Buprenorphine: A Newer Drug for Treating Neonatal Abstinence Syndrome

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NEONATES MAY BE EXPOSED to various legal and illicit substances during gestation, including cigarettes, alcohol, narcotics, benzodiazepines, antidepressants, and stimulants. Many of these substances can result in varying degrees of drug withdrawal after delivery. Polysubstance use can complicate the clinical evaluation of a newborn both in terms of assessment of withdrawal and treatment of symptoms. For the purpose of this column, the focus is on those infants with in utero narcotic exposure. The primary circumstances under which pregnant women use narcotics are illicit drug abuse, prescribed narcotic maintenance as treatment for abuse, and treatment of chronic pain conditions.

Fifty-five percent to 94 percent of neonates with in utero narcotic exposure will develop neonatal abstinence syndrome (NAS).[1] Neonatal abstinence syndrome is characterized by respiratory, gastrointestinal, central nervous system, and autonomic symptoms.[2] In a national survey in the United Kingdom and Ireland, researchers found that the majority of clinicians in neonatal units prescribed morphine sulfate as the first-line agent for both opiate (92 percent) and polysubstance (69 percent) withdrawal in neonates.[3] Similar results were found in an earlier survey of chiefs of neonatology in the United States; tincture of opium or morphine sulfate were most commonly used for management of both opioid (63 percent) and polysubstance (52 percent) use withdrawal in neonates.[4] Recently, there has been interest in buprenorphine as an alternative to morphine sulfate or other drugs to manage NAS. This column will describe buprenorphine and explore the research literature on the use of buprenorphine for NAS.

BUPRENORPHINE

Buprenorphine is a narcotic analgesic and opioid partial agonist (see sidebar, "Opioid Pharmacology Basics"). The U.S. Food and Drug Administration (FDA) has approved two sublingual formulations for treatment of opioid addiction in adults: Subutex buprenorphine monotherapy and Suboxone buprenorphine/naloxone combination therapy.[5,6] As an opioid partial agonist, buprenorphine produces the typical narcotic effects, such as euphoria and respiratory depression, but the maximal effects are less than those of heroin or methadone. At low doses, buprenorphine facilitates cessation of opioid misuse without causing withdrawal symptoms.[6] Buprenorphine is metabolized in the liver into norbuprenorphine and other metabolites. The half-life of buprenorphine in adults is 24 to 60 hours.[6]

The safety and efficacy of injectable buprenorphine (Buprenex) has been established for the management of pain in children aged 2 to 12 years.[5] There is a single report of pharmacokinetic parameters for buprenorphine in premature infants requiring opioid analgesia.[8]

Review of the Literature

Because of the relative novelty of buprenorphine as a treatment for NAS, there currently are a limited number of studies of this drug in neonates. Searching both Ovid MEDLINE and PubMed from 2000 to 2011 using keywords *buprenorphine* and *NAS* and limiting the search to English language resulted in only two studies.[9,10] These studies are described later.

Opioid Pharmacology Basics[13]

Opioid receptors—molecules on the surface of cells to which opioid compounds attach and exert their effects. Although there are several opioid receptors in the brain, the mu (μ) receptor is the receptor most relevant to opioid abuse and its treatment.

Full opioid agonists—an opiate that binds to the opioid receptor in the brain and turns it on to produce an effect in the organism. Increasing the dose of a full agonist increases the effects until a maximum effect is reached, or the receptor is fully activated. Morphine, methadone, heroin, oxycodone, and hydrocodone are examples of full opioid agonist.

Opioid antagonist—a substance that binds to opioid receptors to block activation by preventing the attachment of an agonist to the receptor. Naloxone (Narcan, Endo Pharmaceutical, Newark, NJ) is the opioid antagonist with which NICU nurses are most familiar.

Partial opioid agonist—an opioid with some of the properties of both agonist and antagonists. Partial agonists bind to the receptors and activate them but not the same degree as a full agonist. At lower doses, agonists and partial agonist produce the same effects. With increasing doses of a partial agonist, there is an increasing effect but only up to a point. At this point, increased doses do not produce increased effects. This is known as the *ceiling effect*. Additionally, partial opioid agonist displace or block full agonist from the receptors. Buprenorphine is an example of a partial opioid agonist.

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Kraft and colleagues sought to demonstrate feasibility and safety of sublingual buprenorphine for the treatment of NAS.[9] Additionally, the researchers sought to evaluate the efficacy of buprenorphine relative to standard therapy of neonatal opium solution (NOS) for the endpoints of length of treatment and length of stay. Because of the preliminary nature of the study, the study was not adequately powered to detect a difference in these efficacy endpoints. The researchers also explored buprenorphine pharmacokinetics "within the limits of what [could] be accomplished in this sized otherwise healthy neonatal study population." [9(pe602)]

Twenty-six infants, ≥37 weeks gestation with in utero exposure to opioids and demonstrating signs and symptoms of NAS, were randomly assigned in a 1:1 ratio to receive either buprenorphine or NOS. Exclusion criteria were major congenital malformation or intrauterine growth retardation; medical illness that required escalation of medical therapy, concomitant maternal benzodiazepine, or severe alcohol abuse; maternal benzodiazepine or alcohol use in the 30 days prior to enrollment; or concomitant neonatal use of cytochrome P450 inducers or inhibitors before the initiation of NAS treatment, seizures, or other neurologic abnormality. Neonatal abstinence syndrome was scored using the modified Finnegan scale,* which is standard of care at the study facility. (Treatment was initiated based on any three consecutive modified Finnegan scores ≥24.)[9]

Infants in the buprenorphine group received an initial dose of 13.2 mcg/kg/day sublingual in three divided doses. This dose was selected for this clinical trial using a pharmacokinetic model that determined a target steady-state buprenorphine concentration of 2 ng/mL.[9] The dose was increased by 20 percent for a combined Finnegan score of >24 on two or three measures or a score of 12 on a single measure of the Finnegan score. Infants in whom inadequate control had been achieved could receive a rescue dose of 50 percent of the previous dose; the subsequent dose was increased by 20 percent of the previous maintenance dose. Adjuvant therapy with phenobarbital was added if an infant reached a maximum buprenorphine dose of 39 mcg/kg/day. After three days at a stable dose, weaning was begun for modified Finnegan scores <8. The dose was weaned by 10 percent, and dosing was stopped when the dose was near or at the original starting dose. The researchers did not describe the frequency of weaning.[9]

Infants in the standard treatment group received a starting NOS dose of 0.4 mg/kg divided in six doses. The dose was escalated by 10 percent for a Finnegan score of >24 on two or three measures or a single score of 12. If a rescue dose was needed, the dose was the equivalent of one extra NOS dose. If an infant reached a dose of NOS of 1 mg/kg/day, phenobarbital was added as an adjuvant. Weaning from NOS began when infants demonstrated control of their NAS for 48 hours. Control of NAS was measured by the modified Finnegan scale; however, the researchers did not mention a specific score as a criterion for weaning. All infants, regardless of treatment allocation were observed for at least two days following the cessation of medication. The addition of phenobarbital in either group was considered a treatment failure but not an adverse event.[9]

Thirteen infants were assigned to each group. All of the mothers had been maintained on methadone. One infant in the buprenorphine group did not complete the treatment caused by onset of seizures. This infant was withdrawn from the study and treated with phenobarbital and NOS. The researchers reported that the cause of the seizures did not appear to be related to either undertreatment of withdrawal or a dose-dependent effect of the buprenorphine. The researchers reported no drug-related adverse events.[9]

The lengths of treatment and stay trended lower in the buprenorphine group than in the NOS group, but the differences between the two groups were not statistically significant. The mean length of treatment in the buprenorphine group (n = 12) was 22 days (r = 11–47 days). The mean length of treatment in the NOS group (n = 13) was 32 (r = 14–60 days). The mean length of stay in the buprenorphine group (n = 12) was 27 days (r = 17–51 days). The mean length of treatment in the NOS group (n = 13) was 38 (r = 19–66 days). Three infants in the buprenorphine group required adjuvant treatment with phenobarbital compared to one in the NOS group.

The study target steady-state concentration for buprenorphine was 2 ng/mL. Nine of the 12 infants in buprenorphine group had concentrations of <0.6 ng/mL. There were three outliers with steady-state concentrations ranging of 0.85, 1.80, and 3.69 ng/mL. Interestingly, these concentrations were not dose-dependent. The highest steady-state concentration (3.69 ng/mL) was in an infant at the initial 13.2 mcg/kg dose. The other outlying concentrations were in infants who received the protocol-specified maximum dose of 39 mcg/kg. Despite the lower steady-state concentration in the majority of the infants, the researchers reported good control of withdrawal symptoms. The researchers also noted significant dose-to-dose intrasubject variability in buprenorphine and norbuprenorphine concentrations. They suggested that the variability could not be explained only by developmental ontogeny of metabolic enzymes, but that it was likely a reflection of the extent of sublingual dosing. That is, variable amounts of each dose may have been swallowed and metabolized presystemically. The researchers further noted that morphine pharmacokinetics is also variable in neonates, and therefore clinical efficacy, rather than pharmacokinetics, will ultimately determine dose selection.[9]

In a subsequent study to build upon the study described earlier, Kraft and associates randomized 24 term infants,

*For more information on the modified Finnegan scale, see Zimmermann-Baer U, Nötzli U, Rentsch K, Bucher, HU. Finnegan neonatal abstinence scoring system: normal values for first 3 days and weeks 5–6 in non-addicted infants. *Addiction.* 2010;105(3):524–528. http://dx.doi.org/10.1111/j.1360-0443.2009.02802.x

≥37 weeks gestation with in utero exposure to opioids and a need for pharmacologic management of NAS, in a 1:1 ratio to receive either sublingual buprenorphine or oral morphine.[10] The goal of this study was to optimize the dose of sublingual buprenorphine for the treatment of NAS. Exclusion criteria were major congenital malformation or intrauterine growth retardation, medical illness that required escalation of medical therapy, concomitant maternal benzodiazepine or severe alcohol abuse, maternal benzodiazepine or alcohol use in the 30 days prior to enrollment or concomitant neonatal use of cytochrome P450 inducers or inhibitors before the initiation of NAS treatment, seizures or other neurologic abnormality. Neonatal abstinence syndrome was monitored using a modified Finnegan scale which is standard of care at the study facility. Treatment was initiated based on any three consecutive scores ≥24 or a single score ≥12 on the modified Finnegan scale.[10]

Infants randomized to the buprenorphine group received an initial dose of 15.9 mcg/kg/day sublingual divided in three doses. Several factors lead the researchers to the dosing regimen used in this study. In their previous study, the researchers observed that infants in the buprenorphine group required an initial rapid up-titration of dosing and that the infants frequently attained maximum dosage.[9] Additionally, pharmacokinetic studies revealed lower than anticipated plasma buprenorphine levels. Finally, opioid toxicity related to buprenorphine was not observed.[10] The researchers' goal was to optimize dosing by increasing the initial dose, increasing rate of dose up-titration, and increasing the maximum daily dose.[10] The dose was increased by 25 percent for combined NAS score of ≥24 total on three measures or a score of ≥12 on a single measure. Infants who demonstrated inadequate control between scheduled doses could receive a rescue dose equal to 50 percent of the previous dose; subsequent doses were increased by 25 percent of the previous maintenance dose. When the dose was stable for at least three days, buprenorphine weaning could begin for scores <8. The weaning interval was 10 percent daily. Buprenorphine was discontinued when the dose was within 10 percent of the initial dose. All dose calculations were based on birth weight. If NAS was not controlled on a maximum buprenorphine dose of 60 mcg/kg/day, the infant received a 20 mg/kg loading dose of phenobarbital followed by 2.5 mg/kg doses every 12 hours for at least two days. Phenobarbital was discontinued prior to weaning buprenorphine. Once scores were <8, the phenobarbital dose was reduced by 50 percent, and then discontinued as tolerated based on scores. The researchers reported that phenobarbital was generally discontinued two days following the initial 50 percent reduction.[10]

Standard treatment consistent of morphine 0.4 mg/kg divided in 6 doses. The dose was escalated by 10 percent for a Finnegan score of ≥24 on three measures or a single score ≥12. All dose calculations were based on daily weights. If a rescue dose was needed, the dose was the equivalent to one extra morphine dose. If an infant reached a dose of morphine 1 mg/kg/day, phenobarbital was added as an adjuvant. Phenobarbital was also discontinued as described earlier prior to weaning morphine. Morphine was weaned by 10 percent per day and discontinued when a dose of 0.15 mg/kg/day was reached. Infants in both groups were observed for a minimum of two days following discontinuation of the drugs.[10]

The infants in both groups were similar in relation to gestational age, race, gender, birth weight, and Apgar scores. All mothers had been treated with methadone. None of the adverse events reported in the study were felt likely to be related to either drug. One infant in the buprenorphine group had cytomegalovirus infection, prolonged reflux and poor feeding, elevated liver function tests (LFTs), aminoaciduria, and paronychia of a finger. The study's data safety monitor board (DSMB) reviewed the case and determined that buprenorphine was not responsible for this infant's clinical course. The DSMB did agree with the researchers' suggestion to monitor LFTs in future study participants. Predose, 7 day, and 21-day postrandomization LFTs were normal in six subsequent patients; three in buprenorphine group and three in the morphine group.[10]

The length of treatment in the buprenorphine group was 23 ± 12 days versus 38 ± 14 days in the morphine group (p=.01) representing a 40 percent reduction in length of treatment. The length of stay for the buprenorphine group was 32 ± 24 days versus 42 ± 13 days in the morphine group (p=.05). This represents a 24 percent reduction in length of stay. Three infants in the buprenorphine group and one infant in the morphine group required phenobarbital. None of the infants was readmitted for withdrawal after initial discharged.[10]

PHENOBARBITAL AS AN ADJUVANT

In the study by Kraft and colleagues published in 2008, the researchers asserted that need for phenobarbital in 3 of the 12 neonates in buprenorphine group suggested that the maximal dose of 39 mg/kg/day used in this study may not have been high enough to control symptoms of NAS. The researchers also judged the need for phenobarbital as a treatment failure.[9] However, in the subsequent study, Kraft and associates argued that the need for adjuvant phenobarbital might not be an indication of treatment failure in infants with more severe withdrawal.[10] It is still not clear where the maximum buprenorphine dose lies on the dose-response curve in this population. More infants in the buprenorphine group required phenobarbital than in the morphine group (three vs one). Because buprenorphine is a partial agonist, it is possible that it "may not be able to induce the dense signal generation at the mu opioid receptor obtained with morphine."[10(p578)] Alternatively, as asserted by the researchers, a higher maximum dose of buprenorphine may eliminate the need for phenobarbital. Kraft and associates concluded their discussion related to phenobarbital by noting that short-

term use of phenobarbital has few adverse effects and that a short course may be a useful adjunct for neonates who experience more severe withdrawal.[10]

POSSIBLE ADVANTAGES OF BUPRENORPHINE

The advantages of buprenorphine over morphine for treatment of NAS still need to be determined. Because buprenorphine has a longer duration of action and resides on the mu opioid receptor for a longer period of time, buprenorphine use may decrease sudden shifts in receptor antagonism and thus, reduce withdrawal symptoms. Additionally, a prolonged persistence of drug effect following discontinuation may also reduce symptoms. The higher up-titration of buprenorphine versus morphine (25 percent vs 10 percent) may result in more rapid attainment of symptom control in infants receiving buprenorphine. A 10 percent per day weaning schedule is used for both drugs, however, buprenorphine is discontinued sooner, within 10 percent of the starting dose, whereas morphine is weaning to 0.15 mg/kg/day before discontinuing; this is significantly lower than the initial starting dose of 0.4 mg/kg/day. Finally, because buprenorphine dosing is based on birth weight, not daily weight as morphine dosing is, there is a relative decrease in the buprenorphine dose per kilogram of current weight as the infant grows.

The results of the initial trail by Kraft colleagues suggested improved efficacy of buprenorphine over morphine in terms of length of stay and length of treatment.[9] In the second study with the revised dosing schema, the researchers reported a statistically significant difference between the buprenorphine and morphine groups in both length of stay and length of treatment, thus, demonstrating an advantage of buprenorphine over morphine in this sample of infants with NAS.[10]

Adverse Events

In the study published in 2008, Kraft and colleagues reported adverse events in two infants.[9] One infant in the buprenorphine group had generalized seizures 78 hours after the initial dose resulting in discontinuation of the buprenorphine. The trial was also placed on hold at that point. This infant had normal serum hematology, chemistries, C-reactive protein, and cerebrospinal fluid laboratory values and negative cultures. The electroencephalogram was normal. Magnetic resonance imaging revealed a small subdural hemorrhage in the posterior fossa felt to be related to the birthing process; there was no parenchymal abnormality. The researchers did not feel that there was a causal link between undertreatment of withdrawal or a dose-dependent effect of the drug. An independent review determined that the trial could resume using the established protocol.[9] A second infant in the buprenorphine group experienced a mild fungal paronychia that was deemed unrelated to the drug.[9]

In the subsequent study, the researchers reported two cases of oral thrush, one case of conjunctivitis, and one case of reflux among the infants in the morphine group. None of these adverse events were related to the drug. One infant in the buprenorphine group had a fractured clavicle at birth, which was clearly unrelated to the study drug. Another infant in buprenorphine group experienced several adverse events. Paronychia of the finger, cytomegalovirus infection, and aminoaciduria were judged to be unrelated to the drug; reflux and poor feeding and elevation of liver transaminases were deemed probably not related to the drug.[10]

CONCLUSIONS

The published studies at the time of this printing were both open label studies of buprenorphine and morphine in small samples at one center. Blinded randomized clinical trials comparing morphine to buprenorphine are needed. Several questions need to be answered before buprenorphine becomes standard therapy for NAS, including:

- Is buprenorphine safe and efficacious for treating NAS in the presence of maternal polysubstance use?
- Is buprenorphine safe in preterm infants?
- How is dosing adjusted when scores begin to rise during weaning?
- Is buprenorphine useful in preventing and treating withdrawal associated with iatrogenic physiologic opioid tolerance in infants receiving narcotics for pain management?

Jones asserted the importance of reexamining our methods for measuring neonatal abstinence.[11] Is it possible for one tool to assess withdrawal from opioids alone and in combination with other substances? The items used for measures should be clearly defined and quantifiable. Tools should be easy to use and place limited burden on the neonate, the family, and the staff.

Neonatal abstinence syndrome is a serious health issue. A recent report from SAMHSA noted that 4.4 percent of pregnant women between the ages of 15 and 44 years used illicit drugs.[7] The rate is highest among the youngest group (15.8 percent or 14,000 15- to 17-year-olds; the rate for 18- to 25-year-olds is 7.4 percent and 1.9 percent for 26- to 44-year-olds.[7,12] Assessing and managing NAS is labor intensive and fiscally costly. It is essential that research continues to focus on effective means of assessing and managing NAS with the goal of safely decreasing both the lengths of treatment and the lengths of hospitalization for these infants.

REFERENCES

1. Burgos AE, Burke BL Jr. Neonatal abstinence syndrome. *NeoReviews.* 2009;10(5):e222–e228. http://dx.doi.org/10.1542/neo.10-5-e222
2. Wong S, Ordean A, Kahan M; Society of Obstetricians and Gynecologists of Canada. SOGC clinical practice guidelines: substance use in pregnancy: no. 256, April 2011. *Int J Gynaecol Obstet.* 2011;114(2):190–192.
3. O'Grady MJ, Hopewell J, White MJ. Management of neonatal abstinence syndrome: a national survey and review of practice. *Arch Dis Child Fetal Neonatal Ed.* 2009;94(4):F249–F252. http://dx.doi.org/10.1136/adc.152769
4. Sarkar S, Donn SM. Management of neonatal abstinence syndrome in neonatal intensive care units: a national survey. *J Perinatol.* 2006;26(1):15–17. http://dx.doi.org/10.1038/sj.jp.7211427

5. Reckitt Benckiser Pharmaceutical, Inc. *Buprenex Injectable—RX only—Schedule III*. 2007. Available at: http://www.naabt.org/documents/buprenex_PI.pdf. Accessed October 1, 2011.
6. United States Department of Health and Human Services, Substance Abuse and Mental Health Services Administration. *About buprenorphine therapy*. Available at: http://buprenorphine.samhsa.gov/about.html. Accessed October 2, 2011.
7. Substance Abuse and Mental Health Services Administration. *Results from the 2010 National Survey on Drug Use and Health; Summary of National Findings*. Rockville, MD: Substance Abuse and Mental Health Administration; 2011. NSDUH Series H-41, HHS Publication No. (SMA) 11-4658.
8. Barrett DA, Simpson J, Ruter N, Kurihara-Bergstrom T, Shaw PN, Davis SS. The pharmacokinetics and physiological effects of buprenorphine infusion in premature neonates. *Br J Clin Pharmacol*. 1993;36(3):215–219.
9. Kraft WL, Gibson E, Dysart K, et al. Sublingual buprenorphine for treatment of neonatal abstinence syndrome: a randomized trial. *Pediatrics*. 2008;122(3):e601–e607. http://dx.doi.org/10.1542/peds.2008-0571
10. Kraft WK, Dysart K, Greenspan JS, Gibson E, Kaltenbach K, Ehrlich ME. Revised dose schema of sublingual buprenorphine in the treatment of the neonatal opioid abstinence syndrome. *Addiction*. 2011;106(3):574–580. http://dx.doi.org/10.1111/j.1360-0443.2010.03170.x
11. Jones HE. Commentary on Kraft et al. (2011): Treatment of neonatal abstinence syndrome—morphine, buprenorphine, and beyond. *Addiction*. 2011;106(3):581–582. http://dx.doi.org/10.1111/j.1360-0443.2010.03236.x
12. National Institute on Drug Abuse. *Topics in brief: prenatal exposure to drugs of abuse—May2011*. Available at: http://drugabuse.gov/sites/default/files/prenatal.pdf.
13. National Alliance of Advocates for Buprenorphine Treatment. *Thorough technical explanation of burprenorphine* [sic]. Available at: http://www.naabt.org/education/technical_explanation_buprenorphine.cfm. Accessed November 18, 2011.

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