^{157}Dy-HEDTA FOR SKELETAL IMAGING

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The two most popular agents for skeletal imaging, ^{85}Sr and ^{18}F, are not ideal for gamma camera systems because the counting efficiency for their high-energy photons of 0.51 MeV is relatively low. Moreover, ^{85}Sr has a very long physical half-life of 65 days whereas the positron emitter, ^{18}F, has an inconveniently short half-life of 1.83 hr. Because of these drawbacks, several other radionuclides with more desirable physical properties have been tried for skeletal imaging. Durbin et al (*1*) previously showed that the heavier lanthanons localize in the skeleton of rodents when administered carrier-free as citrates. Thereafter, HEDTA chelates of several reactor-produced rare earth nuclides, including ^{171}Er and ^{153}Sm, were successfully used (*2*) in both experimental animals and in patients with osseous malignancies. Exploration of the physical characteristics of all of the rare-earth radionuclides which have been prepared (*3*) indicated that cyclotron-produced ^{157}Dy should be a superior agent for skeletal scanning or camera imaging. It has no beta emission. Its monoenergetic gamma emission of 326 keV undergoes little internal conversion, and its external photon yield is high (91% of all distintegrations). It has a half-life of 8.1 hr and decays by electron capture to ^{157}Tb (half-life, 150 years), which decays in turn to stable ^{157}Gd. This report describes our preliminary results obtained with ^{157}Dy as a bone seeker.

MATERIALS AND METHODS

Dysprosium-157 was produced in the 60-in. cyclotron at Brookhaven National Laboratory by irradiating natural terbium metal foil with 33-MeV protons [^{159}Tb(p,3n)^{157}Dy] (*4*). Very high yields of ^{157}Dy (approximately 30 mCi/μA-hr for a target thickness of 825 mg/cm^2) were obtained by this method of production. After irradiation, the target was dissolved in concentrated HCl; then the ^{157}Dy was separated from the terbium using a cation exchange column and α-hydroxy butyric acid as the eluant. The ^{157}Dy solution was twice evaporated to dryness after adding concentrated nitric acid to completely break up the α-HYBA by oxidation. The residue was redissolved in 1 *N* HCl solution. Aliquots were examined for radioactive contaminants and for stable terbium. The only radiochemical impurity detected was ^{156}Tb (half-life, 5.1 days), and its activity was less than 10^{-5} the ^{157}Dy activity at the time of production. The amount of stable terbium in the solution was less than 0.1 mg per batch. The HEDTA chelate of ^{157}Dy was prepared according to the method described previously for other rare earth nuclides (*2*).

Organ distribution of this preparation was studied in adult New Zealand albino rabbits with an average weight of 3 kg. It was shown previously by several authors that the localization of bone-seeking compounds in the skeleton differs considerably with the age of animals. Consequently, ^{85}Sr (as chloride) was used simultaneously with the radioactive dysprosium in these experiments as a "biological" standard. In a typical study, 10–200 μCi of ^{157}Dy-HEDTA and 10–20 μCi of ^{85}Sr were administered to each animal through the marginal ear vein as separate injections, each in a volume of 1 ml. The animals were sacrificed serially from 1 to 24 hr after injection. The radioassay was carried out by counting multiple samples from each organ in a scintillation well counter first for ^{157}Dy and then for ^{85}Sr. The ^{157}Dy counts were corrected for the Compton contributions from the ^{85}Sr activity in the ^{157}Dy energy window. To determine skeletal activity, multiple samples were counted from the tibia, femur, spine, and pelvic bones. The total activity in the skeleton was estimated by assum-

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TABLE 1. DISTRIBUTION OF ^{157}Dy-HEDTA AND ^{85}Sr IN RABBITS SIMULTANEOUS STUDY (3 EACH)

Organ	% dose in whole organ							
	1 hr		3 hr		6 hr		24 hr	
	^{157}Dy	^{85}Sr	^{157}Dy	^{85}Sr	^{157}Dy	^{85}Sr	^{157}Dy	^{85}Sr
Blood	9.10	8.04	1.68	3.49	0.77	1.86	0.07	0.21
Liver	4.70	2.75	4.17	1.32	3.47	0.63	1.13	0.07
Muscle	7.34	11.10	2.28	6.87	4.24	4.63	0.52	0.64
Kidneys	1.97	0.77	1.49	0.36	0.99	0.20	0.58	0.03
Marrow	0.89	0.86	0.53	0.46	0.49	0.40	0.49	0.38
One whole femur	0.85	1.17	1.38	2.13	1.36	1.89	1.06	1.33
Urine	33.8	10.90	40.8	16.80	—	—	—	—
	% dose/1% body weight							
Blood	1.30	1.15	0.24	0.50	0.11	0.27	0.01	0.03
Liver	1.09	0.64	1.17	0.36	1.17	0.22	0.29	0.02
Muscle	0.17	0.26	0.053	0.16	0.097	0.11	0.012	0.015
Kidney	3.56	1.39	2.48	0.59	1.86	0.36	0.96	0.04
Marrow	0.40	0.39	0.24	0.21	0.23	0.18	0.23	0.17
Bone (average)	3.27	4.93	4.80	7.13	5.06	6.39	4.11	5.29
Femur	3.46	4.76	5.40	8.3	4.85	6.65	4.21	5.33
Tibia	2.23	3.38	3.32	4.18	3.58	4.65	2.78	4.22
Pelvis	3.62	5.35	5.65	7.60	6.40	6.75	5.50	5.92
Spine	3.77	6.22	4.81	7.17	5.41	7.52	4.02	5.53
Ratios								
Bone/blood	2.5	4.3	20	14	46	24	411	176
Bone/marrow	8.2	12.6	20	34	22	36	18	31
Bone/muscle	19	19	91	45	52	58	343	353

TABLE 2. DISTRIBUTION OF ^{157}Dy-HEDTA AND ^{85}Sr IN RABBITS WITH FRACTURED TIBIA SIMULTANEOUS STUDY AT 24 HR

Organ	% dose		% dose /1% BWT	
	^{157}Dy	^{85}Sr	^{157}Dy	^{85}Sr
Blood	0.12	0.12	0.017	0.016
Liver	0.05	0.04	0.011	0.008
Muscle	0.35	0.32	0.008	0.008
Kidneys	0.02	0.01	0.024	0.017
Marrow	0.05	0.05	0.024	0.023
One whole femur	1.72	1.76	6.37	6.53
Tibia	—	—	3.68	3.81
Fract. femur	—	—	4.99	5.16
Fract. tibia	—	—	9.33	9.61
Callus	—	—	17.4	17.8
Ratios				
Callus/blood	—	—	1,042	1,100
Callus/liver	—	—	1,782	2,209
Callus/muscle	—	—	2,289	2,379
Callus/marrow	—	—	815	809
Callus/N. femur	—	—	2.78	2.78
Callus/N. tibia	—	—	4.83	4.78

ing the whole skeleton consisted of equal proportions by weight of tibia, femur, spine, and pelvis and that 10% of the body weight constituted the entire skeleton. The red marrow was sampled from the femur. The total marrow was assumed to be 7% and skeletal muscle 43% of the body weight. The whole liver and both kidneys were weighed, and multiple samples were weighed and counted to obtain the total activity in each organ.

In addition, the localization of ^{157}Dy-HEDTA complex in comparison with ^{85}Sr was determined in the callus of 3-week-old fractures of tibia in albino rabbits. Again, multiple samples from each organ along with samples of the callus were counted in a well scintillation counter as described above. Imaging of the skeleton of a rabbit with 3-week-old fracture of tibia was performed with the gamma camera, demonstrating the distribution of ^{157}Dy-HEDTA both in the normal skeleton and the fracture site at 4 and 24 hr after injection of 3 mCi of ^{157}Dy. In addition, a normal dog was imaged with the Anger camera 6 hr after administration of 3 mCi of ^{157}Dy-HEDTA.

RESULTS

The results of the simultaneous distribution studies of ^{157}Dy-HEDTA and ^{85}Sr are summarized for normal rabbits in Table 1, whereas Table 2 shows their 24-hr distribution in rabbits with tibial fractures 3 weeks old. The soft tissue and blood concentrations of ^{157}Dy-HEDTA are less than those for ^{85}Sr, whereas the skeletal concentrations are similar. The cumulative urinary excretion of ^{157}Dy at 3 hr is approximately three times higher than for ^{85}Sr (40.8% compared with 16.8%). Table 2 shows that the con-

centrations of ^{157}Dy-HEDTA in the callus and normal skeleton are almost identical to those of ^{85}Sr. Furthermore, the ratios of the activity in callus to other major organs also are comparable.

The skeletal concentration of ^{157}Dy-HEDTA is high enough to obtain excellent camera images of both normal bones and callus even at 4 hr (Fig. 1).

DISCUSSION

The tissue localization of different members of Group IV F trivalent rare-earth elements in the carrier-free state varies in a predictable fashion. The lighter lanthanons (Ce to Gd) have larger ionic radii, are more basic, localize primarily in the liver and secondarily in bone, and are excreted chiefly in the feces. On the contrary, the heavier lanthanons (Tb to Lu) including dysprosium have smaller ionic radii, are more acidic, localize primarily in the skeleton, and are excreted in the urine (*1*). In addition, the tissue distribution of the rare earths is greatly influenced by minute amounts of carrier, colloid formation, chelate stability, and plasma protein-binding (*5*). Without chelating agents, they form hydroxycolloids in vivo at the pH of blood, tend to form aggregates and macromolecules by interaction with plasma proteins, and consequently undergo reticuloendothelial localization. Chelates with a high stability constant like DTPA, particularly for elements with smaller ionic radii, undergo prompt urinary excretion without osseous or reticuloendothelial localization. On the other hand, chelates of intermediate stability, such as Dy-HEDTA, prevent colloid formation but allow bone localization to occur. The site of osseous localization is still a controversial issue. Jowsey (*6*) believes the rare earths become adsorbed on exposed mineral surfaces at sites of active bone resorption, whereas others believe there is significant deposition in the protein of bone matrix (*7*). Like other bone-seeking cations, the rare earths deposited in bone have a large slow biological component in their excretion pattern. In the rat skeleton, for example, the biological half-time of the slow component is about 2.5 years (*1*).

The toxicity of rare-earth metals is low to intermediate (*8*) compared with others used in nuclear medicine. The intravenous toxicity of ionic compounds of the rare earths decreases with increasing atomic weight, and the LD_{50} of the heavier lanthanons in rats lies in the range of 30–60 mg/kg (*9*). Hepatosplenic degeneration from repeated large doses in animals is seen only with the lighter lanthanons (*8*). In the 1940s certain rare-earth salts were used extensively as anticoagulants in Europe and occasional instances of hemoglobinuria were noted. Minimal anticoagulant effects were produced for 6–8 hr with doses of 5–8 mg/kg, and slight transient elevation of the plasma hemoglobin level was occasionally detected with doses as low as 1–2 mg/kg (*10*). The residual terbium in the administration of the carrier-free ^{157}Dy used in this study, however, are only about 7 ng/kg. This is approximately 2,000 times less than the dose required for minimal pharmacological effects.

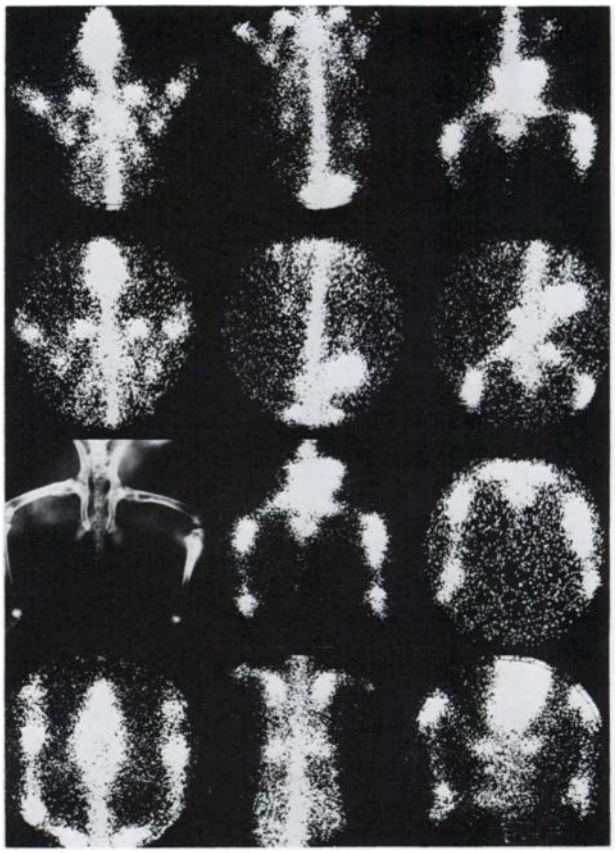

FIG. 1. Camera images after 3-mCi ^{157}Dy-HEDTA. Rabbit at 4 hr (top row) and 24 hr (second row). Radiograph, 4- and 24-hr images of tibial fracture site shown in third row. Images obtained in normal dog at 6 hr (bottom row).

Estimated average skeletal and bone marrow radiation dose levels for ^{157}Dy-HEDTA are shown in Table 3 and compared with other agents. Although the immediate daughter nuclide, ^{157}Tb, is radioactive, its contribution to the radiation dose is negligible because only 6 nCi are produced from the decay of 1 mCi of ^{157}Dy. The biologically important bone marrow and gonadal radiation doses from ^{157}Dy are about the same as for ^{18}F. For diagnostic examinations in humans, therefore, administered doses of 10 mCi appear reasonable. In Table 3, ^{99m}Tc also is listed because a new compound of this nuclide potentially useful for skeletal imaging is under investigation in our laboratory.

TABLE 3. PHYSICAL PROPERTIES OF RADIONUCLIDES SUITABLE FOR SKELETAL IMAGING

Radionuclide	Half-life	Gamma energy (keV)	External photon yield (%)	Average beta energy Eβ (MeV)	Σγ (gm rads/μCi-hr)	Recommended dose (mCi)	Estimated skeletal dose (rads)*	Estimated marrow dose (rads)
^{18}F	1.83 h	511	194	0.25	2.18	10	1.5	0.4
^{87m}Sr	2.7 h	388	78	0.082	0.682	10	0.71	0.21
^{171}Er†	7.5 h	296	91	0.38	0.81	4	3.0	0.76
^{139m}Ba	28.7 h	268	16	0.200	0.125	3	4.08	0.87
		308						
^{153}Sm	47 h	103	28	0.290	0.132	1	3.3	0.85
^{131}Ba†	11.7 d	124	28	0.043	1.221	0.3	4.28	1.35
		216	19					
		373	13					
		496	48					
^{85}Sr	65 d	512	99	0.015	1.08	0.15	3.89	1.35
^{157}Dy†	8.1 h	326	91	0.014	0.741	10	1.27	0.55
^{167}Tm†	9.6 d	208	49	0.126	0.258	0.5	3.45	0.91
^{99m}Tc	6 h	140	90	0.015	0.273	10	0.45	0.10

* Assuming 50% of injected activity remains in the skeleton.
† Includes radiation from radioactive daughters.

SUMMARY AND CONCLUSIONS

Dysprosium-157 appears to be the best rare-earth nuclide available for skeletal imaging using either rectilinear scanner or scintillation camera. It is readily produced in a cyclotron from natural terbium, but the p,3n reaction requires protons of 33 MeV. Its monoenergetic gamma emission of 326 keV, with an external photon yield of 91%, is more suitable for use with the Anger camera than the higher energy photons of ^{18}F or ^{85}Sr. Its half-life (8.1 hr) is 4.4 times greater than ^{18}F, so that shipping problems are not as great. Imaging studies may be performed 4–6 hr, or 18–24 hr after administration. The skeletal localization of the HEDTA chelate is similar to other heavier lanthanons studied previously. Fortunately, there is no gastrointestinal excretion to obscure the abdominal or pelvic bones, as occurs with nuclides of strontium or barium. Fracture sites in experimental animals were well demonstrated by imaging, so that it is likely that other lesions including skeletal metastases will be detected also.

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