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

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Abstract

Background: Recent reports suggest that high doses of methadone may prolong QTc interval and occasionally cause torsades de pointes; however, few of these studies involved the palliative care population.
Objective: The purpose of this study was to determine the effect of initiation of methadone on QTc interval in patients with cancer pain seen at the palliative care setting.
Methods: We enrolled 100 patients with cancer in this prospective study. Patients were followed clinically and electrocardiographically for QTc changes at baseline, 2, 4, and 8 weeks. Contributing factors for QTc prolongation such as medications, cardiovascular diseases, and electrolytes disturbances were documented. QTc prolongation was defined as greater than 430 ms in males and greater than 450 ms in females, and significant QTc prolongation was defined as QTc interval greater than 25% increase from baseline or 500 ms or more.
Results: Electrocardiographic (ECG) assessments were available for 100, 64, 41, and 27 patients at baseline, 2-, 4-, and 8-week follow-up, respectively. At baseline prior to initiation of methadone, 28 (28%) patients had QTc prolongation. Clinically significant increase in QTc occurred in only 1 of 64 (1.6%) patients at week 2, and none at weeks 4 and 8. There was no clinical evidence of torsades de pointes, ventricular fibrillation, or sudden death. QTc prolongation was more frequent among patients with increased baseline QTc interval.
Conclusions: Baseline QTc prolongation was common, whereas significant QTc interval 500 ms or more after methadone initiation rarely occurred, with no evidence of clinically significant arrhythmias. This study supports the safety of methadone use for pain control in patients with advanced cancer in the palliative care setting.

Introduction

Methadone is a synthetic opioid analgesic frequently used in pain management and for maintenance in drug addicts.[1–3] Methadone exerts its analgesic affects by activating both μ and δ opioid receptors.[4] Furthermore, it has been shown to have N-methyl-D-aspartate (NMDA) receptor antagonist activity, with implications for management of neuropathic pain syndrome. Given its high potency and broad spectrum of activity, methodone is frequently used as an alternative opioid to reduce opioid-induced neurotoxicity or other side effects, while maintaining or improving pain control.[5]

Methadone has been shown to be as effective as morphine for cancer pain relief.[6,7] In addition, methadone has a number of advantages compared to other opioids. It is available in oral, sublingual, rectal and intravenous formulations, with excellent oral bioavailability.[8] In addition, methadone has a rapid onset of action, with prolonged analgesic effect. Methadone also has incomplete cross-tolerance with other opioids. This property, coupled with its high potency, makes methadone an excellent agent for opioid rotation.[9] Methadone is the opioid of choice for patients with renal impairment because of the lack of known active metabolites and accumulation in renal failure.[10,11] Finally, methadone is less expensive than other opioids, making it an affordable choice for many patients.[12]

Adverse effects of methadone include sedation, nausea, and constipation. At higher doses, symptoms of opioid-induced neurotoxicity, such as myoclonus, hallucinations and nightmares, and even respiratory depression may occur.[13,14]

Recently, concerns have been raised regarding methadone and QTc prolongation.[15–18] This occasionally has been shown to cause torsades de pointes, polymorphic ventricular tachycardia, and sudden death. The frequency of methadone-induced long QTc interval varied widely between 9% and 83%, depending on the patient population and the methadone dose (higher risk if >300 mg/d or >600 mg/d).[18–21] Most of these studies were performed in the methadone maintenance

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population, in which the average methadone dose was generally high.

For patients with advanced cancer, it remains unclear if the incidence of QTc prolongation reaches the magnitude seen with patients on methadone maintenance programs. The average dose typically given for pain management by palliative care specialists seems to be far less compared to the dose for methadone maintenance.[22] A better understanding of the risk associated with methadone use would guide palliative care specialists to use methadone to manage cancer pain on a daily basis. In this prospective longitudinal study, we determined the prevalence of QTc prolongation at baseline prior to initiation of methadone, and the incidence of QTc prolongation after methadone has been started at 2, 4, and 8 weeks.

Method

Subjects

The Institutional Review Board at M. D. Anderson Cancer Center approved this study. Patients were eligible if they had a diagnosis of cancer, age greater than or equal to 18, had no prior history of methadone use, and were being started on methadone for pain management either as initial opioid or as a switch from other opioids. Exclusion criteria included history of arrhythmias, pacemaker or defibrillator, any contraindications to methadone (e.g., hypersensitivity) and abnormal cognitive status based on a Mini-Mental State Examination (MMSE) score of less than 24. At our cancer center, palliative care is provided to patients with advanced cancer on a referral basis. Patients seen at our service have a median survival of 6 months. Consecutive patients who were seen by the palliative care services (outpatient clinic, pain clinic, or inpatients seen by the palliative care consult team) at M. D. Anderson Cancer Center were approached if they met the eligibility criteria, and subsequently enrolled onto the study if they signed the informed consent.

Electrocardiographic assessments

To determine the QTc interval, we obtained resting 12-lead electrocardiogram (ECG) from subjects at baseline, and at 2 weeks, 4 weeks, and 8 weeks after methadone initiation. At each assessment, three ECGs were performed 5 minutes apart using the ECG machine (Nihon Kohden Cardiofax Q 9130K, Tokyo, Japan). We did not find any significant variations (>5 ms) in QTc interval between the measurements. The QT interval was corrected (QTc) for heart rate using the Bazett formula[23] and the average of three measurements was used for analysis. Each ECG was reviewed by our institutional cardiologists.

We determined upper limit of QTc prolongation using four different definitions: (1) QTc greater than 430 ms for males or QTc greater 450 ms for females, (2) QTc greater 500 ms regardless of gender, (3) QTc increase of 10% from baseline, and (4) QTc increase of 25% from baseline. Clinically significant QTc prolongation was defined as QTc interval 500 ms or more or greater than 25% increase from baseline.

Contributing factors to QT prolongation

Among patients with QT prolongation before the initiation of methadone, we reviewed the chart for risk factors of QT prolongation, including structural heart disease such as myocardial infarction, heart failure and valvular heart disease, and electrolyte abnormalities. Medications associated with QT prolongation were also classified by risk of causing torsades de pointes based on the Arizona Center for Education and Research on Therapeutics.[24] This website identifies three different risk categories including (1) drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of torsades de pointes, (2) drugs that prolong the QT interval and/or in some reports have been associated with torsades de pointes but at this time lack substantial evidence for causing torsades de pointes, and (3) drugs that carry a risk of torsades de pointes and/or QT prolongation under certain conditions, such as patients with congenital long QT syndrome, drug overdose, or coadministration of interacting drugs.

Statistical analysis

We summarized baseline demographics, QTc prolongation, and related causes using descriptive statistics, including medians, means, standard deviations, ranges, and frequencies together with 95% confidence intervals.

We compared the characteristics between patients with and without QTc prolongation before methadone initiation (at baseline). Comparisons were made using the Student's t test for continuous variables that were normally distributed (i.e., QTc interval), the Mann Whitney test for continuous, nonparametric variables (e.g., methadone dose), and the Pearson χ^2 test for categorical variables (e.g., proportion of patients with greater than 10% of QTc prolongation above baseline). We also examined the association between methadone dose and QTc interval using the Spearman correlation test. A two-sided p value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

Table 1 highlights the characteristics of patients included in this study. One hundred patients were enrolled onto the study, although only 66 patients completed at least one follow-up assessment. At 2, 4, and 8 weeks, follow-up ECG was available for 64, 41, and 27 patients, respectively. In total, 26 patients completed 2 assessments, 15 had 3 assessments, and 25 had all 4 assessments. Of the 36 patients who did not have follow-up at 2 weeks, the reasons were hospice transfers or return to local community ($n = 17$, 47%), discontinuation of methadone due to side effects other than arrhythmia or hospital admissions ($n = 11$, 30%), atrial flutter ($n = 1$, 3%), voluntary withdrawal from study ($n = 3$, 8%), nonadherence ($n = 2$, 5%), and death ($n = 1$, 3%). The reason for lost of follow-up was unknown in 1 (3%) patient.

Methadone dose

The median methadone daily dose at 2 weeks was 23 mg (range, 3–90 mg, interquartile range, 10–30 mg). Of note, none received a methadone dose of 100 mg or more. No significant association was found between QTc interval and methadone dose ($p = 0.45$).

QTc prolongation prior to methadone initiation

The frequency of QTc prolongation at baseline, 2, 4, 8 weeks is listed in Table 2. Twenty-eight out of 100 (28%) patients had baseline QTc prolongation before methadone was started,

Table 1. Baseline Characteristics of One Hundred Patients

	Inception cohort n = *100 (%[a])*	*Patients at 2nd follow-up* n = *64 (%[a])*
Median age (range)	56 (28–83)	56 (29–83)
Female	54 (54%)	34 (53%)
Race		
White	70 (70%)	45 (70%)
Black	20 (20%)	10 (16%)
Hispanic	9 (9%)	8 (12%)
Others	1 (1%)	1 (2%)
Cancer diagnosis		
Breast	11 (11%)	7 (11%)
Gastrointestinal	11 (11%)	9 (14%)
Genitourinary	14 (14%)	10 (16%)
Gynecologic	10 (10%)	5 (8%)
Hematologic	6 (6%)	4 (6%)
Head and neck	14 (14%)	9 (14%)
Lung	25 (25%)	14 (22%)
Other	9 (9%)	6 (9%)
Median QTc in ms (Q1–Q3)	429 (411–444)	429 (411–444)

[a]Unless otherwise specified.

although none were greater than 500ms. Risk factors of QTc prolongation were identified in 22 of 28 (79%) patients in this group (Table 3).

QTc prolongation after methadone initiation

At 2 weeks, 20 (31%) patients had prolonged QTc interval, with 1 (2%) having an increased of QTc interval of greater than 500 ms. At 4 week, 3 (8%) patients had an abnormal QTc interval. At 8 weeks, 3 (11%) patients were found to have abnormal QTc. Five (8%), 1 (3%), and 1 (4%) of the patients had an increase in QT interval of greater than 10% from baseline at 2, 4, and 8 weeks, respectively. None of the patients experienced greater than 25% increase of QT interval from baseline. No torsades de pointes or ventricular fibrillation were documented during the study period.

Patients with baseline QTc prolongation have a higher chance of developing QTc prolongation at 2 weeks compared to those without baseline QTc abnormalities (71% versus 17%, $p < 0.001$, Table 4).

Discussion

The United States Food and Drug Administration (FDA) issued a black box warning for methadone, highlighting its risk of QTc prolongation and sudden death. While this adverse effect exists for patients on high doses of methadone and/or with preexisting risk factors for QTc prolongation,[25] there is no convincing evidence that methadone poses a major risk for patients with cancer who have already transitioned into palliative and hospice mode. Hence, we undertook a study in patients with cancer who were initiated on methadone for pain control. Most patients in our study were deemed to have a very limited prognosis of less than 3 months. We found that baseline prolongation of QTc interval in patients with advanced cancer was relatively common, although significant QTc prolongation 500 ms or more only occurred during follow-up in one patient (1.6%). Torsades de pointes, severe arrhythmia, and sudden death were not detected. Results from this study support that methadone can be safely used for pain control in the palliative care setting.

Our study is the largest prospective series to date in the palliative care setting on the issue of QTc prolongation with methadone use, and adds to the body of literature that supports its safe application as an analgesic. Previously, two retrospective studies and one prospective trial have examined the phenomenon of QTc prolongation in methadone for pain management.[22,26,27] Our group reviewed 56 patients with cancer started on methadone by palliative care at an average daily dose of 30 mg, and found no clinically significant QTc prolongation.[22] In another retrospective series, 47 patients with cancer taking an average methadone dose of 18 mg/d did not develop any significant increase in QTc interval (>500 ms).[27] Fredheim and colleagues[26] prospectively examined 8 patients initiated on methadone with a median dose of 51 mg for chronic nonmalignant pain. Although a statistically significant increase in QTc interval was observed, no clinically significant QTc prolongation or arrhythmia was detected. To date, all the studies on methadone for pain control have consistently shown that the risk of methadone induced-QTc prolongation and arrhythmia is minimal.

The dose of methadone appears to be an important determinant of the risk of QTc prolongation.[19,27] The literature regarding QTc prolongation with methadone consists primarily of studies of patients on methadone maintenance programs, who tend to receive higher doses of methadone (>300 mg of methadone).[18] In regard to methadone for pain control, one case series reported 3 patients who developed torsades de pointes while on high doses of oral methadone greater than 600 mg/d.[21] The median dose of methadone in our cohort was only 23 mg. Indeed, our dose is a realistic representation of the actual doses used clinically pain control,[7,28–30] and is consistent with current clinical practice.[31] The palliative care

Table 2. Longitudinal QTc Interval Assessments at Baseline Two, Four, and Eight Weeks

	Baseline (n = *100)*	*2 week* (n = *64)*	*4 week* (n = *39)*	*8 week* (n = *28)*
Median methadone dose in mg (Q1–Q3)	—	23 (10–30)	15 (10–23)	28 (11–38)
Mean QTc in ms (SD)	427 (27)	430 (22)	375 (41)	373 (41)
Median QTc in ms (Q1–Q3)	430 (411–444)	431 (421–441)	380 (344–404)	380 (341–396)
QTc >ULN[a]	28 (28%)	20 (31%)	3 (8%)	3 (11%)
QTc >500 ms	0 (0%)	1 (2%)	0 (0%)	0 (0%)
QTc >10% above baseline	—	5 (8%)	1 (3%)	1 (4%)
QTc >25% above baseline	—	0 (0%)	0 (0%)	0 (0%)

[a]QTc >430 for males and >450 for females.
SD, standard deviation; ULN, upper normal limit.

Table 3. Risk Factors for QTc Prolongation in Twenty-Eight Patients with Prolonged QTc at Baseline Prior to Initiation of Methadone

	Number of patients (%)
Medications[a]	21 (75)
1. Generally accepted to carry a risk of torsades de pointes	3 (11)
2. Prolong the QT interval and/or in some reports have been associated with torsades de pointes	7 (25)
3. Carry a risk of torsades de pointes and/or QT prolongation under certain conditions	11 (39)
Structural cardiac diseases	7 (25)
Coronary artery disease	5 (18)
Congestive heart failure	2 (7)
Valvular heart disease	1 (4)
Female sex	5 (18)
Electrolyte abnormalities	3 (11)
Hypokalemia	2 (7)
Hypocalcemia	2 (7)
No identifiable risk factors	6 (21)

[a]Medications associated with QT prolongation were classified based on criteria set forth by the Arizona Center for Education and Research on Therapeutics.[23]

approach to pain management over the years has evolved into a true multidisciplinary approach, which includes identifying risk factors for cancer pain, with an emphasis on psychosocial interventions in addition to pharmacotherapy. Our team utilizes multiple methodical assessment tools, including the Edmonton Pain Classification System to screen risk factors,[32] the CAGE questionnaire to detect history of alcoholism,[33] and mental status examination to exclude delirium[34] in every patient consulted. This usually leads to identification of patients at risk of opioid escalation for psychosomatic symptoms. This multiprong approach not only helped us to use methadone discreetly, but also required lower doses compared to methadone maintenance.[35,36] No association between QTc prolongation and methadone dose was found in our study, which could be explained by the relatively low dose of methadone in our cohort.

One interesting observation in our study was the high incidence of QTc prolongation (28%) at baseline even before the initiation of methadone, with potential risk factors identified in the majority of individuals. Common risk factors included use of other medications associated with QTc prolongation, structural cardiac abnormalities, and electrolyte disturbances. Using a more stringent criteria of greater than 450 ms for males and greater than 470 ms for females, Walker et al.[37] reported the prevalence of QTc prolongation in the palliative care population as 16%. However, the proportion of patients who were already on methadone was not documented in this study. Another study of general internal medicine patients revealed the prevalence of QTc interval greater than 450 ms to be 25%.[38]

Fredheim and colleagues[26] found that 1 in 8 (12.5%) patients in their prospective series of chronic pain patients had QTc prolongation (>460 ms) at baseline. Larger, prospective studies in patients with cancer are needed to confirm our findings.

We were surprised to find that QTc interval decreased by over 50 ms between baseline and the fourth week and eighth week of follow-up, which is too large a difference to be explained by normal fluctuations. The exact reason for this observation is uncertain, although we postulate that it may be due to medication changes by the palliative care team and/or correction of electrolyte abnormalities. Regression towards the mean from a high baseline is also another potential explanation. Further longitudinal studies are required.

We found that patients with baseline QTc abnormalities were more likely to have QTc prolongation at 2 weeks. Only one patient developed QTc prolongation greater than 500 ms (509 ms) at 2 weeks, and this patient had a baseline QTc interval of 498 ms at baseline. Importantly, our results suggest that even patients with baseline QTc prolongation can be treated safely with conventional doses of methadone, provided that they are monitored carefully.

The risk of QTc prolongation associated with methadone has important practical implications regarding the need of ECG monitoring before and during methadone treatment.[39] A recent clinical practice guideline from an expert panel discussed the implications of QTc prolongation in methadone users, and suggested regular counseling, screening and monitoring of all patients started on methadone.[40] However, the recommendations were predominantly formulated based on published studies on methadone maintenance programs, which may not be applicable to the palliative care setting. Two other guidelines from United Kingdom and Canada, which were also not specific for palliative care patients, recommended ECG screening if patients are on high doses of methadone greater than 100 mg/d and greater than 150 mg/d, respectively.[41,42] Given the significant differences in patient characteristics, methadone dose, risk factors for QTc prolon-

Table 4. Differences in Methadone Dose and QTc Interval at Two Weeks between Patients with and without Baseline QT Prolongation

	No baseline QTc prolongation (n = *47*)	*Baseline QTc prolongation* (n = *17*)	p *value*
Median methadone dose in mg (Q1–Q3)	21 (10–30)	20 (10–34)	0.56
Mean QTc in ms (SD)	426 (18)	440 (28)	0.063
Median QTc in ms (Q1–Q3)	429 (420–435)	435 (425–451)	0.042
QTc > ULN	8 (17%)	12 (71%)	<0.001
QTc > 500	0 (0%)	1 (6%)	0.094
QTc > 10% above baseline	4 (9%)	1 (6%)	0.73
QTc > 25% above baseline	0 (0%)	0 (0%)	—

gation, goals of care and expected survival between the two populations, special considerations should be given to palliative care patients. While ECG may be warranted in patients still undergoing active cancer treatments, and those with significant risk factors for QTc prolongation or on high doses of methadone (>100 mg/d), routine ECGs may not be practical or warranted in patients who have transitioned to the palliative mode of care.

Our study has several limitations. First, our sample size was relatively small. Torsades de pointes and sudden death are both infrequent events, and are not captured in our study. Second, we had a high dropout rate of approximately 30% at each assessment time point, which reflects the nature of palliative care practice in general and specifically at our institution. Patients seen by our palliative care service generally have a poor prognosis, with a rapidly evolving symptom profile that necessitates frequent medication changes. Furthermore, many patients were referred to hospice due to sudden deterioration in their condition. This study cannot rule out arrhythmia in the patients who were lost to follow-up. However, we found similar baseline characteristics and QTc interval between the patients who completed a second assessment and those lost to follow-up. Given this unique challenge in the palliative care population, provision of follow-up in the community utilizing portable ECG may represent an option for future research. Third, this is a single center study in a tertiary care cancer center. The patient characteristics and pattern of methadone use may not apply to other settings. Finally, our findings cannot be extended to patients on methadone doses of greater than 100 mg. Future longitudinal research is required to better characterize the risk of QTc prolongation at higher doses.

To conclude, clinically significant QTc prolongation rarely occurred among palliative care patients prescribed methadone less than 100 mg/d for cancer pain. While the absence of any major electrocardiographic abnormalities in this population is not proof that such complications do not occur, our preliminary findings are encouraging. Given the benefits associated with methadone significantly outweighs the risk of QTc prolongation in this specific population, we believe that methadone should be prescribed without reservations in the palliative care population. For patients with significant risk factors for QTc prolongation or on high doses of methadone (>100 mg/d),[25] monitoring with ECGs at baseline and at subsequent intervals may be reasonable.

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Author Disclosure Statement

No competing financial interests exist.

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