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ARTICLE

Use of clonidine in the prevention and management of neonatal abstinence syndrome

JERROLD B. LEIKIN[1], WILLIAM P. MACKENDRICK[2], GERRY E. MALONEY[3,4], JAMES W. RHEE[5], ELAINE FARRELL[2], MICHAEL WAHL[6], and KAREN KELLY[7]

[1]*Director of Medical Toxicology, Glenbrook Hospital, NorthShore University HealthSystem – OMEGA, Glenview, IL, USA*
[2]*Department of Pediatrics, Evanston Hospital, NorthShore University HealthSystem, Evanston, IL, USA*
[3]*Toxikon Consortium, Chicago, IL, USA*
[4]*Case Western University, Cleveland, OH, USA*
[5]*Section of Emergency Medicine, University of Chicago, Chicago, IL, USA*
[6]*Division of Emergency Medicine, Evanston Hospital, NorthShore University HealthSystem, Evanston, IL, USA*
[7]*Department of Pharmacy, Evanston Hospital, NorthShore University HealthSystem, Evanston, IL, USA*

Introduction. Neonatal abstinence syndrome (NAS) is a complicated medical condition with treatment regimens that traditionally have included methadone and other opioids, barbiturates, and benzodiazepines. We describe a case series in which clonidine was used for the prevention and management of patients with NAS. *Patients and Methods*. Medical records of infants treated with clonidine for NAS from January 2003 to March 2006 were reviewed for gestational age, birth weight, NAS score, dose of clonidine, duration of treatment, and additional medications required. *Results*. Fourteen patients were identified. The mean gestational age was 30.1 weeks (range 24.4–40.7 weeks); three patients were full-term. Eleven had been on intravenous fentanyl for sedation; three were born to opioid-dependent mothers. All patients were treated with clonidine, administered in doses of 0.5–1.0 mcg/kg orally every 6 h. No patient received opioids. Mean duration of treatment was 6.8 days (range 4–15). Mean abstinence scores were 6.4 pretreatment (range 0–20) and 1.9 posttreatment (range 0–5). No patients suffered an adverse event (hypotension, bradycardia, excessive sedation, and oxygen desaturation) from clonidine administration, and no seizures were identified. *Conclusions*. Our data suggest that clonidine may be a reasonable alternative to more traditional agents used to prevent or treat NAS. We agree with the statement of the American Academy of Pediatrics Committee on Drugs that states that larger trials and pharmacologic data are needed before the routine use of clonidine can be recommended.

Keywords Neonatal; Withdrawal; Opioids

Introduction

Neonatal abstinence syndrome (NAS) is a complex clinical problem that occurs in infants, who have a prolonged exposure to certain drugs, either *in utero* or in the postnatal period. Opioids, barbiturates, and benzodiazepines are commonly used in the treatment of NAS. All these regimens utilizing these drugs have the potential disadvantages of respiratory depression, over-sedation, and prolonged tapering of doses. Clonidine is a potentially attractive therapy for NAS because of its safety profile, ease of administration, and lack of a requirement for tapering. However, reports of clonidine use in NAS are limited. In this report, we present our experience of using clonidine for the prevention and management of NAS.

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Address correspondence to Jerrold B. Leikin, Director of Medical Toxicology, Glenbrook Hospital, NorthShore University HealthSystem – OMEGA, 2150 Pfingsten Rd. 3000, Glenview, IL 60026, USA. E-mail: jleikin@northshore.org

Patients and methods

All cases of clonidine use in the NICU were identified retrospectively using the electronic medical record system for clonidine use in the NICU during the study period (January 2003–March 2006). One investigator (JL) recorded gestational age (GA), birth weight, NAS score, dose of clonidine, duration of treatment, additional medications required, and adverse events.[1,2]

Toxicology consultation was performed at the NICU attending physician's discretion; there was no set protocol. During the period of this study, one toxicologist (JL) provided all consultations. An oral clonidine suspension was administered in individual cases in doses of 0.5–1.0 mcg/kg orally every 6 h. Clonidine was discontinued based on

Table 1. Neonatal abstinence score chart

Date	Time	Time	Time	Time	Time	Time	Time	Time
Parameter								
Cry								
High pitch, not continuous (2)								
Continuous high pitch (3)								
Sleep after feeding								
3 or more hours (0)								
2–3 h (1)								
1–2 h (2)								
<1 h (3)								
Moro reflex								
Hyperactive (2)								
Markedly hyperactive (3)								
Tremor								
Mild when disturbed (1)								
Marked when disturbed (2)								
Mild when undisturbed (3)								
Marked when undisturbed (4)								
Generalized convulsion (5)								
Increased muscle tone (2)								
Frantic sucking of fists (1)								
Feeding								
Fair to good (0)								
Poor (2)								
Regurgitation								
Increased (2)								
Projectile vomiting (3)								
Stools								
Loose (2)								
Watery (3)								
Dehydrated (2)								
Frequent yawning (1)								
Sneezing (1)								
Nasal Stuffiness (1)								
Sweating (1)								
Mottling (1)								
Temperature								
>99.5 but ≤ 101 (1)								
>101 (2)								
Respiratory rate								
>60/min without retractions (1)								
>60/min with retractions (2)								
Excoriation (1)								
Total score								
Initials of scorer								

Adapted from Finnegan.[3]

the stability of the patient and the NAS scores at 24–48 h. Finnigan's NAS scoring system (Table 1) was used according to NICU protocol (every 3–4 h during the pharmacological intervention and for 48 h after discontinuation of the intervention).[3] Vital signs and oxygen saturations were recorded hourly in the nursing flow sheets. There were no exclusion criteria. The project was approved by the Institution Review Board of Evanston Northwestern Healthcare (EH 06-178).

Results

The NICU is a 44-bed level III facility, to which 1896 infants were admitted during the study period. A toxicology consultation (with JL) was requested for all suspected withdrawal patients. A total of 14 infants were identified as being at risk for or having NAS. All 14 patients received clonidine as a pharmacologic intervention specifically for NAS or for potential NAS. Tables 2 and 3 display the demographics and

Table 2. Demographic characteristics of patient cohort

Pt	Sex	GA	Drug	Starting age[a]	Apgar[b]	BW	Intubated[c]
1	F	24 w 3 d	Fentanyl	7 w	2/5	1200	Yes
2	F	39 w	Fentanyl	1 w	6/9	3600	Yes
3	F	39 w	Fentanyl	2 w	8/9	3540	Yes
4	F	25 w 1 d	Fentanyl	7 w	4/6	1200	Yes
5	M	24 w 6 d	Fentanyl	5 w	7/7	700	Yes
6	M	25 w 4 d	Fentanyl	7 w	2/5	800	No
7[d]	F	25 w 1 d	Fentanyl	6 w	6/7	740	Yes
8	M	40 w 5 d	Fentanyl	3 w	5/8	3,465	Yes
9	F	26 w 2 d	Fentanyl	10 w	4/6	650	Yes
10[d]	M	25 w	Maternal heroin	5 h	5/6	1000	Yes
11	M	35 w 2 d	Maternal methadone	5 h	6/8	2240	No
12	M	29 w	Fentanyl	6 w		0.74	Yes
13	F	34 w 4 d	Maternal methadone	5 h	7/9	2310	No
14	F	26 w 2 d	Fentanyl	4 w	3/6	500	Yes

GA, gestational age (w, weeks; d, days); BW, birth weight (g).
[a]Initiation of clonidine.
[b]At 0.5 min post-birth.
[c]At time of clonidine dosing.
[d]Intended for prophylaxis.

Table 3. Withdrawal characteristics of patient cohort

Pt	Adjunct drugs	Maximum clonidine dose[a]	Duration of use	NAS score pre-clonidine	NAS score post-clonidine
1		0.5	6 d	10	3
2		1	4 d	20	5
3		1	4 d	7	1
4	L	0.5	7 d	12	2
5	L	1	5 d	4	4
6	L	1	4 d	9	0
7	L	0.5	4 d	3	3
8	CH	1	6 d	11	4
9	L, P	1	10 d	3	0
10		0.5	11 d	0	0
11		0.5	7 d	1	1
12		1	14 d	–	–
13		1	15 d	5	0
14		0.5	6 d	4	2

L, lorazepam; P, phenobarbital; CH, chloral hydrate.
[a]mcg/kg given orally every 6 h.

withdrawal characteristics. The mean GA was 30.1 weeks (range 24.4–40.7 weeks) and the median GA was 26 weeks and 2 days; three patients were full term. Eleven patients had been on continuous intravenous fentanyl for sedation (from 1 to 6 weeks duration at continuous infusion doses up to 5 mcg/kg/h) in the NICU, and three patients were born to opioid-dependent mothers. Treatment was started in anticipation of development of NAS in 10 patients and at the onset of NAS in the remaining four. Clonidine was stopped abruptly in 12 patients and tapered (by 0.25 mcg/kg every 6 h) in two patients (patients 10 and 11) without adverse effect. The mean NAS score was 6.4 before treatment with clonidine (range 0–20) and 1.9 within 4 h after the cessation of clonidine therapy (range 0–5). The greatest improvements were seen in the patients with the highest NAS scores. Six patients were receiving additional drugs primarily for sedation: all but one of these infants were intubated (Table 3). These medications were started before clonidine was started and continued after clonidine was discontinued. Chloral hydrate (81.25 mg/day orally or by suppository) was given to one infant for 6 days prior to clonidine therapy, and one infant was treated with phenobarbital (initially 5 mg/kg then decreased to 3 mg/kg/day)

for cholestasis. The lorazepam dose was 0.1 mg/kg orally or intravenously every 4 h (as needed, up to 4 doses/day). No patient received an opioid agent. The mean duration of clonidine treatment was 6.8 days (range 4–14 days). No patient suffered an adverse event from clonidine administration and no seizures were reported. No infants had any conditions that might mimic NAS (e.g., hyperthyroidism, hypocalcemia, hypoglycemia, and sepsis).

Discussion

The treatment of NAS varies widely among institutions and may include opioid agents (tincture of opium and morphine sulfate solution), phenobarbital, or methadone.[4–6] However, these agents have several potential disadvantages, including respiratory and central nervous system depression and need for a prolonged dosage taper. One recent study noted that the average duration of outpatient phenobarbital use was 3.5 months.[5]

Clonidine, an α-2-adrenergic agonist, has been utilized for decades in adults for opiate detoxification and as a transitional agent from opiate dependence to an opiate antagonist (e.g., naltrexone).[6–8] However, its use in NAS has been limited to only a few studies.[9–11] In a case series, a total daily clonidine dose of 3–4 mcg/kg was used to treat seven neonates exposed to maternal methadone use. Six of these infants exhibited amelioration of major symptoms, and no side effects were reported.[10] Another study used a clonidine infusion (at an approximate dose of 7.5 mcg/kg/h) initiated 5 days after cardiac surgery in children (aged 0–24 months) to reduce benzodiazepine and opioid withdrawal.[12] A decrease in withdrawal signs (lower mean arterial pressure, heart rate, and core temperature) as well as reduction in opioid analgesic doses was noted. No adverse effects on cardiac rhythm were documented. It should be noted, however, that abstinence scoring was not performed.[11] Neonatal rodent studies using clonidine doses of 0.2 mg/kg demonstrated a decreased severity of tremor and a reduction in overall intensity of morphine withdrawal.[12]

Clonidine does not exhibit the sedative or respiratory depressive properties of opioid or barbiturate agents. Tapering of clonidine is not necessary, thus allowing the overall duration of therapy to be shorter. At the doses used in our cases, bradycardia or hypotension was not noted in any patient.

Most of our patients were on continuous fentanyl infusions for more than 1 week. Withdrawal occurs frequently after continuous infusions of fentanyl (especially those more than 8 days duration),[13] and the addition of naloxone to fentanyl infusions does not clinically affect opioid tolerance.[13–15]

Limitations

As a retrospective medical record review, the study is subject to incomplete information documentation, inaccurate information transcribing, and biased data abstraction. Other limitations include a lack of long-term follow-up of these patients following hospital discharge and no control (or placebo-matched) group; every neonate deemed at risk was treated.

Our results may not be generalizable. Our series consisted of a relatively small select group of patients. Our patients tended to be premature infants, most of whom were given clonidine due to prolonged postnatal use of fentanyl infusions for sedation. The limited size of the study population precludes drawing firm conclusions about how well clonidine really worked or the nature of complications that may have been missed.

The concomitant use of other sedatives may have had a modulating effect on NAS scores, although these medications were primarily used for sedation of intubated infants and were not adjusted according to NAS scores. Finally, the clonidine doses and durations were at the discretion of the attending neonatologists and the medical toxicologist.

Conclusions

Based on this series, we suggest that clonidine may be a reasonable alternative to more traditional agents used to prevent or treat NAS. Our data are similar to the findings of other studies of clonidine use for NAS: reduction in abstinence scores without the use of adjunctive opioid agents, shorter duration of treatment, and no adverse sequelae. We agree with the American Academy of Pediatrics Committee on Drugs that larger trials and pharmacologic data are needed before the routine use of clonidine can be recommended.[6] Our data add support for such trials of clonidine use in NAS.

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