

## Methadone and corrected QT prolongation in pain and palliative care patients: A case-controlled study

**Reference:** Juba K, Khadem T, Hutchinson D, Brown J. J Palliat Med 10 Feb 2017 (e-pub ahead of print)

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### Abstract

**Background:** Methadone (ME) is commonly used in pain and palliative care (PPC) patients with refractory pain or intolerable opioid adverse effects (AEs). A unique ME AE is its corrected QT (QT<sub>c</sub>) interval prolongation risk, but most evidence exists in methadone maintenance therapy patients.

**Objective:** Our goal was to identify QT<sub>c</sub> interval prolongation risk factors in PPC patients receiving ME and other medications known to prolong the QT<sub>c</sub> interval and develop a risk stratification tool.

**Design:** We performed a case-control study of adult inpatients receiving ME for pain management.

**Settings/Subjects:** Adult inpatients receiving ME with a QT<sub>c</sub> >470 msec (males) and >480 msec (females) were matched 1:2 according to age, history of QT<sub>c</sub> prolongation, and gender with ME patients who did not have a prolonged QT<sub>c</sub> interval. QT<sub>c</sub> prolongation risk factors were collected for both groups.

Covariates were analyzed using conditional logistic regression. Classification and regression tree analysis was used to identify the ME dose associated with QT<sub>c</sub> prolongation.

**Results:** Predictors of QT<sub>c</sub> prolongation included congestive heart failure (CHF) (OR: 11.9; 95% CI: 3.7–38.2; p < 0.00), peptic ulcer disease (PUD) (odds ratio [OR]: 8.3; 95% confidence interval [95% CI]: 2.4–28.9; p < 0.00), hypokalemia (OR: 6.5; 95% CI: 1.5–28.2; p < 0.01), rheumatologic diseases (OR: 4.7; 95% CI: 1.6–13.9; p < 0.00), taking medications with a known torsades de pointes (TdP) risk (OR: 4.4; 95% CI: 1.8–10.7; p < 0.01), malignancy (OR: 3.3; 95% CI: 1.2–9.3; p < 0.03), hypocalcemia (OR: 2.1; 95% CI: 0.9–4.8; p < 0.07), and ME doses >45 mg per day (OR: 1.9; 95% CI: 0.8–4.8; p < 0.16). Mild liver disease was protective against QT<sub>c</sub> prolongation (OR: 0.05; 95% CI: 0.0–0.46; p < 0.01).

**Conclusions:** Predictors of QT<sub>c</sub> prolongation in our multivariate conditional logistic regression model included CHF, PUD, hypokalemia, rheumatologic disorders, use of medications with a known TdP risk, malignancy, hypocalcemia, and ME doses >45 mg per day.

**Strengths of study:** Study had a large sample size but a heterogeneous cohort. No conflicts of interest were reported. The authors defined QT<sub>c</sub> prolongation.

**Weaknesses of study:** The authors acknowledge several limitations to the study. Data was collected and coded by a single investigator, which ensured reliability but introduced potential for incomplete or miscoded data. Baseline ECG's and methadone start dates were not available for all patients. Bazett's formula was used to calculate QT<sub>c</sub> which may not be accurate in bradycardic or tachycardic patients. Risk factors such as valvular heart disease were not recognized due to low frequency. Cardiac arrest and cardioversion data were not always available as palliative patients have DNR orders. The impact of pharmacogenomics was not considered. CYP2C19 variants have shown to increase QT<sub>c</sub> intervals in other studies. Palliative patients in the cohort were more likely to accept a longer QT<sub>c</sub> interval and less likely to reduce modifiable risk factors.

Additionally doses were not taken into account. Generally, increasing doses of any medication, with the potential to increase QT<sub>c</sub> will increase the risk of elongated QT<sub>c</sub> values.

### **Relevance to palliative care**

Methadone is a potent, synthetic analgesic useful in treating malignant pain, particularly when neuropathic features are present and is frequently used in palliative care for these reasons. It is therefore useful to be able to recognize some of the risk factors of prolongation of QT<sub>c</sub> interval and to try to eliminate as many as possible when prescribing methadone. Dose reduction and using alternative opioids as co-analgesics can be tried as well as correcting electrolyte imbalances and dose-reducing or eliminating other medications with similar effect. Methadone's effect on the QT interval is dose dependent and ECG changes have been seen in patients taking higher doses.

Many of the palliative patients taking methadone are also taking neuroleptics, antidepressants and antiemetics which may also have the potential to increase the QT interval and this should be monitored. Additionally, if antimicrobial therapy is required, and agents such as levofloxacin or fluconazole are prescribed, these also have the capacity to prolong the QT<sub>c</sub> interval significantly. Frequently, in these cases, pharmacists will suggest alternatives, to avoid increasing the QT<sub>c</sub> risk further. If we cannot avoid using these agents it is prudent to run the ECG prior to administration and frequently during treatment to ensure QT<sub>c</sub> is not sufficiently prolonged to risk torsades de pointes or sudden cardiac death. As the size of effect of each of these factors is unknown, and probably dose dependent, it is impossible to determine what the accumulated risk may be. Therefore, we need to balance the risk vs benefit in individual cases and prescribe accordingly and be prepared to monitor ECG as frequently as necessary.