Calculation of the total number of radiation decay of Radiolabelled-Octreotate using non-linear mixed effect models

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Abstract. Non-Linear Mixed Effect (NLME) is a method used in the area under the measured time-activity curve (AUC) calculations. The calculation of an accurate AUC is needed for an accurate determination of the radiation absorbed dose. In NLME, the error model might affect the accuracy of the estimation of the AUC. Therefore, the aim of this study was to determine the effect of error models on AUC calculations using NMLE. The data used in this study were from biokinetic data of the ^{111}In-DOTATATE biodistribution in the tumour collected from the literature. The data were fitted using published bi-exponential function $f(t) = \frac{(k_e \times k_a)}{c\,(k_a - k_e)}\left[e^{-(k_e)t} - e^{-(k_a)t}\right]$ with several error models, namely constant, proportional, combined and exponential errors. The mean and standard deviation were determined from the AUC for each error model AUC values obtained from constant, proportional, combined, and exponential error were (4.40 ± 1.93) nmol·min, (3.13 ± 2.74) nmol·min, (3.22 ± 2.85) nmol·min and (3.14 ± 2.75) nmol·min, respectively. Based on the research results, the proportional, combined and exponential error were relatively produced better results compared to the constant error model in our dataset.

Keywords. NLME, Radiolabelled-Octreotate, AUC

1 Introduction

In nuclear medicine, molecular radiotherapy is used to optimize radiation delivery to target tumors and minimize radiation to normal tissue [1-7]. Calculation of an accurate area under the measured time-activity curve (AUC) is desirable in molecular radiotherapy [1-5]. In Medical Internal Radiation Dose (MIRD), the absorbed doses consist of two components which are the AUC and S-value [2, 8]. AUC corresponds to the total number of radiation decay. Therefore, it is critical to estimate the AUC accurately to determine the absorbed dose [9]. One of the methods that can be used to determine the AUC value is the non-linear mixed

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effect (NLME) method [10, 11]. The NLME method can be used to analyze a number of non-linear data [12]. In addition, data analysis using NLME enables to identify of inter-individual variability [13] and can explain each individual's different response to a given drug [14]. In 2021, Devasia et al. had applied NLME method for AUC calculation in kidneys. The data were used 10 patients of neuroendocrine tumors with injection of the ^{177}Lu-DOTATATE radiopharmaceutical. The result showed good performance for simulation using NLME which obtained time-activity curve were greatest precision and accuracy [10].

In NLME, the difference between the observed value and the predicted value is defined as the error model [15, 16]. The error models consist of 4 error models, such as constant, proportional, combined and exponential error [17]. Misspecifications of the error model might impact both the estimation and the simulation of the AUC [14]. In previous research to our knowledge, AUC calculations with different error model has not been investigated, error model with proportional function is usually used in the literature [18, 19]. Therefore, the aim of this study was to determine the effect of 4 error models for AUC calculating in tumor using NLME method. This study focuses on treatment efficacy by calculating AUC using 4 meningioma and 5 neuroendocrine tumor data injected with ^{111}In-DOTATATE and the results obtained might be used as a dosimetry guide in the hospital.

2 Materials and method

2.1 Materials

The data used in this study were the secondary biokinetic data of tumors from 9 patients who were injected with the ^{111}In-DOTATATE (Supplemental file from ref [3]). The research data has obtained ethical approval from the Ulm University Institutional Review Board. The patient data obtained from 4 meningioma and 5 neuroendocrine tumors, each patient had 5 time points. ^{111}In-DOTATATE with 140±14 MBq were intravenously injected in pre-therapeutic process. The patient data were measured at 2 hours, 4 hours, 1 day, 2 days, and 3 days after injection using planar whole-body scintigraphy. The data were digitized using Web Plot Digitizer software from the results of Kletting's research in 2016 [3]. The data processing is shown in the flowchart in Fig. 1:

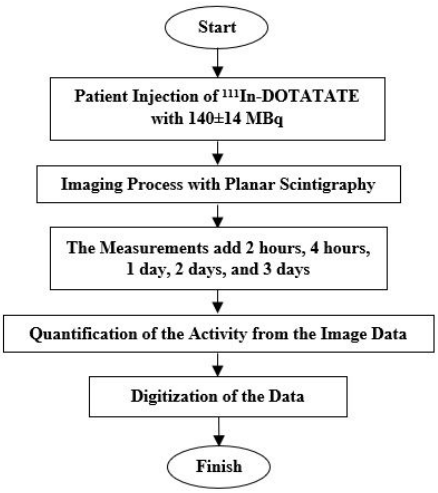


Fig. 1. The data processing flowchart

2.2 Data fitting

The biokinetic data from 9 patients were fitted using the Devasia function in Equation (1) [10]:

$$f(t) = \frac{(\mathrm{k}_e \times \mathrm{k}_a)}{c\,(\mathrm{k}_a - \mathrm{k}_e)}[e^{-(\mathrm{k}_e)t} - e^{-(\mathrm{k}_a)t}] \quad (1)$$

where $f(t)$ is fitted function with 3 parameters, c is prefactor, k_a is absortion rate and k_e is clearance rate [10]. The data fitting was used for simulating the NLME method with the nlmefitsa algorithm approach in Toolbox Matlab R2022a-Simbiology software [17].

2.3 Error model

The error value shows the difference between each individual's the observed and predicted values. Computational simulations were used to fit all biokinetic data with 4 types of error models, namely constant (Equation (2)), proportional (Equation (3)), combined (Equation (4)), and exponential error (Equation (5)) [11].

$$y = f + ae \quad (2)$$

$$y = f + bfe \quad (3)$$

$$y = f + (a + bf)e \quad (4)$$

$$y = f \cdot \exp(ae) \quad (5)$$

where f is the fitting function, a and b are the parameters of the error model and each model defines the error using a standard normal (Gaussian) variable which is represented by e [17]. The best error model was selected based on the Goodness of Fit and the results of the AUC calculation.

2.4 Evaluation of goodness of fit

Evaluation of Goodness of fit was selected based on visual inspection of the fitted graph and the coefficient of variation value (CV). The CV value represented the precision level of the fitted parameters, and the CV tolerance limit is less than 50 %.

2.5 Calculation of the AUC and standard-devition of the AUC

The AUC values can be calculated using Matlab R2022a-Simbiology software with Equation (6) [8] for each model error.

$$AUC = \int_0^\infty A(r_s, t)dt \quad (6)$$

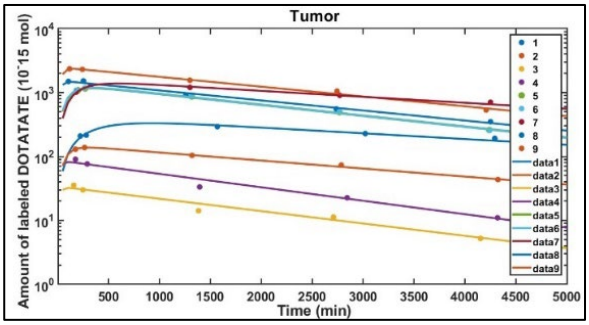
where $A(r_s, t)$ is accumulated activity in the source organ which is function of the time t, integrated from 0 to infinity. The result is to calculate the amount of radiopharmaceutical decay represented by the AUC value. After obtaining the AUC, the standard deviation of AUC was calculated by Equation (7).

$$SD = \sqrt{\frac{\sum_{i=1}^{n}(AUC_i - \overline{AUC})}{n-1}} \tag{7}$$

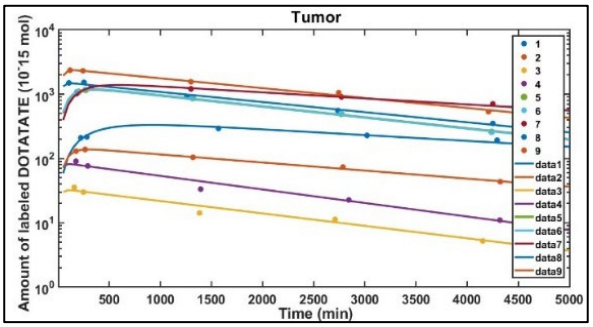
where n is number of data points, AUC_i is the area under the curve value from each patient data and $\overline{AUC}$ is the mean AUC value. Evaluation of AUC and SD of AUC showed the accuracy level of AUC from the error model that selected for the NLME method simulation.

3 Results and discussion

First step, 9 biokinetic data in tumor was population fitted using NLME method and obtained the graph shown in Fig. 2. The observed biokinetic data represented by the dots sign (·) and the fitted curve of each patient was represented by the line. Next, the goodness of fit was evaluated based on visual inspection of the fitted curve. The proportional (Fig. 2b) had similar curves with combined (Fig. 2c) and exponential error (Fig. 2d) which illustrated the data fit closely approximate the shape of the fitted curve. In contrast, the constant error relatively showed lower fitting quality compared to proportional, combined and exponential error model based on the visualization of fitted curve (Fig. 2a), especially in patient 2, patient 3 and patient 4.

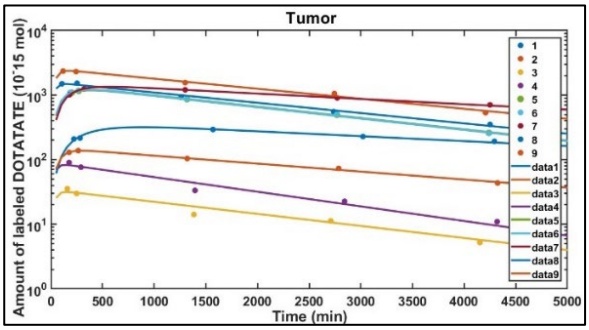


(a)

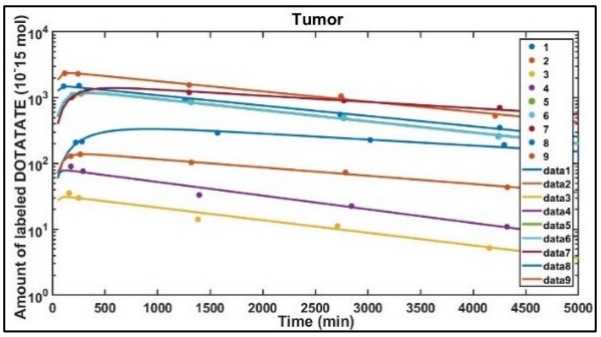


(b)

Fig. 2. Goodness of fit graphs (Amount of radiolabeled with DOTATATE (10^{-15} mol) versus time (min)) for error models such as constant (a), proportional (b), combined (c), and exponential error (d).



(c)



(d)

Fig. 2 (continued). Goodness of fit graphs (Amount of radiolabeled with DOTATATE (10^{-15} mol) versus time (min)) for error models such as constant (a), proportional (b), combined (c), and exponential error (d).

From all fitting process, the estimated parameters of the CV value were shown in Table 1. The CV value was obtained from the comparison between the estimated parameter values obtained with the standard error caused by the parameter estimates. The goodness of fit was analyzed by comparing the obtained CV with the tolerance limit (CV < 50 %). The CV values indicate the precision of the fitted parameters. All the fitted parameters of the error models meet criteria of goodness of fit. The k_a parameters of the proportional error had greatest the CV value that was indicated less precision (within tolerance).

The results of the AUC calculation for each error are shown in Fig. 3, the AUC value obtained from constant, proportional, combined and exponential error were (4.40 ± 1.93) nmol·min, (3.13 ± 2.74) nmol·min, (3.22 ± 2.85) nmol·min and (3.14 ± 2.75) nmol·min, respectively.

Table 1. Coefficient of variation of fitted parameter.

Fitted Parameter	Constant Error	Coefficient of Variation (%)		
		Proportional Error	Combined Error	Exponential Error
k_e	7.51	1.40	1.69	23.69

k_a	6.06	35.85	14.17	1.37
A_1	1.08	3.68	3.69	3.69

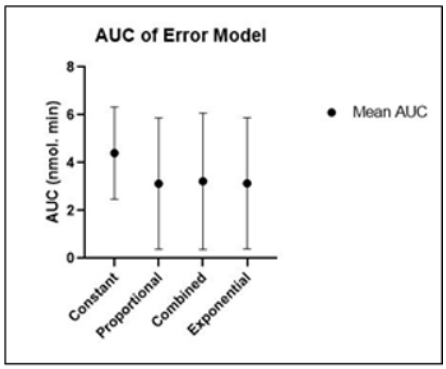


Fig. 3. The AUC value for each model

4 Conclusion

Based on the fitted curve, our results suggest that the proportional, combined and exponential error were relatively produced better results compared to the constant error model in our dataset. In Addition, our results suggest that all error models produced similar AUC values calculated using NLME method in meningioma and neuroendocrine tumors with ^{111}In-DOTATATE radiopharmaceutical.

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