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Effects of Methadone on Corrected Q-T Interval Prolongation in Critically Ill Children

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OBJECTIVES This study aimed to determine the association between methadone use and corrected Q-T interval (QTc) prolongation in critically ill children

METHODS A retrospective cohort study of critically ill children receiving methadone at a tertiary care pediatric hospital was conducted. Patients younger than 19 years who had been admitted to the intensive care unit between January 1, 2009, and June 21, 2013, who had received methadone while inpatients, and who had had electrocardiograms (ECGs) performed within 30 days before and after methadone initiation were included. The primary outcome was the net change in QTc interval between baseline and postmethadone ECGs. Secondary outcomes included percent change in QTc interval and the proportion of patients whose QTc intervals changed from normal to prolonged following methadone initiation. We also evaluated potential predictors of QTc interval prolongation, including age, sex, admission diagnosis category, exposure to other QTc-prolonging medications, presence of congenital heart disease or known arrhythmias, and methadone daily dose and route of administration.

RESULTS Sixty-four patients met the inclusion criteria. The median (25th, 75th percentiles) change in QTc interval following methadone initiation was −8 msec (−34, 13.5 msec; p = 0.19). Five patients (8%) had a baseline normal QTc interval that became prolonged after methadone initiation. We identified no statistically significant predictors of QTc prolongation after methadone initiation.

CONCLUSIONS In this dedicated pediatric safety study, methadone initiation did not result in prolongation of the QTc interval. Although these findings suggest methadone initiation may not have a substantial effect of QTc prolongation in critically ill children, a controlled, prospective evaluation in this population remains warranted.

ABBREVIATIONS ECGs, electrocardiograms; FDA, US Food and Drug Administration; HERG, human ether-a-go-go-related gene; QTc, corrected Q-T interval

KEYWORDS adverse drug effect; electrocardiogram; methadone; pediatrics; QTc interval; QTc prolongation; torsades de pointes

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Introduction

Methadone is frequently used in infants and children for the treatment of neonatal abstinence syndrome, iatrogenic opiate withdrawal, and chronic pain.[1] Despite its frequent use in children in the United States, methadone only has US Food and Drug Administration (FDA) approval for use in adults because of limited information regarding the efficacy and safety of methadone in children.[2] The potential for QTc prolongation in critically ill children is an important determinant of its safety profile because of the increased risk of syncope, seizures, and potentially fatal arrhythmias, such as torsades de pointes; and those with critical illness and underlying cardiac disease may be the most vulnerable to such effects.[3,4] Multiple studies have correlated methadone with QTc prolongation in adults, and the FDA currently recommends providers carefully consider potential cardiac risks prior to prescribing it.[3]

Existing evaluations of the QTc-prolonging effects of methadone in children are limited to very small studies and case reports (73 total children) that reach varying conclusions regarding the degree of QTc prolongation induced by methadone.[4–8] Notably, existing studies have largely excluded critically ill children, including those with underlying cardiac disease. Critically ill children are among the most frequent recipients of methadone therapy.[9,10] In the recently completed RESTORE trial, 30% of patients in the control group received methadone; however, no data regarding the effects of methadone on QTc prolongation have been reported to date from this study.[11] Furthermore, critically ill children are likely to receive other QTc-prolonging drugs, have electrolyte derangements, and have end-organ dysfunction known to be associated with increased risk for QTc prolongation.[12–17]

Table 1. QTc Intervals Based on Age and Sex

Age	QTc Interval for Males, msec, Median (2nd Percentile, 98th Percentile)	QTc Interval for Females, msec, Median (2nd Percentile, 98th Percentile)
0–1 mo	413 (378, 448)	420 (379, 462)
1–3 mo	419 (396, 458)	424 (381, 454)
3–6 mo	422 (391, 453)	418 (386, 448)
6–12 mo	411 (379, 449)	414 (381, 446)
1–3 yr	412 (383, 455)	417 (381, 447)
3–5 yr	412 (377, 448)	415 (388, 442)
5–8 yr	411 (371, 443)	409 (375, 449)
8–12 yr	411 (373, 440)	410 (365, 447)
12–16 yr	407 (362, 449)	414 (370, 457)

QTc, corrected Q-T interval
Adapted from Rijnbeek et al.[13]

Because methadone administration is prevalent in pediatric intensive care units, we must ensure that existing clinical practice of methadone administration does not cause undue, life-threatening harm. Therefore, we aimed to determine the effects of methadone initiation on QTc interval in critically ill children, including those with underlying cardiac disease.

Materials and Methods

Data Source and Cohort. A retrospective, single-center cohort study was conducted, including all patients who met the following criteria: younger than 19 years upon admission; admitted to the pediatric intensive care unit or pediatric cardiovascular intensive care unit between January 1, 2009, and June 21, 2013; initiated on methadone (intravenous or enteral) during hospitalization; and having had at least one 12-lead electrocardiogram (ECG) within 30 days before and 1 ECG within 30 days after methadone initiation. Patients must have been on methadone at the time of the second ECG. The typical practice at our institution is to initiate methadone for opioid withdrawal prophylaxis when patients have received at least 5 days of continuous opioid infusions.

The Duke Enterprise Data Unified Content Explore, a data repository of Duke patient data, was used to identify pediatric patients prescribed methadone and to collect all necessary information to conduct our analyses. Patients were excluded if they were maintained on methadone prior to admission to the intensive care unit. Approval was obtained to conduct this study from the Duke Institutional Review Board under a waiver of consent because of the retrospective nature of this study.

Outcomes and Definitions. The primary outcome was the net change in QTc interval between baseline and post–methadone initiation ECGs. If a patient had multiple eligible ECGs, the change in QTC interval was identified based on the last ECG performed immediately prior to initiation of methadone and the first ECG performed after initiation of methadone during a single hospital admission. Qualifying ECGs must have been obtained between 30 days before and 30 days after methadone initiation.

Secondary outcomes included: 1) percent change in QTc interval (calculated as: [QTc prior to methadone initiation − QTc after methadone initiation] / QTc prior to methadone initiation × 100), and 2) the proportion of patients whose QTc interval changed from normal to prolonged following methadone initiation. The following potential predictors of QTc prolongation were assessed: age, sex, admission diagnosis, exposure to other QTc-prolonging medications, presence of congenital heart disease (CHD) or arrhythmias, and methadone duration, dose, and route of administration on the day of postmethadone ECG analysis.[18] The CredibleMeds database (Azert, Oro Valley, AZ) was used to identify QTc-prolonging medications.[18]

Congenital heart disease was defined as the presence of any congenital structural heart, valve, or large vessel abnormality as documented in the medical record. A prolonged QTc interval was defined as an interval greater than the 98th percentile for age (Table 1).[13] QTc intervals below this threshold were considered normal. A short QTc interval was defined as a QTc interval <340 msec. The pediatric cardiologist on service independently determined all QTc interval measurements, correcting QT intervals using Bazett formula.[19]

Statistical Analyses. Demographic data were characterized using counts and percentages for categoric variables, and medians and 25th to 75th percentiles for continuous variables. QTc intervals prior to and after methadone initiation were compared using the Wilcoxon signed-rank test. In addition, the percent and net change in QTc interval following methadone initiation were calculated for each patient. The Wilcoxon rank sum test was used to determine the association

Table 2. Patient Characteristics (N = 64)

Demographic	Result
Male, n (%)	35 (55)
Age, yr, median (range)	0.5 (0–18)
Ethnicity, n (%)	
White	27 (42)
African American	29 (45)
Hispanic	2 (3)
Asian	6 (9)
Admission diagnostic category, n (%)	
Cardiovascular	39 (61)
Hematology/oncology	7 (11)
Infectious disease	6 (9)
Respiratory	8 (13)
Other	4 (6)
Dosing weight, kg, median (interquartile range)	5.1 (3.2–19.5)
History of congenital heart disease, n (%)	39 (61)
History of arrhythmias, n (%)	24 (38)
QT-prolonging medications prior to methadone initiation, n (%)	25 (39)

between possible predictors and change in QTc interval. The p values less than 0.05 were considered to indicate statistical significance.

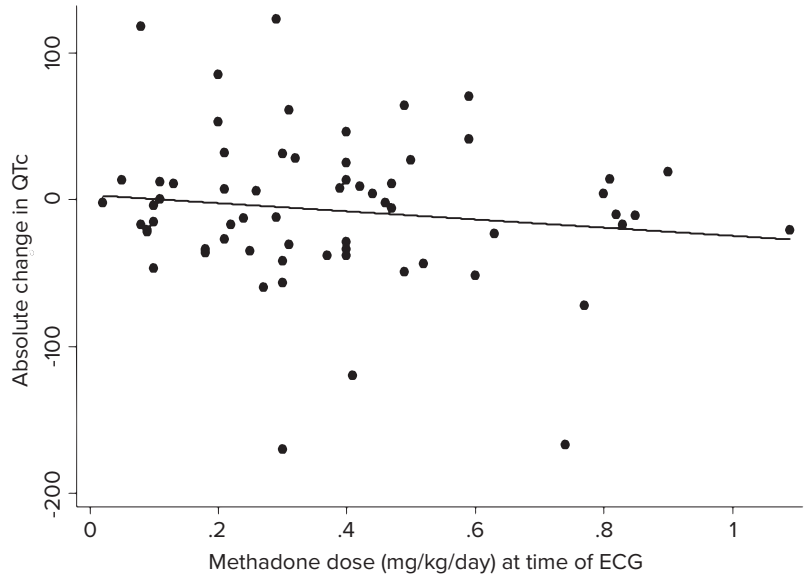
Results

A total of 285 patients admitted during the specified time frame who were treated with methadone were identified. Of these patients, 221 (78%) were excluded. Most patients (207 of 221; 94%) were excluded because of a lack of ECGs within the defined interval, and others were excluded for the following reasons: 7 (3%) were on methadone prior to admission, 5 (2%) had orders for but did not receive methadone, and 2 (1%) had incomplete medical records. The remaining 64 of 285 patients (22%) were included in the study cohort, all of whom received methadone for opiate withdrawal. The median (25th, 75th percentile) age of the cohort was 6 months (0, 60 months), and most patients were male (35 of 64; 55%). A total of 39 included patients (61%) had congenital heart disease (Table 2). The median dosage of methadone was 0.32 mg/kg/day (0.21, 0.49 mg/kg/day). Most of the included patients received methadone multiple times per day (58 of 64; 91%), including 17 (27%), 15 (23%), and 26 (41%) patients administered methadone 2, 3, or 4 or more times daily, respectively. Most patients also received methadone through the enteral route (42 of 64; 66%). The median time of post–methadone initiation ECG was 5 days (3, 10 days).

The median QTc interval at baseline was 446 msec (428, 474 msec). After methadone initiation, the median QTc was 435 msec (413, 479 msec), with a net change of −8 msec (−34, 13.5 msec; p = 0.19) and a percent change of −1.8% (−7.3%, 3.3%) from baseline to after methadone initiation. The 3 patients with the greatest increase in QTc interval had increases of 123, 118, and 85 msec. Of these 3 patients, 2 patients initially had a normal QTc interval and transitioned to a prolonged QTc interval after methadone initiation. None of these 3 patients were on other QTc-prolonging medications. Two of these patients were administered methadone for 1 day and the other for 17 days prior to postmethadone QTc interval assessment.

A total of 30 patients (47%) had a prolonged QTc interval at baseline, with a median value of 474 msec (458, 506 msec), and 21 patients (33%) had a prolonged QTc interval after methadone initiation, with a median value of 496 msec (476, 517 msec). Only 5 of 64 patients (8%) had a normal QTc interval at baseline followed by subsequent prolongation of the QTc interval after methadone initiation. All 3 patients with the longest baseline QTc intervals (588, 559, and 546 msec, respectively) had underlying cardiovascular or congenital heart disease. None of these 3 patients were on other QTc-prolonging medications, and their QTc intervals all decreased after methadone initiation. A total of 25 patients (39%) were on other QTc-prolonging medications at baseline, with these medications discontinued in 13 of 25 of these patients (52%) by the time of postmethadone ECG. Only 1 patient (2%) had a baseline QTc interval that met the definition for short QTc, and no patients met this definition after methadone initiation.[20]

Figure. Absolute change in QTc interval as a function of total methadone daily dosage at time of ECG.



QTc, corrected Q-T interval; ECG, electrocardiogram.

The patient with baseline short QTc had a 118-msec increase in QTc after methadone initiation.

None of the following statistically predicted net or percent change in QTc interval from baseline to postmethadone ECG: age, sex, admission diagnosis category, presence of congenital heart disease, exposure to other QTc-prolonging drugs, history of arrhythmias, and methadone route or method of administration. No significant association was identified between methadone daily dosage and net or percent change in QTc interval (Figure). There was also no association between length of therapy and QTc interval prolongation ($p = 0.67$). There were no documented cases of torsades de pointes or other arrhythmias in our cohort.

Discussion

To our knowledge, this is the first study to systematically investigate QTc prolongation associated with methadone use in critically ill children. We identified no significant change in QTc interval from baseline ECG to postmethadone ECG and no diagnoses of torsades de pointes despite the large proportion of our cohort with underlying cardiac disease or concomitant exposure to other QTc-prolonging drugs.

Our findings are generally consistent with those of other reports in non-critically ill children. Among reports of 27 newborns with *in utero* exposure to methadone, 1 developed bradycardia and 4 transiently developed QTc intervals greater than 460 msec.[5,6] In a study of intravenous methadone in 7 neonates between 33 and 45 weeks postmenstrual age, the maximum QTc interval prolongation was 10.4 msec; however, all QTc intervals remained within the normal range.[12] In 2 pediatric patients (ages 11 and 17 years) receiving methadone for chronic pain, 1 had no change in QTc interval and the other had QTc prolongation in the setting of concomitant QTc-prolonging drugs.[7] In a recent retrospective review of 37 children with cancer-related pain, the mean QTc during methadone treatment was longer than at baseline (447 vs. 437 msec, respectively).[8]

Our findings are inconsistent with data in adults, in whom methadone has been associated with varying degrees of QTc prolongation (16%–23% change in QTc interval), and with torsades de pointes in up to 4% of patients.[14–16,21–26] Further, methadone dose, presence of interacting or other QTc-prolonging drugs, electrolyte abnormalities, and underlying cardiovascular disease have been identified as risk factors for QTc prolongation in adults, but we did not identify these associations in our population.[14–16,21–26]

The observed differences in methadone-associated QTc prolongation may be due to physiologic differences between children and adults. Specifically, the human ether-a-go-go-related gene (HERG) encodes fast potassium channels and is an important catalyst in methadone-associated QTc prolongation through facilitation of delayed repolarization.[3,17,27] Previous investigators have identified decreased HERG gene expression in adults compared with children.[28] The difference in mRNA expression in these patients was nearly 3-fold.[28] Such decreased expression is thought

to be an important factor contributing to differences in QTc prolongation between adults and children.[28] It is currently unknown when HERG gene expression reaches adult levels.[28]

It is also plausible that characteristics of our population contributed to our inability to observe QTc interval prolongation associated with methadone use. Females are known to have longer baseline QTc intervals and are at higher risk for QTc prolongation compared with males.[29] Although such differences between the sexes are normally not apparent until after puberty and we did not identify sex as a significant predictor of QTc prolongation in our study population, developmental changes in the QTc interval have not been studied in critically ill patients.[29] Finally, a high proportion of patients in our study had baseline prolongation of their QTc intervals, potentially precluding significant additional prolongation. Notably, previous investigators have reported prolonged QTc intervals in up to 33% of pediatric patients presenting to the emergency department.[30] It is unclear why such a high proportion of the patients had a prolonged QTc interval at baseline.

Our study has several limitations. Most importantly, our study population was limited in number because a large portion of potentially eligible patients did not have ECGs within the specified time frame. No protocol exists at our institution for ECG monitoring in patients receiving methadone. Therefore, it is possible that our study initially selected for patients perceived to be at higher risk for QTc prolongation because of underlying disease processes or concomitant medications. However, the absence of significant QTc prolongation or related arrhythmia in our most high-risk population may lend support to the short-term safety of methadone in critically ill children**.** Additionally, more patients were on concomitant QTc-prolonging medications at the time of their baseline ECGs compared with their postmethadone ECGs, suggesting that providers discontinue other QTc medications when administering methadone. This practice may have masked an overall effect of methadone on QTc prolongation. Per our study protocol, patients in our study only had 2 ECG measures, including the first ECG after methadone initiation; therefore, we were not able to determine the extent to which intrapatient variation in QTc interval influenced our results. Also, the median duration of methadone at the time of postmethadone ECG was relatively short (5 days) and may not have allowed adequate time for QTc prolongation most frequently described in adults with chronic use (e.g., ≥1 to 6 months).[31,32] Very limited electrolyte data were available at the times of the ECGs, thereby limiting the ability to determine the effects of any electrolyte derangements on the amount of QTc prolongation.

We did not account for medications that may have induced or inhibited the metabolism of methadone. Additionally, we were not able to account for any potential pharmacogenomic differences between patients, which have been associated with variable metabolism of methadone in adult patients.[33] Finally, although we did not identify a relationship between methadone dosage and QTc interval prolongation, we did not obtain serum concentrations, which are more indicative of biologic effect in critically ill children and may have provided additional information regarding the effect of methadone in critically ill children.[12]

Conclusions

To our knowledge, our study is the largest available that evaluates the association between methadone use and QTc prolongation in pediatric patients. We identified no significant change between baseline and postmethadone QTc intervals for included patients, nor did we identify risk factors for prolongation, despite a high proportion of patients with underlying cardiac disease and concomitant QTc-prolonging drugs. Although these findings suggest a favorable safety profile for methadone, a larger, multicenter, retrospective study may be warranted to further evaluate the incidence of torsades de pointes or other severe adverse effects in pediatric patients treated with methadone.

ARTICLE INFORMATION

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