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EVALUATING RENAL TIME-INTEGRATED ACTIVITY COEFFICIENT IN [^{177}Lu]Lu-DOTA-TATE THERAPY: SIMULTANEOUS VS. SEPARATE KIDNEY MODELING USING NON-LINEAR MIXED-EFFECTS MODELING

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Abstrak

Penelitian ini bertujuan untuk membandingkan *time-integrated activity coefficients* (TIACs) dari ginjal pada terapi [^{177}Lu]Lu-DOTA-TATE menggunakan *non-linear mixed-effects modeling* (NLMEM), dengan cara mengeveluasi efek dari metode *fitting* data biokinetic ginjal kiri dan kanan pada estimasi nilai TIACs. Biokinetic data [^{177}Lu]Lu-DOTA-TATE pada ginjal dikumpulkan dari sepuluh pasien dengan tumor neuroendokrin dari literatur (PMID:33443063). Pencitraan SPECT/CT dilakukan antara hari ke-1 dan 7 setelah injeksi radiofarmaka. Parameter fungsi bi-eksponensial di*fitting* ke data biokinetic ginjal menggunakan NLMEM dengan perangkat lunak NONMEM dengan dua metode fitting: secara simultan dan terpisah untuk fitting data biokinetic ginjal kiri dan kanan. TIACs dari fitting secara simultan didefinisikan sebagai *simultaneous* TIAC (siTIACs), dan TIACs yang diperoleh dari fitting biokinetic data secara terpisah didefinisikan sebagai *separated* TIACs (seTIACs), perbedaan antara siTIACs dan seTIACs dievaluasi menggunakan relatif deviasi (RD) dengan seTIACs diaanggap sama dengan siTIACs jika RD dibawah 5%. Fungsi bi-exponensial berhasil mendeskripsikan data biokinetic. seTIACs menunjukkan nilai yang ekuivalen dengan siTIACs, dengan median[min, max] dari RD sebesar -1.6[-4.5, 0.8]%. *Fitting* data biokinetic ginjal kiri dan kanan secara simultan menggunakan metode NLMEM menghasilkan TIACs yang ekuivalen dengan yang diperoleh dari *fitting* biokinetic data ginjal secara terpisah. *Fitting* data biokinetic secara simultan dan terpisah menghasilkan nilai TIACs yang setara dan dapat digunakan secara klinis.

Kata-kata kunci: TIAC, NLMEM, [^{177}Lu]Lu-DOTA-TATE

Abstract

This study aimed to compare renal time-integrated activity coefficients (TIACs) in [^{177}Lu]Lu-DOTA-TATE therapy using non-linear mixed-effects modeling (NLMEM), by evaluating the effect of the fitting setting method of left and right kidney biokinetic data to TIAC calculation. Renal biokinetic data of [^{177}Lu]Lu-DOTA-TATE were collected from ten patients with neuroendocrine tumors from literature (PMID:33443063). SPECT/CT imaging was performed between days 1 and 7 after-injection. The bi-exponential function parameters were fitted to biokinetic data using NLMEM performed using NONMEM software, with two fitting approaches: simultaneous fitting of both kidneys and separate fitting of the left and right kidneys. TIACs from the simultaneous fitting were defined as simultaneous TIACs (siTIACs), and those from separate fitting as separated TIACs (seTIACs). The differences between siTIACs and seTIACs were assessed using relative deviations (RDs), with seTIACs considered equivalent to siTIACs if RD was below 5%. The bi-exponential function successfully describes the renal biokinetic data. seTIACs showed good agreement with the siTIACs, with median[min, max] RD of -1.6[-4.5, 0.8]%. Simultaneous fitting of left and right kidneys biokinetic data using the NLMEM approaches produced similar TIACs to those obtained from separate fittings. Therefore, TIACs from simultaneous and separate fittings of renal biokinetic data are comparable and clinically applicable.

Keywords: TIAC, NLMEM, [^{177}Lu]Lu-DOTA-TATE

INTRODUCTION

Time-integrated activity coefficients (TIACs) are essential dosimetric quantities that represent the cumulative radioactive decay in target organs over time. Accurate estimation of TIACs is important for treatment-safety and efficacy [1], [2], [3]. Typically, TIACs are estimated by fitting a sum-of-exponential function to biokinetic data from quantitative imaging, such as SPECT/CT. Among various functional forms, the bi-exponential function is widely used sum-of-exponential function to describe the kinetic of radiopharmaceuticals [4], [5].

In renal dosimetry, the biokinetic data in each patient could be defined as two kidneys (left and right kidneys), leading to multiple options for data analysis. One common approach is to treat both kidneys as unique individuals and fit them independently, as employed in several previous studies [6], [7], [8]. Alternatively, both kidneys' data may be merged as a single kidney [9], [10], [11], [12]. When employing a bi-exponential function within the non-linear mixed-effects modelling (NLMEM) framework, these two strategies translate to what we refer to as separate fitting (left and right kidneys are modeled individually) and simultaneous fitting (left and right kidneys are fitted in a pooled dataset).

Despite the widespread use of both strategies in renal biokinetics modeling, their comparative performance in the context of NLMEM, has not been systematically evaluated. It remains unclear whether the separate fitting of each kidney introduces substantial differences or uncertainty in the estimated pharmacokinetic parameters and derived dosimetric quantities (e.g., TIACs) compared to simultaneous fitting. This gap in methodological assessment raises important questions about potential discrepancies in renal dosimetry between simultaneous and separate data fitting approaches.

In this study, we address this gap by applying both simultaneous and separate fitting approaches exemplified in renal biokinetic data of [^{177}Lu]Lu-DOTA-TATE within the NLMEM framework. Using a bi-exponential function as the structural model, we evaluate the agreement of the obtained TIACs between the two methods. The findings aim to inform the potential difference of the TIACs from simultaneous and separate renal biokinetic data fitting.

MATERIALS AND METHODS

Biokinetic Data

The renal biokinetic data of [^{177}Lu]Lu-DOTA-TATE used in this study were derived from previously published research by Devasia et al. (PMID: 33443063) [5]. The dataset comprised ten patients with neuroendocrine tumors (NETs) treated at the University of Michigan Medical Center. SPECT/CT imaging was performed to all patients between day 1 and day 7 (at around 3 h, 24 h, 100 h, 167 h) following radiopharmaceutical administration. Eight patients underwent imaging at four time points, while the remaining two had only two imaging time points (only on day 1 and day 7). The comprehensive description of image acquisition and accumulation profile in the kidneys was described in the previously published article [5]. In this study, renal activity data were normalized to the administered activity in all cases.

Non-linear Mixed-effects Modelling

The bi-exponential function (Eq. (1)) was used as the structural fit function to describe the renal biokinetic data. This function was selected as being considered as the gold standard for representing the current dataset, as established in the previous study by Devasia et al. [5].

$$f(t) = \frac{k_e \times k_a}{c(k_a - k_e)}\left(e^{-k_e t} - e^{-k_a t}\right) \tag{1}$$

In Eq. (1), k_e denotes the effective elimination (or decay) rate of [^{177}Lu]Lu-DOTA-TATE in the kidneys; k_a represents the uptake rate in the kidneys; and c is a scaling parameter [5]. The TIACs were calculated analytically by integrating time activity curve (TAC) defined by Eq. (1) from time zero to infinity, as follows:

$$\begin{aligned} \mathrm{TIAC} &= \int_0^\infty \frac{k_e \times k_a}{c(k_a - k_e)}\left(e^{-k_e t} - e^{-k_a t}\right)\, \mathrm{d}t \\ \mathrm{TIAC} &= \frac{1}{c} \end{aligned} \tag{2}$$

Within the NLMEM, the parameters of the structural fit function were described using a combination of fixed-effects (FE) and random-effects (RE) [13]. Individual-specific parameters were modeled using an exponential error model, which ensures parameter positivity and is commonly employed in the modeling of pharmacokinetic data [11], [14], [15]:

$$\begin{aligned} \theta_{ki} &= \theta_{\mu k} e^{\eta_{ki}} \\ \eta_{ki} &\sim N(0, \omega^2) \end{aligned} \tag{3}$$

Here, θ_{ki} denotes the individual-specific parameter value; $\theta_{\mu k}$ represents the FE (i.e., the population mean value); and η_{ki} is the RE, which indicates the individual deviation from the mean. The RE η_{ki} is assumed to be normally distributed with a mean of zero and variance of ω^2. Intra-individual variability (i.e., the discrepancy between the model prediction for individual i $\left(Y_{\mathrm{pred},i}\right)$ and the corresponding observed data $\left(Y_{\mathrm{obs},i}\right)$) was described using a proportional error model [14], [16]:

$$\begin{aligned} Y_{\mathrm{obs},i} &= Y_{\mathrm{pred},i}(1 + a \times \varepsilon) \\ \varepsilon &\sim N(0,1) \end{aligned} \tag{4}$$

In this formulation, a denotes the fractional standard deviation, and ε is a normally distributed random number with a mean of zero and a variance of one.

Study Workflow

Figure 1 shows the overall workflow of the study. In brief, renal biokinetic data were fitted to the bi-exponential function (Eq. (1)) within NLMEM framework.

During the initial model development, all parameters in the structural model were assumed to possess the RE (i.e., inter-individual variability) as described in Eq. (3). Following the successful minimization in the first fitting evaluation, parameters possessing negligible variability (i.e., variance $< 10^{-6}$) were set to have only the FE as recommended in the literature [17]. This approach facilitates the identification of parameters that should be estimated as fixed or vary among population within current dataset [12], [13], [18]. The applied goodness-of-fit criteria were visual inspection of the TAC, relative standard errors (RSEs) of the fitted parameters < 50%, and the absolute value of the off-diagonal in the correlation matrix < 0.8 [19], [20], [21].

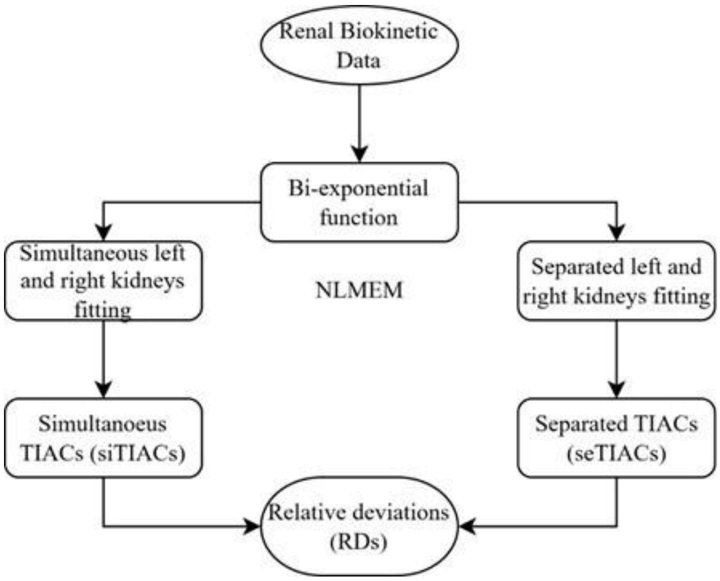

Figure 1. Workflow of the study. Renal biokinetic data were described using a bi-exponential function within the NLMEM framework, implemented in NONMEM software version 7.6.0. Two fitting approaches were employed: simultaneous and separate fitting. In the simultaneous fitting approach, biokinetic data from both kidneys (left and right) were fitted concurrently. In the separate fitting approach, data for the left and right kidneys were fitted independently.

Renal biokinetic data were fitted in two scenarios: (1) simultaneous fitting, and (2) separate fitting of left and right kidneys. In simultaneous fitting approach, each kidney was treated as a unique individual (resulting in 20 kidneys from 10 patients) and all data were fitted simultaneously within NLMEM framework. The TIACs derived from this method are referred to as simultaneous TIACs (siTIACs). In addition, the TIACs obtained from separate fitting of left and right kidneys were referred to as separate TIACs (seTIACs). The discrepancy of seTIACs relative to siTIACs was evaluated using the relative deviation (RD) metric, defined by Eq. (5):

$$\mathrm{RD_j} = \frac{\mathrm{seTIAC_j} - \mathrm{siTIAC_j}}{\mathrm{siTIAC_j}} \tag{5}$$

where $\mathrm{RD_j}$ is the relative deviation of j^{th} kidney. The seTIACs were considered equivalent to the siTIACs if the RD was less than 5%. In Eq. (5), the siTIAC was defined as a reference for calculating RD values, as it was derived from the pooled dataset (20 kidneys). Thus, it was expected to yield more robust results, given the higher ratio of data point (N) to fitted parameters (K) [6], [22]. The precision of both siTIACs and seTIACs was assessed using the RSEs, calculated as the ratio of standard error to the corresponding mean value [12].

RESULTS

Figure 2 illustrates the renal biokinetic curves for the left and right kidneys from the typical patients (i.e., median value of TIAC), obtained using both simultaneous and separate fitting approaches. The maximum value of RSE of FE and RE parameters was observed as 40% for all fitting methods. The maximum absolute values of the off-diagonal elements in the correlation matrix were 0.53, 0.62, and 0.53 for simultaneous fitting, left kidney fitting, and right kidney fitting, respectively. Therefore, the proposed bi-exponential function (Eq. (1)) satisfied the predefined goodness-of-fit criteria.

Figure 3 presents the TIAC and their associated uncertainties for both kidneys obtained from the simultaneous and separate fitting scenarios. TIAC values obtained from both approaches were considered as equivalent, as evidenced by the median [min, max] RD of -1.6[-4.5, 0.8]%.

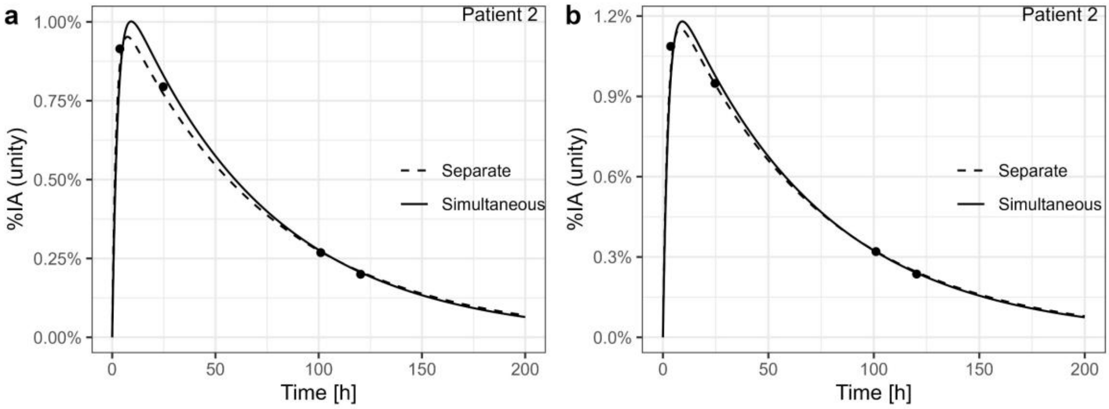

Figure 2. Biokinetic curves for the left and right kidneys in a typical patient (represented by the median TIACs), obtained using both simultaneous and separate fitting within the NLMEM framework. Dashed and solid lines almost overlap, indicating strong agreement between the two methods. (a) Left kidney; (b) Right kidney.

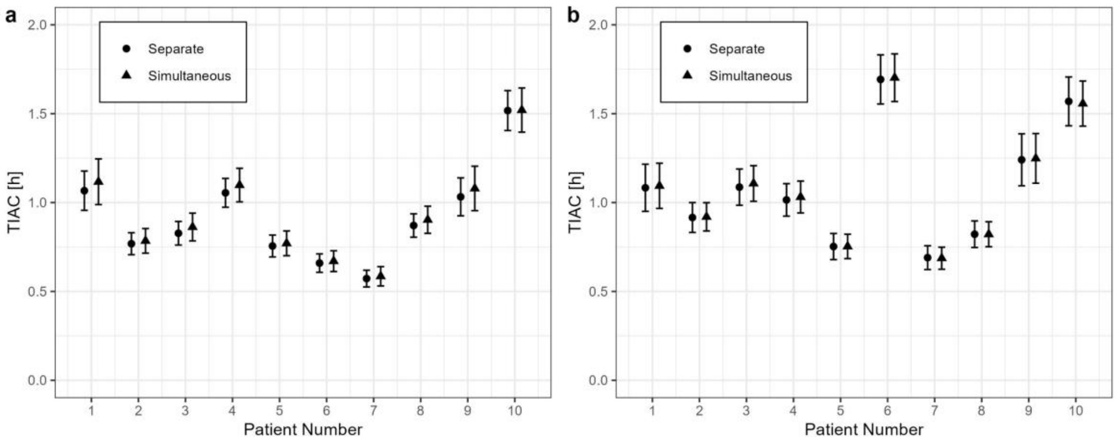

Figure 3. TIACs and their associated uncertainties obtained using the bi-exponential function (Eq. (1)) within the NLMEM framework. (a) TIACs for left kidneys. (b) TIACs for right kidneys.

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DISCUSSION

This study demonstrates that the bi-exponential function within the NLMEM framework adequately describes biokinetic data of [^{177}Lu]Lu-DOTA-TATE in the kidneys, as evidenced by its fulfillment of the predefined goodness-of-fit criteria: adequate visual agreement with the observed data (Figure 2), RSEs of the fitted parameters below 50%, and maximum absolute values of the off-diagonal elements in the correlation matrix below 0.8 for all methods. Two fitting approaches were applied (simultaneous and separate fitting of the left and right kidneys) and both yielded comparable TIACs, as indicated by the small RDs observed between the two methods.

The true biological and physiological processes governing the behavior of radiopharmaceuticals in the human body remain unknown [23], [24], alternative functions may exist that better describe the current dataset than the bi-exponential function employed in this study. In this study, the bi-exponential function was chosen under the assumption that it was the reference for modeling [^{177}Lu]Lu-DOTA-TATE in the kidneys, as previously reported [5]. Nevertheless, the most appropriate sum-of-exponential function form for describing the data could be more objectively determined through a model selection methods [19], [20], [25], [26], [27]. This approach compares multiple candidate models and selects the one with the highest Akaike weight, thereby identifying the best fit function. Moreover, employing model selection enhances reproducibility in the fitting process and reduces subjectivity that may arise from choosing a function based solely on researcher preference [6], [22]. Therefore, the application of model selection is recommended for future studies to ensure more robust and generalizable models.

The simultaneous fitting approach, which treats each kidney as an individual observation, benefits from increased statistical power due to the pooled dataset, e.g., a greater number of individual data points within the population. Consequently, this approach is expected to improve the estimation of both FE and RE parameters. However, in this study, the estimation of RE was comparable between the simultaneous and separate fitting approaches. This outcome may be attributed to the limited population size, which may have reduced the advantage of increased statistical power offered by simultaneous fitting.

Despite the theoretical benefits of simultaneous fitting, the separate fitting approach may offer practical value in clinical settings, particularly in situations where data from only one kidney are available, for instance due to anatomical or pathological conditions. The separate fitting allows independent modeling of each kidney without compromising the accuracy and precision of the estimated TIACs.

CONCLUSION

In this study, TIACs were estimated with bi-exponential function within the NLMEM framework, employing both simultaneous and separate fitting approaches for left and right kidney datasets. The results demonstrated that both approaches yielded similar results as evidenced by the small RD values. Therefore, either simultaneous or separate fitting within the NLMEM framework may be considered suitable for clinical application, as both produce consistent and reliable TIAC values.

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