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Available online at [www.sciencedirect.com](http://www.sciencedirect.com)**ScienceDirect**journal homepage: <http://www.elsevier.com/locate/rpor>**Original research article****Modeling the time dependent biodistribution of Samarium-153 ethylenediamine tetramethylene phosphonate using compartmental analysis**

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**ARTICLE INFO****Article history:**

Received 20 April 2013

Received in revised form

21 July 2013

Accepted 4 December 2013

**Keywords:**

Biodistribution modeling

Compartmental analysis

[<sup>153</sup>Sm]-EDTMP**ABSTRACT**

**Aim:** The main purpose of this work was to develop a pharmacokinetic model for the bone pain palliation agent Samarium-153 ethylenediamine tetramethylene phosphonate ([<sup>153</sup>Sm]-EDTMP) in normal rats to analyze the behavior of the complex.

**Background:** The use of compartmental analysis allows a mathematical separation of tissues and organs to determine the concentration of activity in each fraction of interest. Biodistribution studies are expensive and difficult to carry out in humans, but such data can be obtained easily in rodents.

**Materials and methods:** We have developed a physiologically based pharmacokinetic model for scaling up activity concentration in each organ versus time. The mathematical model uses physiological parameters including organ volumes, blood flow rates, and vascular permeabilities; the compartments (organs) are connected anatomically. This allows the use of scale-up techniques to predict new complex distribution in humans in each organ.

**Results:** The concentration of the radiopharmaceutical in various organs was measured at different times. The temporal behavior of biodistribution of <sup>153</sup>Sm-EDTMP was modeled and drawn as a function of time.

**Conclusions:** The variation of pharmaceutical concentration in all organs is described with summation of 6–10 exponential terms and it approximates our experimental data with precision better than 2%.

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## 1. Background

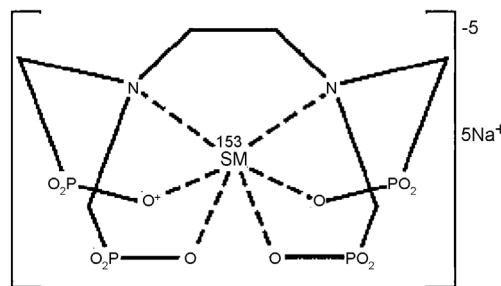
According to the principles of humane experimental technique, the use of other researchers' data has been one of the mainly recommended actions allowing the 3Rs concepts to reduce the number of experimental procedures involving animal and improve results.<sup>1</sup> In the same way, compartmental analyses support the radiopharmaceuticals design permitting a mathematical separation of tissues and organs to determine the concentration of activity in each fraction of interest and pointing toward inconsistency in biodistribution and dosimetry studies. Additionally, by compartmental analysis it is possible to consider different chemical species and to predict metabolites.<sup>2</sup>

Mathematical models that describe the kinetic processes of a particular agent may be used to predict its behavior in regions where direct measurements are not possible but where sufficient independent knowledge about the physiology of the region is available to specify its interrelationship with the regions or tissues in which uptake and retention can be measured directly. These models can account for the presence of metabolic products.<sup>3-6</sup> Compartmental modeling is the most commonly used method for describing the uptake and clearance of radioactive tracers in tissue.<sup>7-9</sup> These models specify that all molecules of tracer delivered to the system (i.e., injected) will at any given time exist in one of many compartments. Each compartment defines one possible state of the tracer, specifically its physical location (for example, intravascular space, extracellular space, intracellular space, synapse) and its chemical state (i.e., its current metabolic form or its binding state to different tissue elements, such as plasma proteins, receptors). Often, a single compartment represents a number of these states lumped together. Compartments are typically numbered for mathematical notation.<sup>10</sup>

The compartmental model also describes the possible transformations that can occur to the tracer, allowing it to move between compartments. The model defines the fraction or proportion of tracer molecules that will move to a different compartment within a specified time. This fractional rate of change of the tracer concentration in one compartment is called a rate constant and has units of inverse time.<sup>10</sup>

The physiological interpretation of the source and destination compartments defines the meaning of the rate constants for movement of tracer between them. For a freely diffusible inert tracer, the rate constant of transfer from arterial blood to the tissue compartment will define local blood flow. By determining these rate constants (or some algebraic combination of them), quantitative estimates or indices of local physiological parameters can be obtained. The underlying goal of all modeling methods is the estimation of one or more of these rate constants from tissue radioactivity measurements.<sup>2,10</sup>

In this study, the compartmental analyses were used to generate a time-dependence model of biodistribution of [<sup>153</sup>Sm]-EDTMP, an agent for bone palliation radiotherapy. Chemotherapy or hormonal therapy may be used for both soft tissue and bone metastases and can be effective until the disease becomes refractory to these agents. External beam radiotherapy provides effective pain control with short courses of high dose per fraction and a low toxicity, if the



**Fig. 1 – Chemical structure of [<sup>153</sup>Sm]-EDTMP.**

metastatic disease is not extensive; however, the toxicity rapidly increases with wide radiation fields.<sup>11</sup>

Systemic therapy with radionuclides linked to bone seeking agents is a treatment option for patients with disseminated skeletal metastases, owing to its efficacy, low cost and low toxicity.<sup>12</sup> Radionuclides suitable for systemic metabolic radiotherapy of bone pain include Phosphorous-32 (P-32), Strontium-89 (Sr-89), Rhenium-186 (Re-186) chelated with hydroxyethylidene diphosphonate (HEDP) and Samarium-153 (Sm-153) chelated with ethylenediamine tetramethylene phosphonate (EDTMP).<sup>13-16</sup>

Considerable bone marrow suppression due to the presence of higher energy  $\beta$  particles is a major constraint toward a widespread use of P-32 (mean  $\beta$ =695 keV,  $t_{1/2}$ =14.3 days) and Sr-89 (mean  $\beta$ =583 keV,  $t_{1/2}$ =50.5 days). Apart from that, the absence of imageable  $\gamma$  photons and long half life (especially in case of Sr-89) are often cited as drawbacks. Beta emitters with short half-lives, like Re-186 (mean  $\beta$ =362 keV,  $\gamma$ =137 keV,  $t_{1/2}$ =3.7 days) and Sm-153 (mean  $\beta$ =233 keV,  $\gamma$ =103 keV,  $t_{1/2}$ =1.9 days), deliver their radiation dose at higher dose rates, which may be therapeutically more effective than equivalent doses given at lower dose rates. The short range of beta emission of these radionuclides may be of advantage in limiting red marrow irradiation.<sup>17</sup> Beside beta ray, <sup>153</sup>Sm emits gamma radiation and conversion electrons with 103 keV and 55 keV energies, respectively. Gamma ray at this energy range makes nuclear imaging feasible, while the process of radiotherapy is carried out. Finally, <sup>153</sup>Sm decays to stable nuclide <sup>153</sup>Eu.<sup>18,19</sup> <sup>153</sup>Sm-ethylenediamine tetramethylene phosphonic acid ([<sup>153</sup>Sm]-EDTMP) (Fig. 1) localizes in the skeleton by chemo-absorption of the tetraphosphonate by hydroxyapatite and by the formation of Samarium oxide involving oxygen on the hydroxyapatite molecule. Early phase I/II studies were published more than ten years ago and since then, this agent has been clinically used worldwide for pain palliation in symptomatic bone metastases from several cancers, mainly prostate and breast.<sup>20-22</sup>

Mathematical biodistribution models are an alternative approach to the direct calculation of cumulated activity in the field of radiopharmaceuticals dosimetry. Often, it is impractical to measure the time-activity curves of all the source regions. When the physiological interactions of these regions with the blood or with other directly measurable tissues are known, the time-activity curves of unmeasured tissues can be inferred by these models. Biodistribution modeling can also be used to separate the activities in the regions that overlap

on imaging studies, such as the renal cortex and renal pelvis or the liver and right colon.<sup>6</sup> In the future, the biodistribution modeling will play an important role in molecular imaging and in vivo dosimetry.

## 2. Aim

Samarium, being a lanthanide metal, concentrates in bone, especially tissues with high osteoblastic activity. This gives the benefit of its absorption in metastatic tissues in bone cancer. As a rule of thumb, concentration of Samarium in metastatic bone tissues is five times higher than in normal tissue.<sup>23</sup>  $[^{153}\text{Sm}]$ -ethylenediamine tetramethylene phosphonic acid ( $[^{153}\text{Sm}]$ -EDTMP) is a major therapeutic agent which is widely used in the world.<sup>2</sup> In this work, time dependant biodistribution model of  $[^{153}\text{Sm}]$ -EDTMP was procured by using compartmental analysis with respect to anatomic data from ICRP Report 89.

## 3. Materials and methods

Data used in the present work were: original percentage of internal dose per gram data from Goeckeler et al.<sup>24</sup>  $[^{153}\text{Sm}]$ -EDTMP long-term biodistribution studies in 160–220 g male Sprague–Dawley rats.

### 3.1. $^{153}\text{Sm}$ -EDTMP complex preparation

Stable Samarium,  $^{152}\text{Sm}$ , is a lanthanide with high absorption cross section for thermal neutrons (204 barns) leading to production of  $^{153}\text{Sm}$ .<sup>2</sup> The radionuclide was prepared by neutron irradiation in the University of Missouri Research Reactor using a thermal flux of  $8.5 \times 10^{13} \text{ n/cm}^2 \text{ s}$  and a resonance flux of  $1.7 \times 10^{12} \text{ n/cm}^2 \text{ s}$ . The radioisotope was dissolved in 1–4 N HCl and brought to a stock concentration of approximately  $1.2 \times 10^{-3} \text{ M}$  with deionized water.<sup>24</sup>

To form  $[^{153}\text{Sm}]$ -EDTMP complex, 50 mg/ml of EDTMP that was prepared by Dow chemical company was used. The amount of ligand needed to achieve a quantitative complex formation<sup>25</sup> was first dissolved in deionized water followed by the addition of concentrated base. The  $^{153}\text{Sm}$  stock and carrier solutions were added so that the final samarium concentration was  $\sim 3.0 \times 10^{-4} \text{ M}$  with a specific activity of 185 MBq/ml. The pH was adjusted to  $>10$  and the solution heated to  $60^\circ\text{C}$  for  $\sim 30$  min to facilitate complexation. After heating, the pH was adjusted to 7.0 with 4–5 M HCl.<sup>24</sup>

Complex yield was determined by separating the complexed metal and uncomplexed  $^{153}\text{Sm}$  species on a 0.5-ml C25 Sephadex cationic exchange column. The ionic samarium ( $\text{Sm}^{+3}$ ) and insoluble  $\text{Sm(OH)}_3$  were retained on the column while the anionic complex was eluted with two 9-ml volumes of isotonic saline.<sup>24</sup>

The elution and columns were counted using the 103-keV gamma photon of  $^{153}\text{Sm}$  and the complex yield (% complex) was obtained from the formula<sup>24</sup>:

$$\text{Complex } (\%) = 100 \times \left( 1 - \frac{\text{column count}}{\text{total count}} \right).$$

Samples were counted in a NaI(Tl) well counter and corrected for background.

### 3.2. Biodistribution of $[^{153}\text{Sm}]$ -EDTMP in rats

Samarium-153 EDTMP was prepared as previously described using a ligand concentration of  $8.0 \times 10^{-2} \text{ M}$  and a samarium concentration of  $3.0 \times 10^{-4} \text{ M}$ , the complex yield was  $>99\%$ . Fifty microliters of the complex were injected into the tail veins of male Sprague–Dawley rats. Each rat was housed in a metabolic cage equipped to collect urine. They were killed in groups of five by cervical dislocation at 2 h, 5 h, 24 h, 48 h, and 72 h post-injection. A 1-ml sample of blood was drawn from the heart and weighed immediately after killing. The whole animal was then weighed and subsequently dissected with special care being taken to separate the blood and urine on the kill papers, the tissue washings and the urine collected from the cages. All tissues were washed with isotonic saline, blotted, weighed, and counted. Animals maintained for 24 h or more were provided with ad lib. standard rat chow and water.

Counting was performed for all tissues in the longer time period groups which were counted in a NaI(Tl) well detector and compared with diluted standards.

### 3.3. Biodistribution modeling of $[^{153}\text{Sm}]$ -EDTMP

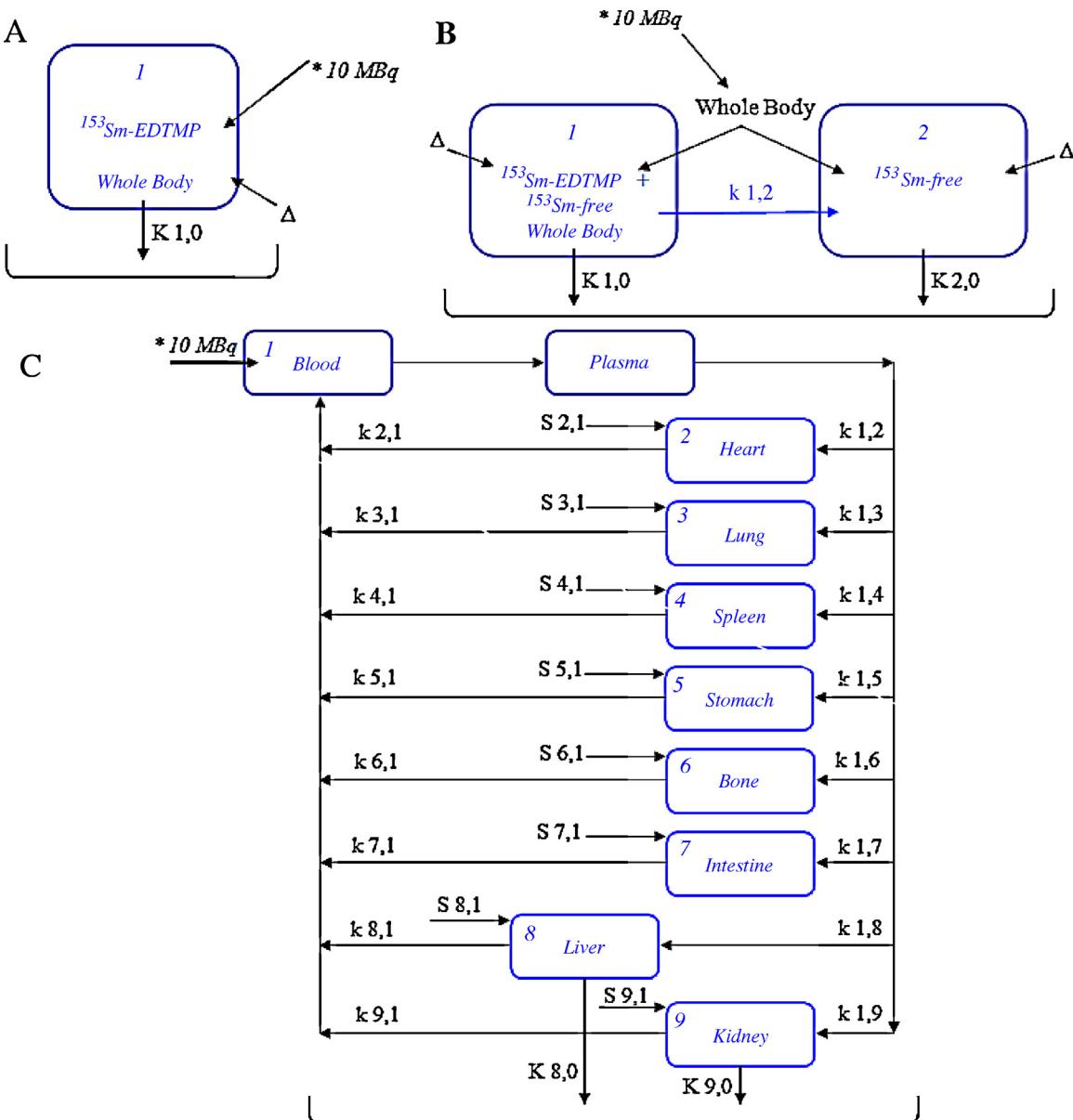
The first approach of the modeling studies included the knowledge of chemical kinetics and mimetism of the Samarium and possible targets of the diagnosis/therapy to choose possible models to apply over the sampling standard methods used in experimental works.

Biodistribution modeling consisted of two steps. At the first stage, a model with only one physical compartment (whole body) and one chemical compartment ( $[^{153}\text{Sm}]$ -EDTMP) were generated with the compartmental analysis. The values used in this work were residence time from three different kinds of study with free  $^{153}\text{Sm}$ : whole body, average excretion and maximum excretion as a chemical compartment. Activity concentration values as a time function in measurements of total whole body and activity measurement in samples of blood with projection to total circulating blood volume with  $[^{153}\text{Sm}]$ -EDTMP. Considering the two sources of data in the same modeling a better consistence was obtained.

The second step was a statistic treatment of biodistribution and dosimetry in rats considering three chemical fractions of the designed radiopharmaceutical:  $[^{153}\text{Sm}]$ -EDTMP, free  $^{153}\text{Sm}$ , and total radiopharmaceutical (free  $^{153}\text{Sm}$  + ( $[^{153}\text{Sm}]$ -EDTMP)) (Fig. 2). Using a mamillary models with six compartments and Human anatomic data from ICRP Report 89, these studies were also performed in rats. The selected parameters were very critical, considering the blood flux in each body region and tissue.

## 4. Results

With the concentration of ligand used in preparation of  $[^{153}\text{Sm}]$ -EDTMP, complex yield was  $>99\%$ . Before the complex was injected into the animals, its pH was lowered to  $\sim 7$  with no detectable complex dissociation. The activity concentration in



\*→ 10 MBq injection of the  $[^{153}\text{Sm}]$ -EDTMP intravenously in the blood (time=0),

$\Delta$ : Sampling for biokinetics calculations,

$K_{i,0}$ : Removal constant from organs to extra,

$k_{1,i}$ : Transfer constant from blood to tissues and organs,

$k_{i,1}$ : Transfer constant from tissues and organs to body fluids.

**Fig. 2 – Selected compartmental analysis models scheme. (A)** One physical compartment (whole body) and one chemical compartment ( $[^{153}\text{Sm}]$ -EDTMP). **(B)** One physical compartment (whole body) and two chemical compartments ( $[^{153}\text{Sm}]$ -EDTMP and  $[^{153}\text{Sm}]$ -free). **(C)** Six compartment model of a rat.

each organ was measured with the use of detectors at specified time after injection. The results show variation with time. Table 1 includes the uptake (%ID/g) data of the  $[^{153}\text{Sm}]$ -EDTMP in various organs of rats.

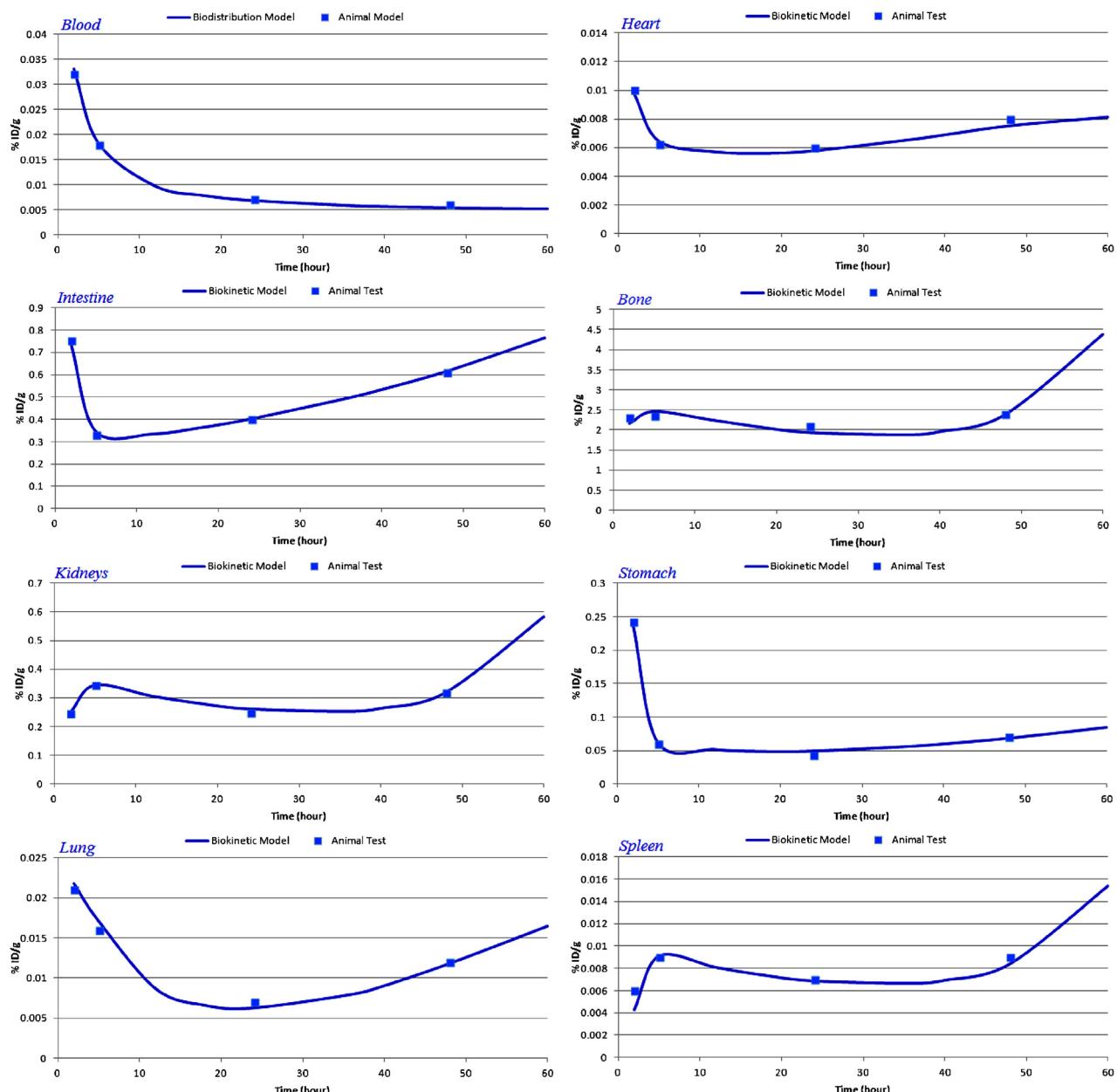
$[^{153}\text{Sm}]$ -EDTMP demonstrated high skeletal uptake with low blood concentration at 2 h post-injection. Localization of  $[^{153}\text{Sm}]$ -EDTMP in nonosseous tissues was also low. The bone to blood activity concentration ratio was about 300

at 24 h and 72 h post-injection. The bone to muscle ratios were more than 16 at 24 h and more than 23 at 72 h post-injection.

The compartmental model was used to produce a mathematical description of these variations. The following equations were obtained for each organ. In each case,  $t=0$  corresponds to the time of injection (Fig. 3).

**Table 1 – Biodistribution of [<sup>153</sup>Sm]-EDTMP in rats as a function of time after injection.**

Organs	Injected dose per gram (ID/g% ± SD) [ <sup>153</sup> Sm]-EDTMP				
	2 h	5 h	24 h	48 h	72 h
Blood	0.032 ± 0.016	0.008 ± 0.019	0.007 ± 0.002	0.006 ± 0.001	0.006 ± 0.001
Heart	0.010 ± 0.009	0.006 ± 0.003	0.006 ± 0.002	0.008 ± 0.004	0.007 ± 0.003
Lung	0.021 ± 0.007	0.016 ± 0.005	0.007 ± 0.002	0.008 ± 0.002	0.008 ± 0.001
Liver	0.252 ± 0.038	0.370 ± 0.080	0.349 ± 0.021	0.458 ± 0.079	0.492 ± 0.097
Spleen	0.006 ± 0.004	0.007 ± 0.005	0.007 ± 0.002	0.009 ± 0.003	0.007 ± 0.004
Stomach	0.241 ± 0.015	0.059 ± 0.003	0.024 ± 0.005	0.081 ± 0.008	0.058 ± 0.002
Intestine	0.095 ± 0.021	0.270 ± 0.017	0.055 ± 0.001	0.081 ± 0.007	0.058 ± 0.002
Kidneys	0.254 ± 0.035	0.364 ± 0.055	0.250 ± 0.087	0.286 ± 0.028	0.216 ± 0.036
Muscle	0.223 ± 0.037	0.064 ± 0.004	0.125 ± 0.008	0.120 ± 0.020	0.097 ± 0.004
Bone	2.308 ± 0.162	2.341 ± 0.173	2.082 ± 0.116	2.381 ± 0.151	2.276 ± 0.160

**Fig. 3 – Temporal behavior of biodistribution of <sup>153</sup>Sm-EDTMP in various organs of wild-type rat.**

## (1) Blood

$$f_1 = (5.175E-3)e^{-(9.9E-3)t} + (9.89E-3)e^{-0.077t} + (3.956E-5)e^{-0.07t} \\ + (2.254E-4)e^{-0.001t} + (2.1275E-2)e^{-0.38t} \\ - (5.964E-6)e^{-5.14t} - (3.266E-8)e^{-0.24t}$$

$$- (2.3941546E-2)e^{-0.42t} - (3.1412E-4)e^{-0.017t} \\ - (2.3141412E-2)e^{-1.18t} - (2.58E-5)e^{0.0999t}$$

## (2) Heart

$$f_2 = (7.70133E-2)e^{-1.64t} + (4.14687E-4)e^{-0.14t} \\ + (4.21848E-4)e^{0.006t} + (3.22896E-3)e^{0.019t} \\ + (3.6456E-3)e^{-0.091t} - (3.7107E-5)e^{0.0706t} \\ - (1.03509E-1)e^{-3.04t}$$

## (8) Spleen

$$f_8 = (6.846E-3)e^{-(9.9E-3)t} + (3.36E-3)e^{-0.047t} - (4.83E-5)e^{0.0911t} \\ - (5.019E-3)e^{-9.14t} - (2.0328E-3)e^{-1.13t} - (1.68E-5)e^{-0.18t} \\ - (8.232E-4)e^{-0.00612t} - (8.309847E-2)e^{-1.38t}$$

## (3) Bone

$$f_3 = 1.956e^{(9.9E-3)t} + (29.6E-1)e^{-0.047t} + (1.26E-2)e^{0.0911t} \\ - (2.34E-1)e^{-9.14t} - (6.00E-4)e^{-1.13t} - (3.24E-1)e^{-0.18t} \\ - (2.352E-2)e^{-0.00612t} - 3.34242e^{-1.08t}$$

## (9) Stomach

$$f_9 = (3.686627E-3)e^{-5.04t} + (3.0899E-1)e^{-1.64t} \\ + (3.9061E-3)e^{-0.14t} + (3.4344E-3)e^{0.006t} \\ + (2.544E-2)e^{0.019t} + (4.558E-2)e^{-0.091t}$$

## (4) Intestine

$$f_4 = 14.54703e^{-1.64t} + (7.230306E-1)e^{-0.45t} \\ + (3.538337E-2)e^{-0.14t} + (3.111048E-2)e^{0.006t} \\ + (2.30448E-1)e^{0.019t} + (4.60896E-3)e^{-0.191t} \\ - (7.63359E-2)e^{-5.04t} - 1.9204e^{-0.777t}$$

## (5) Kidney

$$f_5 = (2.608E-1)e^{(9.9E-3)t} + (1.28E-1)e^{-0.047t} + (1.84E-3)e^{0.0911t} \\ - (3.12E-2)e^{-9.14t} - (6.4E-5)e^{-1.13t} - (6.4E-3)e^{-0.18t} \\ - (3.136E-2)e^{-0.00612t} - 1.885656e^{-1.38t}$$

## (6) Liver

$$f_6 = (2.7873E-2)e^{(9.9E-4)t} + (1.368E-1)e^{-0.037t} \\ + (1.9665E-3)e^{0.0911t} - (3.3516E-4)e^{-0.00512t} \\ - (3.1635E-2)e^{-9.14t} - (4.8564E-2)e^{-1.13t} \\ - (1.6074E-2)e^{-0.06t} - 1.33129485e^{-1.18t}$$

## (7) Lung

$$f_7 = (8.00E-4)e^{-(9.9E-6)t} + (3.8736E-2)e^{-0.26t} \\ + (1.376E-4)e^{-0.062t} + (2.4784E-3)e^{-0.001t} \\ - (1.08E-2)e^{-0.077t} + (1.12E-3)e^{0.0523t}$$

The deviation of  $[^{153}\text{Sm}]$ -EDTMP concentration in all organs and tissues is described with summation of seven to nine exponential terms. Comparison with animal data showed that our experimental data with precision better than 2%. It should be noted that the concentration of activity had been in a good statistics range of measurement.

**5. Conclusion**

In this work, time dependant biodistribution model of  $[^{153}\text{Sm}]$ -EDTMP was procured by using compartmental analysis with respect to anatomic data from ICRP Report 89. Biodistribution studies of  $[^{153}\text{Sm}]$ -EDTMP were carried out in wild-type rats comparing the critical organ uptakes. Comparative studies for the labeled compound were conducted up to 48 h, demonstrating a more rapid wash out of activity for the labeled compound. The radioactivity in the case of the labeled compound is significantly removed from the blood and bone.

As a result of modeling, the variation of pharmaceutical concentration in all organs is described with summation of 6–10 exponential terms and it approximates our experimental data with precision better than 2%.

There are many future studies that can be done in order to add to these models. Eventual goals include incorporating the action of beta-emitting nuclides in order to observe the toxicity and its effect on the killing of cells. A stochastic approach can be taken to model beta emission, because the distance a particle is emitted varies randomly over time; this theoretical, improved model can be implemented into a full simulation involving dosimetry calculations.

**Conflict of interest statement**

None declared.

**Financial disclosure statement**

None declared.

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