RARE EARTH NUCLIDES AS POTENTIAL AGENTS FOR SKELETAL IMAGING

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Almost all of the nuclides used for skeletal imaging to date have the drawback of being high-energy gamma emitters. As a result, they are not particularly suited for use with the Anger camera. Even when used with rectilinear scanners, the detection efficiency is lower with high-energy gamma emitters than with weaker gamma emissions because collimators with greater depth and thicker septa must be used for good resolution.

In addition, the physical half-lives of these agents are at two extremes—very long, as in the case of ^{85}Sr, or very short, as in the case of ^{18}F or ^{87m}Sr. A physical half-life between these extremes may be more desirable to avoid excessive radiation dose on the one hand and to allow more time for radiopharmaceutical preparation and clearance of the radionuclides from the soft tissues on the other.

Durbin (*1*) has demonstrated that citrate complexes of the heavier lanthanons in the carrier-free state concentrate primarily in bone. The lighter lanthanons (Ce to Gd) localize primarily in the liver and to a lesser extent in the skeletal system. Current studies in rabbits indicate that reactor-produced lanthanons with even minimal amounts of carrier localize in the reticuloendothelial system rather than in the skeleton.

From the heavier lanthanon group, we have evaluated four as possible bone-imaging agents—lutetium (^{176m}Lu and ^{177}Lu), samarium (^{153}Sm) and erbium (^{171}Er). All are economically produced in a nuclear reactor with a high specific activity. Their essential physical characteristics, proposed administered doses and resultant radiation doses are given in Table 1. These are also compared with the nuclides currently used as bone-scanning agents.

The decay schemes of these nuclides are complex (*2*). The two nuclides of lutetium decay to stable hafnium. ^{153}Sm decays to stable ^{153}Eu, and ^{171}Er decays to ^{171}Tm (1.92 years) which in turn decays to stable ^{171}Yb. None of these agents are ideal from a physical standpoint because all are beta-gamma emitters and the ratio of external photons per disintegration is relatively low for ^{176m}Lu, ^{177}Lu and ^{153}Sm but higher for ^{171}Er (Table 1). However, they all possess a predominant gamma emission with an energy highly suitable for imaging applications.

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TABLE 1. PHYSICAL CHARACTERISTICS AND RADIATION DOSE ESTIMATES FOR SKELETAL-IMAGING NUCLIDES

	Physical characteristics					Radiation dose estimates (rads) (A.F. Method)							
						Skeleton				Marrow			
	Half-life	$\bar{E}_\beta$ MeV	Gamma-energy MeV (% photon yield)	Γ r/mc-hr @ 1 cm	Σ_γ gm rads mc-hr	Administered dose	D_β	D_γ	Total	D_β intrinsic	D_β trabecular	D_γ skeletal	Total
^{85}Sr	65 d	0.015	0.51 (99%)	2.69	1.08	150 μCi	0.77	3.12	3.89	0.03	0.15	1.17	1.35
^{87m}Sr	2.7 h	0.082	0.388 (78%)	1.85	0.682	10 mCi	0.49	0.23	0.71	0.02	0.02	0.09	0.1
^{18}F	1.85 h	0.25	0.51 (194%)	4.95	2.18	10 mCi	1.01	0.50	1.5	0.025	0.2	0.19	0.4
^{176m}Lu	3.7 h	0.52	0.088 (9.2%)	0.055	0.029	10 mCi	4.2	0.02	4.2	0.2	0.1	0.01	0.3
^{177}Lu	6.7 d	0.15	0.208 (6.1%)	0.094	0.038	1 mCi	5.3	0.09	5.4	0.27	1.06	0.04	1.3
^{153}Sm	47 h	0.29	0.103 (28%)	0.496	0.132	1 mCi	3.1	0.23	3.3	0.16	0.6	0.09	0.85
^{171}Er	7.5 h	0.38	0.296, 0.308 (91%)	1.9	0.81	4 mCi*	2.7	0.36	3.0	0.12	0.52	0.12	0.76

* Radiation dose estimates include 1.92-year daughter nuclide ^{171}Tm (0.45 μCi/mCi ^{171}Er).

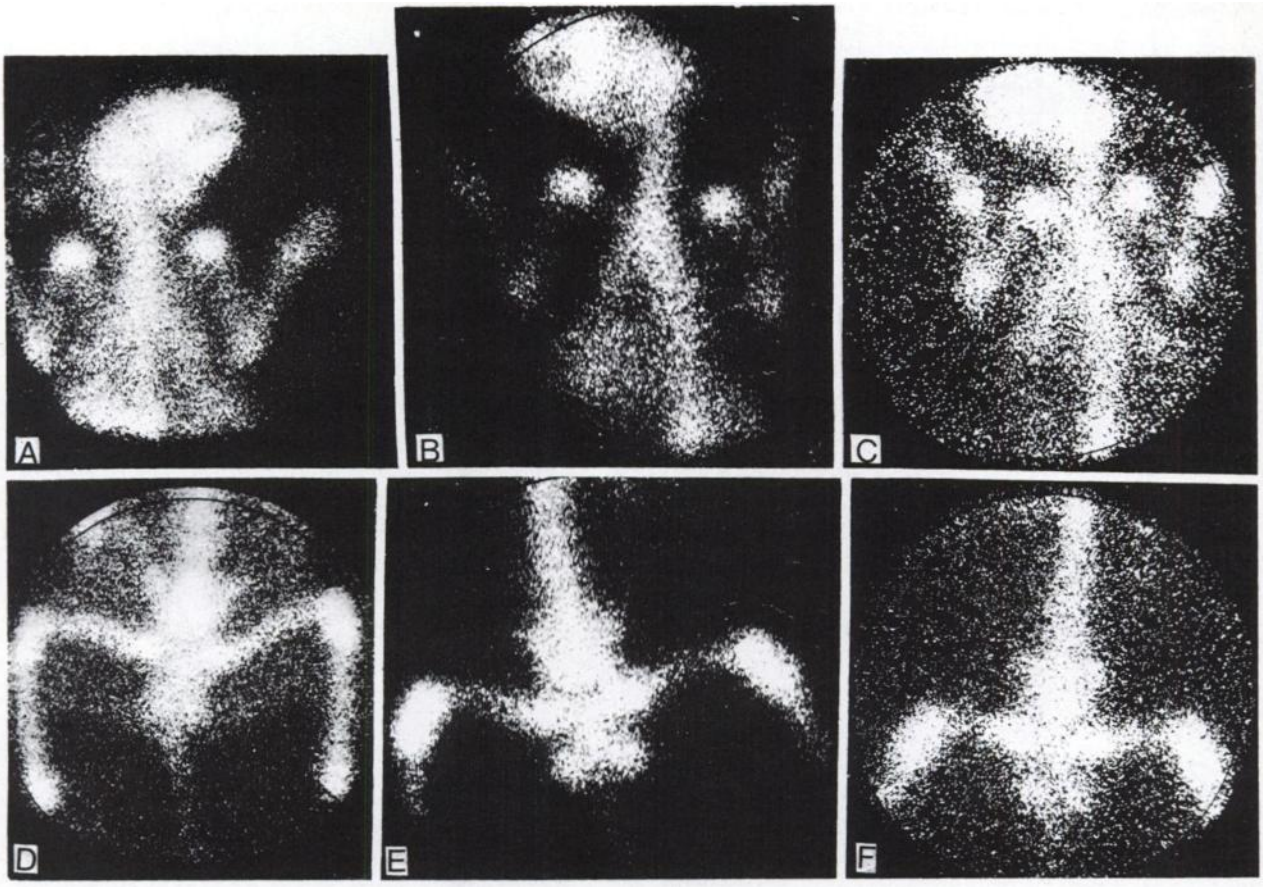

FIG. 1. Skeletal images of adult rabbits obtained on Anger camera 24 hr after i.v. injection of 1 mCi. A and D are made with ^{177}Lu (7-min exposure), B and E with ^{153}Sm (2 min) and C and F with ^{171}Er (4 min).

Another rare earth, dysprosium (^{157}Dy) offers ideal physical characteristics but is cyclotron-produced. Evaluation of this nuclide is in progress.

The biological localization of the rare earths is greatly altered by chelation. When complexed with chelating agents possessing a high stability constant such as DTPA (diethylene triaminepentaacetic acid), these nuclides are rapidly excreted in the urine without reticuloendothelial or skeletal localization. When complexes of low stability are formed, "radiocolloid" formation apparently takes place *in vivo,* and reticuloendothelial localization is the result. However, HEDTA (hydroxyethylenediamine tetracetic acid, analytical grade, J. T. Baker Chemical Co., Phillipsburg, N.J.), or NTA (nitrolacetic acid) form chelates of "intermediate" stability with the rare earths. When these agents are used, approximately 50% of the administered dose localizes in the skeleton. The remainder is promptly cleared from the plasma by the kidneys, and the rate of clearance is similar to that of ^{85}Sr.

The rare earth nuclides are available (Nuclear Science and Engineering Corp., Pittsburgh, Pa.) as chlorides in 0.1–1 *N* HCl solution with specific ac-

TABLE 2. TISSUE DISTRIBUTION IN RABBITS AFTER I.V. INJECTION

	1 hr				3 hr				24 hr			
Nuclide	Bone	Muscle	Marrow	Liver	Bone	Muscle	Marrow	Liver	Bone	Muscle	Marrow	Liver
	% Dose/1% Body Weight											
^{177}Lu	5.12	0.21	0.74	1.93	5.04	0.044	0.32	1.07	5.38	0.032	0.18	0.311
^{153}Sm	7.33	0.14	0.22	1.36	6.34	0.11	0.29	1.74	4.58	0.022	0.13	0.642
^{171}Er	4.79	0.27	0.54	0.89	5.74	0.11	0.35	0.84	7.10	0.10	0.34	0.81
	% Dose in Whole Organ*											
^{177}Lu	51.20	9.13	2.98	7.34	50.40	1.89	1.15	1.31	53.81	1.40	0.73	1.23
^{153}Sm	73.30	6.02	0.89	5.15	63.42	4.58	0.98	9.93	45.70	0.92	0.51	2.51
^{171}Er	47.90	11.66	2.16	4.70	57.40	4.91	0.53	3.27	71.00	4.45	1.36	2.91

Each value represents the mean of 3 animals.
* Total skeleton assumed to be 10% of animal weight, muscle 43%, and marrow 4%.

tivities of 20–200 mCi/mg. The complex is prepared by adding HEDTA in the molar ratio 10:1 (to the metal) and adjusting the pH to 7.5 using 1 *N* NaOH. An equivalent amount of calcium gluconate (Calcium Gluconate Injection, N.F., 10% solution, Parke Davis & Co., Detroit, Mich.) is added and the pH is readjusted to 7.5. The preparation is sterilized either by autoclaving for 20 min at 20 psig or by Millipore filtration.

The toxicity of these metals is low to intermediate when compared to other metals used in nuclear medicine (In, Hg or As). The $LD_{50/30}$ from parenteral doses of lutetium in rodents is 300–325/mg/kg body weight (*3*). No evidence of tissue damage has been found in studies of chronic toxicity with oral doses as high as 1% of the diet for 90 days or in our studies following the single intravenous administration of 100 times the proposed diagnostic doses.

Anticoagulant and hemolytic effects observed with larger pharmaceutical doses (*4*) have not been noted in our animal studies with dose levels 50 times the proposed diagnostic doses or in our limited number of patients to date.

Estimated average skeletal and bone-marrow radiation dose levels are shown in Table 1. The biologically important bone-marrow and gonadal radiation doses are intermediate between those of the nuclides used presently.

Tissue-distribution studies in rabbits following intravenous administration are summarized in Table 2. The skeletal concentration compares favorably with ^{18}F, ^{87m}Sr and ^{85}Sr. Although satisfactory osseous visualization is obtained with the Anger camera after 2 hr, imaging is usually performed at 3, 6 or 24 hr postinjection to take advantage of the higher bone-to-soft-tissue concentration ratios. The average skeletal localization at 3 hr is 50–55%.

The legs of rabbits were fractured and callus-to-normal bone (contralateral tibia) ratios were obtained 14–17 days postfracture for ^{177}Lu, ^{18}F and ^{85}Sr. The ratio for ^{177}Lu is slightly higher than that of ^{85}Sr but somewhat inferior to that of ^{18}F.

Examples of animal skeletal scintiscans are shown in Fig. 1. Our early clinical studies suggest that ^{171}Er and ^{153}Sm produces better images than ^{176m}Lu or ^{177}Lu.

SUMMARY

Good skeletal images can be obtained on the Anger camera using certain radionuclides of the heavier lanthanons as chelates of HEDTA. With rectilinear scanning, slow scanning speeds and long collimators with thick septa necessary for high-energy gamma emissions need not be used. These nuclides are readily and cheaply produced in a nuclear reactor without significant radioactive impurities.

Of the rare-earth nuclides evaluated, ^{153}Sm and ^{171}Er have physical characteristics best suited for imaging in man. ^{153}Sm has the advantage of greater convenience because its half-life is 47 hr and it has higher efficiency with the Anger camera. ^{171}Er has the advantage of a lower estimated radiation dose and a higher ratio of external photons per distintegration.

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