Drug-induced QT interval prolongation and torsades de pointes: Role of the pharmacist in risk assessment, prevention and management

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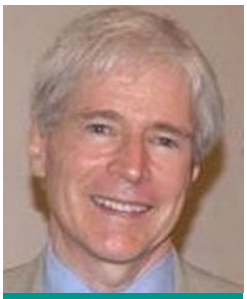

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ABSTRACT

Torsades de pointes (TdP) is a life-threatening arrhythmia associated with prolongation of the corrected QT (QT_c) interval on the electrocardiogram. More than 100 drugs available in Canada, including widely used antibiotics, antidepressants, cardiovascular drugs and many others, may cause QT_c interval prolongation and TdP. Risk factors for TdP include QT_c interval >500 ms, increase in QT_c interval ≥60 ms from the pretreatment value, advanced age, female sex, acute myocardial infarction, heart failure with reduced ejection fraction, hypokalemia, hypomagnesemia, hypocalcemia, bradycardia, treatment with diuretics and elevated plasma concentrations of QT_c interval–prolonging drugs due to drug interactions, inadequate dose adjustment of renally eliminated drugs in patients with kidney disease and rapid intravenous administration. Pharmacokinetic drug interactions associated with the highest risk of TdP include antifungal agents, macrolide antibiotics (except azithromycin) and drugs to treat human immunodeficiency virus interacting with amiodarone, disopyramide, dofetilide or pimozide. Other important pharmacokinetic interactions include antidepressants (bupropion, duloxetine, fluoxetine, paroxetine) interacting with flecainide, quinidine or thioridazine. Pharmacists play an important role in minimizing the risk of drug-induced QT_c interval prolongation and TdP through knowledge of drugs that are associated with a known or possible risk of TdP, individualized assessment of risk of drug-induced QT_c interval prolongation, awareness of drug interactions most likely to result in TdP and attention to dose reduction of renally eliminated QT_c interval-prolonging drugs in patients with kidney disease. Treatment of hemodynamically stable TdP consists of discontinuation of the offending drug(s), correction of electrolyte abnormalities and administration of intravenous magnesium sulfate 1 to 2 g. *Can Pharm J (Ott)* 2016;149:139-152.

QT interval prolongation may provoke the life-threatening arrhythmia torsades de pointes (TdP), which may be induced by many widely prescribed drugs. Pharmacists can minimize the likelihood of drug-induced TdP through knowledge of high-risk drugs, assessment of risk factors and intervening to modify risk or recommend alternate, non–QT interval–prolonging therapy where appropriate.

De nombreux médicaments prescrits couramment peuvent entraîner un allongement de l'intervalle QT, lequel peut provoquer des torsades de pointes (TdP), un type d'arythmie potentiellement mortel. Les pharmaciens sont en mesure de réduire la probabilité des TdP dues aux médicaments grâce à leurs connaissances sur les médicaments à haut risque, l'évaluation des facteurs de risques et des interventions afin de modifier les risques ou de recommander d'autres traitements n'entraînant pas d'allongement de l'intervalle QT, le cas échéant.

Drug-induced prolongation of the QT interval on the electrocardiogram (ECG) increases the risk of the life-threatening ventricular arrhythmia known as torsades de pointes (TdP). Over the past 20 years, several drugs, including terfenadine, astemizole, cisapride and grepafloxacin, have been withdrawn from the Canadian market as a result of causing deaths due to TdP.[1] However, more than 100 drugs with the potential to cause TdP remain available in Canada.[2,3] Pharmacists should be aware of drugs that can cause QT interval prolongation and TdP, risk factors and methods for reducing the risk. The objectives of this article are to 1) describe and define the QT interval and TdP, 2) identify commonly used drugs that may cause QT interval prolongation and TdP, 3) describe risk factors for QT interval prolongation and TdP and 4) provide practical recommendations

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KNOWLEDGE INTO PRACTICE

- Torsades de pointes (TdP) may result in sudden cardiac death. More than 100 drugs available in Canada, including widely used antibiotics, antidepressants, cardiovascular drugs and many others, may cause QT_c interval prolongation and TdP.
- Pharmacists can play an important role in minimizing the risk of drug-induced QT_c interval prolongation and TdP through knowledge of drugs associated with TdP, assessment of risk of QT_c interval prolongation via the QT_c interval prolongation risk score, awareness of drug interactions most likely to result in TdP and attention to dose reduction of renally eliminated QT_c interval–prolonging drugs in patients with kidney disease. Analysis of these factors informs the pharmacist's clinical judgment regarding the need for intervention for patients receiving potentially QT_c interval–prolonging medications.

for pharmacists regarding methods of reducing the risk of QT interval prolongation and TdP and treating TdP.

ECG and the QT interval

The ECG is a noninvasive method of evaluating the heart's electrical activity and represents the phases of the atrial and ventricular action potentials (Figure 1). The P wave represents depolarization of the atria, which precedes and is necessary for atrial contraction. The QRS complex represents depolarization of the ventricles, which precedes and is necessary for ventricular contraction. The QRS complex corresponds to phase 0 and phase 1 of the ventricular action potential. Phase 0 represents ventricular depolarization. The T wave represents the final component (phase 3) of ventricular repolarization (Figure 1). However, ventricular repolarization begins as soon as phase 0 depolarization ends and is complete at the end of phase 3. Therefore, the entire period of ventricular repolarization is represented by the interval from the Q wave to the end of the T wave, known as the QT interval (Figure 2).[4] As phase 3 ventricular repolarization becomes prolonged, the left ventricle becomes more susceptible to premature electrical impulses known as early afterdepolarizations. When an early afterdepolarization occurs during the latter portion of an extended phase 3 ventricular repolarization, represented on the ECG by a prolonged QT interval, this can trigger TdP. Therefore, the longer the QT interval, the greater the likelihood of TdP.

The QT interval varies as heart rate varies. As the heart rate increases, the QT interval shortens and vice versa. Therefore, to be certain that changes in QT interval actually represent changes in ventricular repolarization, rather than simply changes in heart rate, the QT interval must be corrected to account for heart rate variations. The heart rate–adjusted QT interval is known as the corrected QT (QT_c) interval. The most common QT interval correction equation, and that which is used in routine clinical practice, is Bazett's formula[5]:

$$QT_c = \frac{QT}{\sqrt{RR}}$$

where QT_c is the heart rate–corrected QT interval and RR interval is the interval between the R waves on the ECG; the RR interval is the heart rate but expressed in milliseconds or seconds of time on the ECG. The normal QT_c interval in adults is 0.36 to 0.47 s (360–470 ms) in men and 0.36 to 0.48 s (360–480 ms) in women.[6]

Torsades de pointes

TdP is a polymorphic ventricular tachycardia (VT) associated with QT_c interval prolongation. The majority of patients who experience VT, which is most commonly associated with myocardial infarction, myocardial ischemia or heart failure, exhibit monomorphic VT; that is, the QRS complexes manifest a consistent shape and amplitude (morphology). TdP is a polymorphic arrhythmia; that is, the morphology of the QRS complexes is variable and not constant. TdP was initially described in the 1960s by the French physician François Dessertenne and was termed *twisting of the points* because the "points" of the QRS complexes on the ECG appeared to "twist" around the isoelectric baseline (Figure 3).[7]

TdP results in heart rates of 160 to 240 beats per minute.[6] Symptoms of TdP are primarily related to the rapid heart rate and the resulting effects on blood pressure and cardiac output[2] and include palpitations, dizziness, lightheadedness, shortness of breath, near-syncope and syncope. In some cases, TdP may be nonsustained and terminate spontaneously. However, TdP often degenerates rapidly into ventricular fibrillation, resulting in sudden cardiac death. Therefore, TdP can be a catastrophic occurrence. Consequently, strategies for minimizing the risk of TdP are important.

QT_c interval prolongation and the risk of TdP

QT_c interval prolongation may be congenital or acquired. Congenital long QT syndrome (LQTS),

for which as many as 13 distinct genetic mutations have been identified,[8] occurs in approximately 1 in 2000 live births.[9] Acquired QT_c interval prolongation is most often caused by drugs.[2]

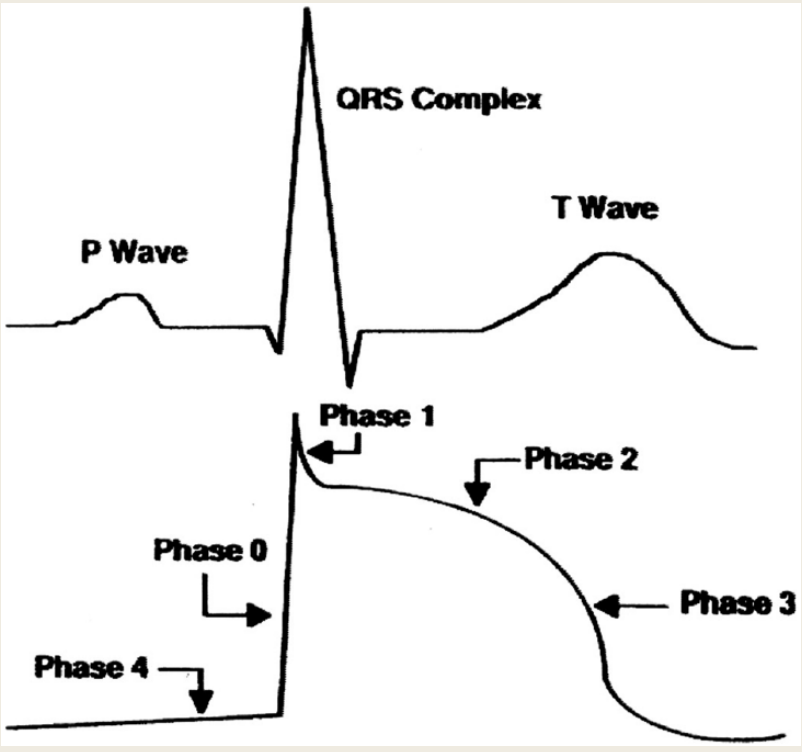
QT_c interval prolongation increases the risk of TdP, particularly when the QT_c interval exceeds 500 ms.[10-12] The majority of reported or published cases of TdP have occurred in patients with a QT_c interval >500 ms, and TdP is rare when the QT_c interval is less than 500 ms.[13] The risk of TdP is also increased when the QT_c interval becomes prolonged greater than 60 ms compared with the pretreatment value.[13]

The incidence of TdP in the general population is unknown. In a study conducted in Sweden, the annualized incidence of TdP in the general population was estimated to be 4 in 100,000.[14] Assuming a similar incidence in Canada, this translates to approximately 1400 TdP cases annually. The incidence of TdP associated with specific QT_c interval–prolonging drugs ranges from 2% to

MISE EN PRATIQUE DES CONNAISSANCES

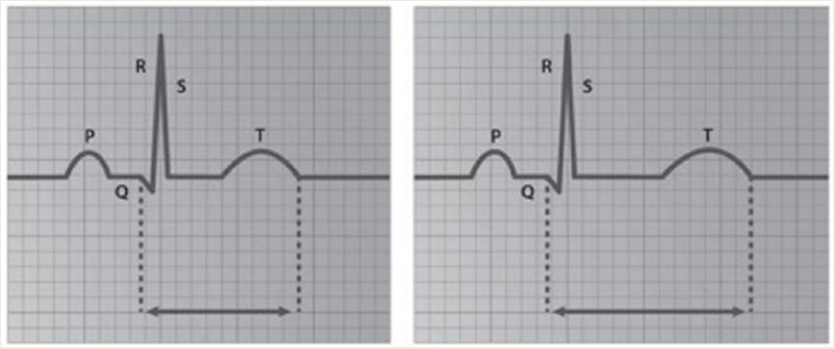
- Les torsades de pointes peuvent causer un arrêt cardiaque soudain. Plus d'une centaine de médicaments en vente au Canada peuvent provoquer un allongement de l'intervalle QT_c et des TdP, y compris des antibiotiques, antidépresseurs, médicaments cardiovasculaires et autres produits largement utilisés.
- Les pharmaciens peuvent jouer un rôle important pour atténuer les risques d'allongement de l'intervalle QT_c et de TdP provoqués par des médicaments, grâce à leurs connaissances sur les médicaments entraînant des TdP, à l'évaluation des risques au moyen d'une échelle de risque d'allongement de l'intervalle QT_c, à la connaissance des interactions médicamenteuses qui sont susceptibles d'entraîner des TdP et à la réduction posologique des médicaments qui allongent l'intervalle QT_c et qui sont éliminés par les reins chez les patients atteints d'une néphropathie. Le pharmacien fonde son jugement clinique sur l'analyse de ces facteurs pour déterminer les cas qui nécessitent une intervention chez les patients recevant des médicaments pouvant allonger l'intervalle QT_c

FIGURE 1 Relationship between the electrocardiogram and the ventricular action potential



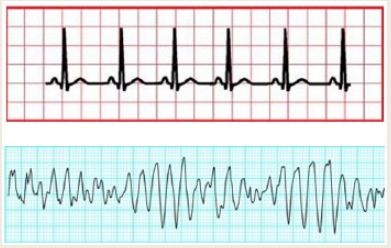
Upper frame: Major waves and complexes on the electrocardiogram. P wave represents atrial depolarization; QRS complex represents ventricular depolarization and the initial portion of ventricular repolarization; T wave represents the final phase of ventricular repolarization; the interval from the Q wave to the end of the T wave (QT interval) represents the complete period of ventricular repolarization. Lower frame: Phases of the ventricular action potential: phase 0 represents ventricular depolarization, which occurs as a result of rapid flow of sodium into the cardiac myocyte; phase 1 represents the initial phase of ventricular repolarization, due to transient movement of potassium out of the cell; phase 2 represents the plateau phase of ventricular repolarization, due to movement of sodium and calcium into the cell; phase 3 represents the final phase of ventricular repolarization, resulting from movement of potassium out of the cell; phase 4 represents the resting phase, maintained by the sodium-potassium pump.

FIGURE 2 The QT interval



(Left) Normal electrocardiogram. (Right) Prolonged QT interval. Reprinted with permission from Trinkley KE, Page RL II, Lien H, et al. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr Med Res Opin* 2013;29:1719-26. Publisher: Taylor & Francis, Ltd, www.tandfonline.com.

FIGURE 3 Torsades de pointes compared with normal sinus rhythm



(Top) Normal sinus rhythm. (Bottom) Torsades de pointes. Reprinted with permission from Tisdale JE. Review of cardiac arrhythmias and rhythm interpretation. In: Wiggins BS, Sanoski CA, editors *Emergency cardiovascular pharmacotherapy. A point of care guide.* Bethesda (MD): American Society of Health-System Pharmacists; 2012. pp 23, 38.

12% depending on the drug, dose administered and the presence of other risk factors.

Hospitalized patients, particularly those in intensive care units (ICUs), are at higher risk of developing QT_c interval prolongation and TdP because of a greater preponderance of risk factors.[6] The incidence of QT_c interval prolongation in patients in ICUs ranges from 24% to 28%[15,16]; as many as 18% of patients in ICUs are admitted with preexisting QT_c interval prolongation. Among 154 patients in adult ICUs and progressive care units during a 2-month period, 1 case of TdP (0.6%) was reported.[16]

Drugs associated with TdP

More than 100 drugs available in Canada are associated with a known or possible risk of TdP. An excellent source of information regarding drugs that may cause TdP is provided at https://www.crediblemeds.org. Anyone can access the QT drugs list on this website; registration is necessary and requires a username and password, but access is free of charge. This website categorizes drugs that may cause TdP into "Known," "Possible" and "Conditional" risk and "Drugs to avoid in congenital LQTS."[3] Definitions of these categories are provided in Table 1. Based on these definitions, a list of drugs with a known or possible risk of TdP is provided in Table 2.

QT_c interval–prolonging drugs are commonly prescribed. Several drugs that cause TdP are among the top 200 medications prescribed annually in the United States, including azithromycin, trazodone, sertraline, fluconazole, citalopram, escitalopram, ciprofloxacin, venlafaxine, aripiprazole, pantoprazole, risperidone and paroxetine.[17] In an analysis of nearly 5 million outpatients, 23% filled prescriptions for QT_c interval–prolonging drugs.[18]

Risk factors for drug-induced QT_c interval prolongation and TdP

Risk factors are important for the development of QT_c interval prolongation and TdP. In comparison with patients who have no risk factors, the odds ratio for QT_c interval prolongation in patients with 1 risk factor is 3.2 (95% confidence [CI] 2.1–5.5); the odds ratio increases markedly in patients with 2 or ≥3 risk factors (7.3 [4.6–11.7] and 9.2 [4.9–17.4], respectively).[19] In an analysis of 144 published articles describing 249 patients with TdP associated with noncardiovascular drugs, nearly 100% had ≥1 risk factor and 71% had ≥2 risk factors.[20] Therefore, risk

TABLE 1 Categories of drugs that may cause TdP[3]

Category	Definition
Known risk	Substantial evidence supports the conclusion that these drugs prolong the QT interval AND are clearly associated with a risk of TdP, even when taken as directed in official labeling.
Possible risk	Substantial evidence supports the conclusion that these drugs can cause QT interval prolongation BUT there is insufficient evidence at this time that these drugs, when used as directed in official labeling, are associated with a risk of causing TdP.
Conditional risk	Substantial evidence supports the conclusion that these drugs are associated with a risk of TdP BUT only under certain conditions (e.g., excessive dose, hypokalemia, congenital LQTS or by causing a drug-drug interaction that results in excessive QT interval prolongation).
Drugs to avoid in congenital LQTS	Substantial evidence supports the conclusion that these drugs pose a risk of TdP for patients with congenital LQTS. Drugs on this list include those in the above 3 risk categories and other drugs that do not prolong the QT interval per se but have a theoretical risk of causing arrhythmia that is based on their known stimulant actions on the heart.

LQTS, long QT syndrome; TdP, torsades de pointes.

factor assessment is critical for evaluating the risk of QT_c interval prolongation and TdP,[6] and risk factor modification, where possible, is important for reducing the risk of drug-induced TdP.

Risk factors for drug-induced TdP are presented in Table 3. A QT_c interval >500 ms and/or prolongation of the QT_c interval ≥60 ms are risk factors. Women are at higher risk of TdP than men; this is most likely related to the fact that testosterone shortens QT_c intervals and is protective against QT_c interval prolongation in men.[21] In addition, some evidence indicates that estrogen may lengthen QT_c intervals in women.[22] Older patients (generally >65 years of age) are at higher risk for drug-induced TdP,[23,24] which may be related to declining serum testosterone concentrations in men[25] and lower serum progesterone concentrations in women.[26] Acute myocardial infarction prolongs ventricular repolarization during the infarction; however, QT_c intervals are not permanently prolonged and return to baseline when the acute myocardial ischemia has resolved. Heart failure due to reduced ejection fraction is associated with lengthening of the QT_c interval and increases the risk of TdP by 2- to 3-fold compared with that in patients with normal left ventricular function.[27-30] Hypokalemia, hypomagnesemia and hypocalcemia increase the risk for TdP. Therapy with diuretics also increases the risk, most likely by provoking electrolyte abnormalities. Some evidence indicates that concomitant administration of ≥2 QT_c interval–prolonging drugs may increase the risk. Conditions that lead to elevated plasma concentrations of QT_c interval–prolonging drugs increase the risk of drug-induced TdP, including pharmacokinetic drug interactions (Table 4), inadequate dose adjustment of renally eliminated QT_c interval–prolonging drugs in patients with acute kidney injury or chronic kidney disease (Table 5) and rapid infusion of intravenously administered QT_c interval–prolonging medications. Some patients may have a genetic predisposition to experiencing drug-induced TdP; genetic polymorphisms known to be associated with some forms of the congenital LQTS may be present in 10% to 15% of patients who experience drug-induced TdP.[31]

When is pharmacist intervention necessary?

Pharmacists may minimize the risk of drug-induced QT_c interval prolongation and TdP primarily through attention to risk factors. Methods of reducing the risk of drug-induced TdP are listed in Table 6. It is recognized that some community pharmacists may not have access to some information, such as the current or pretreatment QT_c interval, left ventricular ejection fraction and/or history of TdP or sudden cardiac death, but these factors are listed in case this information is available. Areas in which pharmacists may have the most impact on reducing the risk of QT_c interval prolongation/TdP include maintaining normal serum electrolyte concentrations, avoidance or mitigation of high-risk drug interactions (Table 4) and appropriate dose adjustment of renally eliminated QT_c interval–prolonging drugs in patients with kidney disease.

TABLE 2 Drugs associated with a known or possible risk of torsades de pointes[3]

Drug class	Known risk	Possible risk
Alpha-blocker		Alfuzosin
Anesthetic, general	Propofol Sevoflurane	
Antiarrhythmic	Amiodarone Disopyramide Dofetilide Flecainide Ibutilide Procainamide Quinidine Sotalol	
Anticonvulsant		Felbamate
Antidepressant	Citalopram Escitalopram	Clomipramine Desipramine Imipramine Lithium Mirtazapine Nortriptyline Trimipramine Venlafaxine
Anticancer	Arsenic trioxide Eribulin Vandetanib	Bortezomib Bosutinib Certinib Crizotinib Dabrafenib Dasatanib Lapatanib Nilotinib Pazopanib Sorafenib Sunitinib Vemurafenib Tamoxifen Panobinostat Vorinostat
Antiemetic	Ondansetron Droperidol	Dolasetron Granisteron Promethazine
Antifungal	Fluconazole Pentamidine	
Antihypertensive		Isradipine Moexipril/ hydrochlorothiazide Nicardipine
Antimalarial	Chloroquine Halofantrine	Artenimol/piperaquine

(continued)

TABLE 2 (continued)

Drug class	Known risk	Possible risk
Antipsychotics	Chlorpromazine Haloperidol Pimozide Thioridazine	Aripiprazole Clozapine Iloperidone Olanzapine Paloperidone Quetiapine Risperidone Sertindole Ziprasidone
Antibiotic	Azithromycin Clarithromycin Erythromycin Ciprofloxacin Levofloxacin Moxifloxacin	Bedaquiline Gemifloxacin Norfloxacin Ofloxacin Telavancin Telithromycin
Antiviral		Atazanavir Foscarnet Rilpivirine Saquinavir
Antispasmodic		Mirabegron
Cholinesterase inhibitor	Donepezil	
Dopamine agonist		Apomorphine
Estrogen agonist/antagonist		Toremifene
Gonadotropin receptor agonist/antagonist		Leuprolide
Gonadotropin-releasing hormone agonist/antagonist		Degarelix
Histamine H_2 receptor antagonist		Famotidine
Immunosuppressant		Tacrolimus
Illicit drugs	Cocaine	
Muscle relaxants		Tizanidine Tolterodine
Norepinephrine reuptake inhibitor		Atomoxetine
Oxytocic		Oxytocin
Opiates	Methadone	
Phosphodiesterase 3 inhibitors	Anagrelide Cilostazol	
Phosphodiesterase 5 inhibitors		Vardenafil
Progesterone antagonist		Mifepristone
Sedative		Dexmedetomidine
Somatostatin analog		Pasireotide
Sphingosine phosphate receptor modulator		Fingolimod

TABLE 3 Risk factors for torsades de pointes[2,4,6]

- QT_c interval >500 ms
- Increase in QT_c interval >60 ms compared with pretreatment value
- Advanced age
- Female sex
- Acute myocardial infarction
- Heart failure with reduced ejection fraction
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia
- Bradycardia
- Treatment with diuretics
- Concurrent administration of >1 QT_c interval–prolonging drugs
- Elevated plasma concentrations of QT_c interval–prolonging drugs
  - Inadequate dose adjustment of renally eliminated drug in patients with acute kidney injury or chronic kidney disease
  - Rapid intravenous infusion of QT_c interval–prolonging drug
  - Drug interaction(s)
- Possible genetic predisposition

Potential drug interactions are common in patients taking QT_c interval–prolonging medications. Of approximately 1.1 million outpatients who filled prescriptions for QT_c interval–prolonging drugs, 9.4% filled overlapping prescriptions for 2 or more of those drugs or for a QT_c interval–prolonging agent and a drug that inhibits its clearance.[18] Pharmacokinetic drug interactions with the highest likelihood of leading to QT_c interval prolongation/TdP are listed in Table 4. Particular attention to and avoidance of these drug interactions is important for risk minimization. Pharmacokinetic interactions not listed in this table are much less likely to result in QT_c interval prolongation or TdP. In addition, as mentioned previously, avoidance of concomitant use of ≥2 QT_c interval–prolonging drugs, to prevent additive lengthening of the QT_c interval, is also recommended whenever possible. Appropriate dose adjustment of renally eliminated QT_c interval–prolonging drugs is extremely important for minimizing the risk of drug-induced QT_c interval prolongation/TdP in patients with kidney disease. QT_c interval–prolonging drugs for which dose adjustment is required in patients with acute kidney injury and chronic kidney disease are listed in Table 5.

As risk factors are important for the development of QT_c interval prolongation/TdP, quantification of risk may be helpful in targeting patients at greatest need of pharmacist intervention/monitoring. A risk score for predicting the development of QT_c interval prolongation in patients hospitalized in cardiac care units has been developed and validated (Table 7).[32] Roughly 50% of patients with a risk score ≥7, in the moderate-to-high range, proceeded to develop QT_c interval prolongation. This risk score was incorporated into a clinical decision support computer alert; when a patient was admitted to the cardiac care units, a computer alert was generated when the patient was prescribed a QT_c interval–prolonging drug and the calculated risk score indicated that the patient was at moderate or high (but not low) risk of developing QT_c interval prolongation. Upon receiving the alert, the pharmacist entering the order for the QT_c interval–prolonging medication contacted the physician to discuss obtaining more frequent ECGs for QT_c interval monitoring, assuring the correct dose and maintenance of adequate serum electrolyte concentrations or substituting a drug that does not prolong the QT_c interval, where possible and appropriate. This computer alert process resulted in modification of prescribing of noncardiovascular QT_c interval–prolonging drugs and significantly reduced the risk of QT_c interval prolongation in patients in these cardiac care units.[33]

While this risk score was developed and validated in a population of patients hospitalized in cardiac care units, it may be of value to community pharmacists and hospital pharmacists not practising in cardiac care units. Pharmacists may use this risk score to assess the risk of QT_c interval prolongation in patients receiving QT_c interval–prolonging medications. Using this risk score, awareness of

TABLE 4 Pharmacokinetic drug interactions associated with the highest risk of drug-induced QT_c interval prolongation and torsades de pointes

Precipitant drug	Mechanism	QT_c interval–prolonging drug
Antifungal agents: Itraconazole Ketoconazole Posaconazole Voriconazole	Inhibition of CYP 3A4	Amiodarone Disopyramide Dofetilide Pimozide
Macrolide antibiotics*: Erythromycin Clarithromycin Telithromycin	Inhibition of CYP 3A4	Amiodarone Disopyramide Dofetilide Pimozide
HIV drugs: Atazanavir Darunivir/ritonavir Fosamprenavir Indinavir Nelfinavir Ritonavir Saquinavir Tipranavir	Inhibition of CYP 3A4	Amiodarone Disopyramide Dofetilide Pimozide
Antidepressants: Bupropion Duloxetine Fluoxetine Paroxetine	Inhibition of CYP 2D6	Flecainide Quinidine Thioridazine
Others: Terbinafine	Inhibition of CYP 2D6	Flecainide Quinidine Thioridazine

*Not azithromycin.
CYP, hepatic cytochrome P-450 enzyme; HIV, human immunodeficiency virus.

the drug interactions listed in Table 4 and paying diligence to appropriate adjustment of drug doses in patients with kidney disease, pharmacists can determine the need to contact prescribers to discuss the risk pertaining to individual patients or, in the case or pharmacist-prescribers, make monitoring and prescribing decisions. If the patient's QT_c interval risk is low and there are no important drug interactions or dose adjustments necessary, then pharmacist intervention is unnecessary. If the risk is moderate or high, then pharmacist intervention in the form of communication with the prescribing physician may be of benefit. In this situation, pharmacists should discuss with the physician the importance of maintaining normal serum potassium, magnesium and calcium concentrations; ECG monitoring for determination of QT_c intervals when appropriate and feasible; and, for patients with a risk score in the high range, whether it is possible to prescribe an alternative, non–QT_c interval–prolonging drug for the therapeutic indication. It should be emphasized that this risk score does not take into account pharmacokinetic drug interactions or appropriate dosing of renally eliminated QT_c interval–prolonging drugs. If the patient is taking a drug combination listed in Table 4, or is receiving a drug in Table 5 for which the dose has not been appropriately adjusted for acute kidney injury/chronic kidney disease, then pharmacist communication with the prescribing physician is warranted irrespective of the calculated QT_c interval risk score.

Recommendations regarding the appropriate frequency of ECG monitoring for determination

TABLE 5 Drugs known to cause torsades de pointes that require dose adjustment in patients with acute kidney injury or chronic kidney disease

- Ciprofloxacin
- Disopyramide
- Dofetilide
- Eribulin
- Flecainide
- Fluconazole
- Levofloxacin
- Procainamide
- Sotalol
- Vandetanib

TABLE 6 Methods of reducing the risk of drug-induced torsades de pointes

- Where possible, avoid use of QT_c interval–prolonging drugs in patients known to have pretreatment QT_c intervals >450 ms.
- Discontinue QT_c interval–prolonging drug(s) if QT_c interval prolongs to >500 ms.
- Reduce dose or discontinue QT_c interval–prolonging drug(s) if the QT_c interval increases ≥60 ms from pretreatment value.
- Maintain serum potassium concentration within normal range.
- Maintain serum magnesium concentration within normal range.
- Maintain serum calcium concentration within normal range.
- Where possible, avoid the use of QT_c interval–prolonging drugs in patients with heart failure and a left ventricular ejection fraction <20%.
- Avoid important drug interactions (Table 4).
- Adjust doses of renally eliminated QT_c interval–prolonging drugs in patients with acute kidney injury or chronic kidney disease (Table 5).
- Avoid rapid intravenous administration of QT_c interval–prolonging drugs.
- Where possible, avoid concomitant administration of >1 QT_c interval–prolonging drug.
- Avoid use of QT_c interval–prolonging drugs in patients with a history of drug-induced torsades de pointes or those who have previously been bresuscitated from an episode of sudden cardiac death.
- Avoid use of QT_c interval–prolonging drugs in patients who have been diagnosed with one of the congenital long QT syndromes.

of the QT_c interval in community-based patients receiving QT_c interval–prolonging drugs have not been widely promulgated. Patients who require therapy with methadone should undergo a pretreatment ECG to determine QT_c interval, another at 30 days following initiation of therapy and annually thereafter.[34] To guide pharmacists' discussions with prescribers or decision-making by pharmacist-prescribers, it seems reasonable to recommend that patients with a QT_c risk score ≥7 and those taking drug combinations in Table 4 for whom therapy cannot be altered should have an ECG to determine QT_c interval when the plasma concentration of the QT_c interval–prolonging drug is estimated to be at steady state, that is, 5 half-lives following the initiation of therapy.[4] For hospitalized patients receiving therapy with QT_c interval–prolonging drugs, it is recommended that the QT_c interval be documented prior to initiation of therapy and at least every 8 to 12 hours following the initiation of therapy, dose increase or overdose.[6] If QT_c interval prolongation is observed, then more frequent monitoring is recommended.

Management of TdP

A treatment algorithm for TdP is presented in Figure 4. Drugs known to prolong the QT_c interval should be discontinued immediately. Serum potassium and/or magnesium should be replaced if the patient is hypokalemic or hypomagnesemic. If the patient is hemodynamically unstable (systolic blood pressure <90 mmHg, heart rate >150 bpm, unconscious or losing consciousness and/or experiencing

TABLE 7 Risk score for identifying patients at greatest risk of QT_c interval prolongation[32,*]

Risk factor	Points
Age ≥68 years	1
Female	1
Loop diuretic	1
Serum potassium ≤3.5 mmol/L	2
Presenting QT_c interval ≥450 ms	2
Acute myocardial infarction†	2
Heart failure with reduced ejection fraction	3
1 QT_c interval-prolonging drug‡	3
≥2 QT_c interval-prolonging drugs‡	3
Sepsis†	3
Maximum score	21

*Risk score category: low risk = <7; moderate risk = 7 to 10; high risk = ≥11.

†During acute event/disease; QT_c interval generally returns to normal following resolution.

‡Three points for taking 1 QT_c interval–prolonging drug; 3 additional points for taking ≥2 QT_c interval–prolonging drugs (for a total of 6 points).

chest pain), asynchronous defibrillation should be performed, rather than synchronized electrical cardioversion, as synchronization of shocks to the QRS complex/T wave is often impossible in patients with polymorphic ventricular arrhythmias.[35,36] In patients with hemodynamically stable TdP, intravenous magnesium 1 to 2 g administered over 15 minutes may terminate the arrhythmia, regardless of whether the patient is hypomagnesemic or has a normal serum magnesium concentration.[37,38] In patients unresponsive to intravenous magnesium, intravenous isoproterenol or rapid overdrive pacing via a temporary transvenous pacemaker may be used if the patient has TdP that is associated with bradycardia. Increasing the heart rate via isoproterenol or rapid pacing facilitates restoration of sinus rhythm. In patients with hemodynamically stable TdP unresponsive to magnesium and, where appropriate, isoproterenol or rapid pacing, sedation followed by elective defibrillation may be indicated. Sotalol-associated TdP that is unresponsive to conventional therapy has been successfully managed with hemodialysis[39] or peritoneal dialysis.[40]

Conclusion

In summary, more than 100 drugs available in Canada may cause QT_c interval prolongation, which increases the risk of sudden cardiac death due to TdP. Risk factors for drug-induced QT_c interval prolongation and TdP include older age, female sex, acute myocardial infarction, heart failure with reduced ejection fraction, hypokalemia, hypomagnesemia, hypocalcemia, bradycardia, diuretic therapy, concomitant therapy with multiple QT_c interval–prolonging drugs, elevated plasma concentrations of QT_c interval–prolonging drugs (due to drug interactions or inadequate dose adjustment of renally eliminated drugs in patients with kidney disease) and a possible genetic predisposition. Pharmacists may play an important role in minimizing the risk of drug-induced QT_c interval prolongation and TdP through knowledge of drugs that are associated with TdP, assessment of risk with the QT_c interval prolongation risk score, awareness of drug interactions most likely to result in TdP and attention to dose reduction of renally eliminated QT_c interval–prolonging drugs in patients with kidney disease. ■

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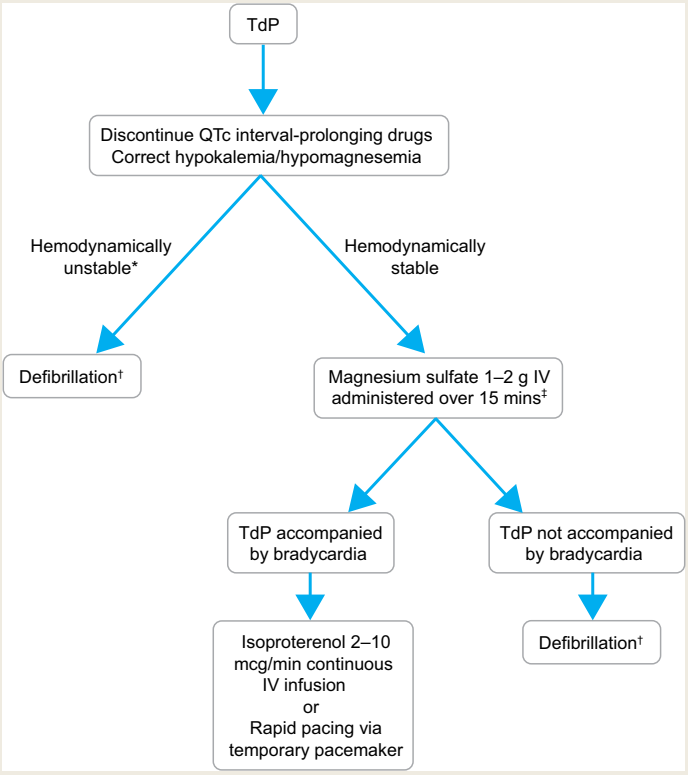
FIGURE 4 Algorithm for management of torsades de pointes



*Often defined as 1 or more of the following: systolic blood pressure <90 mmHg, heart rate > 150 beats per minute, unconscious or losing consciousness or chest pain.
†Polymorphic arrhythmias do not permit synchronization; therefore, defibrillation is recommended, rather than synchronized direct current cardioversion.[35,36] Administer sedation when possible.
‡Even if patient is not hypomagnesemic
IV, intravenous; TdP, torsades de pointes.

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