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Thorium and Actinium Polyphosphonate Compounds as Bone-seeking Alpha Particle-emitting Agents

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Abstract. *The present study explores the use of α-particle-emitting, bone-seeking agents as candidates for targeted radiotherapy. Actinium and thorium 1,4,7,10 tetraaza-cyclododecane N, N', N'', N''' 1,4,7,10-tetra(methylene) phosphonic acid (DOTMP) and thorium-diethylene triamine N,N',N'' penta(methylene) phosphonic acid (DTMP) were prepared and their biodistribution evaluated in conventional Balb/C mice at four hours after injection. All three bone-seeking agents showed a high uptake in bone and a low uptake in soft tissues. Among the soft tissue organs, only kidney had a relatively high uptake. The femur/kidney ratios for ^{227}Th-DTMP, ^{228}Ac-DOTMP and ^{227}Th-DOTMP were 14.2, 7.6 and 6.0, respectively. A higher liver uptake of ^{228}Ac-DOTMP was seen than for ^{227}Th-DTMP and ^{227}Th-DOTMP. This suggests that some demetallation of the ^{228}Ac-DOTMP complex had occurred. The results indicate that ^{225}Ac-DOTMP, ^{227}Th-DOTMP and ^{227}Th-DTMP have promising properties as potential therapeutic bone-seeking agents.*

Bone-targeting radiopharmaceuticals involving the energetic beta-emitters ^{32}P and ^{89}Sr have been used clinically for several decades to palliate pain in patients with skeletal metastases (1,2). The major dose-limiting factor with these radiopharmaceuticals is toxicity to the bone marrow (3-6), presumably caused by the long range of the beta-particles. Radionuclides that emit particles of a shorter range are therefore of interest.

The clinical use of the low-energy beta emitters ^{153}Sm (7,8) and ^{186}Re (9,10) and the conversion electron emitter ^{117m}Sn (11,12) has been explored. The results indicate that there is still room for improving the pain relieving and therapeutic potential of bone-targeting radiopharmaceuticals (4-6,13)

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α-particles, due to their short range (< 0.1 mm) and high linear energy transfer (14), may be better suited as radiation sources in bone-targeting radiopharmaceuticals. This was confirmed in a preclinical study where the radiation doses to bone surface and marrow were compared for α-emitting ^{211}At and β-emitting ^{131}I linked to bone-seeking bisphosphonates (15).

α-particle-emitting bone-seeking compounds of ^{212}Bi ($t_{½}$ = 60.6 m) have also been evaluated (16,17). However, the short physical half-lives of ^{212}Bi and ^{211}At and the relatively long times required to localize in bone result in undesirable radiation exposure to normal tissues. Bone-seeking α-emitters, having a longer half-life, should be attractive because a smaller fraction of the total radiation dose will be delivered to the bone marrow and soft tissues of the body during the bone uptake and soft tissue elimination phases.

Recently α-particle-emitting ^{223}Ra ($t_{1/2}$=11.4 d) was shown to give a selective uptake and retention in bone as compared to soft tissues in rodents (18, 19). Moreover, a significant antitumour activity from ^{223}Ra was observed in a nude rat skeletal metastases model resistant to chemotherapy and a β-emitting bone-seeker (18). Other candidate α-emitters with half-lives of several days are ^{225}Ac ($t_{1/2}$=10.0 d) and ^{227}Th ($t_{1/2}$=18.7 d). These radionuclides decay to stability *via* several daughters, releasing a total of 4 and 5 α-particles, respectively. The large amounts of α-energy released (~28 MeV for the ^{225}Ac- and ~32 MeV for the ^{227}Th-series) indicate a potential to produce the desired effect from relatively low amounts of radioactivity.

Unlike Ra^{2+}, Ac^{3+} and Th^{4+} give a more pronounced soft tissue uptake (20,21). Hence, for these elements to be useful they must be combined with a bone-targeting carrier molecule.

In the present study the biodistribution of ^{227}Th and ^{228}Ac as polyphosphonate chelates was studied. Because of the low availability of ^{225}Ac at the time of the experiment, ^{228}Ac was used as the actinium tracer. Systemically administered polyphosphonates are known

to target calcified tissue (22-24). The uptake of polyphosphonates is high in regions with an elevated bone turnover (25), which makes them appealing for use as carriers of radionuclides in the targeting of bone-forming tumors or calcified metastases in the skeleton. The goal of the current work was to investigate if relevant *in vivo* stability and bone-targeting could be obtained with Th- and Ac-polyphosphonates.

Materials and Methods

Reagents and equipment. The ^{232}Th-nitrate (J.T. Baker, Phillipsburg, NJ, USA) used in this study had been stored for more than 20 years. AG50W-x 12 and Chelex-100 ion-exchange resins were both obtained from Bio-Rad, Hercules, CA, USA. Amberchrom XAD-7HP resin was purchased from Rohm & Haas (Frankfurt, Germany). Diethylene triamine N,N',N'' penta(methylene)phosphonic acid (DTMP) was obtained from Fluka, Buchs, Switzerland.1,4,7,10 tetraazacyclododecane N,N',N'',N''' 1,4,7,10-tetra(methylene) phosphonic acid (DOTMP) was purchased from Macrocyclics, Richardson, TX, USA. All water used was purified through a Milli-Q system (Millipore, Bedford, MA, USA).

Preparation of ^{227}Th. ^{227}Th was selectively retained from a ^{227}Ac decay mixture in 7 M HNO_3 solution by anion exchange chromatography (26). A column of 2 mm internal diameter, length 30 mm containing 70 mg of AG-1 x 8 resin (200-400 mesh, nitrate form) was used.

After ^{227}Ac, ^{223}Ra and daughters had eluted from the column, ^{227}Th was extracted from the column with 12 M HCl. The eluate containing ^{227}Th was evaporated to dryness and the residue dissolved in 0.1 M HNO_3.

Preparation of ^{228}Ac. ^{228}Ra ($t_{1/2}$=5.75 years), which served as generator material for ^{228}Ac, was isolated by solvent extraction from ^{232}Th (27). By this procedure thorium is selectively extracted into the organic phase while radium remains in the aqueous phase. Briefly, ^{232}Th-nitrate was dissolved in 20 ml of 0.1 M HNO_3 and extracted by shaking the aqueous phase three times with 70 ml of a 2 M solution of di-(2-ethylhexyl) orthophosphoric acid (HDEHP) in heptane. The aqueous phase was subsequently washed with 3 x 30 ml heptane. After this, the aqueous solution was concentrated to 10 ml by evaporation and the concentrate applied to a column of 4 mm internal diameter and a length of 70 mm filled with Amberlite XAD-7HP resin for removing residual organic compounds. For further purification, the solution containing ^{228}Ra and ^{224}Ra was applied to a 3 x 40 mm column containing 0.2 g of AG50W-X12 cation exchange resin (200-400 mesh, H+-form). The column was washed with 10 ml of 1 M HNO_3 followed by stripping ^{228}Ra, ^{224}Ra, ^{212}Pb and ^{212}Bi with 5 ml of 3 M HNO_3. The last eluate was left for one month in order to allow ^{224}Ra to decay.

^{228}Ac were separated from ^{228}Ra on a fresh 3 x 40-mm column of AG50W-X12. ^{228}Ra was eluted in 5 ml 3 M HNO_3 before eluting ^{228}Ac with 5 ml of 6 M HNO_3. In preparation for chelation chemistry, the solution containing ^{228}Ac was evaporated to dryness and ^{228}Ac dissolved in 0.1 M HNO_3. The ^{228}Ac produced in this manner contained less than 0.5 Bq ^{228}Ra / kBq ^{228}Ac, as measured by γ-spectroscopy on samples stored for a time corresponding to >10 half lives of ^{228}Ac.

Preparation of thorium and actinium polyphosphonate chelates. A 50 mM aqueous solution of the desired chelating agent was made and the pH adjusted to 5-5.5 by adding 3 M ammonium acetate. Twenty to thirty μl of this solution was mixed with 50-100 μl of a 0.1 M HNO_3 solution containing the radionuclide. The pH was adjusted to 5-5.5 using 3 M ammonium acetate and the reaction mixture was kept at 60˚C for one hour. After this, the solution was applied to a 2 x 20-mm column containing 40 mg of Chelex-100 cation-exchange resin, (100-200 mesh, ammonium form) for isolation of radionuclide complexes.

More than 80% of the ^{227}Th eluted from the column with both the DTMP and DOTMP chelators. The corresponding value obtained with ^{228}Ac-DOTMP was in the order of 60 %.

^{228}Ac-DOTMP, ^{227}Th-DTMP and ^{227}Th-DOTMP solutions for injection were prepared by diluting the complex in a 0.1 M solution of 2-[N-morpholino]ethanesulfonic acid (MES), sodium salt, followed by filtration through sterile 0.22-μm nylon filters (Whatman, Maidstone, UK). The final concentration of DOTMP and DTMP was 5 mM.

Preparation of ^{227}Th-acetate/MES solution. A solution containing ^{227}Th as a weakly complexed cation was prepared in the following manner: 0.1 M HNO_3 solution containing ^{227}Th was added to 3 M ammonium acetate to obtain a pH of 5.5. This solution was diluted to the desired activity concentration and to a pH of 7.4 by using 0.1 M MES buffer. Finally, the solution was filtered through sterile 0.22-μm nylon filters.

Biodistribution experiments. The biodistribution of ^{227}Th-acetate, ^{227}Th-DTMP, ^{227}Th-DOTMP and ^{227}Ac-DOTMP were studied in conventional mice. All procedures and experiments involving animals in this study were approved by the National Animal Research Authority and carried out according to the European Convention for the protection of Vertebrates used for Scientific Purposes.

Young Balb/C mice with an average body weight of 14 g were used in the biodistribution experiments. The preparations were administered by tail vein injection of 100 μl solution to each animal containing approximately 5 kBq of ^{227}Th or ^{228}Ac. Groups of three animals were sacrificed by cervical dislocation after 4 h and the tissue distribution of radionuclides was determined.

^{227}Th was measured by its 236 keV γ-ray (12.3 % probability) employing a HPGe detector (Canberra, Meriden, CT, USA) coupled to a multichannel analyzer (EG&G ORTEC, Oak Ridge, TN, USA) and also by liquid scintillation counting using a Beckmann LS 6500 (Beckmann, Fullerton, CA, USA) after dissolution of tissue samples. Before the liquid scintillation counting, soft tissue samples were dissolved by adding 1-3 ml of Soluene 350 (Packard, BioScience BV, Groningen, The Netherlands) per 100 mg tissue and bone samples were dissolved in $HClO_4$:H_2O_2 1:2 ($^{v}/_{v}$). All tissue samples were kept at 50˚C until they were completely dissolved. If required, soft tissue samples were bleached by adding H_2O_2. Finally, Instagel Plus II scintillation cocktail (Packard) was added and the samples were then stored in the dark to allow decay of luminescence.

^{228}Ac was measured by the HPGe detector by its 911.2 keV γ-ray (26.6% probability) and by a NaI(Tl) well-type detector (Harshaw Chemie BV, De Meern, Holland) combined with a Scaler Timer ST7 (NE Technology Ltd, Reading, UK) digital unit.

Samples of the radionuclide preparations were used as references in the measurement procedures.

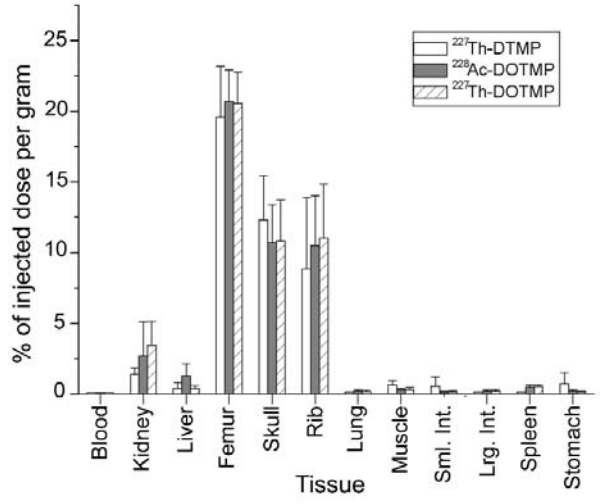

Figure 1. *Uptake of ^{227}Th–DTMP, ^{227}Th-DOTMP and ^{228}Ac-DOTMP in normal tissues from mice 4 h after injection, N=3. The error bars represent the standard deviation.*

Table I. *Biodistribution of ^{227}Th[1].*

Tissue	% of ID/g
Blood	1.2 ± 0.4
Kidney	7.7 ± 0.7
Liver	56.5 ± 9.4
Femur	23.4 ± 6.9
Skull	18.9 ± 7.6
Rib	14.6 ± 4.4
Lung	2.6 ± 0.4
Heart	2.6 ± 0.2
Brain	<0.1
Small Intestine	2.3 ± 0.1
Large Intestine	1.7 ± 0.1
Spleen	14.2 ± 2.8
Stomach	4.6 ± 1.0

Data are presented as percent of injected dose per gram tissue in female Balb-C mice, weight 11-16 g at 4 h after injection. The data are presented as mean ± s.d., N=2.

[1]Thorium-227 was injected as an ammonium acetate/N-morpholine ethane sulphonic acid solution.

Results

Actinium and thorium chelated to polyphosphonates were shown to give high bone to soft tissue ratios indicating adequate stability of the coordination compounds for *in vivo* targeting (Figure 1). The bone samples from femur, skull and ribs all had much higher uptake than the soft tissue organs studied, reflecting a strong and selective bone affinity of the compounds (Figure 1). Among the soft tissue organs, only kidneys had a relatively high uptake 4 h after injection, which is consistent with the rapid excretion of the polyphosphonate chelates from the soft tissues. The femur/kidney ratios for ^{227}Th-DTMP, ^{228}Ac-DOTMP and ^{227}Th-DOTMP were 14.2, 7.6 and 6.0, respectively. Furthermore, the femur/ liver ratio for ^{228}Ac-DOTMP was 16.4. The liver uptake of ^{228}Ac-DOTMP was higher than the corresponding data for ^{227}Th-DTMP and ^{227}Th-DOTMP (Figure 1). This suggests that some demetallation of the complex had occurred.

For comparison, tissue distribution data for ^{227}Th in actetate/MES solution are presented in Table I. It can be seen that the bone uptake of cationic thorium was comparable to that obtained with the bone-seeking polyphosphonate coordination compounds in this study. However, the affinity of the thorium cation for the soft tissue organs, especially liver and spleen, renders this chemical form unsuitable as a bone-targeting agent.

Discussion

^{225}Ac and ^{227}Th are attractive α-particle emitters for use in targeted radiotherapy for several reasons:

1) The relatively long physical half-lives of 10 days and 18.7 days are advantageous by allowing sufficient time for preparation, shipping and administration of radiopharmaceuticals.
2) They can be produced from radionuclide generators securing continuous supply based on long-lived source material.
3) More than 90 % of the total energy emitted in the decay cascade stems from α-particles. Thus, it may be possible to deliver an intense and highly localized irradiation dose to bony surfaces if the nuclide can be targeted to bone.

In the current study it was found that the bone uptake of actinium-DOTMP, thorium-DOTMP and thorium-DTMP in mice was high and selective compared to the uptakes in the soft tissues. Biodistribution of actinium in mice has recently been published (28). These data revealed that this element, as a weakly complexed cation, does not show sufficiently selective bone uptake relative to soft tissue uptake to be suitable as a bone-targeting endoradiotherapeutic agent.

Figure 2 illustrates the localisation index of the chelates *versus* the respective free radionuclide. Actinium-DOTMP and thorium-DTMP/DOTMP all showed improved bone to soft tissue ratios compared to the corresponding data for the free radionuclide.

The biodistribution of ^{225}Ac has been reported for various concentrations of ethylene diamine *N,N'* tetra methylene phosphonic acid (EDTMP) (29). However, at the concentration of EDTMP required to prevent a high soft tissue uptake, the femur uptake was below 10% of I.D./g (29). The results from the present study with ^{228}Ac-DOTMP show that conditions can be found which result in a low soft tissue uptake with concurrent high uptake of actinium in bone. This shows that DOTMP is a more effective bone-targeting carrier for actinium than EDTMP.

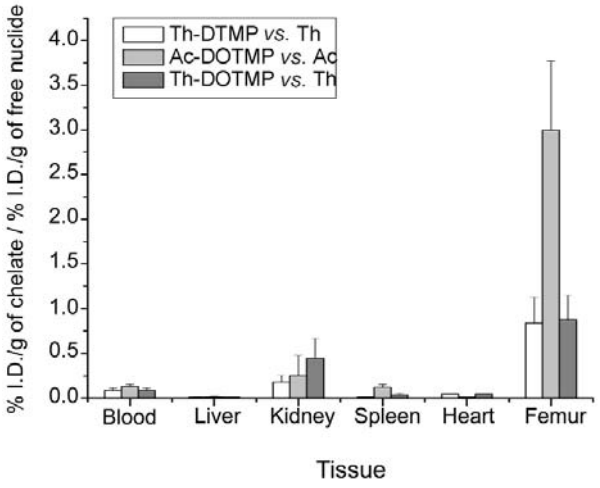

Figure 2. *The figure presents localisation index, i.e., the ratio of tissue uptake of thorium-DTMP vs. free thorium, thorium-DOTMP vs. free thorium and actinium-DOTMP vs.free actinium 4 h after injection. Data for the ^{227}Th-DTMP, ^{228}Ac-DOTMP and ^{227}Th-DOTMP chelates and ^{227}Th-acetate (dissolved) was obtained from this work. Data for actinium-acetate was taken from the work of Davis et al. (28) (^{225}Ac-acetate, female Balb-C mice).*

An alternative approach to achieve bone-targeting with ^{225}Ac could be to use the bone-seeking β-emitter ^{225}Ra ($t_{1/2}$=14.8 d), which decays to ^{225}Ac. Because of the significant half-life of ^{225}Ra, the major transformation from ^{225}Ra to ^{225}Ac would take place after incorporation into the skeleton (and skeletal metastases) and elimination from soft tissues have occurred. The initial beta particle dose from ^{225}Ra would be low since only low levels of radioactivity are required to deliver therapeutically relevant alpha-particle doses.

An interesting mother nuclide/daughter nuclide situation exists also when a bone-targeting compound is based on ^{227}Th as this nuclide decays to ^{223}Ra, another α-particle emitter with high bone affinity. If the ^{227}Th –labeled bone-seeker was free from ^{223}Ra at the time of administration, the total radioactivity in bone should increase as the decay of the parent proceeds. Furthermore, the results from the current study suggest that, with ^{227}Th-DTMP/DOTMP, the maximum dose rate to bone occurs at a time when most of the ^{227}Th has cleared from blood and soft tissues, hence further increasing the bone to soft tissue dose ratios.

In a recently reported biodistribution study with ^{223}Ra in mice, it was shown that at early times after injection only a very low fraction of daughter nuclides from ^{223}Ra located in bone were redistributed (18). Also, the redistribution decreased with time from about 2% at 6 h to less than 1% at 3 days. Evaluation of the long-term retention of actinium and thorium radionuclides and their daughters was not made in this study. It is known from the literature that the skeletal retention half-times of Ac^{3+} and Th^{4+} are very long (20, 21) compared to the half-life of ^{225}Ac and ^{227}Th. Based on the half-life similarities with ^{223}Ra, it can be expected that ^{227}Th- and ^{225}Ac-labeled bone-seekers would have sufficient time for incorporation into the bone matrix for their daughters to be stably retained as well.

In conclusion, a high and selective uptake in bone of actinium-DOTMP, thorium-DOTMP and thorium-DTMP was demonstrated, indicating that polyphosphonate complexes of ^{225}Ac and ^{227}Th could have a relevant *in vivo* stability and be useful to deliver alpha-particle radiation to primary bone cancer and skeletal metastases from soft tissue cancers.

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