Published in final edited form as:

Paediatr Anaesth. 2014 June ; 24(6): 591–601. doi:10.1111/pan.12385.

The Pharmacokinetics of Methadone and its Metabolites in Neonates, Infants and Children

Robert M. Ward¹, David R. Drover², Gregory B. Hammer³, Christopher J Stemland⁴, Steve Kern⁵, Martin Tristani-Firouzi⁶, Ralph A. Lugo⁷, Kristin Satterfield⁸, and Brian J. Anderson⁹

¹Dept Neonatology & Pediatric Clinical Pharmacology, University of Utah, Salt Lake City, USA

²Department of Anesthesia, Stanford University School of Medicine, Stanford, USA ³Departments of Anesthesia and Pediatrics, Stanford University School of Medicine, Stanford, USA

⁴Department of Anesthesiology, University of Virginia, Charlottesville, Virginia, USA ⁵Department of Pharmaceutics, University of Utah College of Pharmacy, Salt Lake City, USA and Department of Anesthesiology, University of Utah, Salt Lake City, Utah 84132. Present Address: Bill & Melinda Gates Foundation, Seattle, USA. ⁶Divison of Pediatric Cardiology, University of Utah, Salt Lake City, USA ⁷Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, USA. Present address: Department of Pharmacy Practice, East Tennessee State University College of Pharmacy, Johnson City, USA ⁸Department of Pharmaceutics, University of Utah College of Pharmacy, Salt Lake City, USA, Present address: Department of University of California – Irvine, Anesthesiology & Perioperative Care, 333 City Blvd. W, Suite 2150, Orange, USA ⁹Department of Anaesthesiology, University of Auckland, New Zealand

Abstract

Background—The lack of methadone pharmacokinetic data in children and neonates restrains dosing to achieve the target concentration in these populations. A minimum effective analgesic concentration of methadone in opioid naïve adults is 0.058 mg.L⁻¹, while no withdrawal symptoms were observed in neonates suffering opioid withdrawal if plasma concentrations of methadone were above 0.06 mg.L⁻¹. The racemate of methadone which is commonly used in pediatric and anaesthetic care is metabolized to EDDP (2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine) and EMDP (2-ethyl-5-methyl-3,3-diphenylpyrroline).

Methods—Data from 4 studies (age 33 weeks PMA-15 years) were pooled (n=56) for compartment analysis using nonlinear mixed effects modeling. Parameter estimates were standardized to a 70 kg person using an allometric model approach. Investigation was made of the racemate and metabolite (EDDP and EMDP) dispositions. In addition, neonatal data (n=7) allowed further study of R and S enantiomer pharmacokinetics.

Correspondence: Brian J Anderson, PICU, Starship Children's Hospital, Auckland 1023, New Zealand, brian@adhb.govt.nz, Telephone +64-9-3074903, Fax +64-9-3078986.

Disclosure

Conflict of Interest: Drs. Hammer and Anderson are Section Editors for the journal Pediatric Anesthesia. The other authors declare no conflict of interest

IRB approval for these studies were given by the Universities of Stanford, Utah and Virginia

Results—A three-compartment linear disposition model best described the observed time-concentration profiles with additional compartments for metabolites. Population parameter estimates (between subject variability) were central volume (V1) 21.5 (29%) L.70kg⁻¹, peripheral volumes of distribution V2 75.1 (23%) L.70kg⁻¹, V3 484 (8%) L.70kg⁻¹, clearance (CL) 9.45 (11%) L.h⁻¹.70kg⁻¹ and inter-compartment clearances Q2 325 (21%) L.h⁻¹.70kg⁻¹, Q3 136 (14%) L.h⁻¹.70kg⁻¹. EDDP formation clearance was 9.1 (11%) L.h⁻¹.70kg⁻¹, formation clearance of EMDP from EDDP 7.4 (63%) L.h⁻¹.70kg⁻¹, elimination clearance of EDDP was 40.9 (26%) L.h⁻¹.70kg⁻¹, and the rate constant for intermediate compartments 2.17 (43%) /h.

Conclusions—Current pharmacokinetic parameter estimates in children and neonates are similar to those reported in adults. There was no clearance maturation with age. Neonatal enantiomer clearances were similar to those described in adults. A regimen of 0.2 mg.kg⁻¹ per 8 h in neonates achieves a target concentration of 0.06 mg.L⁻¹ within 36 h. Infusion, rather than intermittent dosing should be considered if this target is to be achieved in older children after cardiac surgery.

Keywords

modeling; pharmacokinetics; pharmacodynamics; paediatrics; opioid; analgesia

Introduction

Methadone is a drug that is increasingly used in many areas of paediatric medicine, including anaesthesia, neonatology, paediatric critical care, and oncology because it provides a longer duration of analgesia than other common opioids; its metabolites are inactive. Methadone's N-methyl-D-aspartate (NMDA) receptor antagonism is advantageous in children suffering chronic pain and its high enteral bioavailability is useful in both neonates and children in intensive care suffering opioid withdrawal syndrome. The major metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) is often measured in urine as part of a drug abuse testing program. The other metabolite is 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP), but concentrations of this metabolite have little clinical value. Despite the widespread use of this drug, there are few studies describing maturational changes in clearance with age, enantiomer clearance differences between children and neonates, or rate constants that link metabolite production to the parent drug.

Although methadone enantiomer disposition has been described in children 5-18 years, the use of noncompartment kinetics did not enable estimation of rate constants for metabolite production and elimination.⁽¹⁾ Neonatal pharmacokinetics are commonly described using an elimination half-life of the parent racemate (e.g. 16-25 h (2); 41 SD 22 h (3)). This confounded parameter is dependent on both clearance and volume. Consequently, it tracks developmental changes poorly if both volume and clearance change independently with age. Physiologically based pharmacokinetic modeling has been used to predict changes with age, but published reports currently lack supporting data from neonates and infants (4) and so remain speculative.

Methods

Data pooled from 4 studies

We have pooled data from 4 individual studies (three new studies and one published study) in an effort to describe developmental changes in methadone pharmacokinetics and metabolite production using compartment modeling.

Study 1 (University of Virginia; NCT 01205256)—Stemland et al studied adolescents aged 12-19 years (mean age 14 SD 1.2 years and weight 47.9 SD 10.4 kg) undergoing idiopathic scoliosis correction who were administered 0.25 mg.kg⁻¹ racemic methadone IV prior to surgical incision. (5) Institutional Review Board (IRB) approval was given by the University of Virginia. Legal guardian consent was obtained for all patients and children's assent was obtained. Arterial blood samples for methadone assay were obtained at 0 min, 5 min, 10 min, 15 min, 20 min, 40 min, 1 h, 2 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 24 h, and 48 h. Gas chromatography mass spectrometry was used for assay. The limit of quantitation was determined to be 10 mcg.L⁻¹ and the upper end of the linear range is 3000 mcg.L⁻¹. Intra-assay (within run) precision and inter-assay (between run) precision was < 10% throughout the analytical range.

Study 2 (Stanford University; NCT 01094522)—Methadone was administered as the primary analgesic agent in children during the 24-hour period following congenital heart surgery. Following IRB approval, 20 patients (5 days-4 years) were recruited. Legal guardian consent was obtained for all patients. Assent was not sought. Exclusion criteria were (a) single-ventricle physiology, (b) weight < 3 kg, (c) significant renal, hepatic or neurologic impairment, (d) anticipated mechanical ventilation < 24 h, and (e) administration of either morphine or methadone during the 12-hour period prior to the study or chronic opioid therapy for 30 days prior to study enrolment. Intraoperative anesthetic management was guided by standard practice of the anesthesiology faculty. After the child had been transferred to the Cardiovascular Intensive Care Unit (CVICU) and demonstrated the need for analgesia, an initial blinded intravenous dose of methadone 0.2 mg.kg⁻¹ IV was given. Subsequent doses were delivered by a nurse-operated PCA pump with a lock-out interval of 30 min. The initial PCA dose was 0.025 mg.kg⁻¹ IV; increases or decreases in the methadone dose were made in increments of 0.01 mg.kg⁻¹ or 10% as guided by the CVICU physician providers. If additional analgesia was indicated less than 30 minutes after a PCA dose, fentanyl 1-2 mg.kg⁻¹ IV was given. Lorazepam 0.025 mg.kg⁻¹ IV was administered for sedation. Excessive movement despite dosing of these agents was treated with sedative medications (e.g. propofol, dexmedetomidine, ketamine and midazolam), per CVICU provider practice. Neuromuscular blocking drugs were administered for persistent movement despite adequate analgesia and sedation. Blood samples were obtained prior to the initial dose and at 5, 15, 30, and 60 minutes as well as 2, 4, and 6 hours thereafter. Sampling was continued every 6 hours for up to 90 hours according to availability of vascular access.

Methadone and its two major metabolites, EDDP and EMDP, were simultaneously quantified using LC-electrospray ionization-tandem mass spectrometry in combination with

online column switching extraction (LC/LC-MS/MS). One hundred μL EDTA plasma was transferred into a 96- 1mL-well plate and a protein precipitation solution (methanol/0.2M ZnSO_4 , 7:3, v/v) containing deuterated internal standards was added. After centrifugation, injection directly from the 96-well plate into the LC/LC-MS/MS system, online extraction and separation on the analytical column, methadone and its metabolites was detected in the mixed reaction mode.(6) Depending on the compound (methadone or metabolites) the lower limit of quantification was 10-50 mcg.L^{-1} . The inter-assay precision was within 85-115% and total imprecision, except at the lower limit of quantitation, was better than 15%. No matrix inferences, ion suppression or carry-over was detected.

Study 3 (University of Utah; NCT 00715988)—Neonates with stable cardiovascular function, a serum K^+ 3.0 mEq.L^{-1} and older than one week of age at 33-45 weeks postmenstrual age (PMA) were studied during mechanical ventilation and analgesic treatment with fentanyl or morphine. The study was approved by the University of Utah and Primary Children's Medical Center IRBs, and all patients were studied after written informed parental consent. A single intravenous dose of methadone was substituted for one dose of the patient's current opioid and infused with a mechanical infusion pump over 15 minutes. Four to five plasma samples (0.5 mL each) were collected from an arterial line during the 48 hours following the dose with a population-based sampling scheme. Plasma concentrations of methadone, EDDP and EMDP were measured at the University of Utah Center for Human Toxicology by LC/MS/MS using a previously published assay.(7) Accuracy varied from 97% to 107% with an interassay precision of 6%. Effects on cardiac repolarization were measured from a digitized signal recorded continuously with a Mortara H12+™ holter monitor (Milwaukee, Wisconsin WI 53224, USA). The QT interval was calculated as described (8) and corrected for heart rate using Bazett's formula (7).

Study 4 (University of Utah)—The study protocol was approved by the Institutional Review Board from the University of Utah. Patients who were hemodynamically stable were screened for study enrolment based on the need for mechanical ventilation and continuous infusion of opioid. All children were enrolled in the study after consent was obtained from both parents. Due to the critical nature of the children's disease or postoperative condition, assent was not obtained. The children were classified into one of two groups depending on their weight being greater than 10 kg. A liver function panel, basic metabolic panel, and hemoglobin and hematocrit were measured prior to administration of methadone. The patients received a single intravenous dose (0.1 mg.kg^{-1} , maximum 5 mg) of methadone administered over 10 minutes by syringe pump followed by 5 minutes of saline flush. Venous blood samples were collected from an already existing vascular catheter over the next four days for methadone assay. The number and volume of blood samples were dependent on the patient's weight. For children whose body weight was 10 kg or greater, 12 blood samples were collected (Predose, then times 0, 0.25, 0.75, 1.5, 3, 6, 12, 24, 36, 48, 72, and 96 hours). The first 8 samples were 1.6 mL and the final 4 blood samples were 2.0 mL. For children less than 10 kg, 9 blood samples (1.0 mL) were collected (Predose, then time 0, 0.25, 1, 4, 12, 24, 48, 72, and 96 hours).

Pharmacokinetic Analysis

Population parameter estimations—Population parameter estimates were obtained using non-linear mixed effects modeling (NONMEM 7.1, Globomax LLC, Hanover, MD, USA). This software accounts for population parameter variability (between subjects) and residual variability (random effects) as well as parameter differences predicted by covariates (fixed effects). The population parameter variability (CV) for structural model parameters was modelled by a proportional variance model. Residual unknown variability was modelled using additive and proportional terms. The variances of the residual unidentified variability ($\eta_{RUV,i}$) were estimated. The first order conditional interaction estimate method with differential equations using ADVAN6 was used to estimate population mean parameters, between subject variance and residual variance. Convergence criterion was 3 significant digits.

The population parameter variability was modelled in terms of random effect (η) variables. Each of these variables was assumed to have mean 0 and a variance denoted by ω^2 , which was estimated. The covariance between two elements of η (e.g. CL and V) is a measure of statistical association between these two variables. Their covariance is related to their correlation (R) i.e.

$$R = \text{covariance} / \sqrt{(\omega_{CL}^2 \omega_V^2)}$$

The covariance of parameter variability was incorporated into the model.

a) Racemic methadone analysis: A three-compartment (central and two peripheral) linear disposition model was used to fit the parent drug. A metabolite compartment for EDDP (M1) was linked to the central compartment by a series of intermediate compartments to account for formation time delays. A further compartment for EMDP (M2) was linked to the EDDP compartment (figure 1). The volume of distribution for these two compartments was fixed relative to the volume of distribution at steady state (V_{ss}) based on AUC ratios for parent and metabolite analyses determined by others.⁽⁹⁾ Metabolite clearance from both EDDP and EMDP compartments were investigated as a common clearance (CLM) and as individual clearances (CLM1, CLM2). Direct formation clearance of EMDP from the methadone parent (CLPM2) was also investigated.

b) Neonatal stereoisomer analysis and effect on QTc: Data from neonates were in study 3 were limited (n=7) and were analysed using a simpler two-compartment model with an additional compartment for the EDDP metabolite. We assumed that all parent methadone was converted to EDDP and the metabolite volume was given a volume scaled (FVM) to V_1 (Figure 2). Neonatal data included QT_c (also known as QT_{Bazett}) changes with time after methadone administration. An integrated PK-PD model using an additional effect compartment for the R-enantiomer linked to the central compartment using a rate constant (Keo) for R-methadone was investigated. A sigmoid Emax model was used to describe QT_c changes with concentration in the effect compartment (C_e) (Figure 2).

$$QT_c = E_0 + E_{max} \frac{C_e^N}{EC_{50}^N + C_e^N}$$

Where E_0 is the baseline QTc before methadone administration, E_{max} is the maximum QTc change EC_{50} is the effect compartment concentration of the R-enantiomer at 50% of E_{max} and N is a parameter that describes the slope of this response.

c) Covariate analysis: The parameter values were standardised for a body weight of 70 kg using an allometric model (10, 11).

$$P_i = P_{std} (W_i / W_{std})^{PWR}$$

where P_i is the parameter in the i th individual, W_i is the weight in the i th individual and P_{std} is the parameter in an individual with a weight W_{std} of 70 kg. This standardisation allows comparison of child parameter estimates with those reported for adults. The PWR exponent was 0.75 for clearance, 0.25 for half-times and 1 for distribution volumes.(12)

The effect of age on clearance (maturation function, MF_{CL}) was investigated using the Hill equation (13)

$$MF_{CL} = \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}}$$

where MF_{CL} is the maturation factor, TM_{50} is the maturation half time and Hill is the Hill coefficient. The effect of age on distribution volume (MF_V) was investigated using an exponential function

$$MF_V = 1 + \beta_{VOL} \exp(-(PMA - 33) \frac{\ln(2)}{T_{VOL}})$$

where β_{VOL} is a parameter estimating the fractional difference from V_{std} at 33 weeks PMA (the youngest neonate) and T_{VOL} describes the half-time of the age-related changes V .

The quality of fit of the pharmacokinetic model to the data was sought by NONMEM's objective function and by visual examination of plots of observed *versus* predicted concentrations. Models were nested and an improvement in the objective function was referred to the Chi-squared distribution to assess significance e.g. an objective function change (OBJ) of 3.84 is significant at $\alpha = 0.05$. Bootstrap methods provided a means to evaluate parameter uncertainty.(14) A total of 1000 replications were used to estimate parameter confidence intervals. A visual predictive check (VPC) (15), a modeling tool that estimates the concentration prediction intervals and graphically superimposes these intervals on observed concentrations after a standardized dose, was used to evaluate how well the model predicted the distribution of observed plasma concentrations. Simulation was performed using 1000 subjects with characteristics taken from studied children. For data

such as these where covariates such as dose and weight are different for each patient, we used a prediction corrected VPC (PC-VPC).(16)

c) Simulation: Simulation was used to demonstrate the time-concentration profiles for a given dosage regimen. These profiles were performed using Berkeley Madonna™ modeling and analysis of dynamic systems software (Robert Macey and George Oster of the University of California) using pharmacokinetic parameter estimates from this current analysis for a neonate (3.5 kg) given methadone to manage opioid withdrawal and a child (20 kg) given methadone for pain relief after cardiac surgery. A target concentration of 0.06 mg/L was used for both neonate and child.

Results

Population parameter estimates for the parent drug and its two metabolites standardised to a 70 kg person using allometric models are shown in Table 1. The racemate analysis comprised 1248 observations from 56 children (geometric mean age 3.3 years, coefficient of variability [CV] 124%, range 33 weeks PMA – 15 years; geometric mean weight 10.7 kg CV 125%, range 3-76 kg). The addition of intermediate compartments to account for formation time delays that was characterised by a rate constant (RateMI) decreased the objective function (OBJ 102.552) over the model without delays. The use of separate clearances from each metabolite compartment (CLM1, CLM2) rather than a single common clearance (CLM) also decreased the objective function (OBJ 15.543). An additional estimate for direct formation clearance of EMDP from the parent methadone was low (CLPM2 0.35 L.h⁻¹.70kg⁻¹), but also reduced the objective function (OBJ 10.86). The correlation of between parameter variability introduced to increase stability of the model in shown in Table 2. Figure 3 demonstrate the quality of fit of pharmacokinetic data for the parent drug, methadone. We were unable to demonstrate methadone clearance changes with age (Figure 4), but age did have an impact on V2 (Figure 4) (OBJ 12.216, p<0.005). This decrease with age reached 80% of its final value by 5 years.

Enantiomer parameter predictions for neonates (n=7, observations=183) are shown in Table 3. The correlation of between parameter variability introduced to increase stability of the model in shown in Table 4. Neonates had an age of 40 SD 3.6 weeks PMA and weight 3.2 SD 0.99 kg. The volume of distribution for the EDPP metabolite was scaled (FVM) to V2. A simplified 2-compartment model was adequate to describe time-concentration profiles because early concentration assays immediately after dose administration were not available. Similarly, the introduction of a formation delay rate constant (RateMI) had minimal impact on the objective function (OBJ 2.9). It is noteworthy that formation and elimination clearances of metabolites differed for R and S isomers. The effect on QT_c was assumed due to effect compartment R-methadone linked to plasma methadone by a T_{1/2} keo of 3 min. This effect was minimal (E_{max} 10.4 msec) and sustained throughout the study period. Despite the methadone-induced increase in QT_c, the QT_c for all neonates remained within the normal neonatal range (400 SD 20 ms)

Simulation for a neonate shows that the target concentration can be achieved rapidly using a bolus of 0.6 mg.kg⁻¹ followed by 0.15 mg.kg⁻¹ 8 h. Alternatively this target concentration

can be achieved within 36 hours without the bolus by dosing regularly with methadone 0.2 mg.kg^{-1} 8 h (Figure 5). A single dose of methadone 0.2 mg.kg^{-1} given for postoperative analgesia in a child is unlikely to achieve long duration of analgesia because concentrations are below 0.03 mg.kg^{-1} within 1.5 h. Infusion may be a better option. A regimen comprising methadone bolus 0.15 mg.kg^{-1} followed by $0.15 \text{ mg.kg}^{-1}.\text{h}^{-1}$ for 1 h, $0.075 \text{ mg.kg}^{-1}.\text{h}^{-1}$ for 2 h and $0.025 \text{ mg.kg}^{-1}.\text{h}^{-1}$ for 6 h maintains a concentration of 0.06 mg.L^{-1} (Figure 5) An alternative approach would be a bolus of 0.5 mg.kg^{-1} followed by 0.05 mg.kg^{-1} 4 hourly.

Discussion

Methadone is cleared by the cytochrome P450 mixed oxidase (CYP3A4, CYP2B6 and CYP2D6) enzyme systems; all of which are immature at birth.(17) We anticipated reduced clearance in neonates, but found that neonatal clearance was similar to that observed in children and adolescents, when expressed using allometric models. We suspect that CYP3A7 may contribute to clearance in the neonate.(18) Fetal liver microsomes are reported to show extremely high CYP3A7 levels ($311\text{--}158 \text{ pmol.mg}^{-1}$ protein) and significant expression through 6 months postnatal age; the decrease in activity mirrors the rise of CYP3A4 activity.(18)

Consistent with our findings of a “mature” clearance (similar to adults) at birth, we report neonatal clearance estimates for the R and S isomers (Study 2) that are similar to those reported in adults and teenagers (CL R-methadone $7.25 \text{ L.h}^{-1}.\text{70kg}^{-1}$; CL S-methadone $8.2 \text{ L.h}^{-1}.\text{70kg}^{-1}$). Australian adults enrolled in a methadone maintenance program given oral methadone had a mean clearance (CL/F) of 8.7 (95%CI 7.9, 9.6) L.h^{-1} and 8.3 (95%CI 7.3, 9.5) L.h^{-1} for the R and S isomers respectively.(19) We might assume that clearance is higher, given a relative bioavailability 0.86 for the oral formulation.(20) Clearance in methadone naïve teens was less after intravenous administration (R-methadone $6.9 \text{ SD } 2.8 \text{ L.h}^{-1}.\text{70kg}^{-1}$, S-methadone $5.7 \text{ SD } 2.5 \text{ L.h}^{-1}.\text{70kg}^{-1}$) and closer to neonatal estimates. Our volume of distribution at steady state (V_{ss}) estimates (V_{ss} R-methadone 685 L.70kg^{-1} , 95%CI 538, 663; S-methadone 438 L.70kg^{-1} , 95%CI 312, 382) were similar to those in adults on chronic therapy (V_{ss}/F R-methadone 597 L , 95%CI 538, 663; S-methadone 345 L , 95%CI 312, 382). There was a decrease in the peripheral volume of distribution that reached 80% of an “adult” estimate by the age of 5 years. Methadone has high lipid solubility (octanol-water partition coefficient $\text{LogP}=3.93$), similar to fentanyl ($\text{LogP}=4.05$) and sufentanil ($\text{LogP}=3.95$) (21) and such drugs rapidly distribute into fat tissues (including that in CNS). Distribution to V_2 mirrors these fat changes in childhood.

Drug-induced prolongation of the QT interval is a recognized risk factor for ventricular arrhythmias. While methadone prolonged the QTc with an estimated maximum increase of 10.4 ms, the QTc for all neonates remained within the normal range ($400 \text{ SD } 20 \text{ ms}$) (22). The established threshold for regulatory concern by the Food and Drug Administration includes a mean effect on QTc of 10 ms (23). Our study involves a small number of neonates in a critical care setting. Given the limited number of neonates evaluated, it is difficult to extrapolate the observed changes to a larger population of newborns and children. While methadone is known to prolong the QT interval by blocking the cardiac human ether-a-go-go-related (hERG) potassium channel, the effect of methadone on QTc is

associated with chronic dosing in adults rather than an isolated dose and it is the daily methadone dose that correlates positively with the QTc interval (24, 25). QTc prolongation by hERG channel blockers such as methadone provides the substrate for torsade de pointes arrhythmia, but an additional trigger is typically required to initiate arrhythmia. These triggers include electrolyte imbalances, underlying cardiac disease, hypothyroidism or concurrent medications.

Scant data exist to define the target concentration for either opioid withdrawal management in children or for analgesia after cardiac surgery. No withdrawal symptoms were observed in neonates if plasma concentrations of methadone were above 0.06 mg/L.(2) Similarly, an estimate of the EC₅₀ (the steady-state methadone concentration eliciting 50% of maximum pain relief), obtained after administration to relatively naïve subjects, was 0.058 SD 0.015 mg.L⁻¹ (range: 0.035-0.08 mg.L⁻¹). (24) Dosing in neonates will depend on the clinical scenario. Rapid establishment of target concentration can be achieved using a bolus dose strategy (0.6 mg.kg⁻¹ followed by 0.15 mg.kg⁻¹ 8 h). Alternatively a dose of 0.2 mg.kg⁻¹ 8 h will achieve the target concentration within 36 h; 4 hourly dosing (0.1 mg.kg⁻¹) will avoid high peak concentrations by administering the next dose before completion of distribution of the preceding dose.

Analgesic response in adults on chronic methadone programs suggests a steep concentration-response relationship (gamma slope function) for pain relief (4.4 SD 3.8) with very rapid equilibration between plasma methadone concentrations and the sites mediating pain relief.(25) Consequently the drug rapidly loses effect as concentrations fall below the EC₅₀. A single dose of 0.2 mg.kg⁻¹ will contribute little analgesia after a few hours. An infusion has been suggested for analgesia in teenagers after spinal instrumentation surgery (5) and consideration could be given to this technique after cardiac surgery in children.

Acknowledgments

Financial support:

Dr Lugo was supported during this study, in part, by a grant from the National Institutes of Health (NIDA) - 5 RO1 DA10779-02.

Drs. Ward, Satterfield and Kern (University of Utah) were supported during this study in part by grants from the National Institutes of Health (NICHD) - U10 HD045986-01 and 3U10HD045986-05S1 and an unrestricted grant from the University of Utah Vice President for Health Sciences. The neonatal study was registered with ClinicalTrials.gov, NCT 00715988.

Drs. Drover and Hammer (Stanford University) received support for this study through a NCCR/NICHD CTSA consortium project grant via the Stanford University Center for Clinical and Translational and Educational Research Sponsor: NIH ref: 3 UL1 RR025744-02S3. The study was registered with ClinicalTrials.gov NCT 01094522

The adolescent methadone study from the University of Virginia was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) NCT 01094522

All other support was provided from institutional and/or departmental sources

We gratefully acknowledge the skilled study coordination by Jeanne Francis, RN, CCRC for the neonatal study from the University of Utah.

References

- Sharma A, Tallchief D, Blood J, et al. Perioperative pharmacokinetics of methadone in adolescents. *Anesthesiology*. 2011; 115:1153–1161. [PubMed: 22037641]
- Rosen TS, Pippenger CE. Pharmacologic observations on the neonatal withdrawal syndrome. *J Pediatr*. 1976; 88:1044–1048. [PubMed: 1271174]
- Mack G, Thomas D, Giles W, et al. Methadone levels and neonatal withdrawal. *J Paediatr Child Health*. 1991; 27:96–100. [PubMed: 1883657]
- Yang F, Tong X, McCarver DG, et al. Population-based analysis of methadone distribution and metabolism using an age-dependent physiologically based pharmacokinetic model. *J Pharmacokinet Pharmacodyn*. 2006; 33:485–518. [PubMed: 16758333]
- Stemland CJ, Witte J, Colquhoun DA, et al. The pharmacokinetics of methadone in adolescents undergoing posterior spinal fusion. *Paediatr Anaesth*. 2013; 23:51–57. [PubMed: 22978825]
- Clavijo C, Bendrick-Pearl J, Zhang YL, et al. An automated, highly sensitive LC-MS/MS assay for the quantification of the opiate antagonist naltrexone and its major metabolite 6beta-naltrexol in dog and human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2008; 874:33–41.
- Himes SK, Goodwin RS, Rock CM, et al. Methadone and metabolites in hair of methadone-assisted pregnant women and their infants. *Ther Drug Monit*. 2012; 34:337–344. [PubMed: 22495425]
- Lux RL, Sower CT, Allen N, et al. The Application of Root Mean Square Electrocardiography (RMS ECG) For The Detection Of Acquired And Congenital Long QT Syndrome. *Plos One*. 2014
- Kharasch ED, Hoffer C, Whittington D, et al. Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. *Clin Pharmacol Ther*. 2004; 76:250–269. [PubMed: 15371986]
- Holford NHG. A size standard for pharmacokinetics. *Clin Pharmacokinet*. 1996; 30:329–332. [PubMed: 8743333]
- Anderson BJ, Meakin GH. Scaling for size: some implications for paediatric anaesthesia dosing. *Paediatric Anaesthesia*. 2002; 12:205–219. [PubMed: 11903934]
- Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol*. 2008; 48:303–332. [PubMed: 17914927]
- Hill AV. The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. *J Physiol*. 1910; 14:iv–vii.
- Efron B. Bootstrap methods: another look at the jackknife. *The Annals of Statistics*. 1979; 7:1–26.
- Post TM, Freijer JI, Ploeger BA, et al. Extensions to the visual predictive check to facilitate model performance evaluation. *J Pharmacokinet Pharmacodyn*. 2008; 35:185–202. [PubMed: 18197467]
- Karlsson MO, Savic RM. Diagnosing model diagnostics. *Clin Pharmacol Ther*. 2007; 82:17–20. [PubMed: 17571070]
- Hines RN. Developmental expression of drug metabolizing enzymes: Impact on disposition in neonates and young children. *Int J Pharm*. 2012
- Stevens JC, Hines RN, Gu C, et al. Developmental expression of the major human hepatic CYP3A enzymes. *Journal of Pharmacology & Experimental Therapeutics*. 2003; 307:573–582. [PubMed: 12975492]
- Foster DJ, Somogyi AA, White JM, et al. Population pharmacokinetics of (R)-, (S)- and rac-methadone in methadone maintenance patients. *Br J Clin Pharmacol*. 2004; 57:742–755. [PubMed: 15151520]
- Dale O, Sheffels P, Kharasch ED. Bioavailabilities of rectal and oral methadone in healthy subjects. *Br J Clin Pharmacol*. 2004; 58:156–162. [PubMed: 15255797]
- Grassin-Delye S, Buenestado A, Naline E, et al. Intranasal drug delivery: an efficient and non-invasive route for systemic administration: focus on opioids. *Pharmacol Ther*. 2012; 134:366–379. [PubMed: 22465159]
- Schwartz PJ, Paul AG Jr, Stramba-Badiale M, et al. Report from the Task Force of the European Society of Cardiology for the interpretation of the neonatal electrocardiogram. *Cardiol Young*. 2002; 12:592–608. [PubMed: 12739597]

23. FDA. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs 10903 New Hampshire Avenue. Silver Spring, MD: 20993 US Department of Health & Human Services; 2005. Guidance for Industry.
24. Gourlay GK, Willis RJ, Wilson PR. Postoperative pain control with methadone: influence of supplementary methadone doses and blood concentration--response relationships. *Anesthesiology*. 1984; 61:19–26. [PubMed: 6742480]
25. Inturrisi CE, Portenoy RK, Max MB, et al. Pharmacokinetic-pharmacodynamic relationships of methadone infusions in patients with cancer pain. *Clin Pharmacol Ther*. 1990; 47:565–577. [PubMed: 2188771]

Figure 1.

The racemate methadone 3-compartment PK model. V1 is the central compartment while V2 and V3 are peripheral compartments. Intercompartment clearances are expressed as Q2 and Q3. The EDDP metabolite is linked to the parent drug central compartment by a series of intermediate compartments (Rate MI). Formation clearance from the parent drug methadone to the EDDP metabolite was described using CL2M1 with subsequent formation clearance to EMDP by CL2M2. Formation clearance from parent to the EMDP metabolite

was characterised by CLPM2. Clearance of EDDP and EMDP were described by parameters CLM1 and CLM2.

Figure 2.

Neonatal enantiomer PK model. Dose has been split equally and enters central compartments for each enantiomer (V1R, V1S). The inter-compartment (QR, QS) clearances describe flow into peripheral compartments (V2R, V2S). EDDP metabolite formation clearances are CL2M1R, CL2M1S). FVM is a scale factor relating central volume to metabolite volume. Clearance of metabolites is described by CLM1R and CLM1S. The effect compartment is linked to the central compartment V1R by a rate constant Keo.

Figure 3.

Visual predictive check for the methadone parent racemate model. All plots show median and 90% intervals (solid and dashed lines). Left hand plot shows all observed concentrations. Right hand plot shows prediction percentiles (10%, 50%, and 90%) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (gray shaded areas)

Figure 4.

The upper panel shows individual predicted paracetamol clearances, standardised to a 70-kg person, from the NONMEM *post hoc* step, are plotted against postmenstrual age. No relationship between age and standardised clearance was found.

Individual predicted paracetamol peripheral compartment volume of distribution (V2), standardised to a 70-kg person, from the NONMEM *post hoc* step, are plotted against postmenstrual age in the lower panel. The solid line represents the non-linear relation between V2 and age ($p < 0.005$).

Figure 5.

The upper panel shows a simulation for a 3.5 kg neonate given a methadone loading dose of 0.6 mg.kg^{-1} followed by a maintenance dose of 0.15 mg.kg^{-1} 8 h. EDDP concentrations track parent drug concentrations. The methadone target concentration of 0.06 mg.L^{-1} is achieved rapidly when compared to the neonate given 0.2 mg.kg^{-1} 8 hourly without a loading dose.

A single dose of methadone 0.2 mg.kg^{-1} given for postoperative analgesia in a child is unlikely to achieve long duration of analgesia because concentrations are below 0.03

mg.kg⁻¹ within 1.5 h (lower panel). Infusion may be a better option. A regimen comprising methadone bolus 0.15 mg.kg⁻¹ followed by 0.15 mg.kg⁻¹.h⁻¹ for 1 h, 0.075 mg.kg⁻¹.h⁻¹ for 2 h and 0.025 mg.kg⁻¹.h⁻¹ for 6 h maintains a concentration of 0.06 mg.L⁻¹. EDDP concentrations after this infusion regimen are also shown.

Table 1

Standardised methadone population pharmacokinetic parameter estimates (BSV is the between subject parameter variability, 95% CI is the 95% confidence interval).

Parameter	Estimate	%BSV	95%CI
V1std (L.70kg ⁻¹)	21.5	29	11.6, 37.9
Q2std (L.h ⁻¹ .70kg ⁻¹)	324.6	21	185.6, 475.6
V2std (L.70kg ⁻¹)	75.1	23	33.4, 114.1
Q3std (L.h ⁻¹ .70kg ⁻¹)	136.4	14	101.8, 168.2
V3std (L.70kg ⁻¹)	484	8	400.3, 553.1
Rate M1std (h ⁻¹ .70kg ⁻¹)	2.17	43	1.09, 4.39
CL2M1 (L.h ⁻¹ .70kg ⁻¹)	9.1	11	7.6, 10.76
CLM1 (L.h ⁻¹ .70kg ⁻¹)	40.9	26	22.3, 62.1
CL2M2 (L.h ⁻¹ .70kg ⁻¹)	7.4	63	0.76, 18.9
CLPM2 (L.h ⁻¹ .70kg ⁻¹)	0.35	93	0.004, 1.05
CLM2 (L.h ⁻¹ .70kg ⁻¹)	775.9	38	46.9, 997
T _{VOL} weeks	107	70	27.2, 323.7
β _{VOL}	1.63	60	0.57, 4.08
Residual Error Additive mcg.L ⁻¹	1.09	η _{RUV,i} 0.278	0.21, 1.63
methadone proportional	14.8%		12.3, 17.5
Residual Error Additive mcg.L ⁻¹	0.322	η _{RUV,i} 0.373	0.129, 0.626
EDDP proportional	18.9%		14.4, 23.6
Residual Error Additive mcg.L ⁻¹	0.025	η _{RUV,i} 0.154	0.016, 0.035
EMDP proportional	11.4%		2.3, 17.0

See Figure 1 for model details. The effect of age on distribution volume (MFV₂) was investigated using an exponential function

$$MF_{V_2} = 1 + \beta_{VOL} x EXP(-(PMA - 33) x \frac{Ln(2)}{T_{VOL}})$$

where β_{VOL} is a parameter estimating the fractional difference from V_{std} at 33 weeks PMA (the youngest neonate) and T_{VOL} describes the half-time of the age-related changes V₂.

Table 2

The correlation of parameter between-subject variability

	CL2M1	Q2	V1	V2	V3	Q3	CL2M2	CLM	RateM1
CL2M1	1								
Q2	0.246	1							
V1	0.025	0.806	1						
V2	0.026	0.903	0.782	1					
V3	0.488	0.503	0.407	0.434	1				
Q3	0.454	0.487	0.342	0.323	0.745	1			
CL2M2	0.050	0.880	0.751	0.873	0.478	0.449	1		
CLM	0.527	0.729	0.546	0.581	0.507	0.475	0.612	1	
RateM1	0.277	-0.639	-0.574	-0.787	-0.551	-0.369	-0.710	-0.302	1

Table 3

Standardised methadone Stereoisomer parameter predictions in neonates. See Figure 2 for model details (BSV is the between subject parameter variability, 95%CI is the 95% confidence interval)

Parameter		Estimate	%BSV	95%CI
R-enantiomer				
CL2MRstd other (L.h ⁻¹ .70kg ⁻¹)		7.25	53.7	5.42, 11.3
V1Rstd (L.70kg ⁻¹)		342	95.8	37.5, 498
V2Rstd (L.70kg ⁻¹)		343	84.7	182, 795
Q2Rstd (L.h ⁻¹ .70kg ⁻¹)		62.7	158.7	22.8, 245
CLMRstd (L.h ⁻¹ .70kg ⁻¹)		18.3	64.0	14.9, 33.1
FVMR		0.156	-	0.003, 0.457
S-enantiomer				
CL2MSstd other (L.h ⁻¹ .70kg ⁻¹)		8.19	53.7	5.23, 11.7
V1Sstd (L.70kg ⁻¹)		152	95.8	10.5, 293
V2Sstd (L.70kg ⁻¹)		290	84.7	136, 529
Q2Sstd (L.h ⁻¹ .70kg ⁻¹)		104	158.7	22.7, 200
CLMSstd (L.h ⁻¹ .70kg ⁻¹)		15.3	64.0	11.6, 30.1
FVMS		0.334	-	0.037, 6.61
Residual Error				
Residual Error methadone	additive	0.53 mcg.L ⁻¹	$\eta_{RUV,i}$ 0.38	0.005, 1.05
	proportional	13.2%		8.2, 15.3
Residual Error EDDP	additive	0.001 mcg.L ⁻¹	$\eta_{RUV,i}$ 0.003	0.0006, 0.00106
	proportional	27.8%		6.3, 30.6
Effect				
T _{1/2} keo	3 min	202%		0.09, 7.89
E0	389	4.8%		374, 404
E _{max}	10.4 ms	-		5.06, 52.9
N	8.15	-		0.586, 10.0
EC50	0.68 mcg.L ⁻¹	-		0.05, 25.8
Residual error	additive	9.53	$\eta_{RUV,i}$ 0.95	3.67, 12.4

Table 4

The correlation of parameter between-subject variability

	CL2M	Q	V1	V2	CLM
CL2M	1				
Q	0.070	1			
V1	0.498	-0.363	1		
V2	0.589	0.825	0.132	1	
CLM	0.748	0.353	-0.205	0.560	1