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Route of administration and formulation dependent pharmacokinetics of 17-hydroxyprogesterone caproate in rats

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Abstract

1. Weekly intramuscular injections of (250 mg/week) of 17-hydroxyprogesterone caproate (17-OHPC) are the only treatment option for prevention of preterm birth in women with a prior history of preterm delivery.
2. The objective of the current study was to evaluate the use of an alternate formulation and the feasibility of an alternate route of administration of this agent. 17-OHPC was administered to adult female SD rats, as marketed oily formulation intramuscularly, or as a solution IV, IM, or PO.
3. Plasma concentrations of 17-OHPC were measured by LC-MS-MS and pharmacokinetic parameters were calculated by non-compartmental analysis, using WinNonLin (Certara, St. Louis, MO).
4. After IV or IM administration as a solution, the mean half-life of 17-OHPC was around 11 h. The bioavailability was nearly 100% after IM administration, but was very low (<3%) after PO administration of a solution dosage form.
5. Intramuscular injection of the oily formulation resulted in low levels of 17-OHPC that were sustained for a prolonged time period with a projected bioavailability close to 100%.
6. The pharmacokinetics of 17-OHPC is dependent on the formulation and the route of administration.

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Declaration of interest

The authors report no conflict of interest.

7. The low bioavailability after oral administration indicates that oral administration of 17-OHPC may not be feasible with simple formulations of this drug.

Keywords

Absorption; CYP 3A 4/5 metabolism; jugular vein cannulation; LC-MS/MS; pharmacokinetics; preterm birth; 17-OHPC

Introduction

Nearly 12% of the babies born in United States are born prematurely (Mattison et al., 2001). Despite vigorous efforts at treatment of preterm labor with labor-inhibiting drugs (tocolytics), intensive prenatal care, patient education, and bed rest, rates of preterm birth have not decreased significantly over the past 40 years. Preterm birth is associated with mortality and long-term morbidity, and both are inversely related to gestational age at birth. In a sentinel article that has changed clinical practice, Meis et al. (2003) demonstrated a 34% reduction in delivery before 37 weeks, in women with a prior preterm birth, who received weekly injections of 17-Alpha hydroxyprogesterone caproate (17-OHPC). Treatment with 17-OHPC has proven effective in reducing the rate of preterm birth in women with a history of spontaneous preterm delivery, but it appears to be ineffective in other high-risk categories such as women with a short cervical length and those with multifetal gestation (Caritis et al., 2011).

17-OHPC, which was clinically introduced in 1956 under the trade name Delalutin[®], is the caproic acid derivative of 17-hydroxyprogesterone, a natural progestogen. Originally promoted for the treatment of gynecological and obstetrical disorders, such as threatened abortion and repeated early pregnancy loss, the drug is now offered to all pregnant women with a prior history of preterm delivery. Currently only an intramuscular dosage form is available for clinical use. Intramuscular administration is associated with pain at the local site of administration, and a large variation in the trough plasma concentrations of 17-OHPC. Moreover, it is also very inconvenient to the patients. In this context, alternate routes of administration and alternate formulations of 17-OHPC may overcome some of the limitations of the intramuscular administration and may benefit a larger population of women with prior history of preterm delivery. The aim of this study was to characterize the pharmacokinetics and bioavailability of 17-OHPC after different routes of administration in order to investigate potential alternative routes of delivery and to evaluate alternate formulations of 17-OHPC, using an animal model.

Materials and methods

Chemicals

17-OHPC USP reference standard was purchased from United States Pharmacopoeia, Rockville MD. 17-OHPC was purchased from Eminent Services Corporation, Fredrick, MD. Cremophor EL, ethanol, formic acid, medroxyprogesterone acetate, and ammonium acetate were purchased from Sigma Chemicals, St. Louis, MO. LC-MS/MS grade solvents of highest purity and all other chemicals were obtained from Sigma Chemicals, St. Louis, MO.

17-OHPC oil formulation and placebo for oil formulation were obtained from Heber's Compounding Pharmacy, Pittsburgh, PA. Blank female SD rat plasma was purchased from Biochemed Services, Winchester, VA. Oasis® HLB 1cc (30 mg, 30 µm particle size) extraction cartridges were obtained from Waters, Milford, MA.

Animals

Adult female Sprague–Dawley (SD) rats (250–300 g) were obtained from Charles River Laboratories, Inc (Wilmington, MA). All the procedures were performed in accordance to a protocol approved by the University of Pittsburgh's Institutional Animal Care and Use Committee and were consistent with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996, Washington, District of Columbia). The rats were housed in the animal facility with 12 h light/dark cycle with free access to food and water at all times.

Experimental groups

A total of 30 rats were used for *in vivo* pharmacokinetic studies. Animals were randomly assigned to different groups ($n = 3$ –6 per group) and were administered either 5 mg/kg IV or IM or PO as a solution or as IM of an oil formulation of 17-OHPC. Additionally, rats were administered 25 mg/kg 17-OHPC PO as a solution.

Procedures

The rats were acclimated for at least 72 h in the animal facility before conducting any experiments. The jugular vein cannulation procedure was similar to that reported by Shaik et al (Shaik & Mehvar, 2011). Briefly, under isoflurane anesthesia, the right jugular veins of all the rats were cannulated with a silicone tipped PE50 polyethylene tubing for blood sample collection. Normally, a sample of ~200 µl was collected for each time point and the isolated plasma was ~100 µl. For the IM oil and the PO group, ~400 µl blood sample was collected which provided ~200 µl plasma sample, as we needed a larger volume sample to improve LLOQ. A total of less than 15% of total blood volume was collected during blood sampling to avoid anemia in the rats and this has been shown not to influence the overall health of rats (Diehl et al., 2001).

Dosing

IV dosing and sampling—17-OHPC was dissolved in cremophor:ethanol mixture (200 mg:638 mg) and diluted 10-fold with sterile saline. Under isoflurane anesthesia, rats ($n = 6$) were given 2.5 ml/kg of a diluted solution to get a dose of 5 mg/kg 17-OHPC via sublingual vein and blood samples were collected from jugular vein cannula. Periodic blood samples were collected before dosing and at 5, 15, 30 min, 1, 2, 4, 8, 12, and 24 h post dose. Plasma was separated by centrifugation and stored at -80°C until further analysis.

PO dosing and sampling—Oral administration of 17-OHPC was done with the aid of an intra-gastric feeding needle. 17-OHPC solubilized in cremophor:ethanol was diluted 10-fold with saline and given at 2.5 ml/kg orally for a dose of 5 mg/kg ($n = 4$) group, whereas the 25 mg/kg ($n = 4$) group received undiluted cremophor:ethanol solution. Blood samples were

collected from jugular vein cannula before dosing, and at 15, 30, 60, 90 min, 2, 4, 8, 24, and 48 h post dose and plasma was separated and stored at -80°C until further analysis.

IM dosing and sampling—17-OHPC (5 mg/kg) was given IM either as the diluted cremophor:ethanol solution ($n = 4$) or as the commercial oil formulation ($n = 3$). 17-OHPC (250 mg/ml) oil formulation was diluted with placebo to get a 2 mg/ml concentration and was given at 2.5 ml/kg dose. Blood samples were collected from jugular vein cannula before dosing and at 0.5, 1, 2, 4, 8, 24, and 48 h post dose for the IM solution group and before dosing and at 2, 4, 8, 12, 24, 48, 72, 96, and 120 h post dose for the IM oil group. Plasma was separated and stored at -80°C until further analysis.

Sample analysis—17-OHPC and its metabolite levels in plasma samples were analyzed using a validated LC-MS/MS method previously reported by our group with minor modifications (Zhang et al., 2008). Partial validation was performed for the modified assay.

Standards—Stock solutions for primary standards were prepared in methanol (1 mg/ml). The primary stock solution was diluted with rat plasma to get routine working standards and controls. Working solution for the internal standard (medroxyprogesterone acetate (MPA) 1 $\mu\text{g/ml}$) was prepared in methanol. The range of working standards was from 5 ng/ml to 1000 ng/ml. The quality control standards were 15, 400, and 900 ng/ml. The working standards, quality controls, and internal standard were stored at -20°C .

Sample preparation—The working standards, rat plasma samples, and internal standard solution were thawed at room temperature. To 50 μl of working standard or plasma sample, 25 μl of internal standard (1 $\mu\text{g/ml}$ in methanol) was added, diluted with 1 ml water and vortex mixed for 15 s. Oasis[®] HLB 1cc cartridges were preconditioned with 1 ml of methanol followed by 1 ml water and then the entire sample mixture was passed through the cartridge. The cartridge was washed with 1 ml of 50% methanol and dried under vacuum. 17-OHPC and IS were eluted into 1 ml methanol, collected in a glass tube and evaporated to dryness under stream of air. The resultant residue was dissolved in 100 μl of 50% methanol and 20 μl samples were injected into the HPLC system connected to a mass spectrometer. To measure 17-OHPC in samples after administration of PO solution and IM oil formulation, 200 μl of plasma sample was used for solid phase extraction. After reconstitution, 40 μl sample was injected on to the column.

Chromatography and mass spectrometry conditions—The chromatography system used for analysis of 17-OHPC was equipped with a Waters 2795 console (Waters Corporation, Milford, MA). The compounds were separated on 3.5 μm 2.1 mm $\times$ 50 mm Waters C18 Symmetry analytical column at 40°C attached to 2.1 mm $\times$ 10 mm Waters C18 Symmetry guard column (Waters Corporation, Milford, MA). The mobile phase consisted of [A] 5% methanol in water supplemented with ammonium acetate (2 mM) and formic acid (0.1%) and [B] methanol containing ammonium acetate (2 mM) and formic acid (0.1%). The sample run time was set to 10 min at a flow rate of 0.25 ml/min with a gradient program starting from 50% solution [B] to 90% [B] over 2 min, held until 6.0 min, after which returned to the initial condition of 50% [B] over 0.1 min, to achieve the base line until 10 min.

Analysis was performed on a Micromass Quattro Micro triple quadrupole mass spectrometer (Waters Corporation, Milford, MA) in positive electrospray ionization mode (+ESI) using multiple reaction monitoring (MRM). For 17-OHPC, its metabolites and the internal standard, the following MRM setting was employed: capillary voltage 3.5 kV; source temperature 100 °C; de solvation temperature 450 °C; cone gas flow (l/h) 50; de solvation gas flow (l/h) 550; argon pressure 20 ± 10 psig; nitrogen pressure 100 ± 20 psig. The extracted ions following MRM transitions monitored were m/z 429.06→313.05 for 17-OHPC, m/z 444.94→313.05 for 17-OHPC metabolite, and m/z 387.21→327.26 for MPA (IS). The LC and mass spectrometer were controlled and data collected by Masslynx[®] software version 4.1 (Waters Corporation, Milford, MA). The cone and collision energy for HPC, its metabolite, and MPA are presented in Table 1.

Data analysis—The plasma concentration versus time profiles were analyzed by non-compartmental approach using Phoenix-WinNonLin software (Certara, St. Louis, MO). The estimated pharmacokinetic parameters were the area-under-the-plasma concentration–time curve from time zero to t (AUC_{0-t}), area-under-the-plasma concentration versus time curve from last time point to infinity ($AUC_{t-\infty}$), total body clearance (CL), apparent clearance (CL/F), volume of distribution at steady state (V_{ss}), bioavailability (F), and plasma half-life ($t_{1/2}$). The terminal disposition rate constant (K) was calculated from the slope of the log linear terminal portion of plasma concentration versus time profile. The slope of the terminal portion was determined using the last 3–4 points in the plasma concentration versus time profile in each rat. The absorption rate constant (K_a) was calculated by the method of residuals. Area under the curve (AUC_{0-t}) was calculated using the linear trapezoidal method and area under the curve from t to infinity was obtained by dividing the plasma concentration at time t by K . $AUC_{0-\infty}$ was calculated as the sum of AUC_{0-t} and $AUC_{t-\infty}$. Various pharmacokinetic parameters among the groups were compared using one-way analysis of variance (ANOVA), followed by Fisher's post hoc analysis or unpaired Student's t -test. A p value <0.05 was considered to be significant.

Results

Mass spectroscopic analysis

The relative retention times of 17-OHPC, metabolite M1, and MPA were 7.4, 5.9, and 6.2 min, respectively. The observed mass to charge transitions for parent ion and product ions were m/z 429.06 → 313.05 for 17-OHPC and m/z 387.21 → 327.26 for MPA (IS). A standard compound for the most abundant metabolite of 17-OHPC was not available commercially. In the absence of a reference for this metabolite, characterization of the metabolite at m/z 444.97 → 313.05 was performed in accordance to previously reported method from our group (Sharma et al., 2010, 2008).

Assay validation

Linearity—There was a linear relationship between the peak area ratios of 17-OHPC to MPA ($R^2 = 0.993$) in the concentration range of 5–1000 ng/ml. The intra- and inter-day precision expressed as the coefficient of variation at LLOQ (5 ng/ml) was $<17.4\%$ and met the acceptance criterion of 20%.

Precision and accuracy—The coefficient of variation for intra- and inter-day accuracy and precision for the assay, presented in Table 2, are in accordance with acceptable limits of FDA guidelines for the bioanalytical assay method validation. The intra- and inter-day precision at all the concentrations met the acceptance criterion of 20% CV. The assay is sensitive, accurate, and reproducible. Sample analysis revealed that all the measured samples were within the standard curve range. Recovery, ion suppression, and stability of the samples were similar to the previously reported method (Zhang et al., 2008).

Pharmacokinetics—The plasma concentration–time profiles of 17-OHPC after different routes of administration are shown in Figure 1 and the corresponding pharmacokinetic parameters are presented in Table 3. After IV administration of 5 mg/kg 17-OHPC, the highest measured plasma concentration was seen in the first collected samples. The plasma concentration versus time profile showed an initial distribution phase depicted by a sharp decline in plasma concentration, followed by a slower disposition phase. The terminal disposition half-life of 17-OHPC after IV administration was 10.6 ± 4.3 h. The area-under-the-plasma concentration–time curve ($AUC_{0-\infty}$) was 1000 ± 360 ng h/ml. The clearance of 17-OHPC was 1.45 l/h. The corresponding V_{SS} was 23 ± 13 l.

Intramuscular administration of a solution dosage form of 17-OHPC showed an initial rapid absorption phase with a time to reach maximum plasma concentrations of around 2 h and the plasma concentrations of 17-OHPC subsequently decreased over time. The elimination half-life calculated from the slope of the terminal portion of plasma concentration–time profile was 16 ± 5 h, which was similar to the $t_{1/2}$ obtained after IV dosing ($p = 0.62$, compared by unpaired Students' t -test). The $AUC_{0-\infty}$ of 17-OHPC was 1150 ± 150 ng h/ml indicating the bioavailability to be approximately 100% ($F = 1$) after IM administration of the solution dosage form. The apparent clearance (CL/F) and V_{SS}/F of 17-OHPC were 1.13 l/h and 18.3 ± 5.7 l, respectively.

After oral administration of 5 mg/kg of 17-OHPC, the plasma concentrations were below quantitation limits, but measurable concentrations of 17-OHPC were seen in plasma after the 25 mg/kg dose. The plasma concentration–time profile of 17-OHPC after 25 mg/kg dose, presented in Figure 1, shows an increase in the plasma concentration with time, followed by a disposition phase. The time to reach maximum concentration was between 1 and 1.5 h. The maximum plasma concentration reached was ~10 ng/ml. The $AUC_{0-\infty}$ of 17-OHPC was around 151 ng h/ml and the calculated apparent oral clearance (CL/F) was 45 l/h. The bioavailability of 17-OHPC after PO administration was ~3%.

Intramuscular administration of 5 mg/kg 17-OHPC in oil formulation showed very low concentrations in plasma. The sample volume for the assay was increased to be able to properly measure the concentrations after administration of this formulation. The plasma concentration of 17-OHPC indicated slow and sustained absorption from the IM injection site. The AUC_{0-120} of 17-OHPC after IM injection was 340 ng h/ml. As the slope of terminal portion of IM oil injection could not be estimated accurately, $t_{1/2}$, $AUC_{t-\infty}$, $AUC_{0-\infty}$, CL , and V_{SS} values were not estimated after this route of administration.

Discussion

The present study evaluated the feasibility of alternate route of administration for the only drug that is currently available to prevent preterm delivery. In patients, trough plasma concentrations have reported to range from 3.7 to 8.1 ng/ml (Caritis et al., 2014). In order to measure low concentrations of 17-OHPC, a sensitive, specific, and accurate assay was necessary. Zhang et al. (2008) had previously reported a validated LC-MS/MS assay for the measurement of 17-OHPC in human plasma utilizing a sample volume of 400 μ l. We have modified the previously published assay for the measurement of 17-OHPC in rat plasma and performed partial validation of the assay. The assay methodology reported in the manuscript is more sensitive than other reported methods in the literature. The lowest amount of 17-OHPC loaded on the column for accurate measurement using the assay reported by Zhang et al. was 50 pg, whereas our assay methodology requires only 25 pg on the column, making the assay suitable for studies with limited volume of sample. Our assay is two times more sensitive, accurate and requires 2–8 times smaller volume of plasma sample for analysis. For PO and IM oil groups, by using larger volume of sample for extraction and increasing the injection volume, we could measure HPC levels in the range of 1.25 ng/ml.

Currently 17-OHPC is administered as an IM injection of an oily solution at a dose of 250 mg/week starting at 16–20 weeks of gestation and continuing until 36 weeks or delivery, whichever happens first. Based on this dosing regimen, the typical steady-state maximum plasma concentrations range from 12.5 to 56 ng/ml and the steady-state minimal plasma concentrations range from 3.7 to 8.1 ng/ml. The selection of the dose of 17-OHPC for this study was based on the clinically used dose of 250 mg and assuming an average body weight of 70 kg. Allometric scaling indicates a dose of 22.5 mg/kg for studies in rats in order to evaluate the pharmacodynamic effects. Given the focus of our study was to estimate the pharmacokinetic parameters, a dose of 5 mg/kg was selected initially. After IV injection of 5 mg/kg, we observed plasma concentrations of 17-OHPC that are clinically relevant. However, this dose resulted in plasma concentrations that were not quantifiable after PO administration. Therefore, an additional group of rats were tested at a PO dose of 25 mg/kg, a dose close to what is predicted by allometric scaling.

In the present study, the clearance of 17-OHPC was 1.45 ± 0.4 l/h. The hepatic blood flow in rat is around 0.9 l/h. This indicates that 17-OHPC is a high clearance drug in rats. This observation is consistent with the rapid metabolism (short half-life) of 17-OHPC in hepatocytes and hepatic microsomes (Sharma et al., 2008). The plasma clearance of 17-OHPC is more than the hepatic blood flow in rats indicating potential extra-hepatic metabolism of 17-OHPC. The volume of distribution of 17-OHPC after IV administration was 23 ± 13 l. The vascular volume in rat (300 g) is approximately 25 ml. A volume of distribution of 23 l suggests that the 17-OHPC is extensively distributed outside the vascular system. This is consistent with the physicochemical properties of 17-OHPC, such as high lipid solubility. IM administration of a solution dosage form showed an initial rapid absorption and a slower disposition phase with half-life and clearance values similar to IV route. The K_a (0.61 ± 0.31 h⁻¹) was significantly higher than K (0.05 ± 0.04 h⁻¹) for IM administration of a solution of 17-OHPC ($p < 0.012$, unpaired t -test). Given that after IV and IM administration of a solution similar half-lives were observed, this indicates absorption of

the drug from the solution dosage form appears to be faster than the disposition of the drug. In addition, AUC after IM administration was similar to the AUC seen after IV administration, indicating 100% bioavailability after IM administration of the solution dosage form.

PO dosing of 17-OHPC solution at 5 mg/kg did not show measurable levels of HPC in plasma, but increasing the dose to 25 mg/kg and utilizing higher volumes of samples for analysis resulted in measurable plasma concentrations of 17-OHPC. The oral bioavailability of the solution dosage form was very low. This low oral bioavailability is consistent with and as predicted by the high clearance of 17-OHPC observed after IV administration. It is known that CYP 3A4 and 3A5 are the major enzymes responsible for metabolism of 17-OHPC in humans (Sharma et al., 2008). These enzymes are expressed in large quantities in both the liver and the intestine in the rats (Mitschke et al., 2008). High first-pass hepatic and intestinal metabolism could have significantly contributed to the low oral bioavailability of 17-OHPC in rats. We anticipated higher concentrations of the metabolites after oral administration of 17-OHPC compared with IV or IM administration. However, even at an oral dose of 25 mg/kg, the concentrations of metabolites were below the limit of quantitation. This is not surprising in the light of the fact that 17-OHPC is known to be metabolized to 21 metabolites in hepatic and placental microsomes of humans and baboons (Yan et al., 2008) and that the concentrations of monohydroxy metabolite of 17-OHPC in human plasma is much smaller compared with the plasma concentrations of 17-OHPC (unpublished observations). Given the poor aqueous solubility of 17-OHPC, both first pass metabolism and poor absorption from the gastrointestinal tract could have contributed to the low oral bioavailability.

Although the IM injection of the oily formulation showed very low levels of 17-OHPC over extended duration, the plasma concentrations were measurable and the $AUC_{0-120\text{ h}}$ after IM injection of 17-OHPC oil was $340 \pm 30\text{ ng h/ml}$. The plasma concentration versus time profile after IM administration of the oil formulation and the long apparent terminal half-life indicates that the rate of absorption of 17-OHPC from the injection site is the rate-limiting step after administration of oily formulation of 17-OHPC. Kimbel et al. (1958) studied mass balance of 17-OHPC in rats after subcutaneous injection of 100 mg/kg C^{14} -labeled 17-OHPC. Similar to our observations after IM injection of the oily formulation, rats showed consistently low levels of 17-OHPC with comparable variability.

Our observation in rats after IM administration of 17-OHPC is consistent with the observations in humans. The plasma concentrations in human are low and relatively constant over a week period with a half-life in the range of 10–16 d in pregnant women (Caritis et al., 2011). Prolonged half-life of 17-OHPC has also been observed in patients with endometrial cancer who were on 1000 mg biweekly dose of 17-OHPC (Onsrud et al., 1985). In light of the *in vitro* observations of short half-life in human liver microsomes and human hepatocytes, we hypothesized that the observed plasma concentration versus time profile of 17-OHPC in humans after IM administration is rate limited by absorption from the site of injection. This current study provides evidence for this and supports our hypothesis.

In conclusion, this is the first study to systematically characterize the pharmacokinetics of 17-OHPC, the only drug available for the prevention of preterm delivery after various routes of administration. 17-OHPC is a drug with high volume of distribution and high clearance. It has a very low oral bioavailability, making this route of administration and the formulation used unsuitable in routine clinical setting. The elimination half-life of the 17-OHPC was $\sim 10.6 \pm 4.3$ h after administration in a solution dosage form. Much longer $t_{1/2}$ after administration of the IM oil formulation indicates absorption rate-limited plasma concentration versus time profile for the IM oily solution. This observation supports our hypothesis that the prolonged half-life observed in humans after IM administration of 17-OHPC in oily formulation is due slow and sustained absorption rate limited pharmacokinetic profile from the site of administration.

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Figure 1.

Plasma concentration-time course of 17-OHPC in adult female rats after administration of 17-OHPC in cremophore solution via IV (5 mg/kg), IM (5 mg/kg), and PO (25 mg/kg); and 17-OHPC in oil formulation (IM, 5 mg/kg).

Table 1

Conditions set for 17-OHPC, its metabolite and MPA analysis on LC-MS/MS.

Ion	Parent m/z	Daughter m/z	Dwell (s)	Cone energy (V)	Collision energy (eV)
17-OHPC	429.06	313.05	0.1	30	18
Metabolite (M1)	444.94	313.05	0.1	25	14
MPA (IS)	387.21	327.26	0.1	30	14

Table 2

Intra-day and inter-day accuracy and precision of 17-OHPC assay in rat plasma.

17-OHPC	Added concentration (ng/ml)		
	15	400	900
Intra-day assay	14.8 ± 1.1	404.6 ± 3.9	913.7 ± 9.8
Mean ± SD			
CV (%)	7.3	1.0	1.1
Bias (%)	-1.1	1.1	1.5
Inter-day assay	14.0 ± 1.5	400 ± 27.9	894.7 ± 28.9
Mean ± SD			
CV (%)	10.7	7.0	3.2
Bias (%)	-6.9	-1.3	-0.6

Table 3
Pharmacokinetic parameters 17-OHPC in female SD rats after IV, IM, and PO administration.

Parameter route	K (h^{-1})	K_a (h^{-1})	$T_{1/2}$ (h)	AUC_{0-4} (ng h/ml)	$AUC_{0-\infty}$ (ng h/ml)	$AUC_{0-\infty}$ (ng h/ml)	CL or CL/F (l/h)	V_{ss} or V_{ss}/F (l)	F
IV – sol – 5 mg/kg	0.082 ± 0.05	–	10.6 ± 4.3	910 ± 340	90 ± 40	1000 ± 360	1.45 ± 0.4	23 ± 13.5	1
IM – sol – 5 mg/kg	0.05 ± 0.004	0.61 ± 0.31	16.0 ± 5.0	950 ± 130	200 ± 60	1150 ± 150	1.13 ± 0.08	18.3 ± 5.7	1
IM – oil – 5 mg/kg ^a	–	–	–	340 ± 40	–	–	–	–	1
PO – sol – 25 mg/kg	0.05 ± 0.04	0.2 ± 0.06	19.4 ± 14	65 ± 20	67 ± 60	151 ± 60	50 ± 16.5	1387 ± 336	0.03

^a Absorption rate limited terminal disposition rate constant.