as avoidance of QT-prolonging medications.

Conflicts of Interest

The authors declare no conflicts of interest relative to this article.

Funding

This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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