

Journal Watch
The Effect of Oral Methadone on the QTc Interval in Advanced Cancer Patients: a Prospective Pilot Study

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Reference: eddy S *et al* . . J Pall Med 2010;13 (1): 33-38

Background: Methadone is a synthetic opioid, effective for the treatment of cancer pain and is a good option for many patients. One of the adverse effects of methadone is a prolongation of the QTc interval which can lead to severe arrhythmias and sudden cardiac death. Based on previous studies, with maintenance programs, this phenomenon appears to be dose related (300-600mg/day). It is unknown if this applies to the palliative patients, whose doses tend to be lower. Therefore an improved understanding of the risk of this population would be of use to their clinicians.

Methodology:

Inclusion: ≥18rs, cancer diagnosis, no previous methadone use, medthadone used for pain control (either as initial therapy or opioid rotation).

Exclusion: Hx of arrhythmias, pacemaker or defibrillator, contraindications to methadone use (hypersensitivity) and MMSE <24.

Subjects may be inpatients or outpatients as referred to the team.

Electrographic assessments: Resting 12-lead ECG (q 5 mins x 3) at baseline, 2 4 & 8 weeks, QTc calculated and reviewed by institutional cardiologists.

Definition of QTc

1. > 430 ms (male) & > 450ms (female)
2. > 500mg regardless of gender*
3. > 10% above baseline
4. >25% above baseline*

*clinically significant.

Contributing factors to QTc prolongation:

Structural heart disease (MI, CHF & valvular heart disease) & electrolyte abnormalities

Medications associated with QTc prolongation (classified by the QT drugs.org University of Arizona)

3 risk categories:

1. Drugs which carry a risk of torsades de pointes
2. Drugs which prolong the QTc and/or have been associated with torsades de pointes
3. Drugs which carry a risk of torsades de pointes and/or prolong QTinterval under certain conditions (congenital prolonged QTc, overdose, or coadministration of interacting drugs)

Statistical Analysis. Many methods used depending on the data type: seems appropriate

Results:

100 patients enrolled

2 week f/u available to 64 patients 2 assessments: 26 patients

4 week f/u available to 41 patients 3 assessments: 15

8 week f/u available to 27 patients 4 assessments: 25

36 who did not fu at 2 weeks: hospice transfers or return to local community n = 17 (47%). Non-adherence [n=2 (5%)] A flutter, voluntary withdrawal, death & unknown each [n=1 (3%)]

Methadone dose: at 2 weeks mean = 23mg (range 3-90mg)

No significant association between QTc Interval & methadone dose (p=0.45)

QTc prolongation prior to methadone initiation

28 /100 had Tc prolongation prior to methadone administration (none > 500 ms

Risk factors identified in 22/ 28 (79%). (Table 3)

QTc prolongation post methadone initiation

Week 2: 5/64 (8%) had prolonged QTc 1/64 (2%) > 500ms. 11/64 (17%) >10% above baseline

Week 4: 3/39 (8%) abnormal QTc . 1/39 (3%) > 10% above baseline

Week 8: 3/28 (11%) abnormal QTc 1/28 (4%) > 10% over baseline

No patients experience > 25% =above baseline. No torsades or V fib documented during study period.

Patients with baseline QTc prolongation have a higher chance of developing QTc at 2 weeks compared normal subjects (71% vs 17%) p= 0.001 Table 4)

Discussion:

Existing evidence regarding the association of methadone and QTc interval prolongation, possibly resulting in death, has been gleaned from a non-palliative population. This study was to determine if these concerns applied to an advanced cancer palliative population with limited prognosis (< 3 months). Baseline prolongation was relatively common, but significant increases from baseline were not seen and the group concluded methadone safety in this population. The group also noted patients at high risk for opioid escalation due to psychosomatic symptoms may not be offered methadone.

The group concluded methadone was safe to use in the population studied but those significant risk (high doses or with significant risk factors) ECG's at baseline and subsequent intervals may be reasonable.

Study Strengths

Prospective study.

Good pilot project, which may elicit larger studies.

Study Weaknesses

Small sample size.

Torsades de pointes and sudden cardiac death are infrequent & may not have been captured in the small sample.

High attrition rate: typical of the population.

Study cannot identify arrhythmias in those lost to follow-up .

Single center study in a tertiary cancer centre, which may not be representative of the entire palliative population

Relevance to Palliative Care

Study Population is similar to that at the TPCU. We now have evidence that methadone prescribing is appropriate to this population., although we should always be mindful to eliminate any unnecessary QTc prolonging factors.