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Article

Neonatal Abstinence Syndrome: The Use of Clonidine as a Treatment Option

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ABSTRACT

Infants exposed to opioids in utero and postnatally are at risk for developing withdrawal symptoms upon discontinuation of the drugs. This condition is known as the neonatal abstinence syndrome (NAS). Different medications have been used to ameliorate the symptoms of withdrawal, most commonly opioids. Clonidine has also been evaluated both as an additive and alternative option for the treatment of opioid withdrawal symptoms. Data evaluating the use of clonidine for the treatment of NAS are limited; only six studies have been published. The α -2 adrenergic receptor agonist clonidine is believed to reduce the excessive noradrenergic activity that results from opioid withdrawal. Clonidine has the potential to serve as an attractive option to treat NAS because it possesses a favorable adverse effect profile, is easy to administer, and does not require a long tapering period, unlike other agents currently used to treat NAS. Blood pressure and heart rate must be monitored with clonidine use.

OBJECTIVES

After completing this article, readers should be able to:

- 1) Describe the signs and symptoms associated with neonatal abstinence syndrome (NAS).
- 2) Describe the methods for assessing NAS.
- 3) Discuss the possible role of clonidine as a therapy of NAS.
- 4) Describe the adverse effect profile of clonidine in the neonate.

INTRODUCTION

Substance abuse during pregnancy is a growing public health concern, with approximately 4.5% of women using illicit drugs while pregnant. (1) According to reports published by the United States General Accounting Office, the overall incidence of illicit drug exposure in utero is highly underestimated. (2) Infants exposed in utero to opioids may suffer from acute withdrawal after birth, generally known as NAS. NAS can also occur with prescription medications such as amphetamines, benzodiazepines, chloral hydrate, and pemoline. (3) Infants who have NAS are predisposed to prematurity, low birthweight, and delay in growth and neurodevelopment. (4)

SIGNS AND SYMPTOMS

The typical signs and symptoms associated with NAS include hyperexcitability of the central and autonomic nervous systems and gastrointestinal dysfunction (Table 1). (3) The onset of withdrawal symptoms depends on the drug abused by the mother and the time of last exposure to the drug. Withdrawal symptoms present later with medications that have longer elimination half-lives. For example, withdrawal symptoms from heroin may become evident as early as 24 hours after delivery, whereas withdrawal symptoms associated with methadone may not be seen for at least 48 hours and may be delayed up to 4 weeks after delivery.

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Table 1.
 Signs and Symptoms of Neonatal Abstinence Syndrome (3)

DIAGNOSIS

If NAS is suspected, a detailed drug history should be obtained from the mother. Self-reporting by mothers usually underestimate fetal drug exposure. (3) Neonatal samples of urine and meconium may also be tested for drugs. The use of urine drug screens is limited by their ability to only detect drugs recently abused by the mother, leading to many false-negative results. Meconium testing is more sensitive, but it may delay diagnosis because passage of the meconium may take several days. Maternal and neonatal hair have also been used to detect fetal drug exposure. (5) In a study by Ostrea and colleagues, (6) maternal hair and meconium analyses provided the highest sensitivities in detecting fetal opioid and cocaine exposure compared with maternal interview. On the other hand, neonatal hair analysis was found to be as sensitive as meconium analysis in detecting opioid exposure but slightly less sensitive in detecting cocaine and cannabis exposure. (7) Neonatal hair can only be used to detect drug exposure that occurs after the third trimester. (5)

In addition, assessment scoring systems may be used to measure the severity of the withdrawal symptoms and to determine if pharmacologic therapy is needed. The most commonly used scale is the Finnegan Scoring System, consisting of 31 weighted items scored 1 to 5 and evaluated every 4 hours (Table 2). (8)(9) Pharmacologic therapy is recommended if the score is at least 8 or if three consecutive scores are more than 8. (10) The Finnegan Scoring System is more complex and time-consuming than other scoring methods. (3) The Lipsitz tool is an 11-item weighted scale (scored 0 to 3) that is easier to use but more subjective. (8) A score of at least 4 is needed to recommend the use of medications. The Ostrea tool is a 6-item ranking scale that also is easier to use but has no recommendation for when to initiate pharmacologic therapy. (8) Newer options include the Neonatal Withdrawal Inventory and the Neonatal Narcotic Withdrawal Index. If pharmacologic therapy is needed, these scoring systems also may be used to evaluate the need for an increase or decrease in the dose of the medication used. (11)

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Table 2.
 Example of Neonatal Abstinence Syndrome Assessment Tool Based on the Finnegan Scoring System (9)

TREATMENT OPTIONS

Supportive care is the initial treatment for patients suffering from NAS because pharmacologic therapy exposes neonates to medications that may not be needed and increases the length of hospital stay after birth. (3) Supportive care includes, but is not limited to, decreasing sensory stimulation such as swaddling the child and ensuring a quiet room and providing small frequent feedings (neonates experiencing NAS have increased metabolic requirements). In the acute phase, intravenous (IV) fluids with electrolyte replacement may also be necessary.

Pharmacologic therapy is indicated if the neonate experiences poor feeding with insufficient weight gain, fever, inability to sleep, gastrointestinal upset (eg, diarrhea or vomiting) associated with weight loss or hypovolemia, or seizures. (3) As mentioned previously, an assessment tool such as the Finnegan Scoring System may be used to assess signs and symptoms and determine if pharmacologic therapy is needed.

Several pharmacologic agents have been used to ameliorate the symptoms associated with NAS. Opioids are the most widely used, and a comparison of the commonly used opioids is shown in Table 3. One national survey reported that tincture of opium and morphine were the most commonly used agents for both opioid and polydrug withdrawal, followed by methadone for opioid withdrawal and phenobarbital for polydrug withdrawal. (13) No head-to-head trials have been conducted yet to determine the opioid of choice. The adverse effect profile of opioids has stimulated further research into the use of other agents, including benzodiazepines, barbiturates, naloxone, chlorpromazine, and clonidine (Table 4). (3)(12) Most of the alternatives have been found to be useful only when added to opioids rather than being used alone. (3) The updated Cochrane review of sedatives for NAS treatment recommends opioids as the initial therapy and phenobarbital as the preferred sedative if a sedative is used. (10) The review also proposes that the addition of phenobarbital and clonidine to an opioid may reduce the severity of withdrawal signs and symptoms. However, reviewers advise that more studies are needed to evaluate the safety and efficacy of clonidine and phenobarbital.

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Table 3.

A Comparison of Commonly Used Opioids for Neonatal Abstinence Syndrome (3)(12)

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Table 4.

A Comparison of Alternative Agents Used for Neonatal Abstinence Syndrome (3)(12)

CLONIDINE

Background

Clonidine has been studied as a potential addition to and an alternative to opioid in the treatment of NAS. It is an attractive option because of its mechanism of action and adverse effect profile. Clonidine also has the advantage of only needing a short tapering period if one is even needed.

Clonidine is an α -2 adrenergic receptor agonist that stimulates the activation of an inhibitory neuron, leading to a reduction in sympathetic manifestations, ultimately resulting in a decrease in blood pressure and heart rate. (14) Many clinicians have a misconception that decreasing blood pressure and heart rate is the reason for using clonidine to treat NAS. Although increased heart rate and blood pressure are two potential symptoms of withdrawal, they are not usually the reason for treatment. Treating the blood pressure and heart rate does not influence the clinical course of the withdrawal. Many investigators have postulated that the neurotransmitter norepinephrine is involved in NAS. (15)(16)(17)(18) During opioid withdrawal, noradrenergic transmission becomes hyperactive in the major noradrenergic nucleus such as the locus coeruleus. As an α -2 adrenergic receptor agonist, clonidine reduces such noradrenergic activity, thus reversing the cause of opioid withdrawal.

Clonidine has also been used in the treatment of hypertension, pain management, and attention-deficit/hyperactivity disorder in pediatric patients (Table 5). Its adverse effects include drowsiness, bradycardia, dry mouth, gastrointestinal upset, orthostatic hypotension, and rebound hypertension. Generally, a short tapering period is needed to prevent rebound hypertension. Immediate-release clonidine is not commercially available in suspension; it must be compounded extemporaneously (Table 6). (20)

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Table 5.
 Basis for Dosing Clonidine in Neonatal Abstinence Syndrome (14)(19)

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Table 6.
 Formula for Oral Clonidine Suspension 0.1 mg/mL (19)

Little data exist regarding the pharmacokinetics and pharmacodynamics of clonidine in neonates and children. Clonidine is eliminated primarily by the kidney, and its half-life decreases as the child's renal function matures. (14) One analysis of five studies found that clonidine clearance was slow at birth and slowly increased as the children's renal function matured. (21) Recently, a study also suggested that the clearance of clonidine (L/h per kg) actually doubled over the first postnatal month. (22) Other pharmacodynamic and pharmacokinetic data for clonidine in pediatrics are included in Table 7.

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Table 7.
 Pharmacodynamics and Pharmacokinetics of Clonidine (14)(21)(22)

Evidence

Gold and colleagues (22) first studied clonidine in the treatment of opioid withdrawal in adults in the late 1970s and early 1980s. In one placebo-controlled, double-blind crossover trial, clonidine significantly reduced symptoms of withdrawal. Study participants included 30 hospitalized opioid addicts who had participated in a methadone clinic for at least 6 months. The patients received 6 µg/kg of oral (PO) clonidine or placebo on the first day. Withdrawal signs and symptoms, such as perspiration, tremors, tachypnea, and restlessness, were assessed every hour by a research nurse clinician, who rated each sign and symptom as either present (1) or absent (0). Each patient subsequently received open-label clonidine 17 µg/kg per day in three divided doses. After the first dose, withdrawal signs and symptoms were significantly decreased at 90 minutes, with further decreases at 120 minutes ($P < 0.01$ at both time points) that were sustained for an additional 240 minutes. Systolic and diastolic blood pressures also decreased significantly ($P < 0.01$). Withdrawal symptoms remained controlled throughout the treatment and taper periods as well as upon discontinuation on day 14. Blood pressure remained significantly decreased throughout the treatment period but was managed successfully in the hospital. Clonidine doses were held in the setting of severe hypotension. The other primary adverse effect was difficulty falling asleep, which was experienced by 21 of the participants. These data supported the theory that clonidine decreases the amount of norepinephrine released through stimulation of the α -2 adrenergic receptors, thereby potentially ameliorating symptoms of opioid withdrawal.

Hoder and colleagues (23) tested this theory in an open-label pilot study of seven neonates whose mothers had all participated in a methadone maintenance clinic throughout their pregnancies. Clonidine was initiated at 0.5 to 1 µg/kg PO and subsequently titrated over 1 to 2 days to a target dose of 3 to 5 µg/kg per day divided every 4 to 6 hours. The nursing staff evaluated withdrawal symptoms, including high-pitched crying, poor feeding, insomnia, sweating, and mottling, at the end of every 8-hour shift and rated each as either mild, moderate, or severe. Once signs and symptoms were deemed to be controlled, clonidine was slowly tapered by 25% of the total daily dose every other day as the infant tolerated the decrease. A significant reduction in

symptoms was observed in six of the seven neonates. The mother of the one infant who failed to respond to clonidine was also taking haloperidol, desipramine, and theophylline. The average length of therapy for the six neonates was 12.2 days and ranged from 6 to 17 days. No significant changes were observed in blood pressure, heart rate, or atrioventricular conduction. As seen in the adult trials, sleeping difficulties were observed more often in the clonidine-treated neonates. Four of the infants had follow-up examinations at 4 to 9 months, and all were appropriately developing in motor, language, and social skills.

More recently, a multicenter, block-randomized, placebo-controlled, double-blind trial was conducted comparing clonidine to placebo in 80 infants prenatally exposed to heroin or methadone. (24) All 80 patients also received diluted tincture of opium (DTO). Oral clonidine 1 µg/kg every 4 hours or placebo of an equal volume was given to each patient. All infants initially received 0.2 mL DTO (0.08 mg morphine equivalent) PO every 4 hours. DTO was titrated by 0.1 to 0.2 mL every 3 to 4 hours to a maximum dose of 0.9 mL if symptoms were uncontrolled. Once the withdrawal symptoms were controlled, the patients were continued on the same doses of DTO and clonidine or placebo for at least 48 hours. The DTO dose subsequently was tapered by 0.05 mL/dose every 24 hours. If symptoms became uncontrollable, the previous DTO dose was reinitiated. The modified Finnegan Scoring System was used to assess withdrawal symptoms and determine if doses of DTO needed to be increased or decreased. The DTO/clonidine group had a significantly shorter duration of therapy compared with the DTO/placebo group (11 d versus 15 d, range of 4 to 28 versus 4 to 100 d, respectively; $P=0.02$). The clonidine group also required significantly less DTO/kg per day than the placebo group ($P<0.03$); the divergence occurred after the fifth day of treatment. Only five infants failed treatment, and all were in the DTO/placebo group. Seven of the infants, all in the clonidine group, experienced rebound symptoms requiring reinitiation of DTO but were still able to be tapered off DTO. Whether these rebound episodes were due to withdrawal from DTO, clonidine, or both remains unclear.

Esmaili and colleagues (25) conducted a retrospective study in infants prenatally exposed to methadone, comparing clonidine and morphine in the treatment of NAS. In the clonidine group, which consisted of 29 patients, clonidine was administered as a continuous IV infusion initiated at a rate of 0.5 µg/kg per hour. The infusion rate could be gradually titrated to a maximum rate of 3 µg/kg per hour if withdrawal symptoms were not controlled. Oral chloral hydrate 30 to 50 mg/kg was added via nasogastric tube if symptoms persisted at the maximum clonidine infusion rate. A maximum of three doses of chloral hydrate per day was allowed to control symptoms. In the morphine group, which consisted of 64 patients, PO morphine was initiated at 0.3 mg/kg per day in three divided doses and could be titrated to a maximum dose of 0.8 mg/kg per day. Phenobarbital PO could be added to the morphine group if withdrawal symptoms remained uncontrollable. Phenobarbital was initiated at 20 mg/kg per day on day 1, decreased to 5 mg/kg per day on day 2, and maintained at 5 mg/kg per day or increased to 10 mg/kg per day if symptoms were not ameliorated. The clonidine group had a significantly shorter median duration of hospitalization compared with the morphine group (32 d versus 44 d, range of 14 to 56 d versus 16 to 100 d, respectively; $P<0.00001$). The median duration of therapy was also significantly shorter in the clonidine group compared with the morphine group (14 d versus 35 d, range of 6 to 40 d versus 6 to 92 d, respectively; $P<0.00001$). After 1 week of treatment, the median Finnegan score was significantly lower in the clonidine group (7 versus 10, $P=0.01$). Blood pressure did decrease more in the clonidine group, but the difference was not significant when compared with the morphine group.

In a retrospective case series, 14 infants were treated with clonidine 0.5 to 1 µg/kg PO every 6 hours for the prevention and treatment of NAS. (26) Whereas previous trials had excluded preterm infants, this study included them, with a mean gestational age of 30.1 weeks. Only 3 of the 14 patients were born term. Also notably different from previous trials, this study included 11 patients exposed to fentanyl postnatally for sedation. The other three patients were exposed to opioid in utero. No infant was exposed to opioid while using clonidine, but six infants received additional drugs for sedation, including lorazepam, chloral hydrate, and phenobarbital. Chloral hydrate was given to one patient for 6 days before clonidine treatment, and phenobarbital was used in one infant for treatment of cholestasis. Five infants, including the one who

received phenobarbital, received lorazepam. Clonidine therapy still provided clinical benefit, even after discontinuation of the medication. Using the Finnegan Scoring System, the mean NAS score decreased from 6.4 before clonidine treatment to 1.9 within 4 hours of clonidine discontinuation. Twelve of the patients' therapy was abruptly discontinued, and two infants' therapy was tapered by 0.25 µg/kg every 6 hours. None of the 14 patients experienced rebound symptoms after clonidine was discontinued. No infant experienced an adverse effect from clonidine.

Clonidine was also shown to be effective for controlling symptoms associated with tramadol withdrawal in a case report of a 34-week gestational age male. (27) The neonate began exhibiting signs and symptoms of withdrawal, including irritability and myoclonic jerks, within 48 hours of delivery. After seizures and infection were ruled out, a detailed maternal drug history was obtained, which revealed the mother had been taking high-dose tramadol (600 to 800 mg daily) for a shoulder injury. Clonidine 1 µg/kg PO every 3 hours was initiated on postnatal day 5 and titrated to a maximum of 3 µg/kg PO every 3 hours. The Lipsitz tool was used to assess the severity of withdrawal and evaluate the effectiveness of clonidine in controlling the withdrawal signs and symptoms. Clonidine was tapered to discontinuation by postnatal day 12, but within 72 hours, it had to be restarted at 1 µg/kg PO every 8 hours due to increasing signs and symptoms of withdrawal. The neonate was discharged from the hospital 18 days after birth and was able to taper off of clonidine 3 weeks later without further withdrawal symptoms.

DISCUSSION

Opioids, benzodiazepines, and barbiturates are commonly used medications in the treatment of NAS at many pediatric hospitals. (13) Even though these regimens have been used for a long time, they are not without problems. For example, all can cause oversedation and respiratory depression. (14) Because of these adverse effects, potential prolonged tapering of the medications is required, especially for barbiturates, which have long elimination half-lives. (14) A study by Coyle and colleagues (28) found that most patients who received phenobarbital for the treatment of NAS required an average of 3.5 months of outpatient therapy.

Clonidine may be a good option to treat NAS because it does not cause oversedation and respiratory depression, and it usually does not require a taper. (14) It can be easily administered as an oral tablet or an extemporaneously compounded suspension. The concentration of the extemporaneously compounded clonidine suspension is 100 µg/mL or 0.1 mg/mL. (20) The unit of the suspension's concentration requires special attention when prescribing or compounding the formulation because thousands-fold errors have occurred when the prescribers or the pharmacists misinterpreted the unit as mg/mL instead of µg/mL. (29)

Clonidine can cause hypotension and bradycardia, but the doses that were used in clinical trials were not associated with significant differences in the incidence of these adverse effects in the treatment group compared with the control group. (19)(24)(26) Nonetheless, these potential adverse effects can limit the use of this regimen for the treatment of NAS or increasing its dose to optimal efficacy. Patients receiving clonidine require close monitoring of their vital signs.

The optimal dosing of clonidine for the treatment of NAS should be evaluated further. Most studies (19)(24)(26) performed in the past used an initial dose of 0.5 to 1 µg/kg PO every 4 to 6 hours. A recent study by Xie and colleagues (21) showed that a dose of 1 µg/kg may result in a suboptimal clonidine plasma concentrations of less than 0.8 to 1 ng/mL in neonates at postnatal ages of 3 to 4 weeks. A target plasma concentration of 0.8 to 1 ng/mL was confirmed by previous studies to provide adequate sedation in pediatric patients ages 1 to 11 years. (21)(30) Xie and colleagues (21) suggested increasing the initial dose of clonidine to 1.5 µg/kg in neonates starting the second postnatal week; an initial dose of 0.5 to 1 µg/kg may not be adequate for all age groups. Monitoring of the drug's plasma concentration may be warranted. If patients continue to exhibit withdrawal symptoms after reaching the target concentration deemed adequate to provide sedation in clinical studies (ie, 0.8 to 1 ng/mL), an alternative agent for the treatment of NAS may be considered rather than increasing the clonidine dose. Further clinical studies are required to

evaluate this dosing strategy.

CONCLUSION

Clonidine provides an alternative to opioids, benzodiazepines, and barbiturates in the treatment of NAS. As an alternative or an addition to commonly used opioid therapy, clonidine reduces symptoms associated with withdrawal and provides a shorter duration of therapy with limited adverse effects. Evidence remains limited, with only one randomized, controlled trial conducted and no long-term studies available. Larger, prospective, long-term studies are needed to assess the efficacy and safety of clonidine in the treatment of NAS.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the effects on the fetus and/or newborn infant of maternal substance abuse (eg heroin, cocaine, cannabis, methamphetamines, tobacco).
- Know the therapeutic indications for, and toxicity of, commonly used autonomic agonist and antagonist drugs.
- Recognize drugs that cross the placenta and are known to present health risks to the developing fetus or to the newborn infant.
- For therapeutic drugs commonly used in the neonate (eg, opiates, methylxanthines, barbiturates, etc), know indications for their use, clinical effects, pharmacokinetics, side effects, and toxicity.



FOOTNOTES

Author Disclosure

Drs Broome and So have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

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