Pharmacy Friday Pearls

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Antiemetics & QT Prolongation

Introduction

1. Prolonged QT interval reflects prolonged myocyte repolarization due to ion channel malfunction and gives rise to early after-depolarizations.[1]
2. Prolonged QTc is defined as > 470 msec in males and > 480 msec in females.[1]
3. The danger of a prolonged QTc interval is a life-threatening polymorphic ventricular rhythm known as Torsades de Pointes (TdP), the risk of TdP is 2-3 times higher when QTc is > 500 msec.[1]
4. Multiple factors can contribute to QTc prolongation including advancing age, bradyarrhythmias, underlying cardiac disease, electrolyte abnormalities (e.g. hypokalemia, hypomagnesaemia, hypocalcemia), and medications (e.g. antiarrhythmics, antidepressants, antimicrobials, antipsychotics, and many others).[1-2]
5. **Medication induced QT prolongation is dose and route related, with higher doses and IV administration being associated with more QT prolongation**

Pharmacology				
Medication	**Ondansetron (Zofran®)**	**Promethazine (Phenergan®)**	**Metoclopramide (Reglan®)**	**Prochlorperazine (Compazine®)**
Dose	4 mg	12.5 mg	5 to 10 mg	5 to 10 mg
Route of Administration	PO (ODT + Tab), IV, IM	PO, IV, IM, Rectal	PO, IV, IM	PO, IV, IM, Rectal
PK/PD	**Onset:** ~30 min **Half-life:** 3-6 hours **Metabolism:** Extensive hepatic, CYP1A2/2D6/3A4 **Excretion:** Urine (44-60%), feces (~25%)	**Onset:** PO/IM ~20 min, IV ~5 min **Duration:** 4-6 hours **Metabolism:** Hepatic, CYP2D6/2B6 **Excretion:** Urine & feces as inactive metabolites	**Onset:** PO 30-60 min, IV 1-3 min, IM 10-15 min **Duration:** 1-2 hours **Metabolism:** Hepatic, CYP2D6 **Excretion:** Urine (~85%), feces	**Onset:** PO 30-40 min, IM 10-20 min, rectal 60 min **Duration:** 3-4 hours **Metabolism:** Primarily hepatic **Excretion:** Feces
Adverse Effects	Headache, fatigue, malaise, constipation	Injection reactions (vesicant), CNS depression	Flushing (common w/ high IV doses), injection reactions, dystonic reactions, restlessness	Anticholinergic effects, extrapyramidal symptoms, risk of aspiration
Drug Interactions and warnings	CYP3A4 inducers, QT prolongating medications, serotonin syndrome, caution in hepatic disease (Child-Pugh class C)	**BBW: Severe tissue injury** (including gangrene) with injection administration (IM preferred over IV) CNS depressants, anticholinergics	**BBW: Tardive dyskinesia** (dose & duration related), CYP2D6 inhibitors, serotonin modulators, anti-Parkinson agents, CNS depression, extrapyramidal symptoms	**BBW: Elderly patients with dementia** (increased risk of death CNS depression), orthostatic hypotension, caution in seizure disorders
Crediblemeds Classification	Known risk of TdP	Possible risk of TdP	Conditional risk of TdP	No classification

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Medications Associated with QT Prolongation				
Antiarrhythmics	**Antidepressants**	**Antimicrobials**	**Antipsychotics**	**Others**
Amiodarone Propafenone Procainamide Flecainide Dronedarone Sotalol	Citalopram Escitalopram Amitriptyline Sertraline Fluoxetine	Azithromycin Clarithromycin Levofloxacin Ciprofloxacin Fluconazole	Chlorpromazine Haloperidol Ziprasidone Olanzapine Quetiapine	Ondansetron Metoclopramide Sumatriptan Methadone Loperamide

Overview of Evidence			
Author, year	Design/ sample size	Intervention & Comparison	Outcome
Li, 2018	Prospective, observational study (n=20)	IV ondansetron 4 mg	**A single administration of ondansetron was associated with a mean QTc increase of 16.2 msec (p=0.01)** • Zero related cardiac events reported
Moffett, 2016	Prospective, observational study (n=22)	IV ondansetron 4 mg	A single administration of ondansetron was associated with a mean QTc increase of 20 msec • **Zero related cardiac events reported**
Owczuk, 2009	Prospective, double-blind, randomized study (n=40)	IV promethazine 25 mg IV midazolam 2.5 mg	**Promethazine had a statically significant increase in QTc interval compared to midazolam at 5,10,15,& 20 min (p<0.001)** Significantly higher number of patients with a QTc > 450 in the promethazine group compared to the midazolam group (11 vs 7; p=0.007) • No cardiac events were reported
Charbit, 2008	Prospective, double-blind, randomized study (n=16)	IV 1 mg droperidol IV ondansetron 4 mg IV droperidol 1 mg + ondansetron 4 mg placebo	Compared to placebo both droperidol and ondansetron significantly prolonged the QTc interval by 25 msec and 17 msec respectably (p=0.014) **Droperidol and ondansetron combined prolonged the QTc by 28 msec compared to placebo**
Ellidokuz 2003	Prospective, double-blind, cross-over (n=10)	IV metoclopramide 10 mg	Metoclopramide administration resulted in steeper QT/RR slopes compared with the pre-drug values (0.0037 ± 0.004 vs 0.064 ± 0.012, p=0.041). The QT variance increased after metoclopramide administration (46 ± 9 vs 164 ± 27, p=0.003) • **No cardiac events were reported**
Czekalla 2001	Four controlled, double-blind, randomized controlled trials (N=2700)	olanzapine 5-15 mg Placebo	Olanzapine 15 ± 2.5 mg/day dose group had increase of QTc of 8.44 msec vs 4.71 msec in placebo group (p=0.038); **no difference in olanzapine group dosing < 15 mg/day** No cardiac events were reported were reported in post marketing data

Summary

- The danger of QT prolongation is a life threatening arrhythmia known as Torsades de Pointes risk and the treatment is IV magnesium sulfate 1-2 gm over 15 minutes
- Recommend obtaining EKGs for patients receiving multiple doses of antiemetics, or antiemetics in the setting of electrolyte abnormalities, QT prolonging home medications, or extensive cardiac history
- **Per crediblemeds.org the risk of TdP is the highest with ondansetron > promethazine > metoclopramide> prochlorperazine**
  - Keep in mind all of these medications and other antiemetics have the potential to prolong the QT interval
- **Recommend using metoclopramide or prochlorperazine in place of ondansetron in patients with QT prolongation**
- **Recommend using the lowest effective dose of medication and PO or IM administration instead of IV when possible**

References

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