Tc-99m HMDP (Hydroxymethylene Diphosphonate): A Radiopharmaceutical for Skeletal and Acute Myocardial Infarct Imaging. II. Comparison of Tc-99m Hydroxymethylene Diphosphonate (HMDP) with Other Technetium-Labeled Bone-Imaging Agents in a Canine Model

John A. Bevan, Andrew J. Tofe, James J. Benedict, Marion D. Francis, and Bobby L. Barnett

Miami Valley Laboratories, The Procter & Gamble Company, Cincinnati, Ohio

Technetium-99m hydroxymethylene diphosphonate (Tc-HMDP) was compared with the two other diphosphonates (Tc-MDP and Tc-HEDP) and Tc-99m pyrophosphate (Tc-PPi) in a canine model of acute myocardial infarction. The TC-HMDP showed higher uptake in infarcted myocardium than the other two diphosphonates, and uptake equivalent to that of Tc-PPi.

J Nucl Med 21: 967–970, 1980

Since its introduction by Bonte et al. in 1974 (*1*), myocardial scintigraphy with the Tc-99m phosphorus bone-seeking agents has become a useful adjunct in the diagnosis of acute myocardial infarction (AMI). The mechanism of uptake in damaged myocardium remains the subject of investigation, but the phenomenon has been shown by Buja and colleagues (*2*) to be related to the presence of calcium deposits in the infarct. In that respect AMI uptake is quite consistent with the known properties of the phosphate skeletal tracers. The predominant view is that bone agents are taken up on bone-mineral surfaces (*3*) and hence are indicators more of calcium phosphate surface structure and area, rather than of bone mass or calcium content *per se*. A contrary and controversial view is that the technetium is actually taken up in the collagen moiety of bone (*4*).

The canine model of acute myocardial infarction, in which the left anterior descending (LAD) coronary artery is occluded, has been used by other investigators (*1,5,6*) to evaluate potential infarct-imaging agents. In this study we have used the permanently occluded model to compare four Tc-99m-labeled phosphate agents; pyrophosphate (PPi), methylene diphosphonate (MDP), (1-hydroxyethylidene) diphosphonate (HEDP), and hydroxymethylenediphosphonate (HMDP) (*7*).

Received Sept. 14, 1979; revision accepted May 28, 1980.

For reprints contact: Andrew J. Tofe, PhD, Miami Valley Laboratories, P.O. Box 39175, Cincinnati, OH 45247.

MATERIALS AND METHODS

The administered solutions were prepared either from commercially available skeletal-imaging agents or, in the case of Tc-99m HMDP, commercially equivalent kits (*8*).

Twenty adult purebred beagle dogs (average weight 8.9 ± 1.5 kg) were studied. Rather than adjust dose levels for body weight in our dogs, we chose to approximate adult human dose levels. This was justified on the grounds that the Tc-99m-labeled phosphates function over a wide dose range (*8*), and that we were therefore able to compare the various compounds under clinical conditions of volume, concentration, activity, etc. Variations in anatomical size and the severity of myocardial infarction were circumvented by use of an internal control. The details of the doses used for imaging myocardial infarcts in dogs are given in Table 1.

All the dogs were anesthetized and the chest opened. The proximal left anterior descending coronary artery was dissected free 1 to 2 cm from its origin and ligated. Forty-eight hours after the experimentally induced infarct, each dog received a 1-ml dose (10–15 mCi/ml) of

TABLE 1. DOSE DETAILS IN COMPARISON STUDY

Compound	Type of formulation	Dose vol. (ml)	Amount of active (mg)	Tc-99m (mCi)
HMDP	Lyophilized kit*	1.0	0.5	10–15
MDP	Commercial kit†	1.0	0.5	10–15
	Dry-mix‡	1.0	1.1	
HEDP	Commercial kit‖	1.0	1.2	10–15
PPi	Commercial kit§	1.0	3.1	10–15

* Experimental formulation (see Ref *8*).
† Osteolite, New England Nuclear Corp, Boston, MA.
‡ MDP substituted for HEDP in Osteoscan formulation: 5 mg MDP, 0.16 mg $SnCl_2$, 0.56 mg sodium ascorbate.
‖ Osteoscan, Procter & Gamble, Cincinnati, OH.
§ Technescan PYP, Mallinckrodt Nuclear.

one of the Tc-99m-labeled test agents by bolus injection into the cephalic vein. To provide an internal control (v.i.), 15 min later each dog received 1 ml of C-14 HEDP (1 mg/ml; 37 μCi/ml) by bolus injection into the contralateral cephalic vein. Ninety minutes after the initial dose, each dog was anesthetized with pentobarbital disodium, and scintiphotos were made with an Anger camera. A blood sample was obtained, and the animal was then killed with a lethal dose of pentobarbital. Scintiphotos of cross sections of the excised heart were taken to help differentiate infarcted from normal myocardium. Representative tissue samples included rib, femur, normal heart, infarcted heart, and femoral muscle. Both Tc-99m and C-14 were assayed in each tissue sample: Tc-99m in a gamma spectrometer and C-14 as previously described (*9*). The results were expressed as percent administered dose (Tc-99m or C-14) per gram tissue.

The data were analyzed using the experimental agent (Tc-HMDP) as the control in an analysis of variance. This reversal of normal practice was adopted for convenience, since we wished to compare each of the current agents against the new one. Differences between group mean values were tested for significance by Student's t-test and in a nonparametric analysis by the Wilcoxon signed rank sum test.

RESULTS AND DISCUSSION

Technetium-99m assay data for rib, femur, infarct, normal myocardium, femoral muscle, and blood are summarized in Table 2. Beneath these results are listed the ratios (Tc-99m agent)/(C-14 internal control) for rib, femur, and myocardial infarct.

A major problem with the AMI dog model is the large variation in size and severity of the infarct from animal to animal. Because of temporal effects upon the degree of necrosis, it is rarely feasible to study more than one agent in each dog. Therefore, it is highly desirable to have some method of normalizing the distribution data to allow for the variation. Buja et al. (*2*) have reported a high correlation between the Tc-99m pyrophosphate agent and H-3-labeled HEDP localization in two dogs. We have adopted this approach by administering a standard dose of C-14-labeled HEDP as an internal control 15 min after the dose with the Tc-99m-labeled agent. This procedure assumes that the 15-min interval precludes interference with the uptake of the Tc-99m tracer and that the C-14 HEDP uptake is a valid index of "calcification." The physiological dose of HEDP, calculated as usual in terms of the disodium salt, was 1 mg, approximately equal to the amount usually injected in a single dose of Tc-HEDP. This is not considered to be a pharmacologically significant dose (*10*).

The value of the internal standard is immediately apparent when one compares the Tc-99m data with the Tc-99m/C-14 concentration ratios in Table 2. The range of the ratios is considerably less than for Tc-99m alone, confirming that there is substantial animal-to-animal variation in these studies, even though purebred beagles from the same supplier were used. The raw Tc-99m data do not account for this variation, which tends to obscure the true nature of the agent-to-agent differences. The normalization procedure of taking the Tc-99m/C-14 ratio permits a more reliable comparison. For example, the superiority of the Tc-HMDP for osseous uptake is evident in the Tc-99m results and is made particularly clear in the Tc-99m/C-14 concentration ratios. Infarcted myocardium uptake of the agents is variable, but when normalized to the C-14 content, the Tc-PPi is shown to be superior to the HEDP and MDP agents ($p < 0.01$), in agreement with clinical experience (*11,12*). At the same time, the uptake ratio of the HMDP agent is not significantly different from that of PPi for infarct uptake. Recent clinical data (*13*) slightly favored PPi over HMDP for infarct imaging.

Although normalization is achieved by calculating the Tc-99m/C-14 ratios for bone and infarcted heart, it

TABLE 2. DISTRIBUTION OF Tc-99m SKELETAL/MYOCARDIAL IMAGING AGENTS IN DOGS (ACUTE MYOCARDIAL INFARCT MODEL)

Tissue	Tc-99m HMDP (n = 8)	Tc-99m MDP (n = 3)	Tc-99m HEDP (n = 4)	Tc-99m PPi (n = 5)
	Tc-99m content (and range) in % dose/g in tissue × 10^3			
Rib	5.37 (3.15–7.36)	4.32 (2.71–5.64)	2.27 (1.76–2.96)*	4.95 (3.07–8.29)
Femur	1.76 (1.34–2.58)	1.30 (0.46–1.94)	0.42 (0.38–0.46)*	1.30 (0.61–2.51)
Infarcted myocardium	5.05 (1.03–11.6)	3.20 (2.40–4.95)	0.97 (0.72–1.53)*	4.44 (0.03–8.20)
Normal myocardium	0.15 (0.09–0.26)	0.21 (0.18–0.23)	0.15 (0.11–0.20)	0.31 (0.13–0.62)
Femoral muscle	0.07 (0.04–0.10)	0.109 (0.08–0.14)	0.07 (0.05–0.11)	0.14 (0.09–0.200)*
Blood	0.49 (0.31–0.82)	0.74 (0.60–0.95)	0.58 (0.37–1.01)	0.78 (0.63–0.84)†
	Tc-99m/C-14 concentration ratios			
Rib	1.00 (0.92–1.10)	0.69 (0.64–0.74)*	0.78 (0.58–1.01)*	0.84 (0.59–1.01)†
Femur	1.09 (0.91–1.15)	0.64 (0.55–0.72)*	0.56 (0.43–0.65)*	0.81 (0.57–0.91)*
Infarcted myocardium	1.18 (0.98–1.56)	0.53 (0.50–0.57)*	0.65 (0.57–0.73)*	1.27 (0.94–1.52)

Significance of difference compared with Tc-99m HMDP value, *: $p < 0.01$; †: $p < 0.05$.

serves little purpose when applied to the tissues in which uptake of both tracers is low; the concentration ratio is then the ratio of two small numbers. In an attempt to normalize the biodistribution data in such a way as to preserve the contrast between calcified and noncalcified tissues, we have done the following. The average C-14 HEDP values (% dose/g) were calculated for each tissue, the average being calculated over all the animals in the study ($=[C\text{-}14]_{avg}$). Then the Tc-99m value in each tissue was adjusted according to the formula.

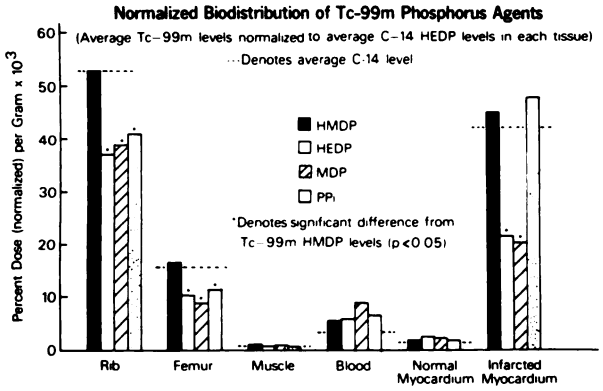

FIG. 1. Comparative distributions of Tc-99m phosphate agents in canine model of acute myocardial infarction.

$$[Tc]_{adj} = [Tc] \cdot \frac{[C\text{-}14]_{avg}}{[C\text{-}14]},$$

Where [Tc] is the measured Tc-99m concentration and [C-14] is the measured C-14 concentration.

The results, which better indicate the scintigraphic properties of the various agents as predicted by this animal model, are shown in Fig. 1.

The Tc-HMDP shows significantly higher uptake than the other three agents in rib and femur, significantly higher uptake in myocardial infarcts than Tc-MDP and Tc-HEDP, and approximate equality with Tc-PPi. This, coupled with the previous finding (*8*) that the blood clearance of Tc-HMDP is equal to or slightly faster than that of Tc-MDP, indicates that the former should provide excellent imaging of both skeletal disease and acute myocardial infarction.

REFERENCES

1. BONTE FJ, PARKEY RW, GRAHAM KD, et al: A new method for radionuclide imaging of myocardial infarcts. *Radiology* 110:473-474, 1974
2. BUJA LM, TOFE AJ, KULKARNI PV, et al: Sites and mechanisms of localization of technetium-99m phosphorus radiopharmaceuticals in acute myocardial infarcts and other tissues. *J Clin Invest* 60:724-740, 1977
3. JONES AG, FRANCIS MD, DAVIS MA: Bone scanning: radionuclide reaction mechanisms. *Semin Nucl Med* 6:3-18, 1976

4. ROSENTHALL L, KAYE M: Observations on the mechanism of ^{99m}Tc-labeled phosphate complex uptake in metabolic bone disease. *Semin Nucl Med* 6:59-67, 1976
5. ZWEIMAN FG, HOLMAN BL, O'KEEFE A, et al: Selective uptake of ^{99m}Tc complexes and ^{67}Ga in acutely infarcted myocardium. *J Nucl Med* 16: 975-979, 1975
6. POLINER LR, BUJA LM, PARKEY RW, et al: Comparison of different noninvasive methods of infarct sizing during experimental myocardial infarction. *J Nucl Med* 18:517-523, 1977
7. BEVAN JA, TOFE AJ, FRANCIS MD, et al: Tc-99m hydroxymethylene-diphosphonate (HMDP): A new skeletal imaging agent. *Radiopharmaceuticals II.* New York, Society of Nuclear Medicine, 1979, pp 645-654
8. BEVAN JA, TOFE AJ, BENEDICT JJ, et al: Tc-99m HMDP (hydroxymethylene diphosphonate): A radiopharmaceutical for skeletal and acute myocardial infarct imaging. I. Synthesis and Distribution in animals. *J Nucl Med* 21:961-966, 1980
9. TOFE AJ, FRANCIS MD: Optimization of the ratio of stannous tin: ethane-1-hydroxy-1,1-diphosphonate for bone scanning with ^{99m}Tc-pertechnetate. *J Nucl Med* 15:69-74, 1974
10. TOFE AJ, FRANCIS MD: Toxicity of ^{99m}Tc-Sn-EHDP. *J Nucl Med* 16:444-445, 1975 (Letter to the Editor)
11. KELLEY RJ, CHILTON HM, HACKSHAW BT, et al: Comparison of Tc-99m pyrophosphate and Tc-99m methylene diphosphonate in acute myocardial infarction: Concise communication. *J Nucl Med* 20:402-406, 1979
12. MAKLER PT, LEDERMAN S, CHARKES ND, et al: Myocardial infarct imaging with ^{99m}Tc-pyrophosphate and ^{99m}Tc-methylene diphosphonate: lack of correlation. *Clin Nucl Med* 4:89-91, 1979
13. WAKAT MA, CHILTON HM, HACKSHAW BT, et al: Comparison of Tc-99m pyrophosphate and Tc-99m hydroxymethylene diphosphonate in acute myocardial infarction: Concise communication. *J Nucl Med* 21:203-206, 1980