Supplementation with exogenous creatine (Cr) has shown physiological benefits in humans, but little is known about the pharmacokinetics of Cr in humans. Six healthy males completed an open-label study consisting of a full pharmacokinetic analysis following a single oral dose of Cr monohydrate (71 mg kg⁻¹) and at steady-state after 6 days of Cr administration (71 mg kg⁻¹ qid). After the single oral dose, the clearance (CL/F) was 0.20 ± 0.066 L h⁻¹ kg⁻¹, t_max was 1.9 ± 0.88 hours, and C_max = 102.1 ± 11.2 mg h L⁻¹. At steady-state, CL/F decreased to 0.12 ± 0.016 L h⁻¹ kg⁻¹, t_max did not change, and C_max increased to 162.2 ± 30.0 mg L⁻¹. Penetration (AUC_MUSCLE/AUC_PLASMA) of Cr into the interstitial muscle space, as determined by microdialysis, was 0.47 ± 0.09 and 0.37 ± 0.27 for the single dose and at steady-state, respectively. Plasma and muscle data were simultaneously fitted with a model incorporating a saturable absorption and first-order elimination process. In conclusion, repeated dosing of Cr caused a reduction in clearance that could result from saturation of the skeletal muscle pool of Cr.


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jected to a prestudy examination. Both males and females were recruited for the study, but only males volunteered. Inclusion criteria consisted of males or females ages 17 to 35 years who have not used Cr in the previous 3 months and had no self-reported history of kidney dysfunction. The University of Florida’s institutional review board on human subject testing approved all protocols. After determining the subject’s suitability and prior to enrollment, written informed consent was obtained in response to a written and verbal explanation of the nature of the study.

### Study Design

For single-dose pharmacokinetics (Day 1), all volunteers received a single morning dose (11:00 a.m.) of 71 mg creatine monohydrate (CM) powder (62 mg creatine) (CreaTeam, Nutrasense Company, Shawnee Mission, KS) per kilogram body weight (BW) (~5-g creatine monohydrate for 70-kg human). CM powder was dissolved in 250 mL of water, and an additional 50 mL of water was used for the residual Cr left in the container. Starting 24 hours after the initial Cr dose (Day 2), volunteers received 71 mg kg$^{-1}$ BW, four times daily (qid) (~20-g daily dose for 70-kg human), for 6 days (Days 2-7). During these 6 days, the first dose of each day was taken in the presence of the investigator, and remaining doses were taken without supervision. Times of all doses were recorded (average dosing interval = 6.5 h). On Day 8, steady-state pharmacokinetics was assessed after giving a single morning dose of 71 mg kg$^{-1}$ of CM. This dosing regimen has been previously shown to increase Cr muscle stores to therapeutic levels (> 17% increase in total Cr).$^{4,14}$ Body weight was tracked daily for the duration of the study.

Subjects were instructed to maintain a similar activity level and diet for the duration for the study. Physical activity of subjects was assessed using Bouchard et al’s 3-day physical activity record.$^{19}$ In addition, subjects completed a 3-day diet record for 2 weekdays and 1 weekend day. Daily dietary intake of Cr was based on animal protein intake, assuming 1 kg of animal protein contains 5 g of Cr.$^{20}$ Diet analysis was performed using Nutrition Data System for Research (NDS-R) software, version 4.01 (Food and Nutrient Database 28, Minneapolis, MN).

### Dietary Control

On the days of pharmacokinetic assessment (Day 1 and Day 8), diet was controlled. The Metabolic Kitchen at the Clinical Research Center prepared meals on these days consisting of low glycemic carbohydrates, similar to a diabetic diet. Volunteers also abstained from caffeine on these days. After an overnight fast, breakfast was given at least 3 hours prior to Cr administration to ensure fasting state at the time of Cr administration. Food was provided 1.5 hours after Cr administration, and subsequent meals were given every 2 hours to control for the effects of insulin by minimizing insulin fluctuation. Each meal contained similar amounts of carbohydrate (50.5 ± 6.44 g per meal). Total daily calories for the 2 pharmacokinetic days were 1893 ± 74 kcal with 16.7% ± 7.4% from protein, 29.7% ± 4.5% from fat, and 54.1% ± 6.7% from carbohydrate. Subjects’ diet was not controlled on Days 2 through 7 because (1) dietary influence (i.e., carbohydrate and caffeine) may be limited to early Cr doses,$^{11,21}$ and (2) regardless of diet, this dosing regimen (71 mg kg$^{-1}$ qid) can sufficiently saturate muscle stores.

### Blood Sampling

The volunteers were in a supine position throughout the study period on Days 1 and 8. A plastic cannula was inserted into an antecubital vein for blood sampling at 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 3, 4, 5, 6, 7, and 8 hours after Cr administration. Blood samples were also collected every morning of the loading phase (Days 2-7) prior to the first dose of the day. Blood samples were collected in heparinized tubes and centrifuged immediately after they were obtained. Plasma samples were frozen immediately and stored at −70°C until analyzed.

### Table I Subject Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.3 ± 2.8</td>
</tr>
<tr>
<td>Body weight (pre) (kg)</td>
<td>82.3 ± 16.3</td>
</tr>
<tr>
<td>Body weight (post) (kg)</td>
<td>83.1 ± 16.6*</td>
</tr>
<tr>
<td>Body mass index (pre) (kg m$^{-2}$)</td>
<td>26.9 ± 4.7</td>
</tr>
<tr>
<td>Diet (daily intake)</td>
<td></td>
</tr>
<tr>
<td>Calories (kcal)</td>
<td>3323 ± 1051</td>
</tr>
<tr>
<td>% carbohydrate</td>
<td>53.5 ± 6.1</td>
</tr>
<tr>
<td>% fat</td>
<td>29.2 ± 5.1</td>
</tr>
<tr>
<td>% protein</td>
<td>15.8 ± 2.0</td>
</tr>
<tr>
<td>Cr intake (g)$^{a}$</td>
<td>0.49 ± 0.21</td>
</tr>
<tr>
<td>Baseline plasma creatine (mg L$^{-1}$)</td>
<td>10.8 ± 3.1</td>
</tr>
<tr>
<td>Interstitial muscle creatine (mg L$^{-1}$)</td>
<td>1.23 ± 0.3</td>
</tr>
<tr>
<td>Dose (mg) (single dose)</td>
<td>5867 ± 1129</td>
</tr>
</tbody>
</table>

$^{a}$ Estimated from animal protein intake from 3-day diet record. $^{*}p < 0.01$ comparing pre- to post-supplementation.
Microdialysis

Unbound concentrations in the interstitial space in thigh muscle (vastus lateralis) were measured by microdialysis. The skin at the site of probe insertion was cleaned and disinfected. One dialysis probe (CMA 60, CMA Microdialysis, Sweden) was inserted into a thigh muscle by the following procedure: the surface of the skin was punctured by the probe at an approximate 45° angle, and the angle was reduced after puncturing the muscle fascia. The steel mandrin was removed, leaving the dialysis probe imbedded in the muscle. The microdialysis system was connected and perfused with normal saline at a flow rate of 2 µl/min using a syringe pump (Harvard Apparatus, Holiston, MA). After a 30-minute equilibrium time, in vivo probe calibration was performed according to the “no net flux” method starting at 7:30 a.m. and ending at 10:30 a.m. The principle of this method relies on the assumption that the diffusion process is quantitatively equal in both directions through the semipermeable membrane. Therefore, Cr was added to the perfusion medium in a concentration of 0, 7, and 15 mg L⁻¹. The disappearance rate through the membrane was taken as the in vivo recovery by plotting the concentration into the probe or perfusate (Cₜₚ) against the difference between the concentration out of the probe or dialysate and the perfusate (Cₜₒ-Cₜₚ). The in vivo recovery value was the slope of regression, and the point of no net flux or when Cₜₒ-Cₜₚ = 0 was taken as the endogenous Cr levels.

Thirty minutes after probe calibration, CM was administered (11:00 a.m.). Microdialysis samples were collected in 30-minute intervals after the administration of the dose. Dialysate samples were frozen immediately and stored at −20°C and analyzed within 3 days of collection. The probe was removed after the last blood sample was taken.

Creatine Determination

Reverse-phase HPLC was used to quantify plasma and microdialysis samples. Plasma samples were precipitated with 6% perchloric acid in a 1:2 ratio of acid to plasma, and supernatant was injected for analysis. Microdialysis samples were directly injected into the HPLC system without pretreatment. The HPLC assay consisted of a mobile phase of KH₂PO₄ (50 mM, 6.8 g L⁻¹) adjusted to pH 4.0 with H₃PO₄. Chromatography was performed using a Waters C₁₈ ODS(2) 250 × 4.6 mm 5-µm analytical column (Millipore Corporation, Milford, MA) with a 10-mm guard column packed with Pellicular ODS (Whatman International Corporation, Maidstone, England). A Perkin Elmer 200 Series liquid chromatograph system equipped with a UV-Vis detector (Shimadzu SPD-10A) was used at 210 nm. The injection volume was 25 µl for microdialysis samples and 50 µl for plasma. Peak height was used to calculate Cr quantities using the TurboChrom software package (Perkin Elmer, Norwalk, CT). Lower limits of quantification for microdialysis and plasma samples were 1 and 5 mg L⁻¹, respectively. Calibration curves and quality controls were prepared using creatine monohydrate (Sigma, St. Louis, MO) in human plasma or normal saline for blood and microdialysis analysis, respectively. The assay was linear from 1 to 75 mg L⁻¹ for microdialysis samples and 5 to 50 mg L⁻¹ for plasma samples. Within this linear range, the coefficient of variation and accuracy were both below 12%.

Estimation of Pharmacokinetic Parameters

Noncompartmental Pharmacokinetic Analysis

Noncompartmental analysis was performed for each subject after their respective baseline Cr levels (time₀ min = 7.2-14.8 mg L⁻¹) were subtracted from all data points as basal Cr levels remain constant over time. The following parameters were calculated using the noncompartmental module of the Kinetica software package (Inna-phase, Philadelphia, PA).

Plasma. For Day 1, the terminal elimination rate constant (kₑ), terminal half-life (tₑ), area under the curve (AUCₗ), area under the first moment curve (AUMC), mean residence time (MRT), peak plasma concentration (Cₘ₉₉), the respective time of maximum concentration (tₚ), and clearance (CL/F) (Dose/AUCₗ) were calculated. On Day 8, assuming steady state, the area under one dosing interval (AUCₘ₉₈) was calculated from the concentration-time profile from 168 to 174 hours. Using Microsoft Excel, steady-state clearance was calculated as Dose/AUCₘ₉₈, trough values (Cₘ₉₈) were taken directly from the Day 8 concentration-time profile, and the average steady-state concentration (Cₘ₉₈) was calculated by AUCₘ₉₈/τ, where τ is the dosing interval (6 h). MRT at steady state was calculated using Excel by the following:

\[
MRT = \frac{AUC_{168-174 \ h}}{AUC_{168-174 \ h} + \tau \cdot AUC_{174-\infty}}
\]

where AUC₁₇₄₋₇₈ is the last measured data point (Cₜ) divided by the terminal rate constant.
Muscle. Unbound concentrations in muscle were calculated from the measured dialysate concentrations and the measured recovery from the no net flux samples. Parameters (k_e, t1/2, AUC, AUMC, MRT, C_max, t_max) were calculated as described for plasma for a single dose (Day 1) and steady-state (Day 8). The tissue penetration ratio (F) was calculated as the ratio of the unbound AUC in plasma and the unbound AUC in muscle (AUC_TISSUE/f_u • AUC_PLASMA), where f_u is the fraction unbound in plasma. Fraction unbound was assumed to be negligible (< 10%).

Compartmental Pharmacokinetic Analysis

Various models were attempted to simultaneously fit the mean plasma and microdialysis data on Day 1 and can be found in the Results section.

Plasma. From the various models tested, a one-compartment body model with Michaelis-Menten absorption and first-order elimination was selected to describe the multiple-dose data (Figure 1). The respective equation for the change in the amount in body (X_p) with respect to changes in time (T) was as follows:

\[
\frac{dX_p}{dT} = \frac{V_{\text{max}} \cdot X_A}{K_M + X_A} - k_e \cdot X_p,
\]

and plasma concentration is \( C_p \):

\[
C_p = \frac{X_p}{V_D} + P_0,
\]

where \( V_D \) is the volume of distribution, \( X_A \) is the amount to be absorbed, \( k_e \) is the first-order elimination rate constant, \( V_{\text{max}} \) and \( K_M \) are the Michaelis-Menten parameters, and \( P_0 \) is the baseline levels of Cr.

Interstitial muscle concentrations (\( C_I \)), as measured by microdialysis, were fitted simultaneously with the respective plasma concentrations. The equation for the free concentration of Cr in the interstitial muscle space was as follows:

\[
C_I = \frac{F \cdot X_A}{V_D} + I_0,
\]

where \( F \) is the penetration factor that describes the ratio of Cr that partitions out of the circulation into the interstitial space, and \( I_0 \) are the baseline interstitial levels.

As stated previously, plasma protein binding was not taken into account because binding is assumed to be minimal.

The data were analyzed by using nonlinear regression software (Scientist, MicroMath, Salt Lake City, UT) employing the Euler integration method. Average plasma and tissue concentrations were fitted, including endogenous levels. The coefficient of determination (CD) and the model selection criterion (MSC) were used as a criterion for the goodness of the resulting curve fits. The higher the MSC, the more appropriate the selected model.

Statistics

Paired t-tests were performed to determine changes over time in pharmacokinetic parameters with the assumption that the change between a single and steady-state condition is normally distributed; \( p \)-value was set at 0.05.

RESULTS

Subjects reported not using Cr supplements within the past year. Cr supplements and all procedures were well tolerated with no reports of gastrointestinal distress, muscle cramps, or bruising at the site of probe insertion. Body weight significantly increased by 0.8 kg (\( p < 0.01 \)) between the first and last day of the study (Table I).

There was some difficulty with the microdialysis calibration procedure, especially at steady-state. The calibration was started 30 minutes after insertion of the probe to allow for local equilibrium. In 1 of 6 subjects on Day 1 and 3 of 6 subjects on Day 8, probe insertion caused increased Cr in the interstitial space that persisted for > 30 minutes, possibly due to the release of
intracellular Cr from microdamage to skeletal muscle. The persistence of elevated local Cr concentrations did not allow for proper probe calibration; therefore, data were analyzed for the subjects with complete single to steady-state profiles (n = 3).

Pharmacokinetics

**Noncompartmental Analysis: Plasma**

Pharmacokinetic profiles and noncompartmental analysis are found in Figure 2 and Table II, respectively. Peak concentrations of Cr after oral dosing on Day 1 (Figure 2A) and Day 8 (Figure 2C) were found between 80 and 180 minutes post-ingestion. Steady-state was reached approximately after 3 days, as demonstrated from the lack of statistical difference between trough plasma levels on Days 3 and 4 (planned comparison, p > 0.90) (Figure 2B). Steady-state Cmax values were statistically higher on Day 8 than those on Day 1 (p < 0.01). Apparent systemic clearance (CL/F) decreased 40% from Day 1 to Day 8 (p < 0.05), indicating time dependency. The change in clearance was significant with or without scaling to body weight. CL/F did not correlate with any body size parameter (i.e., body weight, ideal body weight, body mass index, or body surface area). Dietary intake of Cr as well as physical activity did not correlate with any pharmacokinetic parameters. An accumulation factor of 1.60, as calculated by the ratio of Cmax at steady state and Cmax on Day 1, was found.

**Noncompartmental Analysis: Microdialysis**

There were no significant differences in any parameters from Day 1 to Day 8 for the interstitial muscle pharmacokinetics (Table II). Penetration of blood Cr into the interstitial space (F) was 47% and 37% for Day 1 and Day 8, respectively, but values were not significantly different. Average probe recovery of interstitial Cr was 48%.

**Compartmental Analysis: Plasma and Microdialysis**

Various models, including linear and nonlinear processes, were evaluated to characterize the single-dose data for mean plasma and microdialysis data (Day 1) (Table III). The MSC of the models indicate that Model 4 best described the observed data, and it was selected to model the multiple-dose data set. In addition, modeling was best accomplished by allowing the clearance (CL/F), the apparent volume of distribution (VD), or the affinity constant for absorption (KM) to change over time using the following exponential relationship:

\[ X = X_s + e^{-K_{act} \cdot t} + X_f, \]  

where X is CL, V_d, or K_m; K_{act} is the rate constant of change; t is time; X_s is the lower limit; and the initial value (X_i) is X_s + X_f (Table IV). Even though the MSC indicated a better mathematical fit for Model 4A, Model 4B was selected (Figure 2) as the appropriate model based on a stronger physiological basis (see Discussion).

**DISCUSSION**

This is the first study to perform a detailed pharmacokinetic analysis after a single oral dose and multiple oral doses of creatine monohydrate. Previous studies have examined the plasma concentration-time profile predominantly after administration of a single oral
dose but have not reported detailed pharmacokinetic analysis. The $t_{\text{max}}$ values did not change from single dose (Day 1) to steady-state (Day 8). This is in agreement with earlier studies showing a $t_{\text{max}} < 2$ hours after oral administration of doses of < 10 g. Preceding reported Cmax values after a single 5-g dose were between 65 and 160 mg L–1. The terminal half-life from Day 1 in the present study was slightly longer than a previous report of 1.2 hours after a single 5-g dose. At steady-state (Day 8), terminal half-life was 2.7 hours, which compared well with a previous report of 2.9 hours following 3 days of Cr administration. There are no previous calculations of clearance following creatine administration, and noncompartmental analysis in this study suggested systemic clearance decreases with repeated Cr administration. This decrease is most likely a function of saturation of Cr muscle stores, but increases in oral bioavailability cannot be excluded with the present data.

Total Cr clearance for Cr is the sum of renal elimination ($C_{\text{REN}}$), degradation to creatinine ($C_{\text{METAB}}$), and peripheral irreversible skeletal muscle uptake ($C_{\text{MUSCLE}}$). Degradation of Cr to creatinine ($C_{\text{METAB}}$) is a small contribution to the overall clearance with a half-life of ~40 days ($k_{\text{CRN}} = 0.017$ d$^{-1}$) and would be assumed to be part of $C_{\text{MUSCLE}}$ since the majority of degradation occurs in the muscle compartment. The individual contribution of the kidney and skeletal muscle to overall clearance is still unknown. Poortmans et al. reported a renal clearance of 0.3 to 0.8 L h$^{-1}$ without supplementation that increased to 9 to 22 L h$^{-1}$ when taking Cr supplements. To be noted, in one of these studies, Cr excretion rate was 682.5 µmol min$^{-1}$ or 128 g d$^{-1}$ and may overestimate the true clearance since at this excretion rate, the total Cr pool (120 g) would be removed in a day. The current study reports a total

---

Table III  Goodness-of-Fit Data for Compartmental Analysis of Single Oral Dose Data (Day 1)

<table>
<thead>
<tr>
<th>Model</th>
<th>1</th>
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<tbody>
<tr>
<td>Absorption</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>Vmax/KM</td>
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<td></td>
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<td>Elimination</td>
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<tr>
<td>First order</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vmax/KM</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td></td>
</tr>
<tr>
<td>MSC</td>
<td>3.31</td>
<td>3.43</td>
<td>3.33</td>
<td>3.74</td>
<td>3.66</td>
<td>3.61</td>
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</tbody>
</table>

Mode selection criteria (MSC) were used to determine the best model. Model 4 was chosen to model the multiple-dose data because of the highest MSC.
clearance for a single dose (Day 1) of 16.3 L h⁻¹, and assuming CLRENAL of 0.3 to 0.8 L h⁻¹,26,27 then the renal clearance would contribute < 5% to total clearance. At steady state (Day 8), Harris et al.14 reported ~80% of the clearance would contribute < 5% to total clearance. Therefore, at steady state, renal clearance = 782 mg h⁻¹. Therefore, at steady state, renal clearance would contribute 80% of the total clearance. This is based on using the steady-state plasma concentration, the CLRENAL can be estimated at 8 L h⁻¹ (or around the glomerular filtration rate). This is based on using the steady-state plasma values from this study, with C₀ = 97.4 mg L⁻¹ and rate of excretion = 782 mg h⁻¹. Therefore, at steady state, renal clearance would contribute 80% of the total clearance. Over time with repeated Cr dosing, muscle stores become saturated, forcing a clearance shift from almost exclusively muscle uptake to predominantly renal elimination.

This was the first study to perform compartmental analysis after oral administration of Cr. Various models were derived to describe the plasma and microdialysis data. These models ranged from simple one-compartment body models with first-order processes to one-compartment body models with saturable processes and/or zero-order processes or some combination thereof. Of the many models tested, two models described the data best. Model 4A integrated changes over time for systemic clearance and the volume of distribution. This latter model was used as the final model because of a stronger physiological foundation. A decrease in Km as in Model 4A may support the concept of increased bioavailability if there is an absorption window for Cr in the gastrointestinal tract. However, from a physiological standpoint, it is unlikely that bioavailability would increase with supplementation, as seen in the case of adaptive regulation with respect to amino acids absorption.28 In addition, it is currently believed that the same transporters found in muscle are also located in the gastrointestinal tract based on mRNA evidence,29 and therefore regulation of these transporters may be similar. The exact mechanism of CreaT regulation is not fully understood but may involve feedback mechanisms to down-regulate transporter number or function. Studies in cell culture have shown that cells with increased intracellular Cr or cells placed in a surrounding with high extracellular Cr exhibit a reduction in Cr uptake.30-32 This decrease in Cr uptake was a result of reduced maximal transport activity (Vmax) and not reduced affinity (Km).30,32 The cell culture data are supported by data from intact, perfused skeletal muscle that showed that the most rapid uptake occurs within the first 30 minutes of Cr exposure.33 High extracellular levels of Cr have also been implicated in the production of an inhibitory protein that reduces CreaT activity by reducing Vmax.30-32 Attempts were made to model the data having Vmax change over time, but none of the models sufficiently fit the data. Therefore, the results indicate that high levels of Cr should reduce CreaT activity and possibly reduce and not increase bioavailability, as suggested by Model 4A. Two-compartment body models were also attempted to incorporate the interstitial muscle levels as a separate compartment (data not shown). This model was unsuccessful as the microdialysis data were best modeled using the plasma model with a penetration factor rather than treating the microdialysis data as a separate compartment. However, intracellular Cr data rather than interstitial data may elicit the need for a second compartment.

Interstitial muscle concentrations typically reflect free drug concentrations in the plasma34 and would indicate the amount of Cr at the site of CreaT. This current study found significantly lower interstitial levels than free plasma concentrations, which is consistent with molecules that are subject to transporter-based mechanisms of removal from the interstitial space as in the case of glucose.35,36 It would be expected, however, that a change in transporter function, as suggested by noncompartmental analysis, would also affect the interstitial concentrations. This, however, was not the

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Results of Compartmental Analysis of Multiple-Dose Data from Applying Model 4 from Table III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 4A</td>
<td>Model 4B</td>
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<tr>
<td>VMAX AB (mg h⁻¹)</td>
<td>3769</td>
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<tr>
<td>KM AB INITIAL (mg L⁻¹)</td>
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<td>KM AB FINAL (mg L⁻¹)</td>
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<td>VD FINAL (L)</td>
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</tr>
<tr>
<td>CL INITIAL (L h⁻¹)</td>
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<td>CL FINAL (L)</td>
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<tr>
<td>F</td>
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<tr>
<td>KCL (h⁻¹)</td>
<td>0.029</td>
</tr>
<tr>
<td>MSC</td>
<td>3.60</td>
</tr>
</tbody>
</table>

Model 4A incorporates changes in clearance and the absorption parameter, Kma over time. Model 4B incorporates changes in clearance and volume of distribution over time. CL, clearance for early doses (INITIAL) and steady-state doses (FINAL); VMAX AB, Michaelis-Menten constant for maximum absorption velocity; KM AB Michaelis-Menten constant for affinity of absorption transporters for early doses (INITIAL) and steady-state doses (FINAL); VD, apparent volume of distribution for early doses (INITIAL) and steady-state doses (FINAL); kCL, rate of change fitted to describe changes in KCL; CL, or MSC.
case and may indicate a possible limited ability of Cr to partition from the blood into the interstitial space, or the time to reach equilibrium between the blood and interstitial space is slow. Even though the interstitial concentrations are 30% to 40% lower than plasma, intracellular muscle levels are 200 times higher than plasma, and it is the intracellular muscle concentrations that need to be targeted for dose optimization. In either instance, it is difficult to draw any firm conclusions given the small sample size for the muscle microdialysis data.

In conclusion, repeated dosing of Cr causes time-dependent pharmacokinetics, with clearance being affected by skeletal muscle accumulation of Cr. Noncompartmental and compartmental analyses suggest that interstitial muscle levels at the site of the Cr transporter are lower than plasma, but the reasons for the differences are unclear. Further studies are needed to clarify the absorption kinetics and mechanism(s) that may result in time dependency and most likely dose dependency. In addition, the relationship between plasma levels and the rate of change of intramuscular levels needs to be elucidated, as this relationship would determine dose amount. Dietary influence of simultaneous carbohydrate ingestion and caffeine on the pharmacokinetic parameters needs also to be investigated for both single and multiple doses.

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