Study Protocol
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Title
Clonidine versus Phenobarbital as Adjunctive Therapy

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Location
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Objective
To compare clonidine versus phenobarbital as adjunctive therapy in those infants who have failed monotherapy with morphine sulfate for neonatal abstinence syndrome (NAS).

Background/Significance/Intervention to be studied
Neonatal abstinence syndrome (NAS) is the result of sudden discontinuation of substances used or abused by the mother during pregnancy after delivery[6]. Opioids are the most common of these substances. The signs and symptoms associated with NAS include disturbances in the gastrointestinal, autonomic and central nervous systems[7]. Up to 80% of infants will fail behavioral intervention and require pharmacologic treatment to control the symptoms associated with NAS[6]. The American Academy of Pediatrics (AAP) supports the use of opioids as first-line pharmacotherapy for NAS[6]. Morphine sulfate is most commonly used in the United States for the treatment of NAS[8]. Despite appropriate treatment with opioids, many infants will often require adjunctive or second-line therapy. Phenobarbital and clonidine are both considered as adjunctive therapy for the treatment of NAS. Phenobarbital is considered the drug of choice for nonopiate withdrawal[6] and is often used as adjunctive therapy in infants experiencing withdrawal due to maternal polysubstance abuse. However, there are concerns about the long-term neurodevelopment and exposure to alcohol in infants who receive phenobarbital. Studies have found clonidine to be an effective adjunctive therapy while a few recent studies have evaluated clonidine as initial therapy for the treatment of NAS[2]. The limited data and concern for potential hypotension along with rebound hypertension may limit its use. Studies have compared morphine sulfate versus clonidine as initial therapy[2] and clonidine versus phenobarbital as in combination with morphine sulfate as initial therapy[1]. However, there are no current studies comparing clonidine and phenobarbital as adjunctive therapy in infants who have failed monotherapy with morphine sulfate for the treatment of NAS.

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Study Endpoints

The primary endpoint of this study is the length of morphine sulfate therapy ~~time from initiation of adjunctive therapy until hospital discharge in the two groups~~. Secondary end points include time from initiation of adjunctive therapy until hospital discharge in the two groups, length of stay, ~~length of morphine sulfate therapy~~, percentage of patients requiring triple therapy, safety and readmission rates.

Number of subjects

Approximately 50 patients will be enrolled in the study.

Inclusion / Exclusion Criteria

Inclusion Criteria

Infants greater than or equal to 35 weeks admitted to the neonatal intensive care unit (NICU) who have failed monotherapy with morphine sulfate will be eligible for enrollment in the study. Infants considered to have failed morphine sulfate therapy are those whose dose exceeds 0.15 mg (0.4 mL) q3h or have failed two attempts at weaning after initial stabilization.

Exclusion Criteria

Infants who develop NAS due to iatrogenic causes (analgesia or sedation), are unable to take oral medications at any point during their treatment or are in the custody of the department of child protective services with no legal guardian identified at the time of enrollment will be excluded.

Recruitment Methods

Subjects will be identified through medical record screening, contact with investigators patients in the clinical setting and referral from non-investigators (physicians, nurse practitioners or physician assistants).

Consent process

- An informed consent will be obtained from the parent or legal guardian for all infants enrolled in the study.
- A notice of research will be provided with the admission documents to the parent/legal guardian of all infants being admitted for NAS. If the patient fails monotherapy, the informed consent interview will be conducted and consent obtained over the phone. The full signed consent will be left at the patient bedside and given to the parent/legal guardian at their next visit to the hospital.

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- The informed consent interview will be conducted over the phone by study personnel if the legal guardian is not present at the time it is determined that an adjunctive agent is needed to control the study participants' symptoms of NAS. Documentation of consent by the legal guardian will be noted by the study investigator and a witness. A copy of the informed consent will be left at the subject bedside to be provided to the legal guardian at the next visit to the NICU.

Methodology

Study Design

This study will be a prospective, single-site, randomized, open-label study with institutional review board (IRB) approval. The study will be conducted in the neonatal intensive care unit (NICU) at the University of Tennessee Medical Center.

Study Treatment

Infants who have failed monotherapy with morphine sulfate and have documented informed consent will be randomized to receive phenobarbital (20 mg/kg load, then 5 mg/kg/day divided q12h) or clonidine (6 mcg/kg/day divided q3h). The phenobarbital and clonidine suspensions are 4 mg/mL and 10 mcg/mL, respectively. Study agents will be titrated to achieve control of symptoms (previous 24-hour average FS less than or equal to 8). The phenobarbital dose will be adjusted to obtain a desired trough of 25 to 30 mcg/mL. Levels will be obtained on Day 6, then weekly thereafter. Infants with a trough less than 25 will receive an adjusted load of phenobarbital 1 mg/kg for every 1 mcg/mL increase from obtained level to achieve a desired level of 25 mcg/mL and a change in the maintenance dose using a ratio of desired to measured phenobarbital level. Clonidine will be escalated by 1.5 mcg/kg/day every 24 hours (maximum 12 mcg/kg/day) to achieve control of symptoms. Blood pressure (BP) is documented prior to each clonidine administration. If hypotension occurs while receiving clonidine, the current dose will be held. If more than 2 clonidine doses are held in the previous 24 hours the total daily dose will be decreased by 1.5 mcg/kg/day. After control of symptoms, morphine sulfate will be weaned by 0.02 mg (0.05 mL) every 24 hours as tolerated until off. Morphine sulfate will be weaned if symptoms are controlled, and no rescue doses are required in the previous 24 hours. A rescue dose of morphine sulfate 0.02 mg (0.05 mL) may be given every 3 hours for consecutive FS greater than or equal to 11 while morphine sulfate is being weaned and after discontinuation. Infants who experience return of symptoms and require more than 2 rescue doses in the preceding 24 hours after discontinuing morphine will be placed back on the 0.02 mg (0.05 mL) until symptoms are controlled. Once symptoms are again controlled, a second attempt to discontinue morphine sulfate will occur. After morphine sulfate has been discontinued for 24 hours and symptoms are still controlled, the study agent can be weaned. Clonidine will be weaned by 25% (based on the dose at time of morphine sulfate discontinuation) every 24 hours over 72 hours. Infants will be observed for return of symptoms and rebound hypertension for 48 hours prior to discharge. Blood pressure will be measured every shift for 48 hours after discontinuation of clonidine. Infants who experience rebound hypertension or fail to maintain control of symptoms after

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discontinuation of clonidine will be placed back on the last effective dose until symptoms are controlled. Once symptoms are controlled, weaning will resume. Infants receiving phenobarbital will also be observed for 48 hours after the discontinuation of morphine sulfate prior to discharge. Phenobarbital will be weaned as an outpatient based on the standard taper used in the NICU for over 5 years (Table 1).

Table 1: Standard phenobarbital taper based on dose at discharge

Phenobarbital dose on day of discharge	*Standardized phenobarbital taper initiated upon discharge*
5.1 to 7 mg every 12 hours	6 mg two times a day for 1 week, then 4 mg two times a day for 1 week, then 2 mg two times a day for 1 week, then 2 mg once a day for 1 week, then stop
7.1 to 9 mg every 12 hours	8 mg two times a day for 1 week, then 6 mg two times a day for 1 week, then 4 mg two times a day for 1 week, then 2 mg two times a day for 1 week, then stop
9.1 to 11 mg every 12 hours	10 mg two times a day for 1 week, then 8 mg two times a day for 1 week, then 4 mg two times a day for 1 week, then 2 mg two times a day for 1 week, then stop
11.1 to 13 mg every 12 hours	12 mg two times a day for 1 week, then 8 mg two times a day for 1 week, then 6 mg two times a day for 1 week, then 2 mg two times a day for 1 week, then stop
13.1 to 15 mg every 12 hours	14 mg two times a day for 1 week, then 10 mg two times a day for 1 week, then 6 mg two times a day for 1 week, then 4 mg two times a day for 1 week, then stop

If symptoms are unable to be controlled with the study agent alone, the addition of the nonrandomized medication (phenobarbital/clonidine) may be initiated to control symptoms. Morphine, clonidine and phenobarbital, in that order, will be weaned per protocol.

The patient medical record will be reviewed to collect data about the subjects. This includes the patient's electronic medical record and chart.

Risks to subjects

Risks to participants include side effects associated with study medication, potential increased length of stay/treatment compared to those patients receiving comparative medication and loss of confidentiality. Both of the study medications are commonly used in this patient population and considered standard of care with no evidence of superiority in the treatment of NAS.

Benefits to subjects

It is not known if one of the study medications will better control withdrawal symptoms, allow us to wean oral morphine faster, have fewer side effects or allow the infant to be

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discharged from the hospital sooner. The knowledge gained from this research will help us determine if clonidine or phenobarbital could better control symptoms of withdrawal, have less side effects or allow children to be discharged from the hospital sooner.

Data Management

- The ~~primary~~ endpoint of time from initiation of adjunctive therapy until hospital discharge will be assessed using Mann-Whitney U test. ~~Secondary~~ Endpoints of length of stay and length of morphine therapy will also be assessed via Mann-Whitney U test. Side effects and readmission rate via chi-squared with an unadjusted odds ratio with 95% CI for 30-day readmission.
- A power analysis was completed for sample size (based on Surran et al findings with power to detect a 5-day difference in treatment time):

t tests - Means: Difference between two independent means (two groups)

Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size d	=	3.0666667
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	Allocation ratio N2/N1	=	1
Output:	Noncentrality parameter δ	=	4.3369216
	Critical t	=	2.4469119
	Df	=	6
	Sample size group 1	=	4
	Sample size group 2	=	4
	Total sample size	=	8
	Actual power	=	0.9475121

It is predicted that a sample size of 25 in each treatment group will be powered to detect 1.2-day difference in time from initiation of adjunctive therapy until hospital discharge.

- All paper research records containing data from individual subjects will be locked and stored. All electronic research records containing data from individual subjects will be computer password protected. All records will be accessible only to research personnel.

Withdrawal of Subjects

Subjects may withdraw their permission for participation in research at any time. Subjects will contact Dr. Carrie Brusseau in writing to let us know they are withdrawing their permission. The mailing address is 1924 Alcoa Highway, U-41, Knoxville, TN 37920. At that time, we will stop further collection of any information. However, the health information collected before this withdrawal may continue to be used for the purposes of reporting and research quality.

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