Research Report

Use of Methadone Versus Oxycodone to Facilitate Weaning of Parenteral Opioids in Critically Ill Adult Patients

Annals of Pharmacotherapy
2023, Vol. 57(10) 1129–1136

DOI: 10.1177/10600280221151106
journals.sagepub.com/home/aop
SAGE

Hanna A. Azimi, PharmD[1,2], Kelli R. Keats, PharmD, MPA, BCCCP[1], Essilvo Sulejmani, BS[1,2], Kristina Ortiz[1,2], Jennifer Waller, PhD[3], and Nathan Wayne, PharmD, BCPS, BCCP[1]

Abstract

Background: No previous literature has compared methadone with oxycodone for intravenous (IV) opioid weaning. **Objective:** To determine if a weaning strategy using enteral methadone or oxycodone results in faster time to IV opioid discontinuation. **Methods:** This was a single-center, retrospective, cohort medical record review of mechanically ventilated adults in an intensive care unit (ICU) who received a continuous IV infusion of fentanyl or hydromorphone for ≥72 hours and an enteral weaning strategy using either methadone or oxycodone from January 1, 2020, through December 31, 2021. Differences between groups were controlled for using Cox proportional hazards models. The primary outcome was time to continuous IV opioid discontinuation from the initiation of enteral opioids. Secondary outcomes included the primary endpoint stratified for COVID-19, duration of mechanical ventilation, ICU and hospital length of stay, and safety measures. **Results:** Ninety-three patients were included, with 36 (38.7%) patients receiving methadone and 57 (61.3%) receiving oxycodone. Patients weaned using methadone received IV opioids significantly longer before the start of weaning ($P = 0.04$). However, those on methadone had a significantly faster time to discontinuation of IV opioids than those on oxycodone, mean (standard deviation) 104.7 (79.4) versus 158.3 hours (171.2), $P = 0.04$, and, at any time, were 1.89 times as likely to be weaned from IV opioids (hazard ratio, HR 1.89, 95% confidence interval, CI 1.16-3.07, $P = 0.01$). **Conclusion and Relevance:** This was the first study showing enteral methadone was associated with a shorter duration of IV opioids without differences in secondary outcomes compared with oxycodone. Prospective research is necessary to confirm this finding.

Keywords

opioid weaning, analgesia, analgosedation, methadone, oxycodone, critical care, COVID-19

Introduction

Intravenous (IV) opioids, such as IV fentanyl, are considered standard of care in providing analgosedation in mechanically ventilated adults.[1] Long-term use and use of high doses of short-acting IV opioids have been associated with iatrogenic complications such as tolerance, withdrawal, and opioid-induced hyperalgesia.[2] In addition, patients who have been exposed to long-term use or high doses of continuous IV opioids may not tolerate an abrupt analgesia holiday, delaying the potential for extubation. Current pain, agitation, delirium, immobility, and sleep guidelines do not give recommendations on the use of enteral opioids to achieve faster weaning of IV opioids.[1]

To date, most of the literature for using methadone to facilitate opioid weaning in those who are critically ill was from the studies conducted in the pediatric population.[3-6] In the adult critically ill population, methadone has previously been associated with faster time to weaning from IV fentanyl and decreased duration of mechanical ventilation (MV) compared with no enteral opioids or scheduled gradual reduction of IV fentanyl.[7,8] No previous literature has evaluated the effects of oxycodone in weaning from IV opioids or compared methadone with oxycodone for IV opioid weaning.

[1]Department of Pharmacy, Augusta University Medical Center, Augusta, GA, USA
[2]College of Pharmacy, University of Georgia, Augusta, GA, USA
[3]Division of Biostatistics and Data Science, Department of Population Health Sciences, Medical College of Georgia, Augusta, GA, USA

Corresponding Author:
Hanna A. Azimi, Department of Pharmacy, Augusta University Medical Center, 1481 Laney Walker Blvd, Augusta, GA 30912, USA.
Email: hazimi@augusta.edu

The purpose of this study was to determine if a weaning strategy using enteral methadone or oxycodone resulted in faster time to discontinuation of IV opioids in critically ill, mechanically ventilated adult patients. Previous studies have demonstrated success using methadone as a weaning strategy; however, oxycodone may be preferable to enteral methadone in some cases as it is not known to increase the QTc interval. Compared with other oral opioids, oxycodone is a readily available alternative with high provider familiarity that is used frequently for weaning of IV opioids.[9] However, as a pure mu receptor agonist, oxycodone has a short half-life, is a prodrug with variable metabolism, and requires potentially high oral doses to achieve analgesia equivalent to that with methadone, which may cause oxycodone to be less effective as an enteral weaning strategy.[10,11] Alternatively, methadone has N-methyl-D-aspartate (NMDA) antagonism and selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor (SSRI/SNRI) activity, which may decrease opioid-induced hyperalgesia and withdrawal.[10,12] In addition, methadone has a long half-life and involves nonlinear equianalgesic dosing, so conversion factors may not be necessary. However, methadone has a higher potential for drug-drug interactions as it is extensively metabolized by CYP3A4 and CYP2B6; oxycodone has significantly fewer drug-drug interactions, which may make it preferable for select patients.[10,11] Alternative opioids to oxycodone were not selected for comparison in this study due to infrequent use at our institution. We hypothesized that the use of enteral methadone would result in faster time to discontinuation of IV opioids in patients with prolonged opioid requirements than the use of oxycodone.

Methods

This single-center, retrospective, observational, cohort review was conducted at Augusta University Medical Center, Augusta, GA, and was approved by the institutional review board. Data were collected for patients admitted between January 1, 2020, and December 31, 2021. Patients included were at least 18 years of age, mechanically ventilated in an intensive care unit (ICU), and received continuous IV opioids for at least 72 hours prior to starting scheduled enteral opioids, which were continued for at least 24 hours. To meet the inclusion criteria, patients had to successfully complete weaning from IV opioids, which was defined as discontinuation of the IV opioid for at least 24 hours prior to discontinuation of the scheduled enteral opioid. Patients were excluded if they were receiving treatment for active alcohol withdrawal, methadone maintenance therapy, total parenteral nutrition, extracorporeal membrane oxygenation, or transitioned to end-of-life care prior to discontinuation of IV opioids. Patients were also excluded if they were paralyzed with a neuromuscular blocking agent for over 24 hours while receiving enteral opioids. Exclusion criteria were selected to ensure that patients included had adequate oral absorption and were candidates for opioid weaning. Demographics and outcomes of the patient were collected through review of the electronic medical record using a generated report of scheduled doses of oxycodone or methadone. REDCap (Research Electronic Data Capture), a secure Web-based software platform specifically designed for research data collection, was used to manage study data.[13,14] Scheduled sedatives were defined as either scheduled doses or receipt of a continuous infusion within 24 hours prior to starting the enteral opioid.

The primary outcome was time to discontinuation of the continuous IV opioid after the initiation of the enteral opioid. Secondary outcomes included the primary endpoint stratified for COVID-19 diagnosis, duration of MV, and hospital and ICU lengths of stay, as well as frequency of oral opioid titrations. Safety outcomes included the incidence of respiratory depression necessitating the use of naloxone within 24 hours after extubation, ileus during oral opioid weaning, and QTc prolongation defined as QTc $>$ 500 milliseconds during oral opioid weaning.

To compare different oral and IV opioids, standard conversion factors were used (Table 2) to convert each opioid to oral morphine milligram equivalents (MMEs).[15,16] Down-titration of IV opioids were completed via a nurse-driven protocol including down-titration of fentanyl by 0.5 μg/kg/min every 30 minutes or hydromorphone by 0.5 mg/h every 30 minutes to target the Richmond Agitation Sedation Scale goal. Infusion rates were documented hourly by nursing staff on the medication administration record.

Statistics

The sample size was determined using a 2-group log-rank test under a Kaplan-Meier survival curve. Assumptions included an accrual of 0 days, follow-up time of 28 days, power of 0.80, and alpha level of 0.05. Previous literature reported median wean time from IV fentanyl to be 4.5 days with methadone compared with 7 days with no intervention, so the estimated time to wean was 4 days for methadone and 6 days for oxycodone.[8] A sample size of 100 subjects per group ($n = 100$ in the methadone group and $n = 100$ in the oxycodone group for a total sample size of $n = 200$) was needed to show the assumed difference in median time to wean between the 2 treatment groups.

Descriptive statistics on all variables were determined within the 2 treatment groups and included frequencies, percentages, means and standard deviations (SD), or medians and interquartile range (IQR), as appropriate. Differences in the primary, secondary, and safety outcomes were assessed using Student's 2-sample *t*-tests, χ^2 tests, or logistic regression, as appropriate. The primary outcome, time to weaning in hours, was assessed using a Kaplan-Meier survival curve with a log-rank test and a Cox proportional hazards (CPH) model, which

Table 1. Baseline Demographics.

	Methadone (n = 36)	Oxycodone (n = 57)	*P* value
Age (year), mean ± SD	49.7 ± 17	50 ± 16	0.92
Sex (male), n (%)	20 (55.6)	28 (49.1)	0.55
Weight (kg), mean ± SD	100.5 ± 36.2	93.1 ± 24.4	0.29
IV opioid, n (%)			
Fentanyl	26 (72.2)	46 (80.7)	0.34
Hydromorphone	10 (27.8)	11 (19.3)	
Diagnoses, n (%)			
COVID-19	21 (58.3)	30 (52.6)	0.59
Trauma	4 (11.1)	14 (24.6)	0.11
Other	11 (30.6)	13 (22.8)	0.41
Scheduled sedatives, n (%)			
Midazolam	16 (44.4)	19 (33.3)	0.28
Propofol	6 (16.7)	26 (45.6)	<0.01
Dexmedetomidine	13 (36.1)	16 (28.1)	0.41
Others[a]	13 (36.1)	7 (12.3)	<0.01
Ketamine	2 (5.6)	5 (8.8)	0.70
Multiple sedatives	15 (47.1)	19 (33.3)	0.42
PRN sedatives, n (%)			
Midazolam	17 (47.2)	30 (52.6)	0.61
Lorazepam	6 (16.7)	1 (1.8)	0.01
Ketamine	0 (0)	1 (1.8)	1.00
Duration of IV opioids prior to the start of weaning (hours), mean ± SD	296.7 ± 194.4	213.6 ± 186.3	0.04
Total IV MMEs 24 hours prior to the start of weaning, mean ± SD	2199 ± 1391.8	1410.2 ± 836.2	<0.01

Abbreviations: IV, intravenous; MMEs, morphine equivalents; PRN, as needed; SD, standard deviation.
[a]Other sedative category includes scheduled phenobarbital, lorazepam, diazepam, and clonazepam.

is a predictive model that was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) controlling for demographic or clinical variables as needed. All statistical analyses were performed using SAS 9.4, and statistical significance was assessed using an alpha level of 0.05. The data analysis for this paper was generated using SAS software. Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Results

A total of 93 patients were included. Table 1 summarizes relevant baseline demographic data. There were no statistically significant differences in demographic variables between the groups with the exception of scheduled sedatives and duration of IV opioids prior to the start of weaning. Patients weaned with oxycodone were more likely to receive scheduled propofol ($P < 0.01$), while patients weaned with methadone were more likely to receive other scheduled sedatives including phenobarbital, lorazepam, diazepam, or clonazepam ($P < 0.01$). Those on methadone received IV opioids for a significantly longer period of time prior to the start of weaning ($P = 0.04$) and a significantly higher dose (in MMEs) of IV opioids 24 hours prior to the start of weaning ($P < 0.01$) than those on oxycodone. Patients on methadone received a higher dose of IV opioids prior to the start of enteral opioids (2199 MMEs, 3.2 μg/kg/h fentanyl equivalents using a mean study body weight of 96 kg) than those who received oxycodone (1410.2 MMEs, 2 μg/kg/h fentanyl, $P < 0.01$).

Table 2 shows characteristics of enteral opioids. Patients were started on higher doses of methadone (in MMEs) than oxycodone ($P < 0.01$). Majority of those receiving methadone were converted to oral MMEs using a ratio of 20:1 oral morphine-to-oral methadone because they received >1200 mg of oral MME prior to the start of weaning (26/36, 72.2%). Those on oxycodone required more titrations of their enteral opioid prior to discontinuing their IV opioid ($P = 0.09$).

Patients on methadone had a significantly shorter weaning time than those on oxycodone (mean [SD] 104.7 [79.4] vs 158.3 hours [171.2], $P = 0.04$) using a 2-sample *t*-test. The Kaplan-Meier curve for time to weaning by opioid type is shown in Figure 1. The unadjusted survival curve shows no statistically significant difference in time to weaning between methadone and oxycodone. Various factors that could have affected weaning times were analyzed for the CPH model and included age, sex, weight, COVID-19 status, admission for trauma, choice of IV opioid, sedation with scheduled midazolam, titration of oral opioid, percentage of IV opioid converted to enteral opioid, MMEs of starting enteral opioid dose, percentage of

Table 2. Characteristics of Enteral Opioids.

	Methadone (n = 36)	Oxycodone (n = 57)	*P* value
Total daily dose of starting enteral opioid, mean ± SD			
MMEs[a]	639.2 ± 332.8	75.4 ± 48.6	<0.01
Milligram	35 ± 15.5	50 ± 32.1	—
Percentage of IV opioid converted to enteral opioid,[a] mean ± SD	43.5 ± 24.7	6.9 ± 6.4	<0.01
Enteral opioid requiring increase in titration, n (%)	7 (19.4)	21 (36.8)	0.09
Percent titration, mean ± SD	59.1 ± 16.6	52.2 ± 16.8	0.37
Milligram titration, mean ± SD	30 ± 17	40 ± 26	—

Abbreviations: IV, intravenous; MMEs, morphine equivalents; SD, standard deviation.
[a]Opioid conversions:
300:1 oral morphine-to-IV fentanyl (mg).
20:1 oral morphine-to-IV hydromorphone (mg).
1:1.5 oral morphine-to-oral oxycodone (mg).
For over 1200 mg of oral MMEs, 20:1 oral morphine-to-oral methadone (mg) was used.
For 1000 to 1200 mg of oral MMEs, 15:1 oral morphine-to-oral methadone (mg) was used.
For 500 to 999 mg of oral MMEs, 12:1 oral morphine-to-oral methadone (mg) was used.

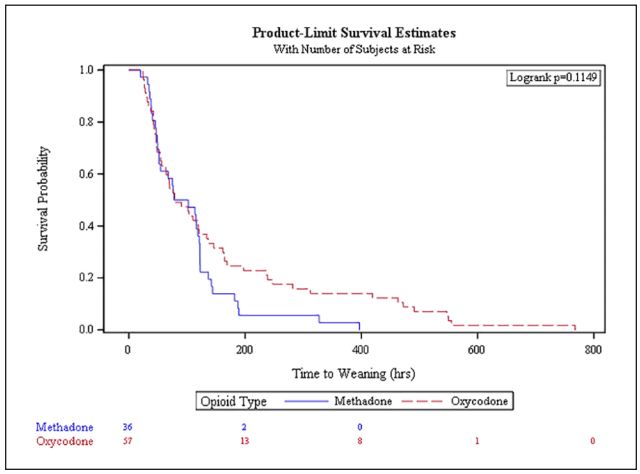

Figure 1. Kaplan-Meier curve for time to weaning between enteral opioid groups.

Table 3. Cox Proportional Hazards Final Model on Time to Weaning.

	Final model, HR (95% CI), *P* value
Methadone	1.89 (1.16-3.07), 0.01
Covariates[a]	
COVID-19 diagnosis	0.64 (0.41-1.02), 0.06
Sedation with scheduled midazolam	0.53 (0.33-0.83), <0.01
Enteral opioid titrated	0.59 (0.36-0.95), 0.03
Total IV MMEs (50-unit)	0.99 (0.976-0.998), 0.02

Abbreviations: CI, confidence interval; HR, hazard ratio; IV, intravenous; MMEs, morphine equivalents.
[a]Additional covariates included in the simple model included age, sex, weight, admission for trauma, choice of IV opioid, percentage of IV opioid converted to enteral opioid, MMEs of starting enteral opioid dose, percentage of enteral opioid titrated, and IV opioid duration.

enteral opioid titrated, total MMEs, and IV opioid duration; however, only those that were statistically significant were included in the final model. In the final CPH model (Table 3), which was adjusted for the COVID-19 status, scheduled midazolam, oral opioid titration, and total IV MMEs prior to the start of weaning, the association between enteral opioid and time to discontinuation of IV opioid was statistically significant. The predictive model was interpreted as, at any given time, those on methadone are 1.89 times more likely to have been weaned from IV opioids than those weaning with oxycodone (HR 1.89, 95% CI 1.16-3.07, $P = 0.01$).

A subgroup analysis was conducted to determine the impact of early initiation of enteral opioids, comparing those who received IV opioids for <7 days prior to the initiation of enteral opioids with those who received IV opioids for ≥7 days prior to the initiation of enteral opioids (Table 4). There was no difference in time to discontinuation of IV opioids after enteral opioid initiation (78.8 vs 102.7 hours, $P = 0.98$). Further stratification to include a more homogenous patient population (eg, excluding patients admitted for trauma, only including patients with COVID-19) found no difference in time to discontinuation of IV opioids between those started early on enteral opioids and those started late. Figure 2 shows a comparison of the duration of IV opioids prior to the start of weaning with enteral opioids versus the time to discontinuation of IV opioids after the start of weaning. There was no association between duration of IV opioids prior to weaning and time to discontinuation of IV opioids after the start of weaning ($R^2 = 0.006$). In mechanically ventilated critically ill adult patients, starting enteral opioids was successful in weaning patients from IV opioid therapy in <5 days from the initiation of enteral opioids, regardless of IV opioid therapy duration.

Table 4. Stratification by Timing of Enteral Opioid Initiation.

	<7 days (n = 41)	>7 days (n = 52)	*P* value
Duration of IV opioid weaning (hours), median (IQR)	78.8 (47.7-145.7)	102.7 (46.6-150.4)	0.98
Excluding trauma patients	79.1 (48.3-153.7)	77.8 (46.2-156.7)	0.80
Only COVID-19 patients	90.5 (67.9-260.3)	76.3 (42.5-197.4)	0.35

Abbreviations: IQR, interquartile range; IV, intravenous.

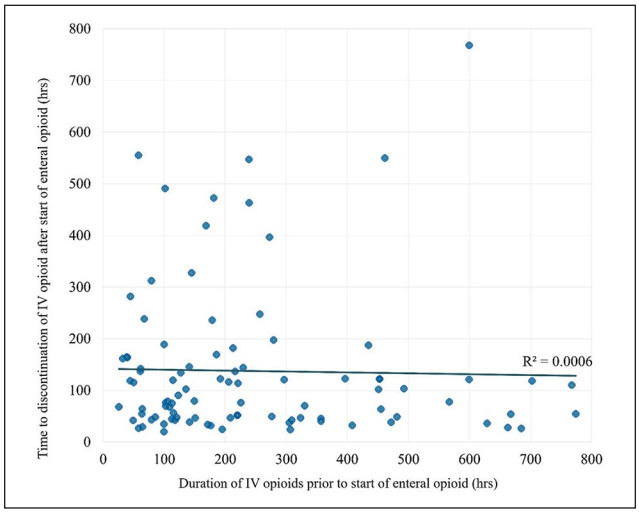

Figure 2. Duration of IV opioids prior to weaning compared with time to discontinuation of IV opioids.
Abbreviation: IV, intravenous.

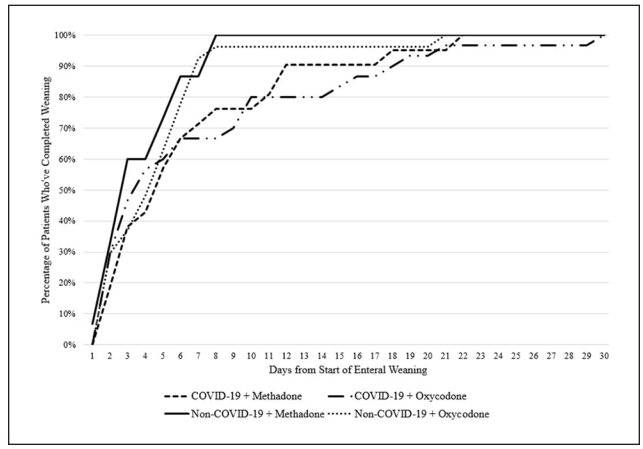

Figure 3. Percentage of patients who completed weaning stratified by COVID-19 diagnosis and enteral opioid weaning choice.

There were no differences in total duration of weaning when stratified by COVID-19 diagnosis and enteral opioid weaning choice. However, when stratified by diagnosis alone, those with COVID-19 took significantly longer time to wean from IV opioids than those without COVID-19 (167.6 vs 101.1 hours, $P = 0.03$) even though there was no difference in duration of IV opioids (257.1 vs 232 hours, $P = 0.53$) or total IV MME prior to weaning (1828.7 vs 1578.2, $P = 0.29$). Figure 3 shows a comparison of the percentage of patients who were successfully weaned between those with and without COVID-19 stratified by the enteral opioid weaning choice. There were no differences in any other secondary outcomes (Table 5), including duration of MV, ICU and hospital lengths of stay, as well as use of naloxone, incidence of ileus, and incidence of QTc > 500 milliseconds during weaning.

Discussion

Currently, there are no clear guideline recommendations on the use of enteral opioids to wean from IV opioids.[1] There have been 2 studies on the use of enteral methadone to wean from IV opioids in the adult critically ill patient population. Al-Qadheeb et al[8] conducted a retrospective, single-center, case-control, preprotocol and postprotocol implantation study that examined time to fentanyl discontinuation for patients in the medical ICU who received ≥72 hours of continuously infused fentanyl. This study included 40 non-methadone patients and 20 methadone patients matched by duration of MV. Patients who had not received oral or enteral methadone (non-methadone) according to the protocol were used as the control; however, receipt of other enteral opioids was not mentioned for either group. Time to IV fentanyl discontinuation was shorter with the addition of enteral methadone for weaning than the control (median [IQR], 4.5 [3.9-5.8] vs 7.0 [4.9-11.5] days; $P = 0.002$) with no differences in QTc prolongation (45% vs 50%, $P = 0.79$), unarousability, duration of MV, or ICU length of stay. The starting dose of methadone was not explicitly stated.[8] The second adult study was a double-blind, randomized, controlled trial of 68 patients receiving IV fentanyl for ≥5 days. There was no significant difference in MV weaning time (HR 1.52, 95% CI 0.87-2.64, $P = 0.11$), which was defined as 48 hours without reintubation; the median weaning time was 5 days in the methadone group (95% CI 2.42-7.58) compared with 7 days in the control group (95% CI 2.87-11.13). When stratified by survivors (29 methadone vs 25 control), the time of MV weaning was lower in the methadone group (HR 2.06, 95% CI 1.17-3.63, $P < 0.004$).[7] Both studies showed success of methadone in reducing the

Table 5. Secondary Outcomes.

	Methadone (n = 36)	Oxycodone (n = 57)	*P* value
Total duration of weaning (hours), median (IQR)			
COVID-19 (n = 51)	113.7 (56.5-189)	64.3 (40-141.3)	0.21
Non-COVID-19 (n = 42)	63.7 (46.8-119.5)	100.4 (58.4-188.5)	0.09
Duration of MV and length of stay measures (days), mean ± SD			
Duration of MV	14.93 ± 6.8	12.78 ± 7.2	0.32
Duration of MV resulting in tracheostomy	18.4 ± 7.1	17.9 ± 8.3	0.32
Hospital length of stay	37.4 ± 23.4	44.6 ± 36.7	0.25
ICU length of stay	27.8 ± 17.9	30.7 ± 19	0.46
Safety outcomes, n (%)			
Use of naloxone after extubation	0 (0)	1 (1.8)	1.00
Incidence of ileus	4 (11.1)	11 (19.6)	0.28
Incidence of QTc > 500 milliseconds	6/32 (18.8)	17/40 (42.5)	0.08

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation; SD, standard deviation.

weaning time from IV opioids and MV without increasing adverse events compared with controls. Several previous studies evaluated the efficacy and safety of oral opioid replacement in the critically ill, pediatric population. A retrospective analysis of 22 critically ill children found that the time to fentanyl discontinuation was a median of 2.6 days when weaning using enteral methadone.[3] A prospective, randomized controlled trial (n = 37) of 5-day versus 10-day opioid weaning using enteral methadone suggested shorter weaning courses with methadone are safe.[6] Finally, a prospective, randomized controlled trial of 68 pediatric patients indicated methadone should be adjusted according to each individual patient response.[4]

This study is the first evaluation comparing enteral methadone and oxycodone in facilitating IV opioid weaning, indicating patients may achieve discontinuation of IV opioids faster when receiving methadone without differences in secondary or safety outcomes. Findings from this study add to the current literature as oxycodone has not previously been studied as an agent to wean patients from IV opioids. This study demonstrates, compared with oxycodone, methadone may be a more appealing option. Methadone was associated with over a 2-day decrease in the duration of continuously infused opioids even though patients on methadone received a significantly longer duration of IV opioids and a higher amount of IV MMEs prior to the start of weaning. It is important to note the variability of methadone's half-life (7-65 hours) and that some patients may not have reached steady state at the time of weaning (the mean weaning time was 158 hours in this study).[10,12] In addition, methadone was not associated with an increase in QTc prolongation, oversedation, or ileus. Although patients who received oxycodone received scheduled propofol more often and patients who received methadone received scheduled phenobarbital, lorazepam, diazepam, and clonazepam more often, the only scheduled sedative that significantly affected time to weaning and was included in the final CPH model was scheduled midazolam. Duration of IV opioids prior to the start of weaning did not appear to affect weaning time; however, starting enteral opioids was successful in weaning patients from IV opioid therapy in <5 days from the initiation of enteral opioids, regardless of IV opioid therapy duration.

Findings from this study may have been observed for several reasons. The first is that methadone was generally dosed more aggressively based on the MMEs of IV opioids prior to the start of weaning. On average, only about 7% of IV MMEs were converted to oxycodone for weaning, whereas almost 44% of IV MMEs were converted to methadone, which may have resulted in the need for more titrations of oxycodone to complete weaning from IV opioids that were observed. However, this difference between groups was accounted for in the CPH model. Clinicians had the tendency to be more conservative with starting enteral weaning doses of oxycodone, although the nonlinear kinetics of methadone could have benefited weaning in this regard. While enteral opioid dosing and other baseline demographics were vastly different between groups, the CPH model, controlling for these differences, showed that methadone resulted in a decrease in the duration of IV opioids. In addition, methadone may have outperformed oxycodone due to its unique pharmacodynamic and pharmacokinetic characteristics. Similar to oxycodone, methadone acts as a mu opioid receptor agonist, which primarily provides its analgesic effects. However, methadone also has NMDA antagonism and SSRI/SNRI activity, which may carry additional antinociceptive effects such as preventing maladaptive responses to acute pain that can develop into chronic pain. Unlike oxycodone, methadone is also lipophilic, so it has rapid absorption, a long duration of action following enteral administration, and produces a depot effect within the tissues, slow releasing into the bloodstream. Methadone has a volume of distribution of 1 to 8 L/kg compared with just 2.6 L/kg for oxycodone. Considering the mean weight of this patient population was over 90 kg, the

lipophilicity and depot effect of methadone could have played a role in successful weaning.[9,12] Compared with the half-life of oxycodone, which is around 3 hours, methadone's half-life varies from patient to patient due to incomplete cross-tolerance with other opioids but can range anywhere from 7 to 65 hours.[10,11] The theoretical benefits of using methadone in critically ill adults are compelling, and this study is hypothesis generating in showing that methadone is a more suitable weaning agent than oxycodone.

Due to the nature of the ICU patient population during our study period, we included those with COVID-19 in our sample. Roughly half of our patient sample had COVID-19, which has been previously been associated with high analgesic and sedation requirements.[17] Although there was no difference in the mean duration of IV opioids or total IV MMEs prior to the start of weaning, patients with COVID-19 took significantly longer time to wean from IV opioids. However, when stratified by COVID-19 diagnosis and enteral opioid weaning choice, there were no differences in time to IV opioid discontinuation. These findings may suggest that patients with COVID-19 may require longer weaning time; however, the choice of enteral opioid for weaning may have less impact on the duration of weaning. These findings should be interpreted cautiously due to the small sample sizes of these subgroups.

Limitations and Future Directions

This study has several potential limitations. First, the nature of the retrospective, single-center design and lack of a sample size sufficient to meet power may preclude external generalizability and cause inference. Due to the retrospective design, the true rates of adverse events are likely underestimated, and patients at risk of QTc prolongation may have been preferentially weaned using oxycodone as our institution had no guidance document for selection of enteral opioid for this purpose. In addition, baseline QTc was not recorded or accounted for in the determination of QTc prolongation while on oral opioids. There are also no current data on reliability of IV infusion rate documentation at this institution, which may preclude the internal validity of the study. The inability to meet sample size may limit the conclusions drawn from this study, particularly when looking at subgroups with smaller sizes, and may be responsible for the wide range of duration of weaning and large SD in the oxycodone group. Second, IV opioid weaning was a nurse-driven titration, which can be a confounder because of variations in practice. While our institution has a protocol for opioid titration, these titrations can be subjective. Next, only patients successfully weaned from IV opioids were included, and patients not completely weaned from IV opioids were not included, so these results may not apply to patients who are not candidates to wean from IV opioids or those who experience challenges in doing so. In addition, the higher rate of IV opioid infusion, indicated by the higher total IV MMEs, in the methadone group at the start of weaning may have encouraged nurses to more aggressively wean IV opioids. The duration of enteral opioid continuation for the purpose of weaning from IV opioids was not taken into consideration and out of the scope of this study; in addition, this study did not evaluate the need to restart IV opioids beyond our definition of successful weaning (24 consecutive hours with no IV opioids). Outpatient follow-up of discharged patients who successfully weaned from IV opioids was not included in this study; therefore, there is limited understanding of the impact of opioid weaning choice on long-term opioid use. Finally, with the exception of chronic methadone use, chronic opioid use was not accounted for and may have affected total opioid consumption and weaning. Regardless of how long patients were on opioids, they were weaned in 4 to 6.5 days across the groups. Although there were several limitations, this study demonstrated a statistically and clinically significant difference in weaning times from IV opioids between both groups.

Conclusion and Relevance

In conclusion, enteral methadone resulted in significantly shorter weaning time from IV opioids than enteral oxycodone in critically ill, mechanically ventilated patients who received at least 72 hours of IV opioids. Large, prospective, multicenter, randomized control trials in critically ill, mechanically ventilated patients are needed to further evaluate if methadone should be considered superior to oxycodone for this indication.

Authors' Note

The contents of this work was accepted for poster presentation at the 2023 SCCM Critical Care Congress and was presented at the 53rd Annual Southeastern Residency Conference as a PowerPoint presentation.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Hanna A. Azimi https://orcid.org/0000-0001-8234-009X

References

1. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult

patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873. doi:10.1097/CCM.0000000000003299
2. Vanjani R, Trimbur MC. Opioid tolerance in critical illness. *N Engl J Med*. 2019;380(16):e26. doi:10.1056/NEJMc1902646
3. Lugo RA, MacLaren R, Cash J, Pribble CG, Vernon DD. Enteral methadone to expedite fentanyl discontinuation and prevent opioid abstinence syndrome in the PICU. *Pharmacotherapy*. 2001;21(12):1566-1573. doi:10.1592/phco.21.20.1566.34471
4. Bowens CD, Thompson JA, Thompson MT, Breitzka RL, Thompson DG, Sheeran PW. A trial of methadone tapering schedules in pediatric intensive care unit patients exposed to prolonged sedative infusions. *Pediatr Crit Care Med*. 2011;12(5):504-511. doi:10.1097/PCC.0b013e3181fe38f5
5. Meyer MM, Berens RJ. Efficacy of an enteral 10-day methadone wean to prevent opioid withdrawal in fentanyl-tolerant pediatric intensive care unit patients. *Pediatr Crit Care Med*. 2001;2(4):329-333. doi:10.1097/00130478-200110000-00009
6. Berens RJ, Meyer MT, Mikhailov TA, et al. A prospective evaluation of opioid weaning in opioid-dependent pediatric critical care patients. *Anesth Analg*. 2006;102(4):1045-1050. doi:10.1213/01.ane.0000202395.94542.3e
7. Wanzuita R, Poli-de-Figueiredo LF, Pfuetzenreiter F, Cavalcanti AB, Westphal GA. Replacement of fentanyl infusion by enteral methadone decreases the weaning time from mechanical ventilation: a randomized controlled trial. *Crit Care*. 2012;16(2):R49. doi:10.1186/cc11250
8. Al-Qadheeb NS, Roberts RJ, Griffin R, Garpestad E, Ruthazer R, Devlin JW. Impact of enteral methadone on the ability to wean off continuously infused opioids in critically ill, mechanically ventilated adults: a case-control study. *Ann Pharmacother*. 2012;46(9):1160-1166. doi:10.1345/aph.1R132
9. Wolters Kluwer. OxyCODONE (Lexi-Drugs). Date unknown. Accessed November 6, 2022. Updated November 6, 2022. https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7416?cesid=83AElIm2lJb&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Doxycodone%26t%3Dname%26acs%3Dfalse%26acq%3Doxycodone#fbnlist
10. Elefritz JL, Murphy CV, Papadimos TJ, Lyaker MR. Methadone analgesia in the critically ill. *J Crit Care*. 2016;34:84-88. doi:10.1016/j.jcrc.2016.03.023
11. Kalso E. Oxycodone. *J Pain Symptom Manage*. 2005;29(suppl 5):S47-S56. doi:10.1016/j.jpainsymman.2005.01.010
12. Wolters Kluwer. Methadone (Lexi-Drugs). Published 2022. Accessed November 6, 2022. Updated November 6, 2022. https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7262?cesid=4Xtpagn3rDj&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dmethadone%26t%3Dname%26acs%3Dfalse%26acq%3Dmethadone
13. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. doi:10.1016/j.jbi.2019.103208
14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010
15. Swarm RA, Paice JA, Anghelescu DL, et al. Adult cancer pain, version 3.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2019;17(8):977-1007. doi:10.6004/jnccn.2019.0038
16. Rakel R, Rakel D. *Textbook of Family Medicine*. 9th ed. Elsevier Saunders; 2015.
17. Balakrishna A, Walsh EC, Hamidi A, et al. An examination of sedation requirements and practices for mechanically ventilated critically ill patients with COVID-19. *Am J Health Syst Pharm*. 2021;78(21):1952-1961. doi:10.1093/ajhp/zxab202