RESEARCH ARTICLE

Biokinetic Model Development of ^{177}Lu-labeled Methylene Diphosphonate as a Radiopharmaceutical Treatment

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Received: 02nd November, 2022; Revised: 20th November, 2022; Accepted: 12th December, 2022; Available Online: 25th December, 2022

ABSTRACT

^{177}Lu is a lanthanide radionuclide. In recent years, the possibility of applying a drug based on the ^{177}Lu radionuclide as a palliative treatment for bone metastases has increased. ^{177}Lu has many prospects in terms of its applications in nuclear medicine. The high-energy beta particles and the relatively short half-life of the radionuclide are used to provide an effective treatment. In this work, a comparison of organ and tissue doses is performed with two different drugs: ^{177}Lu in an ionic radionuclide form and ^{177}Lu labeled methylene diphosphonate (^{177}Lu-MDP). ^{177}Lu in an ionic form actively accumulates in the liver and bones. Phosphonate compounds form stable radio-labeled complexes. This suggests that ^{177}Lu-MDP is a non-dissociated form of the drug. The distribution and elimination of the drug occur according to the kinetics of the carrier, i.e., methylene diphosphonate. It is shown that the use of an osteotropic complex (describing any drug that is attracted to and targets bone) allows for the concentration of a large dose in pathological areas and minimizes damage to healthy organs and tissues.

Keywords: ^{177}Lu, Bone metastasis, Methylene diphosphonate (MDP), Palliative therapy, Radionuclide therapy, Radiopharmaceutical.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.4.52

How to cite this article: Zakaly HMH, Mostafa MYA, Zhukovsky M, Biokinetic Model Development of ^{177}Lu-labeled Methylene Diphosphonate as a Radiopharmaceutical Treatment. International Journal of Drug Delivery Technology. 2022;12(4):1802-1807.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Today, there is an acute problem of ensuring public health against cancer. Cancer affects children and people of working and reproductive age. The percentage of people diagnosed with analogous diseases is growing from year to year. The impact of ionizing radiation is recognized as the most effective method for both the diagnosis and treatment of cancer. The long history of the clinical use of radiation in treating malignant tumors proves this fact. Radiation therapy is preferred in 70–80% of all cancer cases. Today, it is possible to predict with mathematical models and software packages the probability of tumor resorption after exposure to ionizing radiation and the occurrence of radiation complications, as well as to evaluate the biological effects of doses of radiation.[1]

In modern medicine, radiation therapy is a very promising field. In this kind of therapy, the patient, intravenously, orally or *via* inhalation, takes a radioactive drug that affects the pathological state. This is due to a unique chemical compound (the number of acids, monoclonal antibodies, etc.) that targets and destroys malignant cells *via* local irradiation.[2]

However, most known malignant tumors metastasize on the bone and the priority of malignant tumor therapy is not available. Bone metastases are considered complicated cancer types. Their appearance is due to the fact that cancer cells get into the bloodstream, accumulate on bone structures and reproduce inside them. In the presence of multiple metastases in a patient, improving their quality of life is of paramount importance. Traditional methods cannot provide this, so patients are subjected to palliative care to relieve pain.[3]

Undoubtedly, the development of palliative radionuclide therapy in medical practice is necessary. Therefore, the development of new complexes that effectively treat pathological areas in bone tissue is required. Considering exclusively the issue of pain suppression in bone metastases, it is advisable to use osteotropic radiopharmaceuticals containing β-emitting radionuclides.[4-8]

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Due to its various properties, the ^{177}Lu radionuclide is considered one of the most promising radionuclides for therapy and diagnosis. This study aims to develop a biokinetic model of a drug for the palliative treatment of bone metastases and to calculate dose loads for its application. To assess the effectiveness of the complex, a comparison of dose loads of this radionuclide in an ionic form and in combination with MDP on the pathological areas and healthy tissues will be carried out. The action of the drug is based on β-radiation of the ^{177}Lu radionuclide and an osteotropic methylene diphosphonate complex. This combination will reduce the dose load on critical organs because of the rapid delivery of the drug to the pathological area of the bone tissue.

Foundations for the Application of ^{177}Lu in Radionuclide Therapy

The most promising therapeutic agents in radionuclide therapy are short-lived radionuclides such as ^{90}Y, ^{153}Sm, ^{177}Lu, and others. Charged particles resulting from the collapse of these radionuclides possess high energy with a short run-in substance. In this case, there is a sufficient number of α-and β-emitters in the immediate vicinity of tumor cells to ensure their destruction with minimal damage to the surrounding tissues[9,10]

An important feature of lutetium's kinetics is that due to its low penetration range into tissues, it is effective in the treatment of small lesions and minimizes the impact of therapeutic doses on remote cells. ^{177}Lu is a beta-emitting radionuclide with an energy of 0.49 MeV and a half-life of 6.6 days (161 h). The range of these beta particles in tissues smaller than 2 mm gives them the ability to irradiate malignant tissue cells.[11]

Usually, large tumors can be removed surgically, but residual malignant cells are dangerous to human health. Therefore, such cells are often considered as the most suitable target for radiotherapy. In this case, nuclides emitting β-particles of low energy, such as ^{177} Lu are considered to be the most promising. In addition, ^{177} Lu is a radionuclide that, along with beta particles, emits low energy γ-radiation at 112 and 208 Kev, with an intensity of 6.4 and 11%, respectively. This allows for scintigraphy of areas of interest to be conducted during therapy. The spectrum of ^{177} Lu beta-particles provides better irradiation of small tumors when compared to the higher-energy radiation of ^{90}Y, which is successfully used for the uniform irradiation of large tumors.[12]

It is known that in lanthanides, deposition in the liver decreases significantly, while the accumulation of radionuclides in bone tissue increases with an increase in the atomic number and a decrease in the ion radius of the element. This property as it is impossible, by the way for the case considered in work. The radionuclide ^{177}Lu can be safely attributed to the osteotropic. As this paper considers the prospects of using this radionuclide for pain relief in bone metastases, a high proportion of depositions in bone tissue increases the value of ^{177}Lu.[13] 2007

In order to build a biokinetic model for radiopharmaceuticals, it is necessary to know the kinetics of the carrier. The carrier (a ligand) is a compound that defines the vector of the drug's distribution. In radionuclide therapy, ligands can be various acids, peptides, and hormones. The carrier determines the path that the radionuclide-labeled complex will follow.[7]

The literature on radiopharmaceuticals currently used for the palliative therapy of bone metastases was analyzed. The radionuclide^{153} Sm is used to produce radiopharmaceuticals actively used to relieve pain in bone metastases of the skeleton.^{89} Sr is the second radionuclide representative among osteotropic radionuclides. For the diagnosis of bone diseases, phosphate and phosphate complexes labeled with the radionuclide ^{99m} Tc are used in some cases. In humans and animals, these compounds are natural regulators of the formation and decay of mineralized tissues. They also prevent the dissolution of hydroxyapatite: by being included in it, they stabilize its structure. Based on the known data on the kinetics of some phosphate complexes, we consider methylene diphosphonate (MDP). MDP is an osteotropic complex used as a carrier for bone scintigraphy. The accumulation of this drug begins immediately after intravenous administration. An hour later, the skeleton accumulates more than 30% of the administered activity, which indicates an effective treatment of bone anomalies.[14]

Thus, it is interesting to consider how the dose loads on healthy organs and tissues will change when using a phosphate complex of methylene diphosphonate and the ^{177}Lu radionuclide in an ionic form. In the following work, a comparison of absorbed doses in the critical organs of a healthy person and a patient with a bone abnormality will also be made.

METHODOLOGY

To assess the dose load correctly and understand how the radiation damage occurs in organs, the patterns of distribution, exchange and deposition of a radionuclide is necessary to be known. The biokinetic model ^{177} Lu radionuclide dynamics in an ionic form is created by Taylor and Leggett. In such case, the radionuclide is deposited in the liver and bone tissue.

The dynamics data of an osteotropic complex of methylene diphosphonate labeled with the radionuclide ^{99m}Tc behavior are presented in Table 1[15] in the publication of International Commission on radiation protection (ICRP) as transfer coefficients (d^{-1}) for lanthanide models; and ^{177} Lu data have not been found,[8,16] including biokinetic models, biokinetic data, dose coefficients for organ and tissue absorbed doses, and effective dose for major radiopharmaceuticals based on the radiation protection guidance given in publication 60 (ICRP, 1991. The transition coefficients (time constants) are similar for all radionuclides and independent on the accumulation and excretion proportion. The transition coefficients not depend on the properties of the radionuclides itself but on the properties of the carrier (a phosphate complex) that they are attached. In the present case, the values of ^{99m} Tc with MDP are used for ^{177} Lu with MDP for the dynamics scheme in the body.

There are two permanent excretions for the phosphate complex. Therefore, the radionuclide is eliminated from the body by two constant times.

Table 1: Biokinetic data for ^{99m}Tc-labelled phosphates and phosphonate[16] including biokinetic models, biokinetic data, dose coefficients for organ and tissue absorbed doses, and effective dose for major radiopharmaceuticals based on the radiation protection guidance given in Publication 60(ICRP, 1991

Organs	*The proportion of distribution in the organ or tissue*	*Biological half-life (h)*	*Elimination rate*
Bone	0.5	2 72	0.3 0.7
Kidney	0.02	0.5 2.0 72	0.3 0.3 0.04

Table 2: Dose loads on organs and the pathological site of the patients with and without bone abnormalities, mGy/MBq (the mass of the pathological site is accepted as equal to 20 g).

Organs	*^{177}Lu in ionic form (without pathology)*	*^{177}Lu-MDP (without pathology)*	*^{177}Lu in ionic form (with pathology)*	*^{177}Lu-MDP (with pathology)*
Soft tissue	$3.58\ 10^{-1}$	$7.49\ 10^{-3}$	$3.41\ 10^{-1}$	$6.79\ 10^{-3}$
Kidney	2.17	$7.88\ 10^{-1}$	2.07	$6.83\ 10^{-1}$
Liver	1.14	$1.53\ 10^{-2}$	1.09	$1.42\ 10^{-2}$
Red bone	$9.66\ 10^{-2}$	$9.66\ 10^{-4}$	$9.20\ 10^{-2}$	$9.20\ 10^{-4}$
Cort. bone surface	86	18	82	1.70
Trab. bone surface	66	46	62	40
Pathological area	-	-	123	350

The high radiochemical stability of phosphate and phosphate complexes is one of advantage to use.[14] In particular, the ^{177}Lu radionuclide binds to the MDP, ^{177}Lu-MDP, complex actively and remains for a very long time with radiochemical stability of at least 99%[17] a therapeutic radionuclide tagged with a bone seeking ligand is required, while for radiation synovectomy (RS. Figure 1 presents the drug distribution scheme. In this scheme model, the distribution and excretion of 99% of the ^{177}Lu-MDP activity follows the carrier model; only 1% of the activity follows the kinetics of an ionic form of the ^{177}Lu radionuclide.

The biokinetic models were introduced into a WinAct software package. WinAct is a specialized package developed in the US Oak Ridge laboratory that is designed to assess the behavior dynamics of the radionuclides in the body[18,19] an internal dosimetry program for nuclear medicine based on the International Commission on Radiological Protection (ICRP. Each part shown in the biokinetic model diagram belong to a linear differential equation with first order that is included in a general equations system. The solving of such systems of equations for ^{177}Lu radionuclide needs a long time. Therefore, the use of WinAct package is specialized to solve such systems with more accurate and suitable time.[7]

RESULTS AND DISCUSSIONS

Calculation of Radiation Doses of ^{177}Lu as Radiotherapy

The dynamic behavior of radionuclides in the body are estimated with WinAct's program. The output data of WinAct that is necessary for the construction of activity retention curves in healthy organs and the pathological focus of bone tissue in case of ^{177}Lu-MDP are obtained and presented in Figures (2-5).

To reduce the radiation effects on healthy organs and tissues, it is important that the radiopharmathutical quickly leaves the blood system, then followed into the pathological area or excreted through the kidneys. Figure 3 explains that the ^{177}Lu-MDP, as a stable radiopharmathutical, is retained from the blood with a smaller amount.

The pathological area of bone tissue is not a universal structure. Absorption into bone metastases depends on many factors, such as the stage of the disease. In cancer of the first degree of severity, it is proposed to calculate the absorption in the range from 15 to 25%.[2,20,21] In this work, a variant when absorption in the pathological focus of the bone tissue is 20% of the absorption in a healthy person's bone tissue is supposed.

Retention of ^{177}Lu in an ionic form and the drug ^{177}Lu-MDP in the cortical and trabecular bone surfaces in the pathological focus of a patient with bone abnormalities is presented in Figure 6. In the presence of the drug ^{177}Lu-MDP, the trabecular bone surface absorbed the most activity compared to the cortical bone surface. These results mean that the drug is more effective than the ionic form when the activity is distributed equally between the trabecular and cortical bone surfaces.

Next, it is necessary to consider the retention in critical organs (that is, in the organs most sensitive to radiation). These organs include the kidneys and liver. The use of a phosphate complex significantly reduces the activity in the kidneys and liver. Consequently, the time during which there is an impact on the body also decreases. In the pathological area (where increased bone metabolism is present), the value of the retained activity of the drug ^{177}Lu-MDP exceeds the retention when using the radionuclide in an ionic form. This suggests that the area of localization of the bone metastases will have significant and prolonged exposure to beta radiation.

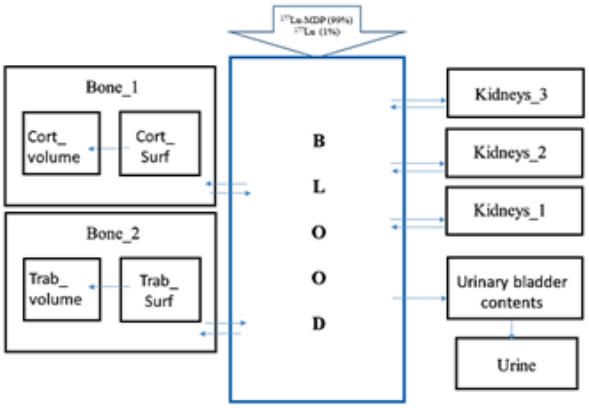

Figure 1: ^{177}Lu-MDP biokinetic model.

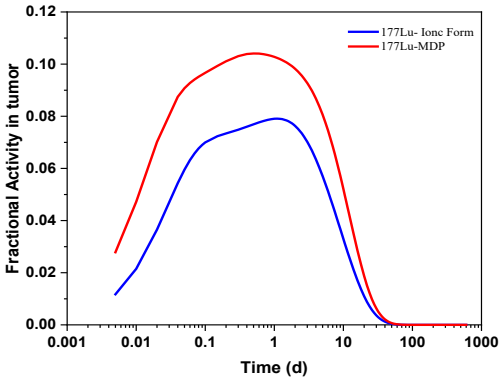

Figure 4: Retention of ^{177}Lu in an ionic form and ^{177}Lu-MDP in the urinary & fecal excretion rates (/d) as a function of time (d).

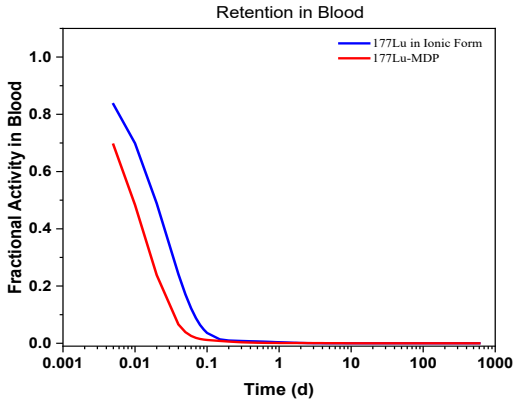

Figure 2: Retention of ^{177}Lu in an ionic form and ^{177}Lu-MDP in the blood

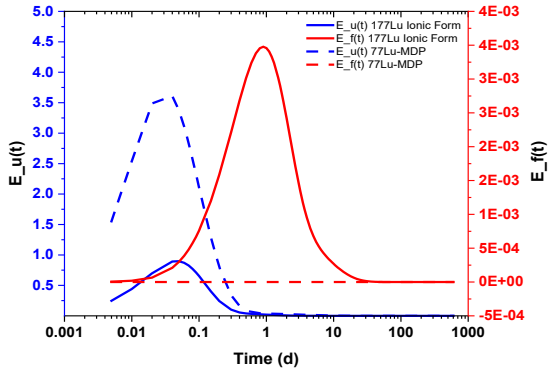

Figure 5: Retention of ^{177}Lu in an ionic form and ^{177}Lu-MDP in the tumor.

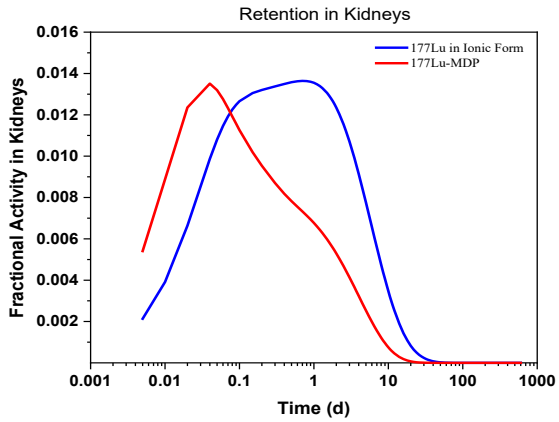

Figure 3: Retention of ^{177}Lu in an ionic form and ^{177}Lu-MDP in the kidneys of a patient with bone abnormalities.

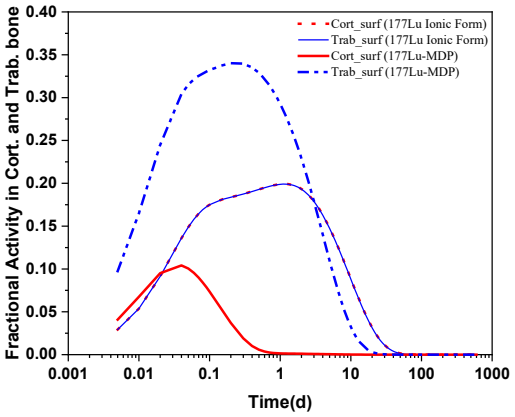

Figure 6: Retention of ^{177}Lu in an ionic form and the drug ^{177}Lu-MDP in the cortical and trabecular bone surfaces in the pathological focus of a patient with bone abnormalities.

In order to assess the risk of the patient's radiation exposure from the radiopharmaceutical, we calculate the absorbed doses for each organ where the radioactive label is deposited to a greater extent, namely, in the kidneys, red bone marrow and liver. Since the ^{177}Lu isotope decays with gamma radiation, it is also necessary to calculate the absorbed doses of neighboring target organs, irradiated by the source organ, with two methods: firstly, through eqs. 1 and 2 and, secondly, with IDAC2.1 software[22,23]the estimated radiation-absorbed dose to organs and tissues in patients undergoing diagnostic examinations in nuclear medicine is derived *via* calculations based on models of the human body and the biokinetic behaviour of the radiopharmaceutical. An internal dosimetry

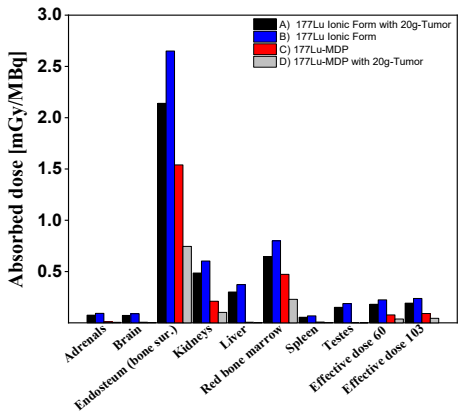

Figure 7: Absorbed dose in mGy/MBq (IDAC2.1) of ^{177}Lu in an ionic form and ^{177}Lu-MDP in two cases with and without a pathological focus in a patient with abnormalities.

computer program, IDAC-Dose2.1, was developed based on the International Commission on Radiological Protection (ICRP.

The general formula for calculating the absorbed dose of an organ or tissue irradiated with ^{177}Lu in an ionic form or the finished radiopharmaceutical ^{177}Lu-MDP (at 1 Bq) is:

$$D_{organ} = N\left(\frac{E_{cp}(\beta)n(\beta)}{m_{organ}} + (E_1(\gamma)n_1(\gamma)SAF_1 + E_2(\gamma)n_2(\gamma)SAF_2)\right), \quad (1)$$

where N is the number of decays in the source organ by 1 Bq; E is the energy of the emitted particle, j; n is the fraction of radiation; M_{organ} is the mass, kg;[24] and SAF (specific absorbed fraction) is the reference data.[25]

When calculating the absorbed dose in red bone marrow and on the surface of bone tissue, self-absorption should be considered as follows:

$$D_{rbm} = N \cdot УЭЭ(T \leftarrow S) = \frac{1}{m_{organ}}\sum_i E_{cp}(\beta)n(\beta) \cdot AF(T \leftarrow S), \quad (2)$$

where AF (T→S) is the fraction of beta - radiation energy that will be absorbed in the target organ, T, upon the decay of the radionuclide in the source organ, S.[25]

The calculation results are given in Table 2. It presents the values of absorbed doses in organs and tissues with the introduction of the radionuclide in an ionic form and with the introduction of the radiopharmaceutical ^{177}Lu-MDP.

It is can be clearly seen that with the introduction of the drug ^{177}Lu-MDP, the absorbed doses in the organs and tissues of a healthy person are much lower in comparison with the absorbed doses after the introduction of the radionuclide in an ionic form. It is necessary to consider the data obtained under the assumption that the patient has a pathological area of bone abnormality. The absorbed dose in the pathological focus when using the radiopharmaceutical exceeds the absorbed dose from radiation-free ^{177} Lu more than 2 times. It can also be noted that in the presence of a pathological area, the absorbed doses in healthy organs are reduced (Table 2 and Figure 7). This is an advantage to this type of therapy.

CONCLUSION

The aim of this article was to compare the dose loads on the organs and tissues of a healthy and sick person after the introduction of the ^{177}Lu radionuclide in an ionic form and the radiopharmaceutical ^{177}Lu-MDP in cases of bone metastases. For this purpose, palliative therapy drugs for bone metastases that are used in modern medical practice were analyzed. A biokinetic model was developed for a methylene diphosphonate complex with an established pattern of behavior in the human body and the ^{177}Lu radionuclide. The absorbed doses in a healthy person's critical organs and soft tissues and in the presence of a pathological area of bone tissue were calculated. It has been shown that by creating the sustainable ^{177}Lu-MDP drug, it is possible to significantly reduce the burden on healthy organs and tissues and to increase the effect on pathological cells. ^{177}Lu-MDP reduced the absorbed dose in the healthy organs ten times compared to the ionic form of ^{177}Lu. The calculation results fully justify the use of a methylene diphosphonate phosphate complex labeled with the radionuclide ^{177}Lu.

Compliance with Ethical Standards

The author declares that they have no conflict of interest.

Ethical Approval

This article does not contain any studies with human participants performed. This article does not contain any studies with animals performed by any of the authors.

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