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ORIGINAL RESEARCH ARTICLE

Oral Morphine Weaning for Neonatal Abstinence Syndrome at Home Compared with In-Hospital: An Observational Cohort Study

Lauren E. Kelly · David Knoppert · Henry Roukema · Michael J. Rieder · Gideon Koren

Abstract

Objective The objective of this observational study was to evaluate the safety and effectiveness of discharging stabilized neonates to complete their oral morphine weaning at home.

Study Design This retrospective cohort study evaluated neonates treated with oral morphine at two hospitals in London, Ontario, Canada. Neonates who completed their morphine wean in hospital were compared with neonates who completed their morphine wean following discharge from hospital (at home).

Results There were 80 neonates treated with oral morphine at two hospitals from 2006 to 2010. The majority (65 %, 52/80) of neonates completed their morphine weaning after hospital discharge and were significantly less likely to return to hospital for further withdrawal treatment (1/52 vs 4/28, $p < 0.05$). Neonates who were treated at home remained on morphine for more days (32 vs 19 days, $p < 0.01$).

Conclusions We present the first North American cohort of neonates weaned with morphine at home for neonatal abstinence syndrome (NAS). We found that more days on oral morphine resulted in fewer returns to hospital for continued withdrawal management. There was no evidence of increased effectiveness, measured by the number of returns to hospital for further NAS management with in-hospital weaning. The estimated cost savings of continued weaning upon discharge was approximately $11,000 per patient (Canadian dollars). While further prospective research is necessary, in some cases morphine weaning at home may present a safe and cost-effective strategy for NAS management.

Key Points

The number of neonates exposed to opioids in utero is increasing and up to 90 % will develop some signs of neonatal abstinence syndrome (NAS).

NAS is currently treated, among other drugs, with a taper of oral morphine in-hospital with a reported median length of stay of 30 days in the neonatal ward.

Oral morphine at home resulted in fewer returns to hospital for continued withdrawal management and there were no signals of increased effectiveness of in-hospital weaning.

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1 Introduction

According to the National Survey on Drug Use and Health, 4.4 % of pregnant women reported using illicit substances within the past 30 days [1, 2]. The incidence of opioid use is increasing, and roughly 90 % of drug abusing women are within the child-bearing age range [3, 4]. In the US, the use of prescription opioids (at least once during pregnancy) has been reported as high 14 % in 2014, which has increased by 2 % since 2011 [5]. Opioids, including methadone and heroin, have been shown to cross the placenta [6, 7] and in utero exposure can lead to neonatal withdrawal. Symptoms of neonatal abstinence syndrome (NAS) include central nervous system effects such as high pitch cry, irritability, tremor and seizures as well as gastrointestinal and metabolic disturbances [8]. Currently, oral morphine is the most frequently used first-line agent to treat NAS and, in severe or unresponsive cases, phenobarbital or clonidine is used as adjuvant therapy [9–11]. In order to ensure careful monitoring and treatment, neonates with suspected NAS are typically admitted to a neonatal intensive care unit (NICU). In the neonatal ward, the severity of NAS symptoms is monitored by using the Finnegan Scale and these scores guide morphine dosing [9, 10, 12]. Morphine is administered until the newborn's Finnegan scores are consistently low (below 8) and are no longer increasing. Gradual tapering of morphine is typically done in hospital and can last from several days up to months (median of 30 days), which has a very high cost of hospitalization that varies between centers [4, 13, 14].

In the UK, roughly 15 % of neonatal hospital units reported discharging neonates on morphine into the community to be managed at home by the primary caregiver [9]. This practice, however, has not been well documented in North America due to concerns surrounding the safety of use of morphine outside the hospital setting. A retrospective cohort by Backes et al. [15] reported that outpatient NAS weaning using methadone decreased hospital stay and substantially reduced the costs associated with NAS management. The objective of this study was to assess the safety and effectiveness of managing NAS at home with oral morphine. The primary outcome variable was a return to hospital following discharge for concerns related to neonatal abstinence syndrome. Secondary outcome measures included an estimation of cost savings.

2 Methods

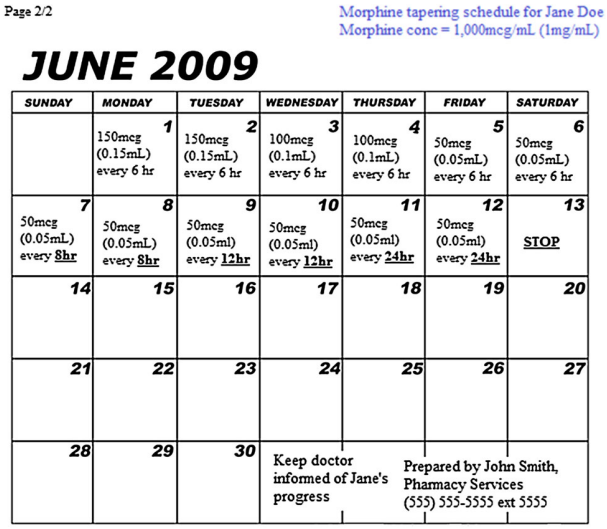
This observational study included all neonates with NAS receiving oral morphine between January 1, 2006 and December 31, 2010 at two academic health centers in London, Ontario, Canada. As per clinical routine, one institution kept most of its neonates in the NICU until morphine tapering was complete ('in-hospital' group) while the other center released stable neonates home with a weaning schedule ('at home' group). Neonates with NAS who required oral morphine were identified through pharmacy records and clinical databases. Anonymized data, from paper and electronic patient records, included the number of days the neonate remained in hospital, oral morphine dosing, Finnegan Scale scores, and concomitant medication use. Demographic and clinical details were also collected. The number of hospital visits for further withdrawal treatment, emergency room visits, specialist referrals and outpatient/in-patient appointments were collected from electronic patient records for the first 2 years of life. The number of in-patient appointments in the first year excluded the initial NAS treatment. Return to hospital for withdrawal management was based on pediatrician/neonatologist assessment upon return to the Emergency Room based on Finnegan Scale Scores.

In both institutions, neonates were treated in accordance with the same non-pharmacologic measures and morphine protocol for the treatment of NAS (Appendix 1, electronic supplementary material [ESM]). Adjuvant therapy was administered based on the decision of the clinical team and varied between centers. Infants with suspected NAS were scored on the Finnegan Scale every 2 hours for the first 48 hours and every 4 hours thereafter. Scores reflected the infants' activity over the previous 4 hours and morphine therapy was initiated for two scores >8 or one score >11. Morphine was started orally at a dose of 240–480 μg/kg orally every 6 hours, unless intravenous (IV) access was already present, in which case an initial morphine loading dose of 50 μg/kg was given over at least 5 minutes and a continuous morphine infusion of 5–10 μg/kg/hour was administered. The full weaning protocol can be found in Appendix 1 (see ESM). Continuous infusion was used in accordance with the institutional protocol for ease of adjustment by the nursing staff. IV morphine was only used if an intravenous port was present for another (non-NAS-related) reason and did not reflect the majority of cases. If, following morphine initiation, the next score was above 8, the dose was increased by 2.5 μg/kg/hour. Medication doses in hospital were not changed for scores of 6 or 7. If the score fell below 5, the dose was reduced by 10–20 % every 48 hours. If multiple drug exposure was suspected (e.g., sedatives, alcohol, barbiturates) or NAS was nonresponsive to morphine, single doses of phenobarbital, clonidine and/or clonazepam were given as per the institution practice. In severe cases, 10 mg of phenobarbital was administered twice daily with clonidine. The term 'nonresponsive' was assigned when NAS Finnegan scale scores continued to increase following morphine administration. At one institution, neonates presenting as medically stable

with persistently low Finnegan Scale scores (below 8) for a minimum of 24 hours were considered for discharge. For the few neonates who remained on IV, they were first converted to oral morphine at a rate of 2× the intravenous dose. Conversion to oral morphine occurred at a minimum of 48 hours prior to discharge to ensure adequate bioavailability was tolerated.

Discharging neonates home to complete the oral morphine tapering was only considered if social stability was demonstrated and caregivers were judged to be competent in administering the morphine doses. This decision was made by the team of doctors, nurses and social workers caring for the child. Social stability included a permanent residence, available arrangements for follow-up with a pediatrician, and family/social support network. Caregivers were trained on morphine administration by the pharmacy team. This included a consultation with a clinical pharmacist, practicing morphine draw/dispense with an oral syringe and training on calculating the amount of morphine required. Specific dosing calendars were prepared by the pharmacy team for each individual neonate upon release home. A sample weaning calendar is presented in Fig. 1. In all cases, caregivers were educated regarding the symptoms of withdrawal. Caregivers were encouraged to return to the hospital with any concerns. Caregivers of children weaned in hospital were also provided with a case worker and a public health nurse. At both sites, non-pharmacologic interventions included minimizing lighting and stimulation, speaking softly, swaddling, and applying ointment cream (nystatin, zinc oxide) to the perianal area following frequent stools. Parents continuing the morphine weaning at home were encouraged to continue these non-pharmacologic interventions after discharge. This retrospective data analysis protocol was approved by the Research Ethics Board at Western University and treatment effectiveness was assessed by the number of hospital readmissions for NAS management.

Cost effectiveness was a secondary outcome. The average daily cost of a bed in the NICU in London Ontario in 2013 was over $1,800/night (Canadian dollars; London Health Sciences Centre, personal communication). This value was used to estimate the cost savings of continuing oral morphine weaning post-hospital discharge. Comparisons of non-parametric continuous data were analyzed using a Mann–Whitney *U* test. Normally distributed data were analyzed using the Students unpaired *t* test. Proportions were compared by Fischer Exact test and linear regression was used to assess correlations between variables.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Morphine tapering schedule for Jane Doe
Morphine conc = 1,000mcg/mL (1mg/mL)

JUNE 2009

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
	1 150mcg (0.15mL) every 6 hr	2 150mcg (0.15mL) every 6 hr	3 100mcg (0.1mL) every 6 hr	4 100mcg (0.1mL) every 6 hr	5 50mcg (0.05mL) every 6 hr	6 50mcg (0.05mL) every 6 hr
7 50mcg (0.05mL) every 8hr	8 50mcg (0.05mL) every 8hr	9 50mcg (0.05ml) every 12hr	10 50mcg (0.05ml) every 12hr	11 50mcg (0.05ml) every 24hr	12 50mcg (0.05ml) every 24hr	13 STOP
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	Keep doctor informed of Jane's progress		Prepared by John Smith, Pharmacy Services (555) 555-5555 ext 5555	

Fig. 1 Example of an oral morphine weaning calendar provided to caregivers. To protect their confidentiality the names and contact number have been changed

3 Results

In a 4-year period, 80 neonates were treated with oral morphine for NAS in the two institutions. There were 45 neonates born at Institution 1, 96 % of whom (43/45) continued weaning post-hospital discharge. At Institution 2 there were 35 babies treated for NAS, of whom 26 % (9/35) completed at-home oral morphine weaning. A total of 52 neonates who completed their oral morphine weaning at home, and 28 who remained in hospital until weaning was completed were analyzed (Table 1). Preterm births (<37 weeks) occurred in 15 % of all cases (12/80) and mothers' median age was 26 years (17–41 years). Gestational age did not correlate with the length of stay in hospital ($r^2 = 0.0038$). In both groups, two-thirds of the babies were delivered vaginally (at-home group 63 % [33/52], in-hospital group 71 % [20/28]) without complications.

The majority of mothers (65 %, 52/80) participated in a methadone maintenance program at the time of delivery. The most common reason for methadone use was addiction to slow-release oxycodone (Oxycontin®) (47 %), followed by oxycodone plus acetaminophen (Percocet®) (26 %), heroin (23 %) and morphine (4 %). Cigarette smoking was reported by 82 % of all mothers; no difference was seen between the two groups. Illicit drug use (marijuana, cocaine, opioids) was highly prevalent in both groups (at-home group 53 % [24/45], in-hospital group 38 % [10/26]) as evidenced by women's reports or positive urine screen. The Children's Aid Society (CAS), a public child welfare agency, apprehended 34 % of all neonates into custody.

In neonates who completed oral morphine weaning at home, the median number of days in hospital was significantly smaller (16 days [3–54] vs 22 days [7–51], $p = 0.042$). The neonates who continued morphine at home remained in hospital for a median of 6 fewer days than those who weaned in hospital. Fewer babies had to

Table 1 Demographic characteristics of neonates treated for NAS with oral morphine at-home and those who remained in-hospital until the morphine taper was complete

	At-home weaning ($N = 52$)	Hospital weaning ($N = 28$)	P value
Maternal age	26 (17–36)	25 (18–41)	NS
Premature (<37 weeks)	11 % (6/52)	21 % (6/28)	NS
Low birth weight (<2500 g)	13 % (7/52)	18 % (5/28)	NS
Smoking	79 % (30/38)	88 % (14/16)	NS
Cocaine	34 % (10/29)	21 % (3/14)	NS
Marijuana	41 % (12/29)	29 % (4/14)	NS
Benzodiazepines	21 % (6/29)	29 % (4/14)	NS
Antidepressants	21 % (6/29)	29 % (4/14)	NS
Initiated breastfeeding in hospital	41 % (17/41)	33 % (7/21)	NS
Father involved in care	72 % (28/39)	75 % (15/20)	NS
Received appropriate prenatal care[a]	25 % (7/28)	47 % (9/19)	NS
Some/minimal prenatal care	35 % (10/28)	11 % (2/19)	NS
Did NOT receive any prenatal care	40 % (11/28)	42 % (8/19)	NS
CAS apprehensions	31 % (16/52)	39 % (11/28)	NS

Data are presented as median (range) or percent of total. The Mann–Whitney U test was used for continuous variables and Fischer Exact for the categorical data. The level of statistical significance was set at 0.05. Denominators vary as all data points were not available for some mothers

[a] 'Appropriate prenatal care' indicates mothers who were followed consistently throughout their entire pregnancy

CAS Children's Aid Society, *NS* not significant

return to hospital for withdrawal treatment in those weaned at home (2 % [1/52] vs 14 % [4/28], $p = 0.044$) compared with those completed their wean in hospital (Table 2). Neonates weaned at home were on oral morphine for significantly more days ($p < 0.001$) and were more likely to have had phenobarbital, clonidine and/or clonazepam while in the NICU ($p = 0.003$). No patients were sent home on adjuvant therapy. When adjuvant therapy was prescribed, the majority of cases only required a single dose (59 %, 10/17). A further 24 % (4/17) required two doses, 6 % (1/17) required three doses and two neonates (11 %) required seven doses of adjuvant therapy.

Although there was no difference seen in the number of NAS scores above 8, neonates weaned at home were significantly more likely to receive an adjuvant therapy in the NICU, indicative of either more severe withdrawal or differences in group practice. Breastfeeding data were available for 61 mother–infant pairs, 40 % of which initiated breastfeeding while in hospital (Table 1). Breast-fed neonates had significantly fewer NAS scores above 8 (median 10 [0–77]) compared with non-breastfeeding neonates (median 16 [1–85]), $p = 0.02$. The number of emergency room visits, in-/out-patient appointments and specialist referrals in the first and second years of life are displayed in Table 3. There was one case of sudden unexpected infant death syndrome in the cohort of children weaned at home attributed to bed-sharing and the presence of an unsafe sleeping environment. Sending neonates home to complete their morphine weaning was associated with a median of 6 fewer days in hospital and provided a potential cost saving of approximately $560,200 ($11,000 per neonate).

4 Discussion

This study, to the best of our knowledge, is the first to describe a North American cohort of neonates who were treated for NAS with morphine outside of a hospital setting. In neonates who were weaned at home, we did not detect an increased risk of emergency room visits or in-/out-patient appointments. The rate of return to hospital for further withdrawal management was significantly lower in those infants weaned at home as compared with those who remained in hospital, suggesting that a slower tapered wean may actually be advantageous in managing NAS. At-home oral morphine weaning may offer several potential advantages including a slower morphine wean, increased mother-infant bonding time, and decrease in hospital costs [16]. Continuing oral morphine weaning post-hospital discharge was associated with potential cost savings of $11,000 per neonate, representing half a million dollars for this small cohort. To better estimate the costs of savings, the more common need for re-hospitalization of neonates treated in hospital should be included. There were no significant differences in the total number of emergency room visits, specialist referrals, or in-/out-patient appointments between those weaned at home and in hospital. As the

Table 2 Clinical response of neonates treated with weaning doses of oral morphine at home and those who remained in hospital until the morphine taper was complete

	At-home weaning ($N = 52$)	Hospital weaning ($N = 28$)	P value
No. days in NICU	16 (3–54)	22 (7–51)	0.04
No. times NAS score was over 8	12.5 (0–132)	10 (0–71)	0.13
No. mothers on methadone	65 % (34/52)	64 % (18/28)	1.00
Methadone dose mg/day	80 (20–115)	80 (25–130)	0.77
Babies receiving adjuvant therapy[a]	31 % (16/52)	4 % (1/28)	<0.01
Return to hospital for withdrawal treatment	2 % (1/52)	14 % (4/28)	0.04
Total number of days on oral morphine	32 (12–117)	19 (6–48)	<0.01

Data are presented as median (range) or percent of total. The Mann–Whitney U test was used for continuous variables and Fischer Exact for the categorical data. The level of statistical significance was set at 0.05

[a] Adjuvant therapy included a single dose of phenobarbital, clonidine or clonazepam given in the NICU

NAS neonatal abstinence syndrome, *NICU* neonatal intensive care unit

Table 3 The median number of emergency room visits, specialist referrals and in-/out-patient appointments from birth until September 1, 2013 as required by neonates weaned at home and those who completed their morphine taper in hospital. The number and type of specialist referrals is also displayed

	At-home weaning ($N = 52$)	Hospital weaning ($N = 28$)
No. times as in-patient in year 1	0 (0–3)	0 (0–3)
No. times as in-patient in year 2	0 (0–1)	0 (0–2)
No. out-patient appointments in year 1	0 (0–21)	0 (0–31)
No. out-patient appointments in year 2	0 (0–8)	0 (0–11)
No. visits to ER in year 1	1 (0–8)	1 (0–6)
No. visits to ER in year 2	1 (0–4)	0 (0–6)
Percentage of children referred to at least one specialist	46 % (24/52)	36 % (10/28)
Specialist referrals (n)		
Allergy/immunology	2	0
Cardiology	3	1
Developmental follow up	5	3
Endocrinology	1	0
Gastroenterology	1	0
Genetics	2	1
Hematology	2	1
Nephrology	2	1
Neurology	3	0
Ophthalmology	4	1
Otolaryngology	3	2
Physiotherapy	1	2
Respirology	1	1
Speech language pathology	3	0
Surgery	4	1
Urology	3	1

Initial NAS treatment was excluded. Year 1 represents the first 12 months of the child's life and excludes return to hospital for further withdrawal management. Year 2 represents months 12–24

ER emergency room, *NAS* neonatal abstinence syndrome

number of infants exposed to opioids with subsequent withdrawal symptoms increases globally it is important to assess safe and cost-effective treatment options.

Our study documents that completing morphine weaning at home may take longer than treatment completed with an exclusively in-hospital morphine wean. The fact that

significantly more in-hospital babies needed to be re-hospitalized suggests that the in-hospital weaning may have been too aggressive, in an attempt to save hospital time. Differences in the use of adjuvant therapy may have resulted from variability in institutional protocols as 83 % of neonates weaned at home were from one institution. Furthermore, neonates weaned at home would have received standard regimented morphine taper as opposed to those who weaned in hospital, whose regimen would have been at the clinical care team's discretion.

There was one fatality in the group of neonates weaned with morphine at home. A previous study by our group suggested that there is no increased risk for mortality under the age of 1 year among infants exposed to methadone in utero [17]. Fatalities attributed to sudden unexpected death in infancy (SUDI) in neonates whose NAS treatment was completed in-hospital have been previously described [17]. There is therefore limited evidence to suggest that at-home oral morphine weaning increased the risk for SUDI.

In this cohort, the reported use of benzodiazepine (33 %) was somewhat lower than previous reported rates of 50 %; however, cocaine and marijuana incidence are similar to rates reported in another cohort [9]. Studies suggest that cocaine increases the severity and frequency of NAS symptoms in those abusing opioids in pregnancy [18]. Furthermore, benzodiazepine use has been shown to increase the length of NAS treatment as symptoms of benzodiazepine exposure often confound NAS [4]. Concomitant use of cocaine and/or benzodiazepines was similar between groups and therefore is likely not a confounding factor for determining length of stay in this cohort. Breastfeeding was significantly associated with a less severe opioid withdrawal course, a finding that has been confirmed by previous studies [19]. As well as providing optimal nutrition, breast milk can provide small amounts of maternal opioid to mitigate withdrawal symptoms. Breastfeeding is recommended and should be encouraged for HIV-free patients on a methadone maintenance program, whether weaned in hospital or at home.

This study has several limitations that require acknowledgement. This report reflects therapy in practice and was not a randomized trial; hence, uncontrolled confounders could have affected the results. The fact that the characteristics of the mothers and their opioid use did not differ between the groups suggests that such bias, if it exists, is not major. Secondly, our study is small and lacks developmental follow-up. Many substance-abusing mothers do not have permanent addresses or cellular phones, which made follow-up difficult. Furthermore, due to the retrospective nature of this study, we were unable to obtain all data, such as child nutrition and social environment. The morphine-weaning protocols were the same at both institutions; however, the use of adjuvant therapy was at the discretion of the attending physician. A limitation of this retrospective study is that the criteria for adjuvant therapy were not specified a priori leading to variability in adjuvant therapy use between centers. The small sample size may have resulted in an inadequate power to support an increased length of stay in hospital for premature and/or low-birthweight babies. A further limitation includes the data source for the number of emergency room visits, in-patient appointments, and hospital visits, which were assessed using electronic patient records and did not include general pediatrician care or specialist appointments outside of the hospital networks. The number of outpatient appointments included pediatrician appointments at both hospital sites. To address these limitations, our findings should be corroborated by a large, prospective, randomized trial before concrete recommendations regarding at-home oral morphine weaning can be made. An important consideration for readers is that NOT all babies will be candidates for at-home oral morphine weaning, mainly due to social factors which are not compatible with caregiver morphine administration.

5 Conclusions

In summary, this observational study assessed the safety of neonatal oral morphine weaning at home for the management of NAS following in utero opioid exposure. A significantly lower return-to-hospital rate for further withdrawal treatment was identified in neonates weaned at home. These data suggest that training caregivers and sending neonates home with an oral morphine weaning calendar may present a safe and cost-effective measure for treating NAS.

Financial Disclosure The authors of this article declare that they have no financial relationships to disclose pertinent to this article.

Conflict of interest LE Kelly, D Knoppert, H Roukema, M Rieder and G Koren have no relevant conflicts of interest to declare.

Contributor's Statement Lauren Kelly is the first author who designed the study, collected and analyzed the data. David Knoppert was the pharmacy team lead and was responsible for overseeing the morphine-weaning calendars. Dr. Henry Roukema is a neonatologist directly involved in patient care at both centers. Dr. Michael Rieder and Dr. Gideon Koren were responsible for the study design, manuscript revisions and study oversight. All authors critically reviewed the manuscript and approved the final draft for submission.

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