Tc-99m HMDP (Hydroxymethylene Diphosphonate): A Radiopharmaceutical for Skeletal and Acute Myocardial Infarct Imaging. I. Synthesis and Distribution in Animals

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Technetium-99m hydroxymethylene diphosphonate (Tc-99m HMDP) is a new diphosphonate skeletal imaging agent. Animal studies show that Tc-99m HMDP has a higher uptake on bone and a more rapid clearance from the blood than any of the three technetium-labeled bone imaging agents in current use: Tc-99m methylene diphosphonate (MDP), Tc-99m (1-hydroxyethylidene) diphosphonate (HEDP), and Tc-99m pyrophosphate (PPi). On the basis of these animal studies, Tc-99m HMDP is a highly promising candidate for skeletal imaging.

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Although new technetium skeletal imaging agents have been reported in the nuclear medicine literature from time to time (*1–3*), none of them have gained wide use because, in one way or another, they were perceived to be inferior to those in current use.

The efficacy of the currently used Tc-99m diphosphonate agents [(1-hydroxyethylidene) diphosphonate (HEDP) and methylene diphosphonate (MDP)] is judged primarily in terms of bone uptake and soft-tissue clearance; pathological lesions are identified as alterations in normal skeletal distribution. Of these agents in current use, Tc-99m MDP has the fastest rate of blood clearance (*4*). Tc-99m HEDP has lower bone uptake, but gives a greater contrast between regions of higher and lower calcification rates (*5*), which would explain reports of better lesion visualization with Tc-99m HEDP (*6,7*) than with other currently used agents.

X-ray diffraction studies in our laboratory (*8,9*) have shown that when a hydroxyl group is attached to the central carbon atom of the MDP structure, tridentate chelation is possible. Figure 1 shows the tridentate ligand nature of HMDP, with its added hydroxyl group, compared with the bidentate structure of MDP. Furthermore, this tridentate pattern is closely similar to that of the three oxygens that coordinate with calcium in the 001-crystal face of hydroxyapatite (HA) (the rapid-growth surface). Thus, in principle, the hydroxydiphosphonates have a unique relationship with rapidly growing HA crystals, which may explain the potency of etidronate (HEDP) in controlling the abnormally high rates of bone formation in Paget's disease (*10*). Rapid bone formation is a characteristic of many skeletal disease states, primary and metastatic, benign and malignant. Therefore, detection of osteogenic abnormalities requires contrast in uptake of Tc-99m phosphorus compounds between the abnormal bone lesion, which contains rapidly forming HA nuclei, and the surrounding normal bone.

Pursuing this hypothesis, we have investigated the skeletal imaging potential of the simplest member of the hydroxydiphosphonates, namely, hydroxymethylene diphosphonate (HMDP).

MATERIALS AND METHODS

Synthesis of HMDP. The disodium salt of hydroxymethylene diphosphonate (Na_2HMDP) was prepared by a modification of the method of Quimby, Prentice, and Nicholson (*11*).

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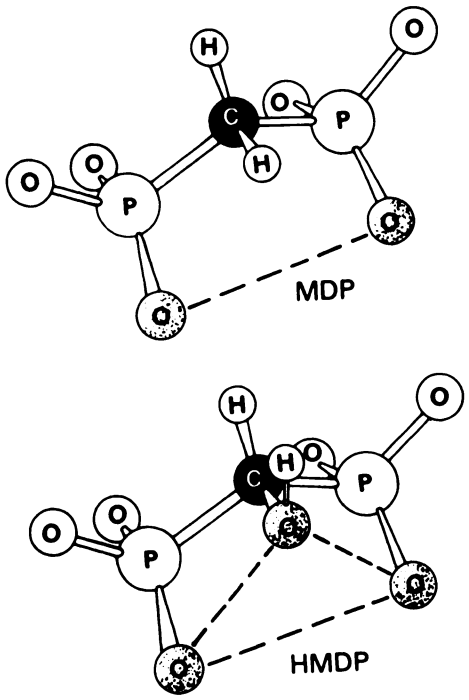

FIG. 1. Structures of HMDP and MDP compared. Phosphate oxygen atoms are shown unprotonated. Tridentate binding potential of hydroxylated molecules is emphasized in heavy print.

Chemical identity was confirmed by ^{31}P-NMR spectrum, S = 15.1 ppm (J = 14 Hz); ^{1}H NMR spectrum, S = 3.88 ppm (J = 14 Hz). Purity was determined by chemical analysis as the stable hemihydrate $[HC(OH)(PO_3HNa)_2 \cdot \frac{1}{2} H_2O)]$.

Formulation of Tc-99m HMDP. The complex between Tc-99m and the HMDP ligand was prepared in the usual manner by reducing pertechnetate (Tc-99m) ion with stannous tin in aqueous solution, in the presence of excess ligand. The initial experiments were carried out with simple liquid preparations. For most of the experimental work, however, an equivalent lyophilized commercial "kit" formulation was prepared in large batches of standard 5-ml dose vials.

Studies to optimize the formulation of Tc-99m HMDP showed that liver uptake of Tc-99m occurred when the Na_2HMDP load was above 0.1 mg/kg in rats, guinea pigs, and dogs. Below this threshold level Tc-99m HMDP appeared to be a promising skeletal imaging agent. These considerations were taken into account in designing a formulation containing 2 mg of Na_2HMDP in a lyophilized vial for human clinical use (maximum possible ~0.03 mg/kg for a whole vial).

The single-vial formulation consisted of: 2.0 mg of Na_2HMDP, 0.16 mg of $SnCl_2$, and 0.56 mg of gentisic acid (antioxidant). This formulation was used throughout the biodistribution studies. Gentisic acid (2,5-dihydroxybenzoic acid) has been found to be an effective antioxidant at these levels of Sn(II), and is equivalent to ascorbic acid in preventing in vitro decomposition (appearance of pertechnetate) (*12*). Neither stabilizer affects the biodistribution of the complex itself (*13,14*).

Biodistribution studies in rats. Dose-level studies were conducted at 0.02, 0.05, 0.10 mg/kg HMDP. Suitable volumes for administration were achieved by saline dilution (1:10) of vials that had been prepared with a specific activity of 1.3 mCi/ml by the usual method. ITLC studies indicated that the dilute formulations were stable in vitro. Three groups (n = 4 per group) of fasted Sprague-Dawley rats (195 ± 7-g females) were given single injections of 0.10, 0.25, or 0.50 ml of diluted Tc-99m HMDP into the jugular vein. Three hours later, the animals were killed and samples of femur (whole), muscle, blood, liver, kidney, and heart were radioassayed for Tc-99m content.

Biodistribution in dogs. These studies were conducted in three purebred male beagles, ages 10, 10, and 13 mo, weighing 10.2, 10.9, and 12.1 kg, respectively. Vials were reconstituted in 4.0 ml of pertechnetate (Tc-99m) in saline (13–15 mCi/ml), and each animal was given a single intravenous dose (1.0 ml) of Tc-99m HMDP into the cephalic vein. Ninety minutes later, a 2-ml blood sample was withdrawn from the contralateral vein, following which the dogs were killed with lethal doses of sodium pentobarbital. With the gamma camera, scintiphotos were taken of the chest and abdomen, both lateral and anteroposterior, and also of the forelegs to ensure that the dose was not extravasated. Samples of rib, femur (diaphysis), muscle, myocardium, liver, spleen, gall bladder, and bile were removed from each dog, weighed, and radioassayed for Tc-99m content.

Blood clearance in dogs. The blood clearance of Tc-99m HMDP in beagles was compared with those of two commercial (kit) bone tracers, MDP* and HEDP,† by radioassay of serial venous blood samples within the period 0.5–4 hr after dose. Sixteen dogs were divided into four equal groups and given single 1-ml doses by cephalic vein of one of the agents, as follows:

Group 1 0.1 mg HMDP (sodium salt)
Group 2 0.5 mg HMDP (sodium salt)
Group 3 0.5 mg MDP (sodium salt)
Group 4 0.5 mg HEDP (sodium salt)

The MDP and HEDP solutions were prepared according to the manufacturer's instructions and aliquots diluted with saline to obtain the desired diphosphonate dose concentration. Blood samples for radioassay (1–2 ml) were withdrawn from the contralateral cephalic vein.

Urinary excretion in dogs. Six beagles were given 1 ml (0.5 mg HMDP) of Tc-99m HMDP by cephalic vein and placed in metabolic cages fitted with Teflon-coated splash shields for urine collection. Cumulative collections were made at 24 and 48 hr after dose, and radioassayed for Tc-99m content.

TABLE 1. BIODISTRIBUTION OF Tc-99m HMDP IN SPRAGUE-DAWLEY RATS AT 3 HR AFTER IV DOSE

Tissue	Tc-99m content in % dose/g × 10^3 0.02 mg HMDP/kg	0.05 mg HMDP/kg	0.10 mg HMDP/kg
Femur	30.1 (28.1–32.5)*	26.2 (23.7–28.3)	29.7 (24.4–35.5)
Blood	0.18 (0.16–0.21)	0.16 (0.14–0.18)	0.19 (0.12–0.23)
Muscle	0.048 (0.043–0.053)	0.039 (0.032–0.044)	0.048 (0.034–0.066)
Kidney	2.76 (2.21–3.29)	3.06 (2.30–4.71)	4.14 (2.97–5.66)
Liver	0.46 (0.23–1.01)	0.41 (0.20–0.77)	0.73 (0.39–1.19)
Heart	0.14 (0.13–0.15)	0.11 (0.10–0.12)	0.13 (0.10–0.15)

* Values in parentheses are range of values per group of 4 rats.

TABLE 2. DISTRIBUTION OF Tc-99m HMDP* IN BEAGLES AT 90 MIN†

Tissue	No. of samples	Animal No. 1	No. 2	No. 3
Rib	3	44.9	32.3	39.8
Femur	3	19.0	12.0	15.4
Blood	1	4.00	2.57	5.65
Muscle	2	0.41	0.38	0.53
Myocardium	4	0.98	0.83	1.46
Liver	1	1.13	2.19	1.18
Spleen	1	1.10	2.01	1.32
Gallbladder	1	1.98	1.74	2.39
Bile	1	1.33	1.54	0.60

* 0.04 mg/kg average dose of Na_2HMDP.
† % dose/g × 10^3.

RESULTS

Biodistribution studies. The average and range of values from the dose-response study in rats are given in Table 1; they show high localization of Tc-99m HMDP agent in bone, moderate levels in the kidney, the principal organ of excretion, and very low retention in the other tissues sampled. Qualitatively, scintiphotos of the rats indicated excellent osseous specificity for Tc-99m HMDP.

The biodistribution data for Tc-99m HMDP in beagles are given in Table 2. As with the rats, the uptake is high in bone and low in other tissues. The mean rib-to-muscle concentration ratio was 89, and the equivalent femor-to-muscle value 35. Again, scintiphotos gave visual support to the radioassay data, with no signs of extra-osseous uptake in these animals.

Blood clearance in dogs. The results of the blood clearance comparison are shown in Fig. 2. The data from Groups 1 and 2 (0.1 and 0.5 mg HMDP) were indistinguishable and have therefore been combined. Tc-99m HMDP and Tc-99m MDP clearances are nearly identical through 2 hr after dose, after which Tc-99m HMDP appears to clear at a slightly faster rate ($p < 0.05$ at 4 hr.). Tc-99m HEDP clearance is significantly slower ($p < 0.05$) than those of both other agents after 1 hr.

Urinary excretion in dogs. The urinary excretion data are given in Table 3 and indicate that about 60% of an i.v. dose is excreted in the first 24 hr, and very little thereafter. This implies that about 40% of the Tc-99m HMDP is retained on the skeleton, since, according to the biodistribution studies, there is no significant retention in soft tissue.

DISCUSSION

Scintigraphic skeletal imaging can be examined in terms of the relative rates of uptake of the tracer on bone and its clearance from the other tissues. Until now, most of the emphasis has been placed on soft-tissue clearance. This is most clearly seen in work comparing the properties of various Tc-99m-labeled phosphate agents by Subramanian, McAfee, Blair et al. (*4*); they concluded that differences in skeletal concentration were relatively minor and that the primary factor affecting skeletal image quality was the rate of renal clearance. While this is consistent with certain aspects of clinical bone-scanning experience, in which image quality is impaired by the effects of delayed clearance, it now seems an overly restrictive view. For instance, Hughes (*15*) measured the

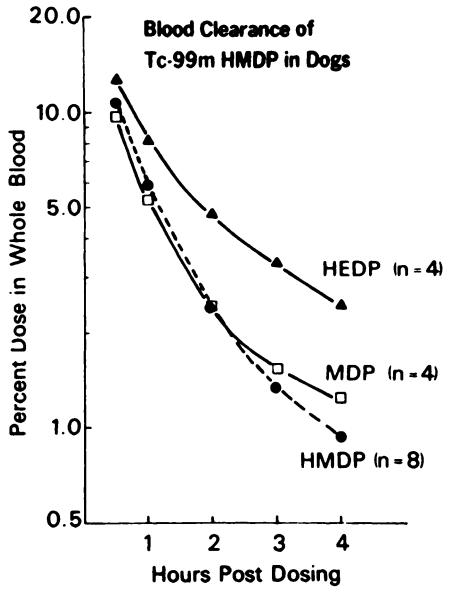

FIG. 2. Blood clearance curves for Tc-99m HMDP, Tc-99m MDP, and Tc-99m HEDP in beagle dogs.

TABLE 3. URINARY EXCRETION OF Tc-99m HMDP IN DOGS (n = 6)

Dog. No.	Percent dose in urine 0–24 hr	24–48 hr
1	53.1	3.1
2	61.8	5.0
3	49.5	7.6
4	59.8	2.3
5	78.8	1.6
6	48.8	1.3
Mean ± s.d.	58.6 ± 11.2	3.55 ± 2.4

renal clearance rate of Tc-99m HEDP in dogs to be 42% of the C-14 inulin clearance rate. Conversely, Troehler (*16*) found, in rats, that C-14 HEDP cleared at 150% of the inulin clearance rate (because of tubular excretion of C-14 HEDP in addition to glomerular filtration). Yet, in spite of this much faster clearance rate for the basic HEDP ligand, its fractional skeletal uptake—i.e., the fraction of the injected dose that is taken up on bone—is considerably higher than for Tc-99m HEDP. In humans (*17*) and animals (*18*), all normal, C-14 HEDP fractional uptake is ~50% of the injected dose. Fractional uptake of Tc-99m HEDP in normal human subjects appears to be about 20% of the injected dose (*19*). Clearly, renal clearance is not the primary determinant of skeletal uptake. This role must logically be assigned to the intrinsic affinity of the tracer for bone.

Studies at Mayo Clinic (*15,20*) have correlated capillary extraction of bone tracers with their diffusion coefficients. This is persuasive evidence (though not proof) that the principal mechanism for the movement of tracer from blood to bone is passive diffusion through the clefts in the capillary walls into the extravascular, extracellular fluid (ECF).

However, it seems unlikely that the initial dilution process determines the ultimate degree of tracer uptake on bone, for the following reasons. If the capillary extraction efficiency of any one tracer is approximately constant in all organs, including bone, one might argue that about the same fraction of the injected dose of any bone agent will be transferred into bone ECF within the first few minutes, over a fairly wide range of transfer rates. This argument assumes that neither renal clearance from the blood nor backflow from ECF to blood is significant in the early dilution phase.

According to blood-flow and dilution considerations, about 20% of the dose will be delivered to bone ECF by dilution alone, i.e., at the end of the first 2 min or so of the blood-clearance curve (*21*). This should be so for *all* tracers, from the simple ions Sr-85 and F-18 to the larger Tc-99m complexes, whatever their diffusion rates. Since fractional uptake for most tracers, certainly in most disease states, is generally higher than this value of 20% (*19*) it means that the additional tracer must come from reflux from nonbone ECF. This is the only substantial source for additional bone uptake beyond the basic 20% level provided by the initial dilution step. Quite obviously, in the second phase of tracer distribution, bone uptake must compete with renal clearance. In order to ensure a continuing flow of tracer into bone ECF, tracer concentration in bone ECF must remain lower than it is in blood plasma. This can happen only if tracer continues to move from bone ECF onto bone surface itself. It follows that the bone-uptake process is the decisive factor that determines the ultimate level of tracer on bone. At the same time, the rate of renal clearance is by no means unimportant. The greater it is, the more rapid the uptake on bone surface must be.

For the pharmacokinetic analysis of bone tracers, Arnold (*5*) has developed a method that overcomes some of the problems that arise when kinetic analysis is based solely on blood clearance. In this method, a specified small volume of bone is studied in vivo, using scintigraphic techniques to measure the net uptake and clearance curves in bone, overlying soft tissue, and, of course, blood. Thus, Arnold is able to base his analysis on the *observed* amount of tracer in the region of interest, bone. Other than this, Arnold chooses not to assign compartments in his model to bone ECF, "bone surface," "deep bone," etc., but adopts the simplest *a priori* model that will fit the data, namely, a rapidly exchanging compartment and a slowly exchanging compartment. Using this experimentally sound approach, Arnold has been able to interpret the observed differences in uptake patterns between Tc-HEDP and Tc-MDP as being due to the relative predominance of the rapidly exchanging compartment. With Tc-99m HEDP, there is a significant fraction of tracer that refluxes from *normal* bone (which is exchangeable) back into blood. This results in a lower ultimate fractional uptake on normal bone, compared with that of Tc-99m MDP, and it is this that is probably responsible for the higher blood levels of Tc-99m HEDP during the first few hours after administration. Accordingly, the higher blood levels of Tc-99m HEDP (compared with Tc-99m MDP), and the resulting lower ratios between normal bone and soft tissue, are due to this rapidly exchanging component, not primarily to greater renal clearance.

The situation in *abnormal* bone appears to be different. Arnold has found that, in osteogenic lesions, the rapidly exchangeable compartment for Tc-99m HEDP is substantially diminished, compared with an equivalent site in normal bone. The slowly exchanging compartment predominates for both Tc-99m HEDP and Tc-99m MDP; hence, the net uptakes for these agents are more nearly similar in abnormal bone. This raises the possibility, mentioned by Arnold (*5*), that Tc-99m HEDP may provide better contrast between abnormal and normal bone. A number of clinical observations tend to

support this (*6,7*). Castronovo (*22*) and Citrin (*23*), using scintigraphic techniques, also studied the pharmacokinetics of Tc-99m HEDP in normal volunteers and patients, and measured the differences in the rate and ultimate level of tracer uptake in normal and abnormal bone.

Charkes (*24*) used a compartmental model of the whole body to investigate bone-scan abnormalities. This work shows that locally increased blood flow alone will not account for the high uptake levels seen in many focal lesions; increased affinity of tracer for reactive new bone must be the principal factor.

Molecular structure and bone affinity. The structural ramifications of the hydroxydiphosphonates (including HEDP and HMDP) have been mentioned earlier in this paper. However, only HMDP appears to have the intrinsically higher uptake on bone mineral. Francis and coworkers (*25*) have studied the uptake affinities of labeled diphosphonates (HMDP, HEDP, MDP) on amorphous calcium phosphate (ACP) and HA in vitro, and in an osteogenic implant model in vivo. They found that HMDP has the highest rate of uptake of the basic ligands (C-14-labeled) on both ACP and HA, and the highest uptake of the Tc-99m complexes on the osteogenic site, at 14 days after implant. These results lend further support to the idea that, in vivo, it is the rate of uptake on bone mineral that will determine the total uptake on bone (ratio of uptake to excretion). The reason for the higher uptake for HMDP, compared with HEDP, is still not clear. It may be related to the absence of a second substituent on the central carbon atom (other than hydrogen). In the case of HEDP and the higher homologs, this group may result in increasing steric hindrance, which could lower the effective uptake. This is true, in our own experience, for the Tc-99m-labeled hydroxydiphosphonates containing alkyl substituent groups CH_3 through $C_{10}H_{25}$.

Radiation dosage. The increased osseous specificity of Tc-99m HMDP will only slightly increase the radiation burden compared with any of the other Tc-99m phosphorus agents.

Any increase in skeletal uptake must of course increase the dose to bone marrow, but this is partly offset by a lower dose to the gonads. In any case, bladder and gonadal dose is affected far more by frequency of voiding than it is by the differences in body distribution discussed in this work.

On the basis of its molecular structure, HMDP appears to combine certain ideal properties for skeletal imaging, which result in a high intrinsic affinity for bone. In animal studies it has demonstrated the necessary prerequisites of high bone uptake, rapid blood clearance, and negligible uptake in other tissues. On that basis, it is a most promising agent.

FOOTNOTES

* Osteolite, New England Nuclear Corp., Boston, MA.

† Osteoscan, Proctor & Gamble, Cincinnati, OH.

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