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Pharmacokinetics and Analgesic Effects of Methadone in Children and Adults with Sickle Cell Disease

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Abstract

Background—Vaso-occlusive episodes (VOE) are a significant source of morbidity among children and adults with sickle cell disease (SCD). There is little information on methadone use for SCD pain. This investigation evaluated methadone pharmacokinetics in children and adults with SCD, with a secondary aim to assess pain relief and opioid consumption.

Procedure—Participants included children (<18 yr) and adults with a VOE requiring hospitalization. Patients were randomly assigned to receive standard care (opioid patient controlled analgesia; control group) or one dose of intravenous methadone (0.1–0.125 mg/kg) in addition to standard care (methadone group). Venous methadone and metabolite concentrations were measured. Pain scores, pain relief scores, and opioid consumption were recorded.

Results—Twenty-four children (12 methadone, 12 controls) and twenty-three adults (11 methadone, 12 controls) were studied. In children, the half-life of R- and S-methadone enantiomers was 34±16 and 24±9 hr, respectively. In adults, R- and S-methadone half-lives were 52±17 and 38±12 hr. Pain scores were lower ($p=0.002$) and pain relief scores were higher ($p=0.0396$) in children receiving methadone vs controls. There was no difference in pain scores and pain relief in adults receiving methadone vs controls. There was no difference in opioid consumption between methadone and control groups, in both adults and children.

Conclusions—Intravenous methadone disposition in children and adults with SCD was comparable to subjects without SCD from prior studies. Methadone produced more pain relief

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than standard care in children with SCD. Higher methadone doses may be more effective and should be evaluated in both children and adults with SCD.

Keywords

Methadone; Pediatric; Sickle Cell Disease; Analgesics

Introduction

Pain due to vaso-occlusive episodes (VOE) is a significant source of morbidity in children and adults with sickle cell disease (SCD).^{1,2} Sixty percent of patients with SCD will have at least one VOE annually and 20% will have multiple episodes requiring hospital care.³ Children with SCD hospitalized for a VOE have an average length of stay of 4.5 days.⁴ Vaso-occlusive episodes can disrupt the quality of life for children with SCD, with psychological ramifications such as posttraumatic stress disorder, poor coping skills, lack of trust in health-care providers, and altered perceptions of future medical procedures.^{5,6} Adequate pain relief in patients with SCD is a medical necessity.

Morphine is the opioid most commonly used to treat pain associated with SCD, and is the only opioid with previously defined intravenous pharmacokinetics in children with SCD.⁷ However, morphine may not be the optimal choice, as it has an increased clearance and shorter half life in patients with SCD,⁸ resulting in increasing doses to achieve analgesia. Morphine use in SCD has also been associated with an increased risk of acute chest syndrome compared to nalbuphine,⁹ and a slower onset of pain relief compared with other opioids. These factors may lead to inadequate analgesia when morphine is used to treat acute pain due to a VOE, either in the Emergency Department or the inpatient unit, where 60–70% of patients continue to experience intense pain.^{10,11}

Methadone is an opioid agonist which may have several therapeutic advantages compared with morphine, including a more rapid onset of effect, longer elimination half-life and duration of effect, greater bioavailability, and absence of active metabolites.^{12–15} Methadone is both a μ -opioid receptor agonist and an N-methyl-D-aspartate (NMDA)-receptor antagonist, and may be given via oral, rectal, nasal or intravenous administration.^{16–18} Methadone is chiral, and is used clinically as a racemic mixture, composed of R and S enantiomers. R methadone has a higher μ -opioid receptor affinity and is 50 times more potent as a μ receptor agonist than the S enantiomer. Methadone is cleared mainly by hepatic biotransformation, via inactivation by N-demethylation to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), which is also chiral¹⁹. Methadone has μ -receptor affinity similar to that of morphine.²⁰ While intravenous morphine has a peak effect 1.5–2 hours after administration,^{21,22} methadone has a peak effect within 5 minutes of intravenous administration.^{15,23} Methadone has a longer elimination half-life (R methadone 48 ± 19 hr, S methadone 34 ± 14 hr in adults^{24–32} compared to morphine (2–3 hours).¹² Methadone may provide more stable plasma concentrations and prolonged analgesia.

In addition, there may be additional benefits of methadone in patients with SCD. For example, 10–20% of adults with SCD may have renal insufficiency as glomerular filtration rate decreases with increasing age.¹ Morphine-6-glucuronide metabolites are

pharmacologically active and undergo renal excretion and morphine doses must be adjusted for renal insufficiency. Methadone, however, is metabolized to inactive metabolites¹⁹ and dose adjustment would not be necessary in patients with renal insufficiency.

Methadone has several advantages compared to morphine; however, there is little information regarding the pharmacokinetics of methadone in children,^{33–35} and, although methadone is commonly used in the treatment of older patients with SCD, no data exists regarding the pharmacokinetics of methadone in children or adults with SCD.

The primary aim of this study was to evaluate the pharmacokinetics of methadone in children and adults with SCD, compared to previously published data on methadone pharmacokinetics in individuals without SCD. The exploratory aim was to assess pain relief and opioid sparing in participants receiving adjuvant methadone compared to controls, in both pediatric and adult patients with SCD. We tested the hypothesis that methadone pharmacokinetics in children and adults with SCD would be similar to the general population. We also tested the hypothesis that children and adults who are experiencing a VOE will have reduced opioid consumption, pain intensity, and improved pain relief when treated with methadone in addition to standard care compared with standard intravenous morphine or hydromorphone alone in control groups.

Methods

This study received approval from Washington University in St. Louis institutional review board. Written informed consent was obtained from adult study subjects and from the legal guardian of pediatric subjects, with children providing assent. There were two arms of the study consisting of participants with SCD: a pediatric arm, with a pediatric methadone group and a pediatric control group; and an adult arm, with an adult methadone group and an adult control group. These two arms were separate during the study, with separate allocations. No comparisons were performed between the pediatric and adult arms.

The eligible study population included children (7–17 years) and adults (18–55 years) with SCD. Inclusion criterion was a confirmed diagnosis of any form of SCD, including sickle cell anemia, sickle-hemoglobin C disease, and sickle- β^+ or β^0 thalassemia. Children were approached for study recruitment and consent during routine outpatient clinic visits, in anticipation of potential future hospitalization for pain and study participation. Adults were approached as inpatients for the study during that admission if they were admitted in the evening hours. Both children and adults who were hospitalized with a history of frequent pain episodes were approached on the day of discharge, to be consented for participation with their next admission for pain. A \$50 gift card to a national retail chain store was offered to patients upon completion of the study.

Patients were eligible for study if they met the following criteria: were experiencing a VOE, defined as acute pain in the extremities, back, abdomen, or chest that is presumed to be due to SCD, with no other identified cause, and admitted to the inpatient unit for further treatment; and started on morphine or hydromorphone patient controlled analgesia (PCA) and infusion for pain management. Previously consented participants were not eligible to

participate in the study during an admission if they were admitted for any of the following: diagnosis of acute chest syndrome, defined as a new lobar pulmonary radiodensity on chest radiograph and two or more of the following: temperature $>38.5^{\circ}\text{C}$, tachypnea, dyspnea, intercostal or supraclavicular retractions, nasal flaring, chest wall pain, oxygen saturation of $<90\%$ on room air by pulse oximetry; new focal neurologic findings or clinical concern of stroke; aplastic crisis with hemoglobin 2 g/dl below steady-state value; allergy or history of adverse reactions to morphine or methadone; any other medical condition that the attending physician deems to be a contraindication to therapy; liver or renal insufficiency or failure, and congestive heart failure.

After a patient was consented and admitted for a VOE, they were randomly assigned to a control group with standard pain therapy (morphine or hydromorphone PCA) or the methadone group, where they received a single dose of IV methadone, in addition to standard pain therapy. Methadone was administered on the morning of the hospital day after admission (due to time required to procure methadone from the pharmacy). Methadone was administered as a bolus to adults and as a 10 minute infusion to children. If a patient in the methadone group was admitted in the afternoon, the study would not be initiated until the following morning. For patients in the control group, the study was initiated the following morning if admitted in the afternoon/evening. If a control patient was admitted in the morning, the study was initiated that morning. The initial methadone dose (0.1 mg/kg) was deliberately low and was chosen to minimize any potential adverse effects, and was based on clinical experience with morphine dosing in pediatrics and potency differences between opioids, as well as experience in adults. The protocol called for a conservative dose escalation to 0.125 mg/kg of methadone in subsequent participants if prior patients continued to have incomplete pain control but no respiratory depression up to 8 hours after methadone administration. The protocol in both the pediatric arm and adult arm was a parallel group randomized study, but participants who had a subsequent admission for a VOE were allowed to be restudied, and were crossed over to the other group.

In participants that received methadone, venous blood samples were obtained at 0.5, 1, 2, 4, 8, 12, 24, 48, 72, and 96 hours after dosing. Plasma was obtained by centrifugation and stored at -80°C until analysis. Plasma concentrations of methadone and the primary (inactive) metabolite 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) were determined by liquid chromatography-tandem mass spectrometry as previously described.³³

Participants' pain scores and pain relief scores were obtained in both control and methadone groups. In the methadone group, pain scores and pain relief scores were obtained at baseline, with each blood draw on study day 1, and twice daily on study days 2–5; in the control group, these data were obtained twice a day for each day of the study. For pediatric patients, pain intensity was assessed using the Wong-Baker FACES scale from 0 (no pain) to 5 (most pain) previously validated in children with SCD.³⁶ For adults, pain was assessed using a 10-cm visual analog scale (VAS) from 0.0 (no pain) to 10.0 (most pain). Pain relief compared to initial presentation to the hospital was also assessed using a colored VAS for both the pediatric³⁷ and adult population, from 0.0 (least pain relief) to 10.0 (most pain relief).

Opioid consumption was recorded for all participants. Emergency department and inpatient opioid consumption prior to initiation of study, as well as opioid consumption during the study, was also recorded in both treatment and control groups using the inpatient medical record. Results are expressed in intravenous morphine equivalents. Opioid equivalence was defined as 10 mg morphine intravenous; 1.5 mg hydromorphone intravenous; 100 ug fentanyl intravenous, and 20 mg of oral oxycodone.³⁸

Participants' background information, including demographic data, hemoglobinopathy phenotype, number of admissions for VOE during the previous 12 months, outpatient medications used for current episode, chronic medical conditions, and other home medications, was obtained from the medical record.

Sample sizes were based on the primary outcome variable: methadone clearance. Interindividual coefficients of variation in methadone clearance were anticipated to be less than 15%. Based on 15% coefficient of variation, we would require at least 10 participants to detect a 20% difference in clearance ($p=0.05$, $\beta=0.8$).

We evaluated continuous variables at each time point by t-test or Wilcoxon non-parametric test, depending on variable distribution, as appropriate. To evaluate the progression in continuous variables over time while accounting for within patient correlation, we fitted repeated measures mixed models for the entire duration of the study. For ordinal variables, such as FACES pain scale and pain relief scores, time trends in cases versus controls were assessed using Cochran-Armitage trend test. Correlations were assessed using a Spearman correlation coefficient. We also repeated all analyses excluding the subjects who were enrolled in the study twice in different study groups, and obtained similar results. Statistical analyses were performed using SAS 9.3 and R statistical software.

Results

Demographics

Participant demographics are shown in Supplemental Table S1. Twenty-four pediatric patients were studied (Figure 1); 12 in the methadone group (15 ± 2 yr) and 12 in the control group (14 ± 3 yr). There were 15 males, 9 females. The majority had Hgb SS phenotype. Four children had an additional admission diagnosis: asthma (2), influenza (1), and headache (1). Of note, 6 pediatric participants were in both the methadone and control groups. Twenty-three adult patients were enrolled (Figure 2): 11 in the methadone group (25 ± 6 yr) and 12 in the control group (25 ± 7 yr). Initially, 14 males and 10 females were enrolled, although 1 female was withdrawn due to agitation and confusion, which was later believed to be a psychiatric episode at the initiation of methadone infusion. Five adults had additional admission diagnosis: pneumonia (1), iron overload (1), fever (2), and urinary tract infection (1). The majority of the adult patients had Hgb SS phenotype. Five adults were in both the methadone and control groups. Methadone patients received 0.1 mg/kg, except three pediatric and one adult patient received 0.125 mg/kg, due to dose escalation. Dose groups were not subdivided for analysis.

Pharmacokinetics

Plasma concentrations of methadone and EDDP (Figure 3) and pharmacokinetic parameters are (Table 1) are shown. Methadone is used clinically as a racemic mixture, but the individual enantiomers have different properties. Consequently, it is standard to quantify the individual enantiomers. Results for both methadone doses were combined, due to the small number of participants receiving the escalated dose of 0.125 mg/kg, thus both observed and dose-normalized results are provided. Most notable was the elimination of methadone, with elimination half-lives of 34 ± 16 and 24 ± 9 hr for R- and S-methadone in children, and 52 ± 17 and 38 ± 12 hr for R- and S-methadone in adults.

Pediatric Pain Scores and Opioid Use

FACES pain scores on a scale from 0 (no pain) to 5 (most pain) for individual pediatric patients were compared between pediatric methadone and control groups. Using a Cochran-Armitage Trend test at each time point, pain scores at baseline (time 0) did not differ ($p=0.234$), but the difference in pain score distribution was significant at 12 hours ($p=0.012$), 24 hours ($p=0.003$), and 48 hours ($p=0.021$). Using a generalized estimating equation (GEE) repeated measures model treating the FACES score as an ordinal value (multinomial distribution), adjusted for age, sex, and time, patients receiving methadone reported significantly less pain ($p=0.002$). Pain relief scores were also compared between methadone and control groups (Figure 4A). Pain relief at baseline did not differ, but pain relief was significantly greater at 12, 24 and 48 hours in patients receiving methadone. Using a repeated measures model treating pain relief a continuous value, adjusted for age, sex, and time, patients receiving methadone reported significantly greater pain relief ($p=0.0396$).

Opioid consumption, including methadone, was also compared in the pediatric patients receiving methadone and the control group (Figure 4B). Data were compared by the Wilcoxon test at each time point to account for the high variance in the data. There were no significant differences in daily opioid consumption between the two groups. Cumulative (day 1–5) opioid consumption was not significantly different between methadone participants (255 ± 155 mg) and controls (309 ± 135 mg). There was no significant correlation between pre-study opioid consumption and total study opioid consumption in either group.

Adult Pain Scores and Opioid Use

VAS pain scores on a scale from 0.0 (no pain) to 10.0 (most pain) for individual adult patients were compared between methadone and control groups. Using a t-test at each time point, mean pain scores at 72 hours were significantly lower in the methadone group (2.6 methadone vs 4.7 control group) ($P=0.04$), but not at any other time point. Using a repeated measures model, adjusted for age, sex, and time, there was no significant difference between the methadone and control groups (4.1 vs 4.8). Pain relief scores were also compared between methadone and control groups (Figure 5A). Pain relief did not differ at any time point. Using a repeated measures model treating pain relief as a continuous value, adjusted for age, sex, and time, there was no significant difference in pain relief between the methadone and control groups (adjusted least square means 5.7 vs 5.4).

Opioid consumption, including methadone, was also compared in the adult methadone group and the control group (Figure 5B). Total opioid consumption was compared by the Wilcoxon test at each time point to account for the high variance in the data. There were no significant differences in daily opioid consumption between the two groups. Using a mixed model accounting for repeated measurements within subjects, daily opioid consumption was not significantly different between the two groups ($p=0.456$). Cumulative (day 1–5) opioid consumption was not significantly different between methadone subjects (469 ± 139 mg) and controls (570 ± 537 mg) ($p=0.499$). There was no significant correlation between pre-study opioid consumption and total study opioid consumption in either group.

Discussion

The primary aim of this investigation was to evaluate methadone pharmacokinetics in children and adults with SCD. Methadone disposition was stereoselective, as expected, with higher plasma concentrations of S-methadone and faster systemic elimination of S-methadone in both children and adults. There are relatively few studies of methadone pharmacokinetics in children, and they have used different methods of data analysis.^{33–35} Published data suggests that methadone clearance is similar in neonates, infants, and children.³⁴ In our patients, methadone and EDDP concentrations and pharmacokinetic parameters in the children with sickle cell disease (15 ± 2 yr) were generally comparable to those in children and adolescents receiving IV methadone during major surgery^{33–35} or sedation.³⁴ Importantly, clearance, volume of distribution, and metabolism (N-demethylation) appear comparable across populations. Together, these results suggest that sickle cell disease does not alter the pharmacokinetics of methadone in children.

Similarly, methadone clearance, volume of distribution, and metabolism (N-demethylation) were also comparable in the adults with SCD and healthy adult volunteers receiving IV methadone.^{24–28} R-methadone half life in healthy volunteers was 48 ± 19 hr,^{24–32} which is comparable to our results in adults with SCD (52 ± 17 hr). Similarly, S methadone half-life was 34 ± 14 hr in healthy volunteers,^{24–32} and 38 ± 11 hr in our adults with SCD. These results suggest that SCD in adults also does not significantly alter the pharmacokinetics of methadone. Thus, available pharmacokinetic data, here and previously published, can be used to guide the use of methadone in sickle cell disease.

One secondary aim was to explore the analgesic effects of methadone in children with SCD. Better analgesia occurred with methadone in children with VOE pain, with a significant reduction in pain scores and an increase in pain relief scores in the pediatric methadone group compared to controls. This is similar to previous studies evaluating methadone for post-operative pain.²³ One possible explanation for better analgesia is that the slower elimination of methadone compared to other opioids (morphine and hydromorphone) leads to a more sustained opioid concentration in the therapeutic range. Another possible explanation is that methadone, unlike morphine and hydromorphone, is an NMDA receptor antagonist. NMDA receptors activation in the spinal cord dorsal horn is important in the generation and maintenance of pain.^{39,40} NMDA-receptor antagonism by methadone may reduce the positive feedback loop associated with hyperalgesia. In addition, NMDA receptors are expressed on red blood cells⁴¹ and are up-regulated in patients with SCD,

particularly during hemolytic crises; NMDA receptor inhibition caused re-hydration and could prevent hypoxia-induced sickling.⁴²

Another secondary aim was to explore the analgesic effects of methadone in adults with SCD. There was no difference between adult methadone and control groups in pain score or pain relief. One possible explanation is that the adults may have been opioid tolerant. Another, more likely explanation, is that the initial low methadone dose (0.1–0.125mg/kg; 4–9 mg, chosen to mirror the pediatric dose) was simply insufficient. For example, in adults with chronic pain, 20mg/day was required to result in a significant improvement in pain compared to placebo.⁴³ Interestingly, however, during an exit interview, 7 of the adults who received methadone subjectively felt that it improved their pain. Lastly, the sample size might have been too small to detect statistically significant pain differences, as the study was powered to obtain pharmacokinetic data.

Another secondary aim was to explore the opioid sparing effects of methadone in children and adults with SCD. In both the pediatric and adult arms, there was no difference between the methadone group versus controls in total and daily opioid consumption. Again, this is likely due to the small methadone dose administered, compared to the total opioid dose which patients received.

Conclusion

The primary goal of the investigation was to evaluate the disposition of methadone, and secondarily to assess pain relief and opioid sparing compared to controls, in pediatric and adult patients with SCD. This study found that the pharmacokinetics of methadone are not altered by SCD in either children or adults, and thus these and previously published pharmacokinetic parameters can be used to guide dosing in this population. The dose of 0.1–0.125 mg/kg was without adverse effects, and safe in both the pediatric and adult populations. While this initial low dose did have improved analgesia versus controls in the pediatric arm, this was not observed in adults. In this pilot study, doses were deliberately chosen to be low. Given the predictable pharmacokinetics, long duration of effect, safety, and early indicators of clinical analgesic effectiveness, further evaluations should be conducted to evaluate the safety and effectiveness of higher methadone doses in children and adults with SCD. Such methadone use may improve analgesia, reduce opioid consumption, and reduce the frequency or duration of hospital admissions for pain treatment in VOE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

VOE	Vaso-occlusive episode
SCD	Sickle cell disease
PCA	Patient controlled analgesia
EDDP	2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine
VAS	Visual analog scale
GEE	Generalized estimating equation
NMDA	N-methyl-D-aspartate

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Figure 1.
Flow diagram for enrollment of pediatric participants.

Figure 2.
Flow diagram for enrollment of adult participants.

Figure 3.

Plasma concentrations of methadone and EDDP. Results are shown as the mean $\pm$ SD for children (left, n=12) and adults (right, n=11). All subjects received 0.1mg/kg methadone, except 3 children and 1 adult, who received 0.125 mg/kg. Children received a 10 minute infusion and adults received a bolus. Times are relative to the start of methadone dosing.

Figure 4.

Effect of methadone on pain relief and opioid consumption in children. Day 1 denotes the day of methadone administration. In controls, data were obtained on the comparable hospital day. (A) Pain relief scores. Results are the mean $\pm$ SD (* $p < 0.05$ between groups) (B) Daily total opioid consumption (morphine equivalents, mg). Results are the median, and upper and lower interquartile ranges. There were no significant differences between groups.

Figure 5.

Effect of methadone on pain relief and opioid consumption in adults. (A) Pain relief scores. Results are the mean $\pm$ SD (B) Daily total opioid consumption. Results are the median, and upper and lower interquartile ranges. There were no significant differences between groups.

TABLE 1

Methadone pharmacokinetic parameters

	Children		Adults	
	R-methadone	S-methadone	R-methadone	S-methadone
$C_{\max}$ (ng/ml)	17 ± 7	28 ± 12	16 ± 7	23 ± 9
$C_{\max}/D$ (ng/ml/mg)	6 ± 2	10 ± 5	5 ± 4	7 ± 4
AUC_{0-96} (ng · hr · ml ⁻¹)	429 ± 248	635 ± 424	421 ± 168	601 ± 276
$AUC_{0-\infty}$ (ng · hr · ml ⁻¹)	523 ± 248	716 ± 439	637 ± 324	790 ± 397
$AUC_{0-\infty}/D$ (ng · hr · ml ⁻¹ · mg ⁻¹)	190 ± 99	262 ± 178	191 ± 94	241 ± 123
CL_{IV} (ml · kg ⁻¹ · min ⁻¹)	2.1 ± 1.2	1.7 ± 1.0	1.6 ± 0.6	1.3 ± 0.5
Elimination $t_{1/2}$ (hr)	34 ± 16	24 ± 9	52 ± 17	38 ± 12
V_{ss} (L/kg)	5.9 ± 3.9	3.3 ± 2.2	6.5 ± 1.7	3.9 ± 1.2
	R-EDDP	S-EDDP	R-EDDP	S-EDDP
$C_{\max}$ (ng/ml)	0.49 ± 0.26	0.90 ± 0.44	0.37 ± 0.20	0.60 ± 0.16
$C_{\max}/D$ (ng/ml/mg)	0.18 ± 0.13	0.33 ± 0.22	0.11 ± 0.06	0.18 ± 0.06
$T_{\max}$ (hr)	6 ± 7	9 ± 8	11 ± 7	11 ± 6
AUC_{0-96} (ng · hr · ml ⁻¹)	19 ± 7	31 ± 12	20 ± 7	32 ± 9
$AUC_{0-\infty}$ (ng · hr · ml ⁻¹)	27 ± 10	41 ± 13	30 ± 10	43 ± 16
$AUC_{0-\infty}/D$ (ng · hr · ml ⁻¹ · mg ⁻¹)	10 ± 3	14 ± 5	12 ± 8	13 ± 4
Elimination $t_{1/2}$ (hr)	42 ± 13	31 ± 8	54 ± 29	41 ± 22
AUC_{0-96} (EDDP/methadone)	0.05 ± 0.03	0.06 ± 0.04	0.05 ± 0.02	0.06 ± 0.02
AUC_{∞} (EDDP/methadone)	0.06 ± 0.04	0.07 ± 0.04	0.06 ± 0.02	0.06 ± 0.02

Adults received 0.1 (n=10) or 0.125 (n=1) mg/kg, and children received 0.1 (n=9) or 0.125 (n=3) mg/kg IV methadone HCl. Results for both doses are within each age group, and are the arithmetic mean · SD. AUC, area under the plasma concentration-time curve (0–96 hr and 0-infinity); $AUC_{0-\infty}/D$, dose-normalized AUC, $C_{\max}$, peak plasma concentration; $C_{\max}/D$, dose-normalized $C_{\max}$, CL_{IV} , systemic clearance; $C_{\max}$, peak plasma concentration; EDDP, 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine; V_{ss} , steady-state volume of distribution.