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The purpose of this column is to explore the use of clonidine as a pharmacologic agent for the treatment of neonatal abstinence syndrome.

Oral Clonidine in the Management of Acquired Opioid Dependency

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ABSTRACT

Clonidine is a nonnarcotic analgesic historically used as a nasal decongestant and more recently established as an antihypertensive agent in adults. Because of its sedative properties with few adverse effects, clonidine has also been reported to be an effective pharmacologic agent for the treatment of neonatal abstinence syndrome (NAS). The use of oral clonidine as a primary or secondary agent in the treatment of NAS has been found to reduce hospitalization and duration of treatment in this population.

Keywords: NAS; clonidine; pharmacology

THE INCIDENCE OF NEONATAL abstinence syndrome (NAS) remains high, with an estimated 55–94 percent of newborns exposed to intrauterine narcotics subsequently developing NAS. Determining the most effective treatment for alleviating the symptoms of withdrawal and minimizing neonatal hospitalization continues to be a challenge for providers of neonatal care. In 1998, the American Academy of Pediatrics (AAP) published guidelines for nonpharmacologic and pharmacologic treatment of neonatal drug withdrawal.[1] Because of the AAP's publication, various pharmacologic treatments have been employed, but no single treatment has emerged that consistently and effectively treats withdrawal symptoms associated with NAS while decreasing the length of hospitalization. Although the AAP's publication in 1998 on neonatal drug withdrawal discusses the use of clonidine for withdrawal in adults and an open trial of seven neonatal patients successfully treated with clonidine for NAS, the AAP stops short of recommending it as a pharmacologic therapy in newborns, citing paucity in controlled research trials. More recent reports in the literature suggest that oral clonidine may be a viable option in the treatment of NAS because it is effective in managing symptoms of withdrawal and decreases length of hospital stay. Clonidine is a nonnarcotic centrally acting α_2-adrenergic receptor agonist used in the treatment of opioid withdrawal in adults and children.[2]

This article will review the incidence of opioid abuse in pregnancy and its effect on the newborn and will examine the research literature surrounding the therapeutic uses of clonidine.

INCIDENCE OF OPIOID SUBSTANCE ABUSE IN PREGNANCY

Opioid substance misuse has increased exponentially over the past 25 years. According to the National Institute on Drug Abuse, 1.85 million Americans are addicted to opioid painkillers such as oxycodone, with an estimated cost to our nation of more than $600 billion annually related to crime, lost work productivity, and health care.[3] More than 475,000 emergency department visits in 2009 were related to the misuse and abuse of prescription painkillers; and prescription painkillers were reportedly involved in 14,800 overdose deaths in 2008.[4] In a review of drug overdose rates by state, New Mexico and West Virginia led the nation in overdose deaths with 27.0 and 25.8 deaths per 100,000, respectively. Nebraska had the lowest rate with a reported 5.5 per 100,000 deaths.[5]

Opioid misuse is particularly problematic when it occurs during pregnancy. The rate of illicit drug use among pregnant women between 2010 and 2011 was highest in pregnant women aged 15–17 years (20.9 percent), followed by 8.2 percent aged 18–25 years, and 2.2 percent aged 26–44 years.[6]

THE EFFECTS OF OPIOID USE IN PREGNANCY

It is estimated that approximately 50,000 newborns in the United States require inpatient pharmacologic treatment each year to treat NAS.[7] Most infants will present with signs and symptoms of withdrawal following in utero substance exposure, requiring pharmacologic treatment, prolonged hospitalization, and uncertain long-term outcomes.

The variable response infants have to the maternal substance used, dosage, and last use further complicates the management of NAS.

The clinical presentation of NAS is generally predictable and well recognized with symptoms of central nervous system irritability; metabolic, vasomotor, and respiratory disturbances; as well as gastrointestinal dysfunction usually presenting within 24 hours to several days after birth.[8]

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Nonpharmacologic and pharmacologic treatments are employed to mitigate the effects of withdrawal and minimize the risk of seizures.

PHARMACOLOGIC TREATMENT OPTIONS FOR NAS

The AAP recommends matching treatment for NAS with the offending maternal substance used.[1] Limited available evidence supports the use of oral morphine solution and methadone for pharmacologic treatment of NAS.[8] Recent studies suggest the use of clonidine as a primary or adjunctive therapy for the treatment of NAS may be as effective as other pharmacologic options and may reduce the length of hospitalization related to neonatal opioid withdrawal. Table 1 offers a comparison of pharmacologic interventions used for treatment of NAS.

CLONIDINE

Clonidine is characterized as a nonnarcotic analgesic, antihypertensive agent with adrenergic agonist and α-adrenergic agonist properties.[9] In adults, clonidine is often used as an antihypertensive known as Catapres. The antihypertensive effect of clonidine is biphasic, with an initial transient rise in blood pressure followed by a sustained fall.[10] Clonidine also acts presynaptically on norepinephrine to inhibit norepinephrine release and block the effects of overexcitation of neurons in the nucleus locus coeruleus, which has been shown to be important in the treatment of narcotic addiction.[11–13] The locus coeruleus located in the forebrain regulates noradrenaline in the brain and is responsible for triggering the "fight or flight" response. Hyperactivity within this region may account for the hyperalertness, alteration in tone, and poor sleep associated with NAS.[14] There are, however, limited data regarding the pharmacokinetics of clonidine use in neonates.

THERAPEUTIC USES IN ADULTS AND CHILDREN

Historically, clonidine was used in the early 1960s as a nasal decongestant but was found to produce side effects such as hypotension, sedation, and bradycardia even with low doses.[15] In 1974, the U.S. Food and Drug Administration (FDA) approved clonidine for use in the treatment of adult hypertension and has incrementally approved its use in various conditions.[16] Gold and colleagues conducted one of

TABLE 1 ■ Comparison of Pharmacologic Interventions Used for Treatment of NAS

Drug Attributes	Morphine[a]	Methadone[b]	Clonidine[c]	Buprenorphine[d]	Diluted Tincture of Opium[e]	Phenobarbital[f]
Class	Opiate	Synthetic opiate	Centrally acting adrenergic	Synthetic opiate	Opiate	Barbiturate
Action	Mu agonist	Mu agonist	α_2-adrenergic agonist	Partial mu agonist	Mu agonist	Decrease hyperactivity in the CNS
Duration of action	Shorter half-life 8 hours	Long-acting half-life 26 hours	Long-acting	Long-acting	Variable	Long-acting
Adverse effects	Respiratory depression	Prolonged Q-T interval	Rebound symptoms of increased BP and HR with abrupt cessation	Respiratory depression	CNS depression, respiratory distress, seizures, and hypotension	Oversedation Impaired sucking reflex
Special considerations	First-line therapy Frequent dosing	First-line therapy	Less sedative effects or respiratory depression	Able to titrate to high doses Needs more research on efficacy	Diluted oral morphine solution No standard formulation: high morphine and opioid concentrations	Adjunctive therapy Outpatient monitoring and weaning Periodic blood level monitoring
Efficacy	More effective than phenobarbital	Trials inconclusive compared with morphine	↓ Finnegan scores with primary or adjunctive therapy	Decrease in duration of therapy when compared with morphine	No difference between diluted tincture of opium and oral morphine	Improved outcomes as an adjunctive agent

Abbreviations: BP = blood pressure; CNS = central nervous system; HR = heart rate.

a 7,32,34,36

b 2,28

c 8,12,20

d 28,35

e 36

f 2,31,33,36

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the first human studies using clonidine to block acute opiate-withdrawal symptoms in adults.[9] Use of clonidine was further expanded to include epidural injection in adults, with FDA approval in 1997. More recently, the FDA approved clonidine for the treatment of attention deficit hyperactivity disorder in pediatric patients ≥6 years of age.[17] Reports of clonidine treatment in children first appeared in the 1970s when clonidine was used in children with migraine headaches.[18] Oral clonidine has been prescribed for attention-deficit disorder and preoperatively in pediatric anesthesia.[18]

REVIEW OF THE LITERATURE

Few neonatal studies have reported using clonidine for the treatment of NAS. A review of the published literature to date using the search term "clonidine for NAS" produced 16 results. Of the 16 results, 15 were related to human subjects, two were Cochrane reviews from 2002 to 2010, and several were updates or review articles. One study reviewed the pharmacokinetic analysis of clonidine and renal clearance in newborns being treated with clonidine for NAS. Only five of the results were feasibility research studies related to the use of clonidine as a primary or secondary agent for the treatment of neonatal withdrawal and ranged from a single case study to the only published randomized controlled trial to date. O'Mara and colleagues published a single case study using clonidine treatment in a 34-week infant after intrauterine exposure to high-dose maternal use of tramadol.[19] Hoder and colleagues published a pilot study involving seven newborns treated with oral clonidine, which was the first published study using clonidine for the treatment of NAS and would become the basis for additional research studies that followed.[13] Another study by Leikin and colleagues reviewed the use of clonidine for iatrogenic-induced NAS following prolonged use of fentanyl, and a study by Esmaeili and colleagues retrospectively reviewed 133 neonates treated with a combination of either clonidine and chloral hydrate or morphine and phenobarbital.[20,21] Of the 15 results, only one is a randomized controlled trial with a sample size of 80 newborns and is described in more detail in the following text.[12] All of the studies reported favorable results with a decrease in treatment therapy and hospitalization. Table 2 summarizes the results of five published studies on the use of clonidine for treatment of NAS, and the 2010 Cochrane review and randomized controlled trial is described in the following text.

A 2010 Cochrane review summarized the results of seven interventional trials from 1977 to 2009, comparing sedatives versus nonopiate controls/nonpharmacologic treatment therapies and sedatives versus other sedatives.[22] The authors concluded that infants with NAS because of opiate withdrawal should receive initial treatment with an opiate. In those infants treated with an opiate, the addition of a sedative (phenobarbitone or clonidine) may help to reduce the severity of withdrawal. Only one of the seven studies investigated clonidine in this review. The study randomized 80 newborns (40 control and 40 placebo) to receive treatment for NAS with either an opiate combined with clonidine or an opiate and placebo, with the primary outcome of decreasing the duration of pharmacotherapy for NAS. The authors found that adding oral clonidine to opioid therapy for neonatal withdrawal related to maternal methadone or heroin use reduced the duration of treatment for neonates with NAS by 27 percent as compared with the opiate/placebo group.[12] Researchers noted that, although the addition of clonidine as an adjunct to opiate therapy may be more effective in treating severe NAS, additional studies are recommended to evaluate its safety and efficacy.[22] Of particular significance is the fact that the only randomized controlled study published to date used clonidine as an adjunct to therapy rather than a first-line agent in the treatment of NAS.[12] In response to Agthe and colleagues' study, Gal and colleagues assert that α_2-agonists such as clonidine have neuroprotective properties and should be considered as a first-line therapy for the treatment of NAS.[23]

Shorter hospitalization and duration of treatment are the observed advantages in recent studies using oral clonidine for NAS. Clonidine also has distinct advantages over other treatment options because it does not possess the same sedative or respiratory depressive properties as other opioid or barbiturate agents, which does not result in oversedation and respiratory depression, and doses do not usually need to be tapered.[20,24]

CLONIDINE DOSING FOR NEONATAL ABSTINENCE SYNDROME

There are no clear-cut recommendations about the use of clonidine for the management of NAS. Most studies have used clonidine in conjunction with opiates to attenuate the symptoms of withdrawal; however, there are no guidelines regarding when to initiate clonidine as an adjunct therapy. In addition, limited data exist regarding optimal neonatal dosing of clonidine. Research studies to date have used clonidine doses between 0.5 and 1 mcg/kg every four to six hours. In a small case series, Gal and colleagues have documented success in using clonidine with daily doses ranging from 1 mcg/kg every six hours to 4 mcg/kg every three hours, noting treatment durations ranging between three and 28 days. Treatment was longest when neonatal abstinence was the result of maternal methadone use.[23] Current recommended neonatal dosing for treatment with clonidine in neonatal opioid withdrawal is divided into dosing regimens according to whether the infant is preterm or term.[11]

For the *preterm* infant, studies have used oral preparations of 0.50–1 mcg/kg/dose of clonidine every six hours with tapering of doses by 0.25 mcg/kg/dose every six hours as the infant stabilizes. Studies in *term* neonates have used doses of 1 mcg/kg/dose every four hours in combination with diluted opium tincture. The AAP reports

TABLE 2 ■ Summary of Studies on the Use of Clonidine for Treatment of NAS

	Purpose	Study	Sample	Dosage	Results
Agthe et al. (2009)[12]	Clonidine/DTO as an adjunct vs placebo/DTO for treatment of NAS	Randomized, double-blinded trial	80 newborn infants (40 control, 40 placebo)	Oral clonidine 1.0 mcg/kg every 4 h or placebo (DTO 1:25 dilution, 0.4 mg/mL morphine equivalent)	Clonidine/DTO stabilized and detoxified infants with moderate-to-severe NAS more rapidly than DTO alone. Length of therapy was reduced 27% in clonidine group.
Esmaeili et al. (2010)[21]	Combination of clonidine/chloral hydrate vs morphine/phenobarbital	Retrospective review	133 neonates from 1998 to 2008 (29 treated with clonidine/chloral hydrate; 64 treated with morphine/phenobarbital)	Clonidine 0.5–3.0 mcg/kg/h continuous IV with addition of chloral hydrate 30–50 mg/kg/dose PO/gavage vs oral morphine 0.3–0.8 mg/kg/d in three divided doses with addition of phenobarbital 20 mg/kg/d, decreased to 5 mg/kg/d following initial loading dose	Duration of treatment 14 d in clonidine/chloral hydrate group vs 35 d in morphine/phenobarbital group; shorter hospital stays (32 d vs 44 d)
Hoder et al. (1984)[13]	Clonidine for treatment of NAS	Pilot study	7 newborn infants	Oral clonidine 3–5 mcg/kg/d in divided doses every 4–6 h	Successful treatment in 6 of 7 infants. Treatment ranged 6–17 d with mean length of 12.2 d. One infant failed to respond to treatment after 27 d, and therapy was discontinued without subsequent treatment.
Leikin et al. (2009)[20]	Clonidine for treatment of NAS	Retrospective review	14 infants (3 term and 11 preterm) from January 2003 to March 2006 Primarily used in preterm infants following prolonged use of fentanyl	Oral clonidine 0.5–1.0 mcg/kg every 6 h	Treatment ranged from 4 to 15 d. No adverse events were reported.
O'Mara et al. (2010)[19]	Clonidine for treatment of NAS following maternal tramadol use	Single case study	34-week infant with NAS	Oral clonidine max to 3 mcg/kg/d (three divided doses)	Discharged home DOL 18 with tapering off of clonidine 7 d following return outpatient visit

Abbreviations: DOL = day of life; DTO = diluted tincture of opium; NAS = neonatal abstinence syndrome; PO = by mouth.

success using an initial dose of diluted opium tincture 0.50–1 mcg/kg/dose (0.4 mg/mL morphine equivalent) followed by 3 mcg/kg/day of clonidine divided every four to six hours.[1] In the randomized controlled trial by Agthe and colleagues, an oral dose of 6 mcg/kg/day of clonidine was used based on the only previously published report in 1984 by Hoder and colleagues.[12] Xie and colleagues studied the renal clearance of clonidine in neonatal patients during the early postnatal period and suggested the initial dose of clonidine be increased to 1.5 mcg/kg starting the second postnatal week because of a rapid clearance of the drug in the newborn period.[25]

Onset of action (by mouth): 30–60 minutes
Maximum effect: 2–4 hours
Half-life: 44–72 hours
Duration: 6–10 hours
Elimination: Excreted primarily by the kidneys
Bioavailability: 90 percent

One of the disadvantages of using clonidine is that it is not commercially available in suspension form and must be compounded.[24]

SAFETY/SIDE EFFECTS

Clonidine has been shown to increase growth hormone secretion in children, but it is unclear what effect, if any, clonidine treatment may have in the subsequent growth of newborns treated with clonidine.[18] Additional side effects of clonidine extrapolated from adult and pediatric studies include hypotension, rebound hypertension, respiratory depression, and bradyarrhythmias.[12] In the first published study using clonidine for the treatment of NAS, Hoder and colleagues reported infants treated with clonidine were considered poor sleepers, which is consistent with the reports of insomnia and nightmares in adult opiate addicts treated with clonidine.[13] More recent studies in neonates, although few, have not reported such findings. The side effects of clonidine, such as hypotension and bradycardia, are easily monitored, and the risk of toxicity is no greater than with the administration of narcotics used to treat NAS.[23]

CURRENT RESEARCH

Currently, two clinical trial studies using clonidine as a primary treatment or adjunct therapy in the treatment of NAS are recruiting patients. One study (NCT01175668) involves the comparison of clonidine versus phenobarbital as an adjunct therapy, whereas the other study (NCT01360450) compares morphine versus clonidine (nonopiate) for the treatment of NAS.[26]

THE FUTURE OF PHARMACOLOGIC TREATMENT FOR PREGNANT WOMEN AND NEWBORNS

Approved in 2002, buprenorphine (Subutex) and buprenorphine with naloxone (Suboxone) are the only two FDA-approved medications for treatment of long-term opioid treatment in adults. They are not recommended for use during pregnancy and therefore have not been studied extensively in this population.[6] Although buprenorphine has not been approved for use during pregnancy, women who are on buprenorphine and become pregnant are often allowed to continue the drug.[27] Studies conducted comparing methadone with buprenorphine for the treatment of opioid dependency in pregnancy have determined that buprenorphine is an acceptable alternative to methadone with a shorter duration of treatment for neonates with NAS.[28] A recent review of the literature on buprenorphine for the treatment of NAS was previously published in this journal.[29]

In October 2010, the FDA approved naltrexone (Vivitrol), a nonnarcotic alternative to methadone and buprenorphine used to prevent relapse in opioid-dependent patients who have undergone detoxification treatment.[6] Naltrexone is a long-acting form of nonnarcotic that blocks opioids and is administered by intramuscular injection monthly. The advantage of naltrexone versus methadone or buprenorphine includes reduced cravings for narcotics with only once-a-month dosing and suppressed opioid use.[30]

Because naltrexone is relatively new to the market, few health care providers are familiar with the drug, and it has not been well studied for use in pregnancy.

CONCLUSION

"Clonidine is a nonnarcotic medication that effectively reduces withdrawal signs in adults; its mechanism of action specifically targets the adrenergic hyperactivity postulated to be the basis of the narcotic withdrawal syndrome. . . . Larger controlled trials and pharmacokinetic data are needed before clonidine can be advocated as routine treatment."[1] Although, anecdotally, morphine remains the mainstay in the treatment of NAS, oral clonidine offers some advantages over other pharmacologic treatment options and may be effective in the treatment of acquired opioid dependency in neonates. Additional investigation is needed in the following areas: (1) neonatal safety data, (2) optimal dosing guidelines, (3) long-term developmental outcomes, and (4) determination about whether clonidine is most effective as a first-line or adjunct therapy in the treatment of NAS.

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