

Evaluation of QTc Interval in Hospitalized Patients Receiving Methadone

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Background

- Methadone is indicated for the treatment of opioid addiction and severe chronic pain, and its use can prolong the QTc interval and lead to torsades de pointes, a life-threatening ventricular arrhythmia.¹
- Methadone was the second most commonly reported drug-related cause of ventricular arrhythmia between 1997 and 2011 according to the United States Food and Drug Administration's Adverse Event Reporting System.²
- Electrocardiogram (ECG) monitoring is recommended upon initiation of methadone, 30 days post-initiation, and annually.³
- More frequent ECG monitoring is indicated if a QTc-prolonging medication is added, new-onset bradyarrhythmias occur, or severe hypokalemia or hypomagnesemia is present.³

Objectives

To describe the frequency of ECG monitoring for adult patients receiving methadone during an emergency room visit or hospitalization, and characterize the patient populations that were more likely to have an ECG ordered during therapy.

Methods

- Retrospective chart review conducted between November 1, 2012 and April 30, 2013.
- Approved by the local Institutional Review Board.
- Inclusion Criteria: 18-89 years old and received ≥ 1 dose of methadone.
- Data collected from the electronic medical record included reason for admission, frequency of ECG monitoring, methadone total daily dose, and the following risk factors for QTc prolongation:
 - Age
 - Sex
 - Comorbid conditions: left ventricular ejection fraction (LVEF) < 40%, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), hypertension
 - Concomitant medications: QTc-prolonging agents, strong cytochrome P 450 (CYP) 3A4 inhibitors, and agents associated with electrolyte disturbances.
- Multiple logistic regression analysis was used to determine an association between patient-specific features and whether an ECG was ordered.

Results

- 500 charts were reviewed; 296 (59.2%) patients received ≥ 1 methadone dose.
- Demographic information is provided in Table 1.
- Data regarding concomitant medication use provided in Table 2.

Table 1. Demographics

Mean age (years)	45
Female gender (n, %)	154 (52%)
Reported LVEF < 40% (n, %)*	5 (7.1%)
Coronary artery disease (n, %)	32 (10.8%)
Chronic obstructive pulmonary disease (n, %)	28 (9.5%)
Hypertension (n, %)	106 (35.8%)
Median methadone total daily dose, mg (range)	57.5 (2.5 - 210)

LVEF = left ventricular ejection fraction. *LVEF reported for 70 patients

Table 2. Concomitant Medication Use

	n (%)
Patients receiving ≥ 1 agents that reduce serum potassium concentrations	77 (26%)
Patients receiving QTc-prolonging medications or CYP3A4 inhibitors	217 (73.3%)
Patients receiving QTc-prolonging medications	201 (67.9%)
1 medication	115 (38.8%)
2 medications	59 (19.9%)
3 medications	20 (6.8%)
4 medications	7 (2.4%)
Patients receiving CYP3A4 inhibitors	26 (8.8%)
1 medication	24 (8.1%)
2 medications	2 (0.068%)

CYP3A4 = cytochrome P 450 3A4

- Data regarding ECG monitoring is presented in Tables 3 and 4.
- Patients receiving methadone doses ≤ 30 mg were 48% less likely to receive a baseline ECG than those receiving doses ≥ 90 mg (Odds Ratio [OR]: 0.52; 95% Confidence Interval [CI] 0.27-0.99; $p=0.0452$).
- One or more risk factors for QTc prolongation was present in 270 (91.2%) of patients, and a baseline ECG was ordered for 97 (35.9%) patients with one risk factor.
- A baseline ECG was ordered for 6 of the 26 (21.4%) patients without risk factors for QTc prolongation.
- Patients with underlying CAD (OR 0.29; 95% CI 0.24-0.62; $p=0.0014$) and hypertension (OR 0.35; 95% CI 0.21-0.59; $p<0.0001$) were more likely to receive a baseline ECG.

Table 3. Factors Associated with > 1 ECG During Hospital Admission	Odds Ratio	95% Confidence Interval	p value
Hypertension	0.50	0.32-0.79	0.0029
4 QTc-prolonging medications	0.21	0.05-0.82	0.0251
Concurrent CYP3A4 inhibitors	0.31	0.11-0.84	0.0214

CYP3A4 = cytochrome P 450 3A4, ECG = electrocardiogram

Table 4. ECG Monitoring	n (%)
Baseline ECG completed	98 (33.1%)
Number of patients with ECG ordered during admission	142
1 ECG per admission	107 (75.4%)
2 ECGs per admission	26 (18.3%)
3 ECGs per admission	3 (2.1%)
4 ECGs per admission	5 (3.5%)
5 ECGs per admission	1 (0.7%)

ECG = electrocardiogram

On the day a QTc-prolonging medication was added, patients with the following risk factors were more likely to receive ECGs:

- Hypertension (OR 0.38; 95% CI 0.21-0.69; $p=0.0012$)
- Concurrent CYP 3A4 inhibitors (OR 0.31; 95% CI 0.10-0.93; $p=0.0362$)
- Four QTc-prolonging medications (OR 0.12; 95% CI 0.02-0.61; $p=0.0107$).

Conclusions

- No guidelines exist for ECG monitoring while patients are receiving methadone in the hospital, but these results suggest a more consistent approach is needed.
- ECG monitoring could be optimized through electronic alerts or automatic orders for hospitalized patients receiving methadone who have one or more risk factors for QTc prolongation.

References

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