A Clinical Comparison of Tc-99m HEDP and Tc-99m MDP in the Detection of Bone Metastases: Concise Communication

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We have compared bone scintigrams made with Tc-99m-tagged HEDP (1-hydroxyethylidene diphosphonate) and MDP (methylene diphosphonate), the former at 4 hr after injection, the latter at both 2 and 4 hr. In 17 patients with skeletal metastases, there was no significant difference in lesion count or scan quality between the 4-hr images. The tumor-to-bone ratio (T/B) was significantly higher with Tc-HEDP ($p < 0.02$). Lesion detection rate and T/B ratios were both lower with Tc-MDP at 2 hr when compared with the 4-hr values for both Tc-HEDP ($p < 0.02$, $p < 0.005$) and Tc-MDP ($p < 0.02$, $p < 0.01$). The 4-hr Tc-MDP scan was of significantly higher quality than the 2 hr Tc-MDP scan ($p < 0.01$). Although Tc-HEDP produces a higher T/B ratio at 4 hr, the present study does not suggest that either agent is superior in clinical practice.

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Since the introduction of the Tc-99m-labeled phosphate and diphosphonate bone-scanning agents, it has been generally accepted that of the available agents the diphosphonates are the most satisfactory (*1-6*). Two diphosphonates are in routine clinical use at present, Tc-99m hydroxyethylidene diphosphonate (Tc-HEDP) and Tc-99m methylene diphosphonate (Tc-MDP). The soft-tissue clearance is apparently more rapid with Tc-MDP than with Tc-HEDP. For this reason it has been suggested that scans may be obtained with Tc-MDP 2 hr after injection, and that Tc-MDP is therefore the agent of choice (*3*). A recent clinical comparison of the two agents has also suggested that Tc-MDP is superior to Tc-HEDP (*7*).

In this report we describe a comparison of 4-hr bone scans obtained with Tc-HEDP and Tc-MDP in 17 patients with bone metastases. Additionally, a comparison has been made between the 2-hr and 4-hr bone scans with Tc-MDP.

PATIENTS AND METHODS

Seventeen patients with bone metastases (Table 1) were studied on two occasions. A radionuclide bone scan was obtained 4 hr after the i.v. injection of 15 mCi of Tc-HEDP*. Approximately one week later a repeat study was performed 2 and 4 hours after the injection of 15 mCi of Tc-MDP†. During the period between the paired studies no patient received specific chemotherapy or radiotherapy.

Bone scans were obtained by recording multiple views of the skeleton on Polaroid film using a gamma camera fitted with a high-resolution medium-sensitivity collimator. Spinal views were obtained with 500,000 counts, and all others with 100,000 counts. In addition, all scintigrams were recorded and stored on a minicomputer by means

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of Laben analog-to-digital converters. Subsequent analysis of the digitized computer images permitted calculation of bone to soft-tissue ratios (B/ST) by selecting regions of interest around lumbar vertebra 2 and an adjacent soft-tissue area clear of renal activity (*8*). Similarly tumor-to-bone ratios (T/B) were measured as ratios of activity in tumor-involved bone to activity in corresponding normal bone.

The bone images were evaluated independently by three observers, (DLC, JHMcK, JGT), without knowledge of patient details or the ratiotracer used. The overall quality of scan image was recorded on a scale of 1–3:1 was considered poor quality, 2 average quality, and 3 a very good-quality image. In addition each physician recorded the total number of focal abnormalities identified in each patient.

All statistical comparisons between Tc-MDP and Tc-HEDP were performed using a paired Wilcoxon test, since each patient was studied with both agents.

RESULTS

The correlation between the lesion counts obtained by the three independent observers was very good for all studies, the correlation coefficient (r) ranging from 0.84–0.96 ($p < 0.001$, in all cases). Regarding image-quality assessment, there was fairly good correlation for both 4-hr studies (r ranging from 0.49–0.76, $p < 0.05$ in all cases). In the 2-hr Tc-MDP study, however, two observers correlated well with each other ($r = 0.60$, $p < 0.01$) but not with the third observer ($r = 0.17$ and 0.45, $p > 0.05$).

Image-quality score (Table 1). Overall there was no significant difference in quality between the 4-hr images obtained with Tc-HEDP and both the 2-hr and 4-hr Tc-MDP images. There was, however, a significant improvement in quality between the images obtained with Tc-MDP at 2 and 4 hr ($p < 0.01$).

Lesion counts (Table 2). There was no significant difference between the number of bone lesions (metastases) identified on the 4-hr Tc-HEDP and Tc-MDP scans. The 2-hr Tc-MDP scans gave significantly fewer identifiable lesions than did the 4-hr studies with either Tc-MDP ($p < 0.02$) or Tc-HEDP ($p < 0.02$).

Bone-to-soft-tissue ratios (Table 3). There was no significant difference in B/ST ratios between the 4-hr Tc-HEDP study and either the 2- or 4-hr Tc-MDP study. However, a significant increase in B/ST ratio was noted between 2- and 4-hr Tc-MDP studies ($p < 0.05$).

Tumor-to-bone ratios (Table 4). The T/B ratios obtained with Tc-HEDP were significantly higher than those obtained in both the 2-hr Tc-MDP ($p < 0.005$) and 4-hr MDP study ($p < 0.02$). In addition, there was a significant increase from 2 to 4 hr in the Tc-MDP studies ($p < 0.01$).

TABLE 1. PATIENT CHARACTERISTICS AND OVERALL SCAN IMAGE QUALITY SCORE*

Patient No.	Age	Sex	Primary Site	HEDP (4 hr)	MDP (2 hr)	MDP (4 hr)
1	62	F	Breast	2.2	1.7	1.5
2	75	F	Breast	2.0	2.0	2.0
3	46	F	Breast	2.0	2.2	2.5
4	58	F	Bladder	2.5	2.2	2.7
5	53	M	Lung	1.5	1.2	1.2
6	72	F	Breast	1.0	1.0	1.7
7	83	M	Prostate	2.5	2.5	2.5
8	55	F	Breast	1.3	1.7	1.7
9	47	F	Breast	3.0	2.7	3.0
10	71	M	Prostate	2.0	1.7	1.7
11	42	F	Breast	1.7	1.7	2.3
12	72	F	Breast	1.0	2.3	2.7
13	49	F	Breast	2.3	2.3	2.3
14	57	F	Breast	2.7	2.0	2.7
15	58	F	Breast	2.0	2.0	2.0
16	41	F	Breast	2.3	2.0	3.0
17	64	F	Breast	1.3	1.0	1.7
Mean ± s.d.				2.0 ± 0.6	1.9 ± 0.5	2.2 ± 0.06
					NSD**	$p < 0.01$**
						NSD**

* Mean of three independent observers.
** Results of comparison by paired Wilcoxon test; NSD = no significant difference.

DISCUSSION

The clinical superiority of the Tc-99m diphosphonate vectors HEDP and MDP, when compared with pyrophosphate and the polyphosphates in terms of quality of scan image and lesion detection rate, is now generally accepted. Since the early work demonstrating that MDP has a slightly faster blood clearance than HEDP, it has been suggested that the former is the preferred agent for routine clinical studies (*3*). Of particular importance in this respect has been the suggestion that a time interval of only 2 hr between injection and scanning is required with MDP, compared with 3 to 4 hr with HEDP (*3*). This suggestion, however, was made by Subramanian (*3*) on the basis of studies of blood clearance in only six healthy volunteers without bone disease, and was not based on any data regarding either the visualization or quantitation of bone lesions. A clinical comparison of MDP and HEDP has been performed in 11 volunteers and 20 patients (*7*). On the basis of faster blood clearance, improved quality of scan image and higher bone to soft-tissue ratios, the authors concluded that MDP was the preferred radiopharmaceutical for bone imaging. However, only seven of their patients had skeletal metastases and in these cases no lesions identified with one compound were missed with the other. Also no quantitative data were presented regarding tumor-to-bone ratios.

The results of the present work, performed as a critical paired study of patients with unequivocal bone metastases, have shown no major difference between the 4-hr HEDP and MDP scans in terms of overall image quality, number of lesions de-

TABLE 2. NUMBER OF BONE LESIONS COUNTED*

Patient No.	HEDP (4 hr)	MDP (2 hr)	MDP (4 hr)
1	15.0	14.7	16.3
2	2.0	2.0	2.0
3	13.3	11.7	14.3
4	28.0	28.3	29.0
5	3.7	4.3	6.0
6	4.3	4.7	4.7
7	29.7	22.7	25.7
8	9.7	10.0	12.3
9	21.3	14.0	16.7
10	17.7	16.0	12.3
11	8.7	8.3	8.7
12	9.7	8.0	9.0
13	12.7	12.7	14.4
14	13.3	12.0	13.0
15	3.0	2.3	2.0
16	3.0	2.0	2.7
17	17.3	16.7	17.7
Mean ± s.d.	12.5 ± 8.4	11.2 ± 7.3	12.2 ± 7.7
		$p < 0.02$**	$p < 0.02$**
		NSD**	

* Mean of three independent observers.
** Results of comparison by paired Wilcoxon test; NSD = no significant difference.

TABLE 3. $\frac{\text{NORMAL BONE}}{\text{SOFT TISSUE}}$ RATIO

Patient No.	HEDP (4 hr)	MDP (2 hr)	MDP (4 hr)
1	5.8	4.7	5.2
2	5.7	6.5	6.8
3	5.3	4.2	5.2
4	4.1	2.8	2.7
5	3.2	2.5	3.8
6	2.9	3.1	4.7
7	7.7	5.1	5.4
8	4.5	3.3	4.1
9	7.0	6.8	8.2
10	4.1	5.5	4.5
11	4.9	6.0	6.0
12	2.7	2.9	2.4
13	12.1	9.9	10.9
14	4.0	4.4	5.5
15	4.7	4.1	5.3
16	4.0	4.7	4.7
17	3.5	3.9	3.3
Mean ± s.d.	5.07 ± 2.26	4.72 ± 1.85	5.22 ± 2.04
	NSD*		$p < 0.05$*
	NSD*		

* Results of comparison by paired Wilcoxon test; NSD = no significant difference.

TABLE 4. $\frac{\text{TUMOR}}{\text{BONE}}$ RATIO

Patient No.	HEDP (4 hr)	MDP (2 hr)	MDP (4 hr)
1	2.0	1.9	1.7
2	2.1	2.0	2.2
3	1.7	1.7	1.8
4	2.1	2.4	2.8
5	2.6	1.8	1.9
6	2.7	2.2	2.2
7	2.2	2.0	2.0
8	1.8	1.7	1.7
9	2.3	2.0	2.1
10	4.5	3.2	3.9
11	3.3	2.5	3.0
12	5.3	3.7	4.1
13	1.5	1.6	1.7
14	2.3	1.8	1.9
15	1.4	1.4	1.3
16	1.8	1.6	1.6
17	1.9	1.6	1.8
Mean ± s.d.	2.45 ± 1.03	2.05 ± 0.61	2.2 ± 0.78
	$p < 0.005$*		$p < 0.01$*
		$p < 0.02$*	

* Results of comparison by paired Wilcoxon test.

tected, and bone to soft-tissue ratios. The only statistically significant difference between the two agents in this study was a high tumor-to-bone ratio with HEDP.

Following the initial independent random evaluation of image quality, the observers reassessed the scan images in sets of three for each of the 17 patients. Overall there was a subjective impression that MDP produced images of higher quality at 4 hr after injection when compared with HEDP. This was supported by a trend towards higher scores for MDP in image quality (Table 1) and bone-to-soft-tissue ratios (Table 3). However, it was felt that there was higher contrast between tumor and normal bone using HEDP, and this was supported by higher tumor-to-bone ratios (Table 4). The subjective impression of a "good image" is influenced by a high bone to soft-tissue ratio, but in clinical practice tumor visualization is paramount. For this purpose the agent with the highest tumor-to-normal-bone ratio may well be superior.

Comparison of the 2- and 4-hr MDP scans shows improvement in all aspects of image quality, lesion detection rate, and tumor-to-bone ratios in the later study. A similar trend was noted in a previous study, which compared 2- and 4-hr scans obtained with HEDP (*9*). Although satisfactory bone scan images are obtained with both HEDP and MDP at 2 hr after injection, 4-hr images are superior.

There was no significant difference for any parameter between the results from the nine patients receiving one commercial MDP and the eight receiving the other MDP. This is similar to our previous experience with HEDP obtained from three different commercial sources, where the products all provided similar, highly reproducible results (*10*).

On the basis of the present study we conclude that, although Tc-HEDP produces higher tumor-to-bone ratios, there is no significant clinical difference between Tc-HEDP and Tc-MDP in terms of image quality and lesion detection rate. In the case of Tc-MDP, scanning at 2 hr will result in some missed lesions, so the longer delay after injection is recommended particularly where subtle abnormalities are anticipated.

FOOTNOTES

* Osteoscan, Proctor and Gamble, Cincinnati, OH.

† Patients Nos. 1–9 with Tc-MDP from Radiochemical Center, Amersham Corp., Arlington Heights, IL; patients Nos. 10–17 with Tc-MDP from New England Nuclear Corp., North Billerica, MA.

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