Cohort Analysis of a Pharmacokinetic-Modeled Methadone Weaning Optimization for Neonatal Abstinence Syndrome

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Objective To evaluate neonatal abstinence syndrome (NAS) treatment outcomes achieved using an optimized methadone weaning protocol developed using pharmacokinetic (PK) modeling compared with standard methadone weaning.

Study design This pre-post cohort study evaluated 360 infants who completed pharmacologic treatment for NAS with methadone as inpatients at 1 of 6 nurseries in southwest Ohio between January 2012 and March 2015. Infants were initially treated with a standard methadone weaning protocol (n = 267). Beginning in July 2014, infants were treated with a revised methadone weaning protocol developed using PK modeling (n = 93). Linear mixed models were used to calculate adjusted mean primary outcomes, including total duration of methadone treatment, total administered methadone dosage, and length of inpatient hospital stay, which were compared between weaning protocols. The use of adjunctive therapy for NAS treatment was examined as a secondary outcome.

Results Infants who received NAS treatment with the revised protocol experienced a shorter duration of methadone treatment (13.1 vs 16.4 days; $P < .001$) and shorter duration of inpatient treatment (18.3 vs 21.7 days; $P < .001$) compared with infants receiving standard methadone weaning. No difference was observed in total methadone dosage administered (0.52 vs 0.52 mg/kg; $P = .97$) or in the use of adjunctive therapy (22.6% vs 25.5%; $P = .68$) between groups.

Conclusion Refinement of a standard methadone weaning protocol using PK modeling was associated with reduced duration of opioid weaning and shortened length of stay for pharmacologic treatment of NAS. *(J Pediatr 2015;167:1221-5)*.

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The incidence of drug withdrawal among infants subsequent to chronic in utero opioid exposure has risen dramatically over the past decade.[1-3] Although the severity of withdrawal associated with neonatal abstinence syndrome (NAS) often necessitates prolonged neonatal hospitalization and gradual opioid weaning,[4-6] recent evidence suggests that improved outcomes, including shortened duration of opioid treatment and reduced length of stay, may be achieved through the adoption of, and adherence to, a stringent NAS treatment protocol.[7,8] Nonetheless, variation remains in NAS treatment approaches, including the selection of first-line treatment opioid, treatment loading dose and subsequent weaning, use of adjunctive therapy with phenobarbital, and outpatient opioid prescriptions.[9-11] In the absence of a national consensus regarding optimal NAS management, there remain opportunities for further refinement and optimization of NAS treatment strategies.[12-14]

Motivated by upward trends in regional rates of in utero drug exposure and NAS in southwest Ohio and throughout the state,[15] researchers at Cincinnati Children's Hospital Medical Center have sought to develop strategies for further improving NAS outcomes beyond those achieved through conventional, standardized weaning. One approach designed to reduce the duration of pharmacologic exposure and improve patient safety was the development of an innovative methadone weaning protocol using pharmacokinetic (PK) computer modeling and simulation.[16] The initiative was motivated by a paucity of available PK data to inform pharmacologic treatment using oral methadone, despite evidence that methadone may support equal or better outcomes than morphine for treating NAS.[7,13] Compared with standard methadone weaning guidelines, the revised protocol prescribed a shorter duration of drug treatment following an initial loading dose. The revised protocol also reduced the total number of prescribed treatment doses from 29 to 17, minimizing opportunities for drug ordering and administration errors. In July 2014, anticipating improvements in patient safety and reduced treatment duration, the revised methadone weaning protocol was adopted by consensus as the standard of care throughout the Cincinnati region.

The objective of the present study was to demonstrate the efficacy of the revised PK-modeled methadone weaning protocol for NAS treatment. We

NAS	Neonatal abstinence syndrome
PK	Pharmacokinetic

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compared NAS outcomes experienced by patients managed with the revised methadone protocol and patients treated with the standard methadone protocol. Evaluated outcomes include duration of methadone treatment, length of inpatient stay, and total dosage of methadone treatment. We examined the use of adjunct therapy as a secondary outcome measure.

Methods

We conducted a pre-post study of neonates who were treated pharmacologically for NAS in southwest Ohio from January 2012 through March 2015. Patients were recruited from 6 nurseries housed within 5 maternity hospitals (Bethesda North Hospital, Good Samaritan Hospital, Mercy Health–Anderson Hospital, Mercy Health–Fairfield Hospital, and University of Cincinnati Medical Center) and 1 children's hospital (Cincinnati Children's Hospital Medical Center). All infants received nursery care under the direction of a single neonatology group representing the children's hospital, who, in collaboration with the Ohio Children's Hospital Association, specified standardized parameters for NAS identification, scoring, and initiation of pharmacologic treatment.[7] In addition, before study initiation, nurses in each nursery received training with D'Apolito Reliability Training for the Finnegan Neonatal Abstinence Scoring Tool,[17] to support standardization of treatment across sites. There were no substantial changes in personnel, leadership, or policies at the participating institutions during the study period.

Infants who were treated pharmacologically for NAS following in utero exposure to opioids and who were at least 34 weeks gestational age at birth were included in the study. Infants included in the analysis received methadone as the first-line weaning agent after receiving 3 consecutive scores $\geq$8 or 2 consecutive scores $\geq$12 with the modified Finnegan Neonatal Abstinence Scoring Tool.[18] All infants completed methadone weaning as inpatients. Before July 2014, infants in all 6 nurseries received treatment according to a single standard methadone weaning protocol (**Table I**; available at www.jpeds.com). From July 2014 through March 2015, infants were treated according to specifications of the revised protocol (**Table II**; available at www.jpeds.com). Six infants who received multiple opioids during treatment (as a result of failed methadone weans) were excluded from the analysis. Six infants failed the standard protocol, and no infants failed the revised protocol.

Study data were collected by research personnel at each nursery, who identified eligible patients using the administrative code for NAS (*International Classification of Diseases, Ninth Revision* code 779.5), and through review of nursery logbooks. Data were abstracted from patient medical records using a standardized data collection form and entered into a REDCap (Research Electronic Data Capture) database hosted at the children's hospital.[19] REDCap is a secure, web-based application designed to support data capture for research studies, providing an interface for real-time data entry validation. Primary measured outcomes were the number of days of methadone treatment, total dosage (mg/kg) of methadone administered throughout treatment, and length of inpatient hospital stay. The use of phenobarbital for adjunct therapy was also recorded. In utero exposure to opioids, including buprenorphine, methadone, and short-acting opioids (including codeine, fentanyl, heroin, hydrocodone, hydromorphone, morphine, and oxycodone), and exposure to nonopioids, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and phencyclidine, was captured. Positive exposures were determined by either maternal self-report or by means of positive toxicology results on regional universal maternal drug screening, which was initiated in May 2012.[20] Polysubstance exposure was defined as exposure to more than 1 opioid or to at least 1 opioid and at least 1 nonopioid substance. In addition, maternal and infant clinical and demographic predictors, along with potential confounders, were captured. As a consequence of incomplete documentation following patient transfer, 17 infants had incomplete outcome data. One infant with missing length of stay, treatment duration, and treatment dosage data was excluded from the analysis. In addition, 2 infants were missing treatment duration and dosage data, and 14 were missing dosage data. These infants were retained for analyses where data were available.

Because a randomized control trial was not feasible for testing the effectiveness of the revised methadone protocol, several adjustments were made to strengthen the study design and statistical analysis. An a priori power calculation determined that to achieve a power of 90% with a 2-sided α value of 0.05, a known treatment duration and length of stay SD of approximately 8 days, and an anticipated 3-day improvement in outcomes,[16] a sample of at least 75 patients in each comparison group was needed. Thus, data collection continued for 9 months after implementation of the optimized methadone protocol until adequate enrollment was achieved. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina). Differences in infant and maternal characteristics comparing those treated by each methadone protocol were tested using the χ^2 test for categorical variables and the t test for continuous variables. Linear mixed models were used to test mean differences in primary outcomes between methadone protocol groups (standard vs revised). Random effects were used to account for clustering within each nursery. The models incorporated potential confounders, including maternal buprenorphine exposure, polysubstance exposure, infant gestational age, highest level of care setting, any feeding of breast milk, and, for the length of stay outcome, discharge disposition. Adjusted mean duration of methadone treatment, total methadone dose, and inpatient length of stay were reported as least squares means with 95% CIs. Other factors not significantly associated with both the treatment protocol group and the outcome were not considered confounders. The χ^2 test was used to identify differences in the use of adjunct therapy between groups. Supplementary subanalyses were performed for 3 mutually exclusive subgroups of infants based on in utero opioid exposures: those with exposure to