

Perioperative Pharmacokinetics of Methadone in Adolescents

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ABSTRACT

Background: Methadone is frequently administered to adults experiencing anesthesia and receiving pain treatment. Methadone pharmacokinetics in adults are well characterized, including the perioperative period. Methadone is also used in children. There is, however, no information on methadone pharmacokinetics in children of any age. The purpose of this investigation was to determine the pharmacokinetics of intravenous methadone in children undergoing surgery. Perioperative opioid-sparing effects were also assessed.

Methods: Eligible subjects were children 5–18 yr undergoing general anesthesia and surgery, with an anticipated postoperative inpatient stay exceeding 3 days. Three groups of 10 to 11 patients each received intravenous methadone hydrochloride after anesthetic induction in ascending dose groups of 0.1, 0.2, and 0.3 mg/kg (up to 20 mg). Anesthetic care was not otherwise changed. Venous blood was obtained for 4 days, for stereoselective determination of methadone and

What We Already Know about This Topic

- Methadone may be a useful perioperative opioid analgesic because of its rapid onset of effect and prolonged duration of effect due to its long elimination half-life
- Methadone pharmacokinetics have been characterized in adults

What This Article Tells Us That Is New

- Methadone pharmacokinetics in adolescents are similar to those in adults
- A single intraoperative dose of methadone did not decrease postoperative opioid consumption in adolescents undergoing major spine surgery

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metabolites. Pain assessments were made each morning. Daily and total opioid consumption was determined. Perioperative opioid consumption and pain was determined in a second cohort, which was matched to age, sex, race, ethnicity, surgical procedure, and length of stay, but not receiving methadone.

Results: The final methadone study cohort was 31 adolescents (14 ± 2 yr, range 10–18) undergoing major spine surgery for a diagnosis of scoliosis. Methadone pharmacokinetics were linear over the dose range 0.1–0.3 mg/kg. Disposition was stereoselective. Methadone administration did not dose-dependently affect postoperative pain scores, and did not dose-dependently decrease daily or total postoperative opioid consumption in spinal fusion patients.

Conclusions: Methadone enantiomer disposition in adolescents undergoing surgery was similar to that in healthy adults.

POSTOPERATIVE pediatric pain management remains a considerable challenge. Physicians, nurses, and parents underestimate the amount of pain experienced by children, often fail to fully treat the pain, and may overestimate the risks of pain treatment.^{1–4} Inadequate pain relief has a significant psychological impact upon children, including alterations in their perceptions of future painful experiences and medical procedures.⁵ Psychological ramifications

of pediatric pain can include lack of adherence to treatment recommendations, poor adjustment and coping skills, long-term changes in willingness and accuracy in self-report of pain, lack of trust in healthcare providers, and posttraumatic stress disorder.⁶ For children, severe pain can occur early in life, and can recur at unpredictable intervals throughout their life. The degree to which this pain is controlled impacts the ability of patients to cope with the next pain episode.

Methadone is a μ opioid agonist and *N*-methyl-D-aspartate receptor antagonist which is highly efficacious and cost-effective in the treatment of acute, chronic, neuropathic, and cancer pain, as well as substance abuse.^{7–10} It is used in adults, children, and even neonates, and can be administered *via* oral, intravenous, nasal, and various other parenteral routes. Methadone is particularly useful in the perioperative period.^{10–13} Methadone is advantageous because it has a rapid onset and slow elimination, which results in prolonged effect and diminished need for postoperative analgesics.¹⁰ Methadone has a long half-life, averaging 24–36 h in adults. It has no active metabolites or prodrug forms. Methadone is metabolized *via* N-demethylation to the inactive metabolite 2-ethylidene-1.5-dimethyl-3.3diphenylpyrrolidine (EDDP) in the liver, primarily by cytochromes P450 CYP2B6 and CYP3A4,^{14–18} although it appears that the latter may be less important clinically in determining single dose methadone metabolism and clearance.^{15,19–22} Methadone is administered clinically as a racemate, but R-methadone is approximately 50-fold more potent than the S-enantiomer.

Methadone use and exposure in children is growing. Clinical applications include acute pain, cancer pain, chronic pain, and palliative care.^{23–27} Similar to adults, methadone is used to treat opioid-dependent adolescents.²⁸ Oral methadone has also been used to treat neonatal abstinence syndrome resulting from either exposure to opioids *in utero* or by chronic administration of opioids in neonatal or pediatric intensive care units. Unintended pediatric exposures to methadone have also increased, as prescribing for pain in the adult population has increased over the last decade.²⁷

Despite the increase in methadone use in pediatrics, there is a paucity of clinical data on its pharmacokinetics and pharmacodynamics in children.^{29–31} The primary purpose of this investigation was to determine the pharmacokinetics of intravenous methadone in children. A secondary purpose was to assess postoperative opioid consumption in pediatric surgical patients who receive methadone.

Materials and Methods

Patients

The investigation was approved by the Washington University in St. Louis Institutional Review Board. Eligible subjects were children 5–18 yr undergoing general anesthesia and surgery, with an anticipated postoperative inpatient stay exceeding 4 days. Exclusion criteria were a history of or known liver or kidney disease, and pregnant or nursing females. Patients' parents or legal guardian provided written informed

consent, and patients provided written assent. Patients received standard monitors for anesthesia and postoperative care. Anesthesia and surgical care were not altered for this investigation, except that a second intravenous catheter was placed in the arm or hand immediately after induction of anesthetic for fluid administration and blood sampling, and subjects received methadone as their initial intraoperative opioid after the placement of the second intravenous line. Methadone administration occurred 27 ± 20 min after propofol induction across all dose groups. A dose-escalation protocol was used. Three groups of 10 patients each received intravenous methadone hydrochloride in ascending dose groups of 0.1 mg/kg, 0.2 mg/kg, and 0.3 mg/kg (up to a maximum of 20 mg). Based on prior experience in pediatrics and adults, these doses were conservatively chosen so additional postoperative pain medication would still be needed, but that increasing methadone doses could result in lessened postoperative opioid use. All other anesthetic care was at the discretion of the anesthesia care team. After induction (typically propofol), anesthesia was maintained with less than 0.5 minimum alveolar concentration of sevoflurane or desflurane in 50:50 oxygen and air, and propofol infusion (50–100 μ g/kg/min) was used to provide additional anesthetic as needed. Muscle relaxation (typically by rocuronium infusion) was monitored by train-of-four ratio, and allowed to wear off before motor stimulation. For analgesia, methadone was supplemented with opioid infusion and/or bolus, at the discretion of the anesthetic provider.

Postoperatively, patients received standard-of-care analgesia (patient-controlled analgesia and oral opioids) as determined by their treating surgeon. Postoperative care was not altered for purposes of this study. Venous blood samples were obtained before methadone and at 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 h after dosing.

Patient assessments were made each morning by a trained member of the research team. Pain intensity was assessed by patients using the Wong-Baker FACES scale and a laminated card, which provides a rating of 0 (no hurt) to 5 (hurts worst).³² Pain was also assessed by patients using a Colored-Visual Analog Scale, which was then scored with a metric ruler from 0 (no pain relief) to 10 (maximum pain relief). The inpatient nursing staff also assessed pain intensity per current institutional practice, using a verbal analog scale (0 being no pain and 10 being the worst pain imaginable). They also assessed sedation using a five-point scale (patient fully alert to not arousable), and itching and nausea using a five-point verbal scale (none, mild, moderate, severe, or excruciating). Information on respiratory depression (less than 8/min), decreased oxygen saturation (less than 92% on room air per pulse oximetry), altered mental status (*i.e.*, confusion, hallucinations, disorientation), and excessive somnolence (*i.e.*, arousability, difficulty staying awake, *etc.*) as observed and documented by inpatient nurses on daily flowsheets was also abstracted from medical records.

The inpatient medical record was used to quantify opiate use by each patient in each 24-h period. Intraoperative opi-

oids, postoperative patient-controlled analgesia use, and oral opioids were quantified separately, and in total. Results are expressed as morphine equivalents.³³ Equivalent to intravenous 10 mg morphine was 1.5 mg hydromorphone, 10 mg methadone, 100 μ g fentanyl, 10 μ g sufentanil, and 20 mg oral oxycodone.

A second cohort of patients, undergoing similar surgical procedures as the methadone cohort, but not receiving methadone, was studied to determine perioperative opioid consumption. Children were selected based on age, sex, race, ethnicity, surgical procedure, and length of stay, to approximate the characteristics of the methadone patients, and medical records were reviewed for intraoperative and postoperative opioids and dose, and postoperative pain assessments and complications. These patients received care during the same period (June 2009 to July 2010) as the methadone patients (June 2009 to June 2010).

Analytical

Plasma methadone and EDDP concentrations were determined by liquid chromatography-tandem mass spectrometry, using a significant modification of a previous method.³⁴ Plasma (500 μ l of patient plasma, calibrator, or quality control sample) was acidified with freshly prepared 4% phosphoric acid (1 ml, containing the internal standards d9-methadone [5 ng] and d3-EDDP [1 ng]) and vortex mixed. Standards were from Cerilliant (Round Rock, TX). Samples were processed by solid phase extraction. Strata-XC strong cation mixed mode 60 mg plates (Phenomenex, Torrance, CA) were conditioned with 1 ml methanol, then 1 ml 0.1N HCl. Acidified plasma was loaded, then washed with 1 ml 0.1N HCl, followed by 1 ml methanol. The plate was dried at full vacuum for 2–5 min, then samples were eluted with

0.5 ml of ammonium hydroxide, 5%, in acetonitrile. Samples were dried under nitrogen stream at 60°C and stored until analysis. Dried samples were reconstituted with 100 μ l of ammonium formate, 20 mM, in water.

Analysis was performed on an API 3200 triple-quadrupole mass spectrometer (Applied Biosystems/MDS Sciex, Foster City, CA) equipped with a Turbo Ion Spray ionization source operated in positive ion mode. The chromatography system was two LC-20AC pumps with a CTO-20A oven, SIL-20A autosampler, DGU-20A3 degasser, FCF-11AL valve, and a CBM 20A controller (Shimadzu, Columbia, MD). Chromatographic separation was performed on a chiral AGP analytical column (100 \times 2 mm, 5 μ m) with a chiral AGP guard column (10 \times 2 mm) (ChromTech, Apple Valley, MN). The injection volume was 70 μ l and the oven temperature was 35°C. Before each injection, the needle was washed with a solution of 50:50 methanol and water. Mobile phase (0.22 ml/min) was (A) 20 mM ammonium acetate (pH 5.7) and (B) methanol using the following program: 10% B for 3 min, linear gradient to 20% B at 4 min, held for 3 min, linear gradient to 50% B at 8 min, held for 2 min, linear gradient to 80% B at 10.5 min, held for 2 min, then reequilibrated to initial conditions between 12.5 and 15 min. Under these conditions, retention times for R- and S-methadone and R- and S-EDDP were 11.5, 12.0, 11.1, and 11.8 min, respectively. Both Q1 and Q3 quadrupoles were optimized to unit mass resolution, and the mass spectrometer conditions were optimized for each analyte. Instrument parameters were: source temperature 600°C, ion spray voltage 5500 V, curtain gas 35, ion source gas 1 at 30, ion source gas 2 at 30, collision gas 5, and entrance and exit potentials 5. Multiple reaction monitoring transitions were m/z 310.2 > 265.2 and 319.3 > 268.2 for methadone and d9-methadone, and

Table 1. Subject Demographics

—	Intraoperative Methadone Dose			
	0	0.1 mg/kg	0.2 mg/kg	0.3 mg/kg
N	30	10	10	11
Age (yr)	15 \pm 2	14 \pm 2	13 \pm 2	14 \pm 2
Sex (M:F)	9:21	2:8	6:4	2:9
Weight (kg)	63 \pm 26	61 \pm 13	50 \pm 8	62 \pm 14
Diagnosis	—	—	—	—
Scoliosis	26	9	9	10
Kyphosis	2	0	1	1
Other	2	1	0	0
Operation	—	—	—	—
Posterior spinal fusion	30	9	10	10
Levels fused	11 \pm 3	10 \pm 5	11 \pm 2	10 \pm 3
Other	0	1	0	0
Anesthesia duration (hr)	5.6 \pm 1.5	5.8 \pm 1.8	5.4 \pm 0.7	5.8 \pm 1.3
Estimated blood loss (ml)	448 \pm 238	555 \pm 269	410 \pm 249	405 \pm 162
Methadone (mg)	0	6.1 \pm 1.3	9.9 \pm 1.4	17.4 \pm 2.3
Total intraoperative nonmethadone opioid (mg morphine equivalents)	81.0 \pm 38.8	61.7 \pm 25.5	76.6 \pm 54.0	64.6 \pm 27.3
Total intraoperative opioid (mg morphine equivalents)	81.0 \pm 38.8	67.8 \pm 25.5	86.5 \pm 54.7	82.0 \pm 26.6
	—	—	—	—

278.2 > 234.2 and 281.2 > 234.2 for EDDP and d3-EDDP, with 250 ms dwell times. For methadone and EDDP, the declustering potential was 40 and 60 V, and the collision energy was 20 and 40 V.

Plasma calibration standards contained 0.1, 0.2, 1, 5, 10, 50, 90, and 100 ng/ml RS-methadone, and 0.02, 0.04, 0.2, 1, 10, 18, and 20 ng/ml RS-EDDP. Plasma quality control samples contained 1, 10, and 80 ng/ml RS-methadone and 0.2, 2, and 16 ng/ml RS-EDDP. Interday coefficients of variation were 5, 7, and 7% for 0.5, 5, and 40 ng/ml R-methadone; 4, 5, and 5% for S-methadone; and 6, 6, and 3% for 0.1, 1, and 8 ng/ml R- and S-EDDP.

Pharmacokinetic data were analyzed using noncompartmental methods (WinNonlin 5.3; Pharsight Inc., Sunnyvale, CA), as described previously.^{15,19,21,22} Dose groups were compared using ANOVA. Differences in methadone and metabolite enantiomer pharmacokinetics parameters (all subjects) were compared using paired Student *t* test or Wilcoxon signed rank tests, as appropriate. Opioid use and pain scores were analyzed by 2-way repeated measures ANOVA. Statistical significance was assigned at *P* < 0.05.

Results

Patient demographics are provided in table 1. The methadone cohort consisted exclusively of adolescents undergoing major spine surgery, usually for a diagnosis of scoliosis. This was influenced by the study aim of 96 h postoperative blood sampling, which required a hospital stay of at least 4 days, which in our institution is comprised largely of patients undergoing major spine surgery. The age range of the final study population (10–18 yr) was a consequence of the age at which scoliosis patients undergo posterior spinal fusion in our institution. Adolescents undergoing spine surgery was not otherwise the target population.

Plasma concentrations of methadone and EDDP enantiomers are shown in figure 1, and pharmacokinetic parameters provided in table 2. There was a secondary peak in methadone plasma concentrations approximately 6 h after dosing, which coincided with the end of surgery and turning supine. Methadone disposition was linear over the dose range 0.1–0.3 mg/kg, with methadone and EDDP peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{∞}) increasing linearly with methadone dose, for both methadone enantiomers. In addition, methadone $C_{max}/dose$, $AUC_{\infty}/dose$, systemic clearance, elimination half-life, and steady-state volume of distribution, and EDDP $C_{max}/dose$, time to peak plasma concentration, $AUC_{\infty}/dose$, and elimination half-life were not significantly different between doses, for both R- and S-methadone. Methadone metabolism also appeared linear with dose, with the EDDP/methadone plasma AUC ratios not significantly different between doses, for both methadone enantiomers. Plasma EDDP concentrations were formation-rate limited, with EDDP enantiomers elimination half-lives not different from those of the corresponding methadone enantiomers.

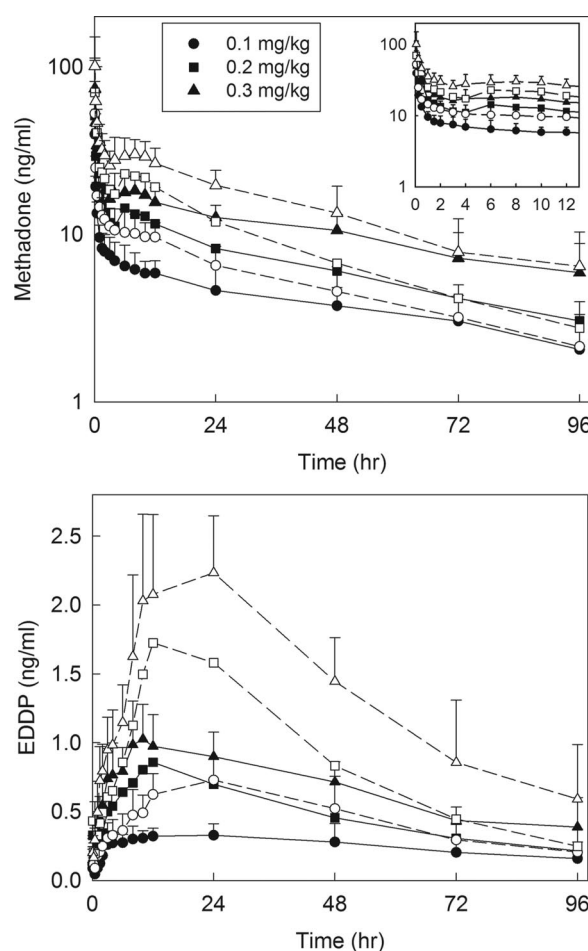


Fig. 1. Methadone and 2-ethylidene-1.5-dimethyl-3.3diphenylpyrrolidine (EDDP) enantiomer plasma concentrations after intravenous methadone. Subjects received 0.1 (circles), 0.2 (squares), or 0.3 (triangles) mg/kg intravenous racemic (R/S)-methadone hydrochloride. Solid symbols and lines show R-methadone and R-EDDP, open symbols and dotted lines show S-methadone and S-EDDP. Each data point is the mean \pm SD (*n* = 10–11). Some SD are omitted for clarity. The inset shows the period from 0–12 h.

Unit dose (dose-adjusted) methadone and EDDP enantiomer plasma concentrations for dose groups, and all adolescents, are shown in figures 2 and 3. Methadone disposition was stereoselective, with S-enantiomer concentrations greater than those of R-methadone and EDDP, related to the smaller volume of distribution for S-methadone. Nevertheless, S-methadone elimination was more rapid, with greater rates of S-methadone N-demethylation (EDDP/methadone ratio); a shorter S-methadone elimination half-life; and time-dependent increase in the plasma R/S-methadone enantiomer ratio (fig. 3).

Perioperative opioid consumption and postoperative pain scores are shown in figures 4 and 5. There were no significant differences between controls (not receiving methadone) and adolescents receiving 0.1, 0.2, or 0.3 mg/kg methadone, in postoperative opioid consumption by patient controlled analgesia, oral opioid administration, or total postoperative opioid con-

Table 2. Intravenous Methadone Pharmacokinetic Parameters

—	(R/S)-Methadone Dose							
	0.1 mg/kg	0.2 mg/kg	0.3 mg/kg	All	0.1 mg/kg	0.2 mg/kg	0.3 mg/kg	All
—	—	R-methadone	—	—	—	S-methadone	—	—
C_{max} (ng/ml)	39 ± 35	56 ± 21	78 ± 27*	—	52 ± 50	75 ± 22	106 ± 40*	—
$C_{max}/dose$ (ng/ml/mg)	14 ± 11	13 ± 5	10 ± 4	12 ± 7	19 ± 16	17 ± 6	14 ± 6	17 ± 10**
AUC_{∞} (ng · hr · ml ⁻¹)	594 ± 389	837 ± 273	1,588 ± 789*	—	679 ± 375	979 ± 245	1,835 ± 757*	—
$AUC_{\infty}/dose$ (ng · hr · ml ⁻¹ · mg ⁻¹)	228 ± 164	189 ± 54	205 ± 102	207 ± 113	256 ± 151	223 ± 58	235 ± 88	238 ± 103**
CL_{IV} (ml · kg ⁻¹ · min ⁻¹)	1.6 ± 0.7	2.0 ± 0.6	1.6 ± 0.8	1.7 ± 0.7	1.4 ± 0.8	1.6 ± 0.4	1.3 ± 0.5	1.4 ± 0.6**
Elimination half-life (hr)	55 ± 38	43 ± 16	59 ± 37	52 ± 31	40 ± 25	28 ± 11	37 ± 17	35 ± 18**
V_{ss} (L/kg)	6.4 ± 1.4	6.6 ± 1.7	6.6 ± 1.5	6.5 ± 1.5	4.0 ± 1.0	3.8 ± 1.1	3.8 ± 0.9	3.8 ± 0.9**
—	—	R-EDDP	—	—	—	S-EDDP	—	—
C_{max} (ng/ml)	0.38 ± 0.11	0.88 ± 0.24*	1.14 ± 0.30*	—	0.76 ± 0.18*	1.79 ± 0.52*	2.35 ± 0.54*	—
$C_{max}/dose$ (ng/ml/mg)	0.06 ± 0.01	0.09 ± 0.04	0.07 ± 0.03	0.07 ± 0.03	0.13 ± 0.03	0.19 ± 0.08	0.14 ± 0.05	0.15 ± 0.06**
T_{max} (hr)	14 ± 14	12 ± 6	11 ± 6	13 ± 9	24 ± 9	17 ± 7	14 ± 6	18 ± 8**
AUC_{0-96} (ng · hr · ml ⁻¹)	23 ± 10	42 ± 11	55 ± 15	—	42 ± 16	78 ± 22	111 ± 32*	—
AUC_{∞} (ng · hr · ml ⁻¹)	46 ± 28	59 ± 20	106 ± 65*	—	60 ± 26	107 ± 49	192 ± 93*	—
$AUC_{\infty}/dose$ (ng · hr · ml ⁻¹ · mg ⁻¹)	7.4 ± 4.0	6.0 ± 1.9	6.1 ± 3.7	6.5 ± 3.3	9.8 ± 3.4	11.4 ± 7.1	11.2 ± 5.5	10.8 ± 5.4**
Elimination half-life (hr)	72 ± 42	41 ± 17	68 ± 57	61 ± 43	41 ± 20	31 ± 14	49 ± 36	41 ± 25**
AUC_{0-96} (EDDP/methadone)	0.06 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.09 ± 0.03	0.09 ± 0.02	0.09 ± 0.02	0.09 ± 0.02**
AUC_{∞} (EDDP/methadone)	0.08 ± 0.03	0.07 ± 0.02	0.07 ± 0.02	0.07 ± 0.02	0.10 ± 0.03	0.12 ± 0.07	0.10 ± 0.04	0.11 ± 0.05**

* Significantly different compared with 0.1 mg/kg ($P < 0.05$). ** Significantly different between enantiomers ($P < 0.05$).

AUC = area under the plasma concentration-time curve; CL_{IV} = systemic clearance; C_{max} = peak plasma concentration; $C_{max}/dose$ = dose-adjusted peak plasma concentration; EDDP = 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine; T_{max} = time to peak plasma concentration; V_{ss} = steady-state volume of distribution.

sumption. Excluding the dose of methadone received intraoperatively, cumulative 0–72 h morphine equivalents (patient controlled analgesia plus oral opioids) were 274 ± 82 , 277 ± 92 , 215 ± 76 , and 221 ± 80 mg in patients receiving 0, 0.1, 0.2, or 0.3 mg/kg methadone, respectively. Differences between groups were not statistically significant.

There were no significant differences between methadone groups in research staff assessments of patient pain, based

either on FACES scores or patient self-reports of pain based on visual analog scales. There were no significant differences between controls (not receiving methadone) and adolescents receiving 0.1, 0.2, or 0.3 mg/kg methadone, in pain scores based on standard assessments of ward nurses and recorded in the medical record.

There were no serious adverse events, or adverse events specifically associated with the use of methadone. Table 3 summarizes the incidence of respiratory depression, decreased oxygen saturation, or altered mental status as observed and documented by inpatient nurses. There were no differences between methadone dose groups, therefore data were combined for ease of reporting. The incidence of adverse events was not different between controls and subjects receiving methadone.

Discussion

This investigation is the first to systematically evaluate methadone pharmacokinetics and perioperative opioid-sparing effects in children 10–18 yr. The protocol used a conservative dose-escalation design, and the 0.1–0.3 mg dose range was chosen, because this was to be the first investigation of methadone pharmacokinetics in children; previous reports of methadone use in children used doses of 0.1 or 0.2 mg/kg,^{30,31} and previous perioperative investigations of methadone in adults had not used doses higher than 20 mg (nominally 0.3 mg/kg, assuming 70 kg patients).^{11–13} Because of the goal of blood sampling for 96 h, and our hospital's surgical demographics, the study population unintentionally

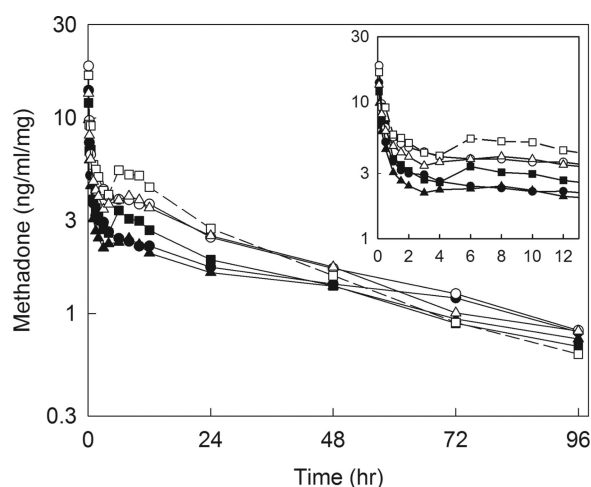


Fig. 2. Dose-adjusted methadone plasma concentrations after intravenous methadone. Subjects received 0.1 (circles), 0.2 (squares), or 0.3 (triangles) mg/kg intravenous racemic (R/S)-methadone hydrochloride. Solid symbols and lines show R-methadone, open symbols and dotted lines show S-methadone. Each data point is the mean. The inset shows the period from 0–12 h.

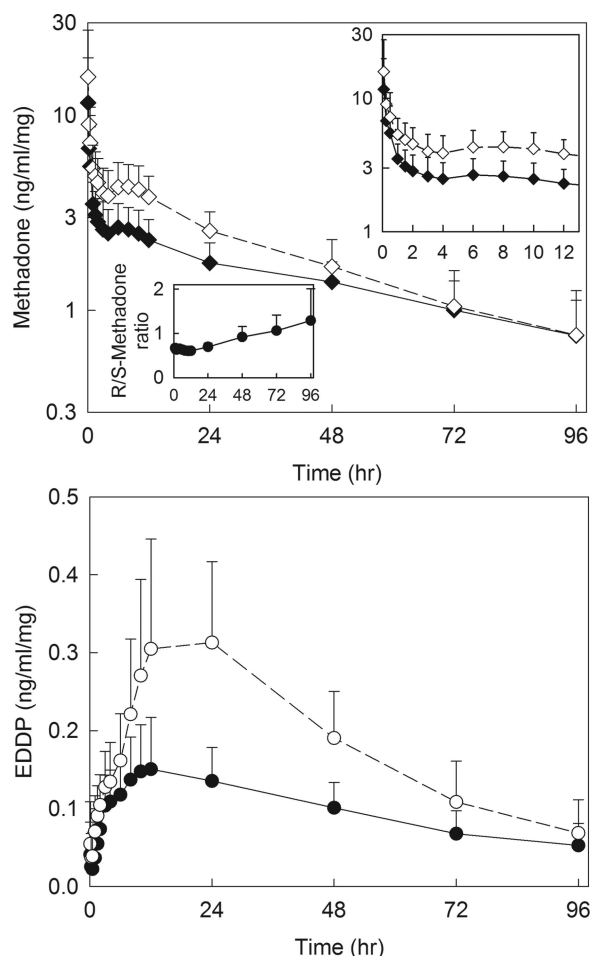


Fig. 3. Dose-adjusted methadone and 2-ethylidene-1.5-dimethyl-3.3diphenylpyrrolidine (EDDP) enantiomer plasma concentrations after intravenous methadone in all subjects. Solid symbols and lines show R-methadone and R-EDDP, open symbols and dotted lines show S-methadone and S-EDDP. Each data point is the mean \pm SD ($n = 31$). The insets show dose-adjusted methadone and EDDP enantiomer plasma concentrations from 0–12 h, and plasma R/S-methadone concentration ratios.

consisted almost exclusively of scoliosis patients undergoing major spinal surgery. Since the most common age for this procedure is adolescence, the final study population unintentionally consisted of adolescents.

Results of this investigation provide several novel findings about methadone disposition. One major finding was that intravenous methadone pharmacokinetics in adolescents in the perioperative period were linear over the dose range 0.1–0.3 mg/kg. For both methadone enantiomers, dose-adjusted methadone C_{max} and AUC, systemic clearance, steady-state volume of distribution, and elimination half-life, were constant over the dose range, as were dose-adjusted EDDP C_{max} and AUC, and the EDDP/methadone AUC ratio. Therefore subsequent discussion refers to parameters averaged across the entire study population. A second major finding was that methadone disposition in adolescents was stereoselective.

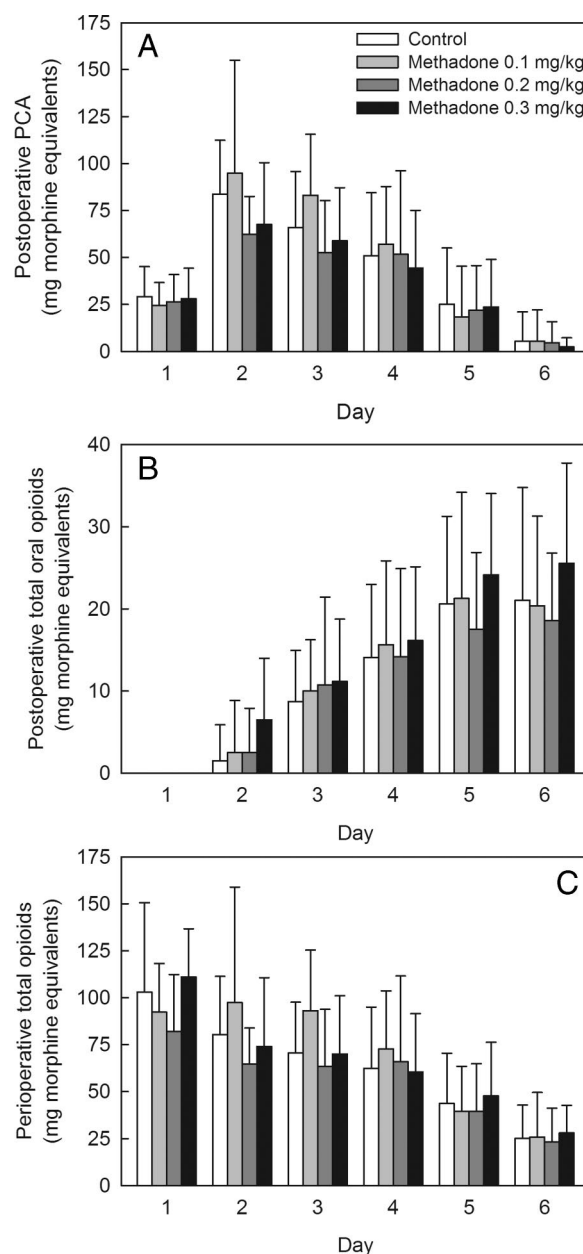


Fig. 4. Influence of intraoperative methadone on analgesic requirements. Subjects received 0.1, 0.2, or 0.3 mg/kg intravenous racemic (R/S)-methadone hydrochloride. Controls received no intraoperative methadone. Day 1 was the day of surgery. Results are shown for (A) postoperative patient-controlled analgesia (PCA) use, (B) postoperative oral opioid use, and (C) total (day 1–6) perioperative opioid use. Intraoperative opioids, patient-controlled analgesia (morphine or hydromorphone), and oral opioids (typically oxycodone) were converted to morphine equivalents. There were no significant differences between controls and patients receiving methadone.

The initial S-methadone concentrations were greater than those of R-methadone. Systemic clearance, elimination half-life, and steady-state volume of distribution were significantly greater for R- than S-methadone. S-methadone N-demethylation was greater than that of R-methadone, ev-

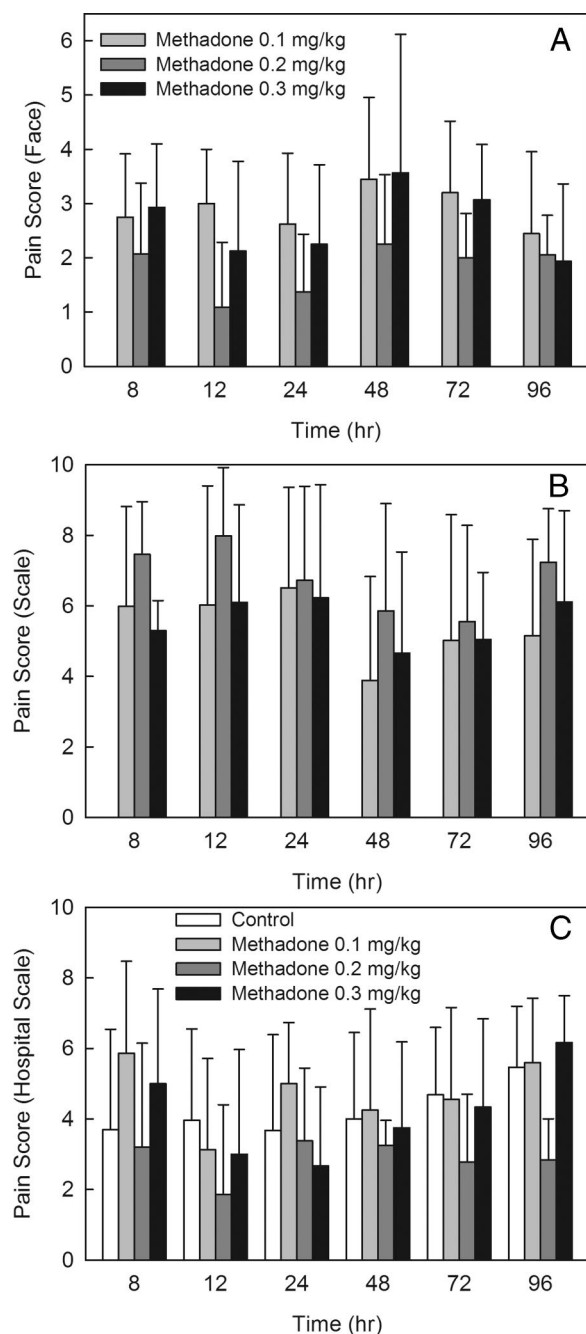


Fig. 5. Influence of intraoperative methadone on pain scores. Time zero was the beginning of surgery. Results are shown for (A) pain scores based on patients' facial expression using the Wong-Baker FACES scale (0–5), (B) pain scores based on patient report using a Colored-Visual Analog Scale (0–10), and (C) ward nurse assessment of pain scores using a verbal analog scale (0–10). Only nurse assessment of pain scores was determined for all groups. There were no significant differences between controls and patients receiving methadone.

identified by greater EDDP/methadone AUC ratios for the R- than S-enantiomers, and a time-dependent increase in the plasma R/S-methadone concentration ratio. A third major finding was that perioperative methadone disposition in adolescents was similar to that in adults. Although there are

numerous studies of methadone pharmacokinetics in adults, most single-dose intravenous studies have evaluated racemic methadone concentrations. Several recent investigations evaluated methadone and EDDP enantiomers concentrations after intravenous dosing in healthy adult volunteers.^{19,21,22} In this investigation, the time-dependent increase in plasma R/S-methadone ratio was similar to that in the healthy adult volunteers, R- and S-methadone clearances (1.7 and 1.4 ml/kg/min) were approximately 15% lower than the averages in the healthy adults (2.0 and 1.6 ml/kg/min), steady-state volume of distribution (6.5 and 3.8 l/kg) were similar to those in adults (6.0 and 3.3 l/kg), and the elimination half-life (52 and 35 h) was longer than the average in adults (39 and 27 h) but consistent with the slightly lower clearances. Methadone N-demethylation (based on the R- and S-EDDP/methadone AUC ratios) was similar in the adolescents (0.07 and 0.11) and adults (0.07 and 0.09). Reasons for the slightly lower methadone clearance in adolescents are not apparent, but the differences are not considered clinically significant. The present results are consistent with the predictions of Yang *et al.*, who used a physiologically based pharmacokinetic model to predict that methadone enantiomer clearances would increase with age in infants but reach plateau values by age 2 yr.²⁹ Additional studies are needed to characterize methadone pharmacokinetics in younger children and infants.

Methadone effects on analgesia and opioid consumption were somewhat unexpected. Methadone administration did not affect postoperative pain scores, and did not decrease daily or total postoperative opioid consumption. The former result could be explained on the basis of access to patient-controlled analgesia throughout the perioperative period, although previous studies did report slightly lower pain scores in adults undergoing abdominal hysterectomy³⁵ and in children³⁰ receiving methadone compared with morphine, although there was no major difference in pain scores between methadone- and sufentanil-treated adults undergoing complex spine surgery.³⁶ The lack of opioid-sparing with methadone, however, was initially more surprising. Previous studies of perioperative methadone in adults and children found longer analgesia, fewer postoperative opioid doses, and lower cumulative postoperative opioid use compared with morphine or other opioids.^{30,31,35,36} For example, adults receiving 0.2 mg/kg intravenous methadone at induction had significantly lower postoperative opioid requirements (median 98 vs. 219 mg morphine equivalents 0–72 h postoperatively) than those receiving sufentanil.³⁶ In this investigation, patient-controlled analgesia use on days 2 and 3 appeared numerically lower, but this did not achieve statistical significance. Nonetheless, the investigation was not powered specifically to evaluate opioid consumption, which was a secondary outcome. In addition, as identified previously, the type of surgical procedure and associated severity of pain likely influence the opioid-sparing effect of methadone.³⁵ For example, after methadone, adults undergoing inguinal

Table 3. Perioperative Opioid-related Adverse Events

Day	Controls (n = 31)			Methadone (All Doses, n = 31)		
	Respiratory Depression	Decreased Oxygen Saturation	Altered Mental Status	Respiratory Depression	Decreased Oxygen Saturation	Altered Mental Status
1	5	8	1	5	4	0
2	3	11	0	2	10	0
3	0	3	0	0	3	0
4	2	7	0	0	1	0
5	0	2	0	0	0	0
6	0	1	0	0	0	0

Results are the number of patient episodes in each group. Information on respiratory depression ($<8/\text{min}$), decreased oxygen saturation ($<92\%$ on room air), and altered mental status (*i.e.*, confusion, hallucinations, disorientation) as observed and documented by inpatient nurses on daily flowsheets was abstracted from medical records. Day 1 was the day of surgery.

herniorrhaphy received no additional opioids³⁷ and those undergoing orthopedic (typically anterior spinal fusion) or general surgery (typically open cholecystectomy) often needed no or minimal postoperative opioids,¹¹ whereas opioid-sparing was less in adults undergoing more painful upper abdominal¹² or complex spine surgery.³⁶ Indeed, in the present population undergoing posterior spinal fusion, the cumulative 0–72 h postoperative morphine equivalent use was 274 ± 82 , 277 ± 92 , 215 ± 76 , and 221 ± 80 mg in adolescents receiving 0, 0.1, 0.2, or 0.3 mg/kg methadone, respectively, where opioid-sparing was not statistically significant, whereas that in adults undergoing multilevel thoracolumbar surgery was a median of 219 mg morphine equivalents, where opioid-sparing occurred,³⁶ suggesting that the present population had more pain compared with other studies. Finally, there was considerable use of other intraoperative opioids (mainly fentanyl and sufentanil), and even at the highest methadone dose, methadone constituted only a small fraction of total perioperative opioid on the day of surgery. Thus, using fixed doses of methadone across the full spectrum of surgical procedures and associated pain may not be optimal; rather, higher doses may be needed for more painful procedures. Use of shorter-duration supplemental opioids (*i.e.*, remifentanyl), use of methadone rather than other opioids in the postanesthesia care unit, or use of higher methadone doses may have decreased daily or total postoperative opioid consumption and demonstrated an opioid-sparing effect of methadone in this investigation.

Despite the absence of specific quantitative analgesic and opioid-sparing effects of methadone, there were clearly observable, albeit anecdotal, differences in patients receiving methadone. Recovery room nurses commented spontaneously on greater comfort in those patients enrolled in the investigation. They requested that whatever had changed be implemented for all patients. Similarly, many pediatric anesthesiologists, who had not previously used methadone, have implemented its use intraoperatively for other painful operations like pectus excavatum repair. Whether the qualitative differences in the adolescents treated with methadone compared with other opioids are related to the unique pharmacology of methadone (*i.e.*, *N*-methyl-D-aspartate receptor

antagonism), as speculated previously,³⁶ remains unknown and merits further investigation.

There was no difference in the frequency of adverse effects associated with the use of methadone in this investigation, consistent with previous report. Indeed, the use of substantial additional intraoperative opioids, and the requirement for substantial postoperative opioids, suggests that even the highest dose used (0.3 mg/kg) was well below the threshold for significant opioid-related adverse events.

There are several potential limitations to the present investigation. The need for several days of venous sampling, and hence inpatient stay, resulted in a patient population undergoing major surgery (posterior spinal fusion), which consequently resulted also in an adolescent study cohort. Characterization of methadone pharmacokinetics and perioperative opioid-sparing effects in younger children would be desirable. Similarly, evaluation of appropriate dosing, analgesia, and opioid-sparing in less extensive and painful operations is also desirable. This investigation did not use methadone in the postoperative period (either the postanesthesia care unit or the ward), and additional benefit might be gained by this approach. Similarly, only single-dose methadone pharmacokinetics and perioperative opioid-sparing effects were evaluated. Anesthetic care was not otherwise changed for this investigation, specifically, a proscription against other intraoperative opioids,¹⁰ which might have masked an opioid-sparing effect from methadone. Two cohorts were studied, a methadone group in a dose-escalation protocol and a nonmethadone group, rather than a single cohort with full randomization across all groups. This was because a conservative, dose-escalation approach was required for safety considerations. The nonmethadone controls were not randomized, but rather taken from a contemporaneous group of adolescents having surgery. They were carefully matched demographically to the adolescents receiving methadone, as evidenced by the similarity of pain scores and opioid use to the lowest dose methadone group.

In summary, this investigation is the first to evaluate the pharmacokinetics of methadone enantiomers in children, specifically adolescents. Methadone disposition in this population was similar to that in adults.

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