Evaluation of the appropriate weaning of neonatal morphine solution (NMS) in the treatment of neonatal abstinence syndrome (NAS) and its effect on length of stay (LOS)

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BACKGROUND

- Neonatal Abstinence Syndrome (NAS) refers to the withdrawal syndrome experienced by neonates born to women who use drugs of abuse (opiates, benzodiazepines, barbiturates, etc.) or who have been treated with methadone for opioid dependency during pregnancy
  - Greater than a three-fold increase in the rate of newborns with NAS was seen between 2000 and 2009 in the United States with an estimated 13,539 newborns with NAS in 2009[1]
  - In 2009, the mean total hospital charges for NAS was $53,400 contributing to an estimated total cost of $720 million nationwide[1]
  - Approximately 5.9% of pregnant women abused illicit drugs from 2011 to 2012[2]
  - Of neonates with intrauterine exposure to opiates, it is estimated that 55-94% will experience withdrawal symptoms[3]
- The most commonly used tool to assess severity of NAS is the modified Finnegan's Scoring System which is based on symptoms including tremors, high-pitched cry, sneezing, increased muscle-tone, poor sleep, loose stools, vomiting, etc.
  - A score of ≥8 is suggestive of in utero opioid exposure as 95% of non-exposed newborns score ≤7[4]
- Many agents have been studied for the treatment of NAS including clonidine, phenobarbital, and buprenorphine, however, opioid-based treatments are well-studied and have the best outcomes
  - Neonatal morphine solution (NMS) is the most commonly used agent in the treatment of NAS due to established pharmacokinetic data and documented efficacy and safety in the neonatal population
  - Morphine should be dosed every three to four hours and requires close monitoring
  - NMS should be weaned slowly by 10-20% of the total daily dose, as tolerated, and can contributes to prolonged hospital courses
- Several studies have shown strict adherence to a protocol when treating NAS has improved outcomes and decreased length of stay (LOS); however, there is limited published data evaluating the process and criteria for weaning neonates and infants off NMS
- NAS management at our institution:
  - NMS (0.4mg/mL) 0.4mg/kg/day divided every 3 to 4 hours
  - Treatment control is defined as achieving an average Finnegan score of <8
  - Dose weaning occurs if the total of three consecutive scores is <24 or if deemed clinically appropriate

OBJECTIVES

Primary objective

- To evaluate the relationship between missed opportunities to wean (MOTW) NMS in NAS patients and LOS

Secondary objectives

- To evaluate the relationship between MOTW NMS in NAS patients and length of treatment (LOT)
- To identify opportunities for improving NAS patient care and to validate the need for revision of current protocol for treating NAS patients in the intensive care nursery (ICN)

Figure 1: Modified Finnegan's NAS Scoring System

SYSTEMS	SIGNS AND SYMPTOMS	SCORE	AM 2	4	6	8	10	12	PM 2	4	6	8	10	12	DAILY WT.
CENTRAL NERVOUS SYSTEM DISTURBANCES	High Pitched Cry	2													
	Continuous High Pitched Cry	3													
	Sleeps < 1 Hour After Feeding	3													
	Sleeps < 2 Hours After Feeding	2													
	Hyperactive Moro Reflex	2													
	Markedly Hyperactive Moro Reflex	3													
	Mild Tremors Disturbed	2													
	Moderate Severe Tremors Disturbed	3													
	Mild Tremors Undisturbed	1													
	Moderate Severe Tremors Undisturbed	2													
	Increased Muscle Tone	2													
	Excoriation (specify area): _____	1													
	Myoclonic Jerks	3													
	Generalized Convulsions	3													
METABOLIC VASOMOTOR/ RESPIRATORY DISTURBANCES	Sweating	1													
	Fever < 101°F (39.3°C)	1													
	Fever > 101°F (39.3°C)	2													
	Frequent Yawning (> 3-4 times/interval)	1													
	Mottling	1													
	Nasal Stuffiness	1													
	Sneezing (> 3-4 times/interval)	1													
	Nasal Flaring	2													
	Respiratory Rate > 60/min	1													
	Respiration Rate > 60/min with Retractions	2													
GASTROINTESTINAL DISTURBANCES	Excessive Sucking	1													
	Poor Feeding	2													
	Regurgitation	2													
	Projectile Vomiting	3													
	Loose Stools	2													
	Watery Stools	3													
SUMMARY	TOTAL SCORE														
	SCORER'S INITIALS														
	STATUS OF THERAPY														

Adapted from Finnegan L. Neonatal abstinence syndrome: assessment and pharmacotherapy. Neonatal Therapy: An update, F. F. Rubaltelli and B. Granti, editors. Elsevier Science Publishers B. V. (Biomedical Division). 1986: 122-146

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METHODS

Inclusion criteria

- All patients treated with oral NMS in the ICN for NAS from July 1, 2012 through June 30, 2013

Exclusion criteria

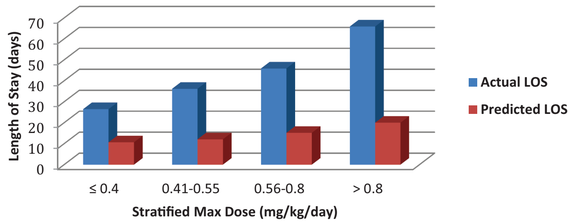
- Patients not tolerating oral medications
- Patients discharged prior to completion of NMS treatment

Study design

- Retrospective chart review of data obtained from electronic medical record of patients receiving oral NMS for the treatment of NAS during the study period
  - Data collected included patient date of birth, birth weight, individual and average modified Finnegan scores, scheduled and rescue NMS doses, adjunct medications, MOTW, LOS, and LOT
  - The average NAS score was recorded for data analysis for each day of treatment; defined as a 24-hour period from 8:00am to 7:59am the following day
  - A MOTW was defined as a 24-hour average modified Finnegan score <8 with no corresponding NMS dose reduction

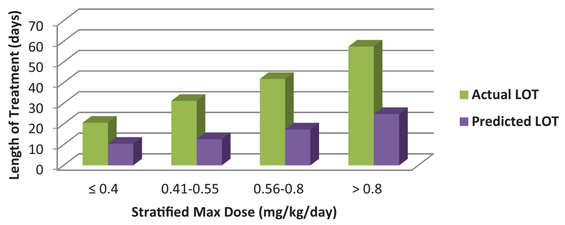
RESULTS

Figure 2: Comparison of the average **actual LOS** to the average **predicted LOS**



*The predicted LOS was calculated using a MOTW value of two in order to account for a 48 hour period before weaning can begin and the average max dose for each group

Figure 3: Comparison of the average **actual LOT** to the average **predicted LOT**



*The predicted LOT was calculated using a MOTW value of two in order to account for a 48 hour period before weaning can begin and the average max dose for each group

- A multiple regression modelwas used to determine that MOTW and MAX DOSE were positively correlated with LOS *(p<0.05)*. MOTW and MAX DOSE can account for 85% of the variance in LOS. The multiple regression model was used to evaluate the relationship between MOTW and MAX DOSE to predict LOS. The model predicted that for every increase of 1 MOTW, the LOS is increased by 1.706 days *(p<0.001)*.
  - LOS = 0.87 + 1.706(MOTW) + 15.974(MAXDOSE)
- A multiple regression model was used to determine that MOTW and MAX DOSE were positively correlated with LOT *(p<0.05)*. MOTW and MAX DOSE can account for 90.7% of the variance in LOT. The multiple regression model was used to evaluate the relationship between MOTW and MAX DOSE to predict LOT. For every increase of 1 MOTW, the LOT is increased by 1.254 days *(p<0.001)*.
  - LOT = -1.871 + 1.254(MOTW) + 24.539(MAXDOSE)
- One patient was excluded from the analysis due to the use of intravenous morphine prior to NMS and was later transferred to another institution prior to completion of NMS therapy

Table 1: Baseline demographics

Patient Population	NAS patient (n=47)
Male, n (%)	23 (49)
Birth Weight (kg), median (IQR)	2.8 (2.35-3.24)
Max Dose (mg/kg/day), median (IQR)	0.59 (0.4 -0.79)
LOS (days), median (IQR)	40 (29-51)
LOT (days), median (IQR)	35 (22-48)
Adjunct Phenobarbital, n (%)	6 (13)

CONCLUSION

When accounting for the maximum dose, the LOS for patients with NAS can be significantly decreased by reducing missed wean opportunities. By confirming that MOTW and LOS are related using statistical analysis, we are able to validate the necessity of a revised protocol for the management of NAS with NMS. After completion of the study, it is evident that there is room for improvement in terms of weaning NAS patients off of NMS. The study results confirm that strict adherence to a protocol, alone, can contribute to a reduction in LOS and consequently decreased NAS-associated hospital costs. There are several limitations to the study including the retrospective analysis, small patient population, unknown in-utero exposure, breastfeeding during NAS treatment, inconsistency in nursing NAS documentation, and unknown gestational age. A future study is warranted to show the economic impact of NAS-associated hospital costs and how they relate to LOS, LOT, and adherence to a protocol.

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DISCLOSURES

Authors have nothing to disclose