PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Clonidine as an Adjunct Therapy to Opioids for Neonatal Abstinence Syndrome: A Randomized, Controlled Trial

Alexander G. Agthe, George R. Kim, Kay B. Mathias, Craig W. Hendrix, Raul Chavez-Valdez, Lauren Jansson, Tamorah R. Lewis, Myron Yaster and Estelle B. Gauda

Pediatrics 2009;123;e849; originally published online April 27, 2009;
DOI: 10.1542/peds.2008-0978

ARTICLE

Clonidine as an Adjunct Therapy to Opioids for Neonatal Abstinence Syndrome: A Randomized, Controlled Trial

Alexander G. Agthe, MD[a,b], George R. Kim, MD[a], Kay B. Mathias, NNP[c], Craig W. Hendrix, MD[d], Raul Chavez-Valdez, MD[a], Lauren Jansson, MD[a,e], Tamorah R. Lewis, MD[a], Myron Yaster, MD[a,f], Estelle B. Gauda, MD[a,c,e]

Departments of [a]Pediatrics, [d]Medicine, and [f]Anesthesiology/Critical Care Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland; [b]Department of Pediatrics, University of Maryland Medical Center, Baltimore, Maryland; [c]Center for Neonatal Transitional Care, Mt Washington Pediatric Hospital, Baltimore, Maryland; [e]Department of Pediatrics, Johns Hopkins Bayview Medical Center, Baltimore, Maryland

The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Little is known about alternative detoxification strategies for the infant with severe NAS. Clonidine has been used to detoxify adults with opioid dependency.

What This Study Adds

This study is the first randomized, placebo-controlled trial using clonidine as adjunct therapy for NAS. It adds an alternative treatment paradigm for these infants.

ABSTRACT

OBJECTIVE. To determine if oral clonidine would reduce the duration of opioid detoxification for neonatal abstinence syndrome.

METHODS. Infants with intrauterine exposure to methadone or heroin and neonatal abstinence syndrome (2 consecutive modified Finnegan scores of ≥9) were enrolled at 2 hospitals during 2002–2005 and followed until final hospital discharge. All enrolled infants (80) received oral diluted tincture of opium according to a standardized algorithm and were randomly assigned to receive oral clonidine (1 μg/kg every 4 hours) (40 infants) or placebo (40 infants). Primary outcome was duration of opioid therapy. Secondary outcomes included the amount of opium required to control symptoms, number of treatment failures, and differences in blood pressure, heart rate, and oxygen saturation.

RESULTS. The median length of therapy was 27% shorter in the clonidine group (11 [95% confidence interval: 8–15 days]) than in the placebo group (15 days [95% confidence interval: 12–17 days]). In the clonidine group, 7 infants required restarting opium after initial discontinuation versus none in the placebo group, with the total length of treatment/observation remaining significantly less in the clonidine group. Higher dosages of opium were required by 40% of the infants in the placebo group versus 20% in the clonidine group. Treatment failures occurred in 12.5% of the infants in the placebo group versus none in the clonidine group. Hypertension, hypotension, bradycardia, or desaturations did not occur in either group. Three infants in the clonidine group died as a result of myocarditis, sudden infant death syndrome, and homicide, all after hospital discharge and before 6 months of age.

CONCLUSIONS. In this randomized, double-blind trial, adding clonidine to standard opioid therapy for detoxification from in utero exposure to methadone or heroin reduced the duration of pharmacotherapy for neonatal abstinence without causing short-term adverse cardiovascular outcomes. A larger trial is indicated to determine long-term safety. *Pediatrics* 2009; 123:e849–e856

www.pediatrics.org/cgi/doi/10.1542/peds.2008-0978

doi:10.1542/peds.2008-0978

This trial has been registered at www.clinicaltrials.gov (identifier NCT00510016).

Key Words
infants, opioid withdrawal, clonidine, tincture of opium

Abbreviations
NAS—neonatal abstinence syndrome
MFS—modified Finnegan score
DTO—diluted tincture of opium
ME—morphine equivalent
SVT—supraventricular tachycardia
JHH—Johns Hopkins Hospital
JHBMC—Johns Hopkins Bayview Medical Center
CI—confidence interval

Accepted for publication Jan 21, 2009

Address correspondence to Estelle B. Gauda, MD, Division of Neonatology Research Laboratories, Johns Hopkins Hospital, CMSC 6-104, 600 N. Wolfe St, Baltimore, MD 21287. E-mail: egauda@jhmi.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

NEONATAL ABSTINENCE SYNDROME (NAS) occurs in 55% to 94% of infants born to substance-dependent women.[1–4] Clinical features include neurologic hyperexcitability (insomnia, irritability, hypertonia, hyperreflexia, tremors, and seizures), enteric symptoms (vomiting, diarrhea, feeding disturbances), and sympathetic/parasympathetic dysregulation (sweating, fever, tachypnea, and congestion). Holding, swaddling, and minimal stimulation may alleviate mild and nonprogressive withdrawal, but may be insufficient for severe NAS.[5–7]

Treatment for severe NAS includes pharmacotherapy,[8–10] the goals of which are to ameliorate hyperactivity and autonomic instability and to promote normal patterns of sleeping, feeding, and weight gain. Pharmacotherapy is most often performed in an inpatient setting,[9,11–13] prolonging hospitalization.

Clonidine, an α_2-adrenergic receptor agonist, is used to ameliorate opiate withdrawal symptoms in older children

and adults.[14,15] However, little is known about its efficacy and safety in treating infants with NAS. We hypothesized that clonidine (in combination with an opioid) would ameliorate withdrawal more rapidly than an opioid alone.

METHODS

Study Subjects and Design

After institutional review board approval and written parental consent, this study was conducted at 3 Baltimore hospitals (Johns Hopkins Hospital [JHH], Johns Hopkins Bayview Medical Center [JHBMC], and Mt Washington Pediatric Hospital) from March 2002 through December 2005. All study infants were born at JHH or JHBMC and were either discharged to home or transferred to the Center for Neonatal Transitional Care at Mt Washington Pediatric Hospital for extended hospitalization. Of 221 eligible infants, 80 (36%) were randomly assigned to 2 treatment groups (Fig 1), which represented 80% (80 of 98) of the infants enrolled. Reasons for nonenrollment included (1) infant-mother dyad participation in another study, (2) starting an infant on diluted tincture of opium (DTO) before enrollment, (3) study staff unavailability to enroll infants, and (4) maternal refusal. Reasons for maternal refusal included (1) negative maternal experience with the sedating effects of clonidine and (2) desire not to involve infant in research or expose infant to "additional drugs."

The study was a prospective, block-randomized, double-blind, placebo-controlled trial of clonidine and diluted tincture of opium (clonidine/DTO) versus opium alone (placebo/DTO) to treat infants with NAS. Infants were potentially eligible for inclusion between 0 and 14 days of age if they were prenatally exposed to opioids and developed moderate to severe NAS (2 consecutive modified Finnegan scores (MFSs)[16] of ≥9) requiring pharmacotherapy. Infants were excluded for (1) gestational age of <35 weeks, (2) intrauterine growth retardation (birth weight below the 5th percentile), (3) congenital anomalies, (4) illness requiring oxygen, intravenous fluids, or medications, and (5) breastfeeding (possible confounder of breast milk opioids).

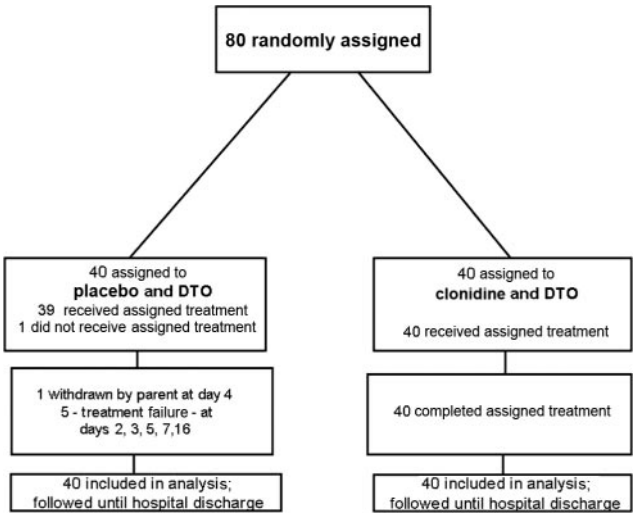


FIGURE 1
Patient randomization. One patient received the initial 3 doses as clonidine instead of the study drug (placebo).

Infants were stratified before randomization to the hospital of birth and maternal methadone use. Urine toxicology was performed on each infant-mother dyad at the time of delivery, and a detailed drug history was obtained from each mother at the time of enrollment. Eligible patients were randomly assigned by the research pharmacist into 2 strata by a computerized random list in blocks of 4. Investigators, parents, and caretakers were blinded to group allocations until the study was completed.

Protocol

Enrolled infants were randomly assigned to receive either clonidine/DTO or placebo (isotonic saline)/DTO. A clear, colorless, liquid formulation of clonidine was diluted 1:10 in saline in the research pharmacy. Study infants received oral clonidine 1 μg/kg every 4 hours or an equal volume of placebo. DTO was given as a 1:25 dilution, 0.4 mg/mL (morphine equivalent [ME]). The dose of clonidine (6 μg/kg per day) used in this study was based on the only published report by Hoder et al[17] who used clonidine (3–5 μg/kg per day divided every 4–6 hours) in 7 newborns with NAS, our previous experience using open-label clonidine (6–12 μg/kg per day divided every 4–6 hours) in 8 infants with intractable NAS, and input and then approval from the US Food and Drug Administration.

The dosing algorithm to guide the escalation and deescalation of DTO was used at all 3 sites. All infants were started on 0.2 mL DTO (0.08 mg ME) orally every 4 hours. NAS symptoms were uncontrolled if there were 2 consecutive MFSs of ≥9. DTO was incrementally escalated to 0.3, 0.4, and 0.5 mL every 4 hours, then to 0.5, 0.7, and 0.9 mL every 3 hours, until withdrawal symptoms (MFS < 9) were controlled. Clonidine/placebo dose was based on measurement of weight (mL/kg) and maintained at that dose.

When symptoms were controlled (mean daily MFS < 9), infants were continued on clonidine/placebo and the DTO dose that controlled symptoms for at least 48 hours. Afterward, DTO was deescalated by increments of 0.05 mL per dose, for each 24-hour period. For example, an infant receiving 0.4 mL of DTO every 4 hours, whose symptoms were controlled for 48 hours, would then receive DTO 0.35 mL every 4 hours for 24 hours, with a reduction of 0.05 mL every 24 hours thereafter. If there were 2 consecutive MFSs of ≥12 during deescalation, the last previous DTO dose that controlled symptoms (MFS < 9) was resumed, with continuation of the protocol. Infants with 2 consecutive MFSs of ≥9 on the highest dose (0.9 mL every 3 hours) were defined as treatment failures, withdrawn from the treatment algorithm, and continued NAS management was at the discretion of the clinical care team. However, total opioid dose, length of treatment, MFSs, and vital signs were still collected, and follow-up calls were made to caregivers

for 6 months after discharge. All infants were included in the intention-to-treat analysis.

Vital signs (temperature, heart rate, respiratory rate, oxygen saturation, blood pressure) were monitored; weights, input, and outputs were measured daily and the MFS was calculated every 3 to 4 hours. Infants were examined by a physician or neonatal nurse practitioner daily. Blood pressure was measured every 4 hours for the first 48 hours on and after stopping clonidine or placebo; otherwise, it was measured every 12 hours. Hypotension was defined as blood pressure below the 5th percentile. Rebound hypertension was defined as an increase of blood pressure above the 95th percentile of age-specific norms. Oxygen saturations ≤ 95% were considered abnormal. Infants were removed from the study if they had an illness necessitating transfer to the NICU.

Outcome Measures

The primary outcome was the total duration of pharmacotherapy for NAS. Secondary outcomes included the amount of DTO required to treat the NAS (with or without clonidine), treatment failure (>0.9 mL of DTO every 3 hours), seizures, weight gain, blood pressure, heart rate, and hemoglobin saturation measured by pulse oximetry.

Statistical Analysis

Before the study, the mean duration of treatment for NAS at the participating centers was 13 days (SD: 5). To demonstrate 25% reduction in the primary outcome with a power of .8 and a 2-tailed α value of .05, 40 infants were needed for each group. All 80 infants were included in the primary intention-to-treat analysis.

Unless otherwise indicated, for descriptive statistics, means and SDs are reported for normally distributed data and medians and interquartile ranges for nonnormally distributed data. Ninety-five percent confidence intervals (CIs) are also reported. Log-rank test is reported for time-dependent outcome data. Fisher's exact test is reported for categorical variables.

Continuous variables were analyzed by using an independent-samples *t* test for between group comparisons and a paired-samples *t* test for within group comparisons corrected for multiple comparisons. Continuous variables following nonnormal distributions were analyzed by using the Mann-Whitney *U* test. All tests were 2-sided with a statistical significance of $P < .05$. All data analyses were performed with SPSS 15 (SPSS Inc, Chicago, IL) and Prism 4.0 (GraphPad Software, Inc, San Diego, CA). The data and safety monitoring board reviewed the data in blocks of 20 patients enrolled, meeting 4 times during the course of the study. No early stopping rules were implemented because of the small sample size.

RESULTS

Patient Characteristics

Forty infants each were assigned to the clonidine/DTO and the placebo/DTO groups. Both groups were similar with regard to maternal and infant demographic factors. Infants in the clonidine/DTO group were lower in average birth weight (mean: 2864 g [SD: 365] vs 3047 g [SD: 395]; $P = .03$) (Table 1). Of the infants, 89% were exposed to methadone, 69% to heroin, and 61% to cocaine plus an opiate during pregnancy. Of the infant-mother dyads, in both groups 3 of 40 either had a positive urine toxicological screen for benzodiazepines at time of delivery or a history of exposure during pregnancy. Exposure to sertraline or paroxetine occurred in 3 of 40 and 6 of 40 in the clonidine/DTO and placebo/DTO groups, respectively. Prenatal exposure to opiates was comparable in both groups as was maternal length of opiate dependency, maternal opiate dose at delivery, and number of mothers enrolled in a methadone treatment program (Table 2).

TABLE 1 Demographics of Study Participants

Infant Characteristic[a]	Clonidine/DTO Group (*N* = 40)	Placebo/DTO Group (*N* = 40)
Birth weight, mean (SD), g	2864 (365)	3047 (395)[a]
Weight at the start of treatment, mean (SD)	2749 (358)	2881 (411)
Gestational age, mean (SD), wk	38.5 (1.5)	38.9 (1.7)
Race or ethnic group, *n* (%)		
Black	19 (47.5)	13 (32.5)
White	21 (52.5)	27 (67.5)
Male gender, *n* (%)	19 (47.5)	18 (45)
Study site, *n* (%)		
JHH	20 (50)	20 (50)
JHBMC	20 (50)	20 (50)
Prenatal exposure, *n* (%)		
Methadone	36 (90)	35 (87.5)
Heroin	26 (65)	29 (72.5)
Other exposures, *n* (%)		
Cocaine	25 (62.5)	24 (60)
Tobacco smoke exposure	36 (90)	35 (87.5)
Age at start of treatment, mean (SD), d	2.3 (1.6)	2.0 (0.9)
MFS at start of treatment, mean (SD)	12 (3)	12 (3)

[a] Birth weight: $P = .03$; otherwise, no statistically significant differences between groups.

TABLE 2 Maternal Demographics

Maternal Characteristic[a]	Clonidine/DTO Group (*N* = 40)	Placebo/DTO Group (*N* = 40)
Age, mean (SD), y	30.6 (6.2)	31.8 (5.3)
Duration of opioid dependency, mean (SD), y	8.3 (5)	7.7 (5)
Enrollment in methadone program, *n* (%)	35 (87.5)	30 (75)
Methadone, mean (SD), mg		
Last dose before delivery	74.8 (43.2)	74 (28.7)
Maximum dose during pregnancy	90.1 (30)	79.1 (26.1)
Epidural or spinal anesthesia, *n* (%)	27 (67.5)	28 (70)
Delivery, *n* (%)		
Vaginal	26 (65)	33 (82.5)
Cesarean	14 (35)	7 (17.5)

[a] There were no statistically significant differences between groups.

Primary Outcomes

For the clonidine/DTO group, the median length of therapy was 27% shorter than for the placebo/DTO group (11 days [95% CI: 8–15] vs 15 days [95% CI: 13–17]), with a range of 4 to 28 and 4 to 100 days (log-rank; $P = .02$, Fig 2), respectively. Although birth weight between the 2 groups differed, weight at the start of treatment did not. We used a symptom-based dosing algorithm for DTO, but both groups received the same dose of DTO/kg at the start of therapy. Infants prenatally exposed to methadone had a median length of treatment 3 times that of infants exposed to heroin alone (15 days [95% CI: 12–18] for methadone versus 5 days [95% CI: 4–6] for heroin, log-rank; $P = .005$). When considering only infants exposed to methadone, clonidine was associated with a shorter length of therapy (12 days [95% CI: 9–16] for clonidine/DTO versus 17 days [95% CI: 11–22] for placebo/DTO, log-rank; $P = .01$). Nine infants in the placebo group had a length of treatment of ≥28 days (median: 32 [range: 29–100]), and all were treated with methadone. At the time of delivery, 5 of 9 and 3 of 9 infant-mother dyads had positive toxicology for heroin and cocaine, respectively, and 1 of 9 of the mothers was on Klonipin and Zoloft.

Secondary Outcomes

There was no difference in maximum weight loss or the time to reach the nadir of weight loss between the 2 groups (Table 3). The total dose (mean [SD]) of DTO required for the clonidine/DTO and placebo/DTO groups was 19.4 (20.1) mL, 7.7 (8.0) mg ME and 47.9 (89.2) mL, 19.2 (3.3) mg ME, respectively. Overall, the clonidine group needed less DTO/kg per day of treatment than the infants in the placebo group ($P < .03$, analysis of variance; Fig 3); the divergence occurred after the fifth day of treatment (Fig 3).

Five of the 80 infants failed treatment (required ≥0.9 mL of DTO every 3 hours). Treatment failures occurred on days 2, 3, 5, 7, and 16, all in the placebo/DTO group (Table 4). Three infants in the placebo/DTO group experienced seizures versus none in the clonidine/DTO group. Diagnosis of seizures was made by the clinical care team; all infants received an electroencephalogram after phenobarbital was administered and no infant had an abnormal electroencephalogram. Seven infants, all in the clonidine/DTO group, rebounded (increasing MFS, necessitating restarting DTO within 12–48 hours after stopping), but most infants were then weaned from DTO within 2 to 5 days (Table 4). Despite the inclusion of these additional days of treatment, the median length of treatment for the clonidine/DTO group was still less than for the placebo/DTO group (Fig 2; $P = .02$, log-rank test).

Blood pressures and heart rates were statistically lower in the clonidine/DTO group but remained in the normal range for newborns,[18] and no infant required intervention for lower blood pressures. The maximum differences in systolic, diastolic, and mean arterial pressures were greatest at 24 and 48 hours after starting the protocol (Table 5). In the 48 hours after discontinuing

TABLE 3 Treatment Outcomes

Variable and Outcome	Clonidine/DTO Group ($N = 40$)	Placebo/DTO Group ($N = 40$)	P
Total daily DTO dose, mL			
Mean (SD)	19.4 (20.1)	47.9 (89.2)	.36[a]
Median (range)	12.0 (3.8–93)	19.4 (2.8–517)	
Total daily ME dose, mg			
Mean (SD)	7.7 (8.0)	19.2 (3.3)	.36[a]
Median (range)	4.8 (1.5–37.5)	7.7 (1.1–207)	
Maximum weight loss, mean (SD), % of birth weight	−6.91 (3.0)	−7.79 (3.6)	.21[b]
Time to weight nadir, mean (SD), d	4.2 (2.8)	4.4 (2.3)	.73[b]
Proportions of infants			
Required ≥0.5 mL of DTO every 4 h, *n* (%)	8 (20)	16 (40)	.09[c]
Seizures, *n* (%)	0	3 (7.5)	.24
Treatment failure, *n* (%)	0	5 (12.5)	.05

[a] Mann-Whitney *U* test, clonidine/DTO group versus placebo/DTO group.
[b] Independent-samples *t* test.
[c] Fisher's exact test.

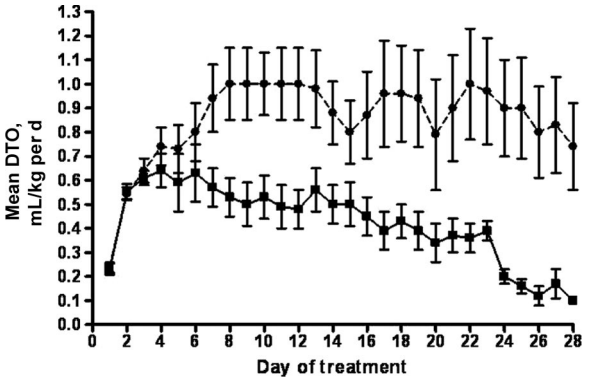
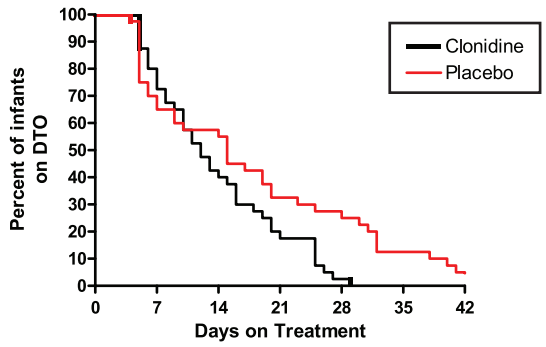


FIGURE 3
Effect of clonidine on the amount of DTO (mL/kg) needed to control symptoms of NAS (mean ± SEM) ($P = .03$, analysis of variance, Bonferroni multiple comparisons). Placebo group, dashed line with circles; clonidine group, straight line with squares.



DAYS	0	7	14	21	28	35	42
No.at Risk PLACEBO	40	28	22	13	10	5	2
CLONIDINE	40	31	16	8	1	0	0

FIGURE 2
Kaplan-Meier curve showing the effect of clonidine on days of DTO treatment for infants with NAS (log-rank; $P = .02$). The graph also includes the total length of DTO treatment for infants who rebounded who were assigned to the clonidine group.

TABLE 4 Treatment Course for Infants in the Clonidine/DTO Group Who Rebounded

Study Identification	Duration of Initial Treatment With DTO, d	Maximum DTO Dose During Initial Therapy, mL Every 4 h	Hours Between Stopping DTO and Resuming DTO, h	Duration of Therapy After Restarting DTO, d	Maximum Dose After Restarting DTO, mL Every 4 h	Prenatal Methadone Exposure Maximum Dose, mg/d
15C	11	0.3	52	2	0.10	75
24C	7	0.3	28	5	0.10	50
26C	6	0.2	48	15	0.10	60
35C	6	0.2	22	2	0.10	65
38C	8	0.2	24	4	0.10	90
66C	19	0.5	36	4	0.05	150
74C	7	0.3	24	3	0.05	120

TABLE 5 Heart Rate and Blood Pressure Measurements

	Clonidine ($N = 40$)	Placebo ($N = 40$)	Difference, Mean (95% CI)
Heart rate, mean (SD), beats per min			
HR: baseline on	144 (7)	146 (9)	1.7 (−2.3 to 4.7)
HR: 24-h on treatment	141 (11)[a]	145 (10)	4.0 (−0.6 to 8.6)
HR: 48-h on treatment	140 (9)[b]	145 (10)	4.7 (0.46 to 8.9)
HR: baseline off	147 (11)	150 (8)	3.9 (−0.5 to 8.2)
HR: 24-h off treatment	149 (10)	153 (8)[a]	4.8 (0.8 to 8.8)
HR: 48-h off treatment	152 (10)[b]	153 (9)	1.4 (−2.9 to 5.6)
Blood pressure, mean (SD), mm Hg			
Systolic: baseline on	75 (8)	74 (11)	−1.0 (5.2 to 3.3)
Systolic: 24-h on treatment	75 (7)	80 (6)[c]	5.2 (2.3 to 8.1)
Systolic: 48-h on treatment	75 (6)	80 (7)[c]	4.7 (1.9 to 7.5)
Systolic: baseline off	81 (8)	85 (7)	3.7 (0.15 to 7.2)
Systolic: 24-h off treatment	81 (8)	85 (8)	4.2 (0.7 to 7.8)
Systolic: 48-h off treatment	86 (6)[b]	87 (8)	1.1 (−2.0 to 4.2)
Diastolic: baseline on	43 (8)	42 (10)	−1.1 (5.2 to 2.9)
Diastolic: 24-h on treatment	42 (7)	45 (9)	3.3 (−0.3 to 6.9)
Diastolic: 48-h on treatment	42 (6)	47 (8)[b]	4.4 (1.1 to 7.6)
Diastolic: baseline off	43 (7)	45 (8)	1.8 (−1.7 to 5.3)
Diastolic: 24-h off treatment	45 (8)	44 (7)	−0.7 (−4.1 to 2.7)
Diastolic: 48-h off treatment	46 (8)[b]	46 (9)	0.4 (−3.2 to 4.1)
MAP: baseline on	55 (6)	53 (8)	−2.1 (−5.5 to 1.2)
MAP: 24-h on treatment	55 (5)	58 (7)[c]	3.3 (0.5 to 6.1)
MAP: 48-h on treatment	55 (5)	59 (7)[c]	4.0 (1.4 to 6.6)
MAP: baseline off	57 (5)	60 (7)	3.1 (0.2 to 5.9)
MAP: 24-h off treatment	59 (6)[b]	60 (5)	1.5 (−1.2 to 4.1)
MAP: 48-h off treatment	61 (6)[c]	60 (6)	−1.2 (−4.0 to 1.5)

Variations in heart rate and blood pressure are shown before starting (on) or stopping (off) clonidine or placebo and at the 24- and 48-hour following periods, respectively. A paired-samples t test was used for within-treatment-group comparisons at baseline versus 24 hours and baseline versus 48 hours. HR indicates heart rate; MAP, mean arterial pressure.

[a] Statistically significant at the .05 level.

[b] Statistically significant at the .01 level.

[c] Statistically significant at the .001 level.

the study drug, the clonidine/DTO group had a mean increase in systolic blood pressure from 81 (8) to 86 (6) mm Hg (Table 5). The clonidine/DTO group had a higher heart rate of 145 (10) versus 140 (9) beats per minute in the placebo/DTO group, which occurred 48 hours after starting the protocol. No difference in heart rate was observed 48 hours after stopping clonidine (Table 5).

Safety and Toxicity

Hypertension, hypotension, bradycardia, or hemoglobin desaturation were not observed during the study.

One infant (79C) in the clonidine/DTO group developed supraventricular tachycardia (SVT) at 5 days of age, 3 days after discontinuing clonidine, requiring 1 dose of adenosine, without recurrence. The infant was discharged from the hospital without additional treatment.

Three infants, all in the clonidine/DTO group, died within 2 months of life, all after discharge from the hospital. The causes of death were myocarditis, SIDS, and homicide (methadone overdose), confirmed by autopsy. These infants died at (1) 50 postnatal days (6 days after discharge and 44 and 23 days after clonidine and DTO were discontinued, respectively), (2) 32 postnatal days (23 days after discharge), or (3) 52 postnatal days (22 days after discharge). All deaths were reported as serious adverse advents to the Food and Drug Administration and the Data Safety and Monitoring Board, which deemed the deaths not likely attributed to clonidine exposure, and the study was allowed to continue.

DISCUSSION

Multiple drug classes (opioids, benzodiazepines, barbiturates, and phenothiazines) have been used alone or in combination to manage NAS in infants born to drug addicted mothers.[9,19] However, this is the first randomized, controlled trial of clonidine[20] and the largest prospective double-blind, randomized trial of any kind in this patient population. Our findings that clonidine in combination with DTO stabilized and detoxified infants with moderate to severe NAS more rapidly than DTO alone confirms the findings of a previously published, small, open-label study in neonates[17] and validates by using α_2-adrenergic receptor agonists in the management of opioid withdrawal symptoms.

Clonidine has successfully been used to treat the symptoms of opioid (and other drug) withdrawal in older children[21] and adults.[22–24] Being a central α_2-adrenergic receptor agonist acting at presynaptic receptors in the midbrain and medulla, clonidine inhibits sympathetic outflow by decreasing central catecholamine release, leading to reduced blood pressure and heart rate.[25,26] Clonidine is well absorbed after oral and transdermal administration, is highly lipid soluble, and readily distributes in the central nervous system.[27] Adverse effects include hypotension, rebound hypertension, atrioventricular block, and bradycardia. Concurrent use of β-blockers increases adverse events in

adults,[28] and toxicity can result from accidental ingestion by children.[29–31]

The transient decrease in blood pressure when starting clonidine/DTO and increase after stopping it was within the range of blood pressure norms for term infants.[18] The differences in blood pressure between the 2 groups may have been directly related to clonidine or attributed to better early control of NAS. Rebound of symptoms of NAS was limited to the clonidine/DTO group (Table 4) and was controlled with small amounts of opioid for a short period. It is unclear if rebound was due to withdrawal from clonidine, DTO, or both. A 2-step reduction of the clonidine dose over 48 hours or weaning of opioids before stopping clonidine may result in fewer rebound events.

The 4 serious adverse events (1 episode of SVT and 3 deaths) all occurred in the clonidine/DTO group and happened after discontinuation of clonidine. The SVT episode occurred 3 days after stopping clonidine and was successfully treated with adenosine; it did not recur. Clonidine has been used to treat cardiac dysrhythmias[32] and is associated with elevations of blood pressure and heart rate after abrupt discontinuation in children[33] and adults,[34] but has only caused SVT in 1 adult with severe heart and renal failure.[35] Although we think it unlikely, we cannot say with certainty that stopping clonidine caused the single episode of SVT in this otherwise healthy infant. Furthermore, whether clonidine contributed to the 3 deaths caused by myocarditis, SIDS, and homicide is not known.

This study was not designed to detect differences in lengths of hospitalization, because hospitalization may be prolonged and discharge delayed even after pharmacotherapy is no longer required in this population. In agreement with other reports,[36] methadone exposure was associated with longer pharmacotherapy for NAS than heroin exposure alone; clonidine shortened the length of treatment of methadone-exposed infants.

Interpretation of our results is limited by the small number of patients, which limited the statistical power to determine the true assessment of the effect of clonidine on short- and long-term adverse events. The short-term follow-up precluded assessment of long-term neurodevelopment. Although the study sample was diverse in gender, ethnicity, and exposure to methadone and heroin, the small number of hospitals in a limited geographic area limits broad generalization of our findings.

Because the pharmacokinetics of clonidine in newborn infants was not available to us at the time of this trial, we chose the dose of 1 μg/kg every 4 hours on the basis of the study of Hoder et al,[17]our experience using clonidine in 8 infants with intractable NAS, and guidance of the Food and Drug Administration who granted the physician-sponsored investigational new drug to perform this trial. As part of the trial, population pharmacokinetics were performed and will be reported in a separate manuscript. The clonidine formulation (100 μg/mL, diluted to 5 μg/mL) administered orally in this study is commercially available for epidural injection; it was selected to ensure accurate dosing as opposed to a suspension made from tablets (0.2 mg).[37] A clonidine transdermal patch is available (in 3 concentrations) but can have problems with bioavailability resulting in nonuniform dosing and has been associated with toxicity in infants.[38]

Dexmedetomindine has 8 times the affinity for the α_2-adrenergic receptor than clonidine and is approved for short-term sedation for adults. Its effective sedative, analgesic, and anxioloytic properties without respiratory depression are desirable properties[39] also for infants,[40] but randomized trials are essential to demonstrate its efficacy and safety.

The American Academy of Pediatrics recommends DTO for treatment of severe NAS, although diluted morphine is frequently used and has similar efficacy.[41] Clonidine, when used in combination with intravenous opioids, reduces total opioid use in infants.[42] Thus, clonidine is likely to be effective when combined with oral morphine. For infants requiring >0.5 mL of DTO or 0.2 mg ME every 4 hours, we added clonidine to facilitate NAS symptom control and weaning of the opioid.

CONCLUSIONS

This prospective, double-blind, randomized, controlled trial supports the efficacy of clonidine in treating moderate to severe NAS in term newborns prenatally exposed to opioids. In conjunction with DTO, clonidine reduces the length of pharmacotherapy without adverse cardiovascular events. A larger trial is indicated to assess long-term safety.

ACKNOWLEDGMENTS

This study was funded by a Thomas Wilson grant, an institutional research grant from JHH, General Clinical Research Center, and was supported by National Institute on Drug Abuse grant IR21DAO16288 (Dr Gauda). None of these institutions were involved in the design, conduct, analysis, or writing of the study. The study was reviewed by the scientific review group at the National Institute on Drug Abuse when it recommended funding for this project. Beyond the review process, neither the National Institutes of Health nor the National Institute on Drug Abuse had a role in the design, conduct, analysis, or writing of this study.

We thank Dr Christoph Lehmann for chairing the Data Safety and Monitoring Board and the other members who ensured the trial was properly conducted and the risks to the infants were minimized. We thank Douglas C. Watson, MD, University of Maryland, Department of Pediatrics, and Frances J. Northington, MD, Johns Hopkins, Department of Pediatrics, for their support and encouragement throughout the process including their helpful suggestions in the presentation of the data and writing of the manuscript. We thank the research pharmacists: Jim Monolakis, PharmD; Henry Choi, PharmD; Bayview Medical Center; Carol Wesolowski, pharmacist at Johns Hopkins; Kathleen Truelove, investigational drug pharmacist and the staff, nurses, and pediatric and neonatal nurse practitioners of the participating centers.

Lastly, we are indebted to the parents of the infants for their willingness to participate in this study.

The study concept and design were devised by Drs Agthe, Gauda, Yaster, Hendrix, Jansson, and Ms Mathias; the data were acquisitioned by Drs Agthe, Gauda, Lewis, and Ms Mathias; the data were analyzed and interpreted by Drs Agthe, Gauda, and Chavez-Valdez; the manuscript was drafted by Drs Agthe and Gauda; the manuscript was critically revised for important intellectual content by Drs Yaster, Hendrix, Jansson, and Ms Mathias; funding was obtained by Drs Agthe and Gauda; administrative, technical, or material support was provided by Ms Mathias and Drs Lewis and Kim; and the study was supervised by Drs Agthe and Gauda. Drs Gauda, Agthe, and Kim had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Fricker HS, Segal S. Narcotic addiction, pregnancy, and the newborn. *Am J Dis Child.* 1978;132(4):360–366
2. Harper RG, Solish GI, Purow HM, Sang E, Panepinto WC. The effect of a methadone treatment program upon pregnant heroin addicts and their newborn infants. *Pediatrics.* 1974;54(3):300–305
3. Madden JD, Chappel JN, Zuspan F, Gumpel J, Mejia A, Davis R. Observation and treatment of neonatal narcotic withdrawal. *Am J Obstet Gynecol.* 1977;127(2):199–201
4. Ostrea EM, Chavez CJ, Strauss ME. A study of factors that influence the severity of neonatal narcotic withdrawal. *J Pediatr.* 1976;88(4pt1):642–645
5. Blinick G, Wallach RC, Jerez E, Ackerman BD. Drug addiction in pregnancy and the neonate. *Am J Obstet Gynecol.* 1976; 125(2):135–142
6. Finnegan LP. Discussion: dilemmas in research in perinatal addiction—intervention issues. *NIDA Res Monogr.* 1992;117: 344–348
7. Levy M, Spino M. Neonatal withdrawal syndrome: associated drugs and pharmacologic management. *Pharmacotherapy.* 1993; 13(3):202–211
8. American Academy of Pediatrics Committee on Drugs. Neonatal drug withdrawal. *Pediatrics.* 1998;101(6):1079–1088
9. Johnson K, Gerada C, Greenough A. Treatment of neonatal abstinence syndrome. *Arch Dis Child Fetal Neonatal Ed.* 2003; 88(1):F2–F5
10. Osborn DA, Jeffery HE, Cole M. Opiate treatment for opiate withdrawal in newborn infants. *Cochrane Database Syst Rev.* 2005;(3):CD002059
11. Ebner N, Rohrmeister K, Winklbaur B, et al. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. *Drug Alcohol Depend.* 2007;87(2–3): 131–138
12. Finnegan LP, Kron RE, Connaughton JF, Emich JP. Assessment and treatment of abstinence in the infant of the drug-dependent mother. *Int J Clin Pharmacol Biopharm.* 1975; 12(1–2):19–32
13. Kron RE, Finnegan LP, Kaplan SL, Litt M, Phoenix MD. The assessment of behavioral change in infants undergoing narcotic withdrawal: comparative data from clinical and objective methods. *Addict Dis.* 1975;2(1–2):257–275
14. Gold MS, Redmond DE Jr, Kleber HD. Clonidine blocks acute opiate-withdrawal symptoms. *Lancet.* 1978;2(8090):599–602
15. Gold MS, Redmond DE Jr, Kleber HD. Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. *Am J Psychiatry.* 1979;136(1):100–102
16. Finnegan L, Connaughton JJ, Kron R. A scoring system for evaluation and treatment of the neonatal abstinence syndrome: a new clinical and research tool. In: Marselli P, Garanttini S, Sereni F, eds. *Basic and Therapeutic Aspects of Perinatal Pharmacology*. New York, NY: Raven; 1995:139–152
17. Hoder EL, Leckman JF, Poulsen J, et al. Clonidine treatment of neonatal narcotic abstinence syndrome. *Psychiatry Res.* 1984; 13(3):243–251
18. Kent AL, Kecskes Z, Shadbolt B, Falk MC. Normative blood pressure data in the early neonatal period. *Pediatr Nephrol.* 2007;22(9):1335–1341
19. Theis JG, Selby P, Ikizler Y, Koren G. Current management of the neonatal abstinence syndrome: a critical analysis of the evidence. *Biol Neonate.* 1997;71(6):345–356
20. Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. *Cochrane Database Syst Rev.* 2005; (3):CD002053
21. Yaster M, Kost-Byerly S, Berde C, Billet C. The management of opioid and benzodiazepine dependence in infants, children, and adolescents. *Pediatrics.* 1996;98(1):135–140
22. Fishbain DA, Rosomoff HL, Rosomoff RS. Detoxification of nonopiate drugs in the chronic pain setting and clonidine opiate detoxification. *Clin J Pain.* 1992;8(3):191–203
23. Fishbain DA, Rosomoff HL, Cutler R. Opiate detoxification protocols: a clinical manual. *Ann Clin Psychiatry.* 1993;5(1): 53–65
24. Gold MS, Pottash AC, Sweeney DR, Kleber HD. Opiate withdrawal using clonidine: a safe, effective, and rapid nonopiate treatment. *JAMA.* 1980;243(4):343–346
25. Sica DA. Centrally acting antihypertensive agents: an update. *J Clin Hypertens.* 2007;9(5):399–405
26. Houston MC. Clonidine hydrochloride. *South Med J.* 1982; 75(6):713–719
27. Timmermans PB, Brands A, van Zwieten PA. Lipophilicity and brain disposition of clonidine and structurally related imidazolidines. *Naunyn Schmiedebergs Arch Pharmacol.* 1977;300(3): 217–226
28. Pettinger WA, Mitchell HC, Gullner HG. Clonidine and the vasodilating beta blocker antihypertensive drug interaction. *Clin Pharmacol Ther.* 1977;22(2):164–171
29. Klein-Schwartz W. Trends and toxic effects from pediatric clonidine exposures. *Arch Pediatr Adolesc Med.* 2002;156(4): 392–396
30. Sinha Y, Cranswick NE. Clonidine poisoning in children: a recent experience. *J Paediatr Child Health.* 2004;40(12): 678–680
31. Spiller HA, Klein-Schwartz W, Colvin JM, Villalobos D, Johnson PB, Anderson DL. Toxic clonidine ingestion in children. *J Pediatr.* 2005;146(2):263–266
32. You-hua Z, You-cheng S, Jun Z, Xian-qi Y. Sympathetic inhibition with clonidine improves autonomic balance in congestive heart failure. *Int J Cardiol.* 1997;59(2):139–144
33. Leckman JF, Ort S, Caruso KA, Anderson GM, Riddle MA, Cohen DJ. Rebound phenomena in Tourette's syndrome after abrupt withdrawal of clonidine. Behavioral, cardiovascular, and neurochemical effects. *Arch Gen Psychiatry.* 1986;43(12): 1168–1176
34. Martin PR, Ebert MH, Gordon EK, Weingartner H, Kopin IJ. Catecholamine metabolism during clonidine withdrawal. *Psychopharmacology.* 1984;84(1):58–63
35. Vignali G, Guadagnucci A, Tulli G. Clonidine abstinence syndrome: a clinical case. *Minerva Med.* 1990;81(9):645–647
36. Kandall SR, Albin S, Gartner LM, Lee KS, Eidelman A, Lowinson J. The narcotic-dependent mother: fetal and neonatal consequences. *Early Hum Dev.* 1977;1(2):159–169
37. Levinson ML, Johnson CE. Stability of an extemporaneously

compounded clonidine hydrochloride oral liquid. *Am J Hosp Pharm.* 1992;49(1):122–125
38. Behrman A, Goertemoeller S. A sticky situation: toxicity of clonidine and fentanyl transdermal patches in pediatrics. *J Emerg Nurs.* 2007;33(3):290–293
39. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. *Pediatr Crit Care Med.* 2007; 8(2):115–131
40. Tobias JD. Dexmedetomidine to treat opioid withdrawal in infants following prolonged sedation in the pediatric ICU. *J Opioid Manag.* 2006;2(4):201–205
41. Langenfeld S, Birkenfeld L, Herkenrath P, Muller C, Hellmich M, Theisohn M. Therapy of the neonatal abstinence syndrome with tincture of opium or morphine drops. *Drug Alcohol Depend.* 2005;77(1):31–36
42. Arenas-López S, Riphagen S, Tibby SM, et al. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. *Intensive Care Med.* 2004;30(8):1625–1629

Clonidine as an Adjunct Therapy to Opioids for Neonatal Abstinence Syndrome: A Randomized, Controlled Trial

Alexander G. Agthe, George R. Kim, Kay B. Mathias, Craig W. Hendrix, Raul Chavez-Valdez, Lauren Jansson, Tamorah R. Lewis, Myron Yaster and Estelle B. Gauda

Pediatrics 2009;123;e849; originally published online April 27, 2009;
DOI: 10.1542/peds.2008-0978