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Tc-99m Methylene Diphosphonate Versus Tc-99m Pyrophosphate: Biologic and Clinical Comparison

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The biologic and imaging characteristics of Tc-99m MDP and Tc-99m PP_i were compared in animals and patients using freeze-dried bone-imaging kits. Biodistribution data in rabbits showed Tc-99m MDP had slightly higher bone uptake, significantly lower blood levels, and faster urinary excretion compared with Tc-99m PP_i. Duplicate studies performed on ten patients showed the following: (a) blood clearance of Tc-99m MDP was more prompt and complete, resulting in significantly lower blood levels at 4 hr; (b) urinary excretion was greater with Tc-99m MDP than with Tc-99m PP_i; and (c) Tc-99m PP_i showed significant red-cell labeling, whereas Tc-99m MDP did not. Image quality was generally better with Tc-99m MDP than with Tc-99 m PP_i, although there was no obvious difference in diagnostic sensitivity between the two agents.

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Since Subramanian's description of Tc-99m polyphosphate for bone imaging in 1971 (*1–3*), a number of Tc-labeled phosphate and phosphonate bone-imaging compounds have been introduced (*4–6*). The agents receiving the widest clinical use include Tc-99m complexes of polyphosphate, pyrophosphate (PP_i), ethylene hydroxy diphosphonate (HEDP), and methylene diphosphonate (MDP). The relative merits of certain of these agents have been compared clinically and in animal models (*7–10*). The most comprehensive comparisons have been done by Subramanian and McAfee (*11,12*) and Davis and Jones (*13*); they suggest that Tc-99m MDP has the best overall characteristics for bone imaging.

We have used an "in house" preparation of Tc-99m pyrophosphate in our laboratories for several years and it has been a reliable and satisfactory agent. Since there were relatively sparse clinical data directly comparing Tc-99m PP_i and Tc-99m MDP, we decided to perform a study comparing the two agents before converting to Tc-99m MDP for clinical bone imaging.

Because MDP was not commercially available at the time of the study, an MDP bone-imaging kit was prepared.* This report consists of two integral parts: (a) formulation and preparation of an MDP bone-imaging kit and comparison with a PP_i kit in an animal model, and (b) clinical comparison of the biologic and imaging characteristics of the two agents.

MATERIALS AND METHODS

Radiopharmaceuticals. Lots of 100 units of MDP and PP_i were formulated, freeze-dried, and sterilized by similar processes. Stannous methylene diphosphonate kits were prepared by dissolving 1 g of methylene diphosphonic acid in 200 ml of sterile pyrogen-free water. The methylene diphosphonic acid solution was combined with a solution of 100 mg of stannous chloride dihydrate dissolved in 1 ml of *N* hydrochloric acid. The solution was adjusted to a volume of 300 ml and pH of 7.0 by the addition of *N* sodium hydroxide solution. The solution was filtered through

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TABLE 1. RABBIT DISTRIBUTION OF Tc-99m MDP AND Tc-99m PP_i 3 HR AFTER INJECTION*

	Whole body	Urine (0–3 hr)	Liver	Spleen	Avg. skeleton	Whole blood	Soft tissue
Tc-99m PP_i	81.8 ± 8.1	18.2 ± 8.1	20.5 ± 3.4	1.39 ± 0.40	44.9 ± 6.3	1.74 ± 0.53	1.26 ± 0.23
Tc-99m MDP	68.1 ± 13.2	31.9 ± 13.2	3.44 ± 2.5	0.18 ± 0.14	47.8 ± 11.2	0.73 ± 0.64	1.13 ± 0.53

* Percent administered dose; mean ± 1 s.d.; n = 6.

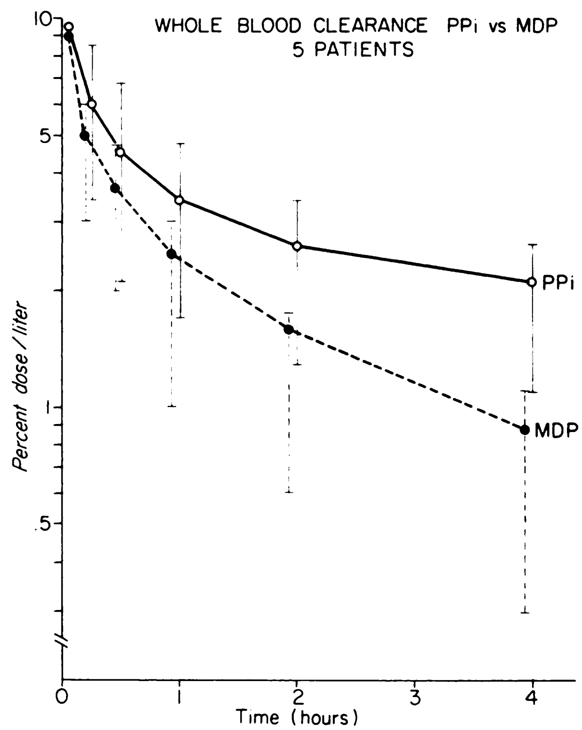

FIG. 1. Comparative blood clearance; activity expressed as percent dose/liter. PP_i—pyrophosphate; MDP—methylene diphosphonate.

a 0.22-μ Millipore filter and dispensed into 3-ml units and freeze-dried in a Virtis Model 800M freeze-dryer for 48 hr. The final shelf temperature of the process was 80°F. Immediately after freeze-drying, the vials were sealed under vacuum. This freeze-drying process was critical to satisfactory kit preparation. Less than 48 hr of drying resulted in significant liver uptake in the animal model.

Because the freeze-drying process is nonsterile, final sterilization was accomplished by cobalt-60 irradiation of the freeze-dried kits. A dose of 4 million rads was given in a single exposure. Comparison of irradiated and nonirradiated kits showed no detectable difference in labeling efficiency or biologic behavior.

Stannous pyrophosphate kits were prepared similarly, using 10 g of sodium pyrophosphate. The final molar ratios of phosphate to stannous chloride were 12.8:1 for methylene diphosphonate and 50.6:1 for pyrophosphate.

Routine quality control on all batches included pyrogen testing (USP rabbit pyrogenicity test and Limulus testing), determination of labeling efficiency (thin layer chromatography), and sterility tests (culture and colony count).

Animal studies. Biologic behavior of Tc-99m MDP and Tc-99m PP_i was compared in New Zealand juvenile (1.5–2.3 kg) albino female rabbits. Six rabbits were given a quantitative intravenous injection of each radiopharmaceutical and killed 3 hr later. Doses were 0.5 mg MDP or 3.0 mg PP_i with 0.05 mg stannous chloride and 1 mCi Tc-99m/kg body weight. Whole-body retention was estimated by a whole-body count immediately following injection and again after the bladder had been removed at necropsy. A flat-field collimated sodium iodide crystal was used at a distance of 1 m. A standard was counted at the time of whole-body counting to correct for physical decay. The liver was counted in similar fashion. The entire spleen, weighed samples of muscle (thigh) and bone (femur, with dried marrow removed), and 1 ml of blood were counted in a standard well counter along with appropriate standards. Activity was expressed as percent of administered dose. The sample activities were then extrapolated to whole-body retention based on the following fractions of body weight: blood 8%, bone 10%, and soft tissue 40%.

Patient studies. Ten cooperative patients referred for bone imaging were asked to participate, with no attempt made to select patients with or without bone disease. Paired bone studies were performed; one with Tc-99m PP_i and one with Tc-99m MDP within a week. Technetium-99m PP_i was the first agent used in five patients and Tc-99m MDP the first in the remaining five. Each patient received a calibrated injection of 15–20 mCi of Tc-99m-labeled MDP or PP_i; appropriate standards were prepared at the time of injection.

Urine collection for the 4 hr following injection and a blood sample at 4 hr after injection were obtained on all patients, and activity was expressed as percent administered dose and percent dose per liter, respectively. In five patients we also determined

TABLE 2. MDP VS. PP_i IN TEN PATIENTS: COMPARISON OF URINARY EXCRETION AND BLOOD LEVELS

Patient No.	Urinary excretion: % dose 0–4 hr			Whole-blood activity: % dose/l @ 4 hr		
	PP_i	MDP	PP_i/MDP	PP_i	MDP	PP_i/MDP
1	36	44	0.82	1.1	0.3	3.7
2	32	47	0.68	2.1	1.0	2.1
3	45	51	0.88	2.1	0.7	3.0
4	18*	66		1.8	0.6	3.0
5	40	47	0.83	1.9	0.8	2.4
6	48	65	0.74	2.5	1.0	2.5
7	43	56	0.77	1.5	0.6	2.5
8	37*	30*		2.0	1.0	2.0
9	27*	—		2.5	1.2	2.1
10	47	63	0.75	1.4	0.5	2.8
Avg.	41	55	0.78†	1.9	0.75	2.6†

* Did not void completely, value not used in computing ratio or avg.
† $p < 0.001$.

blood clearance of radioactivity from immediately following injection up to 4 hr.

Blood and urine samples were counted in a standard well counter with a sodium iodide crystal and single-channel analyzer, calibrated for the 140-keV peak of Tc-99m. Determination of plasma:RBC partition of radioactivity at 4 hr was done by measuring the hematocrit and counting whole blood and plasma.

Each patient received a standard whole-body scan (scintillation camera with whole-body imaging table) 4 hr after injection. In addition, serial images of the left shoulder and lumbar spine were obtained at 1, 2,3, and 4 hr. The images were graded subjectively for overall image quality by three independent observers in two different ways. First, the 20 scans were 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 PP_i and were graded for relative image quality.

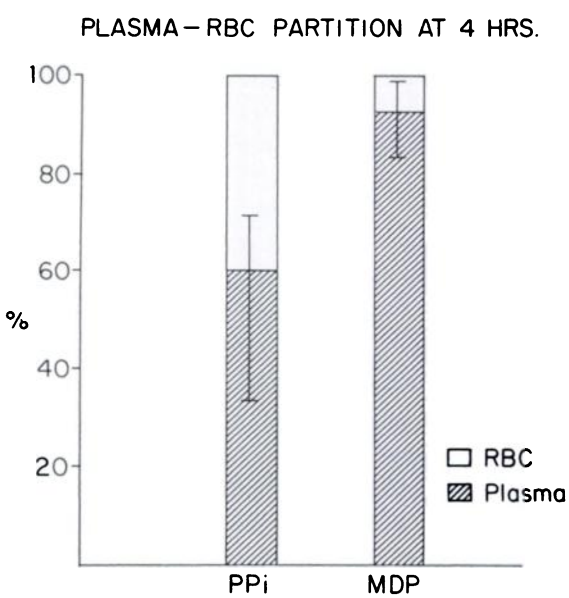

FIG. 2. Shaded area indicates average fraction of blood radioactivity in plasma. Open area is RBC fraction. Values represent average of ten patients. Brackets indicate range.

RESULTS

Animals. Images of the animals showed satisfactory bone labeling with both agents. Biologic data are shown in Table 1. Whole-body retention of MDP is lower, and urinary excretion higher, than that of PP_i. Soft-tissue activity (muscle) was similar with the two agents, but blood activity is significantly lower with MDP. The skeletal data suggest slightly higher MDP bone deposition, but the difference may not be significant. The relatively high PP_i uptake by the liver is a characteristic of this agent in the rabbit.

Patients. The whole-blood clearances are shown in Fig. 1. The curves represent average values, with bars indicating range. Blood levels at 4 hr and cumulative 4-hr urinary excretion data are shown in Table 2. As expected, there was considerable interpatient variability, but in any given patient Tc-99m MDP blood activity was lower and urinary excretion higher than with Tc-99m PP_i. The plasma:RBC partitions at 4 hr are shown in Fig. 2. A significant fraction of Tc-99m PP_i activity is associated with the red cells, whereas Tc-99m MDP is confined primarily to the plasma.

Both agents produced satisfactory bone images. Analysis of relative image quality was necessarily subjective, and although the differences were less impressive than in the measured data, the Tc-99m

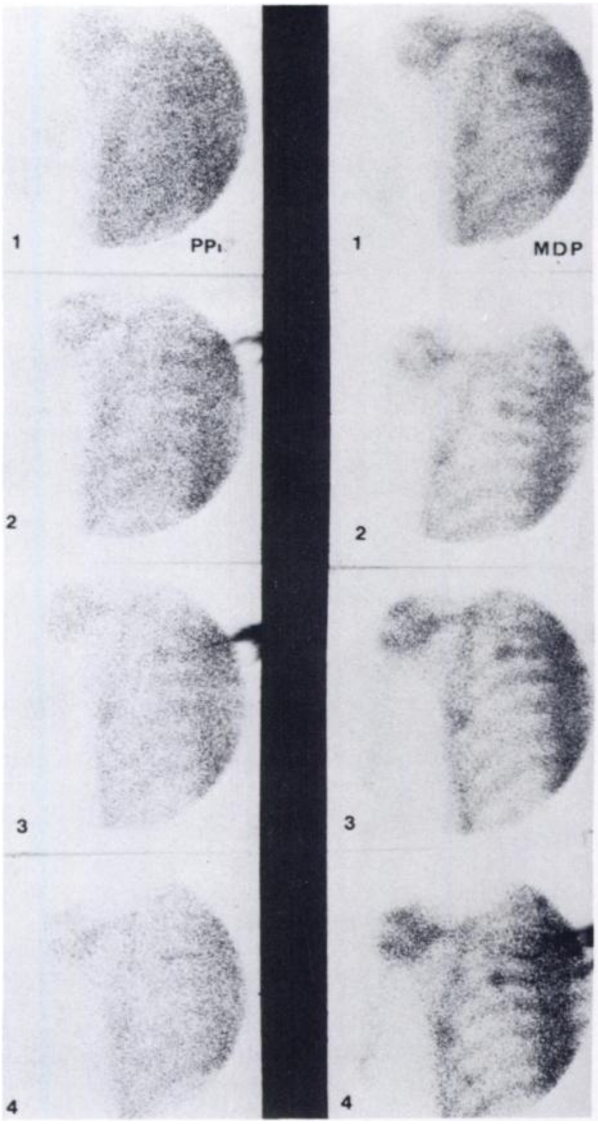

FIG. 3. Comparative hourly images up to 4 hr. PP_i—pyrophosphate; MDP—methylene diphosphonate.

MDP images were generally slightly sharper. Figure 3 compares serial images of the shoulder up to 4 hr, and Fig. 4 compares anterior whole-body images at 4 hr. Tables 3 and 4 show the results of the whole-body images at 4 hr. Tables 3 and 4 show the results of the whole-body image evaluation. Whether compared independently or one against the other, the Tc-99m MDP images were generally judged to be equal or superior to Tc-99m PP_i images, although the independent evaluation differences (Table 3) were not statistically significant. Relative diagnostic sensitivity was not critically evaluated because of the small series and unavoidable differences in imaging technique. But there was no apparent difference in diagnostic sensitivity between the two agents.

DISCUSSION

The biologic behavior of Tc-99m PP_i and Tc-99m MDP found in this study support the findings of Subramanian and McAfee using normal volunteers (*11*). They have indicated that the lower Tc-99m MDP blood levels and increased urinary excretion are due to reduced plasma protein labeling, compared with Tc-99m PP_i (*12*). Our data indicate that these differences may be due primarily to absence of red-cell labeling by Tc-99m MDP, whereas Tc-99m PP_i shows significant red-cell labeling. The phenomenon of in vivo red-cell labeling by pertechnetate following pyrophosphate administration has been reported previously (*14–17*), and is felt to be due to reduction of the pertechnetate by excess circulating tin complexes. Our experience suggests that a small fraction of Tc-99m pyrophosphate activity labels red cells rather promptly following intravenous administration. Whether this is due to direct Tc-99m pyrophosphate labeling or to reduction of free pertechnetate remains to be determined, although the former seems more likely.

Weber and Keyes (*10*) recently performed a comparative study and concluded Tc-99m pyrophosphate

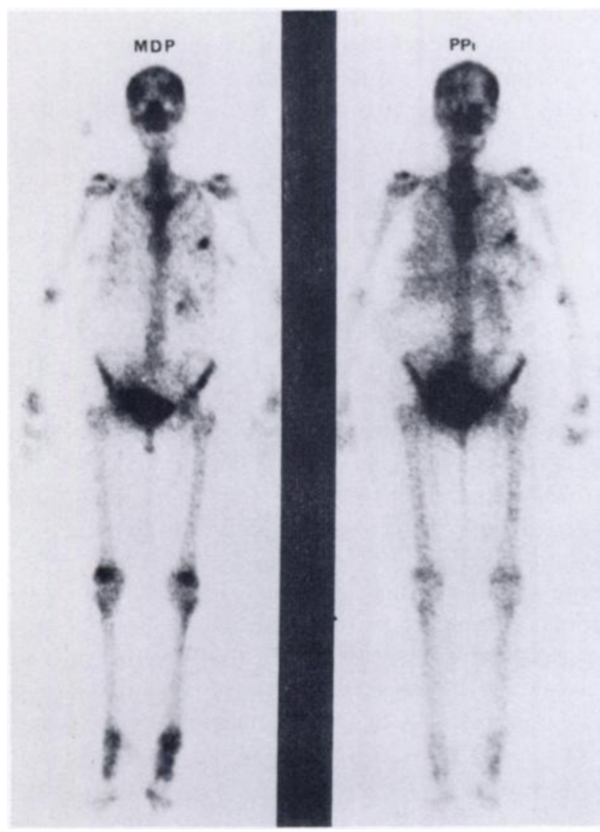

FIG. 4. Comparative anterior whole-body images at 4 hr. PP_i—pyrophosphate; MDP—methylene diphosphonate.

TABLE 3. COMPARATIVE IMAGE QUALITY

	No. scans	No. observations*	Avg. grade†‡
Tc-99m MDP	10	30	3.43 ± 0.81
Tc-99m PP_i	10	30	2.93 ± 0.79

* Each scan graded by three independent observers.
† Scale: 1 (poor) to 5 (excellent).
‡ Differences were not significant.

TABLE 4. COMPARATIVE IMAGE QUALITY*

MDP > PP_i	23
MDP = PP_i	7
PP_i > MDP	0

* Each set of scans (ten sets total) graded by three independent observers.

had the best overall characteristics for bone imaging. Unfortunately, Tc-99m methylene diphosphonate was not included in the agents studied. Their work is further compromised in that the patient studies were in series and not in duplicate, and the well-known interpatient biologic variability of these agents was not controlled. We feel that meaningful results can be obtained only if this variable is eliminated. For this reason we limited our study to two agents and performed paired studies with the patient serving as his own control. Krishnamurthy (*7,8*) and Citrin (*9,18*) have previously used this same approach when making clinical comparisons of bone-imaging agents. Citrin (*9,18*) considers Tc-99m HEDP to be the bone-imaging agent of choice, but he has not compared it with Tc-99m MDP. We intend to perform such a clinical comparison shortly.

The advantages of Tc-99m MDP are several. The rapid blood clearance allows earlier imaging following injection, and we now routinely image at 3 hr with this agent. The lower blood levels offer improved target-to-background ratios and should increase diagnostic sensitivity. This was not apparent in our study, but the series is small. Because of the more rapid clearance and lower background, high-resolution imaging of small bones and joints should be more effective with Tc-99m MDP. Considering the findings of this study, we have converted to Tc-99m MDP for routine bone imaging in our laboratories.

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FOOTNOTE

* This was done for us by the University of Washington Nuclear Pharmacy.

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