QT-INTERVAL PROLONGING DRUGS

Drug-induced QT-interval prolongation is a common cause of hospital admission, withdrawal or relabeling of prescription drugs, and a barrier to the development of new drugs. This is a proarrhythmia that is characterized as a pause-dependent polymorphic ventricular tachycardia also known as torsade de pointes (TdP). This is caused by drugs that increase the time for electrical recovery of myocardial tissue (repolarization) between heartbeats. Pharmacists should understand the levels of risk associated with the varying degrees of QT-interval prolongation and how this can play integral part of drug management to reduce the risk of proarrhythmia. This issue of CLIPs briefly summarizes an article that reviews the physiology of drug-induced QT-interval prolongation and specific drugs that are known to prolong the QT-interval. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Physiology of Cardiac Conduction
- Drug-induced QT-interval prolongation is caused by disruptions in depolarizations, repolarizations, or a combination of both.
- Prolonged depolarization occurs when a drug activates the late component of the cardiac sodium current (I_{Na}) and reduced repolarization occurs through suppression of the delayed rectifier potassium current (I_{Kr}).
- Suppression of the I_{Kr} leads to prolongation of the heart rate-corrected QT (QTc) interval on the ECG.
- QT-intervals exceeding 450 msec or increases greater than 30 msec from baseline are clinical indicators for increased risk of TdP.
- Risk factors for TdP include: hypokalemia, hypomagnesemia, female sex, bradycardia, ion channel polymorphisms, cardiovascular disease, conversion from atrial fibrillation, family history, drugs that prolong QTc-interval, and baseline QT-interval prolongation.

Antiarrhythmic Drugs That Primarily Suppress I_{Kr}
- Ibutilide is one of the most effective agents for rhythm conversion in patients with atrial fibrillation or atrial flutter. However, ibutilide produces extensive QT-interval prolongation ranging from 60-100 msec in clinical trials. Monitoring parameters for the use of ibutilide include: serum potassium and magnesium, drug-drug interactions, p-glycoprotein, and heart rate.
- Sotalol produces QTc-interval increases from baseline of 25 msec with 80 mg, 40 msec with 120 mg, and 50 msec with 160 mg. In turn, sotalol will have an increased risk of 4.3% for TdP.
- Dofetilide (pure I_{Kr} antagonist) has a linear dose QTc-interval relationship of 25 msec for every ng/mL of plasma concentration. Dofetilide has an average increase of 2% for TdP in patients.

Multimechanistic Antiarrhythmics
- Amiodarone the most potent antiarrhythmic as measured by the proportion of patients who remain in normal sinus rhythm for 12 months after cardioversion. Amiodarone prolongs the QTc interval by 30-60 msec, reverses transmural dispersion of repolarization, and suppresses early afterdepolarizations. Amiodarone has the lowest risk of TdP than any other antiarrhythmic (<0.5%). Dronedarone is a deiodinated congener to amiodarone and has a similar electrophysiologic profile; however, use is limited because it does not reduce afterdepolarizations.
- Ranolazine is used as a second-line adjunctive therapy for chronic stable angina when standard care fails. Ranolazine prolongs the QTc-interval by 6-12 msec when dosed 500-1000mg twice daily.
Prophylactic Strategies

- Mexiletine is an orally available lidocaine analog that suppresses I_{Na} channels and is used in conjunction with QT-interval prolonging antiarrhythmic drugs. Mexiletine should be used in patients who have uncontrolled arrhythmias despite optimal therapy with dofetilide, sotalol, or amiodarone.
- Magnesium can be coadministered with ibutilide, 2 grams of magnesium over 10 minutes before the first ibutilide infusion and 2 grams over 60 minutes after the first ibutilide infusion, can be used to increase the efficacy of ibutilide. Magnesium should only be given to patients receiving dofetilide or sotalol when the patient’s potassium level is less than 4 mEq/L or magnesium level is less than 2 mg/dL.

Drugs for Mental Health Disorders

- The S-isomer of methadone suppresses I_{Kr} and prolongs the QTc-interval by 14.1 msec at a mean ± SD dose of 80±32 mg. Patients' serum potassium should be monitored with repletion if concentration falls below 4 mEq/L along with magnesium if below 2 mg/dL.
- First-generation antipsychotics such as haloperidol, thioridazine, and chlorpromazine suppress the I_{Kr} which prolongs the QT-interval by 15-30 msec at recommended therapeutic doses and is also associated with TdP. Haloperidol has a dose-dependent increase in risk of QTc-interval prolongation. Patients should be extremely cautious if when combining any of these with other drugs that prolong the QTc interval or inhibit the CYP2D6 enzyme, principal metabolic pathway for these drugs.
- Second-generation antipsychotics suppress the I_{Kr} to varying degrees. Clozapine, olanzapine, aripiprazole, and paliperidone carry the least risk for QTc prolongation. Quetiapine increases the QTc-interval by an average of 15-20 msec in the presence of CYP3A4 inhibitors. Risperidone increases the QTc-interval by 10 msec, induces early afterdepolarizations, and causes TdP. Ziprasidone prolongs the QT-interval in a dose-dependent manner; however the effect plateaus at 20 msec. The QT-interval should be assessed before initiation of the drug, at day 7, and after any changes in dosing. Genetic polymorphisms may also play a role in the risk of TdP.

Antimicrobial Agents

- The following compounds have been associated with changes in QTc-interval and TdP: macrolides, fluoroquinolones, azole antifungals, and pentamidine.
- Erythromycin and clarithromycin prolong the QTc-interval by suppressing the I_{Kr}. Macrolides act by two ways: through suppressing the I_{Kr} and inhibiting their own metabolism.
- Ciprofloxacin, levofloxacin, and moxifloxacin are associated with the risk of TdP. Moxifloxacin is associated with the greatest risk of QTc-interval prolongation and should be reserved for last line treatment.
- Ketoconazole is the only azole antifungal that suppresses the I_{Kr} but all members of this family are CYP3A4 inhibitors and therefore indirectly contribute to TdP by increasing plasma concentrations of 3A4 substrates.

Antineoplastic Agents

- Tyrosine kinase inhibitors (nilotinib, dasatinib, and sunitinib) prolong the QT-interval by suppressing the I_{Kr} in a concentration-dependent manner. Sudden death was attributed to nilotinib in a clinical trial and the maximum QT-interval prolongation was 18 msec.
- Arsenic trioxide can be used for the treatment of relapsed or refractory acute promyelocytic leukemia but has a high risk of QT-interval prolongation and TdP. In a clinical trial, arsenic trioxide caused QT prolongation of more than 500 msec in 16 of 40 patients, with one patient experiencing TdP.

Conclusion

- Pharmacists should be aware of the medications that have the potential to cause QT interval prolongation to prevent and reduce QT-interval prolongation in patients receiving multiple medications and with certain medications that have the potential to cause QT prolongation.

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