227Th-EDTMP: A potential therapeutic agent for bone metastasis

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^{227}Th-EDTMP: A potential therapeutic agent for bone metastasis

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Abstract

The biodistribution of ^{227}Th-EDTMP and retention of its daughter nuclide ^{223}Ra were examined. ^{227}Th-EDTMP was found to show high uptake and long-term retention in bone. The clearance of ^{227}Th-EDTMP from blood and soft tissues was rapid and the femur-to-tissue uptake ratios reached more than 100 within 30 min for all tissues except the kidney. Seven and 14 days after injection of ^{227}Th-EDTMP, the retention index of ^{223}Ra in bone showed high values, and the differences between these time points were not significant. Therefore, ^{227}Th-EDTMP is a potential radiotherapeutic agent for bone metastasis.

Keywords: α-particle emitter; ^{227}Th; EDTMP; bone metastasis; *in vivo* generator

1. Introduction

Most patients with advanced breast, prostate, or lung carcinoma develop bone metastases [1]. Bone metastasis causes severe pain, so there have been many attempts to develop curative treatment regimens. Various treatment methods, including analgesic therapy, external radiation therapy, hormonal therapy, chemotherapy, and surgical invention, have been used to improve responses, but many of these treatments are limited in their efficacy or duration and have significant side effects [2]. β-emitting radiopharmaceuticals for bone targeting, such as ^{32}P orthophosphate and ^{89}Sr chloride, have been used clinically for treatment of bone pain [2,3].

Although these β-emitters relieve bone pain associated with metastatic lesions in the skeleton, bone marrow toxicity limits use of high dose radiations to prevent tumor progression due to the long radiation range of β-particles. To overcome this drawback, clinical use of several low-energy β-emitters, including ^{153}Sm and ^{186}Re [4-6], and the conversion electron emitter ^{117m}Sn [7], have been examined. Among these radionuclides, ^{153}Sm complexed with ethylenediamine-tetramethylenephosphonic acid (EDTMP) has been approved for use in palliation of bone pain by the U.S. FDA.

Due to the high LET and short range of α-particles in tissue in comparison with β-particles, α-emitting nuclides are promising for the treatment of bone metastases. Reduction of bone marrow exposure can be achieved due to the short range of α-particles. A comparative study using bisphosphonates labeled with α-emitting ^{211}At and β-emitting ^{131}I indicated that the bone surface-to-bone marrow ratio was threefold higher with ^{211}At than with ^{131}I [8]. In addition to their physical properties (short range with high LET), many suitable α-emitting nuclides undergo successive α- and β-cascade disintegrations. These multiple α-emissions at tumor sites are more effective than single α-emission irradiation. In recent studies with α-emitting ^{233}Ra and β-emitting ^{89}Sr, dosimetry also indicated intense and highly localized radiation dose from ^{223}Ra and its progeny to the bone surface with substantially less irradiation of healthy bone marrow as

compared with β-emitting ^{89}Sr [9]. Moreover, only very small amounts of ^{211}Bi, the progeny nuclide of ^{223}Ra, redistributed from the sites of ^{223}Ra decay in the bone [9]. These results suggested the usefulness of cascade α-emission in the treatment of bone metastases.

Thorium-227 ($t_{1/2}$ = 18.72 d) is a promising α-emitting radiotherapeutic nuclide for treatment of bone metastases. It has a more suitable half-life for treatment of bone metastases as compared with other thorium isotopes, such as ^{232}Th ($t_{1/2} = 1.405 \times 10^{10}$ y) and ^{228}Th ($t_{1/2}$ = 1.9116 y). ^{227}Th belongs to the actinium series (Fig. 1), and emits α-particles with an average energy of 5.9 MeV decaying to ^{223}Ra. The daughter nuclide ^{223}Ra also decays to stable ^{207}Pb with emission of about 28 MeV. As the half-lives of ^{227}Th and ^{223}Ra ($t_{1/2}$ = 11.435 d) are similar, it will be possible to avoid the high-dose α-particles of ^{223}Ra and its progeny nuclides during the initial phase of renal clearance after administration of radioactive pure ^{227}Th. In addition, the radioactive growth of ^{223}Ra will prolong the effective irradiation duration. The relatively low energy γ-rays of ^{227}Th will be useful for imaging, and its daughter nuclide ^{223}Ra also emits γ-rays that are available for monitoring. The parent ^{227}Ac ($t_{1/2}$ = 21.773 y) has a long half-life so that ^{227}Th is available from the ^{227}Ac/^{227}Th generator system.

Although Th is a well-known bone-seeking element, it also accumulates in other tissues [10, 11]. However, Larsen *et al.* reported selective accumulation of thorium labeled bis- and polyphosphonate in bone [12]. ^{227}Th was complexed with the ligands diethylenetriamine-*N*,*N'*,*N''*-pentamethylene-phosphonic acid (DTPMP) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylenephosphonic acid (DOTMP), and it was shown to be retained on bone with high uptake ratios of bone-to-soft tissue compared to the acetate salt of ^{227}Th [12]. Although ^{227}Th-polyphosphonates were accumulated selectively in bone, retention of the daughter nuclide ^{223}Ra from ^{227}Th was not clear.

In this study, the biodistribution of ^{227}Th-EDTMP over a period of 14 days in mice was compared with that of ^{227}Th-citrate, and the retention of the daughter nuclide ^{223}Ra in bone was also examined. The potential of ^{227}Th-EDTMP as a therapeutic agent for bone metastasis is

discussed.

2. Materials and methods

2.1. ^{227}Th preparation

^{227}Th was separated from the parent nuclide ^{227}Ac by ion exchange chromatography using strong anion exchange material as described by Müller [13]. ^{227}Ac solution was obtained from the Oarai Branch, Institute for Materials Research, Tohoku University, and sufficiently reached equilibrium state with ^{227}Th and its daughter nuclides. The ^{227}Ac solution prepared in 7 M HNO_3 was loaded onto a 5 × 42 mm column containing Muromac AG1×8 anion exchange resin (Muromachi Technos Co., Ltd., Tokyo, Japan) pre-equilibrated with 7 M HNO_3. The column was washed with 15 mL of 7 M HNO_3 to remove the parent ^{227}Ac and daughter nuclides of ^{227}Th. After purification, ^{227}Th was eluted with 20 mL of 1 M HCl. The eluted ^{227}Th solution was evaporated to dryness, then re-dissolved in 7 M HNO_3 and prepared as a stock solution.

2.2. Preparation of ^{227}Th-EDTMP and ^{227}Th-citrate

EDTMP was purchased from Dojindo Laboratories (Kumamoto, Japan) and used without further purification. Before preparation to ^{227}Th-EDTMP, ^{227}Th solution was purified to remove ^{223}Ra and its daughter nuclides (^{223}Ra-free solution). ^{227}Th solution was finally prepared in 2 mL of 0.2 M HCl. The ^{227}Th solution was added to 0.21 mL of 0.2 M EDTMP in 0.2 M NaOH and heated for 5 min in boiling water after adjusting the pH to 6.6 with 1.45 mL of 1 M NaOH. Finally, pure water was added to adjust the solution to physiologically isosmotic concentration and 4.2 mL of the final ^{227}Th-EDTMP (10 mM EDTMP) solution was prepared. Radiochemical purity of ^{227}Th-EDTMP was determined using miniature paper chromatography [14] with 25%

acetone solvent prior to animal experiments.

^{227}Th-citrate was prepared by adding 1.8 mL of 3.02% (v/v) physiological sodium citrate solution to the purified ^{227}Th fraction.

2.3. Animals

Male ICR mice (n = 51, 7 weeks old, 35.3 ± 1.3 g) were purchased from Japan SLC, Inc. (Hamamatsu, Japan) and housed at the Kanazawa University Animal Experiment Facility. The mice were given certified diet and tap water *ad libitum*. Animal studies were conducted according to the Guidelines for the Care and Use of Laboratory Animals of Takara-machi Campus of Kanazawa University, and the experimental procedures were approved by the Committee on Animal Experimentation of Kanazawa University, Takara-machi Campus.

2.4. Biodistribution of ^{227}Th-EDTMP and ^{227}Th-citrate

Thirty-six mice were administered 100 μL of physiologically isosmotic ^{227}Th-EDTMP containing 60.3 kBq of ^{227}Th *via* the tail vain. Biodistribution was determined in three mice at each of 15 min, 30 min, 1 hr, 3 hr, 6 hr, 12 hr, 1 day, 3 days, 5 days, 7 days, 10 days, and 14 days post-administration. After sacrifice, the following 7 samples were collected from each mouse and weighed: femur, parietal bone, liver, kidney, spleen, lung, muscle, and whole blood.

Fifteen mice were administered 100 μL of physiological ^{227}Th-citrate (3.02% (v/v) sodium citrate) containing 37.2 kBq of ^{227}Th *via* the tail vain. Its biodistribution was determined in three mice at each of 15 min, 1 hr, 6 hr, 1 day, and 7 days post-administration. After sacrifice, the following samples were collected and weighed: femur, parietal bone, liver, kidney, spleen, lung, muscle, stomach, large intestine, small intestine, and whole blood.

The ^{227}Th radioactivity in each sample tissue was determined by γ-ray spectrometry using a

high purity Ge detector (EG&G ORTEC, Oak Ridge, TN, USA) coupled with a multi-channel analyzer, MCA-7800 (Seiko EG&G Co., Ltd., Tokyo, Japan). The most abundant 235.97 keV γ-ray was used for determination (Table 1). The results are expressed as percent injected dose per gram (%ID/g) of tissue.

2.5. Retention of ^{223}Ra generated from ^{227}Th in bone

To evaluate retention of ^{223}Ra generated from ^{227}Th in bone, γ-ray spectrometry was performed on femur samples obtained 7 and 14 days post-administration. The γ-ray spectrometry was performed on femur samples immediately after sacrifice to prevent radioactive growth of ^{223}Ra. The data thus obtained were compared with those of a standard ^{227}Th source prepared from ^{223}Ra-free solution. Analyses were performed using 235.97 keV γ-ray of ^{227}Th and 154.21 keV γ-ray of ^{223}Ra (Table 1). The standard source was measured in the same geometry as the femur sample to be consistent with γ-ray efficiency on Ge detectors. The retention based on relative counting rate (CR) of ^{227}Th and ^{223}Ra in samples *vs*. the standard was determined as (CR of ^{223}Ra in sample/CR of ^{227}Th in sample)/ (CR of ^{223}Ra in standard/CR of ^{227}Th in standard) [9].

3. Results

3.1. Complexation yield

The yield of the carrier free ^{227}Th-EDTMP complex was 99% of the total activity in the original solution.

3.2. Biodistribution of ^{227}Th-EDTMP and ^{227}Th-citrate

The biodistribution of ^{227}Th-EDTMP is summarized in Table 2. The results showed that the uptakes of ^{227}Th-EDTMP by bone were higher than those by other soft tissues. Femur and parietal bone uptake rates rapidly reached the maximum level at 30 min and remained at a constant level throughout the 14-day experimental period. On the other hand, soft tissues except the kidney showed uptakes of less than 1%ID/g at 15 min post-injection. The uptakes by blood, kidney, lung, and muscle decreased with time after administration. Those by the liver and spleen decreased until 1day post-injection, and then increased until day 14.

The biodistribution of ^{227}Th-citrate is shown in Table 3. The results also indicated high uptake rates in the femur and parietal bone during the 14-day experimental period. The maximum uptake level was 28.45%ID/g for the femur at 1 day post-injection. This value was threefold higher than that of ^{227}Th-EDTMP. Although uptake rates of blood decreased rapidly with time after injection, those of the muscle and lung showed slight decreases and those of other soft tissues changed little during the 14-day experimental period.

Figure 2 compares the femur-to-soft tissue uptake ratios of ^{227}Th-EDTMP to ^{227}Th-citrate. The ratios of ^{227}Th-EDTMP were higher than those of ^{227}Th-citrate between 15 min and 14 days after injection. The ratios of ^{227}Th-EDTMP reached more than 100 only 1 hour after injection in all tissues except the kidney.

3.3. Retention of ^{223}Ra generated from ^{227}Th in bone

Table 4 shows the retention index of ^{223}Ra relative to ^{227}Th in the bone at 7 and 14 days compared with a standard radioactive source. The index values were high and the differences between these two time points were not significant. As γ-ray spectrometry was performed within 30 min after sacrifice, radioactive growth of the daughter nuclide ^{223}Ra were ignored due to its relatively long half-life. Fresh ^{227}Th-EDTMP was injected within 2 hours after preparation, and

so it was estimated that mice received less than 0.5% ^{223}Ra radioactivity as compared to ^{227}Th. This value was negligible for evaluation of the retention index.

4. Discussion

The bone uptake of ^{227}Th-EDTMP in mice was found to be high and selective as compared with other tissues. Moreover, ^{227}Th-EDTMP was retained in bone throughout the 14-day experimental period. The clearance of ^{227}Th-EDTMP from soft tissues was rapid compared with its physical half-life. Although Th is a well-known bone-seeking element, it also accumulates in other tissues. There have been several reports regarding the biological behavior of Th isotopes [10, 11], which indicated some retention of Th in soft tissues. Our results using ^{227}Th-citrate also indicated that the %ID/g of ^{227}Th retained in the kidney, liver, spleen, and other tissues was low. The difference in biodistribution between ^{227}Th-EDTMP and ^{227}Th-citrate was due to differences in the bioavailability of these chelates. ^{227}Th-citrate would initially bind to bone according to the chemical absorption of Th(IV) to hydroxyapatite, while ^{227}Th-EDTMP would bind to bone by bridging of ^{227}Th to hydroxyapatite by the multidentate phosphonate chelate system [15]. Therefore, our comparative study of ^{227}Th-EDTMP and ^{227}Th-citrate demonstrated the efficacy of ^{227}Th-EDTMP for bone-affinity radiopharmaceuticals. EDTMP chelate has at least eight protonation sites [16] and it binds readily with bi- and trivalent metal radioisotopes, such as ^{154}Sm, ^{186}Re, ^{177}Lu, ^{105}Rh, ^{212}Pb, and ^{212}Bi, which were thought to have potential for use in treatment of bone metastases [17-21]. Although there were several differences in the uptake rates among these EDTMP complexes, the tendencies to accumulate in bone and to be eliminated rapidly from other tissues were seen in all cases. The uptake rate of ^{227}Th-EDTMP in bone was lower than those of the other ^{227}Th-labeled polyaminophosphonates, ^{227}Th-DTPMP and ^{227}Th-DOTMP [12]. This was most likely due to differences in the body weight of mice between the two studies. However the femur-to-other tissue uptake ratios of ^{227}Th-EDTMP were

high in comparison with those of ^{227}Th-DTPMP and ^{227}Th-DOTMP [12], and reached more than 100 at only 1 hour after injection in all tissues except the kidney. These results showed that the clearance of ^{227}Th-EDTMP from soft tissues through blood flow was superior to those of ^{227}Th-DTPMP and ^{227}Th-DOTMP. Thus, ^{227}Th-EDTMP is promising as a radiopharmaceutical for bone metastases.

In radionuclide therapy, many available α-emitting nuclides undergo successive α- and β-cascade disintegrations [22]. Whether these successive radiations could deliver high-dose irradiation to tumor foci is dependent on retention of daughter nuclides produced *in vivo*. Here, we examined the retention of the daughter nuclide ^{223}Ra produced from ^{227}Th in the femur. The retention index of ^{223}Ra in the femur was determined using γ-ray spectrometry as the relative radiation count rate of ^{223}Ra and ^{227}Th *vs*. standard. The retention index in the femur indicated a high degree of retention of ^{223}Ra on days 7 and 14 after injection of ^{227}Th-EDTMP. Based on the physical and chemical conditions after radioactive disintegration, ^{223}Ra could not remain in chelate form with EDTMP due to the α-recoil energy and/or low chemical stability of Ra with EDTMP. However, Ra is a well-known bone-seeking element [9, 23-25]. Therefore, even if ^{223}Ra is eliminated from the bone after decay of ^{227}Th, ^{223}Ra is redistributed on bone and provides an effective dose to the bone surface. Our results were consistent with those for ^{228}Th and its daughter ^{224}Ra in beagles reported by Stover *et al.* [26] and Lloyd *et al.* [27]. Henriksen *et al.* reported high retention of the progeny ^{211}Bi in bone from ^{223}Ra [9]. As there are no physical or biological differences in the bio-behavior between ^{223}Ra injected directly and that generated *in vivo* after ^{227}Th injection, the progeny generated from ^{223}Ra are expected to also be retained on the bone. There have been several other experiments regarding redistribution of daughter nuclides for treatment of skeletal metastasis. Using ^{212}Pb-DOTMP, it was found that newly generated ^{212}Bi was retained in bone at a rate of 70-85% [28]. Our previous results regarding ^{225}Ra bio-behavior in mice demonstrated that large fractions of ^{221}Fr and ^{213}Bi were eliminated from ^{225}Ra-deposited bone despite the high degree of retention of ^{225}Ac [29]. The

present and previous studies suggest that most radionuclides are distributed first according to their chemical characteristics. In the case of mother nuclides, such as ^{227}Th and ^{225}Ra, which are selectively accumulated in bone, daughter nuclides, such as ^{223}Ra and ^{225}Ac, are also retained selectively on bone according to their bone affinity. Second, even if daughter nuclides have no bone affinity, the relatively short half-lives of daughter nuclides, such as ^{219}Rn and ^{215}Po, compared to ^{220}Rn and ^{221}Fr result in their retention at their site of generation as they show faster disintegration than chemical migration.

In a closed system, the decay and growth of radioactivity of ^{227}Th and ^{223}Ra are expected to be as illustrated in Fig. 5. In the case of ^{223}Ra administration, ^{223}Ra decays according to its half-life with 4 α-emissions due to radioactive equilibrium with its progeny. The highest radiation dose is reached at 4 hours post-injection. On the other hand, in the case of ^{227}Th administration, ^{227}Th also decays according to its half-life, but α-emitted radioactivity increases with time and reaches the maximum level after 17 days, then begins to decrease. Therefore, ^{227}Th administration yields prolongation of effective α-radiation dose. In general, accumulation of ^{223}Ra in bone and its clearance from other tissues are expected to be rapid after ^{223}Ra administration [9], and ^{223}Ra easily reaches secular equilibrium with daughter nuclides, such as ^{219}Rn and ^{215}Po, within 30 seconds and also with ^{211}Pb and ^{211}Bi within 4 hours. Therefore, the kidney, spleen, and other soft tissues might be exposed to large radiation doses from cascade α-emissions in the initial phase. However, in the case of ^{227}Th-EDTMP administration, ^{227}Th contributes a slowly growing radiation dose to bone and a lesser dose of irradiation to non-target tissue. The antitumor effects of ^{223}Ra were examined; this radionuclide was demonstrated to show significantly increased symptom-free survival, and no signs of bone marrow toxicity or body weight loss [25]. There were no significant changes in biodistribution pattern between ^{227}Th-EDTMP and ^{223}Ra. The ^{227}Th chelate would be expected to have effective antitumor activity. We are currently planning to evaluate the antitumor effects of ^{227}Th.

In conclusion, ^{227}Th-EDTMP showed selective accumulation and long-term retention in bone,

with rapid clearance from soft tissues. The retention of the daughter nuclide ^{223}Ra was high during the 14-day experimental period after administration of ^{227}Th, and so it would be expected to administer a much more intense and longer α-emission radiation dose to bone metastases.

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Figure captions

Fig. 1. Decay chain of ^{227}Ac to stable ^{207}Pb.

Fig. 2. The bone-to-tissue uptake ratios of ^{227}Th-EDTMP and ^{227}Th-citrate. ^{227}Th-EDTMP and ^{227}Th-citrate are shown as (○) and (■), respectively. All data are shown with errors based on S.D. for 3 animal experiments.

Fig. 3. The radioactive decay and growth patterns of ^{227}Th and ^{223}Ra in a closed system. Gross α-activities are shown during disintegration of the parent nuclide to stable ^{207}Pb.

Fig. 1.

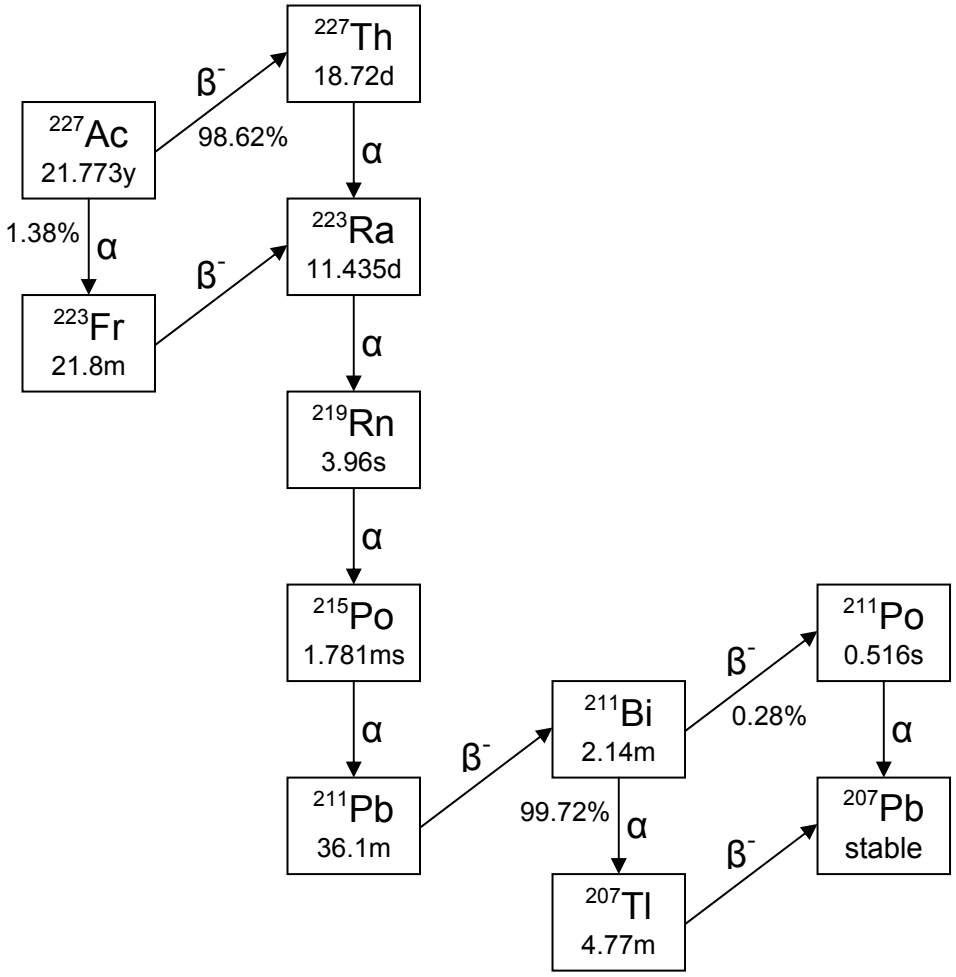
227Th
18.72d
β-
227Ac
21.773y
98.62%
α
1.38%
α
223Ra
11.435d
β-
223Fr
21.8m
α
219Rn
3.96s
α
215Po
1.781ms
α
211Po
0.516s
β-
211Bi
2.14m
0.28%
α
β-
211Pb
36.1m
99.72%
α
207Pb
stable
β-
207Tl
4.77m

Fig. 2.

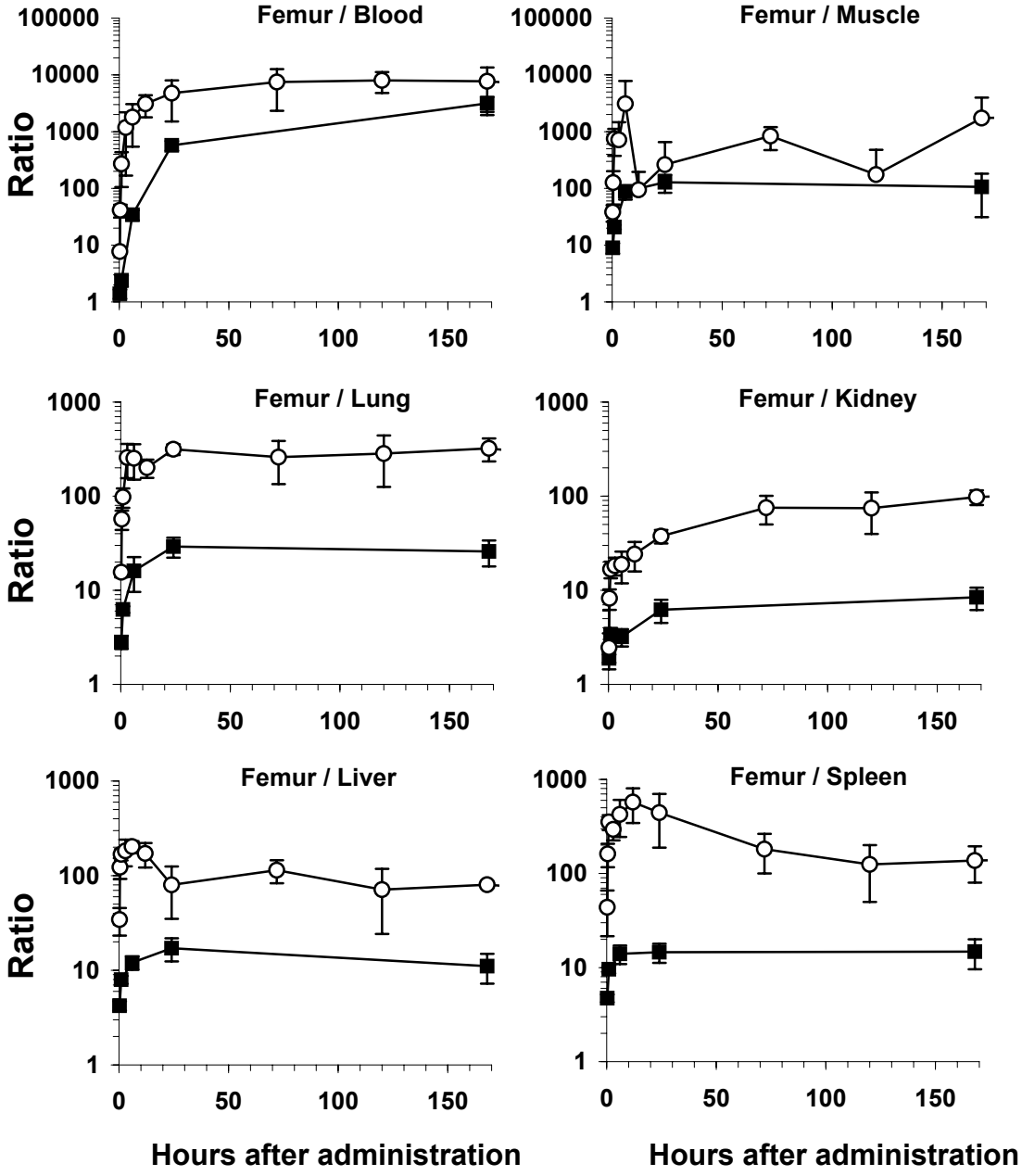
Femur / Blood
Femur / Muscle
Femur / Lung
Femur / Kidney
Femur / Liver
Femur / Spleen
Ratio
Ratio
Hours after administration
Hours after administration

Fig. 3.

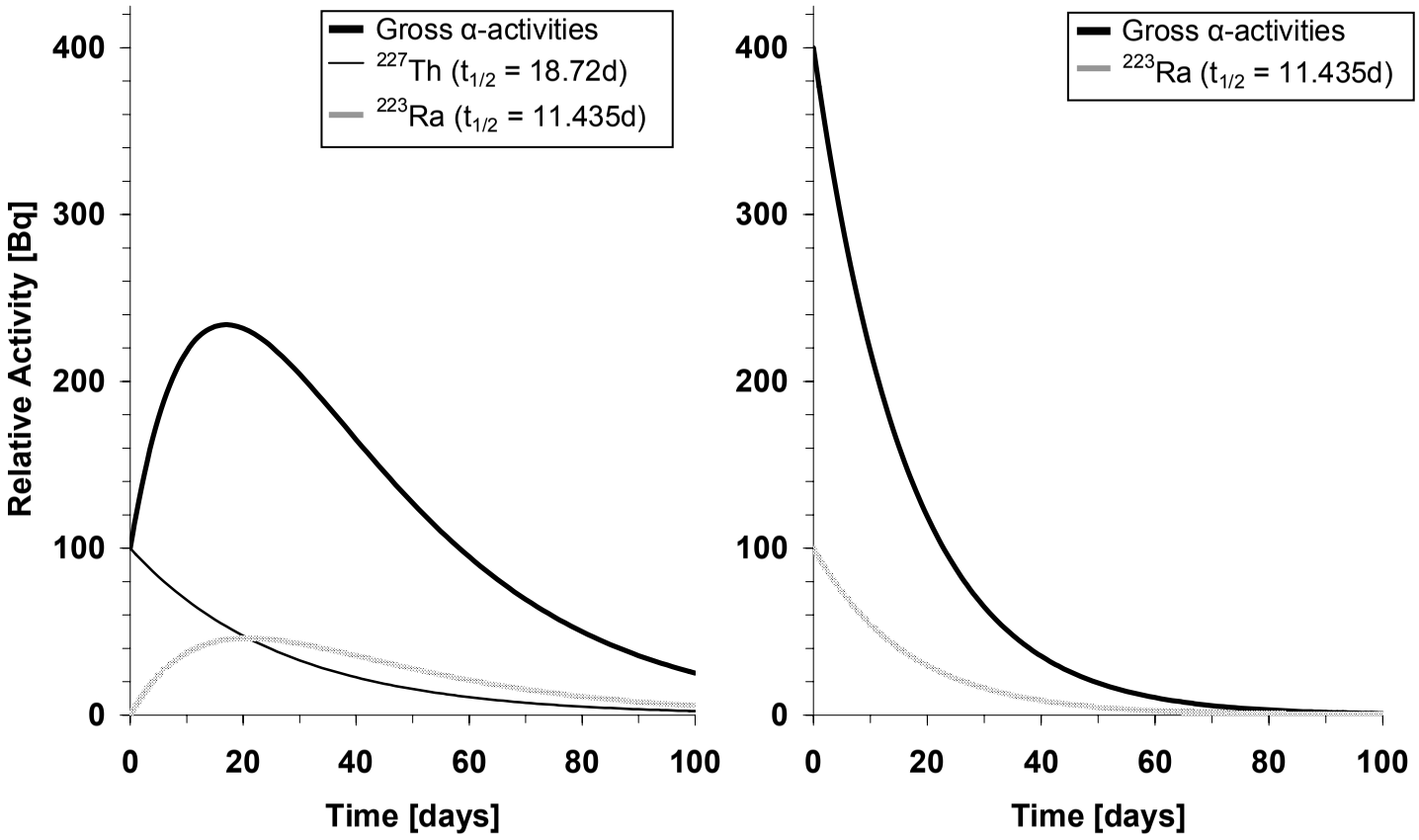
Gross α-activities
227Th (t1/2 = 18.72d)
223Ra (t1/2 = 11.435d)
Relative Activity [Bq]
400
300
200
100
0
0
20
40
60
80
100
Time [days]
Gross α-activities
223Ra (t1/2 = 11.435d)
400
300
200
100
0
0
20
40
60
80
100
Time [days]

Table 1
Decay properties of ^{227}Th and ^{223}Ra

Nuclide	half-life	γ-rays keV (%)
^{227}Th	18.72d	50.13 (7.9)
		235.97 (12.3)
		256.25 (7.01)
		300.00 (2.32)
		329.85 (2.69)
^{223}Ra	11.435d	144.23 (3.22)
		154.21 (5.62)
		269.46 (13.70)
		323.87 (3.93)
		338.28 (2.79)

Data were taken from Table of Isotopes, 8th ed. John Wiley and Sons, Inc., (1996);

a: More than 2% abundant γ-rays are listed for each radionuclide;

b: Percent probability per 100 decays.

Table 2
Biodistribution of ^{227}Th-EDTMP in mice.

	15 m	30 m	1 hr	3 hr	6 hr	12 hr
Blood	0.86 ± 0.01	0.23 ± 0.04	0.029 ± 0.017	0.007 ± 0.006	0.005 ± 0.003	0.003 ± 0.001
Lung	0.43 ± 0.03	0.17 ± 0.02	0.079 ± 0.015	0.033 ± 0.012	0.034 ± 0.013	0.043 ± 0.008
Liver	0.19 ± 0.06	0.08 ± 0.01	0.05 ± 0.00	0.05 ± 0.01	0.04 ± 0.00	0.05 ± 0.01
Spleen	0.15 ± 0.08	0.059 ± 0.012	0.022 ± 0.003	0.029 ± 0.005	0.020 ± 0.008	0.015 ± 0.006
Kidney	2.70 ± 1.08	1.17 ± 0.18	0.46 ± 0.07	0.47 ± 0.06	0.46 ± 0.16	0.35 ± 0.12
Muscle	0.17 ± 0.05	0.076 ± 0.042	0.010 ± 0.005	0.012 ± 0.012	0.003 ± 0.004	0.091 ± 0.097
Parietal bone	4.35 ± 0.21	6.20 ± 1.12	6.29 ± 0.22	6.52 ± 1.01	6.56 ± 0.74	5.52 ± 0.76
Femur	6.64 ± 0.68	9.62 ± 1.88	7.73 ± 1.01	8.54 ± 1.43	8.58 ± 0.83	8.58 ± 1.01

	1 d	3 d	5 d	7 d	10 d	14 d
Blood	0.002 ± 0.001	0.0012 ± 0.0008	0.0012 ± 0.0001	0.0012 ± 0.0009	0.0015 ± 0.0002	0.0007 ± 0.0005
Lung	0.027 ± 0.002	0.034 ± 0.016	0.034 ± 0.013	0.028 ± 0.007	0.035 ± 0.011	0.038 ± 0.002
Liver	0.11 ± 0.06	0.08 ± 0.02	0.13 ± 0.07	0.11 ± 0.00	0.12 ± 0.01	0.18 ± 0.03
Spleen	0.019 ± 0.011	0.048 ± 0.021	0.076 ± 0.034	0.066 ± 0.027	0.051 ± 0.016	0.069 ± 0.008
Kidney	0.23 ± 0.03	0.12 ± 0.04	0.13 ± 0.03	0.09 ± 0.02	0.07 ± 0.01	0.05 ± 0.02
Muscle	0.033 ± 0.049	0.010 ± 0.004	0.054 ± 0.091	0.005 ± 0.007	0.004 ± 0.003	0.001 ± 0.001
Parietal bone	5.37 ± 1.38	6.60 ± 0.53	7.02 ± 2.81	6.11 ± 0.34	6.40 ± 0.29	6.09 ± 0.80
Femur	8.65 ± 0.86	8.75 ± 0.79	9.55 ± 3.82	9.05 ± 0.62	7.50 ± 0.30	9.03 ± 1.15

Uptake rates in various tissues are expressed as % of administered dose per gram of tissue weight.
Values represent the means ± S.D. of four animals.

Table 3
Biodistribution of ^{227}Th-citrate in mice.

	15 m	1 hr	6 hr	1 d	7 d
Blood	5.10 ± 0.82	4.98 ± 1.08	0.60 ± 0.10	0.050 ± 0.004	0.006 ± 0.001
Lung	2.52 ± 0.34	1.91 ± 0.10	1.28 ± 0.49	0.97 ± 0.16	0.75 ± 0.15
Liver	1.68 ± 0.14	1.50 ± 0.11	1.71 ± 0.18	1.66 ± 0.35	1.75 ± 0.45
Spleen	1.50 ± 0.07	1.25 ± 0.09	1.47 ± 0.27	1.95 ± 0.29	1.31 ± 0.34
Stomach	1.87 ± 0.18	2.24 ± 0.20	2.45 ± 0.35	2.16 ± 0.49	1.14 ± 0.29
Large intestine	1.07 ± 0.15	1.24 ± 0.18	1.05 ± 0.32	1.18 ± 0.47	1.05 ± 0.24
Small intestine	1.21 ± 0.31	0.92 ± 0.11	0.73 ± 0.17	0.59 ± 0.09	0.43 ± 0.18
Kidney	3.76 ± 0.22	3.54 ± 0.59	6.44 ± 1.10	4.58 ± 0.97	2.31 ± 0.28
Muscle	0.79 ± 0.15	0.57 ± 0.04	0.23 ± 0.06	0.22 ± 0.07	0.18 ± 0.12
Parietal bone	4.14 ± 0.24	7.48 ± 1.59	12.84 ± 1.27	17.22 ± 0.79	15.63 ± 0.41
Femur	7.11 ± 0.58	11.96 ± 0.71	20.57 ± 2.49	28.45 ± 4.99	19.40 ± 4.62

Uptake rates in various tissues are expressed as % of administered dose per gram of tissue weight.
Values represent the means ± S.D. of four animals

Table 4
Retention index of ^{223}Ra on the femur

	Retenion Index		
day 7	0.85	±	0.04
day 14	0.89	±	0.02