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Drug-Induced QTc Interval Prolongation

The risk of developing a life-threatening arrhythmia at any given QTc interval (the QT interval corrected for heart rate) varies widely between patients. In patients with a high baseline risk, QTc prolonging drugs should be either avoided or the QTc interval should be monitored closely.

QTc Prolongation

- Prolonged QTc interval can lead to Torsades de Pointes (TdP), ventricular tachycardia, ventricular fibrillation, and sudden death.
- QTc prolongation is a QTc interval > 450 milliseconds (ms) in men or > 460 ms in women (definition varies between sources).
- Risk of arrhythmia increases with increasing QTc interval AND predisposing risk factors.
- Some drugs prolong cardiac repolarisation. This usually occurs on starting the offending drug(s), and is apparent within days, it is often dose related and the risk is increased with intravenous administration.

Predisposing Risk Factors

- Congenital long QT syndrome or past history of long QT.
- Family history of sudden cardiac death.
- Structural heart disease (e.g. cardiomyopathy).
- Hypokalaemia, hypomagnesaemia and hypocalcaemia.
- Thyroid dysfunction.
- Bradycardia.
- Female gender.
- Age over 65 years.
- Renal or hepatic impairment can lead to higher drug concentrations of drugs that prolong QTc.

Drug Interactions

- Two or more drugs that cause QTc prolongation independently will have an additive effect and increase the risk of TdP.
- One or more drugs may cause electrolyte disturbance (e.g. diuretics, β-agonists, proton pump inhibitors), bradycardia (e.g. β-blockers, donepezil) or other effects that predispose the individual to the QTc prolonging effects of another drug.
- One drug may increase the plasma concentration of another drug that prolongs the QTc interval.

Some drugs that can prolong the QTc interval. Table is not exhaustive.[1–3]

Drug Class	Drug
Antiarrhythmic	Amiodarone*, flecainide*, sotalol*
Antibiotic	Azithromycin*, ciprofloxacin*, clarithromycin*, erythromycin*, levofloxacin*, moxifloxacin*, roxithromycin*
Antidepressant	Citalopram*, escitalopram* (≥ 30 mg)[4,5], tricyclic antidepressants
Antiemetic	Domperidone* (oral dose > 80 mg daily)[6,7], droperidol*, ondansetron* (IV dose >16 mg)[8]
Antifungal	Fluconazole* (stat doses low risk), ketoconazole, voriconazole
Antipsychotic	Chlorpromazine*, haloperidol*. Most antipsychotics have a dose related risk.
Other	Donepezil*, hydroxychloroquine*, lithium, methadone*, tacrolimus, tamoxifen

*These drugs are classified by CredibleMeds® as a 'known' risk of TdP.

The risk of TdP increases with increasing QTc interval:[3]

- **High risk:** QTc > 500 ms, drugs with a known risk of TdP, or a mean QTc increase > 60 ms from baseline
- **Moderate risk:** QTc 460-499 ms, drugs with a possible association with TdP, or a mean QTc increase 20-59 ms from baseline
- **Low risk:** drugs with minimal evidence of association with TdP, or a mean QTc increase < 20 ms from baseline

Prevention of Drug-Induced QTc interval Prolongation

- Address modifiable risk factors:
  - Limit the use of QTc prolonging drugs in patients with known risk factors.
  - Use the lowest possible dose and/or administer at a slow rate.
  - Avoid drug interactions, particularly multiple drugs associated with QTc prolongation.
  - Avoid electrolyte disturbances.
- Obtain an ECG prior to starting any drug that may prolong the QTc interval. Repeat ECG at steady state (4-5 half-lives). Dose reduction or discontinuation is recommended if the QTc is > 500 ms or if it increases > 60 ms compared with baseline. Consider cardiology review if QTc prolongation doesn't resolve with drug discontinuation.
- Advise patients to seek immediate medical attention if symptoms such as light-headedness, dizziness, palpitations, shortness of breath, or fainting occur.

- Online tools help assess risk in patients e.g. MedSafety Scan® and Tisdale risk score.
- Report suspected adverse effects to CARM.

References

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