Pharmacokinetics of Oral Methadone in the Treatment of Neonatal Abstinence Syndrome: A Pilot Study

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Objective To characterize the population pharmacokinetics of oral methadone in neonates requiring pharmacologic treatment of neonatal abstinence syndrome and to develop a pharmacokinetic (PK) model toward an evidence-based treatment protocol.

Study design Based on a methadone dosing protocol, serum concentrations of methadone and its metabolites were assessed by high performance liquid chromatography-tandem mass spectrometry from dried blood spots. Population PK analysis was performed to determine the volume of distribution and clearance of oral methadone. Methadone plasma concentration-time profiles were simulated from the deduced PK model to optimize the dosing regimen.

Results There was substantial interindividual variability in methadone concentrations. Blood concentrations of methadone were best described by a 1-compartment model with first-order absorption. The population mean estimates (coefficient of variation percentage) for oral clearance and volume of distribution were 8.94 (103%) L/h/70 kg and 177 (133%) L/70 kg, respectively. Optimized dosing strategies were developed based on the simulated PK profiles. We suggest a starting dose of 0.1 mg/kg per dose every 6 hours for most patients requiring pharmacologic treatment of neonatal abstinence syndrome followed by an expedited weaning phase.

Conclusions The proposed dosing regimen may reduce the cumulative dose of opioid and shorten the length of hospitalization. Future studies should aim to validate the simulated dosing schemes with clinical data and expand our understanding of the between-patient PK variability. *(J Pediatr 2015;167:1214-20)*.

Trial registration ClinicalTrials.gov: NCT01754324.

See editorial, p 1189
and related article, p 1221

Neonatal abstinence syndrome (NAS) is a condition unique to the newborn period that results from the abrupt cessation of chronic intrauterine drug exposure following birth. NAS severe enough to require pharmacologic intervention most frequently occurs following opioid exposure. Chronic in utero exposure to opioids is a public health burden because of its increasing prevalence, frequent need for pharmacotherapy to mitigate signs of withdrawal, prolonged hospitalization, and excessive cost.[1-3] Opioid use in the US is highly prevalent[4,5] with a 5-fold increase during pregnancy over the last decade, affecting 5.6 per 1000 births.[6,7] Much of this increase may be attributed to ubiquitous narcotic prescription for pain relief generally and in pregnancy.[8-10] The incidence of NAS has tripled from 1.20-3.39 per 1000 hospital births and is increasing in its geographic distribution.[7,11] In a recent prospective study, as many as 57% of infants born to mothers receiving opioid maintenance therapy required pharmacologic treatment, though the presence of withdrawal symptoms has been reported to be as high as 94%.[1,12]

Opioid replacement is the standard treatment for severe opioid withdrawal in neonates. Many pharmacologic treatment protocols using a variety of drugs have been proposed for the treatment of NAS.[13,14] No standardized, universally accepted treatment exists, though the agents commonly used in the majority of protocols involve methadone (20%) or other opioids (63%).[15] Most infants with NAS respond well to therapy with oral methadone. Strikingly, there are minimal pharmacokinetic (PK) data available to guide pharmacologic treatment strategies with oral methadone despite several studies suggesting that it may be an equivalent, if not superior alternative, to morphine in the treatment of NAS.[16-18] For this reason, the Best Pharmaceuticals for Children Act of the

AUC	Area under the curve
Finnegan	Finnegan Neonatal Abstinence Scoring Tool
NAS	Neonatal abstinence syndrome
PK	Pharmacokinetic

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US Food and Drug Administration includes methadone on its list of priority drugs requiring additional dosing data.[19] The PK of oral methadone has been described for adults receiving methadone for opioid dependence, and the PK of intravenous methadone used for pain control has been reported for adolescents and neonates.[20-22] We aimed to assess the PK of methadone after oral administration in infants progressing through a standardized step-wise methadone tapering protocol. The use of a formal treatment protocol has been shown to decrease hospital length of stay.[16] However, understanding the PK of oral methadone is required for designing evidence-based treatment protocols.

Table I. Oral methadone dosing scheme

Taper step	Dose (mg/kg)	Frequency	Number of doses
1	0.05	q6	×4
1A*	0.1	q6	×4
1B*	0.075	q6	×4
1C*	0.05	q6	×4
2	0.04	q6	×4
3	0.03	q6	×4
4	0.02	q6	×4
5	0.02	q8	×3
6	0.02	q12	×4
7	0.01	q12	×4
8	0.01	q24	×2

*Scheme 2: Used only for infants that are recalcitrant to scheme 1 (weaning directly from step 1 to step 2).

Methods

Institutional review boards at Cincinnati Children's Hospital Medical Center, University of Cincinnati Medical Center, and Mercy Hospital Anderson (Cincinnati, Ohio) all approved the study protocol. Informed consent was obtained from the legal guardians of all the subjects enrolled. Each participant had a history of chronic intrauterine exposure to opioids and required pharmacologic treatment with oral methadone to mitigate signs of NAS. Acutely ill neonates, infants with congenital abnormalities or medical illnesses necessitating opioid treatment for conditions other than NAS, and infants who were wards of the state were excluded.

The decision to treat infants exposed to opioids in utero rested with the medical team and was predicated upon the severity of withdrawal symptoms assessed using the Finnegan Neonatal Abstinence Scoring Tool (Finnegan) in all recruitment sites. Administrators of the Finnegan were educated using the D'Apolito Reliability Training (including an interactive DVD and proctored scoring).[16,23] In general, hospital protocols dictated that Finnegan scores be assigned every 3-4 hours starting within 24 hours of age for all infants exposed to opioids. Neonates with scores ≥8 were transferred to the neonatal intensive care unit for closer observation. Particular effort was exerted to minimize external stimulation including the use of dimmed ambient lighting and swaddling per unit protocol. Pharmacologic therapy with oral methadone was initiated in neonates having 3 consecutive scores ≥8 or 2 consecutive scores ≥12 in a 24-hour period. Administrators of Finnegan scores were not masked to prior scores or treatment.

The dosing guidelines for medications used were the same at all participating institutions and for all patients enrolled in the study (Table I). In brief, all infants were started on oral methadone treatment at 0.05 mg/kg/dose every 6 hours. Infants who responded with reduced withdrawal scores over the first 24 hours were weaned to 0.04 mg/kg/dose every 6 hours (step 2) and continued with the step-wise dosage decreases outlined (scheme 1). The clinical team was at liberty to wean the methadone dose more quickly than scheduled per protocol if there was concern for somnolence or consistently low Finnegan scores. This occurred twice and was done after study-related blood samples were obtained. In contrast, when the Finnegan scores failed to abate over the first 24 hours of treatment, the methadone dose was increased to 0.1 mg/kg/dose every 6 hours (step 1A) and was subsequently weaned per protocol after stabilization of withdrawal scores (scheme 2). Infants who failed to tolerate weaning the methadone dose every 24-48 hours or who backslid on dosing to recapture recurrent symptoms were started on phenobarbital. Subjects receiving phenobarbital were given an oral loading dose of 10 mg/kg followed by a daily dose of 5 mg/kg. The timing of adjunctive therapy with phenobarbital initiation was at the discretion of the clinical team. For the purposes of this study, the time to capture symptoms was documented. The time to capture was defined as the time required to attain 2 consecutive decreases in Finnegan scores below 12 (if therapy was initiated for 2 scores ≥12) or 2 consecutive decreases below 8 (if therapy was initiated for 3 consecutive scores ≥8) after initiation of pharmacotherapy. Blood specimens for PK studies (clearance and volume of distribution) were obtained within 72 hours of commencement of oral methadone regardless of the dosing scheme.

We used a D-optimal sparse blood sampling design with nonparametric population modeling to allow for PK variable estimation while minimizing the need for frequent blood sampling. Three or 4 blood specimens were collected from each patient. The first 3 specimens involved timed collections related to a single methadone dosing (just before a dose of methadone, 1-2 hours after that dose, and just prior to the next dose). Most families consented to an optional fourth blood sample obtained just prior to a methadone dose after the participant failed to respond to treatment as anticipated. Concentrations of methadone and its biologically inactive metabolites in dried blood spots on Guthrie cards were determined using a high-performance liquid chromatography-tandem mass spectrometry assay at the University of Colorado, Aurora, Colorado, as previously published.[24-26] The lower limit of quantitation was 0.25 ng/mL for methadone and