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QT PROLONGATION and TORSADES DE POINTES: DRUGS and SUDDEN DEATH

What is Torsades de Pointes (TdP)?

- TdP or "twisting of the points" refers to a polymorphic ventricular tachycardia
- It is associated with a prolonged QT_c interval and bradycardia; patients may also report shortness of breath or syncope
- TdP is thought to be caused by early after-depolarizations during prolonged repolarization[1]
- It is often self-limiting but may be **potentially fatal**, sometimes leading to syncope and/or sudden death
- TdP can be either 1° (congenital) or 2° (acquired) due to metabolic disturbances, medical conditions, or **most commonly**, drugs [1,10]
- Recent USA black box **FDA WARNINGS** due to QT prolongation: amiodarone, cisapride, droperidol, itraconazole & thioridazine [13]
- Recent drug **FDA REMOVALS** due to QT prolongation: astemizole (Hismanal), grepafloxacin (Raxar) & terfenadine (Seldane). [13]

Who is at risk? [1-6,14]

- The "**multiple hit**" theory suggests that a culmination of several factors is required to induce TdP [2]
- Generally, these factors promote early after-depolarizations or prolongation of the action potential [1]

Table 1: Risk Factors for QT interval Prolongation and TdP [1-6] * greatest significance

Cardiac	Metabolic	Other
Bradycardia < 50 bpm	Altered nutritional status:	***Age** - ↑ risk with ↑ age
***Cardiomyopathy**:	Alcoholism	Cerebrovascular disease
Heart failure	**Anorexia**, starvation	***Female sex** –sex hormones
Left ventricular hypertrophy	Diabetes	regulate channel expression
*Myocardial infarction	Electrolyte disturbances:	Hypothyroidism
***Congenital long QT interval** (incidence ~ 1/5000)[8]	**Hypokalemia**	Obesity
Hypertension	**Hypomagnesemia**	Pituitary insufficiency
Ischemic heart disease	Hypocalcemia	Poisoning –arsenic, organophosphates, nerve gas
	Hypoglycemia	Renal disease
	Hypothermia	***DRUGS (see Table 2)**

Which drugs are implicated?

- Many **drugs** from a variety of therapeutic classes have been associated with **QT interval prolongation** and/or TdP (**see table**)
- All of these drugs have in common their ability to block the *I* kr potassium channel; this results in increased repolarization time and a prolonged QT interval (beginning of QRS complex to end of T wave) on ECG.[1] Inward Na+ and Ca+ influx channels may also be affected [8]
- Prolongation of the QT interval is thought to be **dose-related** and can occur within therapeutic range for some agents (eg amiodarone) but only at supra-therapeutic concentrations for others (eg. clarithromycin)
- Effects of different drugs can be **additive**
- Since many of these drugs are also metabolized by the **cytochrome P450 system**, serious and sometimes lethal drug interactions can occur when combined with drugs which **inhibit** or compete for binding to these isoenzymes (see table)

How to avoid trouble: [2,6]

- **Identify those at risk** (Table 1); be aware however, that individuals' vulnerability can vary greatly due to a complexity of genetic and environmental factors which are not completely understood
- **For patients with major or multiple risk factors, obtain a baseline ECG** and determine the QTc interval (corrected for heart rate – equation described elsewhere[7])
  - **Short [2] QTc $\leq$ 0.41 sec .....VERY LOW RISK**
    -may not require ECG monitoring after initiating a QT-prolonging agent but should have if additional risk factors develop or if a drug interaction is likely
  - **Intermediate QTc 0.42-0.44 sec .....LOW - MODERATE RISK**
    - repeat ECG after initiating any QT prolonging agent, again at steady state, weekly for 1st month, then q6months and when any other QT prolonging agent is added or if a drug interaction is likely
    - if QTc >0.45 sec, reduce dosages or avoid these agents and use alternatives
  - **Prolonged QTc $\geq$0.45 sec .....MODERATE - HIGH RISK**
    - repeat ECG after initiating any QT prolonging agent, again at steady state, weekly for 1st month, then q6months and when any other QT prolonging agent is added or if a drug interaction is likely
    - if QTc >0.50 sec **avoid** these agents and use alternatives
    - regular **monitoring of serum K+ and Mg+** also advised

Rule of thumb [8]: A QTc change of < 10msec is acceptable as long as there are no other significant risk factors; If the QTc change is >10msec, reduce dosage or eliminate the drug(s), monitor more closely.

How to treat TdP:

Emergency: [9]

- *Do not use standard antiarrhythmic agents*
- Give magnesium sulphate 2 grams IV over 2 minutes. If ineffective, consider isoproterenol , dobutamine, or atropine IV
- Consider giving potassium if serum K+ is low; bicarbonate for TCP (phencyclidine) or quinidine poisoning
- Lidocaine & phenytoin have also been used

Later:

- Stop the offending agent
- Maintain normal K+ , Mg++ and HCO_3^-
- Keep out of trouble as above

Table 2: Drugs which can prolong QT Interval [1,3,6,9,12,13,14] -see also www.torsades.org

Cardiovascular Agents	CNS Agents / Psychotropics	Anti-Infective Agents	Miscellaneous Agents	Cytochrome P450 Inhibitors
Anti-arrhythmics	**Anticonvulsants**	**Antibiotics**	Alfuzosin	**CYP3A4**
Amiodarone (low risk of TdP compared to other class III agents such as sotalol; however potential for DIs)	Felbamate	Cotrimoxazole	Amantidine	**amiodarone**
Bepridil	Fosphenytoin	Fluoroquinolones	Arsenic trioxide	**Azole antifungals:**
Bretylium	Lithium	Gatifloxacin	**Cisapride**(Special Access)	*Fluconazole*
Disopyramide		Gemifloxacin	Cocaine	Itraconazole
Dofetilide	**Antipsychotics**	Levofloxacin	Cyclosporin	Ketoconazole
Flecainide	Clozapine	Moxifloxacin	Foscarnet	**Calcium channel blocker**:
Ibutilide	**Phenothiazines (PZs)**	Ofloxacin	Hydroxyzine	Diltiazem
Procainamide	Chlorpromazine	Macrolides	Indapamide	Verapamil
Propafenone	Perphenazine	Azithromycin	Methadone	Cimetidine
Quinidine	Mesoridazine	Clarithromycin	Midodrine	**Ciprofloxacin**
Sotalol	**Thioridazine**	**Erythromycin** [11]	Octreotide	Grapefruit juice
	Butyrophenones	Roxithromycin	Phenylephrine	**HIV: protease inhibitors**
Dobutamine	Haloperidol		**Probucol**	**Macrolides:**
Dopamine	Thioxanthines	**Azole Antifungals**	Pseudoephedrine	**Erythromycin**
Isradipine	**Pimozide**	*Fluconazole*	Ritodrine	Clarithromycin
Moexipril/HCTZ	*Quetiapine*	Itraconazole	Tacrolimus	Troleandomycin (not with Azithromycin)
Nicardipine	*Risperidone*	Ketoconazole	Tamoxifen	Methadone
Norepinephrine	**Ziprasidone**	Voriconazole	Tizanidine	**SSRI's:**
			Triptans(Recently off QT list)	Fluvoxamine
	Chloral Hydrate	**Antimalarials**	Vardenafil	Norfluoxetine
		Chloroquine	**Antihistamines**	Nefazodone
	SSRIs	**Halofantrine**	*Diphenhydramine*	**Paroxetine**
	Fluoxetine	Mefloquine	*Clemastine*	**CYP2D6**
	Paroxetine	Quinine	*Loratidine* (proposed but no reports)	Beta Blockers (BBs)
	Sertraline		Withdrawn: Astemizole & terfenadine	Haloperidol
		Pentamidine	**Appetite suppressant**	Phenothiazines
	SNRI		Ephedrine	Quinidine
	Venlafaxine		Fenfluramine	SSRIs (not interact with citalopram)
			Phentermine	Terbinafine
	TCAs		Sibutramine	TCAs
	Amitriptyline		**Bronchodilators**	---
	Amoxapine		Epinephrine	*less significant*
	Clomipramine		Isoproterenol	**CYP1A2**
	Desipramine		Levalbuterol	Fluoroquinolones
	Doxepin		Metaproterenol	Fluvoxamine
	Imipramine		Salbutamol/albuterol	Grapefruit juice
	Maprotiline		Salmeterol	
	Nortriptyline		Terbutaline	

ADHD agents				
Amphetamine				
Atomoxetine				
Dextroamphetamine				
Methylphenidate				
Antiemetics				
Dolasetron				
Domperidone				
Droperidol				
Granisetron				
Ondansetron				

AVOID COMBINATIONS of PHENOTHIAZINES with TCAs, BETA BLOCKERS, and ANTICONVULSANTS

Some drugs (eg. erythromycin & amiodarone) **prolong the QT Interval AND act as inhibitors to potentially increase levels or QT effects of concomitant medications.**

BOLD=major significance (well-documented) REGULAR=low-moderate significance (fewer case reports) *ITALIC=minor significance (theoretical, few if any case reports)*

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