Technetium-99m-labeled Methylene Diphosphonate and Hydroxyethylidine Diphosphonate—Biologic and Clinical Comparison: Concise Communication

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The biologic and imaging characteristics of Tc-99m MDP and Tc-99m HEDP were compared in ten patients: Tc-99m MDP exhibited lower blood activity, lower 4-hr urinary excretion, and higher normal bone-to-background ratio. Assessment of overall image quality also favored Tc-99m MDP, indicating that the normal skeleton is better visualized with this agent. The total number of lesions seen (18) was not large enough to allow critical comparison of relative lesion-detecting efficacy. However, discrepancies between the two agents were observed, suggesting additional evaluation of the relative lesion-detecting efficacy of these two bone agents.

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Since Subramanian's original description of Tc-99m polyphosphate for bone imaging (*1-3*), a number of Tc-99m-labeled phosphate and phosphonate compounds have been introduced for clinical bone imaging, including pyrophosphate (*4-6*), hydroxyethylidine diphosphonate (*7-10*), methylene diphosphonate (*11,12*), trimetaphosphate (*13*), and monofluorophosphate (*14*). The relative merits of certain of these agents have been evaluated clinically and in animal models (*15-19*). The most comprehensive comparisons have been by Subramanian and McAfee (*12,20*) and by Davis and Jones (*21*). Although there is still some disagreement, the methylene and hydroxyethylidene disphosphonates (MDP and HEDP) are considered superior. These two organic phosphates are closely related and the term "diphosphonate" is occasionally used in the literature without specifying which agent had been actually used (*22,23*). Despite their structural similarity, differences in their biologic behavior have been demonstrated in animals and in normal volunteers (*12*). Arnold and associates have also presented preliminary evidence indicating that the mechanisms of binding of these two agents by bone are different (*24*). They have suggested that Tc-99m MDP may be superior for visualizing the normal skeleton but that Tc-99m HEDP may be better for detecting osteoblastic lesions. It is unknown at present whether these differences are important in routine clinical bone imaging.

Because of these observations, and because clinical data comparing the two agents are sparse, we elected to compare their biological behavior in a series of ten patients.

MATERIALS AND METHODS

Radiopharmaceuticals. Methylene diphosphonate kits, whose formulation has been described earlier (*19*), were obtained from the University of Washington Nuclear Pharmacy. Each unit contained 10 mg of MDP and 0.84 mg of stannous chloride. The kit is freeze-dried immediately after formulation

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and terminally sterilized by cobalt-60 irradiation. Hydroxyethylidine diphosphonate kits were obtained from a commercial supplier* and contained 5.9 mg of HEDP and 0.16 mg of stannous chloride. The molar ratios of diphosphonic acid to stannous chloride were 12.8 for MDP and 36.6 for HEDP. On the initial six patient studies, labeling efficiency for each agent was determined using instant thin-layer chromatography† with methylethylketone as solvent, and averaged >98% for Tc-99m MDP and >99% for Tc-99m HEDP.

Patient material. Patients referred for routine bone imaging were asked to participate in the project. No attempt was made to select a specific group of patients. Sex, age, weight, and clinical diagnoses are summarized in Table 1. All were ambulatory and normally hydrated.

Study protocol. Paired studies were performed on each of the ten patients within a 2-wk period. Technetium-99m MDP was the initial agent in five of the patients, and Tc-99m HEDP in the remaining five. The kits were labeled with 20 ± 1 mCi of sodium pertechnetate immediately before injection, and an appropriate standard prepared. The entire contents of a single kit were used for each study. The following collections were made: a) blood samples were obtained at 5, 15, and 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 percentage administered dose per liter of whole blood and percentage dose per estimated whole-blood volume. Urinary activity was expressed as dose percentage. The degree of red-cell labeling was assessed by measuring plasma-to-RBC partition at 4 hr. Whole-blood and plasma samples were counted and the hematocrit measured.

Imaging studies. Three hours following injection, a spot image was made of the lumbar spine and stored in digital form. From this, a target-to-background ratio was determined by summing the activity over a single normal lumbar vertebra and summing an equal number of channels on either side of the vertebra to represent background. Care was taken to select identical vertebrae in any given patient and to use identical areas for estimation of target and background activities. Immediately afterwards, standard whole-body images were made using a large-field-of-view gamma camera and a moving-bed whole-body table. The whole-body studies were set up to obtain a constant information density. These images were graded by five independent observers in two different ways. First, the 20 scans were qualitatively graded for image quality on a scale from 1 (poor) to 5 (excellent), without knowledge of the patient or agent. Second, the two scans for each patient were compared, without knowledge of which was MDP and which was HEDP, and graded for relative image quality.

RESULTS

Biologic data. The clinical and biologic data are summarized in Table 1. As expected, there was considerable interpatient variability in the biologic

TABLE 1. INDIVIDUAL PATIENT DATA

Patient No.	Sex	Age	Wt (kg)	Diagnosis*	Blood activity % dose/L 4 hr		% dose/WBV† 4 hr		% dose 4-hr urine		Bone-to-background‡	
					MDP	HEDP	MDP	HEDP	MDP	HEDP	MDP	HEDP
1	F	70	59	Osteoporosis (calcitonin)	1.05	2.13	3.59	7.28	51.4	54.2	4.8	4.6
2	F	27	55	ca, + mets	0.89	0.91	2.89	2.96	65.2	67.6	5.8	4.6
3	F	62	48	ca, screen	1.01	1.40	2.86	3.96	51.5	56.4	4.6	2.8
4	M	68	85	ca, screen	0.75	1.04	3.92	5.44	40.0	41.1	5.6	4.4
5	F	37	57	ca, screen	1.16	1.44	3.90	4.83	53.0	52.9	6.2	5.8
6	F	64	54	ca, screen	0.95	1.27	2.97	3.98	44.5	43.3	6.0	6.0
7	M	23	68	Diabetes R/O Osteomyelitis	0.39	0.43	1.63	1.80	61.3	64.6	5.3	4.5
8	M	45	80	Stress fracture	0.74	0.87	3.63	4.27	55.6	58.1	5.0	4.1
9	F	43	63	ca, screen	0.59	0.88	2.19	3.26	56.5	62.5	8.2	6.1
10	M	64	68	ca, + mets (estrogen)	0.92	1.06	3.89	4.43	50.0	53.2	4.7	4.0
Average values					0.85	1.14	3.46	4.22	52.9	55.4	5.62	4.69
Standard deviation					±0.23	±0.46	±0.77	±1.47	±7.4	±8.5	±1.07	±1.03
P value (paired)					< 0.02		< 0.02		< 0.01		< 0.01	

* Indicated in parentheses are drugs patient is receiving, which might affect bone uptake; + mets = known bony metastases; Screen = screening study; ca = known primary carcinoma.

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

‡ Bone-to-background ratio over lumbar vertebra.

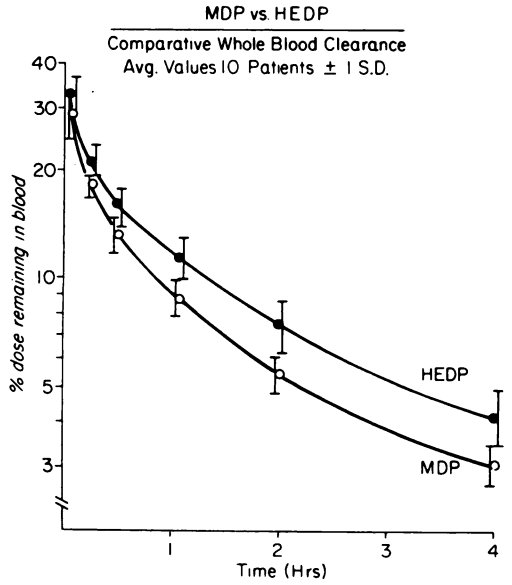

FIG. 1. Comparative whole-blood clearances; average values ± 1 s.d.

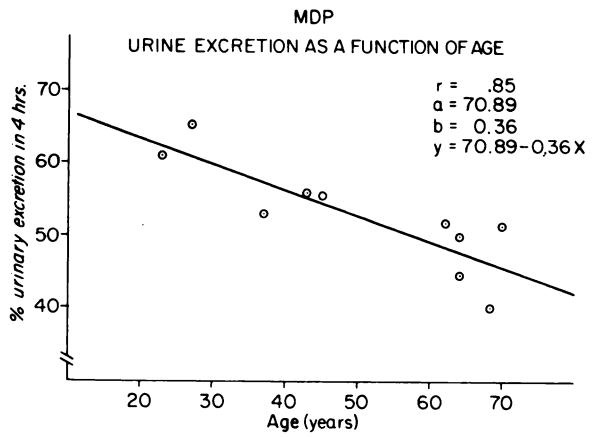

FIG. 2. Urinary excretion of Tc-99m MDP as a function of age. Excretion appears to decline with increasing age.

handling of these two agents. However, the comparative behavior was similar in all patients. Technetium-99m MDP blood activity levels at 4 hr were significantly lower than with Tc-99m HEDP, and the 4-hr urinary excretion of Tc-99m MDP was also slightly lower. The whole-blood clearance curves shown in Fig. 1, indicate that Tc-99m MDP clears more rapidly than Tc-99m HEDP especially during the initial 2 hr. Four-hour urinary excretion varied from 40% to greater than 65% and appeared to be inversely related to the patient's age (Fig. 2). As the blood and urine data suggest, the normal Tc-99m MDP bone-to-background ratio was significantly higher than that of Tc-99m HEDP. Neither agent showed significant RBC labeling: blood activity confined to the plasma fraction at 4 hr was 94% for Tc-99m HEDP and 88% for Tc-99m MDP.

Image quality. In the whole-body images there were no significant differences in imaging time or total counts accumulated. Overall, Tc-99m MDP image quality was judged to be slightly better than Tc-99m HEDP by both methods of evaluation. The results are shown in Tables 2 and 3. In the ten patients studied, only 18 lesions were identified. Technetium-99m MDP identified an average of 1.8 lesions per patient, compared with 1.7 for Tc-99m HEDP. Of the lesions seen, seven (in two patients) were metastatic lesions; the remainder were a variety of benign lesions, including compression fractures, degenerative change, and soft-tissue abnormality (absent kidney). Because of the small number of lesions, no formal comparison of lesion detection efficacy is attempted. However, differences observed between the two agents deserve comment. Figures 3, 4, and 5 show some representative images. In Fig. 3, slightly lower soft-tissue activity and greater skeletal clarity is apparent on the Tc-99m MDP image compared with the Tc-99m HEDP image. In Fig. 4, the metastatic lesion at T-9, and that in the left sacroiliac joint, are definitely more discrete on the Tc-99m HEDP image. Figure 5 shows a patient with osteoporosis and multiple compression fractures, which are better defined on the Tc-99m MDP image.

TABLE 2. COMPARATIVE IMAGE QUALITY

	No. scans	No. observations*	Average grade†
Tc-99m MDP	10	50	3.39 ± 0.85
Tc-99m HEDP	10	50	2.56 ± 0.94

* Each scan graded by five observers.
† Scale 1 (poor) to 5 (excellent); difference significant: $P < 0.01$.

TABLE 3. COMPARATIVE IMAGE QUALITY*

MDP > HEDP	27
MDP = HEDP	7
HEDP > MDP	16

* Each set of scans (10 sets total) compared by five observers; difference significant: $P < 0.02$.

DISCUSSION

The comparative biologic data reported here generally agree with the published literature for blood clearance and the normal ratios for bone to soft tissue. Subramanian and McAfee, using prepared kits "in house," reported slightly greater urinary excretion of Tc-99m MDP than Tc-99m HEDP (*12*), whereas we found the reverse situation. The explanation for this discrepancy is unclear, but the Tc-99m HEDP kit they used provided a different molar ratio of phosphonate to stannous ion. The average

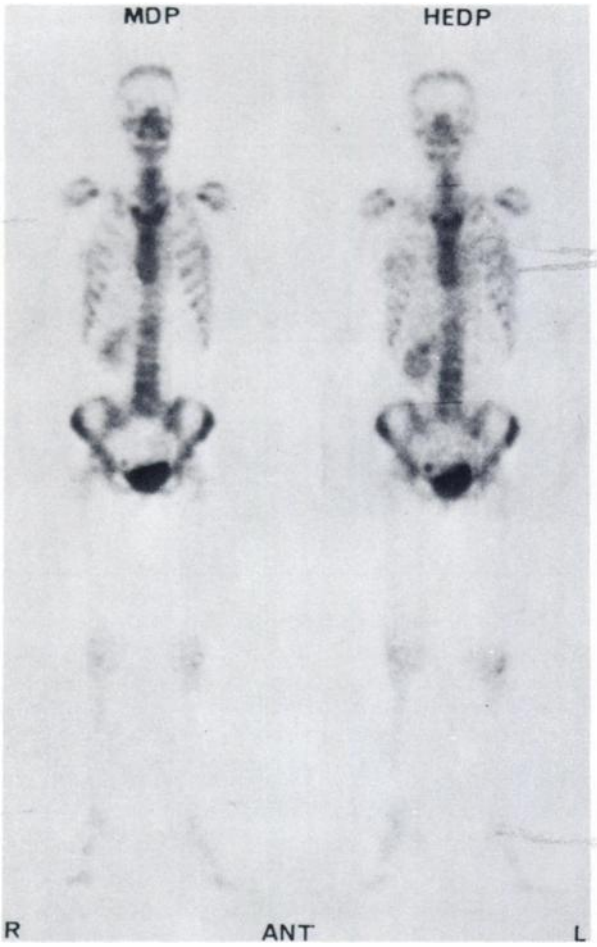

FIG. 3. Comparative whole-body images, Patient 5. Tc-99m MDP soft-tissue activity is lower, and normal skeleton is better seen. Hot spot adjacent to bladder is probably a bladder diverticulum.

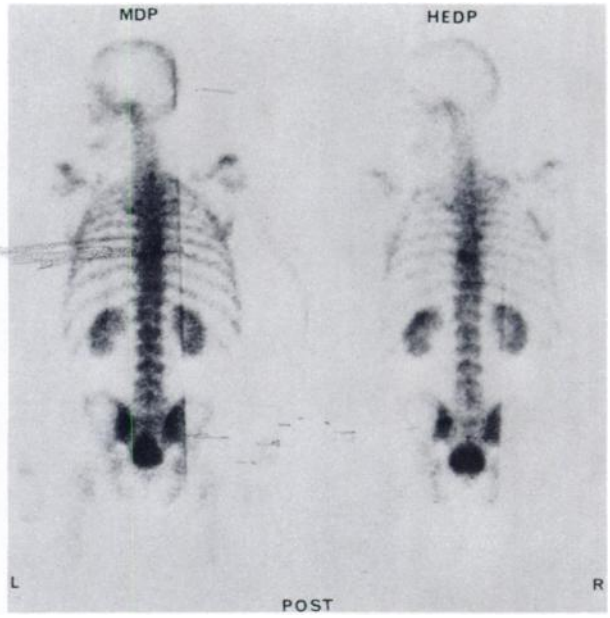

FIG. 4. Comparative whole-body images from Patient 10. Metastatic lesions at T-8 and in left sacroiliac area are more discrete with Tc-99m HEDP.

4-hr urinary excretion of both Tc-99m MDP and Tc-99m HEDP was slightly less than that reported for the normal volunteers by Subramanian and McAfee (*12*). This is probably due to the diversity of our patient population, which included elderly patients. As we have shown, urinary excretion appears to decline with increasing age, most likely because of the gradual aging of renal function (*25*). Blood activity, however, did not show a reciprocal increase with increasing patient age, which suggests that in older patients a relatively greater fraction of the total administered dose is distributed into the skeleton. Castronovo and associates have also demonstrated reduced urinary excretion of diphosphonate in patients with and without bony involvement, compared with normal volunteers (*22*). They postulate that this could be due to increased skeletal uptake in patients with bony involvement, and possibly to other factors in patients with normal scans. However, patient age was not considered. Fogelman has shown that the presence of certain metabolic bone diseases (renal osteodystrophy, Paget's, osteomalacia, hyperparathyroidism) may increase retention (and decrease urinary excretion) of Tc-99m HEDP (*26*); osteoporotics, however, did not show this effect. We cannot exclude the possibility that factors other than simple senescence of the kidneys contributed to the reduced urinary excretion in our patients.

From our data and from others' (*12*), it is clear that the normal skeleton will be better visualized with Tc-99m MDP than with the other bone-imaging agents. Using the rationale that if the normal skeleton is better seen, lesions should also be more easily detected, McAfee and Subramanian have recommended that Tc-99m MDP should be the agent of choice for routine skeletal imaging. Whether this suggestion is sound remains to be determined.

There are few clinical studies in which the comparative efficacy of lesion detection with the various bone-imaging agents has been evaluated. Of the studies that have been done, the findings suggest that Tc-99m HEDP is superior to Tc-99m pyrophosphate and Tc-99m polyphosphate. Citrin and associates have demonstrated Tc-99m HEDP produced higher ratios for tumor-to-normal bone than did Tc-99m polyphosphate and Tc-99m pyrophosphate (*17*). Fogelman and associates compared Tc-99m HEDP with Tc-99m pyrophosphate with similar results (*27*). Lundell and associates have presented suggestive evidence that Tc-99m HEDP is superior to Tc-99m polyphosphate and Tc-99m pyrophosphate for detecting bone metastases in patients with breast carcinoma (*28*). Also, Silberstein

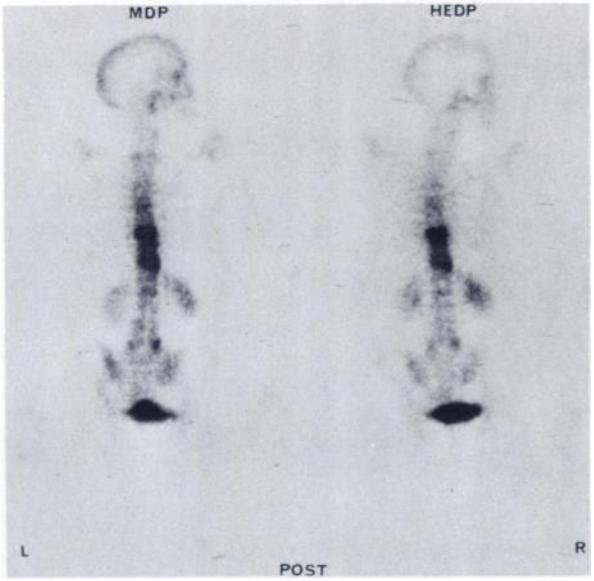

FIG. 5. Comparative whole-body images from Patient 1. Multiple compression fractures are better seen on Tc-99m MDP image.

and associates compared Tc-99m HEDP and Tc-99m pyrophosphate in a series of 30 patients and concluded that Tc-99m HEDP was superior for detecting lesions (*29*). Weber and associates prefer Tc-99m pyrophosphate for routine bone imaging (*18*), but their conclusions are based on imaging the normal skeleton and not on lesion detectability. Likewise, Nelson and associates prefer Tc-99m pyrophosphate and Tc-99m trimetaphosphate over Tc-99m HEDP and Tc-99m polyphosphate (*30*); their conclusions are also based on imaging the normal skeleton.

Only two studies have directly compared Tc-99m MDP with Tc-99m HEDP (*31, 32*). Rosenthall and associates compared them in a small series of patients, seven of whom had bony metastatic disease, and they concluded that lesion detection was similar, but expressed preference for Tc-99m MDP (*31*). Fogelman et al. studied a larger series of patients with bony metastatic disease (predominantly breast carcinoma) and found no significant difference in lesion detection but did find significantly higher tumor-to-normal bone ratios with Tc-99m HEDP (*32*). Fogelman also showed that imaging Tc-99m MDP 4 hr after injection resulted in a significantly higher number of lesions detected than did imaging at 2 hr.

The two discrepancies in lesion visualization in the current study are of interest. In one, metastatic lesions were better seen on the Tc-99m HEDP image (Patient 10, Fig. 4). This patient had prostatic carcinoma, and his data would support Arnold's contention that Tc-99m HEDP may be superior for osteoblastic lesions (*24*). The two patients with prostatic carcinoma in Fogelman's series also appeared to be better imaged with Tc-99m HEDP (*32*); however, the compression fractures in our study were better seen on the Tc-99m MDP image (Patient 1, Fig. 5). These observations suggest a need for additional evaluation of relative lesion detecting efficacy of these two agents in both benign and malignant disease of the skeleton.

There are also experimental data suggesting that the mechanisms and degree of bone labeling may be different for the various bone-imaging agents. Rosenthall and associates have shown differences in the distribution and degree of bone uptake of Tc-99m-labeled HEDP, pyrophosphate, and polyphosphate (*33*). Using the longer-lived Tc-95m and Tc-96 and microautoradiographic techniques, Guillemart and associates have studied the sites of deposition of Tc-pyrophosphate in the rabbit (*34*). Application of this technique to the study of comparative localization of the other phosphate bone-imaging agents would be of considerable interest, and might help to explain some of the differences observed in clinical imaging.

FOOTNOTES

* Osteoscan, Procter and Gamble, Cincinatti, OH.
† ITLC-SG, Gelman Instrument Co., Ann Arbor, MI.

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