

The early plasma concentration of ⁵¹Cr-EDTA in patients with cirrhosis and ascites: a comparison of three models

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Objectives The aim of the study was to determine which of three two-parameter fitting functions (exponential, linear-log, and negative-power function of time) most accurately models early chromium-51-EDTA (⁵¹Cr-EDTA) plasma concentration data prior to 120 min in patients with cirrhosis and ascites and understand how these fitting functions affect the calculation of the area under the plasma concentration curve (AUC).

Methods A bolus, antecubital intravenous injection of 2.6 MBq of ⁵¹Cr-EDTA was given to 13 patients with cirrhosis and ascites. Up to 16 blood samples were drawn at time points ranging from 5 to 1440 min following injection. The concentration data prior to 120 min were used as reference data. Early time concentration values, estimated by fitting exponential, linear-log, and negative-power functions of time to the time samples at 120, 180, and 240 min, were then compared with reference data. The AUC was calculated for each patient using the exponential, Bröchner-Mortensen-corrected exponential, and linear-log functions, and these values were compared.

Results The withheld, observed plasma concentrations were (a) most accurately estimated by linear-log functions (Wilcoxon $P=0.4548$), (b) significantly underestimated by exponential functions (Wilcoxon $P=0.0002$), and (c) significantly overestimated by negative-power functions (Wilcoxon $P=0.0034$). The relative errors when ranked from best to worst were those for the linear-log (12.0%, 9.0%), exponential (22.9%, 14.2%), and negative-power (31.9%, 48.4%) functions of time, respectively (median, interquartile range). For each patient, the values for AUC calculated by the exponential function differed significantly

(range = 3.4–15.3%, median = 8.3%) from those calculated by the corrected Bröchner-Mortensen exponential, as to a lesser extent did those values calculated using linear-log functions (range = 0.4–8.0%, median = 3.0%).

Conclusion In patients with cirrhosis, linear-log functions were significantly more accurate than exponential or power functions in estimating early time plasma concentrations (< 120 min). However, the improved linear-log early time plasma concentration model does not provide as much correction to the total AUC as does the corrected Bröchner-Mortensen exponential method. This is likely because of the large contribution of late time data to the AUC, and future work is suggested to explore the late time fit problem. *Nucl Med Commun* 36:392–397 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Glomerular filtration rate (GFR) is generally accepted as the best overall measure of kidney function. Accurate measurement of GFR is important for diagnosing chronic kidney disease, for monitoring renal transplants, and for selecting appropriate drug dosages to minimize nephrotoxicity [1]. GFR is determined from the plasma clearance (CL) of a GFR marker. A common GFR marker, chromium-51-ethylenediaminetetraacetic acid (⁵¹Cr-EDTA) [2–5], was used in this study. GFR is most often calculated as the bolus-injected marker dose divided by the total area under the curve of plasma concentration (AUC)

from the time of injection to infinite time. However, to find the total AUC, concentration data before the time of the first sample and after the last sample time are extrapolated using mathematical functions [6].

In clinical practice, the extrapolated values are often computed using a monoexponential model of the plasma concentration versus time curve. This permits the use of only two to four plasma samples to calculate the AUC, where for full characterization of the plasma concentration curve more samples are needed; for instance, the British Nuclear Medicine Society guidelines recommend

10 samples for that purpose [5]. For monoexponential fitting, the samples are typically collected at 120–240 or 120–300 min following injection of the radio-pharmaceutical GFR marker [2,7]. Although this method has the benefit of being very simple to implement, it has been shown to underestimate early concentration data [8] and overestimate the CL [9,10]. Moreover, in 41 patients without fluid disturbances using ^{169}Yb -DTPA with eight time samples over 4 h, it was noted that monoexponential and biexponential function fits failed goodness-of-fit testing, especially for early sample times [11]. In patients with ascites or severe renal insufficiency, the overestimation of CL is magnified, suggesting that the monoexponential model is of limited clinical utility in these patients [12,13]. To correct the monoexponential function estimates of CL, it is common to apply empirical correction factors. A variety of correction factors [9,10] have been developed and applied to CL data with varying degrees of success [7]. In addition, these correction factors do not account for the different CL values that are obtained when different initial and final sample times are used with this model [13,14]. Ideally, it would be desirable to use a method that does not require these types of corrections [8].

To test whether there may be a simpler functional explanation for early time data, we examined the back-extrapolation accuracy of three basic, two-parameter fitting functions, and explored the implications for the early time kinetics of mixing. The traditionally used exponential function was compared with two alternative functions that have been used in pharmacokinetic modeling: (a) the linear-log function, in which concentration is a linear function of the logarithm of time [15,16], and (b) the negative-power function model, in which concentration changes as a negative-power function of time [17,18]. Then to more directly explore the clinical utility of these models, we compared the AUC calculated using the exponential model, the Bröchner-Mortensen-corrected exponential model, and the linear-log model.

Methods

Patient population

The patient data have been well characterized [8,19] and were part of a research project that compared methods of assessing renal function in patients with cirrhosis, which was approved by the Royal Free Hospital Research Ethics Committee. Thirteen patients, all with cirrhosis and under assessment for liver transplantation, were given an antecubital intravenous bolus injection of 2.6 MBq of ^{51}Cr -EDTA. Subsequent to the injection, 6–16 blood samples were drawn, with the earliest sample obtained at 5 min ($n=12$) or 30 min ($n=1$), and the latest at 720 min ($n=1$) or 1440 min ($n=12$). These data included one to nine samples drawn before 120 min. Plasma samples were separated from the blood cells by centrifugation and then counted for radioactivity.

Plasma concentration fit functions

The exponential, linear-log, and negative-power functions of time were used to estimate the plasma concentration data generated before 120 min. Each function is defined as follows.

The exponential model

The exponential function is $C(t) = ce^{-\lambda t}$, where $C(t)$ is drug concentration at time t in min and $C(t) = c\epsilon$ and λ are its two parameters, c having units of concentration and λ being in min^{-1} .

The linear-log model

The linear function of the logarithm of time (linear-log) is given as $C(t) = a - b \ln(t)$, where a and b are the two parameters of the model. For $t > e^{a/b}$, $C(t) = 0$ in order to avoid negative concentrations. The physical units of $C(t) = a - b \ln(t)$ are taken from the equivalent relationship $C(t) = -b \ln(t/\tau)$, where t and τ are in min and b has units of concentration, by noting that $a \equiv b \ln(\tau)$.

The negative-power model

The negative-power function is $C(t) = Kt^{-\beta}$, where K and β are the two parameters of the power function. The units of $C(t) = Kt^{-\beta}$ are properly dimensioned in the equivalent relationship $C(t) = \kappa(t/\tau)^{-\beta}$, where $K \equiv \kappa\tau^\beta$, such that κ has units of concentration and t and τ are in min.

Fit function performance testing

For each of the 13 patients in this series, the following procedure was used. The observed plasma concentrations acquired prior to 120 min were withheld as reference data. Each function was then fit to the remaining three time samples drawn at 120, 180, and 240 min ($n=12$) or 120, 360, and 480 min ($n=1$, patient 7) using weighted least squares fitting with a direct $C(t)^2$ weighting factor that was found to have biases toward earlier time sample concentrations. Although the time samples for patient 7 differ from those of the other patients in this data set, this should not have an effect on our statistical analysis as all of the tests are nonparametric and therefore not sensitive to outliers. These fitted functions were used to compute estimates of plasma concentrations at the withheld sample times. The resulting estimated concentrations were compared with the corresponding observed but withheld plasma concentrations. Because the error of estimation was proportional to the withheld, observed concentrations, the relative root mean square error (rRMSE) between the computed and observed plasma concentration data was determined for each patient and used to compare the performance of the three fit functions. The first available plasma samples in this study were always the most concentrated and were used for the comparison as they gave the greatest contribution to AUC within the sample time interval. The differences of the estimated plasma concentrations minus the earliest

withheld concentrations (mostly at 5 min), that is, the overestimates (+) and the underestimates (–), were calculated. Wilcoxon signed-rank sum testing was applied to this difference to calculate the probability of its median value being zero (to the 0.05 level).

Comparing AUC obtained by exponential, corrected exponential, and linear-log models

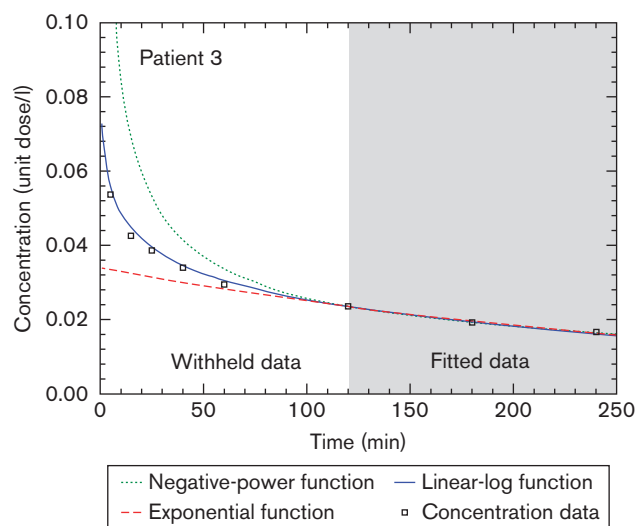
The AUC for each patient was calculated for the exponential and linear-log models as the sum of two incomplete areas delimited by the 240 min sample time data point, that is, $AUC(0-240)$ and $AUC(240-\infty)$. As outlined in the previous subsections, exponential and linear-log functions were used to estimate early data by fitting the three plasma concentration samples drawn at 120, 180, and 240 min. The $AUC(0-240)$ was then calculated for each model by integrating each fit function from time 0 to 240 min. To estimate later time concentrations, the same process was used for both exponential and linear-log models. As is common in clinical practice, a single exponential was fit to the three plasma concentration samples drawn at 120, 180, and 240 min and then extrapolated forward from 240 min to infinite time [5]. Weighted least squares regression, using a $1/C(t)^2$ weighting factor, was used for the fitting in order to bias toward late time concentration data [20]. Thus fit, the exponential curve was then integrated to give $AUC(240-\infty)$. For each model, $AUC(0-240)$ and $AUC(240-\infty)$ were then added together to give total AUC_{exp} for the exponential model and total $AUC_{linear-log}$ for the linear-log model.

In addition, as it is well known that the exponential model underestimates AUC, the AUC_{exp} values were also corrected using the Bröchner-Mortensen method [10], which was performed according to the guidelines of the British Nuclear Medicine Society [5]. Corrected areas ($AUC_{exp-cor}$) were obtained from the reciprocal of CL_{cor} after inverting the normalization of body surface area. For the exponential, corrected exponential, and linear-log methods, the AUC values were then compared using Passing-Bablok regressions.

Results

Figure 1 illustrates the fitting procedure for patient 3 and is indicative of the majority of the results ($n=9$ of 13) for which the linear-log function provided the most accurate model of early concentration data, whereas the exponential and negative-power functions significantly underestimated and overestimated the withheld, observed concentrations, respectively. A representation of special case results from the remaining four patients is shown in Fig. 2, in which the shape of the early time concentration is different from that of the majority of cases. Figure 2a represents results from one of three patients (patient 8) for whom all three of the fitting functions underestimated their early plasma concentrations. In those three cases (patients 1, 2, and 8), the negative-power function most accurately modeled the

Fig. 1



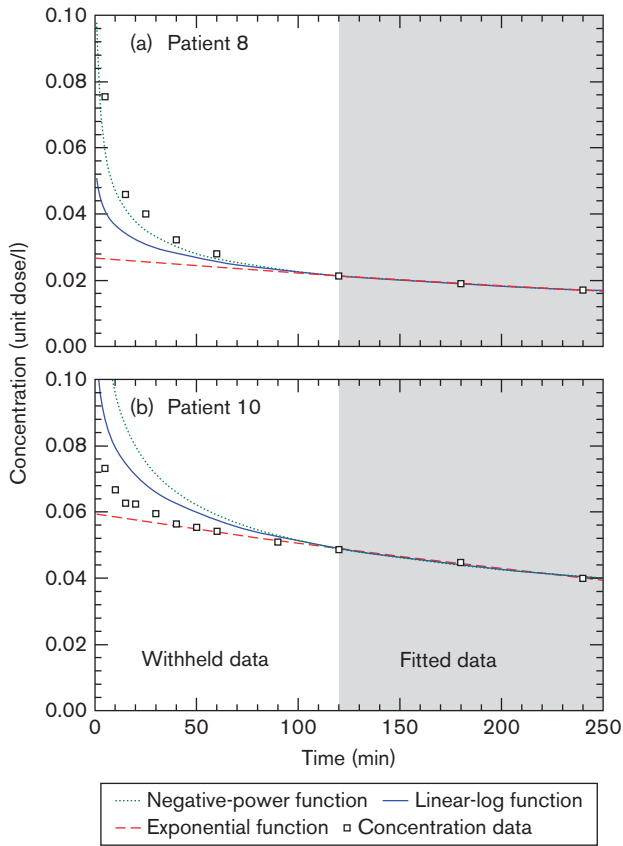
Results for patient 3 are used to show the pattern of back-extrapolation from 120, 180, and 240 min representative of the majority, that is, nine of 13 total study patients. This pattern consists of the most accurate estimation from the linear-log function (solid blue), underestimation from the exponential function (dashed red), and overestimation from the negative-power function (dotted green).

corresponding early plasma concentrations. Shown in Fig. 2b is the single case (patient 10) for which the exponential function, while still underestimating the withheld concentrations, formed the most accurate model and for which both the linear-log and the negative-power functions overestimated the withheld, observed concentrations.

The rRMSE data between the withheld, observed concentrations and the estimated concentrations for each patient and each fitting function are presented in Table 1. The linear-log functions had rRMSE values that ranged from 4.3 to 26.5%, with a median of 12.0% and an interquartile range (IQR) of 9.0%. The rRMSE for the exponential function ranged from 8.6 to 40.5% in all patients with a median value of 22.9% and an IQR of 14.2%, whereas the negative-power functions had rRMSE values ranging from 6.1 to 121.5%, with a median of 31.9% and an IQR of 48.4%.

The results of the Wilcoxon signed-rank sum tests are presented in Table 2. The linear-log functions were found to most accurately model the withheld observed concentrations showing the most balanced sign scores (+7, –6) and whose estimated concentrations did not differ significantly from the withheld, observed concentrations (Wilcoxon $P=0.4548$). The exponential fitting functions were found to consistently underestimate (+0, –13) and significantly differed from the withheld, observed concentrations (Wilcoxon $P=0.0002$). The estimated concentrations computed using the negative-power functions overestimated the withheld observed

Fig. 2



(a) Patient 8 and (b) patient 10 as representations of the special cases, which occurred in four of 13 total study patients. (a) From best to worst performance: the negative-power function (dotted green), the linear-log function (solid blue), and the monoexponential function (dashed red). (b) From best to worst performance: the monoexponential function, the linear-log function, and the negative-power function.

Table 1 Relative root mean square error of estimating observed concentration time samples from each back-extrapolation of three fitting functions

| Patient number | Linear-log function (%) | Exponential function (%) | Negative-power function (%) |
|------------------|-------------------------|--------------------------|-----------------------------|
| 1 | 16.1 | 29.3 | 6.1 |
| 2 | 19.3 | 28.9 | 16.2 |
| 3 | 4.3 | 22.2 | 65.8 |
| 4 | 7.7 | 26.1 | 46.8 |
| 5 | 16.9 | 36.2 | 31.9 |
| 6 | 6.7 | 21.6 | 121.5 |
| 7 | 12.0 | 36.6 | 15.8 |
| 8 | 26.5 | 40.5 | 12.6 |
| 9 | 10.1 | 17.1 | 98.5 |
| 10 | 13.7 | 8.6 | 30.8 |
| 11 | 6.2 | 22.9 | 13.3 |
| 12 | 8.5 | 17.5 | 62.1 |
| 13 | 12.9 | 17.0 | 49.1 |
| Median | 12.0 | 22.9 | 31.9 |
| IQR ^a | 9.0 | 14.2 | 48.4 |

^aIQR is interquartile range.

concentrations in most cases (+10, -3) and significantly differed from the withheld observed concentrations (Wilcoxon $P=0.0034$).

Figure 3 shows Passing–Bablok regression fitting that compares the AUC determined using linear-log, exponential, and Bröchner-Mortensen-corrected exponential methods. The Passing–Bablok regression line of AUC_{exp} and $AUC_{exp-cor}$ shown in Fig. 3a, has a slope that statistically differs from 1 [95% confidence interval (CI) of slope is 0.980 to 0.995] and an intercept that statistically differs from zero (95% CI of intercept is -1.298 to -0.923). For this patient series, the values for AUC_{exp} were 3.4–15.3% (median = 8.3%, Wilcoxon $P=0.0002$, significant median difference), lower than the $AUC_{exp-cor}$. The slope of the Passing–Bablok regression line shown in Fig. 3b, which compares $AUC_{linear-log}$ and $AUC_{exp-cor}$, was statistically indistinguishable from 1 (95% CI of slope is 0.977 to 1.0001), whereas the intercept was statistically different from zero (95% CI of intercept is -0.633 to -0.169). The values of $AUC_{linear-log}$ differed from those of $AUC_{exp-cor}$ to a lesser extent than those of AUC_{exp} , with a range of 0.4–8.0%; however, this difference was statistically significant (median = 3.0%, Wilcoxon $P=0.0002$, significant median difference).

Discussion

Comparison of the three fitting functions

When used to estimate earlier concentrations, the most accurate estimation of concentrations was achieved with linear-log functions with an insignificant difference (to the $P=0.4548$ level) between the withheld, observed concentrations and the estimated concentrations. Moreover, the median differences had the smallest errors among the tested functions. That is, the linear-log function outperformed both the exponential and negative-power function of time models in estimating early concentration data (<120 min). The linear-log model corresponded to a slow-mixing model in which the initial volume of distribution is vanishingly small and, as it has been shown to differ insignificantly from the observed data, serves as a good candidate to explain the kinetic behavior of early plasma concentration in patients with cirrhosis and ascites.

The exponential functions, back-extrapolated from 120 min, were found to significantly underestimate the withheld, observed concentrations for each patient (13 of 13 total) with a large overall difference. This is the most likely explanation for the well-documented need for decreasing the CL values resulting from exponential function fitting of time samples acquired after 120 min [9,10]. As the exponential model of early plasma concentration was significantly rejected for our data ($P=0.0002$), it is unlikely that the instant mixing in a large initial volume of marker distribution implied by that model is the proper kinetic interpretation of early concentration.

Conversely, concentration values estimated from negative-power functions were found to overestimate the withheld, observed concentrations in 10 of 13 patients. The estimated values were found to differ significantly from the

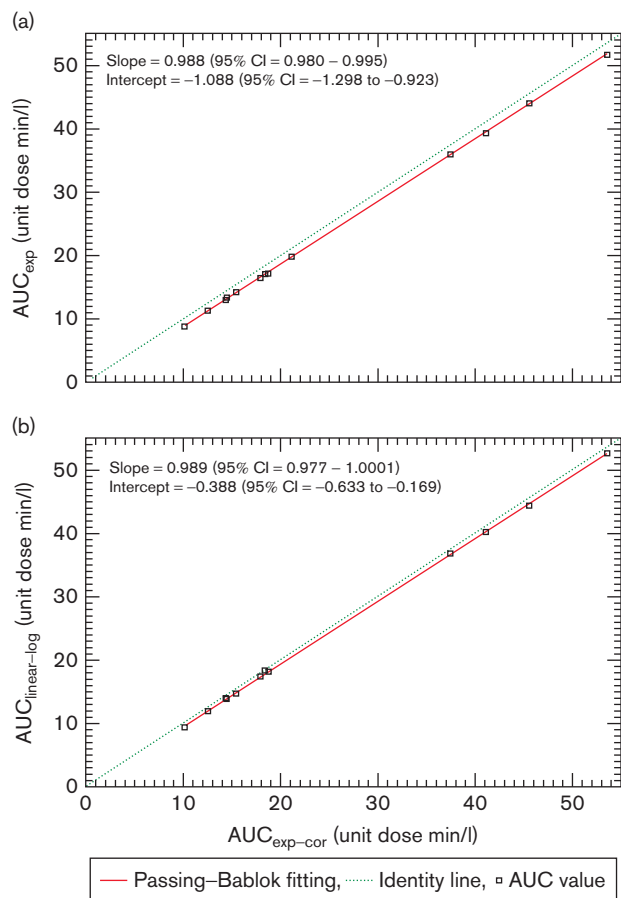
Table 2 Overestimates and underestimates of observed concentrations from back-extrapolation of three fitting functions, with significance

| Function of time | Sign score ^a | | Wilcoxon signed-rank sum | |
|------------------|-------------------------|--------------------|--------------------------|---------------------------------------|
| | Overestimates (+) | Underestimates (-) | P-value ^b | Significance of Δ ^c |
| Linear-log | 7 | 6 | 0.4548 | NS |
| Exponential | 0 | 13 | 0.0002 | S |
| Negative-power | 10 | 3 | 0.0034 | S |

^aThe sign score is the number of back-extrapolations that overestimated (+) and underestimated (-) the measured earlier concentrations.

^bWilcoxon probabilities (P) are for a median difference (Δ) of zero from test functions evaluated at the earliest available sample times, minus the observed concentration at those sample times.

^c Δ = difference; NS, not significant ($P > 0.05$); S, significant ($P < 0.05$).

Fig. 3

Passing-Bablok regression comparison is shown for AUC values obtained by the Bröchner-Mortensen-corrected exponential model ($AUC_{exp-cor}$) with AUC values (a) obtained by exponential fitting without corrections (AUC_{exp}) and (b) obtained by the early time linear-log model ($AUC_{linear-log}$). The confidence intervals (CIs) for the constant difference between these measurements do not include zero for both panels, implying that these AUC measurements differ significantly. AUC, area under the curve.

withheld, observed concentrations ($P=0.0034$), with a large median error between the observed and estimated time samples. Interestingly, in three cases (patients 1, 2, and 8) the negative-power function performed better compared with both the exponential and linear-log function in estimating early time concentration data.

For the majority of $^{51}\text{Cr-EDTA}$ patients studied here, linear-log functions fit to 120 min and later time samples were the most accurate functions for back-extrapolation estimation of observed plasma concentration. However, in four of 13 cases the best back-extrapolated function was not a linear-log as shown in Fig. 2. These patients had either high fluid volume (patient 8), low clearance (patients 2 and 10), or both (patient 1), conditions that are known to increase the difficulty of determining GFR accurately [8,13,19]. It seems likely that the reason for the occasional casewise variability between the estimated and observed plasma concentrations for different functions is the fact that any single, two-parameter model is too simple to estimate the shape of all abnormal plasma concentrations curves.

Clinical implications and limitations

Most clinical studies use a single, two-parameter exponential function to determine CL and do not obtain early plasma concentration data (< 120 min) [5,7]. Our results show that exponential functions significantly underestimated the observed early time concentration data. Underestimation of concentration implies an underestimation of AUC and overestimation of CL [11]. To compensate for this overestimation of CL, it is common clinical practice to apply post-test empirical correction factors, such as the Bröchner-Mortensen algorithm, that artificially increase AUC and decrease CL values [5,9,10,19].

In the current patient data set, the $AUC_{linear-log}$ was found to be significantly greater than the AUC_{exp} , wherein both models used exponential extrapolation for times greater than 240 min. However, when the $AUC_{linear-log}$ was compared directly with the $AUC_{exp-cor}$ it was seen that the linear-log model results in AUC values that are significantly lower than those of the corrected exponential model, suggesting that the linear log model does not correct AUC as much as the Bröchner-Mortensen algorithm. Despite the much-improved performance of the linear log model compared with the exponential model for estimating early concentrations, the median increase in AUC was relatively small. In contrast, underestimation of late time withheld concentrations has been seen even for biexponential fits to GFR marker time samples [11]. In this context, it is not surprising that the Bröchner-Mortensen median correction of 8.3% of the single

exponential term model of concentration is of significantly greater magnitude (Wilcoxon, $P=0.0002$) than the linear-logarithm correction of early concentration alone. In previous works using this same patient data set, it has been shown that extrapolation of plasma concentrations to time points greater than 240 min using monoexponential functions underestimates late time (>240 min) plasma concentration data [8,19]. For these same patients with a high incidence of ascites, the Bröchner-Mortensen correction was also shown to not increase the AUC enough to account for the effects of these fluid disturbances [19]. Consequently, the use of the more accurate and precise linear-log model for early time concentration data alone does not solve the late time fit problem, the investigation of which is beyond the scope of the current work.

Conclusion

We have shown that two-parameter, linear-logarithm functions performed significantly better than both exponential and negative-power functions in estimating early concentration plasma data prior to 120 min following a bolus, antecubital intravenous injection of ^{51}Cr -EDTA. Back-extrapolation with exponential functions, a method typically used in clinical settings when calculating CL, consistently underestimated the observed plasma concentration data. The AUC calculated using the exponential model was also lower than the AUC calculated using the linear-log model; however, the AUC calculated with the Bröchner-Mortensen-corrected exponential model was larger than those calculated with both the exponential and linear-log models. This is likely due to the large contribution of the late time concentration data to the total AUC. As the linear-log model most accurately characterized the early time (<240 min) plasma concentration curve, we suggest further model testing to explore accurate late time (>240 min) plasma concentration.

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Conflicts of interest

There are no conflicts of interest.

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