# DIAGNOSTIC NUCLEAR MEDICINE

## Comparison of Tc-99m Pyrophosphate and Tc-99m Hydroxymethylene Diphosphonate in Acute Myocardial Infarction: Concise Communication

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**A clinical comparison between a new bone seeking radiopharmaceutical, Tc-99m hydroxymethylene diphosphonate (TcHMDP) and the standard agent, Tc-99m pyrophosphate (TcPPi), was performed in 18 patients with acute myocardial infarction. Each patient was imaged initially with either TcHMDP or TcPPi, and imaged 24 hr later with the other tracer. All 18 patients had images positive for acute myocardial infarction with TcPPi, whereas 16 of 18 patients (89%) had positive studies with TcHMDP. The TcPPi images were graded significantly superior to those obtained with TcHMDP in 61% of the patients, and they were equal in 33%. In only one patient (6%) was TcHMDP better. The results indicate that compared with TcHMDP, TcPPi not only has a superior sensitivity for acute myocardial infarction but also has a significantly increased intensity of uptake in positive areas. TcPPi remains the agent of choice for myocardial infarct imaging.**

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Myocardial infarct imaging with Tc-99m pyrophosphate (TcPPi) has proven to be a reliable and highly sensitive procedure for the determination of acute myocardial injury. (*1–7*) Since the introduction of this technique by Bonte et al. in 1974 (*8*), the availability of other Tc-99m-labeled bone-seekers (*9*)—such as methylene diphosphonate (MDP) (*10*) and 1-ethane-1-hydroxy diphosphonate (EHDP) (*11*)—has stimulated considerable suspicion that these agents may also possess an affinity for acutely infarcted myocardium. Recently, in a comparison of TcPPi and TcMDP in 24 patients with proven acute myocardial infarction (*12*), we reported that TcPPi yields the higher sensitivity (86% against 71% for MDP) and remains the current agent of choice. Others have had similar results (*13*). Another recently developed phosphonate analogue, hydroxymethylene diphosphonate (HMDP), has been evaluated in animals for skeletal imaging and the demonstration of myocardial infarcts (JA Bevan, et al., personal communication). Compared with TcMDP, the blood clearance of TcHMDP is slightly faster and the bone accumulation significantly greater. In a dog model of myocardial infarction, the myocardial uptake of TcHMDP was shown to be approximately equal to that of TcPPi. However, the MI/blood ratio of TcHMDP was higher than that with TcPPi. These animal findings have prompted us to perform a prospective clinical comparison between this potentially useful agent, TcHMDP, and the current agent of choice, Tc pyrophosphate, in patients with acute myocardial infarction.

### MATERIALS AND METHODS

The 18 patients selected for inclusion in this study were admitted to our coronary care unit (between Jan. 4 and May 3, 1979) with a diagnosis of acute myocardial infarction (transmural). Each patient exhibited clinical evidence of acute myocardial infarction as documented by clinical history, physical examination, standard electrocardiographic changes, serial enzyme elevations (CPK, SGOT, and LDH), and a positive MB fraction

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of creatine phosphokinase. All patients were carefully screened to prevent the inclusion of persons with significant arrhythmias, cardiogenic shock, left bundle-branch block, or those requiring intracardiac pacing. Written informed consent was obtained from each patient.

In the protocol, each patient was initially imaged with either TcHMDP or TcPPi, then imaged 24 hr later with the other tracer. The order of tracer administration was randomized by computer, with an equal number of patients receiving each agent first. All patients were injected with the first tracer between 2 and 4 days from the onset of myocardial injury (average 3.9 days). TcPPi† and TcHMDP‡ were prepared in a similar manner by adding to each vial between 80 and 100 mCi of sodium pertechnetate in a total volume of 4 ml. All patients were imaged in the coronary care unit approximately 90–120 min following i.v. administration of 20 mCi of each tracer. Anterior, left anterior oblique (45°), and left lateral supine views were obtained using a small-field portable scintillation camera fitted with a general-purpose low-energy collimator. Anterior views were recorded for 4,000 counts/cm$^2$ (over sternum) and subsequent views were obtained for the same period of time.

**TABLE 1. SENSITIVITIES OF Tc-99m HMDP FOR THE DETECTION OF ACUTE MYOCARDIAL INFARCTION IN A TOTAL OF 18 PATIENTS WITH PROVEN INFARCTION**

| Radiopharmaceutical | Positive | Negative |
|---|---|---|
| Tc-99m PPi | 18 (100%) | 0 (0%) |
| Tc-99m HMDP | 16 (89%) | 2 (11%) |

The sequence of the radiopharmaceutical administration was known only to the nuclear pharmacy staff. Although the clinicians were aware of the selection criteria for inclusion in the study, the randomized nature of the tracer administration precluded any knowledge of the one used in each scintiscan. Following completion of the study, the images were interpreted and graded independently by four members of the Nuclear Medicine Section. For each tracer, images were graded on the view showing the most intense myocardial uptake. No discernible myocardial activity was graded 0. Diffuse uptake in the region of the myocardium not clearly distinguishable from blood pool was graded 1+, irrespective of intensity. Focal accumulation less than rib uptake was

**TABLE 2. PATIENTS IN ORDER OF GREATEST DIFFERENCE BETWEEN TcPPI AND TcHMDP**

| Patient | Location of infarction | Average graded intensity* of myocardial uptake | | Difference (PPi − HMDP) |
|---|---|---|---|---|
| | | TcPPi | TcHMDP | |
| 1 | Inferior | 4 | 1.25 | 2.75 |
| 2 | Anterior | 4 | 2.5 | 1.5 |
| 3 | Inferior | 2.5 | 1.0 | 1.5 |
| 4 | Inferior | 3.25 | 2.0 | 1.25 |
| 5 | Anterolateral and anteroseptal | 4.0 | 3.0 | 1.0 |
| 6 | Inferior | 4.0 | 3.0 | 1.0 |
| 7 | Inferior and anterior | 3.75 | 2.75 | 1.0 |
| 8 | Anterior | 3.25 | 2.25 | 1.0 |
| 9 | Inferior | 2.75 | 1.75 | 1.0 |
| 10 | Inferior | 2.75 | 2.0 | 0.75 |
| 11 | Inferior | 3.25 | 2.75 | 0.5 |
| 12 | Inferior | 2.25 | 2.0 | 0.25 |
| 13 | Anteroseptal | 4.0 | 4.0 | 0 |
| 14 | Anteroseptal | 4.0 | 4.0 | 0 |
| 15 | Anteroseptal | 3.0 | 3.0 | 0 |
| 16 | Inferior | 3.75 | 4.0 | −0.25 |
| 17 | Anteroseptal | 3.75 | 4.0 | −0.25 |
| 18 | Inferior | 3.0 | 4.0 | −1.0 |
| Average | | 3.4 | 2.76 | 0.64 |

* Average graded intensity for four observers using a grading scale of 0 = negative, 1+ = diffuse uptake or blood pool, 2+ = focal uptake less than rib, 3+ = focal uptake equal to rib, 4+ = focal uptake greater than rib.

graded 2+, that equal to rib was 3+, and focal accumulation greater than rib was graded 4+ (*6*). The interpreters' scores for each study were averaged, and any study having an average intensity of 1.5+ or greater was considered positive for acute myocardial infarction.

## RESULTS

All 18 patients had positive TcPPi scintiscans, whereas there were 16 of 18 (89%) positive with TcHMDP (Table 1). The averages of the graded intensities for each patient with the two agents are shown in Table 2. In 11 of 18 patients (56%), the images obtained with TcPPi were graded significantly higher (greater than 0.5 difference) than those obtained with TcHMDP. The two studies were graded equal in six of 18 patients (33%). In only one patient was the intensity in the TcHMDP images more than 0.5 greater than in the TcPPi images.

When the gradings for the two tracers were compared using Student's paired t-test of significance, TcPPi showed an intensity of uptake significantly greater ($P < 0.001$) in areas of myocardial infarction. Interobserver agreement, evaluated using Pearson's correlation coefficient, showed good agreement. Only one study, as graded by one observer, differed by more than 1 from the average of the other three observers.

## DISCUSSION

This study confirms the high sensitivity of myocardial infarct imaging well documented in the literature (*1–7*). TcPPi has been the tracer most commonly used for infarct imaging, and has evolved as the present agent of choice. Previous work has established its superiority over Tc-99m methylene diphosphonate, Tc-99m glucoheptonate, and Tc-99m tetracycline (*12–14*).

Variables of concern during comparison of two tracers in the same patient are the effect of time and the sequence of administration. The sensitivity of myocardial infarct imaging is time-dependent. Imaging with TcPPi is believed to be dependably positive in the period from approximately 12 hr to 6 days following infarction. In this study, one patient (No. 17) was imaged on the second day following infarction; the others were initially imaged on either Day 3 or Day 4 following onset. All images were completed by the fifth day. Thus all patients were imaged at a time following their infarction at which the scan should be abnormal. Patients were equally divided between those receiving TcHMDP and those receiving TcPPi for the first imaging, thus minimizing any effect from the sequence of imaging.

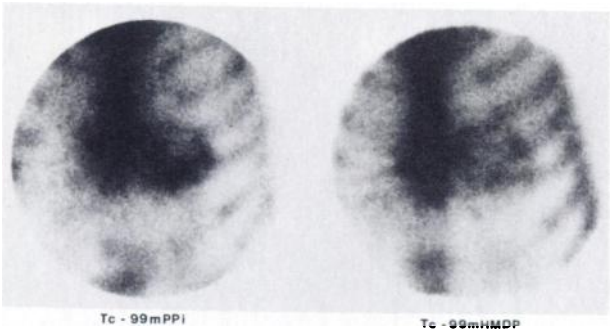


**FIG. 1.** Anterior images of Patient 7, graded 3.75+ for TcPPi and 2.75+ for TcHMDP. There are areas of increased bone uptake in sternum and ribs from prior resuscitation.

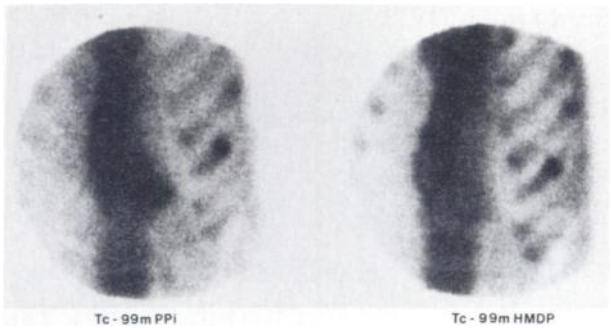


**Fig. 2.** Anterior images of Patient 1, showing 4+ activity for TcPPi and 1.25+ for TcHMDP.

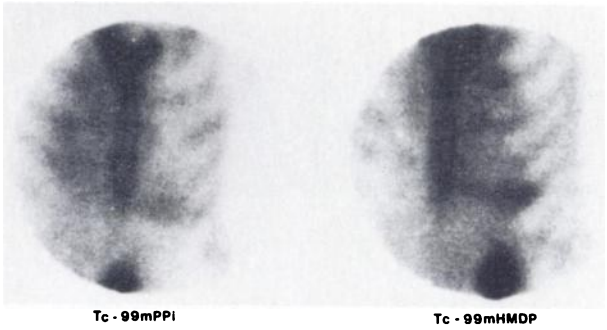


**Fig. 3.** Anterior images of Patient 18, with intensity graded 3+ with TcPPi and 4+ with TcHMDP, thus demonstrating better uptake with TcHMDP. Uptake seen in left upper abdomen is an extra renal pelvis as determined by prior IVP.

To evaluate possible interference with the second study, due to residual activity from the first, patients in the early phases of this series were reimaged 24 hr following the administration of the first tracer, just before administration of the second. Camera settings and counting periods were identical to those used for the initial images. None of these patients showed discernible residual activity over the myocardium. To assure maximum consistency in the grading of images, the examiners individually graded all of the studies in one setting without interruption or distraction.

The anterior images for a typical patient (No. 7) are shown in Fig. 1. This patient had an average graded intensity of +3.75 with TcPPi, whereas the average for TcHMDP was +2.75. The area of uptake in the inferior myocardium is significantly easier to identify on the TcPPi image. The patient with the most dramatic difference (No. 1) is shown in Fig. 2. The average graded

intensity with TcPPi was +4.0, whereas the TcHMDP study on this patient was considered negative for acute myocardial infarction, with a +1.25 average. The one patient (No. 18) whose average grade with TcHMDP was greater than that with TcPPi is shown in Fig. 3.

## CONCLUSION

The results indicated that TcPPi is not only superior to TcHMDP in sensitivity (100% against 89%) but has a significantly increased intensity of uptake in positive areas compared with bone. TcPPi thus remains the agent of choice for acute myocardial infarct imaging. The sensitivity of TcHMDP in this study was 89%, whereas that for TcMDP on our previous study (*12*) was 71%. While this difference in two different patient groups may not be significant, it supports previous animal work, which showed that HMDP, a tridentate ligand, possesses multicoordination potential for calcium ions and would bind more intensely to acutely infarcted myocardium than the bidentate molecule, MDP.

## FOOTNOTES

† Mallinckrodt Nuclear, St. Louis, MO.
‡ Proctor and Gamble Co., Cincinnati, OH.

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## ERRATUM

In the article entitled "Transmission Computed Tomography, Tc-99m MAA Scintigraphy, and Plain Chest Radiography after Experimentally Produced Acute Pulmonary Arterial Occlusion in the Dog" by Zachary D. Grossman, et al., appearing in *J Nucl Med* 20: 1251-1256, 1979, the discontinuous color bar was inadvertently omitted from figure 1. The correct figure and caption are printed below.

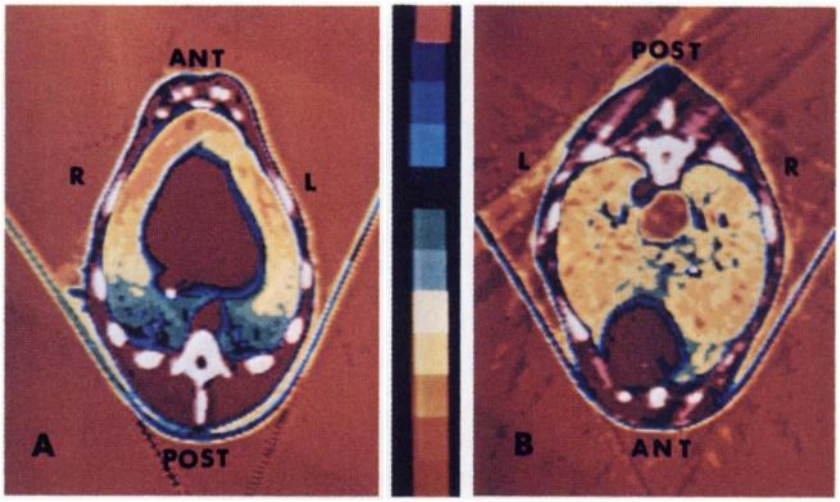


**FIG. 1.** Supine transaxial image (A) of lower thorax of anesthetized dog reveals striking anterior-to-posterior increasing density gradient. Discontinuous color bar is arranged so that progressively greater densities are toward *top*. Note predominance of blues and greens in dependent portions of both lungs, and predominance of yellows and oranges more ventrally. Prone transaxial image (B) of anesthetized dog reveals loss of most of gradient. Lung density is largely uniform from front to back.