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Mice Dosimetry of [18F]DPA-714 based in ex vivo biodistribution data using MCNP

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RESUMO

Biodistribution studies are essential for understanding how radiotracers like [18F]DPA-714 move throughout the body and accumulate in various tissues. In these studies, a controlled dose of the radiotracer is administered, and tissue samples are collected at different times to measure radioactivity. This helps researchers determine the radiotracer's behavior, including its speed of distribution, accumulation in specific organs, and how it is eliminated from the body. For [18F]DPA-714, which targets the TSPO protein, these studies suggest it could be a valuable tool for studying brain inflammation. The data from these biodistribution studies allows researchers to create Time-Activity Curves (TACs) for key organs and tissues, providing a detailed picture of how the radiotracer behaves over time. Using the Monte Carlo method with the MCNP6 code, researchers can then calculate the absorbed radiation doses in different organs based on the TACs. In the case of [18F]DPA-714, the highest absorbed doses were found in the kidneys, adrenals, and lungs, indicating these organs have a higher affinity for the radiotracer. This dosimetric data is critical for ensuring that the radiation dose from the radiotracer is within safe limits, preventing any adverse effects that could compromise experimental results. It also helps in the development and registration of new radiopharmaceuticals, ensuring that they are both effective and safe for future studies.

1. INTRODUCTION

When discussing dosimetric studies, several conditions must be considered to determine the correct use and dose of radiopharmaceuticals. Preclinical studies play a crucial role in assessing the potential toxicity of a drug or treatment before it proceeds to human trials. By determining the dose-response relationship in animal models, researchers can identify safe dosage levels and the potential for adverse effects before advancing to human trials. These studies are conducted in a controlled environment, enabling researchers to evaluate the effectiveness of a treatment by testing different dosages to find the optimal amount that provides the desired therapeutic effect with minimal side effects. Consequently, preclinical dosimetry studies offer essential data on how a drug is absorbed, distributed, metabolized, and excreted in the body. Understanding these processes helps predict how the drug will behave in humans and in designing appropriate dosing regimens. Through preclinical studies, researchers can optimize the dosing schedule and administration route to maximize therapeutic benefits while minimizing toxicity. This information is crucial for designing clinical trials and ensuring patient safety. Additionally,

understanding how the treatment works at a cellular and molecular level is essential for improving and refining therapeutic strategies.

Dosimetric studies are often combined with biodistribution experiments, such as *ex vivo* biodistribution studies, which are essential to understanding how radiotracers move throughout the body over time. In these experiments, a calibrated activity of the radiotracer or radiopharmaceutical is administered and samples from different body parts are collected at specific times. The analysis of the activity in these samples provides valuable insights into how the substance behaves, including its speed of movement, where it accumulates, and how the body eliminates it. Time versus activity (TAC) for the main organs and tissues can be obtained. These data are vital in the development and registration of new radiopharmaceuticals [1, 2].

In this context, a method for synthesizing the radiopharmaceutical [18F]DPA-714 was developed, with radiochemical purity and a yield suitable for preclinical efficacy and safety studies.

Additionally, biodistribution experiments were included to understand how radiotracers move throughout the body over time, fulfilling the preclinical requirements. In the case of the [18F]DPA-714 radiotracer, biodistribution provides data for determining tissues and organs with more affinity to this molecule, particularly the ones expressing the protein called TSPO [3].

It is expected that the [18F]DPA-714 could be a good option for studying brain inflammation [3, 4, 5, 6, 7]. Therefore, in this work, we utilized biodistribution data from a previous experiment involving [18F]DPA-714 to obtain TAC for the main organs and to calculate the Time Integrated Activity Coefficient (TIAC). The mice dosimetry was then obtained using the MCNP Monte Carlo code, which simulates particle interactions to determine the energy deposition patterns in the body. The code models how radiopharmaceuticals or other tracers distribute within biological systems, helping to predict the delivery and retention of radioactive substances in target and non-target tissues. This capability is essential for optimizing treatment planning and understanding the potential risks of radiation exposure.

2. METHODOLOGY

A synthetic route for [18F]DPA-714 was developed, ensuring adequate radiochemical purity and yield for preclinical efficacy and safety studies. The protocol for in vivo studies was approved by the Animal Ethics Committee (CEUA/CDTN-002/2022).

In the biodistribution study, [18F]DPA-714 (~5 MBq) was intravenously administered to 18 male C57Bl/6 mice, 8 weeks old, acquired from the Central Animal Facility of UFMG (CEBIO/UFMG, Belo Horizonte, Brazil). The mice were housed in ventilated cages with controlled light and temperature, with free access to food and water. Efforts were made to minimize unnecessary suffering in accordance with the guidelines of the National Council for Control in Animal Experiments (CONCEA).

The mice were divided into three groups and sacrificed at 15, 30, and 60 minutes post-injection through cervical dislocation. Various organs were collected for the biodistribution experiment, including blood, bone, brain, fat, heart, kidneys, large intestine, liver, lungs, muscle, small intestine, spleen, stomach, thyroid, and lymph nodes. The organs were individually weighed using a precision scale, and blood samples were collected with a 1 mL micropipette.

The radioactivity in the samples was measured using a gamma counter (2480 WIZARD; PerkinElmer (Wallac Oy), Joensuu, Finland.). The data were corrected, processed, and expressed as the percentage of the injected dose per gram of tissue (%ID/g).

Biodistribution data in mice were utilized to estimate absorbed doses. The uptake values of [18F]DPA-714 (%ID/g) were converted into the percentage of the injected dose per organ/tissue, using reference masses for mouse organs/tissues from the DM_BRA mice model, as described elsewhere. Time-activity curves were generated for each measured organ/tissue. The time-integrated activity within the source region, denoted as Ã was calculated for each curve using trapezoidal integration up to 60 minutes post-injection. Beyond the final measured time point (60 minutes), it was assumed that the radiotracer experienced only physical decay, with no further biological elimination from the source organ. The time-integrated activity coefficient (ã) for each organ was calculated by dividing the time-integrated activity in the source region by the injected activity (A_0), as shown in Eq. (1):

$$\tilde{a} = \frac{\tilde{A}}{A_0} \qquad (1)$$

The absorbed dose for animal organs/tissues was calculated using the MIRD formulation, according to Eq. (2):

$$D(r_T) = \sum_S \tilde{A}_s \times S_{(r_T \leftarrow r_s)} \qquad (2)$$

In this formulation, $D(r_T)$ represents the absorbed dose in the target organ r_T, Ã denotes the time-integrated activity in the source organ r_S, and $S_{(rT \leftarrow rS)}$ is the S-value, which is the mean absorbed dose per decay in the source region. The S values for the animal organs/tissues were derived from the DM_BRA mouse voxel model.

The urinary bladder TIAC was estimated using a simplified excretion model [2]. The male mouse voxelized phantom, DM_BRA, was implemented in the MCNP code. Using the TIAC values, the absorbed dose per injected activity in the primary organs of the model was calculated.

3. RESULTS AND DISCUSSION

The Time-Integrated Activities calculated for the different organs and tissues were presented in FIG 1. For all organs and tissues evaluated, 30 minutes was the time with higher uptake. Adrenals, kidneys and lungs were the organs with higher affinity for the radiopharmaceutical. These findings are in accordance with previous work [7]. Gallbladder presented an uptake spike at 30 min. which was not found in that data. These organs exhibit high uptake of radiopharmaceuticals targeting inflammatory receptors, such as TSPO, for several reasons. TSPO is highly expressed in various cells, particularly in glial cells during neuroinflammation. These organs have high metabolic activity and rich vascularization, which enhance the delivery and retention of the radiopharmaceutical. The kidneys' role in filtration and excretion, the adrenal glands' hormone production in response to inflammation, and the stomach's involvement in gastrointestinal inflammation further contribute to their significant radiotracer uptake.

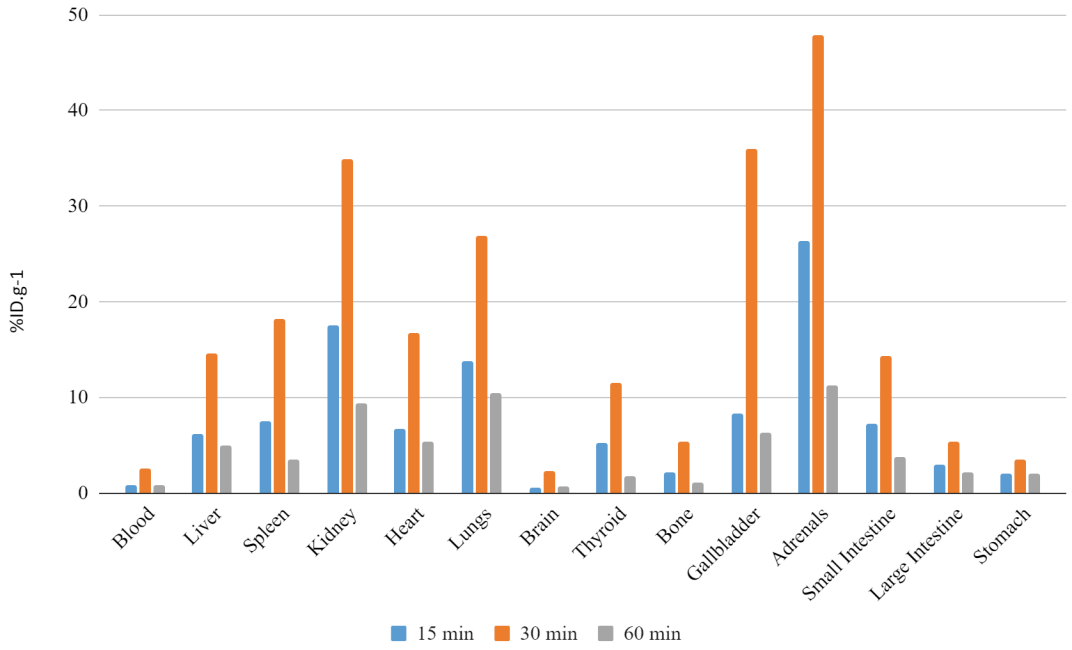

Fig. 1. Time corrected ^{18}F-DPA tissue uptake data (%ID.g^{-1}) from biodistribution study with the gamma counter.

Lower uptake values were observed for brain and blood, as shown in Fig.1. This is in accordance with the study [7]. That fact indicates that the radiopharmaceutical could not pass through the blood-brain barrier. In this work the stomach also presented low uptake. The previous work doesn't evaluate the uptake of this organ.

Time-Integrated Activity Coefficient were presented in Figure 2. Muscle, liver, small intestine and kidney were the main source organs. These organs show high uptake and/or have large mass values.

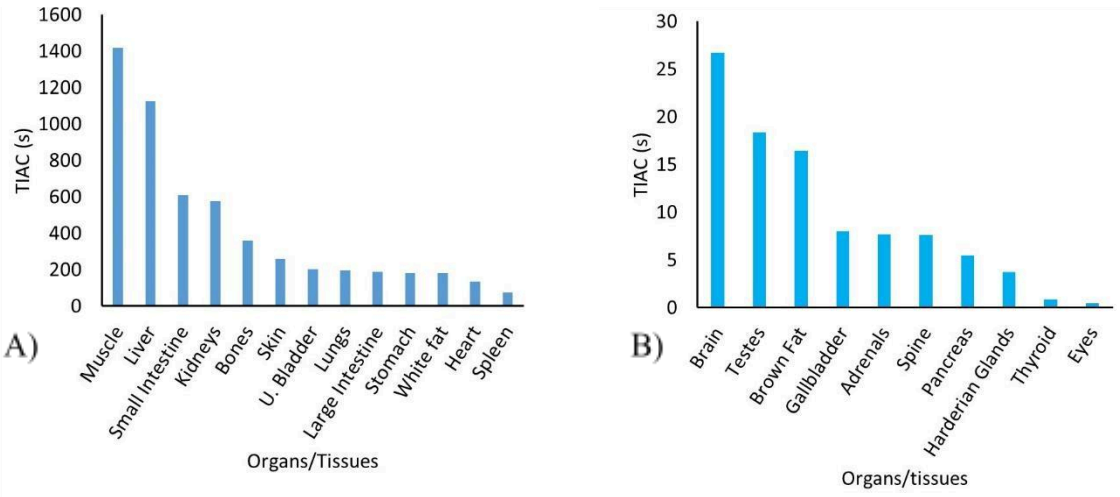

Fig. 2. Time-Integrated Activity Coefficient. A) Main source organs. B) Source organs with low uptake or low mass.

The absorbed dose per injected activity for all organs and tissues of the DM_BRA model was calculated based on the TIAC values of Fig. 2. Kidneys are the main organ at risk. The absorbed dose for 10 MBq of injected activity could result in absorbed doses of approximately 0.5 Gy in these organs. Other organs with relevant absorbed dose values were adrenals, lungs and gallbladder. Brain, eyes and cerebellum show negligible absorbed dose values.

Table 1 – Absorbed dose per unit of injected activity in the organs of DM_BRA mouse phantom.

Organ	Absorbed Dose per Injected Activity (mGy/MBq)	Organ	Absorbed Dose per Injected Activity (mGy/MBq)
Kidney	44,0	Bone	6,4
Adrenal	35,9	Muscle	6,0
Lung	33,8	Brown Fat	5,5
Gallbladder	32,5	Adip. Tis.	5,4
U.B. Cont.	31,7	Testes	5,3
Stom. Cont.	28,6	Hard. Glan.	5,0
Heart	25,5	Spin. Chord	4,6
Liver	22,9	Skin	4,1
Spleen	19,7	Cerebellum	4,0
Int. Cont.	14,0	Eye	4,0
Pancreas	10,7	Brain	3,8

4. CONCLUSIONS

The biodistribution study of [18F]DPA-714 demonstrates its significant accumulation in key organs such as the adrenal glands, kidneys, lungs, and stomach, with the highest absorbed doses observed in the adrenals. This high uptake is attributed to the presence of TSPO in these tissues, their high metabolic activity, and rich vascularization. The data highlights the potential of [18F]DPA-714 for studying inflammatory processes, particularly in neuroinflammation, by targeting TSPO-expressing cells. The dosimetric analysis ensures that the radiotracer's absorbed doses remain within safe limits, providing confidence in its use for future research and clinical applications. Overall, these findings contribute valuable insights into the pharmacokinetics of [18F]DPA-714, supporting its development and optimization as a diagnostic tool.

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