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Original research article

Modeling the time dependent distribution of a new ^{153}Sm complex for targeted radiotherapy purpose

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ABSTRACT

Background: For radioimmunotherapy purposes, a chemical complex with high absorption in cancer tumor is required. New chemicals are to be examined for their concentration in tumor and healthy organs. These are labeled with β-emitting radioisotopes to irradiate the tumor while deposited inside it.

Aim: To study the capability of recently developed chemical complex in targeting cancer tumor and investigate the distribution of ^{153}Sm-TPTTC in rat organs as function of time.

Materials and methods: The chemical complex – [*Tris*(1,10-phenanthroline)Samarium(III)] trithiocyanate was prepared and labeled with ^{153}Sm radioisotope. The labeled complex was injected to a population of tumor bearing mice. In 2, 4, 24, 48, 96 h after injection the animals were sacrificed and the concentration of Samarium complex was measured in various organs such as blood, heart, intestine, colon, liver, spleen, kidney, sternum and bone.

Results: The concentration of the radiopharmaceutical in various organs was measured at different times. The temporal behavior of biodistribution of ^{153}Sm-TPTTC was modeled and drawn as function of time.

Conclusion: It is shown that ^{153}Sm-TPTTC is concentrated in tumor tissue and liver much more than in other organs. The variation of pharmaceutical concentration in all organs is described with summation of eight exponential terms and it approximates our experimental data with precision better than 2%.

1. Background

Targeted radiotherapy has been developing over past two decades.[1,2] In this method, a major proportion of radiation is delivered directly to the cancerous tumor by biological means. The chemical compound with high deposition in tumor is labeled with a beta emitter radioisotope. The high LET (linear energy transfer) of beta particle leads to destruction of cancer cells while the radioisotope is concentrated inside the tumor. The short range of beta particle spares the healthy tissue surrounding the tumor and the major proportion of the radiation dose is absorbed by the tumor.

Among beta emitting radioisotopes is ^{153}Sm with half-life of 46.8 h. Emitted beta ray energies and their abundances are 640 keV (30%), 710 keV (50%), and 810 keV (20%), respectively. Average beta ray energy of 290 keV renders the penetration depth of 3 mm in soft tissue, making it a good candidate for

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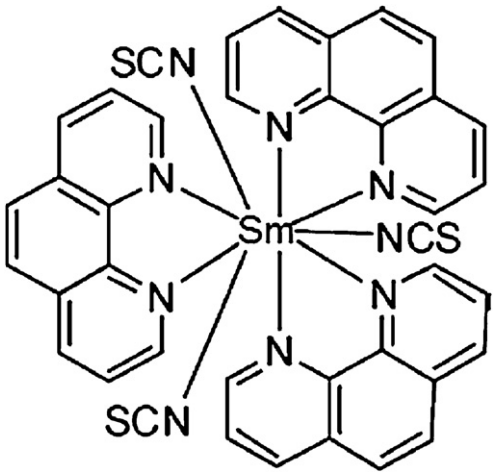

Fig. 1 – Molecular view from Sm-153 complex [*Tris*(1,10-phenanthroline)Samarium(III)] trithiocyanate known as Sm-TPTTC.

application in targeted radiotherapy. Besides beta ray, ^{153}Sm emits gamma radiation and conversion electrons with 103 keV and 55 keV energies, respectively.[3] Gamma ray at this energy range makes nuclear imaging feasible, while the process of radiotherapy is carried out. Finally, ^{153}Sm decays to stable nuclide ^{153}Eu.

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.[4]

Sm-EDTMP has already been produced in our laboratory.[5] In this work, ^{153}Sm-[*Tris*(1,10-phenanthroline)Samarium(III)] trithiocyanate (^{153}Sm-TPTTC) was developed for possible therapeutic applications (Fig. 1) and the variation of its concentration with time in important organs is shown.

3. Materials and methods

3.1. *Radionuclide production*

Stable Samarium, ^{152}Sm, is a Lanthanide with high absorption cross section for thermal neutrons (204 barns) leading to production of ^{153}Sm. The radionuclide was prepared in a research reactor according to regular methods with a specific activity of 350 mCi/mg for radiolabeling use. The radioisotope was dissolved in acidic media as a starting sample and was further diluted and evaporated to obtain the desired pH and volume followed by sterile filtering. Gamma-ray spectrum revealed the presence of ^{154}Eu ($<4.7 \times 10^{-5}$% of ^{153}Sm) and ^{155}Eu ($<2.4 \times 10^{-5}$% of ^{153}Sm) at the end of irradiation.

Radiochemical impurities in the ^{153}Sm sample in the radiolabeling step were checked by two systems. As stationary phase for paper chromatography system, Whatman 2 mm paper was utilized.[6] In 10% ammonium acetate:methanol, the free Samarium cation in $^{153}Sm^{3+}$ form remains at the origin ($R_f = 0.0$), while other ^{153}Sm species migrate to higher ($R_f = 0.8$). Another agent for Sm^{3+} detection was 10 mM DTPA aqueous solution at pH 4 ($R_f = 0.8$).

3.2. *Biodistribution of ^{153}Sm-TPTTC in tumor bearing mice*

The first stage in examining a new pharmaceutical is to study its behavior and effects in the body of a mouse or rat. Due to physiological resemblance between rat and human, the distribution of drugs in a rat body is a good indicator of phenomena appearing in a human body. Thus, the information collected by animal experiments would be applicable for development of pharmaceuticals for human.[6]

In the present study, the biological distribution of newly developed Sm-TPTTC complex in healthy and tumor bearing rats was evaluated.

Fibrosarcoma cells (about 10^4) were injected s.c. to the dorsal area of Balb/C mice weighing 15–20 g. The distribution of $^{153}SmCl_3$ and ^{153}Sm-TPTTC among tissues were determined for untreated mice and for mice with Fibrosarcoma. Briefly, a volume (0.1 ml) of final ^{153}Sm-TPTTC solution containing ($3.5–3.8 \times 10^6$ Bq) radioactivity was injected intravenously into the dorsal tail vein. The animals were sacrificed at the exact time (2, 4, 24, 48, 96 h) after injection and specific activities of different organs were measured as percentage of injected dose per gram of tissue using HPGe detector (%ID/g). The animals were sacrificed by asyxphycation at selected times after injection, the tissues were weighed and their specific activities were determined with scintillation detectors as percentage of injected dose per gram of tissues.

The total amount of radioactivity injected into each mouse was measured by counting 1-ml syringe before and after injection in a radiometer with a fixed geometry. ^{153}Sm-TPTTC was prepared in two steps. At first, $^{153}SmCl_3$ was produced by neutron irradiation of an enriched ^{152}Sm sample in a research nuclear reactor. Biodistribution studies of the complex in wild-type rats and tumor bearing mice were also determined. The radiolabeled complex was prepared in high radiochemical purity (>99% precipitation method) and specific activity of 278 GBq/mmol and demonstrated significant stability at 4, 25 and 37 °C (in the presence of human serum). Initial biodistribution data showed significant liver accumulation in wild-type rat and tumor accumulation in tumor bearing mice of the tracer in 48 h. The properties of ^{153}Sm-TPTTC products suggest an efficiently new liver accumulating therapeutic agent in order to overcome possible liver malignancies with the lowest toxicity.

4. Results

The activity concentration in each organ was measured with the use of detectors at specified time after injection. The results show variation with time which is depicted in Fig. 2. The compartmental model[7–10] 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.

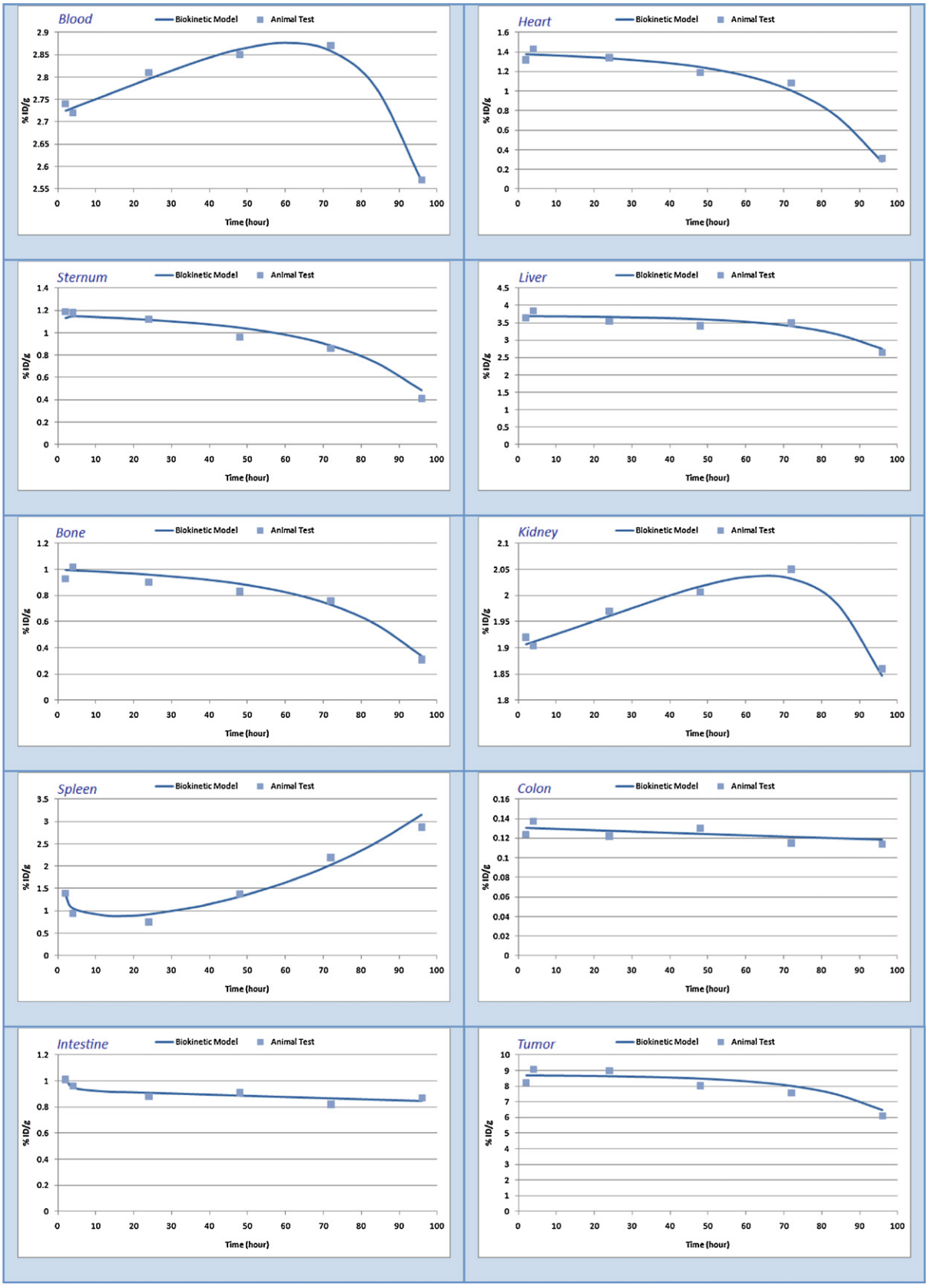

Fig. 2 – Temporal behavior of biodistribution of Sm-TPTTC in various organs of tumor-bearing mouse.

(1) Blood

$$f_1 = 2.6824\,e^{-1.64t} + (5.844E-5)\,e^{-0.06t} + (4.075E-2)\,e^{0.025t} - (4.7201E-2)\,e^{-5.04t} - (4.5559E-6)\,e^{-1.64t} - (5.1499E-6)\,e^{-0.14t} - (4.94E-3)\,e^{0.051t}$$

(2) Heart

$$f_2 = (9.512E-1)\,e^{-0.001t} + (4.408E-1)\,e^{-(9.9E-5)t} - (9.28E-3)\,e^{0.049t} - (4.118E-4)\,e^{-5.04t} - (4.0194E-4)\,e^{-1.64t} - (6.264E-4)\,e^{-0.14t} - (7.598E-4)\,e^{-0.06t}$$

(3) Sternum

$$f_3 = (8.736E-1)\,e^{-0.001t} + (3.172E-1)\,e^{-(9.9E-5)t} - (1.092E-2)\,e^{0.042t} - (4.212E-4)\,e^{-5.04t} - (5.09656836E-2)\,e^{-1.64t} - (5.616E-4)\,e^{-0.14t} - (2.5532E-3)\,e^{-0.06t}$$

(4) Liver

$$f_4 = (8.0444E-5)\,e^{-0.06t} + 3.6924\,e^{-(9.9E-5)t} - (6.80E-3)\,e^{0.051t} - (6.4974E-2)\,e^{-5.04t} - (6.2968E-6)\,e^{-1.64t} - (7.089E-6)\,e^{-0.14t}$$

(5) Bone

$$f_5 = (6.888E-1)\,e^{-0.001t} + (3.192E-1)\,e^{-(9.9E-5)t} - (1.26E-2)\,e^{0.04032t} - (2.982E-4)\,e^{-5.04t} - (2.9106E-5)\,e^{-1.64t} - (4.536E-4)\,e^{-0.14t} - (5.502E-3)\,e^{-0.06t}$$

(6) Kidney

$$f_6 = (4.090814E-5)\,e^{-0.06t} + 1.877694\,e^{(9.9E-5)t} + (2.85285E-2)\,e^{0.025t} - (3.9767E-3)\,e^{0.051t} - (3.375008E-6)\,e^{-1.64t} - (3.604965E-6)\,e^{-0.14t} - (3.321409E-1)\,e^{-5.04t}$$

(7) Spleen

$$f_7 = (6.61608E-2)\,e^{0.06t} + 5.95243\,e^{-1.64t} + (7.52477E-2)\,e^{-0.14t} + (4.9008E-1)\,e^{0.019t} + (5.7176E-1)\,e^{-0.091t} - 5.70739\,e^{-5.04t}$$

(8) Colon

$$f_8 = (2.752E-5)\,e^{-0.06t} + 0.1304\,e^{(-9.9E-4)t} + (1.568E-5)\,e^{-0.001t} - (2.272E-8)\,e^{-0.14t} - (1.48E-5)\,e^{-5.04t}$$

(9) Intestine

$$f_9 = (1.96424E-4)\,e^{-0.06t} + (9.3073E-1)\,e^{(-9.9E-4)t} + (1.11916E-4)\,e^{-0.001t} + (4.568E-1)\,e - 0.077t - (1.62164E-7)\,e^{-0.14t} - (1.05635E-4)\,e^{-5.04t}$$

(10) Tumor

$$f_{10} = (1.8928E-4)\,e^{-0.06t} + 8.688\,e^{(-9.9E-4)t} - (1.668E-5)\,e^{-0.14t} - (1.5288E-1)\,e^{-5.04t} - (1.4816E-5)\,e^{-1.64t} - (1.60E-2)\,e^{0.51t}$$

^{153}Sm-TPTTC imaging performed in the tumor-bearing mice showed a distinct accumulation of the radiotracer in the tumor, while in the first and second hour a background in the liver was absorbed (Fig. 2).

5. Discussion

Among many Samarium compounds, such as EDTA, DTPA, EDTMP, DTPMP, and HEDTA, Sm-153-EDTMP is proven to be a better choice in treatment of metastatic bone cancer[11,12] and is already been used in clinical practice. The criteria to choose this compound were its blood clearance, little concentration in other organs, and practical pain relief in cancer patients. ^{153}Sm was used for pain relief in patients with bone metastases. It was administered proportionally to body weight (37 MBq/kg) in 50 patients, 30 of them in combination with external beam radiation therapy. Complete pain relief was observed in 40% of patients, a more satisfactory figure compared with ^{89}Sr.[13]

Although considered as a negative effect in EDTMP, the remarkable concentration of TPTTC in the liver makes it a good candidate for treatment of liver cancer. The ID/g concentration of TPTTC in the liver is 3 times higher than that in bone. One disadvantage of ^{153}Sm-TPTTC is its slow blood clearance (Fig. 2). In such a case, drinking high amount of liquids is recommended for the patient.

6. Conclusion

Beta emitter radioisotope of a rare earth metal, Samarium, ^{153}Sm, can destroy cancer cells due to its radiation, if deposited inside the tumor. Using nuclear imaging techniques, it was shown that the labeled compound ^{153}Sm-TPTTC concentrates in tumor tissue and is a proper candidate for targeted radioimmunotherapy. Concentration of ^{153}Sm-TPTTC in important organs of tumor bearing mice was measured at time intervals of up to 96 h. It was concluded that its concentration depicts various behavior as function of time in different organs. In the blood, the concentration of radiopharmaceutical increases up to 60 h after injection and after that a sharp decrease is observed. In the heart, the variation is monotonically decreasing and the rate of decrement becomes faster at longer times after injection. The same trend is observed in the liver, sternum, bone and tumor, in the sternum and bone the fall-off region being more rapid than in others. Thus, radionuclide

concentration in tumor is desirably constant until 50 h after injection and decreases to 65% of initial value after 96 h. In the spleen, after a rapid decrease, a minimum is observed at $t = 15$ h after which the concentration curve tends to soar up to reach a level a few times higher than the initial one. Finally, it is concluded that ^{153}Sm-TPTTC might be considered in the future as a radiopharmaceutical for targeted radiotherapy of cancerous tissues located in the liver. For this purpose, more pre-clinical stages, such as rabbit experiment and human toxicity tests must be performed.

Conflict of interest

None declared.

Financial disclosure

None declared.

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