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Variable Patterns of Continuous Morphine Infusions at End of Life

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Abstract

Background: Continuous morphine infusions (CMIs) treat pain and dyspnea at the end of life (EOL). CMIs may be initiated at an empiric rate and/or are rapidly escalated without proper titration.
Objective: The study objective was to evaluate CMI patterns at the EOL.
Methods: This single-center, retrospective chart review evaluated adult patients who died while receiving CMI at EOL. Patient demographics and opioid dosing information were extracted from an electronic medical record. Twenty-four hour IV morphine equivalent was calculated prior to CMI initiation and at the time of death.
Results: Of the 190 patient charts, 63.2% ($n = 120$) received no bolus doses prior to CMI initiation. Mean 24-hour IV morphine equivalent prior to CMI initiation was 49.3 mg (range: 0–1200 mg, SD 384.9) and at time of death was 267.1 mg (12.0–5193.2 mg, SD 442.2), representing an increase of +442%. Mean CMI starting rate was 3.3 mg/hour (0.4–30.0 mg/hour, SD 3.6) with titration at time of death to a mean of 7.7 mg/hour (0.4–70.0 mg/hour, SD 9.4), representing an increase of +130%. Mean number of CMI rate adjustments was 2.5 (0–5, SD 3.3); and number of bolus doses administered between titrations was 4.2 (0–27, SD 4.8). Mean time from CMI initiation to death was 15.5 hours (0.05–126.9 hours, SD 21.7). There was a negative association between rate of infusion increase per hour and total number of hours on CMI ($r = -0.2$, $p = 0.0062$).
Conclusions: Hospitalized patients at EOL had a much higher 24-hour IV morphine equivalents and CMI rates at time of death compared to CMI initiation. Variability was observed in the number of CMI rate adjustments and the number of bolus doses administered.

Introduction

When a patient is identified to be at the end of life (EOL), the medical plan transitions from curative intent to comfort care. Pain management at the EOL is challenged by factors including family pressures, misconceptions about opioid use, recognition of nonverbal signs of pain. and lack of education among health care professionals regarding the treatment of pain.[1] There is sparse literature on EOL pain management.[2,3] Both the public and health care professionals often mistakenly believe opioid use will hasten death, when in fact appropriately dosed opioids can significantly improve pain and extend time until death.[4] According to the World Health Organization, properly dosed and titrated opioids are the medication of choice for pain management at the EOL.[5]

A recent article shows that morphine is the most common opioid used at EOL.[6] With proper titration, morphine can be given both as intermittent bolus doses and as a continuous infusion during EOL.[5] However, no literature exists guiding continuous morphine infusion (CMI) initiation and titration in hospitalized EOL patients, causing a lack of standardization. Intravenously administered morphine has a peak effect at 20 minutes and an elimination half-life of two to four hours.[7] In patients with renal dysfunction, accumulation of the morphine-3-glucuronide and -6-glucuronide metabolites occurs, leading to prolonged serum concentrations and increased toxicities.[7] Given these morphine pharmacological parameters, practice consensus is to give intermittent morphine bolus doses to assess an appropriate and tolerable dose prior to starting a continuous infusion. The rate of the CMI should be uptitrated based on additionally administered bolus doses. Further, there is large interpatient variability on dosing of morphine,[8] making it crucial to observe clinical response of bolus dosing prior to infusion initiation or rate change. In those with renal dysfunction, CMI may not be warranted because of the decrease in elimination.[9] In such cases,

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appropriate alternative options may include closely monitored bolus doses of morphine as needed or use of an alternative opioid such as fentanyl due to absence of active metabolites.[10]

In our clinical practice at two hospitals under a single-academic center, initiation of ''comfort care'' measures with hospitalized patients often leads primary teams to reflexively initiate CMIs without any prior bolus dosing, even in patients who are asymptomatic or opioid-naïve. In the setting of decreased renal function as part of the normal dying process,[11] rapid, unrestricted titration of morphine infusions is not supported by its pharmacokinetic and pharmacodynamic properties, including the time to steady state and the potential for unwanted effects such as respiratory depression and even hastened death. This retrospective chart review aimed to assess current EOL CMI utilization practices at two hospitals under a single-academic center and identify areas for quality improvement.

Methods

The UC San Diego Human Research Protections Program granted institutional review board approval. This retrospective data analysis evaluated adult hospitalized patients who died while receiving CMI from 2012 to 2013 at a single-academic center.

Data collection

All data were collected from a single electronic medical record and captured on an Excel spreadsheet. Patient demographics such as age at time of death, sex, and diagnosis were collected from those patients identified as having died in the hospital between January 1, 2012 until January 1, 2013 who were on a CMI at the time of their death. Kidney function was quantified by glomerular filtration rate (GFR). Data collected were indication for CMI, opioid requirements prior to initiation of the CMI, starting CMI rate, number of rate adjustments, number of bolus doses given between titration, time from CMI initiation to death, and CMI rate at time of death. We defined opioid naive as those patients who did not receive any opioids while in the hospital or as an outpatient prior to CMI. Those patients who were admitted to our academic center without prior knowledge of their opioid use were assumed to be opioid naïve. For uniform comparison, all intravenous opioid totals were converted to 24-hour intravenous morphine equivalent.[11–13] When patients received less than 24 hours of opioids, a 24-hour equivalent was extrapolated.

Statistical analysis

Continuous data such as age (years) and CMI starting and ending doses were reported as means and standard deviations. Frequencies are reported for nominal and/or ordinal data variables such as sex and morphine indication. Pearson correlations were performed for the following: (1) CMI rate increase and total duration patient was on a CMI and (2) 24-hour IV morphine equivalent and total duration patient was on a CMI. A Wilcoxon two-sample test was performed to evaluate GFR (e.g., ≤30 mL/min versus >30 mL/min) on total duration patient was on a CMI, 24-hour IV morphine equivalent, and total number of IV bolus doses administered. A p-value ≤ 0.05 was considered statistically significant. All analysis was conducted with SAS version 9.3 (SAS Institute Inc., Cary, NC).

Table 1. Patient Demographics (n = 190)

Variable	*N (%)*
Mean age (range)	66.4 (19–99)
Sex	
Men	109 (57%)
Women	81 (43%)
Diagnosis	
Trauma	57 (30%)
Active oncology	49 (26%)
Other	84 (44%)
ICU	139 (73%)
Nonacute care	51 (27%)
Kidney function	
GFR ≥30 ml/min	140 (74%)
GFR <30 ml/min	50 (26%)
Opioid naïve	77 (41%)
Opioid tolerant	113 (60%)

Results

Patient charts of patients who died while receiving a CMI ($n = 190$) were identified and analyzed. Mean age was 66.4 years (range: 19–99 years), with inclusion of 109 males and 81 females. Prior to CMI initiation, 41% ($n = 77$) were opioid naïve, 43% ($n = 82$) were on fentanyl, 7% ($n = 13$) were on hydromorphone, 5% ($n = 9$) were on morphine, and the remainder of the patients were on various other opioids including methadone, oxycodone, hydrocodone, and tramadol. At initiation of CMI, 25.8% ($n = 49$) had an oncologic diagnosis and 73.2% ($n = 139$) were in the ICU. Eighty-five percent ($n = 160$) had documented CMI indication for initiation (e.g., compassionate extubation or comfort care with pain/dyspnea), whereas 15.8% ($n = 30$) had no documented indication (see Table 1). Sixty-three percent ($n = 120$) did not receive any bolus doses prior to CMI initiation and of these, 23% were opioid naïve ($n = 44$). The mean CMI starting rate was 3.3 mg/hour (0.4–30.0 mg/hour, SD 3.6). The mean 24-hour IV morphine equivalent prior to CMI initiation was 49.3 mg (range: 0–1200 mg, SD 384.9).

Table 2. Continuous Morphine Infusion Rate and 24-Hour IV Morphine Equivalent at Baseline and Death

	At baseline	*At death*	*Overall change*
Mean CMI rate	3.3 mg/hr (0.4–30.0 mg/hr, SD 3.6)	7.7 mg/hr (0.4–70.0 mg/hr, SD 9.4)	+130%
Mean 24-hr IV morphine equivalent	49.3 mg[a] (0–1200 mg, SD 384.9)	267.1 mg[b] (12.0–5193.2 mg, SD 442.2)	+442%

[a]IV morphine equivalent determined based off oral and/or IV opioid use prior to CMI initiation.
[b]IV morphine equivalent determined based off CMI use at time of death.
CMI, continuous morphine infusion.

Table 3. Renal Function

GFR mL/min	N	# bolus doses given (mean, SD)	# rate changes (mean, SD)	Total number of CMI hours (mean, SD)
0–30	46	2.97, 3.69	1.54, 2.20	10.6, 13.4
>30	139	4.61, 5.15	2.78, 3.60	17.1, 23.8

CMI, continuous morphine infusion; GFR, glomerular filtration rate.

The average number of CMI rate adjustments was 2.5 (0–25, SD 3.3) and number of bolus doses given between titrations was 4.2 (0–27, SD 4.8). Mean time from CMI initiation to death was 15.5 hours (0.05–126.9 hours, SD 21.7). The mean CMI rate at time of death was 7.7 mg/hour (0.4–70.0 mg/hour, SD 9.4), which represents an increase of +130% relative to CMI initiation. The 24-hour IV morphine equivalent at time of death was 267.1 mg (12.0–5193.2 mg, SD 442.2), which represents an increase of +442% relative to CMI initiation. There was a negative association between CMI rate increase per hour and total number of hours on the CMI ($r = -0.2$, $p = 0.0062$ (see Table 2).

In analyzing renal function, 24.2% ($n = 46$) had a GFR ≤30 mL/min, 73.1% ($n = 139$) had a GFR >30 mL/min, and 2% ($n = 5$) were not recorded. Patients with a GFR >30 mL/min received more bolus doses and had more rate changes compared to those with a GFR ≤30 mL/min (see Table 3). However, GFR accounted for no difference in total number of hours on CMI, 24-hour IV morphine equivalent, and number of IV bolus doses administered ($p > 0.05$). There was a negative association regarding number of CMI rate changes ($r = -0.18$, $p = 0.01$) based on GFR.

Discussion

According to best practice standards, opioid naïve patients should be started on bolus doses first to determine opioid requirements. If a CMI is indicated, the initial CMI rate should be determined based on response to the bolus doses. In the current study, about 25% of opioid naive patients were started on a CMI without any knowledge of their opioid requirement. We also observed large variations in the CMI starting rate (see Table 2), as well as the number of rate adjustments and number of bolus doses between titrations. These results suggest that standardized protocols are needed.

Studies by Bailey and Brown[2,3] showed that there were problems and concerns while implementing standardized protocols, including proper symptom documentation regarding justification of upward titration of opioids, questions regarding pain assessment related to underdosing of opioids, correct opioid initiation, and uncertainty among health care professionals on safe opioid doses.[2,3] Such studies indicate the necessity of evaluating how opioids are used in EOL clinical settings and the need to provide education and clarity in the area of creating EOL symptom management protocols. The findings of our study and evaluating previous studies[2,3] have helped our institution focus on creating policies and education for health care professionals managing pain at EOL. With the leadership of a multidisciplinary palliative care team and hospital-wide pain task force, our institution has developed EOL order sets. We have also provided education on EOL symptom management with a focus on the use of bolus dosing prior to initiating or uptitrating opioid infusions and assessing renal function when selecting a particular opioid, starting dose, and infusion rate. We have also reviewed the importance of assessing renal function, starting dose, and infusion rate when selecting and initiating an opioid. We also plan to evaluate our EOL order sets at set intervals after protocol launch to assess any confusion among health care professionals using the protocol.

Limitations

The limitations of our study include its retrospective study design and small sample size. We were limited in collecting certain data of interest, including unclear indication for starting CMI and lack of urinary output information, thus requiring reliance on GFR as a sole means of estimating renal function. Additionally, we observed a lack of consistent documentation of the rationale that may influence the frequency of CMI rate adjustments, such as a concern for pain level or signs of toxicity as reflected by metabolite accumulation due to decreased renal function. Also, this study focused solely on the use of morphine and was not inclusive of other sedatives at EOL. For comparison, opioids prior to CMI initiation were converted to 24-hour IV morphine equivalents. When patients received less than 24 hours of opioids, a 24-hour equivalent was extrapolated, which may have resulted in overestimation of IV morphine equivalents. In addition, patients admitted to our academic center without prior knowledge of their opioid use were assumed to be opioid naïve.

Conclusions

This retrospective analysis observed variability in 24-hour IV morphine equivalents, CMI rates at time of death, number of CMI rate adjustments, and number of bolus doses administered. These results suggest CMIs are not properly initiated and titrated, leading to potential harm. It confirms the need to create and standardize protocols guiding health care providers on symptom management at EOL and education on the appropriate use of opioids and other medications at EOL. Further prospective studies are warranted to confirm our findings.

Author Disclosure Statement

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