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The Use of Very-Low-Dose Methadone for Palliative Pain Control and the Prevention of Opioid Hyperalgesia

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Abstract

Background: Opioid dose escalation may cause hyperalgesia, mediated by the N-methyl-D-aspartate (NMDA) pathway. Methadone is an atypical opioid that inhibits hyperalgesia through NMDA-blockade, especially at low doses.
Objective: To evaluate the efficacy of using very-low-dose methadone as the sole long-acting opioid agent in a hospice practice.
Design: A retrospective, observational study of the use of methadone, ≤15 mg daily, with as-needed short-acting opiates. Adjuvant nonopioid medications included haloperidol, which may have NMDA-blocking effects.
Setting/Subjects: We reviewed the records of 240 patients admitted to a community-based hospice from July 1, 2011 to April 1, 2012, with data collected until hospice discharge or until April 30, 2012.
Measurements: Descriptive statistics were used to summarize patient demographics, medication regimens, and reported pain scores measured on a numeric rating scale from 0 to 10.
Results: All patients received short-acting opiates, in a morphine-equivalent dose of 5 mg every 4 hours as needed, while 40% also received methadone at a median daily dose of 5 mg. Of those on methadone, almost half received scheduled haloperidol. The population had a median reported pain score of 0 and a peak score of 3, with similar results seen for cancer and noncancer groups. Two-thirds of patients never reported a pain score greater than 3.
Conclusion: The use of very-low-dose methadone in conjunction with adjuvant haloperidol resulted in excellent pain control without dose escalation or opioid-induced hyperalgesia, for both cancer and noncancer diseases. We conclude that low-dose methadone should be part of first-line treatment in palliative pain management.

Introduction

Opioid prescription trends have changed dramatically over the past 20 years.[1–6] In the 1980s concerns were voiced about "opiophobia" and inadequate pain management, and physicians were encouraged to use opioid analgesics, at least for the acute treatment of advanced cancer.[7–9] By the 1990s, guidelines recommended more liberal opioid use, fueled by pleas from the World Health Organization and the introduction of newer more expensive opioid analgesics.[1,3–5,10–21] Since then, prescription opioid use has increased by over tenfold worldwide, associated with similar exponential rises in opioid-related hospitalizations and deaths.[2,5,12,22–24]

Despite an increased vigilance toward pain management, higher opioid doses may result in increased rather than decreased pain sensitivity, mediated in part by the pronociceptive N-methyl-D-aspartate (NMDA) pathway.[25–32] This syndrome of opioid hyperalgesia has recently become recognized as a major hurdle in effective pain management and challenges our conventional wisdom of rapid escalation of opiates without a ceiling dose.[33,34]

Methadone is a unique opioid analgesic with high-efficacy opioid-receptor stimulation plus NMDA-blocking effects.[28,35] Methadone at relatively low doses (<30 mg/day) is effective for the long-term management of cancer and noncancer pain, while higher doses result in the development of hyperalgesia.[36–38] We review the use of very-low-dose methadone as the sole long-acting opioid in a hospice practice.

Methods

Study design and subjects

We retrospectively reviewed the electronic records of all patients admitted to a community-based hospice service in San Mateo County, California, from July 1, 2011 to April 1, 2012, with data collected until hospice discharge or until April 30, 2012. The study protocol was approved by the

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institutional review board of Mills-Peninsula Health Services as exempt from further review.

Pain management regimen

Short-acting opiates were prescribed in a morphine-equivalent dose of 5 mg every 4 hours as needed. Once ≥2 daily doses of short-acting opiate was needed, methadone was initiated at 2.5 mg daily and titrated up by 2.5 mg increments every 4–7 days as needed, with a maximum daily dose of 15 mg. The pain regimen was reassessed by the nurse and hospice physician whenever the short-acting opiate was being used more than a few times a day.

Patients receiving long-acting opiates other than methadone who had a life expectancy of ≥1 week were offered conversion to methadone. Methadone was started at a daily dose ranging from 2.5 mg to 15 mg, depending on the degree of pain and the previous opiate dose, and the opiate was tapered off over a few days. Patients who had a life expectancy of <1 week on admission could remain on their previous long-acting opiate.

Pain was assessed and recorded on each nursing visit using a standard numeric rating system, in which patients were asked to rate their pain on a scale from 0 to 10.[39,40] For unresponsive patients, caregivers acted as surrogate to rate the patient's pain using the same scale. The values were entered into the computer database, with other vital signs. A multidisciplinary approach to addressing pain and suffering was utilized, incorporating both pharmacological and nonpharmacological means.[19] Pain and other symptoms were treated with nonopioid medications such as antidepressants, antiinflammatory drugs, and agents thought to block NMDA pathways.[26] Haloperidol was the primary nonopioid medication used, because evidence suggests that it decreases pain sensitivity, possibly through NMDA inhibition.[41–44]

Patients who were imminently dying received regularly scheduled oral or parenteral opiates, sedatives, and neuroleptics, as needed. Those on methadone continued to receive the drug sublingually. Patients with uncontrolled symptoms were admitted to the hospital under a general inpatient contract.

Data analysis

The electronic medical records were reviewed to extract data on patient demographics, medication regimens, and pain scores. Descriptive statistics were used to summarize the results, using the mean and standard deviation (SD) for data with a symmetrical distribution and the median and interquartile ranges (IQR) for data with a skewed distribution.

The median and peak pain scores for each patient were recorded. For the study population and for various subgroups we found the median and IQR of these individual values. Pain scores ≥4 were considered a marker of moderate to severe pain.[40,45] The percentage of total pain scores that were moderate to severe for each patient was recorded, and the median

Table 1. Demographic and Diagnostic Characteristics for Patient Population

	Cancer	*Noncancer*	*Total*
Patient characteristics			
Patients, *n*	103	133	236
Admissions, *n*	105	135	240
Female, *n* (%)	69 (67.0%)	75 (56.4%)	144 (61.0%)
Mean age, years (SD)	75 (14)	86 (10)	81 (13)
Length of stay			
Median, days (IQR)	18 (10–38)	25 (9–59)	19 (9–49)
Range	1–237	1–234	1–237
Discharge status			
Died, *n* (%)	81 (77.1%)	83 (61.5%)	164 (68.3%)
Extended prognosis, *n* (%)	0 (0%)	7 (5.2%)	7 (2.9%)
Revoked, *n* (%)	10 (9.5%)	11 (8.1%)	21 (8.8%)
Transferred, *n* (%)	5 (4.8%)	4 (3.0%)	9 (3.8%)
Still alive, *n* (%)	9 (8.6%)	30 (22.2%)	39 (16.3%)
Disease type, *n* (%)			
	Breast	Cardiac	
	20 (19.4%)	37 (27.8%)	
	Lung	Debility	
	19 (18.4%)	34 (25.6%)	
	Hepatobilliary/pancreatic	Dementia	
	15 (14.6%)	22 (16.5%)	
	Gastrointestinal	Pulmonary	
	13 (12.6%)	10 (7.5%)	
	Urological	Cerebrovascular	
	12 (11.7%)	10 (7.5%)	
	Head/neck/brain	Neurodegenerative	
	9 (8.7%)	9 (6.8%)	
	Female genital	Hepatic	
	7 (6.8%)	5 (3.8%)	
	Other	Other	
	8 (7.8%)	6 (4.5%)	

IQR, interquartile range; SD, standard deviation.

(IQR) of these values were found for the study populations. The number of patients with ≥3 moderate-to-severe pain scores was also assessed.

Results

Patient characteristics

The baseline characteristics of the patient population are shown in Table 1. There were 236 patients admitted to the service, with a total of 240 hospice admissions (4 patients were discharged and then readmitted). The mean age was 81 years (range, 28 to 105 years), with 44% having a cancer diagnosis. During the study period 84% were discharged, due to death (68%) or live discharge (16%), with a median length of stay of 19 days (mean, 38 days). At the end of the study, 16% were still alive.

Pain regimen

Details of the medication regimen are summarized in Table 2. Methadone was used for 53% of the patients with cancer and 27% of those with a noncancer diagnosis (39% of total admissions). The final median dose was 5 mg a day, for both the cancer and noncancer groups, with 81% of patients on methadone receiving ≤7.5 mg a day. The median start date of methadone treatment was two days after admission (IQR, 0–9 days). The dosing schedule was once daily (42%) or in divided doses two to three times a day (58%). The median duration of methadone treatment was 34 days (IQR, 16–59 days).

On admission, 32 patients (13% of admissions) were already receiving a long-acting opiate other than methadone. Of these, 23 were converted to methadone, while 9 remained on their previous regimen, due to imminent death or because of patient or doctor preference. The maximum morphine-equivalent daily dose of opiate prior to conversion was 1200 mg, and the maximum conversion ratio used was 133. Conversion to methadone was started a median of 0 days after admission (IQR, 0–3 days), with the median time for complete conversion of 0 days (IQR, 0–5 days) and a median duration of methadone treatment of 49 days (IQR, 13–89 days). The median final daily dose of methadone for these patients was 7.5 mg.

Haloperidol was the most commonly used adjuvant nonopioid medication, prescribed on a scheduled basis to 23% of patients on the service, to 44% of those treated with methadone, and to 70% of those with methadone conversion. In addition, haloperidol was prescribed as needed for pain. The median daily dose of scheduled haloperidol was 3 mg (IQR, 2 mg to 6 mg). Other adjuvant medications included selective serotonin reuptake inhibitors (14% of admissions), corticosteroids (13%), nonsteroidal antiinflammatory drugs (7%), gabapentin (5%), and tricyclic antidepressants (2%). At least one adjuvant medication was prescribed to 52% of patients on the service, with or without methadone.

Pain scores

For the study population, the median pain score on admission was 2 (IQR, 0–4), with a peak score of 3 (IQR, 1–4) and an overall median score per patient of 0 (IQR, 0–0.1, range, 0–7; see Table 3). When the analysis was restricted to scores between 1 and 10, the median pain score per patient was 2.5 (IQR, 2–3). The percent of total pain scores that were moderate to severe (a score ≥4) per patient was 0% (IQR, 0% to 7.7%). Of the group, 8% reported ≥3 moderate-to-severe scores during the study, while 63% never reported any.

The median pain scores were slightly higher for the methadone group (admission score 3 and peak score 4) than for the nonmethadone group (admission score 0 and peak score 2; see Table 3). The percent of patients with ≥3 moderate-to-severe pain days was 18% for the methadone group and 1% for the nonmethadone group. The percent of patients without any moderate-to-severe pain scores was 39% in the methadone group and 78% in the nonmethadone group.

Table 2. Pain Regimen: Use of Methadone, Adjuvant Haloperidol

	Cancer	*Noncancer*	*Total*
Methadone regimen			
Methadone use, *n* (% of admissions)	56 (53.3%)	37 (27.4%)	93 (38.8%)
Final daily dose, mg, median (IQR)	5 (2.5–8.1)	5 (2.5–7.5)	5 (2.5–7.5)
Use of higher-dose methadone (≥10 mg/day)	14 (25%)	4 (10.8%)	18 (19.4%)
Start date, median days from admission (IQR)	1 (0–6)	3 (1–9)	2 (0–9)
Duration of treatment, median days (IQR)	32 (15–55)	45 (22–63)	34 (16–58)
Opioid conversion to methadone			
Methadone final daily dose, mg, median (IQR)	7.5 (5–15)	7.5 (6.9–9.4)	7.5 (5–15)
Opioid conversion, *n* (% of methadone use)	19 (33.3%)	4 (10.8%)	23 (24.7%)
Conversion start date, median days (IQR)	0 (0–3)	1 (0–11)	0 (0–3)
Conversion duration, median days (IQR)	0 (0–5)	2 (0–5)	0 (0–5)
Duration of treatment, median days (IQR)	19 (12–84)	69 (65–73)	49 (13–89)
Other long-acting opiate use, no conversion			
Patient/doctor chose to continue previous regimen	2 (1.9%)	1 (0.7%)	3 (1.3%)
Death imminent, insufficient time for conversion	4 (3.8%)	2 (1.5%)	6 (2.5%)
Scheduled adjuvant haloperidol use			
Haloperidol use (% of admissions)	27 (25.7%)	28 (20.7%)	55 (22.9%)
Final daily dose, mg, median (IQR)	3 (2–6)	2 (1–4)	3 (2–6)
Use with methadone (% of methadone use)	25 (44.6%)	16 (43.2%)	41 (44.1%)
Use with opioid conversion (% of conversions)	14 (73.7%)	2 (50%)	16 (69.6%)

IQR, interquartile range.

Table 3. Pain Scores, with Range, 0–10

	Cancer	*Noncancer*	*Total*
Admission pain score per patient, median (IQR)			
Methadone	3 (0–4)	2 (0–3)	3 (0–4)
Nonmethadone	0 (0–3)	0 (0–1)	0 (0–2)
Total	2 (0–4)	0 (0–2)	0 (0–3)
Median pain score per patient, median (IQR) [range]			
Methadone	0 (0–1) [0–6]	0 (0–0) [0–6]	0 (0–1) [0–6]
Nonmethadone	0 (0–1) [0–7]	0 (0–0) [0–5]	0 (0–1) [0–7]
Total	0 (0–1) [0–7]	0 (0–0) [0–6]	0 (0–0.1) [0–7]
Median pain score per patient with scores of 0 removed from analysis, median (IQR)			
Methadone	2.75 (2–3)	2.5 (2–4)	2.5 (2–3)
Nonmethadone	2.75 (2–4)	2 (2–3)	2 (2–3)
Total	2.75 (2–3)	2 (2–3)	2.5 (2–3)
Peak pain, median (IQR)			
Methadone	4 (3–6)	4 (3–7)	4 (3–6)
Nonmethadone	2 (0–4)	2 (0–3)	2 (0–3)
Total	3 (2–5)	2 (0–4)	3 (1–4)
Moderate-severe pain days per patient, median % (IQR)			
Methadone	16.5% (0%–17%)	5.6% (0%–9%)	5.9% (0%–14%)
Nonmethadone	0% (0%–8%)	0% (0%–0%)	0% (0%–0%)
Total	0% (0%–17%)	0% (0%–4.4%)	0% (0%–8%)
Patients with ≥3 moderate-severe pain days, *n* (%)			
Methadone	11 (20%)	6 (16%)	17 (18%)
Nonmethadone	0 (0%)	2 (2%)	2 (1%)
Total	11 (11%)	8 (6%)	19 (8%)
Patients with 0 moderate-severe pain days, *n* (%)			
Methadone	22 (39%)	14 (38%)	36 (39%)
Nonmethadone	33 (67%)	82 (84%)	115 (78%)
Total	55 (52%)	96 (71%)	151 (63%)

Moderate-severe pain defined as a score of ≥4.
IQR, interquartile range.

Discussion

This retrospective study reports on the use of very-low-dose methadone as the sole long-acting opioid analgesic in the management of 240 patients admitted to a community-based hospice practice. Methadone, an atypical opioid with NMDA-blocking effects, was used in conjunction with low-dose short-acting opiates and adjuvant nonopioid medications as needed. The hospice population had a median reported pain score per patient of 0 (IQR, 0–0.1) and a median peak pain score of 3 (IQR, 1–4), on a numeric scale from 0 to 10, with similar results seen for the cancer and noncancer groups. Approximately two-thirds of the patients never reported a pain score >3. Our method of pain management was quite different from standard palliative care practice today, and appeared to be successful for managing pain without escalation of opiate dose or hyperalgesia.

All patients on the service were offered short-acting opiates in a morphine-equivalent dose of 5 mg every 4 hours as needed, and the pain regimen was reassessed when more than a few daily doses were used. In addition, 40% of patients received methadone (50% of cancer patients and 25% of noncancer patients). Methadone was started a median of two days after admission, with a median duration of treatment of one month. Patients on other long-acting opiates were offered conversion to methadone immediately upon admission. The maximum morphine-equivalent daily dose of opiate prior to conversion was approximately 1200 mg, and the maximum conversion ratio used was 133. The median daily dose of methadone was 5 mg for the general population and 7.5 mg for those converted to methadone, with a maximum daily dose of 15 mg for all patients. The methadone dosing used was similar for cancer and noncancer groups. Over half of the study population also received at least one nonopioid adjuvant medication that was thought to have analgesic effects, either alone or in combination with opioids. Haloperidol was the most common adjuvant medication prescribed, on a scheduled and as-needed basis, due to its NMDA-blocking effects and its relief of symptoms associated with terminal disease.[41–44]

Our approach of using low-dose methadone for palliative pain management offers the potential for large cost savings compared to more standard practices. The average total medication cost on our service was $2.76 per patient per day. This compares favorably to a national average medication cost of $11.16 per person per day for routine home-based hospice services, with published survey ranges from $7.00 to $20.00.[46,47] The cost of methadone is less than one-tenth that of other long-acting opioid preparations.[48] Pharmaceutical costs of routine hospice care have been rising dramatically over time, thought to be primarily related to the cost of newer long-acting opioid agents such as oxycodone and fentanyl, and of parenteral opioid delivery systems.[46,47]

The standard practice of palliative pain management is quite different from the approach used here, and involves the liberal use of long-acting opioids with frequent breakthrough doses of a short-acting opioid, as often as every 1–2 hours.[13,15,16] The opioid dose traditionally is rapidly titrated upward without a ceiling dose, resulting in doses as high as 15,000 mg of morphine (or equivalent) a day.[13–21] Despite some renewed interest

in using methadone in the hospice setting, it still represents < 5% of prescriptions for long-acting opioids at this time.[1,49–54] When used, methadone doses tend to be quite high, with an average daily dose of approximately 100 mg.[1,53] For patients converted from another opioid to methadone, standard guidelines propose various conversion ratios to use depending on the previous dose of opioid, often resulting in very high calculated methadone doses.[21,55,56,57] Nonopioid adjuvant medications have not received much attention in palliative pain management, and do not traditionally include haloperidol for pain despite its potential NMDA-blocking effects.[17,41–44]

The traditional approach of opioid dose escalation has paradoxically resulted in a decrease in analgesic effect, mediated by two related mechanisms: desensitization of the antinociceptive opioid pathway due to receptor tolerance, and sensitization of the pronociceptive NMDA pathway as a compensatory response to opioid receptor stimulation.[18–21,27,58–63] This syndrome of opioid-induced hyperalgesia results in an increased sensitivity to pain that is proportional to the dose and strength of the opiate used.[27,33,58,62,64–67] Opioid-induced NMDA pathway stimulation also causes other forms of neuroxicity, including cognitive impairment, dysphoria, delirium, hallucinations, myoclonus, and seizures.[30,58,68] Reducing the dose of the opioid agent or using an NMDA antagonist may result in reduction of pain and irritability.[25–28,59,60,66]

Methadone is a unique synthetic high-efficacy opioid agent introduced in the United States in 1946, with a threshold effective dose in humans of 2.5 mg.[69] Methadone is one of the most potent agonists of the μ-opioid receptor, which is thought to be the main mediator of analgesia as well as of the development of tolerance and hyperalgesia through secondary stimulation of the NMDA pathway.[28,35] Methadone is unique among opiates due to its high-efficacy NMDA-receptor blockade, low cost, high bioavailability, and long elimination half-life, and is thought to have a lower risk for constipation than other opiates at equivalent doses.[35,70–75] Daily administration of low-dose methadone results in an increasing analgesic effect for the first few weeks, due to tissue accumulation, and then can maintain effective analgesia over time by balancing opioid-receptor stimulation and NMDA blockade.[69] However, higher doses result in the development of hyperalgesia through overstimulation of μ-opioid receptors, and can result in serious toxicity and death.[36–38,76–78] Hence, we chose to use very-low-dose methadone for safe, effective, low-cost pain control in a palliative care setting. The findings of this study justify prospective studies to define the role of hyperalgesia in chronic opioid dosing and the role of methadone in patients suspected of having hyperalgesia.

Our study has several limitations. We conducted a simple, retrospective, observational study without a comparator group, and the assessment of pain was not as rigorous as is generally required in pain research trials. We used a numeric pain-scale reporting system to evaluate our results, in which reports of pain intensity were elicited regularly by clinicians in the field. This approach is the standard of care in hospice practice, but it is unclear how valid this method is in quantitatively assessing pain control. The median pain scores in this study were very low, even for the cancer group, because for the majority of nursing visits the patients reported little or no pain. When the scores of 0 were removed from the analysis, the median pain score was 2.5 (IQR, 2–3), indicating good pain control.

It is possible that this population is not representative of hospice patients in other communities. Another possibility is that this pain regimen resulted in good pain control for the majority of patients on the service. Half of the patients with cancer (mainly of breast, brain, lung, and liver) did not receive methadone at all, and were controlled on adjuvant medications and rare short-acting opiates. This suggests that opioid hyperalgesia occurs more commonly than is suspected in general palliative practices, due to heavy opiate use.

We pooled patient data to analyze results for the population and various subgroups, but were unable to track results or trends for individual patients or individual pain regimens. We only evaluated patients in a community-based hospice service, so are unable to extrapolate our results to a hospital setting or outpatient palliative care programs. We reported on a pain management protocol used in clinical practice, rather than in a structured trial, with some deviations in the regimen due to individual variability. For example, three patients chose not to convert to methadone from another long-acting opioid due to patient or physician preference.

Over 50% of the patients who received methadone were started within the first few days of admission or even prior to admission, so it is difficult to assess pain prior to the start of treatment. In addition, 75% of the patients on methadone received treatment for at least two weeks, and treatment was rarely started on patients with impending death, so the short-term efficacy of methadone cannot be assessed. Despite these study limitations, we believe this study presents promising results that merit further evaluation.

In conclusion, the use of very-low-dose methadone in conjunction with adjuvant haloperidol provides excellent pain control while minimizing the development of opioid-induced hyperalgesia. Methadone is presently considered a second-line agent for pain management, mainly because of its complicated pharmacokinetic and pharmacodynamic properties, with resultant risk for toxicity at the high doses used in practice today. We propose a simple and safe method of use that could advance methadone as a first-line treatment for the management of both cancer and noncancer pain. Future controlled trials are needed to elucidate the most optimal, cost-effective management approach in these patients.

Author Disclosure Statement

No competing financial interests exist.

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