Methadone and QTc Prolongation

A normal QTc interval is ≤430 msec for men and ≤450 msec for women[1]. Borderline QTc prolongation for men is classified as 431-450 msec and 451-470 msec for women, while QTc prolongation is defined as >450 msec for men and >470 msec for women. As the QTc interval increases, so does the risk for life-threatening arrhythmias such as polymorphic ventricular tachycardia or Torsades de Pointes (TdP). The risk of sudden cardiac death increases 4-fold when QTc is ≥500 msec.[2]

Many studies have reported on QTc interval prolongation caused by methadone. In one literature analysis, patients were using between 2 and 1680 mg/day and the percentage of patients with prolonged QTc intervals varied from 9% to 88%.[1] ECG readings showed QTc intervals of 413-457 msec with a change from baseline of 12-42 msec. The analysis found that some studies showed a dose-dependant effect on increasing QTc interval, while others did not. Some cases of TdP were reported, but there is still debate regarding the clinical significance of mildly prolonged QTc interval. In case reports of patients who did experience TdP, the QTc range was 517-626 msec. Sudden cardiac death has been reported in patients taking as little as 29 mg/day of methadone.[2] The lowest dose of methadone at which an ECG should be performed has not been clearly established.[1] There is increased potential for QTc prolongation with IV methadone compared to oral due to the preservative chlorobutanol with an average increase of 42 msec from baseline.[2, 3]

A prospective trial of 100 cancer patients starting methadone therapy found that although baseline QTc prolongation was common, increases to >500 msec were rare.[4] None of the patients in this study used >100 mg/day of methadone and 28% of patients had QTc prolongation prior to methadone initiation.

Risk Factors for QTc Prolongation[1,2]

- Hypokalemia
- Hypomagnesemia
- Age
- Female sex
- Advanced heart disease
- Congenital and acquired long-QT syndromes
- Family history of sudden death
- Anorexia
- Bradycardia

Drugs that Prolong the QTc Interval

A proposed mechanism for drug induced QTc prolongation is blockade of the human ether-a-go-go potassium channel resulting in inhibition of outward potassium current during myocardial repolarization[5]. Risks and benefits should be considered when a drug with QTc prolonging potential is prescribed. The optimal time to measure QTc is when the QTc-prolonging medication is at steady state.[6] Serious consideration should be given to stopping the drug if the prolongation is more than 40 msec over the patient's baseline QTc.

Following are drugs that may prolong the QT interval:[7]

Methadone (Dolophine)	Amantadine (*Symmetrel*)	Erythromycin
Buprenorphine (*Butrans*, Subutex)	Trimethoprim-Sulfamethoxazole (*Septra, Bactrim)*	Azithromycin (*Zithromax, Z-Pak)*
Octreotide (*Sandostatin)*	Ritonavir (*Norvir*)	Clarithromycin (*Biaxin*)
Tizanidine (*Zanaflex*)	Lopinavir/ritonavir (*Kaletra*)	Ciprofloxacin (*Cipro)*
Lapatinib (*Tykerb*)	Atazanavir (*Reyataz*)	Moxifloxacin (*Avelox*)
Sunitinib (Sutent)	Saquinavir (*Invirase*)	Levofloxacin (*Levaquin*)
Dasatinib (*Sprycel*)	Nortriptyline (*Pamelor)*	Hydroxyzine (*Vistaril*)
Nilotinib (*Tasigna*)	Amitriptyline (*Elavil)*	Diphenhydramine (*Benadryl)*
Tamoxifen (*Nolvadex*)	Desipramine (*Norpramin*)	Aripiprazole (*Abilify*)
Vandetanib (*Caprelsa*)	Doxepin (Sinequan)	Olanzapine (*Zyprexa*)
Levalbuterol (*Xopenex*)	Desvenlafaxine (*Pristiq*)	Risperidone (Risperdal)
Albuterol (*Proventil HFA*, *Ventolin HFA*)	Venlafaxine (*Effexor*, *Effexor XR*)	Quetiapine (*Seroquel*, *Seroquel XR*)
Promethazine (*Phenergan)*	Trazodone (*Desyrel)*	Clozapine (*Clozaril*)
Haloperidol (Haldol)	Fluoxetine (Prozac)	Iloperidone (Fanapt)
Chlorpromazine (*Thorazine)*	Escitalopram (*Lexapro*)	Paliperidone (*Invega*)
Metoclopramide (*Reglan)*	Citalopram (*Celexa*)	Ziprasidone (*Geodon*)
Prochlorperazine (*Compazine)*	Paroxetine (*Paxil*, *Paxil CR*)	Fluconazole (*Diflucan*)
Granisetron (*Kytril*)	Sertraline (*Zoloft*)	Voriconazole (Vfend)
Ondansetron (*Zofran*)	Mirtazapine (*Remeron*)	Dobutamine
Amiodarone (*Cordarone)*	Methylphenidate (*Ritalin)*	

Drugs that Inhibit Methadone Clearance[11]

Methadone is metabolized by cytochrome P450 isoenzymes CYP3A4, CYP2D6, and to a lesser extent, CYP2B6, CYP1A2, CYP2C19, and CYP2C9.[1]

Amitriptyline	Itraconazole
Ciprofloxacin	Ketoconazole
Delavirdine	Omeprazole
Fluconazole	Paroxetine
Fluvoxamine	Voriconazole

Monitoring Recommendations

Depending on a patient's life expectancy and goals of care, ECG monitoring may not be warranted for comfort care patients.

- Identify High Risk Patient Populations
  - IV Methadone use
  - Medically frail

- Concurrent use of interacting medications (e.g. CYP3A4, 2D6 inhibitors) or QTc prolonging agents
- Personal or family history of arrhythmias
- Electrolyte abnormalities
- Age
- Female sex
- Advanced heart disease
- Anorexia

- Patient education at time of prescribing
  - Clinicians should ask patients about any history of structural heart disease, arrhythmia or syncope, and warn patients of the risk of arrhythmia before prescribing methadone[2]
  - Educate patients/caregiver to seek medical attention immediately if any non-specific signs and symptoms of QTc prolongation occur such as syncope, seizures, or palpitations

- Monitoring
  - Inpatients started on methadone should get a baseline ECG, which should be repeated after dose escalation to a oral methadone dose of 60mg/day, if patients are started on IV methadone, or when drugs that can increase the risk for QTc prolongation are added
    - Consider repeating the ECG when steady state is achieved after dose escalation, with IV methadone, or when interacting medications are initated[3]
      - For patients on an oral methadone dose of 60mg/day, consider obtaining a follow-up ECG in 1-2 weeks
      - For patients with a previous ECG indicating boardline QTc prolongation, consider obtaining a follow-up ECG in 4-7 days
  - Stable outpatients should receive a baseline ECG before treatment, 30 days after treatment initiation, and annually[2]. More frequent ECG is should be considered for patients using ≥60 mg/day of oral methadone
  - An ECG should be obtained immediately in patients with unexplained syncope, palpitations, or seizures[2]
  - Consider tapering methadone when QTc is prolonged ≥40 msec from baseline[1]
  - Tapering methadone or eliminating other risk factors is recommended when QTc is >500 msec[2]

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