Nuclear Medicine and Biology 43 (2016) 243–246

Contents lists available at ScienceDirect

Nuclear Medicine and Biology

journal homepage: www.elsevier.com/locate/nucmedbio

Physiologically based pharmacokinetic modeling of ^{18}F-SiFAlin-Asp$_3$-PEG$_1$-TATE in AR42J tumor bearing mice

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ARTICLE INFO

Article history:
Received 7 September 2015
Accepted 4 January 2016

Keywords:
Physiologically based pharmacokinetic (PBPK) modeling
Peptide receptor radionuclide therapy (PRRT)
Neuroendocrine tumor (NET)
Mice

ABSTRACT

Purpose: Peptide receptor radionuclide therapy (PRRT) is commonly performed in the treatment of neuroendocrine tumors (NET), where somatostatin analogs (DOTATATE) are radiolabeled with ^{90}Y, ^{68}Ga or ^{111}In for pre-therapeutic and therapeutic purposes. Quantitative evaluation of the biokinetic data can be performed by using physiologically based pharmacokinetic (PBPK) models. Knowledge about the biodistribution in a pre-clinical setting would allow optimizing the translation from bench to bedside. The aim of this study was to develop a PBPK model to describe the biodistribution of a novel sst2-targeting radiotracer.
Methods: Biokinetic data of six mice after injection of ^{18}F-SiFAlin-Asp$_3$-PEG$_1$-TATE were investigated using two PBPK models. The PBPK models describe the biodistribution of the tracer in the tumor, kidneys, liver, remainder and whole body via blood flow to these organs via absorption, distribution, metabolism and excretion.
A recently published sst2 PBPK model for humans (model 1) was used to describe the data. Physiological information in this model was adapted to that of a mouse. Model 1 was further modified by implementing receptor-mediated endocytosis (model 2). Model parameters were fitted to the biokinetic data of each mouse. Model selection was performed by calculating Akaike weights w_i using the corrected Akaike Information Criterion (AICc).
Results: The implementation of receptor-mediated endocytosis considerably improved the description of the biodistribution (Akaike weights $w_1 = 0\%$ and $w_2 = 100\%$ for model 1 and 2, respectively). The resulting time-integrated activity coefficients determined by model 2 were for tumor (0.05 ± 0.02) h, kidneys (0.11 ± 0.01) h and liver (0.02 ± 0.01) h.
Conclusion: Simply downscaling a human PBPK model does not allow for an accurate description of ^{18}F-SiFAlin-Asp$_3$-PEG$_1$-TATE in mice. Biokinetics of this tracer can be accurately and adequately described using a physiologically based pharmacokinetic model including receptor-mediated endocytosis. Thus, an optimized translation from bench to bedside is possible.

1. Introduction

Peptide receptor radionuclide therapy (PRRT) is commonly performed in the treatment of neuroendocrine tumors (NET), where somatostatin analogs (DOTATATE, DOTATOC, DOTANOC) are radiolabeled with ^{177}Lu, ^{90}Y, ^{68}Ga or ^{111}In for pre-therapeutic and therapeutic purposes [1,2]. Treatment efficacy and outcome rely on the high expression of the somatostatin receptor subtype 2 (sst2) on tumor cells compared to normal tissues, e.g. kidneys, liver and spleen. However, kidneys are the dose limiting organ in this therapy approach as reabsorption processes cause an effective higher absorbed dose value. These processes are mainly receptor-mediated endocytosis (internalization) and diffusion [3,4].

Quantitative evaluation of novel radiotracers is performed in pre-clinical biodistribution studies. These studies require a high number of animals (e.g. mice). After injection of the new tracer, animals are sacrificed at different time points to measure the remaining activity in the tumor and the organs of interest (typically: kidneys, liver) [5]. However, dedicated pre-clinical PET/CT systems enable measuring the biodistribution over a longer time course with both an increased spatial and time resolution.

Physiologically based pharmacokinetic (PBPK) modeling was introduced in radioimmunotherapy with radiolabelled anti-CD66 antibody and peptide receptor radionuclide therapy (PRRT) to describe the biodistribution of pre-therapeutic measurements [6,7]. The application of these models allowed an accurate prediction of therapeutic biodistributions [8,9]. However, to the best knowledge of the authors, no PBPK model for mice exists, which allows describing the biodistribution of sst2 targeting radiotracers. Furthermore, there is

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http://dx.doi.org/10.1016/j.nucmedbio.2016.01.001
0969-8051/

only minor knowledge about the concentration of the sst2 receptors in the tumor and kidneys and internalization rates of the peptide-receptor complex. Typically, these values are determined from in vitro or qualitative in vivo studies [10–13]. However, the application of PBPK modeling would allow describing the biodistribution of sst2 targeting radiotracers and determine physiological relevant parameters (receptor numbers, blood flows, and binding rates) quantitatively. This information is important as it allows optimization of the amount of activity to administer and thus to determine the absorbed dose more accurately. Such a model would also allow the description of new radiotracers and allow the translation to humans, i.e. predicting the biodistribution of this new tracer in a patient.

Therefore, the aim of this work was to develop a PBPK model for mice to describe the biodistribution of ^{18}F-SiFAlin-Asp$_3$-PEG$_1$-TATE.

2. Material and methods

2.1. Mice and radiolabelling

All experiments were performed in compliance with the National Guidelines for Animal Protection, Germany, and the approval of the animal care committee.

Biodistribution of ^{18}F-SiFAlin-Asp$_3$-PEG$_1$-TATE [14,15] in six AR42J tumor bearing mice was obtained from a preclinical PET/CT (Bruker BioSpin MRI GmbH, Ettlingen, Germany). Labeling of ^{18}F to the peptide-TATE was done using the SiFA method [16].

For pre-therapeutic imaging (0.18 ± 0.05) nmol with a mean ^{18}F activity of (4.8 ± 1.3) MBq was injected as an infusion over 30 s. For each mouse, 29 frames were obtained with the following frame duration: 1 × 0.5, 9 × 1, 11 × 2, 5 × 5 and 3 × 10 min. Reconstruction was performed using a maximum likelihood expectation–maximization algorithm with 35 iterations.

To determine the time-activity curves (TAC) for tumor, kidneys, liver and whole body an in-house software for automated organ segmentation of 4D PET/CT images was implemented in MATLAB (R2015a, MathWorks, Natick, Massachusetts, USA). This algorithm clusters TACs voxelwise over all 29 frames using k-means. The optimal number of clusters was determined by comparing the volume of the clustered region to the actual organ volume.

2.2. PBPK model

To describe the biodistribution of radiolabeled peptides a recently developed PBPK model [7] was used. In this model, physiological processes, e.g. absorption, distribution, internalization and excretion (ADME) are implemented. Injected peptide is distributed via blood flow to the organs (tumor, kidneys, liver and spleen). Specific binding to somatostatin receptors subtype 2, physical decay of the label and degradation of bound peptide is considered. The kidney model describes unspecific uptake and release of still intact peptide back into the serum [7]. In this model, the co-administration of amino acids is considered to block unspecific uptake by the kidneys. Thus, this PBPK model was developed to describe the biodistribution of ^{111}In-DTPAOC in humans.

To account for these differences (human–mouse, co-administration of amino acids) the previously published human PBPK model was modified. For this, internalization and subsequent recycling back of receptors to the cell surface was explicitly modeled [10–13]. Thus the following two PBPK models were investigated:

1. Human PBPK model using physiological information of the mouse
2. Mouse PBPK model describing rapid internalization of receptors

2.3. Parameter fitting, model selection and time-integrated activity coefficients

For modeling, fitting and simulation SAAMII (Simulation, Analysis and Modeling) software (version 2.3, The Epsilon Group, Washington, USA) was employed [17]. Model parameters were fitted to pre-therapeutic biokinetic data of each mouse individually.

Adjustable model parameters were the receptor numbers for tumor R_T, kidneys R_K and the remainder of the body R_R, the total blood flow F, the relative excretion fraction of peptide by the kidneys f_{ex}, the degradation rates of tumor and kidneys λ_i and the internalization rate of the kidneys receptors $\lambda_{int,K}$. Preliminary investigations showed that for tumor, liver, spleen and remainder of the body previously published values for the internalization rates are sufficient [7]. The recycling rate of receptors back to the cell surface was set 10 times smaller than the apparent internalization rate [18]. Bayesian terms for the relative blood flow to tumor f_T ((0.2 ± 0.1) ml/min/g) [7], the glomerular filtration rate GFR ((0.14 ± 0.02) ml/min) and the hematocrit value h (0.46 ± 0.02) were introduced [19,20].

Recent work revealed uptake of ^{68}Ga-DOTATOC of less than 0.5% injected dose/g in the liver and spleen [13,21]. Thus, the receptor numbers for liver and spleen were set to zero.

The degradation rates for liver, spleen and the remainder of the body were implemented based on values found in patients [7].

To determine the probability of the model better supported by the data, the corrected Akaike Information Criterion (AICc) was used calculated [22,23].

Time-integrated activity coefficients were determined by integrating the time-activity curves of tumor, kidneys, liver and whole body over 500 min p.i. (<1% remaining activity).

3. Results

Visual inspection showed very good fits for model 2, however, only acceptable results for model 1. A typical biodistribution is shown in Fig. 1 for (left) the human model and (right) the optimized model.

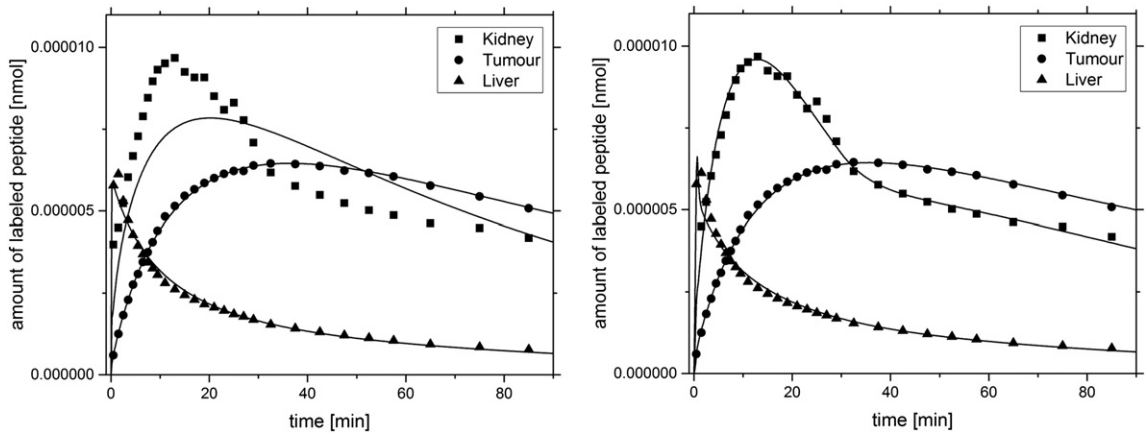

Fig. 1. Typical biodistribution. Typical biodistribution of the novel sst2-targeting radiotracer for kidneys, tumor and liver. Measurements (dots) and model description (lines) for the recently developed human model (left) and the improved mouse model (right).