RAP Conference Proceedings, vol. 4, pp. 36–40, 2019
ISSN 2466-4626 (online) | doi: 10.37392/RapProc.2019.08
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TWO LABELED EDTMP RADIOPHARMACEUTICALS WITH Sm-153 AND Lu-177 FOR HUMAN BONE RADIOTHERAPY

Hesham M. H. Zakaly[1,3*], Mostafa Y. A. Mostafa[1,4], M. Zhukovsky[1,2]

[1]Ural Federal University, Yekaterinburg, Russia
[2]Russia Institute of Industrial Ecology UB RAS, Ekaterinburg, Russia
[3]Al-Azhar University, Faculty of Science, Physics Department, Assuit, Egypt
[4]Minia University, Faculty of Science, Department of Physics, El-Minia, Egypt

Abstract. *^{177}Lu and ^{153}Sm are perspective radionuclides used in nuclear medicine. High-energy beta particles and the relative half-life of the radionuclides are used to achieve an effective palliative treatment of bone metastases. In this paper, the effect of the drug carrier EDTMP (i.e. ethylene diamine tetramethylene phosphonate) on the ionic form of ^{177}Lu and ^{153}Sm is presented. The absorbed doses of ^{177}Lu and ^{153}Sm in ionic form labeled with EDTMP in different organs and tissues are determined by IDAC-Dose 2.1 (Internal Dose Assessment by Computer) software and WinAct software which is used to calculate cumulative activity. ^{177}Lu and ^{153}Sm are lanthanide radionuclides which actively accumulate in the liver and bones when used in ionic form. In the case of labeling with EDTMP, the distribution and elimination of the drug occur according to the kinetics of the carrier, EDTMP. The use of an osteotropic complex (drugs attracted to and targeting bones) allows creating a large dose in the pathological areas and minimizes the damage of healthy organs and tissues. ^{177}Lu and 153Sm labeled with EDTMP decrease the liver dose absorption and increase the bone surface absorption for a more effective treatment and minimizing side effects. The effective dose per administered activity is 0.189 mGy/MBq for ^{177}Lu-ionic form, 0.232 mGy/MBq for ^{153}Sm-ionic form and 0.242 mGy/MBq for ^{177}Lu-EDTMP and 0.139 mGy/MBq for ^{153}sm-EDTMP.*

Keywords**:** *Radiopharmaceutical, Sm-153, Lu-177, EDTMP*

1. INTRODUCTION

Radionuclide therapy (RNT), employing radiopharmaceuticals labeled with β^- conversion electron-emitting radionuclides, is effectively utilized for bone pain palliation, thus providing significant improvement in the quality of life of patients suffering from pain resulting from secondary skeletal metastases. The major challenge in developing effective agents for the palliative treatment of bone pain arising from skeletal metastasis is to ensure the delivery of an adequate dose of ionizing radiation at the site of the skeletal lesion with minimum radiation-induced bone marrow suppression. These in vivo features are governed by the tissue penetration range and, hence, on the energies of the β^- particles of the radionuclides used in the radiopharmaceutical preparations [1,2].

Designing ideal radiopharmaceuticals for use as bone pain palliatives requires the use of a moderate energy β^- emitter as a radionuclide and a suitable polyaminophosphonic acid as a carrier molecule. Owing to its suitable decay characteristics [T1/2 = 6.73 d, Eβ(max) = 497 keV, Eγ = 113 keV (6.4%), 208 keV (11%)] as well as the feasibility of large-scale production inadequate specific activity and radionuclidic purity using a moderate flux reactor, ^{177}Lu could be considered as a promising radionuclide for palliative care in painful bone metastases. Therefore, the present study is oriented toward the comparison of the ^{177}Lu complex of ethylene diamine tetramethylene phosphonic acid (EDTMP) in various models and ^{153}Sm-EDTMP in therapy [1].

^{153}Sm is a radionuclide emitting beta radiation with an average energy of 0.223 MeV and accompanying gamma radiation with an energy of 103 Kev (yield 29 %). The half-life of ^{153}Sm is 46.3 hours, which imposes territorial restrictions. That is, the production of the radionuclide, the preparation of the drug and therapy should be carried out in a very short time. In North America, the drug ^{153}Sm-EDTMP (ethylene diamine tetramethylene phosphonate) has been available for therapy since 1997 [2]. Since the use of this drug is possible with any kind of cancer which is accompanied by bone metastases, the potential market for radiopharmaceuticals is very large. ^{153}Sm-oxabiphore is a drug used presently in Russia for the treatment of bone lesions – similar to the foreign ^{153}Sm-EDTMP. This complex is concentrated in the skeleton in proportion to osteoblastic activity. Pathological foci, where the accumulation is intense, can be visualized using the gamma camera, which enables the scintigraphy of a patient and monitoring of the treatment process. The drug is very quickly excreted from the blood. 0.5-3 hours after intravenous injection only 1 % of the drug remains in the blood. It is excreted from the urine almost completely after 6 hours [3–5]. The behavior of the whole drug in the body is affected by the nature of the ligand distribution, and the

* h.m.zakaly@gmail.com

radionuclide in the complex serves either for the treatment of the disease or for diagnosis. The distribution of the ligand EDTMP is identical to the distribution of other complexes, isotropic to the bone tissue, for example methylene diphosphonate (MDP) [2,3,6]. Nowadays, methylene diphosphonate labeled with radionuclide ^{99m}Tc is used for the diagnosis of bone anomalies. Due to the gamma radiation emitted by the ^{99m}Tc radionuclide, health care professionals can assess bone metabolism in detail and track where the drug accumulates the most, allowing for the therapy to be planned if necessary.

The purpose of this paper is to assess and examine the effect of the drug carrier EDTMP (i.e. ethylene diamine tetramethylene phosphonate) on the ionic form of ^{177}Lu and ^{153}Sm. Even in ionic form, the distribution of ^{177}Lu is better than the distribution of ^{153}Sm being more absorbed in the bone surface, red bone marrow, and kidney with low absorption in life.

2. Materials and methods

The specialized package WinAct is developed in Oakridge laboratory [7] and it is intended for the assessment of the dynamics of the behavior of radionuclides in an organism. A biokinetic model of the drug EDTMP taking into account the conversion is presented in Figure 1. This model can be used for EDTMP labeled with ^{177}Lu or ^{153}Sm. Each rectangle shown in the diagram, Figure 1, corresponds to a linear differential equation of the first order, which is included in the general system of equations. Writing and solving such a system of equations for ^{177}Lu and ^{153}Sm takes a long time. The WinAct package is a specialized package for solving such systems [8,9].

The initial text block in the file is a comment block. For structuring the original design of the file into parts special words-separators are used. These words are the delimiters and are always typed in all uppercase letters. The activity distribution for ^{177}Lu and ^{153}Sm in ionic forms, ^{177}Lu-EDTMP and ^{153}Sm-EDTMP in different organs based on the model in Figure 1 are calculated as shown in Figure 2. The calculation was prepared for the diagnostic pathological area of bone tissue at a patient. The values of the transition factors of the substance from blood to organs are determined on the basis of a number of studies, converted from biokinetics for mice according to human anatomy [1,8,10–12] and are presented in Table 1. The input files of the WinAct software package are created on the base of these results and compiled as shown in Figure 2.

From the output files, the leaves rate of a particular drug from the blood is estimated. This is an important indicator for minimizing dose loads on the body as a whole. In addition, the percentage of activity retention for the preparations of the pathological nidus and organs plays a major role in setting the restrictions for the magnitude of the input activity of the drug.

The main task is the comparison of drugs based on radionuclide ^{177}Lu and drugs that are currently used in medical practice for the treatment of bone metastases, such as ^{153}Sm-EDTMP. As it is noted above, phosphonates form very stable compounds with radionuclides from a number of rare earth elements, such as ^{177}Lu and ^{153}Sm. Based on this, the calculation takes into account that the solution is not more than a 1 % free radionuclide. Using the data mentioned above, the source files for ^{153}Sm are in combination with ethylene diamine tetramethylene phosphonate.

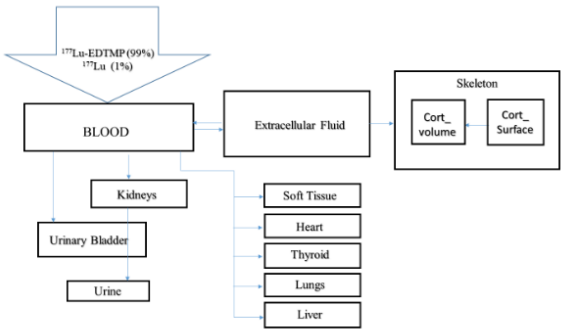

Figure 1. Biokinetic model of the drug ^{177}Lu-EDTMP or^{153}Sm-EDTMP taking into account the conversion

Table 1. Constant transition time between departments of osteotropic drug EDTMP

Path		Transition Rate K, Day^{-1}
From	To	
Blood	-> Ecf	134
Ecf	-> Blood	20.79
Ecf	-> Cort_Boone_Surf	10.39
Ecf	-> Trab_Boon_Surf	10.39
Blood	-> UB_Cont	16.03
Blood	->Soft Tissue	$3.01\ 10^{-1}$
Blood	-> Spleen	$5.20\ 10^{-2}$
Blood	-> Heart	$1.10\ 10^{-2}$
Blood	->Lungs	$3.84\ 10^{-2}$
Blood	-> Liver	$9.04\ 10^{-2}$
Blood	-> Kidneys	$1.12\ 10^{-1}$
Soft Tissue	-> Blood	$1.42\ 10^{-2}$
Spleen	-> Blood	$1.80\ 10^{-2}$
Heart	-> Blood	$7.95\ 10^{-2}$
Lungs	-> Blood	$2.21\ 10^{-2}$
Liver	-> Blood	$7.36\ 10^{-3}$
Kidneys	-> UB_Cont	$5.47\ 10^{-2}$

When using a drug based on radionuclide and a therapeutic agent, the dynamics of behavior in a body completely depends on the carrier. That is, the calculation files for the drug ^{177}Lu-EDTMP and ^{153}Sm-EDTMP are absolutely similar, except for the half-life of the radionuclide. In addition, in the process of further calculation the presence of the 1% free radionuclide in the solution will be taken into account, biokinetic data for which are not the same. A number of studies showed that the radiochemical resistance of drugs is not less than 99 %. Therefore, the free radionuclide ^{177}Lu in each solution will be taken into account separately in the calculations.

WinAct generates three output files and an information file with an extension ".log", which basically duplicates the input data. All files received as a result of the program are located in the \output folder. The file extension ".act" contains information on the activity contained in an organ or tissue as a function of the time since the beginning of the nuclide intake. It is this file that was used to plot the dependence of the activity retention on time after the administration of the drug. The file extension ".ext" contains data on the rate of excretion of the nuclide from urine and feces (1/day)

as a function of time. Additionally, the file tabulates data on the retention of the nuclide in the lungs and in the body as a function of time. The file with the extension ".u50" contains data on the number of nuclear transformations in a particular organ or tissue.

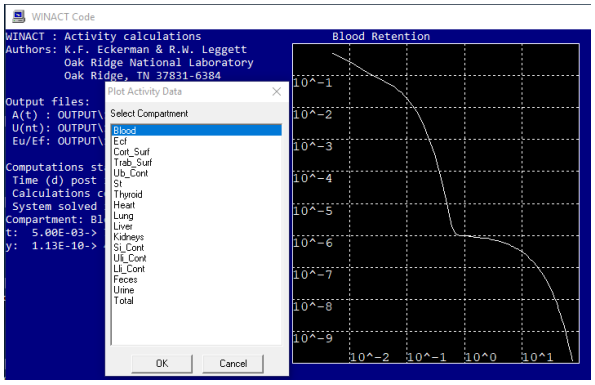

Figure 2. The input file of WinACt

The output results from the WinAct program are used as the input data for IDAC 2.1 software, an internal dosimetry program for nuclear medicine based on the ICRP adult reference voxel phantoms [13,14,15], IDAC 2.1 software was used for dose calculations in organs and tissues. As a result, the absorbed doses of the organs and tissues are estimated.

3. Results and Discussion

To assess the level of radiation exposure risk to a patient due to radiopharmaceutical use, absorbed doses were calculated for the organs wherein the labeled complex accumulates to the greatest extent, namely, the kidneys, ECF, skeleton, spleen, heart, lungs, and liver. Since the ^{177}Lu and ^{135}Sm isotopes decay by emitting beta and gamma rays, it was also necessary to calculate the absorbed doses in the adjacent organs (targeted organ), which received radiation from the source organs. In connection to this, the doses in the lungs from the radionuclide in the liver, as well as the doses in the gonads from the contents of the bladder, were calculated as the most closely related organs. The injection was administered directly into the blood, which circulates throughout the body and to a large extent, in the lungs. The absorbed dose was assessed. Additionally, the contribution to the lungs, red bone marrow, and gonads from the source such as "other organs and tissues" was assessed. The results showed that for the rest of the internal organs, the contribution to the dose was smaller than for the listed organs by one or two orders of magnitude, so a detailed calculation of the doses was not performed for them.

Figures 3 and 4 refer to the time-activity curves of the radiopharmaceutical as fitted by WinAct. The figures show the behavior of fractional activity retention in different organs with ^{177}Lu and ^{153}Sm in Ionic form and when labeled with EDTMP. The pharmaceuticals in ionic form were removed from the blood more slowly than when labeled with EDTMP, which points to the advantages of using ^{177}Lu-EDTMP instead of ionic form. The largest amount of activity was cumulated in bone surface and a small amount was cumulated in other organs in the case of ^{177}Lu-EDTMP, which means that ^{177}Lu-EDTMP is better than ^{135}Sm-EDTMP in the diagnosis of bone metastases diseases. In addition, a long period of removal from the bones indicates that it is also better in therapy.

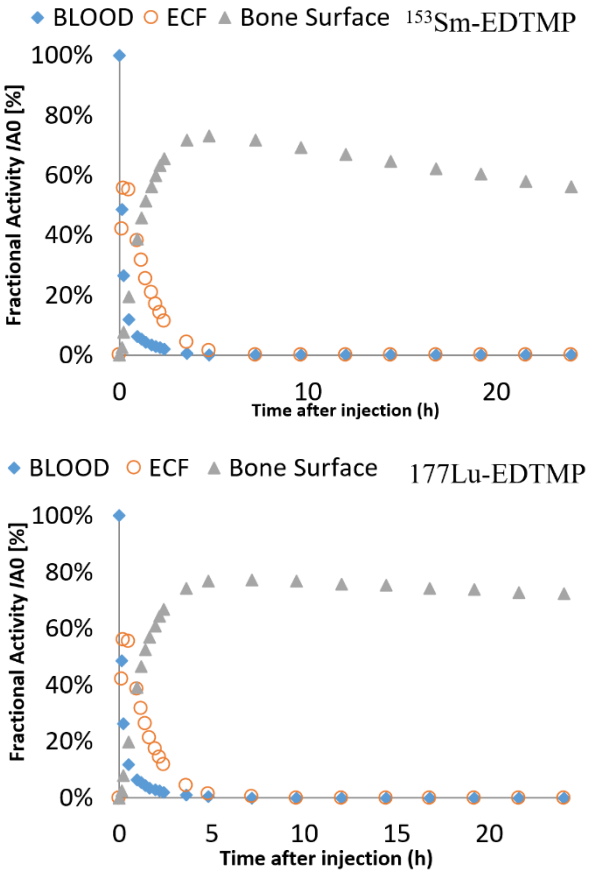

Figure 3. Distribution of activity in blood, ECF and bone surface of ^{177}Lu-EDTMPand ^{153}Sm-EDTMP

The peculiarity of this type of therapy is reasoned by the targeted action of the drug in the focus of the disease, a large dose is created and, very importantly, the dose load on healthy bone tissue, organs and tissues are minimized. The absorption in the bone tissue of a person with metastatic lesions of the skeleton depends on the degree of the disease, the general condition of the patient and many other factors. In the study, it is accepted that the absorption in the pathological area of bone tissue is 20% of the proportion of the substance deposited in a healthy skeleton.

Figure 5 shows the results of comparing a dose calculation conducted using the two drugs.

The ^{177}Lu-EDTMP absorbed dose is two times higher than ^{135}Sm-EDTMP with nearly the same effects on other organs. In addition, ^{177}Lu-EDTMP like ^{135}Sm-EDTMP does not deposit in the liver unlike the ionic forms. The ionic form of ^{177}Lu has the absorbed dose two times lower than the ^{135}Sm ionic form in the liver with a high absorbed dose in the endosteum and red bone marrow. The highest effective dose per administered activity is 0.242 mGy/MBq for ^{177}Lu-EDTMP, followed by 0.232 mGy/MBq for ^{153}Sm-ionic form, followed by 0.189 mGy/MBq for ^{177}Lu-ionic form and then 0.139 mGy/MBq for ^{153}sm-EDTMP.

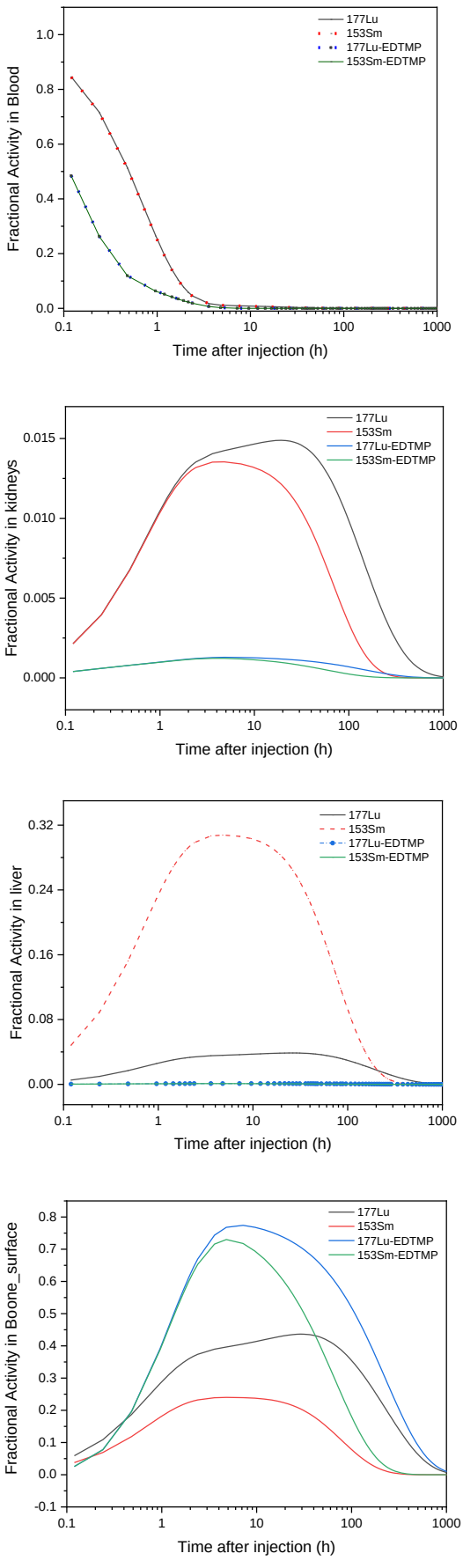

Figure 4. Fraction activities curves in blood and different organs for the three cases of interest

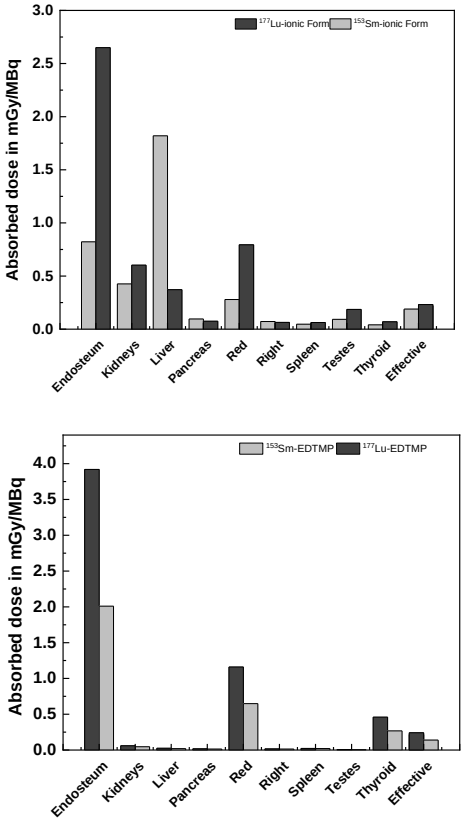

Figure 5. Absorbed Dose in (mGy/MBq) in different organs and tissues

4. Conclusion

- The comparison between the activity behavior and Dose Distribution in Different Organs for one Carrier, EDTMP, labeled with Lu-177 and 153Sm is presented.
- ^{177}Lu-EDTMP and ^{153}Sm- EDTMP are removed from the blood faster than an ionic form of ^{177}Lu and ^{153}Sm. It gives the opportunity to start to accumulate in the target organ with a short time.
- A clear effect of ^{177}Lu- EDTMP in the bone surface is observed compared to ^{153}Sm- EDTMP.
- ^{177}Lu- EDTMP shows fast accumulation and slow removal compared to ^{153}Sm- EDTMP in the distribution of activity in the bone surface.

All these advantages of ^{177}Lu-EDTMP lead to the conclusion that ^{177}Lu can be recommended for diagnosis and therapy instead of ^{153}Sm.

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