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Methadone prolongs cardiac conduction in young patients with cancer-related pain

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Abstract

Objective—Methadone prolongs cardiac conduction, from mild corrected QT (QTc) prolongation to torsades de pointes and ventricular fibrillation, in adults. However, methadone use for pain and its effects on cardiac conduction have not been investigated in pediatric populations.

Methods—A retrospective review of QTc intervals in patients receiving methadone analgesia was conducted. Medical records from a 4-year period (September 2006 to October 2010) at a pediatric oncology institution were reviewed, and correlations were tested between cardiac

conduction and methadone dosage and duration of therapy, electrolyte levels, renal and hepatic dysfunction, and concurrent medications.

Results—Of the 61 patients who received methadone, 37 met our inclusion criteria and underwent 137 electrocardiograms (ECGs). During methadone treatment, the mean QTc was longer than that at baseline (446.5 vs 437.55 ms). The mean methadone dose was 27.0 ± 24.3 mg/d (range, 5–125 mg/d; median, 20 mg/d) or 0.47 ± 0.45 mg/kg per day (range, 0.05–2.25 mg/kg per day; median, 0.37 mg/kg per day), and the mean duration of therapy was 49 days. The authors identified a correlation between automated and manual ECG readings by two cardiologists (Pearson $r = 0.649$; $p < 0.0001$), but the authors found no correlations between methadone dose or duration and concurrent QTc-prolonging medications, sex, age, electrolyte abnormalities, or renal or hepatic dysfunction.

Conclusion—At a clinically effective analgesic dose, methadone dosage and duration were not correlated with QTc prolongation, even in the presence of other risk factors, suggesting that methadone use may be safe in pediatric populations. The correlation between automated and manual ECG readings suggests that automated ECG readings are reliable for monitoring cardiac conductivity during the reported methadone-dosage regimens.

Keywords

methadone; complex pain; cardiac conduction; pediatric oncology

INTRODUCTION

Methadone is a full μ -receptor agonist that is used to treat severe, chronic pain or pain refractory to conventional therapies.^{1–5} Unique among opioids, methadone is also an *N*-methyl-D-aspartate receptor antagonist⁶; this action may mediate the reduction of opioid-induced hyperalgesia and opioid tolerance^{1,4,7,8} and contributes to methadone's beneficial effect on neuropathic pain. These characteristics, in addition to the drug's low cost, long duration of action, higher potency than morphine, and lack of desensitizing/downregulatory effects seen with other opioids, make methadone an excellent choice for the treatment of severe or complex pain, cases of high-dose opioid regimens with opioid tolerance or opioid hyperalgesia, neuropathic pain, and as a long-acting opioid.^{9–13}

Substantial evidence in adult populations has shown that methadone prolongs the corrected QT (QTc) interval and may cause torsades de pointes and ventricular fibrillation, the leading cause of sudden cardiac death.^{2,4,5,14–22} The QTc prolongation in adult studies has been correlated with methadone dose,^{14,15,19,21} though the mean doses cited (80–397 mg/d) are substantially higher than the typical analgesic doses administered to pediatric patients at our institution.¹ A study by Peles et al.²³ demonstrated a correlation between the QTc prolongation and duration of methadone therapy among adult former heroin addicts who were undergoing methadone maintenance therapy for at least 2 weeks. Several studies in adults have reported risk factors such as sex, age, electrolyte abnormalities, and renal and hepatic dysfunction to be correlated with QTc prolongation in conjunction with methadone administration.^{2,18,24–26} Although not all studies of adult populations have corroborated these findings, these are noticeable trends. Our study aimed to determine if methadone, used

at clinically effective analgesic dosing, causes prolonged QTc in a pediatric oncology population, and to explore correlations between prolonged QTc and methadone dosage, duration of therapy, and associated risk factors.

METHODS

Patients

This retrospective review was approved by the St Jude Children's Research Hospital (St Jude) Institutional Review Board. Patients were identified by reviewing the institution's pharmacy records from September 2006 to October 2010.

The study population included all St Jude patients who received methadone therapy for analgesia for at least 7 consecutive days during a 4-year period and excluded those patients who received methadone to facilitate weaning from opioids after prolonged use for sedation during mechanical ventilation. Data extracted from the medical records included demographic characteristics (ie, age, sex, weight, and primary diagnosis) and dosage and duration of methadone therapy. Pain diagnoses (nociceptive, phantom, or neuropathic) were obtained from either the Pain Management Service progress notes or physician notes. Doses of methadone were noted on each day an electrocardiogram (ECG) was recorded.

Electrocardiography

For each patient, all available 12-lead ECG records were reviewed for the automated and manual QTc intervals at the following time points: 1) before or on the first day of methadone treatment (baseline); 2) during methadone therapy (on-therapy); and 3) at 7 or more days after the final dose of methadone (off-therapy). ECGs were ordered as part of standard protocols related to chemotherapy or for evaluations in conjunction with methadone treatment. All ECGs had computer-generated automated readings of the QTc interval. Additionally, all ECG records were manually and independently assessed by two pediatric cardiologists who were blind to the patients' data. Normal QTc intervals based on sex and age were considered in the interpretation of the data. We defined QTc prolongation as more than 450 ms in female patients and more than 430 ms in male patients. Significant QTc prolongation was considered more than 500 ms or more than a 25 percent increase from the baseline measure.

Laboratory studies

Blood chemistry data (eg, creatinine, potassium, and magnesium levels) obtained no more than 24 hours before or after the ECG recordings and liver function data (eg, albumin, alanine-aminotransferase [ALT], and aspartate-aminotransferase [AST]) obtained no more than 7 days before or after the ECG recordings were extracted from the medical records. We chose 24 hours as a cutoff for the blood chemistry measures because fluctuations in those values can have immediate clinical implications. Similarly, we chose 7 days as a cutoff for liver function data because abnormal levels of albumin, ALT, and AST tend to require that much time before having a discernible effect.

Data on concurrent medications that prolong the QTc interval, interfere with methadone elimination, or are cardiotoxic, based on the Lexicomp database,²⁷ were also extracted from each patient's medical record. The laboratory study values were evaluated based on the normal range for specific age groups at St Jude. The medications administered on the same days as ECG recordings were identified and analyzed as single drug versus associations of drugs.

Statistical analysis

Correlations between the automated and manual QTc intervals were examined using the Pearson correlation, as well as simple linear regression. One-way analysis of variance models were applied to study the correlation between QTc readings and categorical clinical features, such as sex and the number of concurrent medications that affect QTc prolongation. A simple linear-regression model was applied to study the relation between the QTc duration and each of the following variables: duration of methadone therapy, methadone dose, and the serum laboratory values (creatinine, potassium, magnesium, albumin, ALT, and AST). Analyses were performed using SAS 9.3 (SAS Institute, Cary NC).

RESULTS

Of the 61 pediatric patients who were treated with methadone during the time of the retrospective study, 37 met the study's inclusion criteria. The cohort underwent a total of 155 ECGs, of which 137 were evaluable. Baseline characteristics revealed a wide range of ages (0.9–27.4 years) and a predominantly (59.4 percent) male study group (Table 1). The most common primary diagnoses were solid tumors (71.1 percent) and hematologic malignancies (18.4 percent).

The automatic ECG readings of QTc interval were strongly correlated with each of the cardiologists' independent manual readings, and the manual readings were highly correlated between the two cardiologists (Pearson $r=0.649$; $p<0.0001$) (Figure 1). The patients' mean automated QTc during methadone therapy, as measured on 104 serial ECGs, was higher than that at baseline (446.5 ± 26.3 ms vs 437.55 ± 28.02 ms). The mean baseline automated QTc was 433.28 ± 24.05 ms for male patients and 443.46 ± 32.84 ms for female patients. Off-treatment automatic QTc measurements were available for seven patients; the mean was 445.2 ± 29.3 ms.

The mean methadone dose was 27.0 ± 24.3 mg/d (range, 5–125 mg/d; median, 20 mg/d) or 0.47 ± 0.45 mg/kg per day (range, 0.05–2.25 mg/kg per day; median, 0.37 mg/kg per day). QTc readings, whether automated or manual measures calculated by either cardiologist, were not correlated with the dose of methadone (mg/kg/d) on the date of each on-therapy ECG. This included 94 ECGs in 37 patients, $p = 0.42$. The mean (SD) duration of methadone therapy was 49 ± 67.25 days (range, 1–427 days; median, 28 days). Patients underwent a mean of 3.7 ± 3.7 EKGs (range, 1–13 EKGs; median, 3 EKGs), including baseline and off-therapy EKGs.

We detected no significant relation between the duration of methadone therapy and ECG readings (automated or manual). Also, we found no correlation between the administration

of methadone and that of as many as three additional medications that prolong QTc, inhibit methadone elimination, or are cardiotoxic. This lack of correlation held when we compared methadone alone with one additional QTc-prolonging medication or methadone alone with two or three QTc-prolonging medications. When we evaluated specific medications known to prolong QTc that were used concurrently in our study population, we found that 28 of 37 (75.7 percent) patients received at least one concurrent QTc-prolonging medication. Ondansetron, granisetron, and fluoxetine were the most common concurrent medications. Ondansetron was given at the time of 98 ECGs in 28 patients; granisetron was given at the time of 16 ECGs in five patients; and fluoxetine was given at the time of 15 ECGs in two patients. Finally, we detected no correlations between QTc interval and the patient's sex, nor between QTc interval and any of the following serum components: creatinine, potassium, magnesium, albumin, ALT, and AST.

DISCUSSION

This retrospective study is the first investigation of the effects of methadone treatment on cardiac conduction in a pediatric population. Many studies have documented the effects of methadone on cardiac conduction in adults,^{3,4,18,19} however, the use of methadone is rarely studied for chronic pain management in children and young adults.^{1,28,29} We found that 1) the mean on-therapy QTc was prolonged compared to that measure at baseline; 2) manual and automated QTc readings were strongly correlated; and 3) QTc prolongation was not correlated with methadone dose or duration or other known risk factors.

Our statement regarding "clinically effective analgesic doses" is based on our previous experience using methadone at our institution.¹ Furthermore, we did not identify a correlation between the concurrent administration of as many as three medications with known QTc-prolongation effects, in addition to methadone, and the clinically significant prolongation of QTc. Also, we did not find any significant dose-dependent or duration-dependent effect on QTc prolongation, in contrast to much of the literature on methadone use in adults. We investigated a comprehensive set of potential risk factors for prolonged QTc and did not find any correlations.

Our results did not show a significant correlation between dose of methadone and automated QTc measurement. Many studies of adult opioid addicts have reported dose-dependent increases in QTc,^{14,15,19,21} but the mean doses used in those studies were substantially higher than what we used to treat our pediatric population. We use conservative dosing regimens when prescribing methadone to our pediatric patients because the available safety data are limited and the population is at high risk due to concurrent blood chemistry abnormalities, radiation therapy, and multiple medications, including chemotherapeutic agents.

Pediatric populations naturally weigh less than adult populations so comparing methadone doses in our study with those reported in the adult literature is difficult. The vast majority of literature reports doses as milligrams per day, whereas we report our findings as milligrams per day and milligrams per kilogram per day. This difference becomes relevant when we consider the recommendation of Krantz et al.,²¹ who claim that only those patients who receive

methadone doses greater than 100 mg/d should be monitored via additional ECGs. Further studies to evaluate the daily methadone dose at which serial ECGs become necessary in a pediatric population would be beneficial to guide clinical practice.

A retrospective study by Ehret et al.¹⁸ evaluated QTc intervals in a large cohort of intravenous drug users, 167 of whom received concurrent methadone therapy (median dose, 100 mg/d; range, 4–600 mg/d). A correlation between dose and QTc was found, and the lowest methadone dose that showed clinically significant QTc prolongation (ie, 460 ms) was 20 mg/d. Considering the large study population and high median dose, one can expect a small number of cases in which QTc prolongation was associated with a low daily dose of methadone, comparable to those used in our study. Peles et al.²³ reported findings in adults that were consistent with those from our study, that is, that there was no correlation between the daily dosage of methadone and QTc interval.

In contrast to most findings in the adult literature, Fredheim et al.³⁰ reported that QTc prolongation was not consistently correlated with duration of therapy in 12 adult patients with chronic nonmalignant pain after switching from morphine to methadone. This finding mirrors our results, which did not demonstrate a correlation between the duration of methadone use and QTc interval.

We found no correlation between the concurrent administration of methadone and as many as three other medications known to prolong QTc. In our study population, the most common concurrent medications with known QTc-prolonging effects, methadone metabolism-inhibiting effects, or cardiotoxicity effects were ondansetron, granisetron, and fluoxetine. This information may be clinically significant to healthcare providers of children with complex illnesses or multiple medical symptoms requiring pharmacologic management, who also suffer from neuropathic or pain that is difficult to manage. No adverse cardiac events were noted in our patients' records, not even for those who received three or more medications with known QTc-prolonging effects. These findings highlight an opportunity for a prospective study of the clinical safety of methadone use in children who require other medications that prolong QTc.

During our investigation of a comprehensive set of potential risk factors for prolonged QTc, including sex, age, electrolyte abnormalities, renal failure, and hepatic dysfunction, we found no correlations. This was unusual, as most studies in adult populations that evaluated some or all of these risk factors in conjunction with administration of methadone found that they were commonly seen in the context of QTc prolongation.^{2,18,24,25,31} The explanation for this variation in our findings may be that laboratory abnormalities identified in our study were not profound—our patients were followed closely, and laboratory abnormalities were corrected early. It is also possible that when comparing results between populations of adult opioid addicts and populations of pediatric patients with cancer, other confounding variables affect cardiac conduction.

Limited pediatric literature addresses methadone use for analgesia,^{1,28,29,32,33} let alone its associated effects on cardiac conductivity, QTc in particular.³⁴ Two case reports have noted complications related to methadone therapy in children, but they did not mention QTc

prolongation: in one report, central sleep apnea developed in a child with leukemia who received methadone for analgesic therapy,³² and in the other, bradycardia developed in an infant for whom methadone was used to facilitate weaning from long-term opioid use in the intensive care unit setting.³⁵ Three other publications have discussed the use of methadone for analgesia in pediatric populations.^{1,28,29} In our previous study of the use of methadone for neuropathic and nociceptive pain in children with cancer, we found that methadone effectively reduced pain and prevented opioid withdrawal; the most common side effect was sedation.¹ Davies et al.²⁸ similarly found that the use of methadone analgesia in children with cancer is both clinically effective and safe with close monitoring. Friedrichsdorf and Kang²⁹ noted the use of methadone for analgesia in children receiving palliative care as “extremely useful.” Boyer et al.³³ indicated that due to known toxic effects on cardiac conduction, methadone may exacerbate medical problems that appear during adolescence, particularly acquired prolonged QT syndromes. This potential for adverse events led the authors to recommend a baseline ECG prior to initiation of methadone therapy in children. Roth et al. noted the lack of existing literature on methadone and surveyed pediatric oncologists regarding their comfort and experience with the use of methadone for analgesia. Respondents stated that the primary reasons they did not often prescribe methadone was a lack of knowledge of methadone’s pharmacodynamics, effectiveness, and/or dosing equivalence.³⁶

Our study suggested that methadone affects cardiac conduction, that is, it prolongs the QTc. Based on commonly accepted standards, however, the QTc prolongation documented in our study was not significant.^{4,7,37} Additionally, we found no instances of torsades de pointes or sudden cardiac death, suggesting that methadone use in children may be safe at clinically effective analgesic doses. In a study by Grodofsky et al.,³⁴ patients who received low-dose methadone therapy showed QTC prolongation during the initiation of therapy, but that difference disappeared at subsequent ECGs performed during the third and sixth months on-therapy.

In our study, automated and manual QTc-interval readings were highly correlated. Although the current gold standard for QTc-interval measurement is manual reading by a cardiologist, our results suggest that when using methadone or other QTc-prolonging medications to treat pediatric patients, automated readings of QTc on ECGs may be sufficient.

Recent recommendations from the American Heart Association suggest that, “in view of the clinical importance of the QT-interval prolongation, it is essential to visually validate QT-interval prolongation reported by a computer algorithm.”³⁸ Although manual reading of the QTc is the currently accepted standard, our results support another recent study that showed a high correlation between manual and automated QTc measurements³⁹ and suggested that in clinical practice it may be acceptable to base decisions on automated QTc measurements rather than requiring manual readings.

The Pain Management Service at St Jude tends to prescribe methadone to treat both nociceptive and neuropathic pain, with less reluctance than other clinicians. This dual use has been substantiated in recent studies demonstrating successful use of methadone in the treatment of neuropathic pain.^{1,40} Despite this dual use and the increasing willingness of

pain management services to prescribe methadone, it is still considered a drug of last resort, which partially explains why the size of our study group was somewhat limited compared to those in other studies. Those studies evaluated adult methadone use during methadone maintenance therapy programs for opioid dependence, a framework within which methadone is much more commonly prescribed.

Although we evaluated electrolyte levels, we did not collect data regarding the patients' cardiac history, specifically whether congenital long-QT syndrome was noted. This type of evaluation has since become common practice at our institution, but it was not the standard approach during the time-frame of our study. Obtaining a baseline ECG at the time of initiation of methadone therapy was also not common practice during that period, though it is the current practice for patients followed by the St Jude Pain Management Service. Because of the retrospective nature of this study, our data were generated from ECGs, most of which were coincidental with methadone therapy and driven by chemotherapy protocols. A literature review by Krantz et al.²¹ established a series of recommendations to follow when considering methadone therapy. The recommendations regarding ECGs include a pretreatment ECG and annual off-therapy follow-up ECGs to monitor fluctuations in the QTc interval. Additional ECGs were recommended if the methadone dosage exceeded 100 mg/d, though as previously mentioned, the dosage-dependent recommendations for adults may not apply to pediatric patients. Although Krantz et al.'s review consisted of primarily adult reports, we do not have enough pediatric data to abandon their recommendations.

CONCLUSION

This study reports that methadone therapy in pediatric patients is associated with prolongation of QTc. Although manual readings of ECGs are the gold standard, we found a significant correlation between automated and manual measurements of the QTc interval. No significant correlations were found among QTc prolongation and methadone dose, duration of therapy, concurrent use of QTc-prolonging medications, or other risk factors reported in the literature on methadone treatment of adult populations. On the basis of our findings, the use of clinically effective analgesic doses of methadone appears to be safe in pediatric oncology patients. Prospective studies in pediatric patients undergoing methadone therapy for the treatment of neuropathic or nociceptive pain are needed to validate these findings.

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References

1. Angheliescu D, Faughnan L, Hankins G, et al. Methadone use in children and young adults at a cancer center: A retrospective study. *J Opioid Manag.* 2011; 7(5):353–361. [PubMed: 22165034]
2. Krantz MJ, Mehler PS. QTc prolongation: methadone's efficacy-safety paradox. *Lancet.* 2006; 368(9535):556–557. [PubMed: 16905001]

3. Krantz MJ, Lewkowicz L, Hays H, et al. Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med.* 2002; 137(6):501–504. [PubMed: 12230351]
4. Reddy S, Hui D, El Osta B, et al. The effect of oral methadone on the QTc interval in advanced cancer patients: A prospective pilot study. *J Palliat Med.* 2010; 13(1):33–38. [PubMed: 19824814]
5. Shaiova L, Berger A, Blinderman CD, et al. Consensus guideline on parenteral methadone use in pain and palliative care. *Palliat Support Care.* 2008; 6(2):165–176. [PubMed: 18501052]
6. Gorman AL, Elliott KJ, Inturrisi CE. The D- and L-isomers of methadone bind to the non-competitive site on the *N*-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett.* 1997; 223(1):5–8. [PubMed: 9058409]
7. Andrews CM, Krantz MJ, Wedam EF, et al. Methadone-induced mortality in the treatment of chronic pain: Role of QT prolongation. *Cardiol J.* 2009; 16(3):210–217. [PubMed: 19437394]
8. Bryson J, Tamber A, Seccareccia D, et al. Methadone for treatment of cancer pain. *Curr Oncol Rep.* 2006; 8(4):282–288. [PubMed: 17254528]
9. Gourlay G, Cherry D, Cousins M. A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. *Pain.* 1986; 25:297–312. [PubMed: 3528988]
10. Ventafridda V, Ripamonti C, Bianchi M, et al. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. *J Pain Symptom Manage.* 1986; 1(4): 203–207. [PubMed: 3537160]
11. Bruera E, Watanabe S, Fainsinger R, et al. Custom-made capsules and suppositories of methadone for patients on high-dose opioids for cancer pain. *Pain.* 1995; 62(2):141–146. [PubMed: 8545138]
12. De Conno F, Groff L, Brunelli C, et al. Clinical experience with oral methadone administration in the treatment of pain in 196 advanced cancer patients. *J Clin Oncol.* 1996; 14:2836–2842. [PubMed: 8874346]
13. Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain. *Pain.* 1997; 70(2–3):109–115. [PubMed: 9150283]
14. Heppel DB, Haigney MC, Krantz MJ. The effect of oral methadone on the QTc interval in advanced cancer patients: A prospective pilot study. *J Palliat Med.* 2010; 13(6):638–639. [PubMed: 20597697]
15. Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: Reports to the FDA spontaneous reporting system. *Pharmacoepidemiol Drug Saf.* 2005; 14(11): 747–753. [PubMed: 15918160]
16. Sekine R, Obbens EA, Coyle N, et al. The successful use of parenteral methadone in a patient with a prolonged QTc interval. *J Pain Symptom Manage.* 2007; 34(5):566–569. [PubMed: 17616330]
17. Anchersen K, Clausen T, Gossop M, et al. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: A mortality assessment study. *Addiction.* 2009; 104(6):993–999. [PubMed: 19392907]
18. Ehret GB, Voide C, Gex-Fabry M, et al. Drug-induced long QT syndrome in injection drug users receiving methadone: High frequency in hospitalized patients and risk factors. *Arch Intern Med.* 2006; 166(12):1280–1287. [PubMed: 16801510]
19. Krantz MJ, Lowery CM, Martell BA, et al. Effects of methadone on QT-interval dispersion. *Pharmacotherapy.* 2005; 25(11):1523–1529. [PubMed: 16232014]
20. Krantz MJ, Martell BA, Arnsten JH, et al. Medications that prolong the QT interval. *JAMA.* 2003; 290(8):1025. author reply 1026.
21. Krantz MJ, Martin J, Stimmel B, et al. QTc interval screening in methadone treatment. *Ann Intern Med.* 2009; 150(6):387–395. [PubMed: 19153406]
22. Zeltser D, Justo D, Halkin A, et al. Torsade de pointes due to noncardiac drugs: Most patients have easily identifiable risk factors. *Medicine (Baltimore).* 2003; 28(4):282–290.
23. Peles E, Bodner G, Kreek MJ, et al. Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients: A cross-sectional study. *Addiction.* 2007; 102(2):289–300. [PubMed: 17222284]
24. Kay GN, Plumb VJ, Arciniegas JG, et al. Torsade de pointes: The long-short initiating sequence and other clinical features: Observations in 32 patients. *J Am Coll Cardiol.* 1983; 2(5):806–817. [PubMed: 6630761]

25. Makkar RR, Fromm BS, Steinman RT, et al. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. *JAMA*. 1993; 270(21):2590–2597. [PubMed: 8230644]
26. Martell BA, Arnsten JH, Ray B, et al. The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med*. 2003; 139(2):154–155. [PubMed: 12859171]
27. Lexicomp Online. Drug Index. Hudson, OH: Wolters Kluwer Health; 2012. Available at <http://www.crlonline.com/lco/action/home/switch> [Accessed July 2, 2012]
28. Davies D, DeVlaming D, Haines C. Methadone analgesia for children with advanced cancer. *Pediatr Blood Cancer*. 2008; 51(3):393–397. [PubMed: 18428431]
29. Friedrichsdorf SJ, Kang TI. The management of pain in children with life-limiting illnesses. *Pediatr Clin North Am*. 2007; 54(5):645–672. x. [PubMed: 17933616]
30. Fredheim OM, Borchgrevink PC, Hegrehaes L, et al. Opioid switching from morphine to methadone causes a minor but not clinically significant increase in QTc time: A prospective 9-month follow-up study. *J Pain Symptom Manage*. 2006; 32(2):180–185. [PubMed: 16877186]
31. Martell BA, Arnsten JH, Krantz MJ, et al. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. *Am J Cardiol*. 2005; 95(7):915–918. [PubMed: 15781034]
32. Amos LB, D'Andrea LA. Severe central sleep apnea in a child with leukemia on chronic methadone therapy. *Pediatr Pulmonol*. 2013; 48(1):85–87. [PubMed: 22431505]
33. Boyer EW, McCance-Katz EF, Marcus S. Methadone and buprenorphine toxicity in children. *Am J Addict*. 2010; 19(1):89–95. [PubMed: 20132125]
34. Grodofsky S, Edson E, Huang S, et al. The QTc effect of low-dose methadone for chronic pain: A prospective pilot study. *Pain Med*. 2015; 16(6):1112–1121. [PubMed: 25644980]
35. Wheeler AD, Tobias JD. Bradycardia during methadone therapy in an infant. *Pediatr Crit Care Med*. 2006; 7(1):83–85. [PubMed: 16395081]
36. Roth M, Davies D, Friebert S, et al. Attitudes and practices of pediatric oncologists regarding methadone use in the treatment of cancer-related pain: Results of a North American Survey. *J Pediatr Hematol Oncol*. 2013; 35(2):103–107. [PubMed: 23242323]
37. Ebert SN, Liu XK, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: Evaluation of clinical and experimental evidence. *J Womens Health*. 1998; 7(5):547–557. [PubMed: 9650155]
38. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part IV: The ST segment, T and U waves, and the QT interval: A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*. 2009; 53(11):982–991. [PubMed: 19281931]
39. Tyl B, Azzam S, Blanco N, et al. Improvement and limitation of the reliability of automated QT measurement by recent algorithms. *J Electrocardiol*. 2011; 44(3):320–325. [PubMed: 21163494]
40. Moulin D, Palma D, Watling C, et al. Methadone in the management of intractable neuropathic noncancer pain. *Can J Neurol Sci*. 2005; 32(3):340–343. [PubMed: 16225176]

Figure 1.

Correlation of automatic and manual QTc interval measurements. QTc intervals (open dots) were measured in 79 ECGs obtained from a pediatric oncology population. The data show a strong correlation between the automated readings and manual readings done independently by two cardiologists. The fit (blue line), 95% confidence interval (blue shading), and 65 percent prediction limits (dotted lines) are shown.

Table 1

Demographic characteristics of 37 pediatric patients treated with methadone

Characteristic	Mean (range)	n (percent)
Sex		
Male		22 (59.4)
Female		15 (40.6)
Age, y *	16.1 (0.9–27.4)	
9		7 (18.9)
9.1–18		13 (35.1)
18.1		17 (46)
Weight, kg †	58.6 (8.6–116)	
35		6 (16.2)
35.1–70		18 (48.7)
70.1		13 (37.1)
BMI ‡	23 (12.8–39)	
23		18 (48.7)
23.1–33		17 (45.9)
33.1		2 (5.4)
Primary diagnosis		
Solid tumor		26 (71.1)
Sarcoma		19 (50)
Carcinoma		2 (5.3)
Other		5 (13.2)
Hematologic malignancies		7 (18.4)
Leukemia ‡		6 (15.8)
Lymphoma		1 (2.6)
Brain tumors		4 (10.5)
Nonmalignant hematologic disorder ‡		1 (2.6)
Pain diagnosis (n = 31) §		
Neuropathic		12 (38.7)
Phantom		6 (15.8)
Nociceptive		13 (41.9)

* Age at the start of methadone therapy is noted.

† Weight and BMI were measured at the time of on-therapy ECGs.

‡ One patient had two primary diagnoses.

§ Thirty-one patients had pain diagnosis data (six patients—missing data).