Initial Dosing and Taper Complexity of Methadone and Morphine for Treatment of Neonatal Abstinence Syndrome

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Abstract

Background: Methadone and morphine are commonly used to treat neonatal abstinence syndrome (NAS). Limited data exist to describe the most appropriate initial doses and taper regimens of these agents. **Objectives:** Describe the median initial dose and frequency of methadone and morphine for NAS. Compare dose adjustments, time to symptom relief, and taper complexity between groups. **Methods:** Retrospective study of neonates receiving enteral methadone or morphine for NAS over a 4-year period. Data collection included medication regimen, abstinence scores based on the Modified Finnegan Neonatal Abstinence Scoring Tool, and adverse events. Planned home taper complexity was assessed using the Medication Taper Complexity Score–Revised (MTCS-R). The primary outcome was initial opioid dose. Secondary outcomes included number of dose adjustments, time to symptom relief, and MTCS-R score. **Results:** Fifty neonates were initially treated for NAS with methadone (n = 36) or morphine (n = 14). The median initial dose was 0.09 mg/kg (range = 0.03–0.2) for methadone and 0.04 mg/kg (range = 0.03–0.4) for morphine. The most common initial dosing interval was q8h for methadone versus q3h for morphine. Number of dose adjustments and time to symptom relief were similar between groups. Median MTCS-R scores were similar between groups. There was no difference in adverse events between groups. Limitations included small sample size, preference toward methadone use, and variability of initial opioid dosing and titration. **Conclusions:** There was significant variability in initial doses of both agents. Neonates receiving methadone required less frequent dosing than morphine, which may result in easier administration and may allow for safer outpatient administration.

Keywords

pediatrics, neonatology, drug abuse, alcohol abuse, substance abuse, withdrawal, narcotics

Introduction

Neonatal abstinence syndrome (NAS) occurs in 55% to 94% of neonates exposed to opioid agents in utero.¹ Infants with NAS present with symptoms that can be classified into 3 separate categories: autonomic dysfunction (eg, diaphoresis, hypertension), gastrointestinal dysfunction (eg, vomiting, diarrhea), and central nervous system irritability (eg, tremors, agitation). The intensity of these symptoms can be scored using the Modified Finnegan Neonatal Abstinence Scoring Tool (Finnegan scores), the most widely used scale to assess symptoms.^{1,2} This tool is utilized by clinicians to determine the need for management.

Methadone and morphine are 2 of the most common opioid agonists used to treat NAS.^{1–4} Methadone's property as a *N*-methyl-D-aspartate (NMDA) receptor antagonist allows

it to block the actions of glutamate, an excitatory neurotransmitter.¹ When compared with morphine, methadone has a more predictable oral bioavailability and a longer half-life.^{3,4} Because limited data exist on the most appropriate initial dose of methadone and morphine, as well as duration of taper, for neonates with NAS, dosing regimens vary among institutions.^{5–11} The purpose of this study was to determine the median initial dose utilized (ie, mg/kg/day)

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for methadone and morphine and the impact that this had on time to symptom control based on Finnegan scores within the first 72 hours of initiation.

Methods

Study Design

This was a descriptive, retrospective, cross-sectional, institutional review board–approved study conducted in a tertiary care academic hospital with an 88-bed neonatal intensive care unit. Neonates were included if they were admitted between January 1, 2009, and December 31, 2013, and received enteral methadone or morphine within the first 14 days of life for the treatment of NAS. Potential subjects were identified through the electronic medical record (EMR), utilizing both Meditech (Medical Information Technology, Inc, Westwood, MA) and Crib Notes (Grand Rounds Software, LLC). Patients were excluded if they received treatment with either medication for pain or iatrogenic opioid abstinence syndrome (IOAS), or had incomplete medical records.

Study Objectives and Data Collection

Demographics included gestational age, weight, sex, and hospital length of stay. An attempt was made to identify the agent(s) to which the infant was exposed in utero through maternal reports or prenatal screens, as well as the infant's urine and meconium drug screen. The specifics of the NAS treatment regimen (ie, initial dose, dosage changes required, duration of therapy, and change in treatment agents) were collected.

Finnegan scores and symptoms were collected from the EMR from birth through the first 72 hours of treatment. Data pertaining to opioid adverse events were collected from the infant's progress notes. For the purpose of this study, an adverse event was defined as documentation of oversedation or respiratory depression noted in the EMR, administration of agent(s) to alleviate the adverse event (eg, naloxone for respiratory depression), or reduction in dosage of the opioid not attributed to the medication taper.

For neonates discharged with a methadone or morphine taper, the complexity of the planned outpatient taper was calculated using the Medication Taper Complexity Score–Revised (MTCS-R).¹² The MTCS-R considers 5 variables affecting taper complexity: (1) number of dosage/interval changes, (2) ease of measurement, (3) number of daily doses, (4) taper duration, and (5) concomitant taper with a benzodiazepine. Each variable is assessed on a scale of 1 to 5 points and is then weighted by a factor of 1 (taper duration), 2 (number of dose/interval changes, ease of measurement, and number of daily doses), or 3 (concomitant taper). A recent study demonstrated that the MTCS-R has good reliability and

validity and can be used to assess complexity of tapers.¹³ Based on the MTCS-R total score, tapers are classified as “easy regimens” (ie, 7–12.9), “medium regimens” (ie, 13–22.9), or “difficult regimens” (ie, 23–42).

The primary objective was to describe the initial median dose of enteral methadone and morphine (ie, mg/kg/day). A number of secondary comparisons were performed that included the number of dosing adjustments made within 72 hours following initiation of therapy and time from therapy initiation to symptom control (defined as 2 consecutive Finnegan scores <8). The incidences of opioid adverse events, as well as MTCS-R scores, were also compared between groups.

Statistical Methods

Descriptive and inferential statistics were utilized. Nominal data were assessed using the Fisher exact test. Continuous data were analyzed via 2-tailed Wilcoxon-Mann-Whitney tests given the nonnormal distribution of the data. Data management and analyses were conducted using Stata v13.1 (StataCorp, LP, College Station, TX) with the α set at $P \leq .05$.

Results

A total of 251 patients received enteral methadone ($n = 133$) or morphine ($n = 118$) during the study period. Thirty-six methadone-treated neonates were included in the analysis with the remaining 97 excluded due to IOAS treatment ($n = 93$) or incomplete data ($n = 4$). Only 14 neonates receiving morphine treatment were included for analysis with the remaining 104 patients excluded due to IOAS treatment ($n = 18$), use for pain or breakthrough withdrawal symptoms ($n = 80$), or incomplete data ($n = 6$).

Table 1 includes a comparison of demographics. There were no statistically significant differences between groups, including length of stay (10 days for methadone vs 11.5 days for morphine, $P = .19$). Eighteen (50%) neonates in the methadone group and 10 (71%) neonates in the morphine group had a confirmed positive drug screen, but this difference was not statistically significant ($P = .17$).

Table 2 describes the treatment regimens of both methadone and morphine. Although there were numerical differences in the mg/kg and mg per dose between groups, these differences are hard to assess given the expected differences in potency between the agents. Neonates who received morphine required more frequent dosing than the methadone group ($P < .001$). There was no difference in the median Finnegan scores on days 1 to 3 of therapy between groups. While there was no difference between groups in the time for symptoms to be controlled or in dose changes required in the first 72 hours, 4 (29%) of those initially receiving morphine were switched to methadone due to a perceived

Table 1. Demographics Based on Initial Opioid Agent Received (N = 50).

Variable	Methadone (n = 36), n (%) or Median (Range)	Morphine (n = 14), n (%) or Median (Range)	P
Age (gestational age in weeks)	37.9 (30.0-40.6)	36.9 (34-39.9)	.230
Sex			
Male	22 (61.1)	7 (50)	.475
Female	14 (38.9)	7 (50)	
Weight (kg)	2.9 (1.0-4.2)	2.5 (1.8-3.7)	.114
Length of stay (days)			
Total	10.0 (3.0-44.0)	11.5 (7.0-33.0)	.194
Prenatal exposure ^a			
Opioids	7 (19.4)	6 (42.9)	.235
Benzodiazepines	2 (5.6)	1 (7.1)	
Cocaine	0 (0)	1 (7.1)	
Cannabinoids	2 (5.6)	0 (0)	
Other	0 (0)	1 (7.1)	
Multiple exposures	7 (19.4)	1 (7.1)	
Negative	10 (27.8)	2 (14.2)	
Not obtained	8 (22.2)	2 (14.2)	

^aDerived from urine and meconium drug screen results.**Table 2.** Comparison of Methadone and Morphine Regimens (N = 50).

Variable	Methadone (n = 36), n (%) or Median (Range)	Morphine (n = 14), n (%) or Median (Range)	P
Initial dose			
mg	0.2 (0.1-0.7)	0.1 (0.06-0.8)	NA ^a
mg/kg	0.09 (0.03-0.2)	0.04 (0.03-0.4)	NA
Initial frequency			
q3h	0 (0)	9 (64.3)	<.001
q4h	0 (0)	3 (21.4)	
q6h	10 (27.8)	2 (14.3)	
q8h	14 (38.9)	0 (0)	
q12h	11 (30.6)	0 (0)	
q24h	1 (2.7)	0 (0)	
Initial dose per day			
mg	0.6 (0.2-2.0)	0.8 (0.4-3.2)	NA
mg/kg	0.27 (0.07-0.6)	0.32 (0.2-1.7)	NA
Dose changes in first 72 hours			
Increases	0 (0-1)	0 (0-1)	.988
Decreases	1 (0-2)	0.5 (0-2)	.627
Total	1 (0-2)	1 (0-2)	.622
Finnegan scores			
Day 1 ^b	6 (1-21)	7 (0-14)	.267
Day 2 ^c	5 (0-15)	4 (0-14)	.624
Day 3 ^d	4 (0-15)	3 (3-14)	.509
Time to symptom control (hours) ^{b,e}	6.8 (3.2-123.0)	9.1 (5.0-78.0)	.129
Oversedation	3 (8.3)	1 (7.1)	.889
Switch to alternate opioid	0 (0)	4 (28.6)	<.001

^aNot applicable; enteral methadone and morphine doses are not equivalent.^bData not available for all patients; methadone n = 28 and morphine n = 12.^cData not available for all patients; methadone n = 30 and morphine n = 11.^dData not available for all patients; methadone n = 27 and morphine n = 11.^eDefined as 2 consecutive Finnegan scores <8.

Table 3. Comparison of Planned Tapers for Outpatient Setting (N = 31).

Variable	Methadone (n = 27), n (%) or Median (Range)	Morphine (n = 4), n (%) or Median (Range)	P
Ending dose			
mg	0.1 (0.03-0.1)	0.1 (0.05-0.1)	NA ^a
mg/kg	0.03 (0.01-0.05)	0.035 (0.01-0.07)	NA
Ending dosing frequency			
q8h	1 (3.7)	1 (25)	.003
q12h	0 (0)	2 (50)	
q24h	26 (96.3)	1 (25)	
Ending dose per day			
mg	0.1 (0.03-0.3)	0.18 (0.1-0.2)	NA
mg/kg	0.03 (0.01-0.2)	0.05 (0.04-0.1)	NA
Duration (days)			
Inpatient	8.0 (3.0-33.0)	5.0 (5.0-12.0)	.208
Outpatient	16.0 (4.0-34.0)	11.0 (11.0-17.0)	.479
Total duration	24.0 (7.0-49.0)	20.5 (16.0-23.0)	.226

^aNot applicable; enteral methadone and morphine doses are not equivalent.

Table 4. Comparison of Medication Taper Complexity Scores for Outpatient Planned Tapers (N = 31).

Category	Methadone (n = 27), Median (Range)	Morphine (n = 4), Median (Range)	P
Number of dosage changes	2 (2-6)	2 (2-2)	.097
Ease of measurement	2 (2-10)	2 (2-10)	.939
Number of daily doses	8 (4-10)	10 (8-10)	.084
Taper duration	4 (1-8)	3 (3-4)	.586
Concomitant benzodiazepine taper	0 (0-6)	0 (0-0)	.417
MTCS-R Total Score	20 (9-29)	17.5 (15-25)	.906

Abbreviation: MTCS-R, Medication Taper Complexity Score–Revised.

lack of symptom control, leaving 10 children completing a morphine taper ($P < .001$). Only one of these was changed to methadone within the initial 72-hour period.

No patients developed respiratory depression within the first 72 hours after treatment was initiated. More methadone-treated ($n = 3$) neonates developed oversedation than morphine-treated patients ($n = 1$), but this was not statistically significant. The doses were decreased in all 4 patients, and no further interventions were made.

Sixty-eight percent ($n = 34$) were discharged home on a planned taper. Eighty-three percent ($n = 30$) of methadone-treated infants and 40% ($n = 4$) of morphine-treated infants were discharged home with a planned taper ($P < .001$). Specifics of the planned taper were missing for 3 methadone-treated patients and details were not included in the analysis in Table 3. There were no differences between groups in the total duration of treatment or in the length of planned taper.

Those finishing a methadone taper were likely to be on daily dosing, while those on a morphine taper were more likely to require at least twice daily dosing ($P = .003$).

Outpatient taper complexity using the MTCS-R data is described in Table 4 for the 31 patients with planned tapers documented in the EMR. There were no statistical differences between groups on either of the domains of the MTCS-R as well as the overall scores. Within the methadone tapers, 3 (11%) were classified as “easy regimens,” 19 (70%) as “medium regimens,” and 5 (18.5%) as “difficult regimens.” For the morphine tapers, none were identified as “easy regimens,” 3 (75%) were “medium regimens,” and 1 (25%) was a “difficult regimen.”

Discussion

The American Academy of Pediatrics (AAP) published guidelines for the management of neonatal drug withdrawal in 2012.¹ These guidelines include recommendations for NAS and IOAS in neonates and suggest that the first-line treatment for NAS would be oral methadone or morphine. The AAP provides initial dosing recommendations for methadone (0.05-0.1 mg/kg/dose every 6 hours) and morphine (0.04 mg/kg/dose every 3-4 hours), but there are

limited data to support these recommendations. This is the first study to compare time to NAS symptom control based on the initial dose of methadone versus morphine. As a result, we wanted to examine the outcomes of symptom control as measured by the Finnegan tool to assess the impact of the agent and initial dose selected.

Three previous studies have compared the use of methadone and morphine for NAS; however, 2 of these focused on hospital length of stay as their primary objective.^{6,14} Lainwala and colleagues⁶ conducted a retrospective study that included 46 neonates (methadone, $n = 17$; morphine, $n = 29$) that utilized a protocol for management of NAS. Patients receiving methadone were initiated on a loading dose of 0.1 mg/kg, and then an additional 0.025 mg/kg was administered every 4 hours for Finnegan scores >8 . The morphine group was initiated at 0.05 mg/kg, and this dose was increased by 0.03 mg/kg/dose every 4 hours for Finnegan scores >8 . Then the investigators calculated a maintenance dose based on the methadone or morphine dose received in the first 24 hours, and this maintenance dose was divided every 12 hours for methadone or 4 hours for morphine. The investigators found no statistical difference in the median length of stay between the methadone and morphine groups, 40 versus 36 days, respectively ($P > .05$). One significant limitation of this study is that the authors included patients receiving tincture of opium and oral methadone in the oral methadone group, converting their dose into morphine equivalents. It should be noted that tincture of opium is no longer recommended in the guidelines. It is difficult to compare this study with our own given that these patients completed their entire taper in the inpatient setting while approximately two thirds of our patients were discharged home on a taper.

Young and colleagues¹⁴ conducted a retrospective study of the length of stay in neonates with NAS receiving methadone ($n = 13$) versus morphine ($n = 13$). Patients were excluded if they were discharged home on NAS treatment. Their study also utilized a standard dosing protocol for morphine but not methadone. The morphine dose was determined by the neonate's most recent Finnegan score with initial doses ranging from 0.04 to 0.12 mg. Doses were increased by 0.02 to 0.06 mg for 2 consecutive Finnegan scores >8 . For those infants receiving methadone, symptoms were evaluated using the Neonatal Withdrawal Inventory score, and methadone dosing was weight-based; however, the investigators did not provide the mg or mg/kg dose. Because they used 2 different scoring tools to assess symptom control, it is difficult to compare our findings with this study. They also found a significant difference in hospital length of stay with those on methadone treatment staying 44.2 days and those on morphine staying 12.1 days ($P < .01$). As noted previously, these results may be reflective of the fact that a standardized approach was not used for the methadone group. The difference in length of stay seems

very surprising given that many clinicians have recommended a taper over 4 to 6 weeks.¹⁵ A mean treatment duration of approximately 2 weeks would likely not be adequate for NAS treatment. Additionally, the study does not provide details on postdischarge outcomes such as hospital readmissions or pediatrician visits for withdrawal episodes.

A third study by Brown and colleagues¹⁶ compared duration of treatment between infants with NAS treated with methadone ($n = 15$) or morphine ($n = 16$). This prospective, randomized trial included infants who were exposed to maternal methadone or buprenorphine. Randomization was stratified by the agent of exposure. This study utilized a standard treatment protocol in which patients in both groups were initiated on methadone or morphine doses of 0.05 mg/kg/dose every 4 hours for Finnegan scores ≤ 12 or 0.1 mg/kg/dose every 4 hours for scores >12 . Doses were increased in increments of 0.05 mg/kg every 12 hours as needed to control symptoms, to a maximum of 0.2 mg/kg. However, the authors did not report the number of infants initiated on each dose, maximum doses to achieve control, or Finnegan scores, which may limit comparison with our study. In addition, this protocol does not take into account differences in half-life and may have resulted in suboptimal dosing frequency for the morphine group. The authors found a significant difference in median duration of treatment, between the methadone and morphine group, 14 (interquartile range = 10-20) versus 21 (interquartile range = 15.8-29.5) days; $P = .008$. Patients in this study remained hospitalized for the duration of treatment. Our median duration of methadone was longer than reported in this study. This could be a result of less aggressive tapering in the out-patient setting.

Our institution uses the Finnegan scoring tool for assessment of symptoms and need for therapy initiation. We do not utilize a standardized protocol for dosing of either medication. The median mg/kg initial doses of morphine and methadone are comparable to the recommendations of the AAP. While not statistically significant, there was a shorter median time to symptom control favoring methadone (6.8 hours) over morphine (9.1 hours). Furthermore, 4 (29%) neonates were converted from morphine to methadone because of a perceived lack of symptom control. It is plausible that the study was underpowered to detect a difference in time to symptom control, and that the results may have differed if these patients continued on morphine. There was no difference in hospital length of stay or overall treatment duration between the 2 medications. In contrast to the previously mentioned studies, clinicians at our institution will frequently discharge neonates with NAS home on a taper after a thorough investigation of the home environment and caregiver understanding. As noted in the results, 68% of patients in this study were discharged home on a taper.

This is also the first study to assess complexity of the planned home tapers of methadone and morphine for NAS. There were no significant differences in the MTCS-R total

scores or other domains between groups. There was no difference in the median total taper duration between methadone (24.0 days) and morphine (20.5 days), $P = .226$. However, as expected, there was a significant difference in the ending dose frequency between methadone and morphine ($P = .003$). It is likely we found no difference between the MTCS-R total scores because of inadequate sample size, as there were only 4 patients receiving a morphine taper. Based on the MTCS-R scores, the majority (90%) of tapers for both agents were classified as “medium” or “difficult” complexity. At this time, there is a paucity of data supporting a clinical correlation of increased MTCS-R scores and negative clinical outcomes (eg, withdrawal, overdose) or caregiver burden. However, until further research can be conducted, these data indicate that treatment plans for neonates discharged home on NAS tapers may be very complex.

There were a number of study limitations, including the retrospective nature of this study. We collected data regarding the planned methadone and morphine tapers, but we were unable to determine if these tapers were followed by the caregivers and/or adjusted by their primary care physician once infants were discharged home. Neonates with NAS at our institution are not treated according to a standardized protocol and the selection of the agent and dosing were determined by the prescriber. In addition, pediatric pharmacy specialists were available to consult to help develop taper plans; however, not all prescribers utilized their services. There remains some controversy regarding the use of a standard dosing protocol for NAS management. First, there is no consensus on a specific protocol that should be used.¹ As with pain management, there is often significant interpatient variability in dosing requirements. There is emerging evidence for genetic variance in the μ -opioid receptor (OPRM1) and catechol-O-methyltransferase (COMT) genes that could result in different opioid requirements and response to therapy.¹⁷ As a result, a one size fits all approach may not be possible in all patients. This was a small study at a single academic institution, and we are limited to the available population. Our infants are more likely to be treated with methadone, so finding a cohort of morphine-treated infants during a comparable timeframe proved difficult.

Conclusions

There was a high degree of variability in initial doses of methadone and morphine for treatment of NAS in this study. Based on the longer half-life, neonates receiving methadone required less frequent dosing than morphine, which may lead clinicians to prescribe methadone over morphine for at-home tapers. Although these data provide some support for the use of methadone over morphine to treat NAS, future prospective studies should focus on the difference between

time to symptom resolution, caregiver adherence to the planned taper, and safety of outpatient tapers.

Authors' Note

Study design and preliminary results presented as a poster at the 48th Annual American Society of Health-System Pharmacists Midyear Clinical Meeting in Orlando, Florida, in December 2013. Final results presented as a poster at the American College of Clinical Pharmacy Annual Meeting in Austin, Texas, in October 2014.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Jamie Miller is on the speaker's bureau for Chiesi, USA, Inc. The rest of the authors declare no conflicts or financial interest in any product or service mentioned in the article, including grants, equipment, medications, employment, gifts, and honoraria.

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