DIAGNOSTIC NUCLEAR MEDICINE

Tc-99m Hydroxymethylene Diphosphonate and Tc-99m Methylene Diphosphonate: Biological and Clinical Comparison: Concise Communication

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The biologic and imaging characteristics of Tc-99m HMDP and Tc-99m MDP were compared in ten patients. Tc-99m HMDP blood levels were marginally lower at 4 hr. There were no significant differences in 4-hr urinary clearance, normal bone-to-background ratio, or ratio of lesion to normal bone. Relative image quality comparison showed a slight preference for Tc-99m HMDP. Biologically Tc-99m HMDP compares favorably with Tc-99m MDP. Under the conditions of this study, Tc-99m HMDP image quality is at least comparable to that of Tc-99m MDP.

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There is continuing interest in developing new bone-imaging agents (*1*,*2*). Currently, Tc-99m methylene diphosphonate (MDP) is the most widely used bone-imaging agent, in part because of its rapid blood clearance and high ratios of bone-to-soft tissue (*3*). Francis and coworkers have recently introduced the derivative hydroxymethylene diphosphonate (HMDP) and have noted its improved physicochemical and biological characteristics (*4*). Other studies have demonstrated higher absolute bone uptake (*5*) as well as improved imaging characteristics in humans (*6*).

Because of these observations, and because clinical data comparing Tc-99m HMDP and Tc-99m MDP are lacking, we have compared their biological and imaging characteristics in a series of ten patients.

MATERIAL AND METHODS

Radiopharmaceuticals. HMDP and MDP kits were obtained from commercial suppliers.* Each HMDP kit contained 2.0 mg of HMDP and 0.16 mg of stannous chloride. Each MDP† kit contained 10 mg of MDP and 0.84 mg of stannous chloride. The molar ratios of diphosphonic acid to stannous chloride were 11.5 to 12.8 for HMDP and MDP, respectively.

Patient material. Ten patients referred for routine bone imaging were asked to participate. No attempt was made to select patients with or without bone disease. All were normally hydrated and ambulatory.

Study protocol. Double-blind paired studies were performed on each of the ten patients within a two-week period. The kits were labeled with 20 ± 1 mCi of Tc-99m immediately before injection, and an appropriate standard was made. The entire contents of a single kit were used for each study. The following collections were then made: (a) blood samples were obtained at 5, 15, 30 min and 1, 2, and 4 hr after injection; and (b) total urine collection was obtained from the time of injection up to 4 hr. Blood activity was expressed as percent dose per liter of blood and percent dose in the estimated whole-blood volume. Urinary activity was expressed as percent dose. Blood and urine aliquots (1 ml) were counted in a standard well counter with a sodium iodide crystal and single-channel analyzer calibrated for the 140 keV photopeak of Tc-99m.

Imaging studies. Images were begun 4 hr after injection. Anterior and posterior whole-body images were obtained using a large-field-of-view gamma camera and a moving whole-body imaging bed.‡ The images were set up to obtain constant information density. Spot images of the lumbar spine and the femurs were obtained and

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TABLE 1. INDIVIDUAL PATIENT DATA

Patient no.	Sex	Age	Wt(Kg)	Diagnosis	Blood activity % dose/l 4 hr MDP	Blood activity % dose/l 4 hr HMDP	% dose/WBV* 4 hr MDP	% dose/WBV* 4 hr HMDP	% dose 4 hr urine MDP	% dose 4 hr urine HMDP
1	F	62	92	Ca. breast	0.900	0.740	4.88	4.02	55	49
2	M	60	86	Osteoarthritis	0.459	0.332	2.43	1.76	57	54
3	M	67	65	Hypernephroma	1.87	1.24	7.48	4.96	12	12
4	F	72	86	Osteomyelitis	0.352	0.565	1.79	2.87	23	22
5	F	72	68	Paget's disease	0.697	0.517	2.80	2.07	Incom.	35
6	M	79	79	Ca. prostate	1.70	0.801	8.26	3.90	38	Incom.
7	M	69	61	Ca. tongue	0.799	0.620	3.00	2.33	50	52
8	M	50	65	Osteomyelitis	0.930	0.747	3.72	2.99	46	44
9	F	54	53	Fracture	0.995	0.804	3.11	2.51	38	42
10	F	52	62	Osteoarthritis	0.570	0.559	2.09	2.04	49	44
Average values					0.930	0.692	3.96	2.95	42	40
Standard deviation					±0.50	±0.24	±2.24	±1.04	±17	±15
p value (paired)					<0.05		= 0.057		>0.10	

* Estimated whole blood volume based on avg. values (61.5 ml/kg men, 59.0 ml/kg women).

stored in digital form. Selected images of abnormally increased bone uptake were similarly acquired. The digitized images were used to generate normal bone-to-background ratios (lumbar vertebra and femur), and ratios of abnormal bone-to-normal bone. Image quality was graded subjectively by two observers in two separate ways. First the two images for each patient were compared without knowledge of which tracer had been given, and were graded for relative image quality. Second, the 20 images were independently graded for image quality on a scale from 1 (poor) to 5 (excellent)—again without knowledge of the patient or agent.

RESULTS

Biological data. The clinical and biological data are summarized in Table 1. At 4 hr Tc-99m HMDP blood activity was marginally lower. Four-hour urinary excretions were not significantly different. Comparative blood clearance curves are shown in Fig. 1. Ratios for normal bone (lumbar vertebra, femur) to soft tissue and for lesion-to-normal bone showed no significant differences between the two agents (Table 2).

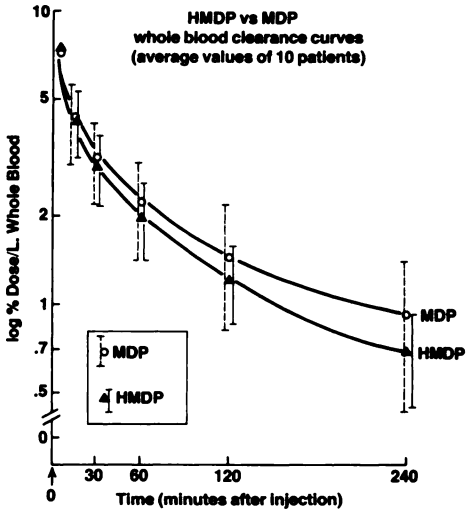

FIG. 1. Comparative whole-blood clearance; average values ±1 s.d.

Image quality. Imaging time and total counts accumulated were not significantly different for the two agents. When the whole-body images were compared side by side, there was a slight but significant preference for the Tc-99m HMDP images (Table 3). When the images were graded independently by random, no significant difference appeared (Table 4). The small number of lesions seen were too few to allow evaluation of the relative efficacy of lesion detection for the two agents. Figures 2, 3, and 4 show representative images of normal and abnormal studies.

DISCUSSION

The biological behavior of Tc-99m MDP found in this series is similar to that previously published (*3*). Clinical data directly comparing Tc-99m HMDP to Tc-99m MDP are sparse. Fogelman has demonstrated significantly higher absolute bone uptake for Tc-99m HMDP than for either Tc-99m MDP or Tc-99m HEDP (*5*). Rosenthall and associates compared Tc-99m HMDP and Tc-99m MDP in normal volunteers and found no significant differences in blood levels, urinary excretion, or image quality (*7*). These last findings differ from ours, but the method of radiopharmaceutical preparation was also different. We used a single kit (reaction vial) for each study, and labeled it with 20 mCi of Tc-99m im-

TABLE 2. INDIVIDUAL PATIENT DATA

Patient no.	Bone/Soft Tissue				Lesion/Normal Bone	
	Femur		Lumbar spine			
	MDP	HMDP	MDP	HMDP	MDP	HMDP
1	2.70	3.24	2.29	3.20	1.58	1.25
2	1.37	1.55	3.21	4.12	1.67	2.14
3	2.03	2.35	4.34	3.39	—	—
4	2.36	1.93	2.96	3.00	1.37	1.40
5	2.77	2.84	3.24	2.95	1.19	1.50
6	3.09	3.09	4.84	3.25	—	—
7	2.64	3.12	4.58	4.62	—	—
8	1.72	2.05	4.13	5.05	2.09	1.45
9	3.42	4.88	3.32	3.98	2.12	2.02
10	6.00	6.44	8.34	10.30	—	—
Average	2.81	3.15	4.13	4.39	1.67	1.63
±1 s.d.	±1.28	±1.48	±1.68	±2.20	±0.38	±0.36
p value (paired)	<0.10		>0.10		>0.10	

mediately before injection. Rosenthall loaded each reaction vial with larger amounts of Tc-99m and then used the contents for several patient doses. Possibly this difference could account for the conflicting results.

The ultimate value of any bone-imaging agent is lesion detection efficacy. Too few lesions were present in our series to allow evaluation of relative efficacy of lesion detection. Silberstein and associates compared Tc-99m HMDP to Tc-99m HEDP and demonstrated no difference in sensitivity, although four lesions (out of 40 lesions total, 20 patients) were better demonstrated by Tc-99m HMDP (*6*). Rosenthall, comparing Tc-99m HMDP and Tc-99m MDP found no significant difference in lesion uptake (*7*).

Tc-99m HMDP is a promising new bone-imaging agent. Biologically, it compares favorably with Tc-99m MDP, and its routine use for diagnostic bone-imaging should result in improved visualization of the normal bony skeleton. Whether this will favor improved lesion detection will require additional carefully controlled clinical studies.

TABLE 3. COMPARATIVE IMAGE QUALITY*

	Scans
HMDP > MDP	13
HMDP = MDP	5
HMDP < MDP	2

* Each set of scans (10 sets total) compared by two observers. p value <0.05.

TABLE 4. COMPARATIVE IMAGE QUALITY

Random, individual evaluation of HMDP and MDP

	No. scans	No. observations*	Average grade†
Tc-99m HMDP	10	20	2.75 ± 0.79
Tc-99m MDP	10	20	2.90 ± 0.72

* Each scan graded by two observers.
† Scale: 1(poor) to 5(excellent), p value >0.10.

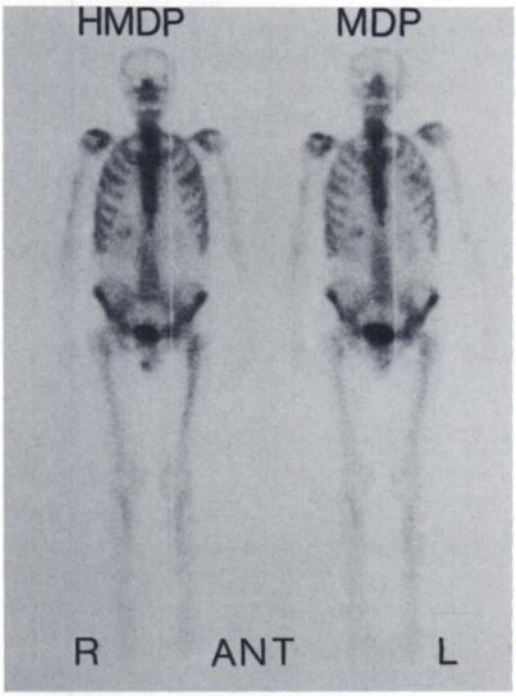

FIG. 2. Comparative whole-body images, Patient 7. Rib detail sharper on HMDP image. Soft-tissue uptake in RUQ seen on both images due to necrotic tumor in liver.

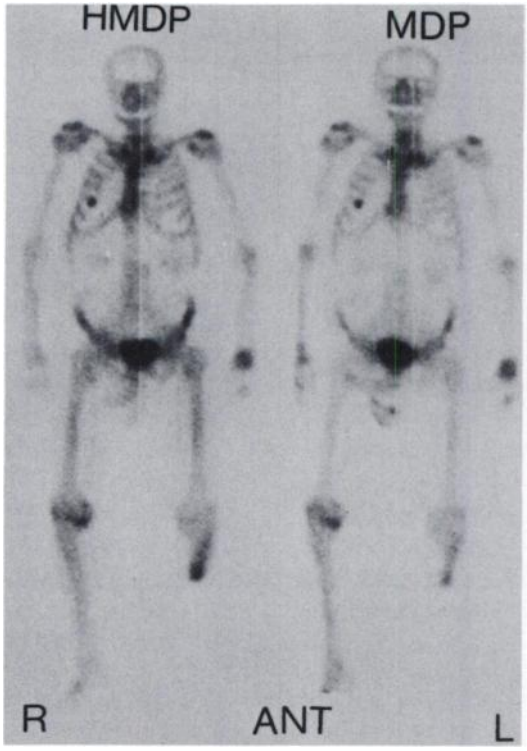

FIG. 3. Comparative whole-body images, Patient 4. Degenerative changes R knee; L wrist and costochondal junction well imaged by both agents. Increased activity in stump on HMDP image thought to be trauma-related and had quieted down at time of MDP image 2 wk later.

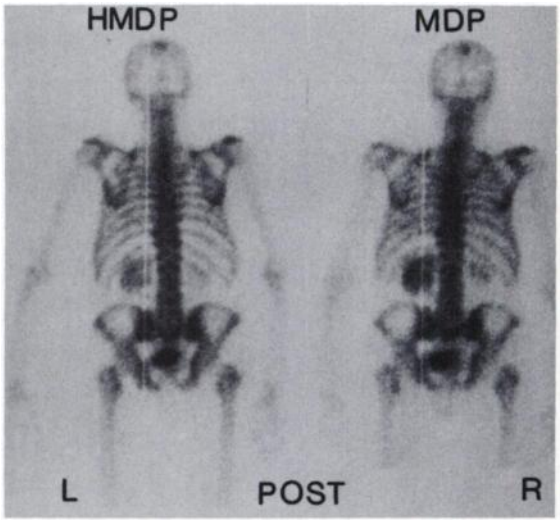

FIG. 4. Comparative whole-body images, Patient 6. Bony detail better on HMDP image. Lesions mid-sacrum, pedicle T-10 and skull well imaged by both agents.

FOOTNOTES

* HMDP-Proctor & Gamble, Cincinnati, OH.
† MDP—New England Nuclear, North Billerica, MA.
‡ Picker 4-15 and Picker Whole Body Table, Northford, CT.

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