

Radiation Absorbed Dose from Technetium-99m-Labeled Bone Imaging Agents

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The estimated absorbed doses from an i.v. administration of technetium-99m methylene diphosphonate (^{99m}Tc]MDP), ^{99m}Tc]hydroxymethylene diphosphonate (HMDP), ^{99m}Tc]hydroxyethylidene diphosphonate (HEDP), and ^{99m}Tc]pyrophosphate (PP_i) are given in Table 1. The data and assumptions used for the calculations follow.

RADIOPHARMACEUTICAL

The four principal radiopharmaceuticals that have been used for bone imaging are ^{99m}Tc]MDP, ^{99m}Tc]HMDP, ^{99m}Tc]HEDP, and ^{99m}Tc]PP_i. These radiopharmaceuticals are prepared by adding ^{99m}Tc]pertechnetate to a preparation containing stannous ions and either a diphosphonate or pyrophosphate ligand. Chromatographic assays conducted by one investigator supplying clearance data for this study showed the radiochemical purity of each radiopharmaceutical to consistently exceed 90% (2).

NUCLEAR DATA

Technetium-99m decays to ^{99}Tc by isomeric transition with a half-life of 6.02 hr. The radioactive daughter ^{99}Tc decays to ruthenium-99 (^{99}Ru) by a beta particle emission of 0.101 MeV average energy with a half-life of 2.13×10^5 yr. The very small radiation dose contribution from the decay of ^{99}Tc is omitted from the dose estimates presented in this report. Further details on

the decay schemes and radiation dose constants for ^{99m}Tc and ^{99}Tc are given in Table 2.

BIOLOGIC DATA AND DOSE CALCULATIONS

Dose estimates in this report are based on data obtained from measurements of activity in blood and urine (and kidney data in the case of ^{99m}Tc]MDP) for each of the radiopharmaceuticals in patients with minimal or no bone disease and in volunteer subjects. Activity assays were made between 3 min and 24 hr (Table 3). These include data on 25 patients studied with ^{99m}Tc]MDP, ten patients with ^{99m}Tc]HMDP, ten patients with ^{99m}Tc]HEDP, and 15 patients with ^{99m}Tc]PP_i. Quantitative kidney data were obtained for ^{99m}Tc]MDP in four patients using conjugate view counting techniques (Thomas SR: unpublished data).

The four-compartment model shown in Figure 1 was used to generate intercompartmental rate constants, k_{ji} , and the residence times, τ , in the individual compartments for ^{99m}Tc]MDP. The k_{43} calculated from these data was used in the model solution for the transfer rate constants for ^{99m}Tc]HMDP, ^{99m}Tc]HEDP, and ^{99m}Tc]PP_i because no kidney data were available for them. Compartment 1 represents blood and extracellular fluid (ECF); compartment 2, bone; compartment 3, kidneys; and compartment 4, urine. More complex models have been proposed to describe the kinetics of radiopharmaceuticals used to study bone (9,10). The four-compartment model that combines blood and extracellular fluid into one compartment appears to be best for the purpose of calculating the absorbed dose from the data used for the four agents presented here. Simplified smaller models often will not answer all the questions addressed by a larger model (11). For this reason, the

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TABLE 1
Estimated Absorbed Dose from Intravenous Administration of Technetium-99m Labeled Bone Imaging Agents

Target organ	Absorbed dose per unit administered activity							
	MDP	HMDP	HEDP	PP _i	MDP	HMDP	HEDP	PP _i
	(rad/mCi)				(mGy/MBq)			
Bone surfaces	0.23	0.34	0.13	0.25	0.061	0.091	0.036	0.068
Bladder wall ¹	0.13	0.081	0.15	0.092	0.034	0.022	0.041	0.025
Kidneys	0.031	0.022	0.035	0.023	0.0084	0.0059	0.0094	0.0063
Red bone marrow	0.034	0.048	0.024	0.040	0.0093	0.013	0.0066	0.011
Ovaries	0.012	0.012	0.014	0.014	0.0032	0.0032	0.0037	0.0037
Testes	0.0082	0.0085	0.0092	0.0096	0.0022	0.0023	0.0025	0.0026
Remainder of the body	0.010	0.013	0.0094	0.013	0.0028	0.0036	0.0026	0.0035

¹ Bladder wall dose is calculated for a constant bladder content of 200 ml (1). The dose was calculated by assuming an initial void at 2 hr and subsequent regular void intervals of 4.8 hr.

rate constants and other values calculated using the current model should not be applied to other bone-imaging radiopharmaceuticals, particularly those with longer-lived radionuclides.

The activity in plasma and ECF was assumed to be in a steady state 30 min after administration. The extracellular fluid volume was estimated for each patient by assuming that the total-body water is 600 ml/kg of body weight in the male and 500 ml/kg of body weight in the female, that 43.3% of the body water is extracellular fluid, and that 7% of the body water is plasma (12). The activity per liter of plasma was available for [^{99m}Tc]MDP, [^{99m}Tc]HEDP, and [^{99m}Tc]PP_i. The values were extrapolated directly to activity in total ECF. Because no plasma values were available for [^{99m}Tc]HMDP, the ECF values were estimated by assuming that 90% of the measured activity in the whole blood was actually in the plasma. This was derived by comparing plasma and whole blood values for the other three agents.

The intercompartmental rate constants, k_{ji} , were calculated using the iterative least squares program, SAAM-27 (13). First-order kinetics was assumed between compartments. Input data for the SAAM program consisted of the percent of the administered activity of each agent in blood and extracellular fluid and urine at various times after injection. The transfer rate constants derived from these calculations are shown in Table 4.

The SAAM program estimates the standard deviations for the calculated transfer rate constants, Table 4. These values are approximations and may not express the true uncertainties in the rate constants because of compensations for nonlinearity and simplifications inherent in multilinear regression analysis (14).

The coefficients α_{hj} and biologic disappearance constants λ_j (Table 5) were determined from the transfer rate constants by solving simultaneously the differential equations associated with each compartment. A computer program called DIFFSOL (15) was used for these

TABLE 2
Nuclear Data

Radionuclide	^{99m} Tc				⁹⁹ Tc	
	E_i	n_i	Δ_i	Δ_i	Δ_i	Δ_i
Physical half-life	6.02 hr				2.13 × 10 ⁵ y	
Decay constant	0.1151 hr ⁻¹				3.25 × 10 ⁻⁶ y ⁻¹	
Mode of decay	I.T.				β^-	
Principal radiations	(keV)		(rad g/ μ Ci h)	(Gy kg/MBq s)	(rad g/ μ Ci h)	(Gy kg/MBq s)
Photon	18-21	0.079	0.0029	2.18 × 10 ⁻¹⁰	—	—
	140.5	0.89	0.266	2.00 × 10 ⁻⁸	—	—
Nonpenetrating	—	—	0.0332	2.50 × 10 ⁻⁹	0.216	1.62 × 10 ⁻⁸

E_i is mean energy per particle or photon.

n_i is mean number of particles or photons per nuclear transition.

Δ_i is mean energy emitted per nuclear transition.

Nonpenetrating radiation for ^{99m}Tc includes conversion and Auger electrons ranging in energy from 1.6 to 140 keV.

Nonpenetrating radiation from ⁹⁹Tc includes beta minus emissions with an average energy of 101.3 keV. Only photons whose mean number per transition is 0.01 or greater are included. See references (3, 4) for sources of nuclear data.

NOTE: Complete decay of one unit of activity of ^{99m}Tc produces 3.2 × 10⁻⁹ units of activity of ⁹⁹Tc.

TABLE 3
Human Subject Data

Radiopharmaceutical	Number of subjects	Observation time duration (hr)	Reference
^{99m}Tc]MDP	6	24	5
	3	24	†
	2	6	†
	10	4	‡
	4	24	§
^{99m}Tc]HMDP	10	4	‡, †
^{99m}Tc]HEDP	10	4	6, ‡
^{99m}Tc]PPi	15	24	7, 8, †

* With the exception of six normal adult volunteers studied with ^{99m}Tc]MDP (5), all subjects were adult patients referred for the bone imaging procedure.

† Personal communication: D. A. Weber.

‡ Personal communication: T. G. Rudd.

§ Personal communication: S. R. Thomas.

† Personal communication: J. Littlefield.

calculations. Cumulated activities per unit administered activity (residence times) for blood and ECF, bone, and kidney were calculated using these values. One-half of the bone residence time was assigned to trabecular bone and one-half to cortical bone because trabecular and cortical bone surface areas are assumed to be equal (16).

The residence time for bladder contents was calculated by solving the differential equation that describes the change in activity in Compartment 4 (urine) and using a model in which the bladder was emptied at 2 hr after administration of the radiopharmaceutical and then at 4.8-hr intervals, integrating the activity

from time of administration to infinity (1). The residence times in trabecular and cortical bone for ^{99m}Tc]HEDP are shorter by factors of 2–3 than those for the other agents. One possible explanation is that blood and urine data used in the calculation were only collected for 4 hr (6); however, when 24-hr data from Subramanian et al. (5) were used in the calculation, the residence time was even shorter. The residence time in the remainder of the body was assumed to be equal to the residence time for the blood and ECF. The residence times in all source organs are given in Table 6 for each radiopharmaceutical.

Absorbed dose estimates were made for various organs using the residence times in the source organs listed in Table 6. The S values for bladder wall, kidneys, ovaries, and testes were taken from MIRD Pamphlet No. 11 (17). Values of S for bone surfaces as the source organ irradiating bone surfaces and red marrow were taken from Johansson's calculations (18). An S value for each target organ from activity in the remainder of the body was calculated according to the method described by Coffey and Watson (19). The remainder of the body is considered to be the total body excluding the source organs (trabecular bone, cortical bone, kidneys, and bladder contents). Table 7 provides the S values that are not available in MIRD Pamphlet No. 11 (17).

Other sources of radiopharmaceutical variability have been omitted here. These include differences between the various commercial and "in-house" kits, the state of ^{99m}Tc and the labeling characteristics of ^{99m}Tc from the various dry-column and wet-column generators, and the age, pathophysiologic state, and drug

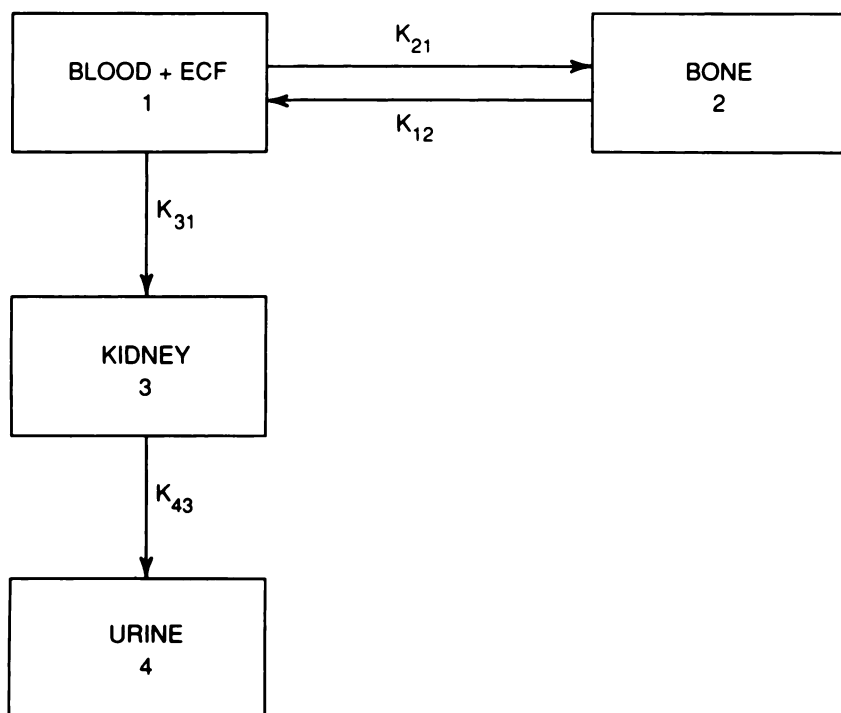


FIGURE 1
Model used for dose estimates of bone imaging agents.

TABLE 4
Transfer Rate Constants (hr⁻¹)

Radiopharmaceutical	k ₁₂	k ₂₁	k ₃₁	k ₄₃ *
Technetium-99m MDP	0.063 ± 0.010	0.295 ± 0.025	0.305 ± 0.012	3.25 ± 0.37
Technetium-99m HMDP	0.154 ± 0.116	0.508 ± 0.15	0.135 ± 0.021	3.25
Technetium-99m HEDP	0.054 ± 0.026	0.110 ± 0.070	0.260 ± 0.025	3.25
Technetium-99m PP _i	0.127 ± 0.022	0.241 ± 0.021	0.104 ± 0.004	3.25

* The transfer rate constant k₄₃ calculated for [^{99m}Tc]MDP was used for the other three agents. See section on Biologic Data and Dose Calculations.

TABLE 5
Biologic Parameters of the Fractional Distribution Function α_n(t)
Single Intravenous Administration of ^{99m}Tc-Labeled Bone Radiopharmaceuticals

Source organ	^{99m} Tc]MDP		
	λ ₁ = 3.25 hr ⁻¹ α _{n1}	λ ₂ = 0.633 hr ⁻¹ α _{n2}	λ ₃ = 0.0304 hr ⁻¹ α _{n3}
Blood + ECF	—	0.946	0.0541
Bone	—	-0.490	0.490
Kidneys	-0.115	0.110	0.00512
Source organ	^{99m} Tc]HMDP		
	λ ₁ = 3.25 hr ⁻¹ α _{n1}	λ ₂ = 0.770 hr ⁻¹ α _{n2}	λ ₃ = 0.0271 hr ⁻¹ α _{n3}
Blood + ECF	—	0.829	0.171
Bone	—	-0.683	0.683
Kidneys	-0.0524	0.0452	0.00718
Source organ	^{99m} Tc]HEDP		
	λ ₁ = 3.25 hr ⁻¹ α _{n1}	λ ₂ = 0.388 hr ⁻¹ α _{n2}	λ ₃ = 0.0361 hr ⁻¹ α _{n3}
Blood + ECF	—	0.949	0.051
Bone	—	-0.315	0.315
Kidneys	-0.0899	0.0858	0.0031
Source organ	^{99m} Tc]PP _i		
	λ ₁ = 3.25 hr ⁻¹ α _{n1}	λ ₂ = 0.443 hr ⁻¹ α _{n2}	λ ₃ = 0.0299 hr ⁻¹ α _{n3}
Blood + ECF	—	0.764	0.236
Bone	—	-0.585	0.585
Kidneys	-0.0358	0.0282	0.00760

TABLE 6
Residence Time (τ) in Source Organs (hr)

Source organ	^{99m} Tc]MDP	^{99m} Tc]HMDP	^{99m} Tc]HEDP	^{99m} Tc]PP _i
Bladder contents	0.782	0.483	0.954	0.545
Kidneys	0.148	0.0861	0.164	0.0923
Trabecular bone	1.36	2.02	0.730	1.50
Cortical bone	1.36	2.02	0.730	1.50
Remainder of body	1.64	2.14	2.22	3.00

TABLE 7
S Values for Remainder of Body, Cortical and Trabecular Bone Surfaces

Target organ	Source Organ, h					
	Remainder of the body* (rad/μCi hr)	Cortical bone surface† (rad/μCi hr)	Trabecular bone surface† (rad/μCi hr)	Remainder of the body* (Gy/MBq sec)	Cortical bone surface† (Gy/MBq sec)	Trabecular bone surface† (Gy/MBq sec)
Bone surfaces	2.4×10^{-6}	8.2×10^{-5}	8.2×10^{-5}	1.8×10^{-10}	6.2×10^{-9}	6.2×10^{-9}
Red bone marrow	2.9×10^{-6}	4.0×10^{-6}	1.6×10^{-5}	2.2×10^{-10}	3.0×10^{-10}	1.2×10^{-10}
Bladder wall	1.9×10^{-6}	—	—	1.4×10^{-10}	—	—
Kidney	1.4×10^{-6}	—	—	1.1×10^{-10}	—	—
Ovaries	2.4×10^{-6}	—	—	1.8×10^{-10}	—	—
Testes	1.7×10^{-6}	—	—	1.3×10^{-10}	—	—
Total body	2.0×10^{-6}	—	—	1.5×10^{-10}	—	—

* In this report remainder of the body refers to total body minus cortical bone surfaces, trabecular bone surfaces, kidney, and bladder contents. See Ref. (19) for details.

† Mass of bone surfaces was assumed to be 120 g evenly divided between trabecular bone and cortical bone surfaces. See Ref. (18) for details. The S values for activity on the bone surfaces irradiating targets other than bone and marrow were taken from MIRD Pamphlet No. 11 using the values for cortical and trabecular bone as the source organs.

history of the patient. However, the short physical half-life of ^{99m}Tc negates to a large extent the importance of differences in biologic half-life resulting from the patient status and the radiopharmaceutical preparation.

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