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Publication Information

Chatham, Megan S.; Dodds Ashley, Elizabeth S.; Svengsouk, Jefferson S.; and Juba, Katherine (2013). "Dose Ratios between High Dose Oral Morphine or Equivalents and Oral Methadone." *Journal of Palliative Medicine* 16.8, 947-950.

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Dose Ratios between High Dose Oral Morphine or Equivalents and Oral Methadone

Abstract

Background: Methadone is a commonly used opioid in hospice and palliative care for patients with refractory pain. Various methadone dose conversion methods utilize progressively higher morphine equivalent dose (MED) to methadone dose ratios to compensate for increased methadone potency with escalating opioid doses.

Objective: The purpose of this study was to determine the dose ratio between equianalgesic doses of high dose oral morphine (daily doses >1200 mg morphine or MED) and oral methadone.

Methods: This study was a retrospective chart review of 324 patients who received methadone at Strong Memorial Hospital or the associated outpatient clinic during a nine-month period in 2011. Ten patients met the study inclusion and exclusion criteria. A Wilcoxon signed-rank test was used to compare the pain scale scores. The Spearman correlation coefficient was used to assess level of correlation between morphine dose and methadone dose.

Results: Patients rotated to methadone from high opioid doses had a two-point improvement in median pain scale scores after conversion ($p=0.039$). However, there was no correlation identified for patients taking daily doses >1200 mg oral morphine or MED prior to methadone rotation ($p=0.19$). There were no reported methadone adverse effects during the study.

Conclusions: No correlation was identified between high MED doses and methadone at dose stabilization after opioid rotation. A fixed maximum methadone dose of 30 mg/day produced clinically meaningful improvements in pain scores without adverse drug effects. Caution should be exercised before considering rotation to methadone doses higher than 30 mg/day in a patient receiving >1200 mg oral MED/day.

Disciplines

Pharmacy and Pharmaceutical Sciences

Comments

This is the authors' manuscript version of the article. The final publication is available from Mary Ann Liebert, Inc., publishers <https://doi.org/10.1089/jpm.2012.0434>.

Abstract

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Introduction

Methadone is a unique opioid that is a delta and mu opioid receptor agonist, N-methyl-D-aspartate (NMDA) receptor antagonist, and inhibits reuptake of serotonin and norepinephrine.¹⁻⁴

It is metabolized via N-demethylation by CYP 3A4, 2B6, 2C8, 2C9, 2C19, and 2D6 to the inactive metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) which is eliminated in the feces and urine.⁵

Methadone is commonly used in hospice and palliative care for patients with refractory pain despite aggressive opioid titration, neuropathic pain, renal failure, morphine allergy, opioid-induced adverse effects, and dysphagia who require long-acting opioids.⁶ Methadone is particularly efficacious for opioid rotation in patients with intolerable opioid induced adverse effects such as myoclonus, opioid-induced hyperalgesia (OIH), hallucinations, sedation, and seizures, or uncontrolled pain. This is attributed to its increased potency with prior exposure to high opioid doses.⁷ Potential reasons for potency differences include incomplete cross-tolerance between other mu opioid receptor agonists and methadone causing changes in receptor binding affinities, reverse opioid tolerance from NMDA receptor antagonism, and elimination of opioid active metabolites such as morphine-3-glucuronide (M-3-G) and hydromorphone-3-glucuronide (H-3-G).

Various methadone dose conversion methods utilize progressively higher morphine equivalent dose (MED) to methadone dose ratios to compensate for increased methadone potency with escalating opioid doses although variations exist among dose range cut-offs.⁸⁻¹⁵ While there are

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many conversion models available, the existing evidence does not support the accuracy of one model over another. Previous methadone conversion studies included small numbers of patients on oral MED $\geq 1200\text{mg/day}$, but to our knowledge no studies have focused exclusively on this patient population.¹⁶⁻²³ At our own institution, we use the American Academy of Hospice and Palliative Medicine (AAHPM) equianalgesic table as a guide, however, there is no guidance for MED $\geq 1200\text{mg/day}$.¹⁵ Our clinical experience suggests that a more conservative oral MED to oral methadone dose ratio is needed for patients receiving these higher oral MEDs. Thus, the primary objective of this study was to determine the dose ratio between equianalgesic doses of high dose oral morphine (daily doses $\geq 1200\text{mg}$ morphine or MED) and oral methadone.

Methods

Sample

We retrospectively reviewed the electronic medical records of 324 patients who received methadone while at Strong Memorial Hospital or the associated Palliative Care Clinic from March 1 through December 31, 2011. Patients were eligible for study inclusion if they were ≥ 18 years and taking high dose oral morphine or MED, defined as $\geq 1200\text{mg/day}$ at the time of methadone rotation. Exclusion criteria included incomplete medical records or lack of a documented pain scale score prior to and post methadone rotation. Patients receiving methadone prior to the start of the study period were also excluded. Data were collected from an electronic medical record database. This study was approved by the University of Rochester Research Subjects Review Board.

Measurements

Methadone Dose Ratios

Pain was assessed on a 0-10 scale with 0 designating “no pain” and 10 indicating the “worst possible pain.” We collected the median pain scale score on the day prior to methadone rotation and at dose stabilization. A methadone dose was considered stabilized when the patient required no dose modifications for 5 consecutive days. . If patient was discharged from hospital earlier than day 5 of methadone therapy, the dose on the day of discharge was used. To determine a morphine to methadone ratio, the daily oral morphine or MED prior to methadone rotation and the methadone dose after stabilization were collected. Adverse events and reason to discontinue methadone were also collected.

Data analysis

Wilcoxon signed rank test was used to compare the median pre-rotation and post-rotation pain scale scores. The Spearman correlation coefficient was used to assess level of correlation between previous morphine dose or MED and stabilized methadone dose.

Results

Baseline characteristics

Of 324 patients, 10 met inclusion criteria. Baseline characteristics are presented in Table 1. The average age was 51 years and most patients (n=7) were male. The underlying diagnosis related to pain was malignancy in all cases.

Reason for methadone rotation

Seven patients were transitioned off of a hydromorphone infusion to methadone for ease of opioid administration upon hospital discharge. Three patients required methadone rotation due to inadequate analgesia from high dose opioids and one patient experienced over-sedation from hydromorphone.

Change in pain scale

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Pain was assessed by a nurse at least every 2 hours in most patients. Table 2 compares median pain scale scores (MPSS) and methadone dose regimens before and after opioid rotation. Seven of the 10 patients experienced improved pain control after switching to methadone. Two patients had no change in MPSS and one had higher pain scale scores after switching to methadone. The patient with increased pain scores was later titrated to a higher methadone dose with improved pain control, but not within the specified 5 day dose stabilization time frame. The titrated methadone dose for this patient was determined based on the patient's as needed short-acting opioid use. The Wilcoxon signed rank test showed a median difference of 2 points on the 0-10 pain scale ($p=0.039$).

Dose ratio

There was no correlation between previous oral morphine dose or MED and stabilized methadone dose ($p=0.19$), as seen in Figure 1. Most patients were started on 30mg of methadone/day (divided every 8 hours) and the majority of patients ($n=8$) were stabilized on this dose. Of the two patients who required higher than 30mg/day of methadone, one patient did not report a difference on the pain scale and the other patient reported worsened pain after methadone rotation.

Adverse events and discontinuation

Methadone was well tolerated in all study patients. There were no reported adverse drug effects during the specified study period. Methadone was not discontinued in any patients.

Discussion

Methadone Dose Ratios

This study further elucidates the underestimated potency of methadone in patients with prior opioid exposure. If the palliative care providers followed the AAHPM dosing card recommendations exactly, the study patients potentially could have been converted to methadone doses exceeding 60mg/day. Based on the palliative care providers' clinical experience and concern about methadone drug accumulation, they utilize a more conservative conversion strategy that rarely exceeds 30mg/day. Clinically meaningful improvements in median pain scores of 2 points on the 0-10 pain scale was noted indicating adequate pain control in the majority of patients with a fixed maximum methadone dose of 30mg/day. No adverse drug effects were observed during the study period. These outcomes support a more conservative approach to methadone rotation in patients with high dose opioid exposure. Although we were not able to determine a specific fixed dose ratio between MED and methadone for high dose opioids, the results of our study are consistent with prior studies examining this relationship.¹⁷ One of our patients was taking >10,000mg MED/day and another was taking only 1200 mg, but both achieved adequate pain control on a fixed maximum methadone dose, suggesting only partial cross-tolerance exists between opioids and methadone. Beyond the threshold of 1200mg MED/day, the cross tolerance between opioids and methadone appears to become very low, as seen in the increasingly large MED to methadone ratios found. This resulted in a potentially predictable methadone dose plateau for these patients with relatively high MED requirements and supports the safety and efficacy of a fixed maximum dose.

There are several limitations of our study. It included a small sample size of patients from one medical center. Given the retrospective nature of the study, data collection relied on electronic records which could potentially contain inaccurate opioid dosing documentation especially regarding as needed patient controlled analgesia use. We did not collect certain patient specific

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factors, such as drug interactions that may have had an effect on methadone metabolism and dosing regimens. Lastly, our providers utilize a very conservative methadone rotation approach in all palliative care patients based on their clinical experience which may have confounded our results.

Conclusions

This study is a retrospective chart review of opioid conversions from a high oral MED $\geq$ 1200mg/day to oral methadone. No correlation was identified between high MED doses and methadone at dose stabilization after opioid rotation. A fixed maximum methadone dose of 30mg/day produced clinically meaningful improvements in pain scores without adverse drug effects. Caution should be exercised before considering rotation to methadone doses higher than 30mg/day in patient receiving >1200 mg oral MED/day.

Author Disclosure

No competing financial interests exist.

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Figure 1. Comparison of Methadone and Morphine Dose

Table 1. Baseline Characteristics

Pt	Sex	Age	Pain diagnosis	Oral MED
1	F	55	Metastatic small cell lung cancer	1200 mg
2	M	58	Metastatic pancreatic cancer	1220 mg
3	F	45	Metastatic colon cancer	1371 mg
4	M	34	Carcinoma of supraglottis	1495 mg
5	M	52	Metastatic adenocarcinoma of lungs	1900 mg
6	M	63	Stage III non small cell lung cancer	2440 mg
7	M	37	Metastatic adenocarcinoma of unknown origin	2578 mg
8	F	43	Metastatic breast cancer	7500 mg
9	M	68	Lung cancer/Pancoast syndrome	8316 mg
10	M	58	Metastatic melanoma	10940 mg

Pt= Patient; M=male; F=female; Age in years; MED = morphine equivalent dose

Table 2. Differences in Pain Scale and Methadone Dose

Pt	Prior MPSS	Stabilized MPSS	Initial Methadone Dose	Stabilized Methadone Dose
1	9	6	5 mg po q6h	10 mg po q8h
2	1	2	15 mg po q8h	20 mg po q8h
3	4	0	10 mg po q8h	10 mg po q8h
4	5	5	10 mg po q8h	15 mg po q8h
5	6	5.5	10 mg po q8h	10 mg po q8h
6	7.5	6.5	10 mg po q8h	10 mg po q8h
7	8	5	10 mg po q8h	10 mg po q8h
8	0	0	10 mg po q8h	10 mg po q8h
9	8	4.5	10 mg po q8h	10 mg po q8h
10	7	0	10 mg po q8h	10 mg po q8h

Pt = Patient; MPSS = Median Pain Scale Score