Brief Report

Attitudes, Beliefs, and Practices of Pediatric Palliative Care Physicians Regarding the Use of Methadone in Children With Advanced Cancer

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Abstract

Context. Methadone is a long-acting opioid known for its unique pharmacokinetic and pharmacodynamic properties. Most research on methadone in children is limited to its effect on the prolongation of the corrected QT (QTc) interval.

Objectives. To better understand the attitudes, beliefs, and practices of pediatric palliative care physicians regarding the use of methadone in children with advanced cancer.

Methods. A survey was sent to the American Academy of Pediatrics Section of Hospice and Palliative Medicine LISTSERV. Information on demographics, dosing of methadone, and the use of electrocardiograms (ECGs) was collected.

Results. One-hundred and five respondents (91%) provide palliative care to children ≥ 50% of the time, and a majority (81, 77%) prescribe methadone. Most (62, 77%) physicians were board certified in Hospice and Palliative Medicine, and most (39, 63%) certified via the direct pathway ("grandfathering"). Most physicians (57, 70%) do not use loading doses of methadone. Board-certified physicians trended toward decreasing methadone dose more (40% ± 19%) than non−board-certified physicians (28%, ±20%) when changing from the oral to intravenous route ($P = 0.07$). Respondents defined a QTc interval as "prolonged" (mean ± SD) at 444 milliseconds (±68 milliseconds). The percentage of patients receiving a baseline ECG was 65% (±33%). The most common reason for not performing a baseline ECG was that the patient was on hospice (13, 36%).

Conclusions. There are consistent practices, attitudes, and beliefs of pediatric palliative care providers with regard to methadone. More education is needed on the accurate value of a prolonged QTc interval. J Pain Symptom Manage 2019;57:260−265.

Key Words

Pediatric palliative care, methadone, pain management, pediatrics, pediatric oncology

Introduction

Methadone is a synthetic long-acting opioid known for its unique pharmacokinetic and pharmacodynamic properties compared with μ-agonist opioids such as morphine, hydromorphone, and fentanyl. It exhibits many mechanisms that modulate pain beyond pure μ-agonist activity including agonist activity at the δ and κ opioid receptors, antagonist activity at the *N*-methyl-D-aspartate receptor, and as a serotonin and norepinephrine reuptake inhibitor.[1,2]

For pediatricians, methadone might be appealing as it is the only long-acting opioid available as a liquid. This might allow them to safely administer it to even the very youngest children.[3] Most research on methadone in children for pain is limited to reports on the prolongation of the corrected QT (QTc) interval.[4−6] The use of methadone for pain in children with cancer is limited to a few case series.[3,6−9] Use by pediatric oncologists is limited because of its variable and unpredictable half-life, and lack of education and

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experience with safely prescribing and monitoring the side effects of methadone.[10] It is unclear whether pediatric palliative care physicians have the same concerns given that they likely prescribe methadone more frequently than pediatric oncologists. The purpose of the study was to better understand the practices, attitudes, and beliefs of pediatric palliative care physicians regarding the use of methadone in children with advanced cancer.

Methods

Design and Subjects

We conducted an electronic survey of demographics, practices, attitudes, and beliefs of palliative care physicians toward the use of long-acting opioids, including methadone, in children with advanced cancer. This is a subgroup analysis of this previous study, and the data collection methods and subjects have been previously detailed.[11] The study was reviewed and approved by the Institutional Review Board at MD Anderson Cancer Center (PA16-0523).

Survey

A web-based survey technology, Qualtrics, was used to create the survey. The presentation and flow of the survey used "adaptive logic," meaning that the number of questions answered by a respondent varied based on their responses to particular questions. Questions for this portion of the survey consisted of three domains: 1) physician demographics, 2) dosing of methadone, and 3) physician practice of obtaining electrocardiograms (ECGs). Six questions asked about respondent demographics, 10 questions inquired about the dosing of methadone, and six explored the respondents' practices, attitudes, and beliefs about the QTc interval and obtaining ECGs. All participating authors reviewed the survey content for validity.

Four weeks after the initial survey was e-mailed, a follow-up reminder e-mail was sent to all eligible physicians who had not yet completed the survey. Six weeks after the initial survey was e-mailed, another follow-up reminder e-mail was sent to all eligible physicians who had not yet completed the survey. Ten weeks after the initial survey was e-mailed, a personal e-mail was sent to nonrespondents. Participants who completed the survey received a $10.00 gift card. The survey closed 12 weeks after the initial e-mail.

Statistical Analysis

Surveys were counted as "completed" if a respondent answered a minimum of 70% of questions available to that respondent about methadone. Physicians were classified as a pediatric palliative care provider if they self-reported that they provided palliative care to children ≥50% of their clinical time.

We compared responses in physicians board-certified versus not board-certified in Hospice and Palliative Medicine (HPM). Subgroup analysis was also performed on HPM board-certified physicians comparing those certified via the direct pathway ("grandfathering") versus those who completed fellowship training. Respondents' age, gender, time of pediatric palliative care practice, method of board certification, patterns of practice, and attitudes and beliefs related to methadone were summarized and presented by descriptive statistics, specifically, a frequency tabulation for discrete variables, and mean, standard deviation, median, and range for continuous variables. We evaluated any differences between/among board certification groups using the Chi-squared test or Fisher's exact test for categorical variables and the Wilcoxon rank sum test or the Kruskal-Wallis test for continuous variables when appropriate.

Results

Figure 1 shows the participation of physicians in the survey. Three hundred thirty-seven physicians were e-mailed the survey; 141 were ineligible as they do not provide palliative care to children with advanced cancer, and eight were excluded as their e-mail addresses were invalid or they opted out of the survey. Of the remaining 188 eligible physicians, 116 completed the survey, making the response rate 62%. Of the 116 respondents, 105 physicians (91%) reported they provide palliative care to children ≥ 50% of their clinical time.

Twenty-four of 105 (23%) pediatric palliative care physicians reported that they do not prescribe methadone at their institution. These physicians were asked to provide possible reasons why they do not prescribe methadone, including a free-text response box. Sixteen of 24 (67%) reported they do not prescribe any long-acting opioid, whereas eight of 24 (33%) reported they can prescribe long-acting opioids but not methadone.

Demographics

Eighty-one physicians (77%) prescribe methadone; the characteristics of these physicians are summarized in Table 1. Most physicians were female (58/81, 72%), in pediatrics for 10 years or less (35/81, 43%) and in HPM for 10 years or less (61/81, 75%). Most physicians were board certified in HPM (62/81, 77%); of those board certified, most (39/62, 63%) received board certification via the direct pathway.

Board-certified physicians were significantly more likely to be practicing HPM for 11 years or more

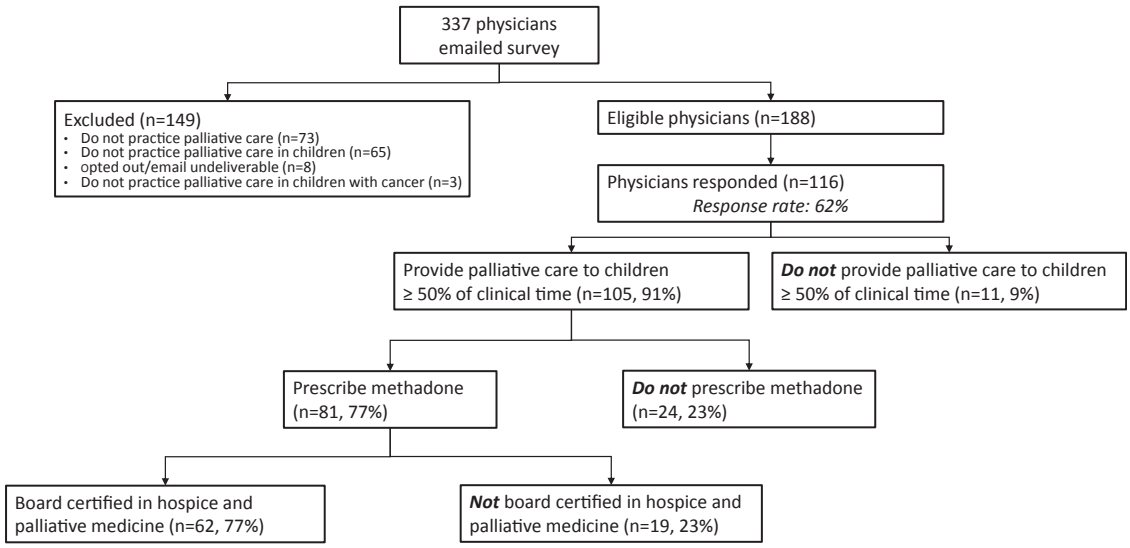

Fig. 1. Physician participant accrual.

compared with non−board-certified physicians ($P < 0.001$). Non−board-certified physicians trended toward being younger ($P = 0.08$) and in pediatrics for 10 years or less ($P = 0.08$). Physicians board certified via fellowship were significantly younger ($P = 0.002$) and had been practicing pediatrics ($P < 0.001$) and HPM ($P < 0.001$) for 10 years or less compared with physicians board certified through the direct pathway.

Methadone Dosing and Electrocardiograms

Table 2 shows practices related to dosing methadone and management of electrocardiograms. We observed no significant difference between board-certified and non−board-certified physicians with a few exceptions.

Most physicians (69/81, 69%) use equianalgesic dosing with dose reduction instead of weight-based formulas to initiate methadone, and most (57/81, 70%) do not use loading doses of methadone, with safety cited as the predominant reason. The mean (±SD) percentage decrease in methadone when switching from the oral to the intravenous route was 37% (±19%). Board-certified physicians trended toward decreasing methadone dose more (40% ± 19%) than non−board-certified physicians (28%, ±20%) when changing from the oral to intravenous route ($P = 0.07$).

Table 1
Characteristics of Methadone-Prescribing Physicians

	All	Board Certified			Board Certification via:		
Question	n (%)	Yes [n (%)]	No [n (%)]	*P*-value	Direct Pathway [n (%)]	Fellowship [n (%)]	*P*-value
Provide palliative care to children ≥ 50% of clinical time and use methadone	81 (100%)	62 (77%)	19 (23%)		39 (63%)	23 (37%)	
How old are you?							
31−40 years old	35 (43%)	22 (35%)	13 (68%)	0.08	7 (18%)	15 (65%)	0.002
41−50 years old	21 (26%)	18 (29%)	3 (16%)		13 (33%)	5 (22%)	
51−60 years old	14 (17%)	13 (21%)	1 (5%)		10 (26%)	3 (13%)	
61 years or older	11 (14%)	9 (15%)	2 (11%)		9 (23%)	0 (0%)	
What is your gender?							
Female	58 (72%)	43 (69%)	15 (79%)	0.56	26 (67%)	17 (74%)	0.55
How many years have you been practicing pediatrics?							
0−10 years	35 (43%)	22 (35%)	13 (68%)	0.08	5 (13%)	17 (74%)	<0.001
11−20 years	26 (32%)	23 (37%)	3 (16%)		18 (46%)	5 (22%)	
21 years of more	20 (25%)	17 (28%)	3 (16%)		16 (41%)	1 (4%)	
How many years have you been practicing in HPM?							
0−10 years	61 (75%)	43 (69%)	18 (95%)	<0.001	21 (54%)	22 (96%)	<0.001
11−20 years	18 (22%)	18 (29%)	0 (0%)		17 (44%)	1 (4%)	
21 years of more	2 (3%)	1 (2%)	1 (5%)		1 (2%)	0 (0%)	

Table 2
Practices of Dosing Methadone and Management of Electrocardiograms

Question	n (%)
Dosing of methadone, $N = 81$	
Determine starting dose of methadone	
Equianalgesic dosing with dose reduction	69 (85%)
Weight-based formula	6 (7.5%)
Other	6 (7.5%)
Do you use loading doses of methadone?	
No	57 (70%)
	Mean ± SD
% decrease in methadone dose when changing from oral to IV route	37 ± 19
% decrease in methadone dose when adding this medication	
Azole antifungals	38 ± 27
Calcium channel blockers	31 ± 19
Macrolides	30 ± 27
Quinolones	31 ± 24
Selective serotonin reuptake inhibitors	31 ± 21
Electrocardiograms (ECGs), $N = 73$	
QTc interval defined as prolonged (millisecond)	444 ± 68
% of patients who receive baseline ECG	65 ± 33
% of patients who receive repeat ECG	42 ± 31
Weeks after baseline ECG repeat is done	3.0 ± 1.7

The mean (±SD) threshold definition of a "prolonged QTc" was 444 (±68) milliseconds. Physicians obtained a baseline ECG in (mean ± SD) 65% (±33%) of children. Repeat ECGs were done in (mean ± SD) 42% (±31%) of children. The most common reason for not performing a baseline or repeat ECG was that the patient is on hospice, or if obtaining the ECG was not consistent with the overall goals of care (13, 36%). Repeat ECGs were done a mean (±SD) of 3 (±1.7) weeks after the baseline ECG. Physicians certified via fellowship were significantly more likely to repeat an ECG (59% of patients) than those certified through the direct pathway (36% of patients) ($P = 0.02$). Physicians certified through the direct pathway were significantly more likely to repeat ECGs in children with underlying cardiac illness ($P = 0.03$) and impaired liver function ($P = 0.03$) compared with physicians certified via fellowship.

Discussion

Our results show that most pediatric palliative care providers prescribe methadone.

Respondents who said that they do not prescribe methadone reported that the primary reason was due to institution-specific policies that limit who can prescribe methadone. Anesthesiology, the pediatric intensive care unit, and the Pain Service were identified as the primary services that prescribe long-acting opioids and methadone at these institutions. The fact that 23% of physicians cannot prescribe methadone, however, is a concerning finding as children who may need this important medication may be limited in receiving it. This provides an opportunity to better understand the workplace barriers that may need to be modified to provide the best care for a child suffering from uncontrolled pain.

Pediatric palliative care is a relatively new discipline when compared with adult palliative care. The historic paucity of specific training in pediatric palliative care led the American Academy of Hospice and Palliative Medicine to create a "direct pathway" ("grandfathering") to board certification in place of ACGME fellowship training. The window for pediatricians to obtain certification via the direct pathway is now closed, and all future board-certified palliative care physicians who provide care to children will need to complete an ACGME-accredited fellowship. This has led to three distinct types of pediatric palliative care physicians: board certified via the direct pathway, board certified via fellowship, and non−board certified. Such a diversely educated workforce might lead to significant variation in the attitudes, beliefs, and practices regarding the use of methadone for pain in children with cancer. Somewhat surprisingly, we found relatively uniform practices with regard to initial dosing and dose reduction of methadone across all groups of pediatric providers.

Most medications in pediatrics are indexed on a per kilogram basis (weight-based formulas), although the initial dose of opioids may be different if a child is already taking, or recently received, opioids. Although there are recommended starting doses of methadone that are weight-based,[12–14] there are also equianalgesic tables to help approximate more physiologic appropriate doses if a child is already on opioid medications, but these are based on adult data[15] and some have found the use of the same conversions to be clinically challenging in pediatric patients.[16] Most pediatric palliative care physicians in this survey preferred equianalgesic dosing with dose reduction over weight-based formulas. This likely reflects that the patients are not opioid-naive, and so equianalgesic dosing is the clinically appropriate manner in which to start methadone. Weight-based formulas are more commonly used when patients are opioid-naive. The World Health Organization recommends weight-based dosing to be started in so-called "loading doses" defined as an initial increased frequency,[13] yet most pediatric palliative care physicians surveyed do not use loading doses, citing safety as the primary reason. Given methadone's long and unpredictable half-life,[17–19] this seems to be prudent and is congruent with recommendations by the American Pain Society (APS).[14]

Although uncommon,[5] methadone may directly increase the QTc interval and lead to torsades de pointes (TdP), a potentially fatal arrhythmia.[20] Adult data show that the risk of TdP with respect to the QTc

interval is linear, becoming exponential when the QTc ≥ 500 milliseconds.[21,22] The APS recommends the use of adult values for assessing the risk of TdP in children given the paucity of data in threshold levels in the pediatrics. Essential threshold values for adults are 450 and 500 milliseconds[14]; for values above 450 milliseconds, it is advised to consider modifying doses or removing medications that may alter the QTc, whereas for above 500 milliseconds, it is advised to discontinue QTc-altering medications. Given the lack of data in children, we inquired about the perception of what defines a prolonged QTc interval. Pediatric palliative care physicians surveyed defined a "prolonged QTc interval" in a bimodal distribution with modes at 450 and 500 milliseconds (Figure 2), suggesting agreement with the APS guidelines. Normative pediatric QTc values (99−99.5th percentile), however, are 460 milliseconds in prepubertal children, 470 milliseconds in adolescent males, and 480 milliseconds in adolescent females,[23] suggesting that threshold values of a prolonged QTc interval in children, and their subsequent risk of TdP, may be higher compared with adults, but this is beyond the scope of this article. The threshold values recommended by the APS, and apparently used by most surveyed pediatric palliative care physicians, may be a cautious choice to minimize the risk of potentially life-threatening arrhythmias. It may have unintended consequences, however, including underprescribing or deprescribing methadone and other QTc interval−prolonging medications prematurely. More education is needed on the upper limits of the normal QTc interval and risk for TdP in children to assist pediatric palliative care providers to make the most informed decisions regarding when it is safe to use methadone.

The APS recommends a baseline ECG before the initiation of methadone in patients with risk factors for QTc interval prolongation, and to consider an ECG if the patient does not have any risk factors. Pediatric palliative care providers appear to follow these general recommendations, with some notable differences between subgroups. There were significant differences between physicians certified via the direct pathway compared with fellowship trained physicians. Those who completed fellowship were more likely to obtain repeat ECGs, which may reflect a more in-depth knowledge about the potential side effects of methadone from their structured education, or may be indicative of a more cautious approach given that fellowship trained physicians were younger, and earlier in their career. Physicians certified via the direct pathway were significantly more likely to repeat an ECG if there was a prior history of cardiac illness (structural or electrophysiological) or if the child had impaired liver function compared with fellowship trained physicians. This finding may be due to these physicians having a longer personal history of prescribing methadone, as direct pathway−certified physicians tended to be older and be practicing in pediatrics and HPM for longer periods of time.

The study has many strengths. First, the response rate of the original full-length study was very high (62%).[11] Although seemingly small compared with adult palliative physician numbers, 81 pediatric palliative physicians is a large sample for this small subspecialty.[24] Second, there are limited data on the use of methadone in pediatrics. This study offers preliminary insights into the practices, attitudes, and beliefs about methadone for pain in children with cancer by pediatric palliative care providers. There are limitations to the study. The sampling process was limited to members of the American Academy of Pediatrics (AAP) and those on the AAP electronic mail listserv. Mid-career and hospice physicians, as well as other pediatric palliative care providers, may have been excluded. Their absence may affect the generalizability of the data reported. In addition, questions about a prolonged QTc interval did not specify whether the QTc value was an automated calculation by the ECG machine or manually calculated. Manual calculation of

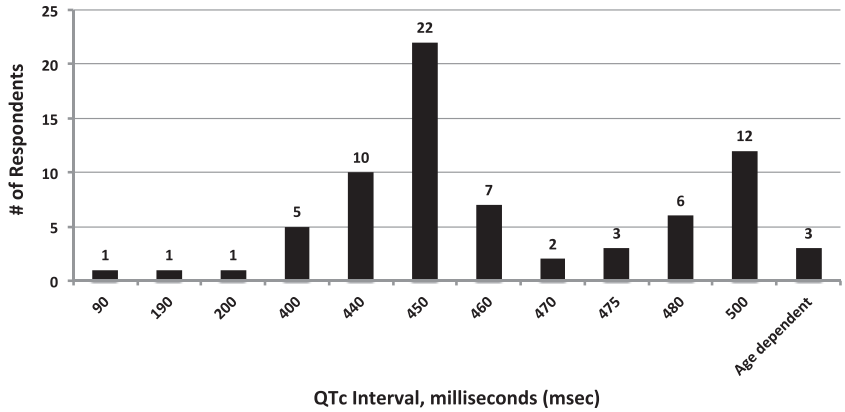

Fig. 2. Distribution of definition of prolonged QTc interval.

the QTc interval is still considered the gold standard despite the prevalence of automated QTc interval calculations.

Conclusions

There are relatively consistent practices, attitudes, and beliefs of pediatric palliative care providers with regard to methadone for pain in children with cancer with very few significant differences in whether these physicians were board certified or not, and how they achieved board certification. More research is needed to understand better the nuanced decisions made when using this effective, inexpensive, and versatile medication in children with cancer who have pain.

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