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The Impact of Barium Isotopes in Radiopharmacy and Nuclear Medicine – from Past to Presence

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Abstract

With the exception of beryllium, every alkaline earth metal is characterized by a calcimimetic behavior. Thus, *in vivo* biodistribution mostly occurs in form of a massive accumulation in bone tissues, consisting of hydroxyapatite to a major extent. Apart from the lightest elements beryllium and magnesium, animal studies and human studies regarding the overall *in vivo* behavior were carried out by using radioisotopes of the elements calcium, strontium, barium, and radium. To date, only strontium with its radioisotopes gained importance for applications in nuclear medicine, mainly for pain-reducing and palliative treatment of bone metastases. In contrast, barium isotopes can be useful imaging agents and possible diagnostic analogues for theranostic approaches. This review focuses on the characteristic and chemical behavior of barium compounds, possible radioactive barium isotopes for future applications in nuclear medicine and radiopharmacy as well as recent results regarding barium-131 as diagnostic match for radium isotopes used in targeted alpha therapy.

Introduction

Heavy alkaline earth metal-containing radiopharmaceuticals, especially containing strontium, barium, and radium radionuclides, have been used in nuclear medicine for a long time. Even today, several important routine applications exist. Due to their affiliation to the second group (alkaline earth metals) of the periodic table (Figure 1), these elements are characterized by their calcimimetic behavior. This refers to the chemical similarities as well as the physiological distribution behavior regarding *in vivo* applications as group 2 metal ions occur as divalent cations. Because of the challenging physicochemical properties regarding a stable complex formation, the scope of applications is mostly limited to the use as bone-seeking elements [1]. Despite their differences in ionic radii (Ra ≥ Ba > Sr > Ca) and slight differences in organ distribution and kinetics, the excretory processes are very similar.

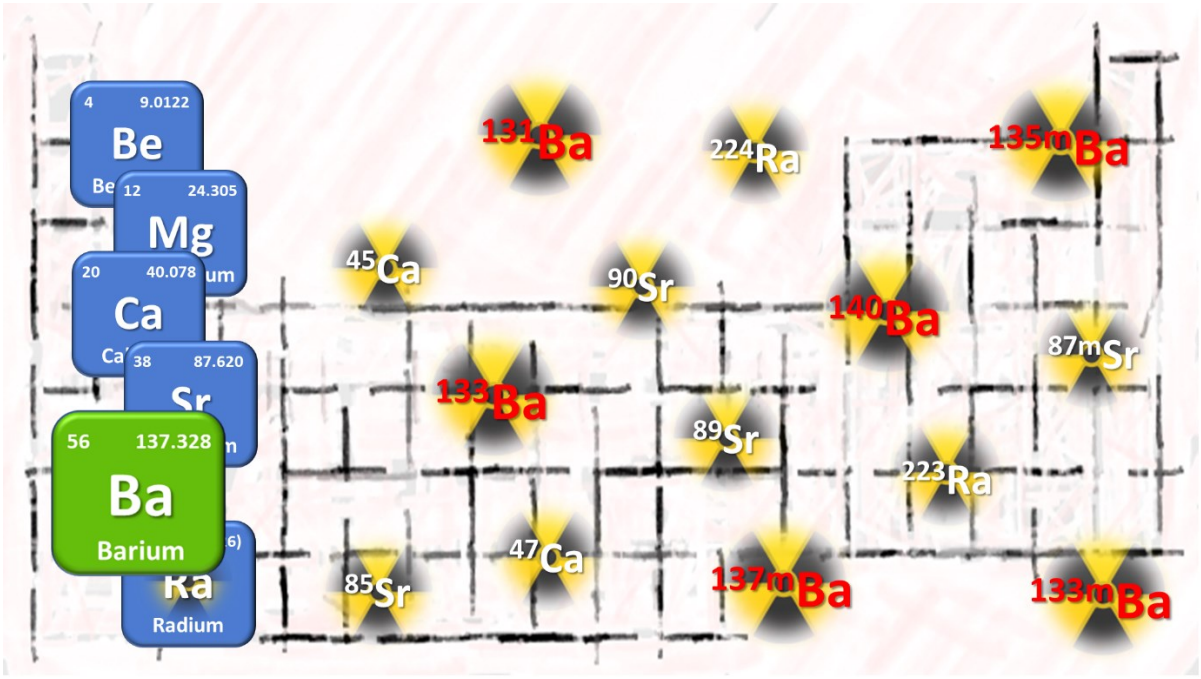

Figure 1. Periodic Table of Elements showing all alkaline earth metal (group 2) elements and radionuclides with radiopharmaceutical background thereof.

In the late 1950s, both beta emitters ^{45}Ca and ^{47}Ca were the starting point of research on alkaline earth radionuclides for later human applications. Both calcium isotopes were mainly used for the investigation of the calcium metabolism in humans [2-5] and furthermore applied as therapeutic agents for palliative care and pain treatment of bones [6-8]. Due to its relative long half-life ($t_{1/2}$ = 163 d), ^{45}Ca was not an ideal candidate for medical use. In this case, ^{47}Ca is preferred ($t_{1/2}$ = 4,7 d), but both still can be considered as the access point for further investigation of other earth alkaline elements and their radioactive isotopes.

Several interesting radioisotopes of strontium like ^{85}Sr, ^{87m}Sr, ^{89}Sr, and ^{90}Sr are known. In current times, FDA-approved Metastron in form of [^{89}Sr]$SrCl_2$ ($t_{1/2}$ = 50.6 d) is in clinical practice for palliative treatment of bone metastases to reduce bone pain [9]. Metastron can be seen as modern alternative for the previously described therapy using calcium isotopes. Furthermore, ^{90}Sr delivers the possibility of preparing a ^{90}Sr/^{90}Y radionuclide generator, thereby delivering ^{90}Y [10], a therapeutic beta emitter of high importance for medical use.

The heaviest group 2 element radium delivers two isotopes of high relevance for targeted alpha therapy: ^{223}Ra and ^{224}Ra. For a number of decades in the past, ^{224}Ra ($t_{1/2}$ = 3.6 d) has been applied as SpondylAT® for the treatment of Morbus Bechterew [11,12], but lost its approval due to regulatory issues. Presently, ^{224}Ra-radiolabeled seeds are in the focus of DaRT (diffusing alpha emitters radiation therapy) research, a new type of brachytherapy using the diffusion potential of cascade-decaying alpha emitters after intratumoral application into squamous cell carcinoma [13,14]. Moreover, ^{223}Ra

($t_{1/2}$ = 11.4 d) as Xofigo® is applied in clinical routine for palliative treatment of bone metastases [15,16].

Unfortunately, none of the presented calcium, strontium, and radium isotopes is suitable for imaging purposes using PET or SPECT techniques. Therefore, numerous isotopes of barium have been investigated in the past, including ^{131}Ba, $^{133m/133}$Ba, ^{135m}Ba, ^{137}Ba, and ^{140}Ba. By combining one of these isotopes with a therapeutic radionuclide, such as one of the radium isotopes, barium can unlock its usefulness as potential diagnostic tool in theranostic approaches for targeted alpha therapy. Recently, ^{131}Ba was reported as nearly ideal match for ^{223}Ra, although the radionuclide pair is still suffering from the lack of a convenient carrier system, no matter if on basis of a chelating ligand or inorganic particle matrices.

Characteristics of the Element Barium and its Compounds

The German pharmacist, Carl Willhelm Scheele was mainly responsible for the discovery of the chemical element barium, by finding an oxygen compound of the well-known mineral “Bologneser Sonnenstein”. His findings were verified by the English chemist Humphry Davy more than 30 years later, who finally gave this element the name barium (greek: barys = heavy). Humphry Davy was able to isolate elemental barium by using an amalgam method. Later on, Robert Wilhelm Eberhard Bunsen and Augustus Matthiessen isolated elemental barium by fused-salt electrolysis from barium chloride as well [17,18].

Barium belongs to the second group of the periodic table also referred as alkaline earth metals. Naturally existing compounds (apart from its appearance as base metal) contain divalent barium cations. Barium occurs in the uppermost earth's crust to a less extent of 0.04–0.05%. Because of its reactivity, Barium never naturally occurs as a pure metal, but in minerals, mostly as Barite (barium sulfate) or Witherite (barium carbonate). The very rare occurring Benitonite (barium titanium silicate) is a blueish fluorescing gemstone and the official state gem of California [17,18].

Barium compounds gained excess in industry. Metallic barium aluminum/magnesium alloys are used as getter in electron tubes and for activation of electrodes. Moreover, lead/barium alloys, that provide a high mechanical resistance, are used as bearing metal. Different barium compounds are applied for several purposes: barium acetate is used as mordant for printing industry and as a catalyst for organic compounds. Barium carbonate is applied in the manufacturing industry of glassware, bricks and ceramic materials. Barium hydroxide is in application for glass fabrication as well, for oil cleansing and water softening. Main applications of the mainly occurring barium sulfate are found as x-ray contrast agent, raw oil industry, plastic and textile industry as well as paint industry [19].

Carrier Systems for Barium Ions

The stable fixation of heavy alkaline earth metal ions is challenging and several approaches have been reported over the last decades. Starting with the examination of standard chelating agents, such as EDTA and DTPA (without any satisfying results and calculated logK values of 8-9) [20,21], those studies were rapidly supplemented by crown ethers and aza-crown ethers. One major advantage of cyclic ligands is the pre-formed macrocyclic template, which is then provided to the relatively large barium cation. Moreover, those ligands can offer several functional entities to strengthen the coordination abilities. Nonetheless, the bulk of tested substances did not lead to any logK value that was seen to be high enough for stable complexation and the use of barium complexes for medical purposes. The range of determined values was logK between 6 and 12 and the highest value was obtained for the Ba-DOTA complex with logK = 11.8, still not high enough compared to other clinically applied pharmaceuticals [22-24]. However, the cavity of the 18-crown-6 moiety seems to be nearly ideal compared to any other sizes of macrocyclic compounds. For this reason, chelating ligands for heavy alkaline earth ions, which are under investigation nowadays, often contain this certain cavity somehow. Some structures that are currently in the research focus are displayed in Figure 2.

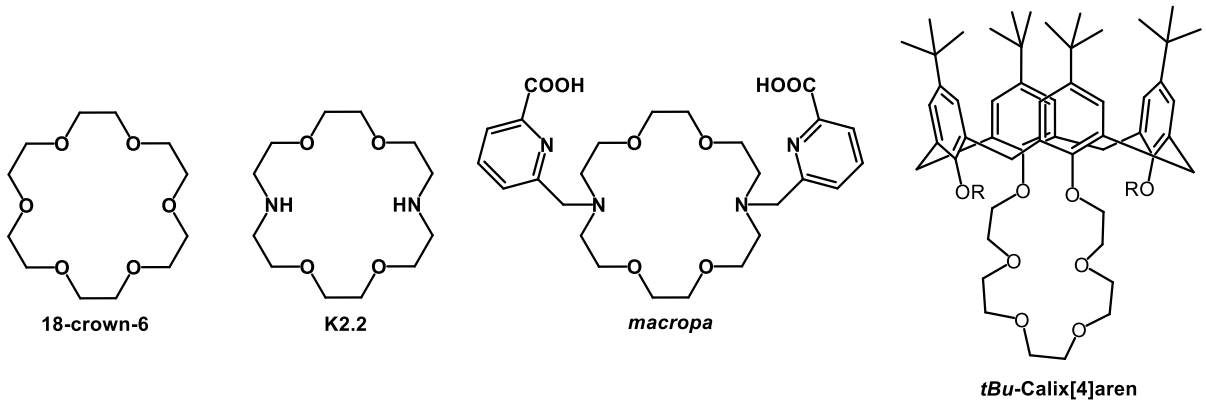

Figure 2. Structural formulas of candidates for barium chelation, that are currently under investigation.

Regarding the potential of calix[4]arenes as chelating ligands for barium ions, no stable complexes were found under physiological conditions. Nevertheless, functionalized calix[4]arenes seem to be excellent extracting agents and could be therefore useful for environmental chemistry [25-27]. Although the logK value of the ligand macropa was determined to be 10.7, which is not the highest value compared to the other chelators, the complexation affinity to barium ions is surprisingly high, even high enough to dissolve the nearly insoluble barium sulfate [28]. Thus, the K2.2-based macrocycle macropa can be seen as an interesting starting point for the development of further chelating agents.

Additionally, several inorganic matrices have been reported for the stable fixation of heavy alkaline earth metal ions, especially for radium isotopes regarding their use in targeted alpha therapy. Matrices

based on titanium dioxide, hydroxyapatite, barium ferrite, barium titanate and barium sulfate nanoparticles have been investigated as metal ion carriers for medical use [29-34]. Despite their ability of appropriate radionuclide binding combined with very high radionuclide retention, none of these materials was reported as a well-working system for radionuclide deposition *in vivo*. Specific binding of targeting biomolecules was not observed for any of the examined nanomaterials. The major obstacle is non-specific binding to serum proteins, followed by accumulation in spleen and liver in any animal experiment, which makes those nanomaterials unusable due to expected major side effects by unwanted irradiation of organs.

From Physiological Behavior to Medical Applications

In contrast to other group 2 metals such as calcium and magnesium, barium is non-essential for humans [35]. On the contrary: even though every human contains approx. 0.3 mg of barium per kilogram body weight; Ba^{2+} is classified as highly toxic even at low concentrations (MAK level 0.5 mg/m^3). Anyway it is assumed, that a certain extent of barium is indispensable for a normal growth [36]. Consequently, each barium compound that is soluble in either water or acidic media (similar to stomach pH) has to be considered as toxic [37]. The lethal dose for barium chloride was determined as 100 mg per kilogram body weight. Oral or inhalation exposure led to muscle cramps (damage of smooth and skeletal musculature), disruption of the circulatory and respiratory system and failures in the central nervous system. Moreover, gastroenteritis, hypoglycemia (driven by intracellular accumulation of potassium) and acidosis are induced [38-40]. All water-soluble compounds are reabsorbed via the gastrointestinal tract and excreted via feces. Renal excretion only occurs to a minor extent of less than 3%. The usage of a sodium sulfate solution as antidote is feasible in an early stage of poisoning, in order to precipitate insoluble and non-toxic barium sulfate [37].

In medical applications, barium sulfate is applied as x-ray contrast agent for imaging of the gastrointestinal tract due to its extremely low solubility in aqueous fluids. For medical examinations, barium sulfate is applied orally and passes through esophagus into the stomach. Barium sulfate is not reabsorbed by the gastrointestinal tract and becomes extracted via defecation [41]. Furthermore, it is applied as contrast agent for computed tomography as well (i.v. injection of a 1%–1.5% solution) [41]. It is a prerequisite to carefully separate the barium sulfate from water-soluble components, which are toxic and would cause severe side effects [42].

Relevant Barium Radioisotopes

According to the Karlsruhe chart of nuclides, there are almost 40 isotopes of the element barium known, owing a mass number between 114 and 153. Six of them are classified as stable, all other radionuclides are radioactive. Only some of them could be interesting for their future use in nuclear medicine, mainly depending on their half-lives and other physical properties such as decay energies and radiation quality. A short overview over potentially relevant barium isotopes is given in Table 1 [43].

Table 1. Overview of selected barium radioisotopes and short characteristics

Isotope	$t_{1/2}$	Decay mode	Decay product(s)	Production
^{126}Ba	100 min	β^+	^{126}Cs → ^{126}Xe	^{125}Cs(p,γ)
^{128}Ba	2.43 d	β^+	^{128}Cs → ^{128}Xe	Cyclotron ^{133}Cs(p,6n)
^{129}Ba	2.23 h	β^+	^{129}Cs → ^{129}Xe	Cyclotron ^{133}Cs(p,5n)
^{129m}Ba	2.16 h	IT	^{129}Ba → ^{129}Cs → ^{129}Xe	^{130}Ba(γ,n)
^{130}Ba	$1.6 \cdot 10^{21}$ a	double ec	^{130}Xe	Natural occurring
^{131}Ba	11.5 d	ec	^{131}Cs → ^{131}Xe	Reactor: ^{130}Ba(n,γ) Cyclotron: ^{133}Cs(p,3n)
^{133}Ba	10.5 a	ec	^{133}Cs	Reactor: ^{132}Ba(n,γ) Cyclotron: ^{133}Cs(p,n)
^{133m}Ba	38.9 h	IT	^{133}Ba → ^{133}Cs	Cyclotron: ^{133}Cs(p,n)
^{135m}Ba	28.7 h	ec	^{135}Ba	Reactor: ^{134}Ba(n,γ)
^{139}Ba	83.06 min	β^-	^{139}La	Fission product of ^{238}U
^{140}Ba	12.8 d	β^-	^{140}La → ^{140}Ce	Fission product of ^{238}U

Both the physical half-life and the decay mode influence the potential use of a particular barium isotope for medical purposes. ^{139}Ba and ^{140}Ba are therapeutic beta emitters and provide simultaneous emission of photons that could be used for imaging and therapy monitoring. Further listed isotopes like ^{129}Ba, ^{131}Ba, $^{133(m)}$Ba, or ^{135m}Ba are diagnostically usable and classified as positron- and gamma-emitting radionuclides. Nevertheless, the application of a number of the presented isotopes is limited by their availability. Either the complex isolation process after nuclear fission reactions or the production starting from a highly expensive enriched target material is hindering the establishment of

an efficient application for the majority of the isotopes, which are shown in Table 1. Moreover, some of these radioisotopes (e.g., ^{129m}Ba, ^{131}Ba, ^{133m}Ba, ^{140}Ba) decay via cascades. In this regard, both the biodistribution of the mother radionuclide (in free ionic form or in a stable complex) and the daughter nuclide(s) are necessary to be considered, which have a different pharmacological behavior *in vivo* in most of the cases.

Apart from these considerations, several approaches, to make barium isotopes accessible for nuclear medicine, have been reported in the past. The starting point of civil usage of barium isotopes can be found after the second World War. Consistently, different research articles focusing group 2 metal radionuclides have been published until today, mainly concentrating on the biodistribution behavior of barium isotopes in comparison with their homologs calcium, strontium, and radium. At the same time, numerous reports were published, dealing with the radioactive fallout and health consequences for the human population. Barium isotopes of particular interest are ^{131}Ba, $^{133/133m}$Ba, ^{135m}Ba, ^{137}Ba and ^{140}Ba. A more detailed profile of these radionuclides is presented in the following sections.

Barium-140

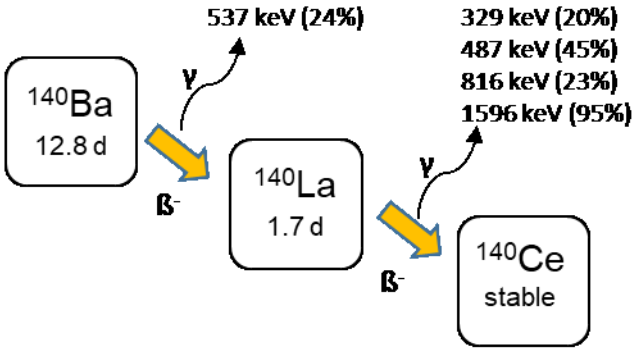

Figure 3. Decay scheme of ^{140}Ba via ^{140}La to stable ^{140}Ce.

The therapeutic beta emitter ^{140}Ba (mean $E_ß$ = 280 keV) is part of the product mixture of various fission reactions, such as ^{238}U fission. It is produced in a reactor and can be separated in high radionuclide purity. One major disadvantage is the emission of high energy photons ($E_γ$ = 1.6 MeV; 95%) caused by the first decay product ^{140}La, that further decays to stable ^{140}Ce. The decay scheme is displayed in Figure 3.

Initial experiments regarding the application of barium isotopes in humans were presented by a Swedish working group in 1952 [44]. This research group also examined the biodistribution behavior of ^{140}Ba in comparison to ^{45}Ca in rats [45]. It was shown that, after intraperitoneal injection, blood clearance as well as bone accumulation kinetics of ^{140}Ba was two-times faster compared to ^{45}Ca. In contrast, the total accumulation of ^{45}Ca was found to be higher than for ^{140}Ba.

Similar studies were performed by an American research group using rats and ^{140}Ba (n.c.a.) in direct comparison to ^{85}Sr [46]. Experimental data were interpreted in dependence of the animals' age. It was demonstrated that, after intravenous injection, older rats (15 months) accumulated less radioactivity compared to younger animals (6-8 weeks). During a long-term study, it was shown that the barium accumulation in the bones occurred to a higher extent than the strontium accumulation. Activity concentration in soft tissues was similar to the concentration in the blood and almost zero even 10 minutes post injection. Furthermore, the same research group provided data on the reabsorption of ^{45}Ca, ^{85}Sr, ^{140}Ba, and ^{226}Ra via the gastrointestinal tract after oral exposure to rats [47]. The strong dependence of radionuclide accumulation kinetics on the age of the used animals was demonstrated again and determined to be significantly lower at a higher age. In general, radionuclide accumulation is completed already seven hours post injection. Maximum radioactivity concentrations in the blood pool were determined 30-60 minutes after intravenous injection. In contrast to the previous observations regarding the behavior of calcium vs. strontium, the distribution and accumulation behavior of barium vs. radium was almost identical.

A similar work, aiming at the comparison of calcium, strontium, and barium radionuclide biodistribution after intravenous injection or oral exposure to dairy cows was published in 1960 [48]. It has been demonstrated that 98% of ^{140}Ba was excreted via feces after oral exposure, in contrast to only 36% of ^{140}Ba after intravenous injection. Eight days after intravenous injection, 10% of the ^{140}Ba was found in the milk and 34% in urine. In general, the blood clearance of ^{45}Ca and ^{89}Sr were comparable, whereas barium radioisotopes showed a clearance, which is 80% of the calcium value.

Barium-137m

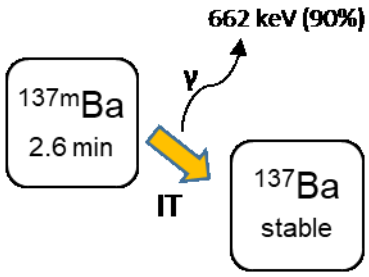

Figure 4. Decay scheme of metastable ^{137m}Ba to stable ^{137}Ba.

^{137m}Ba is obtained from a ^{137}Cs/^{137m}Ba radionuclide generator using the mother nuclide ^{137}Cs ($t_{1/2}$ = 30.3 a), which is immobilized on an ion exchange resin [49]. For separation, the daughter radionuclide ^{137m}Ba is eluted by rinsing the ion exchange resin with a diluted HCl/NH_4Cl solution. Those generators were part of various investigations [50,51] and are still commercially available.

Animal experiments with dogs were carried out by a continuous intraarterial infusion of a ^{137m}Ba-EDTA solution. In this study, a maximal and constant concentration of ^{137m}Ba in the blood was reached, to carry out cardiologic blood pool scans during the infusion using pinhole collimators for gamma radiation filtering [52]. In addition to the high energy photon emissions (Figure 4), ^{137m}Ba is rather inappropriate for medical imaging because of its very short half-life of only 2.6 minutes.

Barium-135m

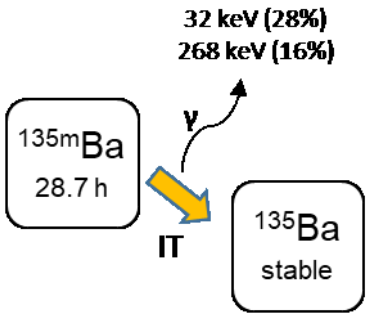

Figure 5. Decay scheme of metastable ^{135m}Ba to stable ^{135}Ba.

^{135m}Ba can be produced by neutron bombardment of stable ^{134}Ba inducing a n,γ-nuclear reaction. High specific activities of the product can be achieved by using a highly enriched ^{134}Ba target, but the natural abundance of ^{134}Ba is only 2.4%. However, the high specific activity is needed for further medical use due to the toxicity of barium compounds in higher concentrations. Regarding its physical properties, ^{135m}Ba can be seen as suitable imaging agent. Providing a half-life of 29 hours, it decays to stable ^{135}Ba. Moreover, photons with an energy of 268 keV are emitted nearly without any other accompanying radiation[53] and thereby enabling SPECT imaging (Figure 5).

Starting from 1970, two research groups intensively investigated the production, physical properties and the scope of possible medical applications of ^{131}Ba and ^{135m}Ba [54-56] One of their main intentions was to compare those “new” radionuclides with already applied $^{85/87m}$Sr and ^{18}F, regarding their qualities in bone tissue imaging. Nevertheless, and due to the higher emission energy, no significant advantages of the barium isotopes over the already examined radionuclides have been demonstrated [57]. Concluding their studies on rodents, dogs, and humans, the pharmacological behavior is mainly dependent on the type of application (intravenous vs. oral). The total accumulation in bone tissue is very high, combined with a very fast blood clearance. Bone-surrounding tissues, such as muscles and the red bone marrow showed a very low accumulation as well. Furthermore, the gastrointestinal excretion profile was pointed out as disadvantage, which is however comparable to previously described studies using calcium and strontium isotopes.

Barium-133 and Barium-133m

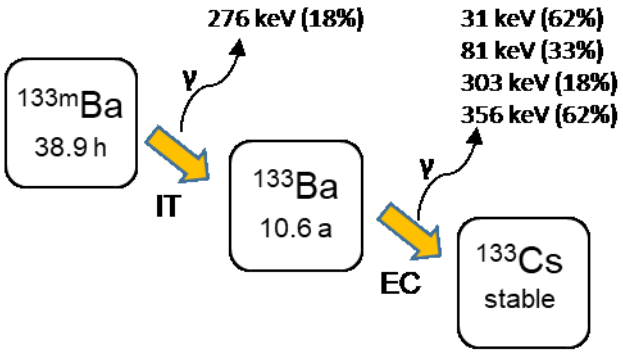

Figure 6. Decay scheme of metastable ^{133m}Ba over ^{133}Ba to stable ^{133}Cs.

The radioisotope ^{133}Ba possesses a long half-life of 10.6 years and decays via electron capture to stable ^{133}Cs (Figure 6). Due to the very long half-life and a higher energy gamma emission (E_γ = 356 keV, 62%), ^{133}Ba is inappropriate for medical applications. However, the metastable form (E_γ = 276 keV, 18%) has a half-life of almost 40 days and is therefore more favorable. Still, the consequent decay to ^{133}Ba can cause the pre-mentioned issues and become an essential disadvantage regarding patient dosimetry and long-lived radioactive waste.

The intestinal discrimination between ^{47}Ca, ^{85}Sr, and ^{133}Ba was compared after oral administration in young albino rats showing that the epithelium has the ability to differentiate between the different M^{2+} ions with an efficiency of absorption of the following order: Ca > Sr > Ba [58].

In 1966, a Polish research group investigated the uptake and retention of ^{133}Ba at different time points after injection [59]. For this purpose, radioactivity values in the blood and in the bones were compared. Besides their work on ^{131}Ba and ^{135m}Ba, Spencer and co-workers also focused on the radionuclide ^{133m}Ba [60]. A much better availability of ^{133m}Ba (no need for highly enriched and expensive target materials) and the possibility of cyclotron production were pointed out as major advantages. Regarding to their studies, the decay to the long-lived ^{133}Ba was tolerable. In vivo studies with dogs pointed out that 60% of the injected radioactivity were accumulated in the bones. Compared to other barium isotopes, an identical behavior was observed, but the uptake it is less compared to the $^{85/87m}$Sr bone accumulation with 70% and a little higher compared to ^{18}F accumulation with 53%.

Comparative studies using ^{47}Ca, ^{85}Sr, ^{133}Ba, and ^{223}Ra were accomplished in human males to study the metabolism of these metal ions after intravenous application. The blood plasma concentrations of these four radionuclides decreased rapidly over time and were generally low. They pointed out that the behavior of ^{47}Ca is similar to ^{85}Sr as well as the behavior of ^{133}Ba compared to ^{223}Ra [61-63].

Moreover, the influence of the chemical form of the applied barium compound was subject of another study published in 1973 [64]. For this purpose, ^{133}Ba-labeled particles (barium aluminosilicate, barium carbonate, barium sulfate) and a [^{133}Ba]$BaCl_2$ solution were administered intramuscular in the hind legs of female rats and the kinetics of the biodistribution was monitored over a period of more than one year. The distribution of barium carbonate particles and the barium chloride solution was similar. Over a period of 50 days, both substances led to a bone accumulation to a major extent (>85%) and no radioactivity at the injection site (<2%) was detectable. After a period of 100 days, barium sulfate particles showed an identical behavior as well. Radioactivity was observed mainly in the skeleton, in contrast to the ^{133}Ba-radiolabeled barium aluminosilicate particles. Even after more than one year, those particles were mainly sticking at the injection site and only a small portion of the injected ^{133}Ba radioactivity was accumulated in the bones (<10% after 399 days).

Barium-131

The neutron bombardment of stable ^{130}Ba in a nuclear reactor by using the n,γ-reaction is described as one production route for ^{131}Ba. An increasing specific activity can be achieved by using a highly enriched ^{130}Ba target, since the natural abundance of only 0.11% ^{130}Ba in natural barium compounds is very low. Due to the toxicity of barium compounds in higher concentration, the use of expensive targets is required in any case. Alternatively, ^{131}Ba can be produced by proton irradiation of a ^{133}Cs target by the p,3n-nuclear reaction. ^{131}Ba decays ($t_{1/2}$ = 11.5 d) via electron capture to ^{131}Cs ($t_{1/2}$ = 9.7 d) which further decays via electron capture to stable ^{131}Xe as displayed in Figure 7. Due to its physical properties and therapeutic potential, the daughter nuclide ^{131}Cs is nowadays in application for brachytherapy [65]. Immobilized on the surface of seeds or needles it is in use for the therapy of prostate cancer (Cesium Blu™) [66].

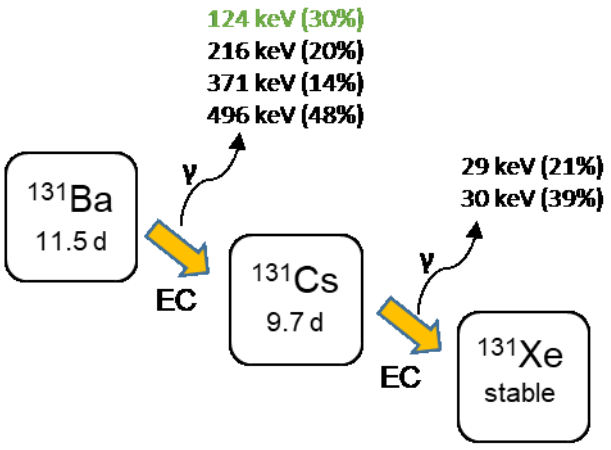

Figure 7. Decay scheme of ^{131}Ba via ^{131}Cs to stable ^{131}Xe.

Several research groups have focused in the past on the use of ^{131}Ba for bone scintigraphy [67]. The research group of Spencer and Treves has investigated ^{131}Ba besides ^{135m}Ba as bone-seeking agent and performed comparative experiments with both isotopes [57]. Nevertheless, the various energy emissions of the first decay (see Figure 7) did not allow sufficient imaging at this time. The influence by the accompanying γ-emission caused by the second decay of ^{131}Cs to ^{131}Xe was reported to be negligible. In vivo experiments with dogs showed a rapid blood clearance with only 8% remaining activity two hours post injection. The main activity fractions accumulated, as expected, in bone tissues. A small portion was excreted via the gastrointestinal excretion route [68]. Distribution studies with humans verified those data, especially the rapid washout from the blood pool and the massive bone uptake. In contrast, activity was excreted for more than 48 hours via the gastrointestinal tract after oral application.

Recently, ^{131}Ba underwent a breaking revival regarding a different focus [69]. On the basis of more than 40 years of barium-related research in combination with the use of modern techniques, this study is focused on the development of a diagnostic match for the therapeutically relevant alpha emitters ^{223}Ra and ^{224}Ra. The preparation of ^{131}Ba was carried out using a cyclotron and the p,3n-reaction. A cesium target (naturally monoisotopic) was irradiated with a 27.5 proton beam for 4 hours to yield up to 300 MBq of ^{131}Ba. ^{133}Ba as isotopic impurity was found with not more than 0.01% in a p,n-side reaction, which is not any disadvantage at all, even in cases of waste disposal and patient dosimetry.

For the first time, SPECT/CT imaging was reported by comparing free ionic ^{131}Ba and the ^{131}Ba-labeled model chelator macropa (see Figure 2) after injection in healthy mice. For image reconstruction, solely the energy emission of 124 keV was used. After energy calibration SPECT/CT-images were obtained for mice receiving both ^{131}Ba tracers. Free ^{131}Ba as divalent cation, as expected, was accumulated in the bones to a major extent and almost no changes in biodistribution was observed by comparing the scans one hour vs. 24 hours post injection. Impressively, the ^{131}Ba-labeled complex showed significant stability *in vivo*. Bone accumulation was substantially lower after 24 hours and the majority of radioactivity was excreted from the body via the renal and hepatobiliary pathways (Figure 8). Therefore, macropa can be seen as a glimmer of hope for the development of suitable complexing agents for barium and radium ions, thereby enabling the chance to follow a theranostic approach using ^{131}Ba for diagnosis and monitoring as well as ^{223}Ra and ^{224}Ra for targeted therapy of various tumor entities.

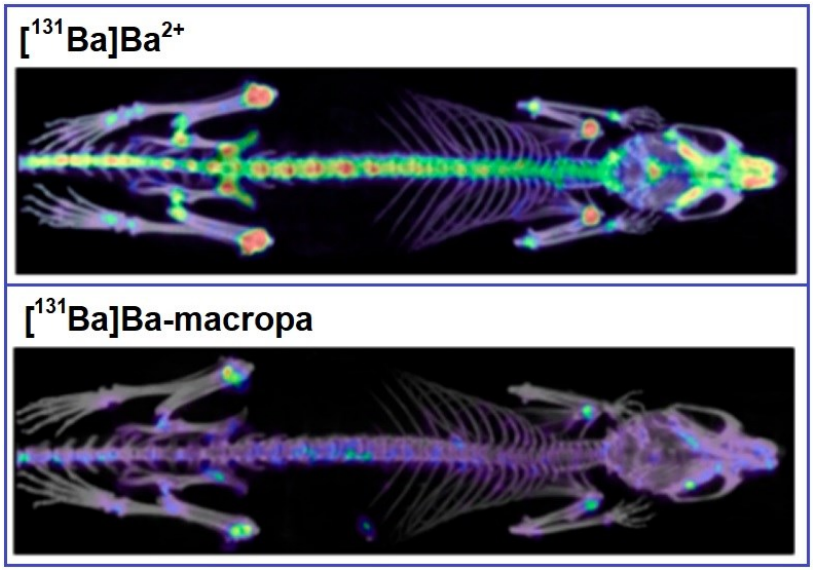

Figure 8. SPECT/CT images of [^{131}Ba]Ba^{2+} and ^{131}Ba-labeled macropa 24 h after intravenous injection in healthy mice using the 124 keV photopeak [69].

Conclusion

Barium isotopes did not yield in any breakthrough for applications in nuclear medicine yet based on their (nuclear) physical and chemical characteristics as well as the partially inappropriate accessibility. Nevertheless, the potential of barium isotopes has been investigated for decades, mainly to better understand the pharmacokinetic behavior *in vivo* and for the evaluation of significant differences compared to other group 2 metal radioisotopes of calcium, strontium, and radium. A similar distribution of the heavy alkaline earth metal ions *in vivo* was reported by many research groups, mainly consisting of massive bone tissue accumulation and excretion pathways. However, the kinetic profile of biodistribution differs; most-likely depending on the different ionic radii. Most recently, the potential use of ^{131}Ba as diagnostic match for $^{223/224}$Ra was reported. A new production method and straight-forward purification procedure enables large-scale availability for future applications in nuclear medicine. First promising approaches to try to overcome the major disadvantage of group two metal ions – the challenging coordination chemistry – have been reported by radiolabeling the model chelator macropa and other K2.2-based complexing agents are still in the focus of current research. In this connection, the application spectrum of barium isotopes, especially ^{131}Ba in stable complexes attached to biomolecules of interest, will be expanded towards new monitoring tools for prospective targeted alpha therapy and theranostic approaches.

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