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# A Comparison of Technetium Etidronate and Pyrophosphate for Acute Myocardial Infarct Imaging

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***Etidronate and pyrophosphate, labeled with Tc-95m and Tc-99m, were studied in experimentally infarcted mongrel dogs. A distribution study was conducted 2 hr after simultaneous administration of both agents in two groups of dogs. In one group, the injection was made 15 min after release of a 2-hr coronary arterial ligation. Another group was injected 48 hr after release of the ligation. The uptakes for each radiopharmaceutical and the ratio of uptakes for each sample were computed. The data show pyrophosphate to be a superior agent for the imaging of acute myocardial infarcts because of the higher uptake by infarcted myocardium and the greater contrast between infarcted myocardium and neighboring organs.***

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A number of Tc-99m radiopharmaceuticals have been shown to concentrate in acutely infarcted myocardium. These include tetracycline, glucoheptonate, polyphosphate, etidronate, and pyrophosphate (*1–5*). Of these compounds, the use of Tc-99m etidronate (HEDP) and Tc-99m pyrophosphate ($PP_i$) predominates in the imaging of acute myocardial infarction due, for the most part, to their superior uptake in infarcted myocardium. The purpose of this study was to determine whether one would be superior to the other.

This comparison was made using the two agents together, one labeled with Tc-99m and the other with Tc-95m, in dogs with surgically infarcted hearts. The ratio of pyrophosphate uptake to etidronate uptake was then computed for the heart and for surrounding organs.

## METHODS AND MATERIALS

**Experimental infarction.** Myocardial infarctions of the left ventricle were induced in mongrel dogs by a 2-hr ligation of the anterior descending coronary artery at the level of the tip of the left atrium, followed by release of the ligation. No dog was found to have an abnormal EKG before the surgical procedure. In one group, injection of HEDP and $PP_i$ was made 15 minutes after release of the ligation and the animal killed two hr later. This time period was chosen since it has been reported previously that uptake of these tracers would occur rapidly in this infarction model (*6*). Each animal was maintained on a mechanical respirator until sacrifice. In a second group of dogs, injection was made 48 hr after release of the ligation. These dogs had their incision closed and were allowed to recover after the operation.

**Radiopharmaceuticals.** [$^{99m}$Tc] sodium pertechnetate was obtained by elution from a generator. [$^{95m}$Tc] sodium pertechnetate was obtained commercially.* The technetium etidronate kit† and technetium pyrophosphate kit‡ were also obtained commercially.

Each kit was labeled with the appropriate isotope of technetium. The Tc-95m activity added to each kit vial was less than 50 $\mu$Ci—that is, less than $1.4 \times 10^{13}$ atoms.

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**TABLE 1. UPTAKE OF HEDP AND $PP_i$ IN THE EARLY-INFARCT GROUP FOLLOWING SIMULTANEOUS INJECTION OF BOTH RADIOPHARMACEUTICALS LABELED WITH Tc-99m AND Tc-95m**

| Tissue | Uptake × 100* | | | |
|---|---|---|---|---|
| | Tc-99m $PP_i$† | Tc-95mTc $PP_i$‡ | 95mTc HEDP† | Tc-99m HEDP‡ |
| Blood | 3.92 (3.59– 4.21) | 5.22 | 4.63 (3.88– 5.07) | 7.51 |
| Diaphragm | 4.06 (2.53– 6.07) | 2.11 | 4.75 (2.43– 8.21) | 2.23 |
| Liver | 4.86 (2.17– 9.97) | 2.55 | 1.73 (1.24– 2.24) | 1.98 |
| Lung | 5.27 (3.70– 7.95) | 2.79 | 3.33 (2.88– 3.97) | 3.36 |
| Normal myocardium | 6.18 (4.11– 7.79) | 1.41 | 2.74 (1.82– 4.39) | 1.88 |
| Rib | 30.5 (20.5 –37.7) | 35.6 | 25.6 (17.5 –32.6) | 35.8 |
| Hemorrhagic infarct | 29.7 (—) | 36.6 | 16.0 (—) | 27.8 |
| Nonhemorrhagic infarct | 56.3 (26.6 –76.1) | 60.8 | 31.3 (15.9 –35.4) | 47.1 |

* Percent kg dose/g tissue.
† Data from three dogs receiving Tc-99m $PP_i$ and Tc-95m HEDP (mean and range).
‡ Data from one dog receiving Tc-95m $PP_i$ and Tc-99m HEDP.

The Tc-99m activity added to each kit vial was less than 2 mCi. Each animal received approximately 40 μCi Tc-95m and 200 μCi Tc-99m. The dose of Tc-99m was made larger because this isotope of technetium decays more rapidly. Another reason is because the Tc-99m photopeak is counted in a window containing Tc-95m counts from Compton scatter. Increasing the activity of Tc-99m reduces the errors of measurement.

Thin-layer chromatography, which is able to distinguish the tagged product from pertechnetate and reduced technetium colloid, was performed (*7*) and the radiopharmaceuticals were always found to be better than 92% radiochemically pure. The quantity of HEDP administered was 0.73 mg and of $PP_i$ 6.9 mg, in accordance with the manufacturers' recommended doses. These quantities (approximately 0.3 mg/kg of $PP_i$ and 0.04 mg/kg of HEDP) are approximately one-tenth of those found to alter liver, bone, and bone-marrow distribution in rabbits (*8*). We therefore feel confident that the available binding sites in the tissue are in sufficient excess to avoid their saturation, which could alter the relative distribution of each radiopharmaceutical. In addition, two other dogs were studied using equal masses of the two tracers (0.73 mg or 0.04 mg/kg in each case), even though this delivers less pyrophosphate than is recommended by the manufacturer.

**Procedure.** In one group of three dogs, 6.9 mg Tc-99m $PP_i$ and 0.73 mg Tc-95m HEDP were administered simultaneously from separate syringes 15 min after release of the coronary obstruction. In a separate study the labels were switched, each being attached to the vector formerly used for the other. No difference in the tissue distribution attributable to this change could be found (Table 1). Consequently, all four dogs (the early-infarct group) were combined into a single group for analysis.

In a second group of three dogs (the aged-infarct group), the same procedure was followed except that the injection was made 48 hr after release of the ligation.

A third group of two dogs (the equal-mass aged-infarct group) had 0.73 mg each of Tc-99m $PP_i$ and Tc-95m HEDP injected 48 hr after release of the ligature. No difference in the tissue distribution caused by altering the mass of $PP_i$ injected could be found (Table 2). Consequently, all five dogs (the aged-infarct group) were combined into a single group for analysis.

In all cases, dogs were killed by overdose of sodium pentobarbital 2 hr after injection. Organs of interest were removed and samples were taken, weighed, and placed in tubes containing 10% buffered formalin.

Multiple samples (two to six samples of each tissue from each animal) of microscopically confirmed normal and infarcted myocardial tissue (hemorrhagic and nonhemorrhagic) and other tissues were counted from each animal. All samples were counted in a dual-channel automatic gamma spectrometer.§ The Tc-95m was counted using a window from 190 to 230 keV and the Tc-99m used a window from 120 to 160 keV with correction for decay and for Compton scatter from the Tc-95m. The photopeak-to-Compton ratio for Tc-95m was computed for different tissue types as well as for the technetium standard, and was not found to vary appreciably between samples. The injected activities were determined by counting aliquots of the radiopharmaceutical, corrected for residual syringe activity following injection, and the concentration of activity in each sample was computed (*9*).

## RESULTS

Two hours after injection, both $PP_i$ and HEDP

**TABLE 2. SIMULTANEOUS UPTAKE OF Tc-99m $PP_i$ AND Tc-95m HEDP IN THE AGED-INFARCT GROUP WITH TWO DIFFERENT ADMINISTERED QUANTITIES OF Tc-99m $PP_i$**

| Tissue | Uptake × 100* | | | |
|---|---|---|---|---|
| | 6.9 mg Tc-99m $PP_i$† | 0.73 mg Tc-95m HEDP† | 0.73 mg Tc-99m $PP_i$‡ | 0.73 mg Tc-95m HEDP‡ |
| Blood | 5.04 (4.79– 5.41) | 5.19 (4.60– 5.72) | 4.30 (3.47– 5.13) | 4.59 (4.12– 5.06) |
| Diaphragm | 1.25 (1.07– 1.57) | 1.32 (1.06– 1.47) | 1.64 (1.07– 2.21) | 1.42 (1.18– 1.66) |
| Liver | 3.38 (2.67– 3.88) | 1.63 (1.16– 1.87) | 4.44 (3.32– 5.55) | 1.63 (1.07– 2.19) |
| Lung | 3.70 (3.10– 4.32) | 3.53 (2.97– 3.85) | 4.76 (2.80– 6.72) | 6.5 (3.63– 9.37) |
| Normal myocardium | 1.97 (1.69– 2.28) | 1.71 (1.53– 1.88) | 3.80 (2.59– 5.01) | 2.44 (1.27– 3.61) |
| Rib | 22.3 (11.8 –35.7) | 20.5 (11.4 –32.1) | 39.1 (19.6 – 58.6) | 35.2 (34.9 –35.5) |
| Hemorrhagic infarct | 36.9 (12.8 –53.4) | 16.9 (6.42–26.1) | 16.1 (—) | 62.9 (—) |
| Nonhemorrhagic infarct | 60.0 (44.2 –79.1) | 20.5 (15.6 –26.5) | 111 (47.7 –175) | 42.9 (37.9 –47.9) |

* Percent kg dose/g tissue (mean and range).
† Data from three dogs.
‡ Data from two dogs.

**TABLE 3. OVERALL UPTAKE OF TECHNETIUM ETIDRONATE AND PYROPHOSPHATE IN DOGS WITH EXPERIMENTALLY INFARCTED HEARTS 2 HR AFTER INJECTION**

| Tissue | Uptake × 100* | | | |
|---|---|---|---|---|
| | Early-infarct group† | | Aged-infarct group‡ | |
| | Pyrophosphate | Etidronate | Pyrophosphate | Etidronate |
| Blood | 4.25 (3.59– 5.22) | 5.35 (3.88– 7.51) | 4.74 (3.47– 5.41) | 4.95 (4.12– 5.72) |
| Diaphragm | 3.57 (2.11– 6.07) | 4.12 (2.23– 8.21) | 1.41 (1.07– 2.21) | 1.36 (1.06– 1.66) |
| Liver | 4.28 (2.17– 9.97) | 1.79 (1.24– 2.24) | 3.80 (2.67– 5.55) | 1.63 (1.07– 2.19) |
| Lung | 4.65 (2.79– 7.95) | 3.34 (2.88– 3.97) | 4.12 (2.80– 6.72) | 4.72 (2.97– 9.37) |
| Normal myocardium | 4.99 (1.41– 7.79) | 2.53 (1.82– 4.39) | 2.70 (1.69– 5.01) | 2.00 (1.27– 3.61) |
| Rib | 31.8 (20.5 –37.7) | 28.2 (17.5 –35.8) | 29.0 (11.8 – 58.6) | 26.4 (11.4 –35.5) |
| Hemorrhagic infarct | 33.2 (29.7 –36.6) | 21.9 (16.0 –27.8) | 31.9 (12.8 – 53.4) | 28.4 (6.42–62.9) |
| Nonhemorrhagic infarct | 57.4 (26.6 –76.1) | 35.3 (15.9 –47.1) | 80.5 (44.2 –175) | 29.5 (15.6 –47.9) |

* Percent kg dose/g tissue (mean and range).
† Results from four dogs.
‡ Results from five dogs.

show substantial uptake in bone and infarcted myocardium for the early- and aged-infarct groups (Table 3). The bone uptake is comparable in magnitude with hemorrhagic and nonhemorrhagic infarcted tissue for both agents, which reduces their value in cardiac studies. The uptake by blood, diaphragm, liver, lung, and normal myocardium is seen to be 1.8–25% of the activity (percent kg dose/g tissue) in infarcted tissue. The data show sizable variation in uptake between animals, which is to be expected since the study used mongrel dogs of varying age.

A more helpful method for comparing the two radiopharmaceuticals is to compute the simultaneous $PP_i$/HEDP ratio for each tissue sample and to compare these ratios (Table 4).

In the early-infarct group, the mean $PP_i$/HEDP ratio is 1.59–1.67 for infarcted tissue, 1.15 for bone, and 0.814–2.24 for other background tissues. Similarly in the aged-infarct group, the mean $PP_i$/HEDP ratio ranges from 2.27 to 3.33 for infarcted tissue, 1.09 for rib, and from 0.975 to 2.40 for other background tissues.

## DISCUSSION

Etidronate and $PP_i$ have previously been shown to be effective in the diagnosis of acute myocardial infarction (*1,2,5*). In this study, to ascertain whether one of them would generally outperform the other, mongrel dogs were chosen because of their size, availability, and variability in an attempt to simulate the clinical setting, in which patients of various races, ages, and weights are encountered. The simultaneous dual-isotope technique is essential because of the variability in uptake from animal to animal, in the degree of experimental infarction created in each animal, and especially in the age of the infarct. With our procedure, each dog and each tissue concentrates $PP_i$ and HEDP at the same time under the same conditions and each sample is counted under identical conditions.

**TABLE 4. $PP_i$/HEDP RATIOS***

| Tissue | Early-infarct group† | Aged-infarct group‡ |
|---|---|---|
| Blood | 0.814 (0.697–0.924) | 0.975 (0.697–1.24) |
| Diaphragm | 1.45 (0.436–3.77) | 1.08 (0.647–1.87) |
| Liver | 2.24 (1.29 –4.50) | 2.40 (1.94 –3.13) |
| Lung | 1.43 (1.04 –2.54) | 1.19 (0.806–1.85) |
| Normal myocardium | 2.14 (0.751–4.28) | 1.38 (0.892–2.09) |
| Rib | 1.15 (0.994–1.26) | 1.09 (0.553–1.68) |
| Hemorrhagic infarct | 1.59 (1.32 –1.86) | 2.27 (1.97 –2.66) |
| Nonhemorrhagic infarct | 1.67 (1.71 –1.88) | 3.33 (1.27 –6.62) |

* $PP_i$/HEDP ratio (mean and range).
† Each ratio is from multiple tissue samples from four dogs.
‡ Each ratio is from multiple tissue samples from five dogs.

The results from this study show that in terms of absolute uptake (percent kg dose/g tissue), infarcted tissue accumulates four to 57 times the activity of any of the neighboring background organs with the exception of rib, in which concentration is from 0.4 to 1.3 times the infarct activity for both tracers.

In the group of dogs containing early infarcts, the $PP_i$/HEDP ratio is approximately 1.6 for both grossly hemorrhagic and nonhemorrhagic infarcts. In each animal, this ratio is significantly greater than one ($p = 0.05$) using a one-sided paired $t$ test. The ratio in blood—a major contribution to image background—is 0.8. These factors demonstrate that $PP_i$ is substantially better than HEDP. The result is weakened to a small extent by a ratio of 1.15 for rib, since the ribs have good uptake and lie directly over the heart. The ratios for other organs—including lung, liver, diaphragm, and normal myocardium—are also greater than 1.0, although they are extremely variable between dogs and relatively unimportant because of their low uptake.

The group of dogs containing aged infarcts shows the desirability of $PP_i$ to a greater extent. The $PP_i$/HEDP ratios for grossly hemorrhagic and nonhemorrhagic infarcts are 2.3 and 3.3. Again, the ratios for infarcts in each animal are significantly greater than 2.0 ($p = 0.05$). The ratios for lung, blood, diaphragm, and normal myocardium are nearly 1.0. These data clearly show $PP_i$ to be superior to HEDP. The ratio for rib and liver again show pyrophosphate to have some disadvantages, although only to a lesser extent. Although comparable to that of infarcted myocardium, the uptake by the rib is only 9% more for $PP_i$ than for HEDP, and therefore little difference will be seen between them in bone. Since liver uptake is only about 10% that of infarcted myocardium and does not lie over the heart, the $PP_i$/HEDP ratio of 2.1 will not seriously affect imaging.

Little difference can be seen between (A) the group of dogs with aged infarcts that received the recommended quantity of $PP_i$ and HEDP, and (B) the group that received equal masses of the two agents. We therefore conclude that in this model the dose of $PP_i$ administered has little effect on tissue distribution in the range tested.

Although both $PP_i$ and HEDP are indicated for use in bone imaging, and more recently have been suggested for the diagnosis of acute myocardial infarction, the $PP_i$/HEDP ratios for bone and infarct are not equal to 1.0, indicating a difference in kinetics or uptake mechanism by these tissues for the two radiopharmaceuticals.

From our experimental canine data, we conclude that both radiopharmaceuticals are useful in the diagnosis of acute infarctions, but that $PP_i$ will yield images with greater infarct intensity and improved contrast compared with HEDP. These findings are in agreement with the animal studies performed by Bonte et al. (*5*), who report a subjective preference for $PP_i$ in myocardial infarct studies performed with $PP_i$, HEDP, and polyphosphate. Since the distribution in animals varies substantially between manufacturers of both HEDP and $PP_i$ (*10*), the results of this study should be carefully considered when using other sources of these drugs.

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FOOTNOTES

* New England Nuclear, Boston, Mass.
† Osteoscan®, Procter and Gamble, Cincinnati, Ohio.
‡ Phosphotec™, E. R. Squibb & Sons, Princeton, N.J.
§ Searle model 1185.

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. PARKEY RW, BONTE FJ, MEYER SL, et al: A new method of radionuclide imaging of acute myocardial infarction. *Circulation* 50: 540–546, 1974

3. HOLMAN BL, DEWANJEE MK, IDOINE J, et al: Detection and localization of experimental myocardial infarction with $^{99m}$Tc-tetracycline. *J Nucl Med* 14: 595–599, 1973

4. ROSSMAN DJ, ROULEAU J, STRAUSS HW, et al: Detection and size estimation of acute myocardial infarction using $^{99m}$Tc-glucoheptonate. *J Nucl Med* 16: 980–985, 1975

5. BONTE FJ, PARKEY RW, GRAHAM KD, et al: Distribution of several agents useful in imaging myocardial infarcts. *J Nucl Med* 16: 132–135, 1975

6. BRUNO FP, COBB FR, RIVAS F, et al: Evaluation of $^{99m}$Technetium stannous pyrophosphate as an imaging agent in acute myocardial infarction. *Circulation* 54: 71–78, 1976

7. ZIMMER AM, HOLMES RA: Radiochemical purity and stability of commercial Tc-99m-Sn-diphosphonate kits using a new chromatography technique. *J Nucl Med* 16: 584, 1975

8. ECKELMAN WC, REBA RC, KUBOTA H, et al: $^{99m}$Tc-pyrophosphate for bone imaging. *J Nucl Med* 15: 279–283, 1974

9. KIRSCHNER AS, ICE RD, BEIERWALTES WH: The Authors' Reply. *J Nucl Med* 16: 248–249, 1975

10. ACKERHALT RE, BLAU M, BAKSHI S, et al: A comparative study of three $^{99m}$Tc-labeled phosphorus compounds and $^{18}$F-fluoride for skeletal imaging. *J Nucl Med* 15: 1153–1157, 1974

## SECOND INTERNATIONAL SYMPOSIUM ON RADIOPHARMACEUTICALS

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This symposium will be held under the auspices of the Radiopharmaceutical Council of the Society of Nuclear Medicine.

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- Proffered papers will be accepted on all aspects of radiopharmaceutical preparation, methodology, and use.

As a guide to prospective attendees who were not present at the Atlanta symposium in 1974, references to the content of that meeting can be obtained from its published proceedings, *Radiopharmaceuticals*, G. Subramanian, B.A. Rhodes, J F. Cooper, and V.J. Sodd, Editors, New York, Society of Nuclear Medicine, Inc., 1975.

The program committee for this meeting includes: Vincent J. Sodd, Ph. D., FDA Nuclear Medicine Laboratory, Cincinnati General Hospital, Cincinnati, OH 45267; David R. Allen, Ph. D., Division of Nuclear Medicine, University of Washington, Seattle, Washington 98195; Dennis R. Hoogland, Ph. D., Nuclear Pharmacy, Mayo Memorial Building, Box 382, Minneapolis, Minnesota 55455; Rodney D. Ice, Ph. D., College of Pharmacy, University of Oklahoma, 644 N.E. 14th Street, Oklahoma City, Oklahoma 73104.