Evaluation of the Cardiovascular Effects of Clonidine in Neonates Treated for Neonatal Abstinence Syndrome

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OBJECTIVES Neonatal abstinence syndrome (NAS) is characterized by withdrawal symptoms in neonates exposed to legal or illegal substances *in utero*, and it is often managed with medications such as opiates, phenobarbital, and clonidine. Clonidine use is increasing, but further safety data regarding its use in neonates are warranted. This study evaluated the effects of clonidine on heart rate and blood pressure in neonates treated for NAS at doses up to 24 mcg/kg/day.

METHODS A retrospective review via the electronic medical record of infants at least 35 weeks' gestation treated adjunctively with clonidine for NAS in the neonatal intensive care unit at St Elizabeth was conducted. Heart rate, and systolic and diastolic blood pressure were recorded at baseline, while on different dose ranges of clonidine (small: ≤ 1.5 mcg/kg per dose every 3 hours; medium: >1.5 to 2 mcg/kg per dose every 3 hours; and large: >2 mcg/kg to 3 mcg/kg per dose every 3 hours), and upon discontinuation.

RESULTS A total of 64 infants treated with clonidine for NAS between August 2015 and December 2016 were included. Heart rate decreased in all clonidine dose ranges compared with baseline (average reduction of 7 bpm [CI: -12 to -2], 9 bpm [CI: -16 to -2], and 10 bpm [CI: -18 to -1] for the small, medium, and large dose ranges, respectively; $p < 0.0001$). Systolic and diastolic blood pressure were not significantly different from baseline when infants were receiving any dose of clonidine, except diastolic blood pressure while on medium-dose range clonidine, where diastolic blood pressure was higher than baseline ($p = 0.0128$). Increases in systolic and diastolic blood pressure were evident upon discontinuation of clonidine ($p < 0.0001$ and $p = 0.0156$, respectively).

CONCLUSIONS Clonidine doses up to 24 mcg/kg/day are well tolerated in neonates ≥ 35 weeks' gestation treated for NAS. Any decreases in heart rate are likely clinically insignificant, and increases in blood pressure upon discontinuing clonidine are mild and may be mitigated further with extended discontinuation protocols. Further trials should be conducted to evaluate the long-term safety of clonidine in this population.

ABBREVIATION NAS, neonatal abstinence syndrome

KEYWORD neonatal abstinence syndrome

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Introduction

Neonatal abstinence syndrome (NAS) is defined as withdrawal signs and symptoms exhibited in a neonate exposed to heroin, opiates, benzodiazepines, or other substances *in utero* and occurs with abrupt cessation of drug exposure after delivery.¹ Neonatal abstinence syndrome can be seen after exposure to a variety of medications, but it is most notably seen with chronic *in utero* opioid exposure.^{1,2} It is characterized by central nervous system excitability or irritability, autonomic nervous system dysregulation and instability, as well as gastrointestinal dysfunction.^{1,2}

Across the United States, the incidence of NAS is increasing, with a recent report describing a 300% increase in NAS from 1999 to 2013.³ Neonatal abstinence syndrome is particularly problematic in our region, with a reported 24-fold increase in hospital NAS diagnosis

in the state of Kentucky from 2001 to 2016, with 46 reported cases of newborns with NAS in 2001 versus 1115 cases in 2016.⁴

Treatment of NAS usually begins with non-pharmacologic modalities, such as breastfeeding, rocking, non-nutritive sucking, and providing a quiet and low-light environment.^{1,2,5} When these measures fail, the American Academy of Pediatrics recommends the use of opioids (e.g., morphine or methadone) to help ameliorate NAS.^{3,6} Occasionally, neonates may require additional treatment modalities when these first-line opioid medications fail to fully control their NAS symptoms.⁷ Of these adjunctive treatments, clonidine and phenobarbital are most commonly used.⁵ Clonidine use appears to be increasing whereas phenobarbital is falling out of favor because of long tapering and potential side effects on the developing brain.^{7–9}

Figure. Patient Selection

NAS, neonatal abstinence syndrome.

Clonidine is a centrally acting α_2 adrenergic receptor agonist.^{2,7} Stimulation of this receptor results in a negative feedback with diminished sympathetic outflow via reduced norepinephrine release.^{2,7} Because many of the manifestations of NAS are believed to be caused by an increased release of norepinephrine, clonidine is hypothesized to directly reduce signs and symptoms associated with NAS.² Several published prospective studies on clonidine for the treatment of NAS demonstrate its efficacy as both adjunctive therapy and monotherapy.^{9–11} Additionally, these studies demonstrate no adverse effects in clonidine-treated neonates, including clinically significant hypotension, bradycardia, or rebound cardiovascular effects with dose reduction or discontinuation.^{9–11} Doses studied ranged from 5 to 12 mcg/kg/day divided every 3–6 hours.^{9–11}

St Elizabeth Healthcare protocol for treating NAS involves use of Finnegan scores, a standardized system for identifying withdrawal symptoms in a neonate.¹² When a neonate has 3 consecutive Finnegan scores ≥ 8 or 2 consecutive scores ≥ 12 , sublingual buprenorphine is initiated as the treatment opioid of choice at a dose of 4.5 mcg/kg per dose every 8 hours. Clonidine is added if NAS symptoms are not controlled with buprenorphine alone. This usually occurs when we escalate the buprenorphine dose without a subsequent

reduction in withdrawal symptoms per Finnegan scoring or in instances where there is difficulty weaning buprenorphine. Clonidine is started at 1.5 mcg/kg per dose administered orally every 3 hours. If Finnegan scores remain elevated (≥ 8), we titrate the clonidine up by 0.5 mcg/kg per dose incrementally to a maximum of 3 mcg/kg per dose every 3 hours. Consideration for switching from buprenorphine to morphine occurs in neonates with average Finnegan scores that fail to fall below 8 on our maximum buprenorphine and clonidine doses (7.5 mcg/kg every 8 hours and 3 mcg/kg every 3 hours, respectively). Once an infant has discontinued opioids or is on small doses of an opioid with low and stable Finnegan scores (average < 8), clonidine is weaned each day by 0.5 mcg/kg per dose to eventual discontinuation. Heart rate is monitored every 3 hours and blood pressure is measured at least every 12 hours while on therapy, as well as when therapy is discontinued up until time of discharge. Lastly, phenobarbital is added in instances of multiple failed attempts to wean off the opioid medication.

There are few pharmacokinetic studies of clonidine in neonates. Xie et al¹³ evaluated clonidine in 36 neonates with gestational age greater than 35 weeks treated for NAS. Their findings suggest the clearance of clonidine dramatically increases within the first few weeks of life,

Table 1. Baseline Demographics

Variable	All Neonates (n = 64)	Small Dose (n = 62)	Medium Dose (n = 29)	Large Dose (n = 22)
Sex, female, n (%)	30 (47)	30 (48)	15 (52)	11 (50)
Gestational age, wk, mean $\pm$ SD	38 5/7 $\pm$ 1 5/7	38 5/7 $\pm$ 1 5/7	39 1/7 $\pm$ 1 2/7	39 3/7 $\pm$ 1 2/7
Postnatal age at clonidine initiation, days, mean $\pm$ SD	4 $\pm$ 2	—	—	—
Duration of clonidine, days, mean $\pm$ SD	10 $\pm$ 6	10 $\pm$ 7	15 $\pm$ 6	16 $\pm$ 6
Birth weight, kg, mean $\pm$ SD	3.02 $\pm$ 0.47	—	—	—
Length, inches, mean $\pm$ SD	19.41 $\pm$ 1.14	—	—	—
Treatment opioid, n				
Buprenorphine	57	57	18	14
Morphine	15	14	9	6
Methadone	6	6	2	2
None	1	1	0	0
Opioid switch from buprenorphine during treatment, n	12	12	11	8
Phenobarbital addition, n	9	8	8	6

and doses larger than 1 mcg/kg per dose every 4 hours may be warranted. However, concerns for hypotension and/or bradycardia may prohibit using increased doses of clonidine. This study sought to provide additional short-term safety data by assessing the cardiovascular effects of oral clonidine up to doses of 24 mcg/kg per day in neonates treated for NAS.

Materials and Methods

This was a retrospective chart review that used the electronic medical record to collect data on neonates admitted to our neonatal intensive care unit for treatment of NAS between August 1, 2015, and December 31, 2016. Approval was obtained from the Institutional Review Board, and consent of a legal guardian was deemed unnecessary for this evaluation.

Patients were included if they were at least 35 weeks' gestational age, received a diagnosis of NAS, and received clonidine per protocol for at least 24 hours. Exclusion criteria included patients who were admitted to the neonatal intensive care unit for a reason

other than NAS (Figure). Furthermore, data collection was stopped once a neonate began phenobarbital or switched opiate therapy to minimize the impact this would have on the data interpretation.

The medical record was used to collect the following: gestational age, sex, birth weight, length, treatment opioids, type of *in utero* exposure, and adjunctive phenobarbital use. Per hospital protocol, heart rate and blood pressure measurements were noted 24 hours prior to starting clonidine, for up to 24 hours on each dosing step of clonidine, and for 24 hours after discontinuation of clonidine. Because clonidine was incrementally titrated, patient data were stratified into 3 different dosing groups (Table 1). These groups include clonidine doses ≤ 1.5 mcg/kg per dose every 3 hours (small), doses >1.5 to 2 mcg/kg per dose every 3 hours (medium), and doses >2 to 3 mcg/kg per dose every 3 hours (large).

Heart rate and blood pressure measurements are presented as means with mean reduction from baseline (95% CI). Repeated-measures analysis of variance was

Table 2. Heart Rate: Baseline and in Each Clonidine Dosage Group

Group	Mean Heart Rate, bpm (95% CI)	Change From Baseline, bpm	95% CI	p value
Baseline (n = 64)	145 (142–148)	—	—	—
Small-dose clonidine (n = 62)	138 (135–141)	–7	–12 to –2	<0.0001
Medium-dose clonidine (n = 29)	136 (131–140)	–9	–16 to –2	<0.0001
Large-dose clonidine (n = 22)	135 (129–141)	–10	–18 to –1	<0.0001
Postclonidine (n = 33)	149 (145–153)	–4	–2 to 10	>0.05

Table 3. Systolic Blood Pressure (SBP) at Baseline and for Each Clonidine Dosage Group

Group	Mean SBP (mm Hg)	Change From Baseline (mm Hg)	95% CI	p value
Baseline (n = 64)	80	—	—	—
Small-dose clonidine (n = 62)	80 ± 1.39	0	−2.88 to 2.57	0.9101
Medium-dose clonidine (n = 29)	84 ± 1.90	4	−0.15 to 7.32	0.0599
Large-dose clonidine (n = 22)	79 ± 2.11	−1	−5.06 to 3.24	0.6672
Postclonidine (n = 33)	88 ± 1.68	8	4.48 to 11.09	<0.0001

used for analyzing both heart rate and blood pressure data. Dunnett pairwise comparisons were used to compare the mean heart rate at the different treatment phases to baseline. Regarding blood pressure, because multiple measurements were taken for each time frame, appropriate contrasts were used to compare each dosage level to the baseline. Models have been adjusted for covariates of age and sex. Statistical analysis was performed by the Northern Kentucky University Burkardt Consulting Center using SAS version 9.3 (SAS Institute Inc, Chicago IL; 2012).

Results

Data were available from 64 neonates for baseline blood pressure and heart rate measurements, 30 of whom were female. Of these, 62 neonates had data while on the smallest clonidine dose range, data were obtained from 29 neonates for the middle clonidine dose range, and 22 neonates received the largest dose range of clonidine. For clonidine discontinuation, 33 neonates had available data for collection. Neonatal abstinence syndrome was most frequently owing to exposure to methadone, heroin, and buprenorphine *in utero*, and 89% received buprenorphine as their initial treatment opioid.

We found that the small, medium, and large clonidine doses all result in a lower heart rate from baseline ($p < 0.0001$; Tables 2, 5). Average baseline heart rate was 145 bpm, and treatment heart rates were an average of 7 bpm lower than baseline (CI: −12 to −2), 9 bpm lower than baseline (CI: −16 to −2), and 10 bpm lower than baseline (CI: −18 to −1) for the small, medium, and large clonidine dose ranges, respectively. Heart rate measurements were on average 4 bpm higher in the

24 hours after clonidine discontinuation, which was not significantly different from baseline ($p > 0.05$).

Mean baseline systolic blood pressure was 80 mm Hg. At all dosage levels, systolic blood pressure was not significantly different from baseline (Tables 3, 5). However, there was evidence of an increase in mean systolic blood pressure of 8 mm Hg (CI: 4.48–11.09, $p < 0.0001$) within the 24 hours after clonidine discontinuation. Average diastolic blood pressure at baseline was 52 mm Hg. For the 3 clonidine dose range groups, difference from baseline was only found in the medium dose group, where there was evidence of an increase in mean diastolic blood pressure of 5 mm Hg (CI: 1.07–8.94; $p = 0.0128$; Tables 4, 5). Diastolic blood pressure was not different from baseline in the small-dose ($p = 0.2571$) and large-dose ($p = 0.6933$) clonidine groups. Upon discontinuation of clonidine, there was a trend toward an increase in mean diastolic blood pressure of 4 mm Hg (CI: 0.8–7.79 mm Hg, $p = 0.0156$).

Discussion

Current literature suggests clonidine is effective for the treatment of NAS and that doses ≤ 12 mcg/kg per day are tolerated in this neonatal population.^{9–11} Our retrospective review indicates that clonidine doses up to 24 mcg/kg/day are well tolerated, from a cardiovascular standpoint, when used in neonates ≥ 35 weeks' gestation for the treatment of NAS (Table 5). Although heart rates were significantly lower in all treatment groups, they were within an acceptable range for neonates (90–164 bpm).¹³ It is unlikely that the small decreases in heart rate are clinically relevant. Moreover, aside from diastolic blood pressure in the medium dose range group, treatment blood pressure was shown to be no

Table 4. Diastolic Blood Pressure (DBP) at Baseline and for Each Clonidine Dosage Group

Group	Mean DBP (mm Hg)	Change From Baseline (mm Hg)	95% CI	p value
Baseline (n = 64)	52	—	—	—
Small-dose clonidine (n = 62)	54 ± 1.46	2	−1.22 to 4.53	0.2571
Medium-dose clonidine (n = 29)	57 ± 1.99	5	1.07 to 8.94	0.0128
Large-dose clonidine (n = 22)	53 ± 2.22	1	−3.50 to 5.25	0.6933
Postclonidine (n = 33)	56 ± 1.77	4	0.8 to 7.79	0.0156

Table 5. Summative Cardiovascular Effects of Clonidine Dosing Groups

	Small-Dose Clonidine (n = 62)	Medium-Dose Clonidine (n = 29)	Large-Dose Clonidine (n = 22)	Postclonidine (n = 33)
Heart rate				
Beats per minute, mean (95% CI)	138 (135–141)	136 (131–140)	135 (129–141)	149 (145–153)
Change from baseline, bpm	–7	–9	–10	–4
95% CI	–12 to –2	–16 to –2	–18 to –1	–2 to 10
p value	<0.0001	<0.0001	<0.0001	>0.05
Systolic blood pressure				
Systolic blood pressure, mm Hg, mean $\pm$ SD	80 $\pm$ 1.39	84 $\pm$ 1.90	79 $\pm$ 2.11	88 $\pm$ 1.68
Change from baseline, mm Hg	0	4	–1	8
95% CI	–2.88 to 2.57	–0.15 to 7.32	–5.06 to 3.24	4.48 to 11.09
p value	0.9101	0.0599	0.6672	<0.0001
Diastolic blood pressure				
Diastolic blood pressure, mm Hg, mean $\pm$ SD	54 $\pm$ 1.46	57 $\pm$ 1.99	53 $\pm$ 2.22	56 $\pm$ 1.77
Change from baseline, mm Hg	2	5	1	4
95% CI	–1.22 to 4.53	1.07 to 8.94	–3.50 to 5.25	0.8 to 7.79
p value	0.2571	0.0128	0.6933	0.0156

different in infants up to the largest dose of 3 mcg/kg every 3 hours. Increase in diastolic blood pressure in the medium dose group was a peculiar finding considering the mechanism of action of clonidine to stimulate α_2 receptors and reduce sympathetic output through inhibition of norepinephrine release. It is possible this finding may be owing to influences on blood pressure from worsening withdrawal in infants within this dose range, because many of these infants proceeded to the largest dose of clonidine shortly after initiation.

When discontinuing clonidine, doses are de-escalated daily or the dosing interval is increased per protocol. The results of this review indicate that although heart rate is not significantly different when discontinuing clonidine from baseline, both systolic and diastolic blood pressures were elevated. Again, this is likely not clinically relevant because no infant was restarted on clonidine because of blood pressure increases, and could likely be mitigated by slowing the rate of de-escalating clonidine.

This study is not without its limitations. The sample size was small, which resulted in fewer neonates in the largest dose ranges of clonidine. Moreover, because of the retrospective nature of the study, there was no blinding or randomization, and results are dependent on the accuracy of the medical record.

Conclusions

These data supplement existing data regarding the safe use of clonidine in infants for the treatment of NAS. Furthermore, the results indicate that larger doses of up to 24 mcg/kg/day are well tolerated in this population; hence, these doses should be considered when managing NAS. By using the larger doses of clonidine as adjunctive management for NAS, institutions may be able to effectively treat withdrawal without using increased opiate doses or phenobarbital, and to reduce the exposure of neonates to these substances. However, these data only provide short-term cardiovascular safety information, and further trials should be conducted to evaluate the long-term safety of clonidine in this population.

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