Drug-induced proarrhythmia and use of QTc-prolonging agents: Clues for clinicians

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Use of drugs with the potential for prolongation of the QTc interval and proarrhythmia is a growing challenge facing clinicians. Many pharmaceutical agents have been denied approval for human use, approved with restrictions and warnings regarding proarrhythmia, or withdrawn from the market based upon arrhythmic risk. Despite known risk factors for QTc prolongation and drug-induced arrhythmia, precise prediction of the risk of torsades de pointes (TdP) in an individual patient remains difficult. The mechanism of drug-induced TdP typically involves use of an agent that blocks the I_{Kr} cardiac potassium current, often in combination with risk-amplifying factors such as high drug levels, reduced drug metabolism, polypharmacy, and patient-specific factors such as gender, age, and genetic polymorphism. For the clinician, an integrated approach involving appreciation of the risk factors for proarrhythmia combined with computer-based risk assessment is the best method for reducing the risk of drug-induced proarrhythmia in clinical practice.

KEYWORDS Arrhythmia; Clinical practice; Drug; QT interval; QTc interval; Torsades de pointes

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Introduction

Drug-induced proarrhythmia is a growing challenge shared by the pharmaceutical industry, prescribing clinicians, and regulatory bodies charged with evaluating and monitoring drug safety. The greatest risk of drug-induced proarrhythmia with current agents is the risk of prolongation of the corrected QT interval (QTc) on the electrocardiogram (ECG), which can be associated with a potentially life-threatening form of polymorphic ventricular tachycardia termed *torsades de pointes* (TdP). Drugs with proven lengthening of the QTc interval or a definite association with TdP are common and are estimated to compose approximately 2% to 3% of all prescriptions written.[1] Among the most common noncardiac drugs with QTc interaction seen in clinical practice are antibiotics and psychotropic drugs,[2] which in the vast majority of cases are prescribed by noncardiologists. Although uncommon in routine clinical practice, TdP is extremely difficult to predict accurately despite known risk factors and mechanism. A large number of drugs in clinical use are associated with QTc prolongation based upon studies in humans, animals, and various experimental preparations (Figure 1).

Because of the risk of drug-induced arrhythmia associated with QTc prolongation, regulatory agencies now require detailed evaluation of the effects of new agents on cardiac repolarization prior to drug approval, as well as postmarketing surveillance of approved drugs with perceived risk. As a result of this scrutiny, a number of drugs have been denied approval for use in humans, have received approval with warnings related to QTc effects (either at the time of approval or relabeled after initial approval), or have been withdrawn from the market after previously unappreciated proarrhythmic effects were detected (Figure 2). The pharmaceutical industry and regulatory bodies are charged with safety monitoring at all stages of drug evaluation, both before and after approval for human use. Despite the industry and regulatory body monitoring, clinicians ultimately are responsible for the safety of the patients to whom they prescribe drugs. Many approved drugs have the potential—either demonstrated or theoretical—for QTc prolongation and TdP. As a result, prescription of all agents must be based upon informed evaluation of the risks and benefits of each drug compared with available alternatives.

A mechanistic understanding of drug-induced arrhythmia has been appreciated only recently. In the 1920s, quinidine (a new antiarrhythmic agent at that time) was associ-

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Anticonvulsants	Fosphenytoin; Felbamate
Antihistamines	Azelastine; Clemastine
Anti-Infectives	Amantadine; Clarithromycin; Chloroquine; Foscarnet; Erythromycin; Halofantrine; Mefloquine; Moxifloxacin; Pentamidine; Sparfloxacin; Quinine; Trimethoprim-Sulfamethoxazole, Ketoconazole
Antineoplastics	Tamoxifen
Cardiovascular: Antiarrhythmics	Amiodarone; Bretylium; Disopyramide; Flecainide; Ibutilide; Procainamide; Quinidine; Sotalol; Dofetilide
Calcium Channel Blockers	Bepridil; Israpidine; Nicardipine
Diuretics	Indapamide; Moexipril/HCTZ
Hormones	Octreotide; Vasopressin
Immunosuppressives	Tacrolimus
Migraine: Serotonin Receptor Agonists	Zolmitriptan; Naratriptan; Sumatriptan
Muscle Relaxant	Tizanidine
Narcotic Detoxification	Levomethadyl
Psychotherapeutics: Antidepressants	Amitriptyline; Desipramine; Fluoxetine; Imipramine; Venlafaxine
Antipsychotic	Chlorpromazine; Haloperidol; Pimozide; Quetiapine; Risperidone; Thioridazine
Antianxiety	Doxepin
Antimanic	Lithium
Respiratory: Sympathomimetics	Salmeterol
Sedative/Hypnotics	Chloral hydrate

Figure 1 Partial list of drugs associated with QTc prolongation subgrouped by drug class. For details, see *http://www.arizonacert.org*. HCTZ = hydrochlorothiazide.

ated with syncope. Advances in ECG monitoring in the ensuing decades identified pause-dependent polymorphic ventricular tachycardia, later termed TdP, as the responsible mechanism.[3–4] Similarly, cases of cardiac toxicity with antipsychotics and antihistamines were reported in the 1960s and 1970s, but the cases were poorly understood, and little regulatory oversight was in practice. In concert with growing appreciation of drug-induced arrhythmia, the first descriptions of heritable syndromes linking a long QTc interval with sudden cardiac death were reported.[4–6] Knowledge of both drug-induced QTc lengthening and the heritable long QTc syndromes has proved complementary in elucidating the mechanisms responsible for the clinical features of TdP.

Terfenadine: a case study

Terfenadine is a nonsedating antihistamine that was widely used (>100 million prescriptions filled while an approved agent) prior to its withdrawal from the market in 1998. Use of terfenadine at therapeutic concentrations produces a measurable increase in the QTc interval, but the increase is relatively modest (6–8 ms average QTc increase across the dosing interval, 18 ms at peak drug levels).[7] Furthermore, terfenadine appeared to be safe in large, postapproval monitoring of approximately 200,000 patients.[7–8] Despite this finding, rare reports of TdP and sudden cardiac death associated with terfenadine sparked regulatory investigation in the late 1980s and culminated in withdrawal of the drug in 1998.[9] The mechanisms responsible for terfenadine-induced TdP are interesting from a pharmacologic perspective and illustrative of the challenges facing the pharmaceutical industry, regulatory bodies, and prescribing clinicians in assessing the proarrhythmic risk of a drug.

Like most drugs associated with QTc prolongation, terfenadine is capable of blocking the cardiac cell membrane potassium current I_{Kr}. However, at typical therapeutic concentrations, terfenadine produces only modest effects on the QTc interval that are not generally associated with significant potential for arrhythmia. The liability for terfenadine proved to be its route of metabolism. Terfenadine is modified by first-pass metabolism in the liver via the cytochrome P450 3A4 (CYP3A4) system to an active metabolite that is an active antihistamine but does not substantially prolong the QTc interval. This hepatic modification of the drug markedly reduces the systemic concentration achieved by a given oral dose of the QTc-prolonging parent compound.[10]

Unfortunately, CYP3A4 activity can be inhibited by a wide range of drugs commonly used in clinical practice, including some macrolide antibiotics, ketoconazole and related antifungals, cimetidine, fluoxetine, protease inhibitors, and amiodarone.[11] In addition, many nondrug factors, including age, smoking, hepatic disease, genetic polymorphism, and grapefruit juice, can lead to CYP3A4 inhibition.[12] In the presence of significant CYP3A4 inhibition, first-pass metabolism of terfenadine is blocked, resulting in up to 20-fold increased systemic terfenadine concentrations (Figure 3). This exposure can produce a marked increase in the QTc interval (up to 82 ms nonpeak),[11] which is sufficient to cause substantial risk of TdP. Because of the impossibility of controlling for all factors that affect terfenadine metabolism in clinical practice and the presence of viable alternatives without comparable arrhythmic risk, terfenadine was withdrawn from the market.

Mechanisms of drug-induced arrhythmia

In order to understand the molecular basis of QTc prolongation, an understanding of the molecular basis of the QT interval is critical (for review, see Fenichel et al.[13]). The QT interval represents a summation of the entire duration of the cardiac action potentials of ventricular cardiomyocytes, from the onset of depolarization until the completion of repolarization. The membrane voltage is governed by

- **Drugs withdrawn because of TdP**
  - **Terfenadine**
  - **Astemizole**
  - **Grepafloxacin**
  - **Cisapride**
- **Nonapproval—several**
- **Complicated approval**
  - **Moxifloxacin**
  - **Ziprasidone**
- **Approved with QT cautions in labeling—numerous**
- **Re-labeling**
  - **Thioridazine**
  - **Droperidol**

Figure 2 Partial list of drugs with risk of QTc lengthening or torsades de pointes (TdP) that has resulted in withdrawal from the market, nonapproval for human use, complications in the approval process, approval with cautions in regard to QT effects, and relabeling after approval based on QT effects and/or TdP.