VIEWPOINT

Long-Acting Opioids for Treating Neonatal Abstinence Syndrome

A High Price for a Short Stay?

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Neonatal abstinence syndrome (NAS) is a generalized multisystem disorder that produces a constellation of symptoms in neonates and results from abrupt discontinuation of opioids used by the mother during pregnancy at the neonate's birth. Approximately 13 500 neonates born in the United States each year develop NAS, and this number has increased nearly 5-fold between 2000 and 2012.[1] The percentage of neonatal intensive care unit (NICU) days attributed to NAS increased 7-fold from 0.6% in 2004 to 4% in 2013; and up to 20% of all NICU days in several centers were attributed to NAS.[2] Although some regional differences exist, this increase has occurred in all communities, all ethnicities, and in all types of hospitals. Because the period of hospitalization for the treatment of NAS now averages 16 days, the treatment costs are substantial.[3] The overall cost of care for a typical neonate with NAS may be $159 000 to $238 000 greater than that of a healthy neonate.

At-risk neonates remain in the hospital for observation, supportive care, and, if needed, opioid replacement therapy. Although neonates born to mothers with opioid use disorders are at high risk (approximately 50%) for developing NAS, there are no well-defined strategies to prevent NAS from occurring in at-risk neonates. If NAS develops, supportive measures are the standard of care, and pharmacotherapy is often initiated in the setting of inability to sleep, lack of weight gain despite adequate caloric intake, or extreme irritability or hypertonicity. If a neonate is treated with an opioid, the drug is gradually tapered as the newborn regains the capacity for self-regulation and weight gain.

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The number of neonates with NAS receiving pharmacotherapy has increased (up to 87%), and morphine is the most commonly used agent (72% in the United States and 92% in the United Kingdom).[3] Recently, however, some NAS treatment protocols have replaced morphine with methadone.[4] At some institutions, methadone has become the treatment of choice for neonates, perhaps influenced by drug replacement programs for addicted adults. The use of methadone may reduce the duration of NAS in at-risk neonates, and a shorter treatment period would substantially reduce the cost of treatment. However, many factors influence the onset, duration, and severity of NAS. These include (but are not limited to) the type and degree of fetal drug exposure, tobacco use during pregnancy, gestational age, genetic and epigenetic factors, sex, maternal autonomic control, and breastfeeding. In a recent analysis of 547 neonates treated for NAS, use of a stringent protocol for NAS treatment had the largest association with the duration of hospital stay,[4] regardless of whether morphine or methadone was used.

When methadone is used for treatment of NAS, the neonate is exposed to an opioid with a long half-life. The half-life of methadone in adults is 12 to 18 hours after the first dose, and 13 to 47 hours for the second and third doses. Although cytochrome P450 enzymes (CYP3A4, CYP2B6, and CYP2D6) that metabolize methadone are immature at birth, the measured half-life of methadone in neonates is similar to that of adults, possibly because a fetal cytochrome P450 enzyme (CYP3A7) may contribute to methadone clearance in the neonate. Because a neonate can alternate between minimal and maximal NAS withdrawal symptoms within a few hours, it is difficult to titrate the dose of methadone due to its long half-life. In contrast, because of its shorter half-life, morphine can be administered every 3 to 4 hours, which enables rapid dose adjustments in response to changes in the severity of NAS. Methadone is known to prolong the corrected QT interval in adults and neonates,[5] which places neonates at increased risk for cardiac arrhythmias. Methadone use in neonates is also associated with reduced brain and somatic growth,[6] intractable nystagmus, altered visual evoked potentials, or delayed encephalopathy. Whether the cardiac and neurological effects of methadone have long-term independent consequences for the neonate is unknown. Morphine therapy is associated with respiratory depression, bradycardia, hypotension, urinary retention, reduced gut motility, and emesis. However, the potential adverse effects for both methadone and morphine have rarely been reported in opioid-tolerant neonates presenting with NAS.

Recent evidence suggests that long-term cognitive development may be impaired in children born to mothers with opioid addiction.[7] Given the many confounding variables frequently present among women with substance use disorders and their neonates and the long period required for performing neonatal follow-up studies, it is uncertain how prolonged exposure

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to opioids affects the developing infant brain. In addition, whether different treatment strategies for NAS that use short- or long-acting narcotics have different detrimental long-term consequences is not known, as studies mostly examine short-term outcomes (ie, incidence, duration, and severity of NAS symptoms).

New strategies are needed that do not require continued exposure of the newborn brain to opiates. As one example, pretreatment of nonaddicted human volunteers with a 5-HT_3 receptor antagonist (ondansetron) reduced or prevented the appearance of experimentally induced opiate withdrawal symptoms. Of note, muscle twitches and abdominal cramping—withdrawal manifestations that are common in NAS—were eliminated after ondansetron treatment.[8]

Ondansetron has an excellent safety record, and its use in pregnant women to treat pregnancy-induced nausea and during labor for anesthetic-induced nausea has not been associated with adverse fetal outcomes. It is possible that treatment of the mother with ondansetron during labor and of the infant after birth could prevent or ameliorate the symptoms of NAS,[9] and a randomized clinical trial (NCT01965704) is under way. Other preventive strategies have been proposed, which include combining ondansetron with other agents, such as with an antihistamine. However, promising new approaches should not be incorporated into NAS treatment regimens without thorough testing of their efficacy and adverse effects.

ARTICLE INFORMATION

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REFERENCES

1. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics*. 2015;135(5):842-850.

2. Tolia VN, Patrick SW, Bennett MM, et al. Increasing incidence of the neonatal abstinence syndrome in US neonatal ICUs. *N Engl J Med*. 2015; 372(22):2118-2126.

3. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *JAMA*. 2012;307(18):1934-1940.

4. Hall ES, Wexelblatt SL, Crowley M, et al; OCHNAS Consortium. A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. *Pediatrics*. 2014;134(2):e527-e534.

5. Parikh R, Hussain T, Holder G, Bhoyar A, Ewer AK. Maternal methadone therapy increases QTc interval in newborn infants. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(2):F141-F143.

6. Welle-Strand GK, Skurtveit S, Jones HE, et al. Neonatal outcomes following in utero exposure to methadone or buprenorphine: a National Cohort Study of opioid-agonist treatment of Pregnant Women in Norway from 1996 to 2009. *Drug Alcohol Depend*. 2013;127(1-3):200-206.

7. Nygaard E, Moe V, Slinning K, Walhovd KB. Longitudinal cognitive development of children born to mothers with opioid and polysubstance use. *Pediatr Res*. 2015;78(3):330-335.

8. Chu LF, Liang D-Y, Li X, et al. From mouse to man: the 5-HT3 receptor modulates physical dependence on opioid narcotics. *Pharmacogenet Genomics*. 2009;19(3):193-205.

9. Elkomy MH, Sultan P, Carvalho B, et al. Ondansetron pharmacokinetics in pregnant women and neonates: towards a new treatment for neonatal abstinence syndrome. *Clin Pharmacol Ther*. 2015;97(2):167-176.