



Pediatric Academic Societies Meeting

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Buprenorphine Cuts Neonatal Abstinence Syndrome Treatment Length by Nearly Half

Clinical trial results presented at the 2017 Pediatric Academic Societies Meeting suggest better alternative than standard morphine treatment

SAN FRANCISCO – Findings of a phase 3 clinical trial being presented at the 2017 Pediatric Academic Societies Meeting show that buprenorphine is just as safe and more effective than morphine when used to treat newborns suffering withdrawal symptoms after prenatal drug exposure.

Researchers will present the study, “A Randomized Controlled Trial of Sublingual Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome,” on Sunday, May 7, at the Moscone West Convention Center in San Francisco. The randomized controlled trial known as B-BORN (Blinded Buprenorphine OR Neonatal morphine solution trial) will be published online in the *New England Journal of Medicine* on May 4.

More than half of infants exposed to opioids during pregnancy require pharmacologic treatment for withdrawal symptoms of neonatal abstinence syndrome, such as seizures and respiratory and digestive problems, that make it difficult for them to adequately eat and sleep. Traditional treatment for these newborns, most often with morphine, requires lengthy hospital stays.

The B-BORN study followed up earlier-phase clinical trials that suggested buprenorphine could reduce the length of treatment and hospitalization needed for babies with neonatal abstinence syndrome. Researchers enrolled 63 infants who were born exposed to opioids—97 percent of whom were exposed to methadone. They compared sublingual buprenorphine to oral morphine treatment outcomes and found similarly promising results.

"This study has large public health implications, since the rate of neonatal abstinence has increased almost 5-fold over the past 15 years," said lead author Walter Kraft, MD, Professor of Pharmacology, Medicine & Surgery at Thomas Jefferson University. In some hospitals, he said, NAS accounts for more than 20 percent of all days patients spend in the neonatal intensive care unit.

Buprenorphine was associated with a 42 percent decrease in the length of treatment compared to standard morphine, according to the trial. Average length of treatment needed for babies given buprenorphine was 15 days compared with 28 days using morphine, he said, while length of hospital stays for babies treated with buprenorphine averaged 21 days, versus 34.5 days for those treated with morphine.

In addition, Dr. Kraft said, there were no readmissions or increased need for "rescue" therapy with phenobarbital when symptoms didn't initially subside. Buprenorphine has a well-established safety record in adults, he said, and no safety issue was identified in this trial. Babies' respiratory rate, liver function and other health indicators, for example, were similar in both groups.

"Our findings provide evidence that buprenorphine can safely and effectively serve to reduce the significant burden of neonatal abstinence syndrome on individual infants and families, and hospitals," he said.

Dr. Kraft will present the study, "A Randomized Controlled Trial of Sublingual Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome," at 8:45 a.m.

Reporters interested in an interview with Dr. Kraft may contact Thomas Jefferson University media relations officer Gail.Benner@Jefferson.edu.

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The Pediatric Academic Societies (PAS) Meeting brings together thousands of individuals united by a common mission: to improve child health and wellbeing worldwide. This international gathering includes pediatric researchers, leaders in academic pediatrics, experts in child health, and practitioners. The PAS Meeting is produced through a partnership of four organizations leading the advancement of pediatric research and child advocacy: Academic Pediatric Association, American Academy of Pediatrics, American Pediatric Society, and Society for Pediatric Research. For more information, visit the PAS Meeting online at www.pas-meeting.org, follow us on Twitter @PASMeeting and #pasm17, or like us on Facebook.

ABSTRACT

TITLE: A Randomized Controlled Trial of Sublingual Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome

Background: Pharmacologic treatment of neonatal opioid abstinence syndrome (NAS) with morphine (MOR) is associated with a long duration of treatment and hospital stay. Phase 1

clinical data suggest that buprenorphine (BUP), a partial mu opioid agonist, may be more effective than MOR for the treatment of NAS.

Objective: This is a Phase 3 clinical trial comparing sublingual BUP to oral MOR as treatment for NAS. The primary outcome was length of treatment (LOT), and secondary outcomes were length of hospitalization (LOS), and need for adjunct therapy with phenobarbital.

Design/Methods: This was a double blind, double dummy, single site, randomized, clinical trial (NCT01452789). Opioid exposed infants \geq 37 wks GA were eligible. Exclusion criteria were: major congenital anomaly, birth wt < 2.2 Kg, medical or neurologic illness, hypoglycemia requiring IV glucose, bilirubin $>$ 20 g/dl, maternal benzodiazepine use $<$ 30 days before birth, or seizures. Infants were scored using a modified Finnegan instrument. Infants with a single score \geq 12 or sum of 3 scores \geq 24 were randomized to receive BUP q8 or MOR q4, and a matched placebo to maintain blinding. If NAS symptoms persisted at maximum doses of opioid, phenobarbital was added. Doses were weaned in 10% steps. The two-sample Wilcoxon rank sum test with continuity correction was used to compare LOT and LOS. Supplemental phenobarbital requirement was compared using Fisher's exact test.

Results: Sixty-three infants were enrolled (BUP = 33, MOR = 30). 97% of infants had in utero exposure to methadone. Patients were analyzed according to *intention to treat, per protocol*, and *as treated* populations. In all analyses, BUP significantly reduced median LOT (15 vs. 28 days, P<0.001) and LOS (21 vs 34.5 days, P<0.001) when compared to MOR. There was no difference (p =0.53) of need for adjunct phenobarbital between BUP (5, 15%) and MOR (7, 23%). Safety measures, including respiratory rate and liver function, were comparable in both groups.

Conclusion(s): In the treatment of NAS, sublingual BUP is associated with shorter LOT and LOS than current standard of care using oral MOR. BUP was as safe as MOR and offers an alternative to treating NAS.