## INSTRUMENTATION

# Computer Analysis of Tc-99m DPD and Tc-99m MDP Kinetics in Human: Concise Communication

Marino Mele, Elio Conte, Angelo Fratello, Domenico Pasculli, Maria Pieralice, and Angelo D'Addabbo

*Centro Interdipartimentale di Biocibernetica e Tecniche Radioisotopiche dell' Università di Bari—Policlinico, Piazza Giulio Cesare, Bari, Italy*

**Technetium-99m DPD and Tc-99m(Sn)MDP were compared regarding the quality of skeletal images and the compartmental kinetic data, in two groups of nine normal subjects. No difference in scan quality was found. Data derived from compartmental kinetic analysis suggest that MDP has a higher bone uptake and a lower soft-tissue retention in comparison with DPD.**

J Nucl Med 24: 334–338, 1983

During recent years many bone-seeking radiopharmaceuticals have been proposed for bone scanning. At present, the Tc-99m phosphonate compounds are used more frequently, but the mechanism of bone uptake is still unclear (*1–7*).

The methylene diphosphonic acid labeled with Tc-99m, used so far, has given the highest blood clearance and highest bone affinity (*8*). The bone uptake has been estimated by whole-body monitoring (*9*), measurement of renal excretion of the tracer (*10–13*), and by compartmental analysis of Tc-99m(Sn)MDP kinetics (*14,15*). Recently a new radiotracer, 2,3-dicarboxypropane-1,1-diphosphonic acid (DPD), has been proposed for bone scanning (*16,17*).

The purpose of this study is to compare the quality of the skeletal image and the compartmental kinetic data of Tc-99m(Sn)MDP with those of Tc-99m DPD. The kinetic analysis was performed using a four-compartmental model for both radiopharmaceuticals.

## MATERIALS AND METHODS

We studied 18 "normal" subjects (age range 20–72 yr) who had neither malignant nor metabolic disease of the bones nor inflammatory joint disease. Nine were given Tc-99m-tagged methylene diphosphonic acid,* reduced with $SnCl_2$, [Tc-99m(Sn)MDP], and nine received the tetrasodium salt of dicarboxylpropane diphosphonic acid† (Tc-99m DPD), reduced with stannous oxide. The two compounds seem essentially alike except for the presence of Cl in the first and of dicarboxypropane in the second.

The tracer dose used was 20 mCi. A large-field scintillation camera with medium-sensitivity low-energy collimator was used. The patients lay on one side, with the detector head over the lateral side of the knee and the distal thigh.

Counts were collected every minute for 2 hr in a 64 × 64 matrix, then corrected for background and physical decay, and stored in a 32K-word computer.

The regions of interest (ROI) for the knee and superior soft-tissue mass of the thigh were selected manually by light pen on computer processing frames, and time-activity curves were then generated.

During data acquisition, blood samples were collected at 2, 5, 10, 20, and 30 min, and at 1, 2, 3, and 4 hr after injection. The urine collection was obtained from the time of injection at 2 to 4 hr. Blood and urinary activities were expressed as a percentage of the blood value at zero time.

All the experimental data were obtained for each subject separately and an analysis of their statistical reliability was performed.

The scans were performed about 3 hr after injection. The mathematical approach to the tracer kinetics was

Received June 7, 1982; revision accepted Nov. 8, 1982.

For reprints contact: Dr. Marino Mele, Cattedra di Medicina Nucleare, Università di Bari—Policlinico, Piazza Giulio Cesare, 70124—Bari, Italy.

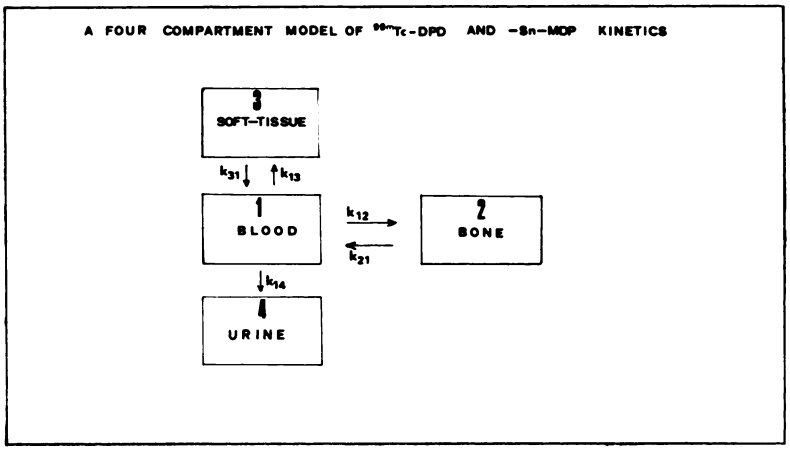


**FIG. 1.** Kinetic pathways of Tc-99m DPD and Tc-99m(Sn)MDP. The tracer, entering blood, is transferred to soft tissue and bone space, and is excreted through urinary compartment. Tracer re-enters blood for subsequent redistribution or excretion.

based on a model of the system that uses plasma activity for "structural" and parameter identification (*18*), a procedure outlined elsewhere (*19*). The computer program used for the compartmental identification fitted the sum of 2, 3, 4 . . . exponential terms to the experimental data from plasma, where the fit to each number of exponentials is that given by the minimization of errors. At each step the computer program determined by F-test whether the addition of another exponential term would significantly reduce the least-square errors.

The differential equations describing the kinetics of Tc-99m DPD and Tc-99m(Sn)MDP using this model (Fig. 1) are the following:

**Blood**

$$\frac{dx_1}{dt} = -(k_{12} + k_{13} + k_{14})x_1 + k_{21}x_2 + k_{31}x_3;$$

**Bone space**

$$\frac{dx_2}{dt} = k_{12}x_1 - k_{21}x_2;$$

**Soft tissue**

$$\frac{dx_3}{dt} = k_{13}x_1 - k_{31}x_3;$$

where $k_{ij}$ ($i = 1, 2, 3$ and $j = 1, 2, 3, 4$) are the kinetic rate constants to be compared for the two tracers. The half-

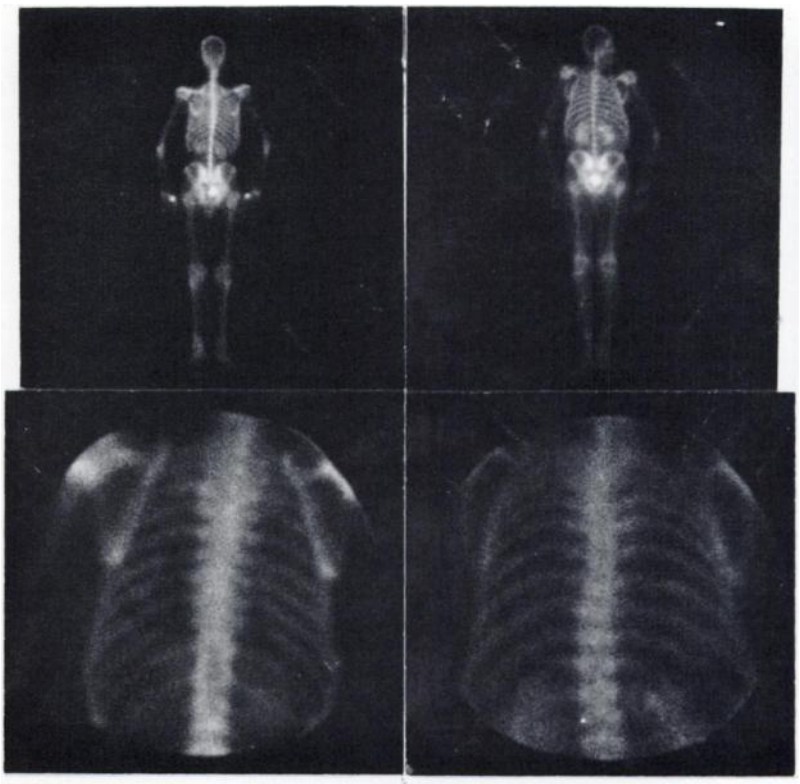

**FIG. 2.** Bone scans 3 hr after injection of Tc-99m DPD (left) and Tc-99m(Sn)MDP (right).

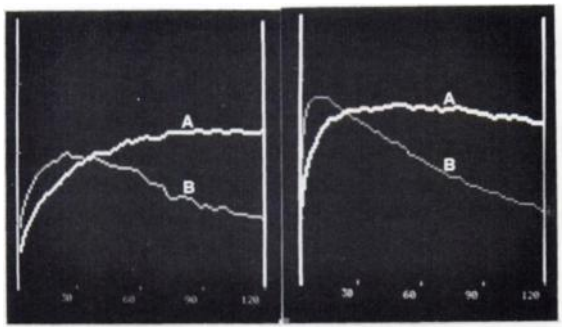


**FIG. 3.** Time-activity curves from two selected regions of interest (knee "A" and soft tissue of thigh "B") of subject treated with Tc-99m DPD (left) and another with Tc-99m(Sn)MDP (right).

time values, intercepts, and rate constants were calculated by computer through minimization of errors (*20,21*), simultaneously fitting the blood data and the experimental values of the activity in the ROI for each tracer. All the data were analyzed for each subject separately, then the average results were calculated. A further computer program was used to calculate the numerical solutions of the above differential equations, which then describe the tracer activity against time in each compartment; in addition the excretion rate constants, half-times, and intercepts were calculated.

## RESULTS AND DISCUSSION

Figure 2 shows the scintigrams of Tc-99m DPD (left) and Tc-99m(Sn)MDP (right), respectively. Considering that the quality of scintigrams can influence our subjective evaluation of the images, it appears that there are no important differences between the tracers, unless one could claim a slightly higher bone uptake for Tc-99m DPD relative to Tc-99m(Sn)MDP.

Preliminary studies suggest that Tc-99m DPD gives scintigrams of better quality (*16*) and with a higher ratio of bone to soft tissue compared with Tc-99m(Sn)MDP (*17,22*).

Figure 3 shows the time-activity histograms relative to soft tissue of the thigh and the knee. With Tc-99m DPD the time of steady-state bone uptake is reached at ~60 min after injection, whereas that with Tc-99m(Sn)MDP is reached after ~30 min. The histograms for soft tissue (Fig. 3) show an earlier peak and a faster elimination for Tc-99m(Sn)MDP.

This external measurement, however, must be recognized as affected by many sources of error, since soft-tissue radioactivity varies according to vascularity, muscle bulk, and plasma clearance, the last depending mainly on the ratio of renal clearance. Consequently the impressions from Fig. 2, the histograms of Fig. 3, and the estimation of Nosslin (*17*) and Buell (*22*) also useful for clinical comparisons of bone-seeking tracers cannot be considered to reflect a final quantification of the actual and total bone turnover. Of course, a quantitative estimation of bone uptake can be obtained only by computer analysis of the Tc-99m(Sn)MDP and Tc-99m DPD kinetics. This approach uses the identification techniques (*23–27*) of a multicompartmental model, in contrast to the technique adopted by Makler (*14*), which fitted the experimental data to a preconceived compartmental model.

**TABLE 1. COMPUTER ANALYSIS OF BLOOD CLEARANCE OF Tc-99m-TAGGED DPD AND (Sn)MDP**

| Phase | $1^{\wedge}$ | $2^{\wedge}$ | $3^{\wedge}$ | $1^{\wedge}$ | $2^{\wedge}$ | $3^{\wedge}$ |
|---|---|---|---|---|---|---|
| | $\lambda$ ($min^{-1}$) | | | $t_{1/2}$ (min) | | |
| DPD (n = 9) | | | | | | |
| $\bar{X}$ | 0.099 | 0.012 | 0.00168 | 7.0 | 57.7 | 412 |
| s.d. | 0.0206 | 0.0045 | 0.000458 | 1.2 | 15.7 | 88 |
| MDP (n = 9) | | | | | | |
| $\bar{X}$ | 0.113 | 0.0148 | 0.00174 | 6.13 | 46.8 | 398 |
| s.d. | 0.019 | 0.0028 | 0.00030 | 1.06 | 9.2 | 71 |

**TABLE 2. COMPUTER ANALYSIS OF Tc-99m DPD AND Tc-99m(sn)MDP KINETICS INTERCEPTS**

| Phase | $1^{\wedge}$ | $2^{\wedge}$ | $3^{\wedge}$ | $1^{\wedge}$ | $2^{\wedge}$ | $3^{\wedge}$ | $1^{\wedge}$ | $2^{\wedge}$ | $3^{\wedge}$ | $1^{\wedge}$ | $2^{\wedge}$ | $3^{\wedge}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Blood | | | Bone | | | Soft tissue | | | Urine | | |
| DPD (n = 9) | | | | | | | | | | | | |
| $\bar{X}$ | 66.2 | 25.0 | 8.75 | 9.0 | 41.2 | 50.2 | 50.2 | 39.8 | 10.3 | 9.2 | 26.8 | 64.0 |
| s.d. | 6.2 | 5.1 | 2.49 | 3.0 | 8.9 | 10.7 | 3.4 | 3.4 | 2.7 | 4.8 | 8.7 | 12.5 |
| MDP (n = 9) | | | | | | | | | | | | |
| $\bar{X}$ | 60.6 | 30.4 | 9.0 | 9.2 | 45.7 | 54.9 | 48.2 | 38.8 | 9.4 | 7.3 | 26.3 | 66.4 |
| s.d. | 10.3 | 10.2 | 2.0 | 2.8 | 6.1 | 6.4 | 9.1 | 4.9 | 4.6 | 2.7 | 4.9 | 7.3 |

**TABLE 3. COMPUTER ANALYSIS OF COMPARTMENTAL KINETICS FOR Tc-99m-TAGGED DPD AND (Sn)MDP**

| | Rate constants ($min^{-1}$) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $k_{12}$* | $k_{21}$† | $k_{13}$‡ | $k_{31}$§ | $k_{14}$‖ | $\alpha$¶ | $\beta$# | $\alpha/\beta$ |
| DPD (n = 9) | | | | | | | | |
| $\bar{X}$ | 0.0130 | 0.0040 | 0.0447 | 0.0405 | 0.0121 | 3.24 | 1.10 | 2.94 |
| s.d. | 0.0061 | 0.0013 | 0.0081 | 0.0126 | 0.0031 | | | |
| MDP (n = 9) | | | | | | | | |
| $\bar{X}$ | 0.0163 | 0.0043 | 0.0497 | 0.0515 | 0.0133 | 3.79 | 1.0 | 3.95 |
| s.d. | 0.0038 | 0.0019 | 0.0061 | 0.0064 | 0.0031 | | | |

* $k_{12}$ = blood → bone.
† $k_{21}$ = bone → blood.
‡ $k_{13}$ = blood → soft tissue.
§ $k_{31}$ = soft tissue → blood.
‖ $k_{14}$ = blood → urine.
¶ $\alpha = k_{12}/k_{21}$.
# $\beta = k_{13}/k_{31}$.

The kinetic data are reported in Tables 1, 2, and 3 and the compartmental curves, generated by our computer analysis, are shown in Figs. 4 and 5. Different average ratios of the rate constants (Table 3) show some basic differences that can be extracted from the kinetics of the two tracers.

The average ratios to and from soft tissue are 1.1 for Tc-99m DPD and 1.0 for Tc-99m(Sn)MDP. Concerning the bone uptake, the average ratio of the rate constants to and from bone are quite similar for the two tracers (3.24 and 3.79 for Tc-99m DPD and Tc-99m(Sn)MDP, respectively).

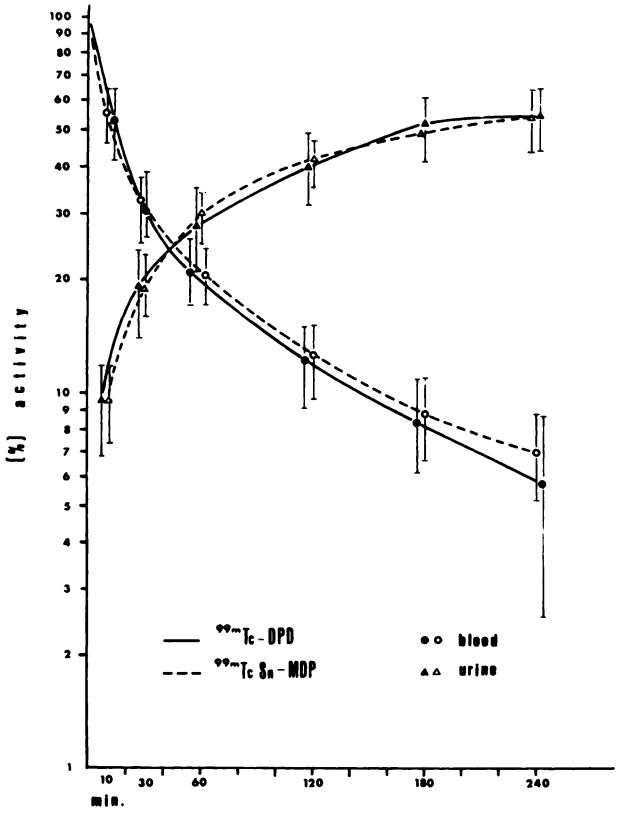


FIG. 4. Computer-generated average curves for compartmental model of blood and urine.

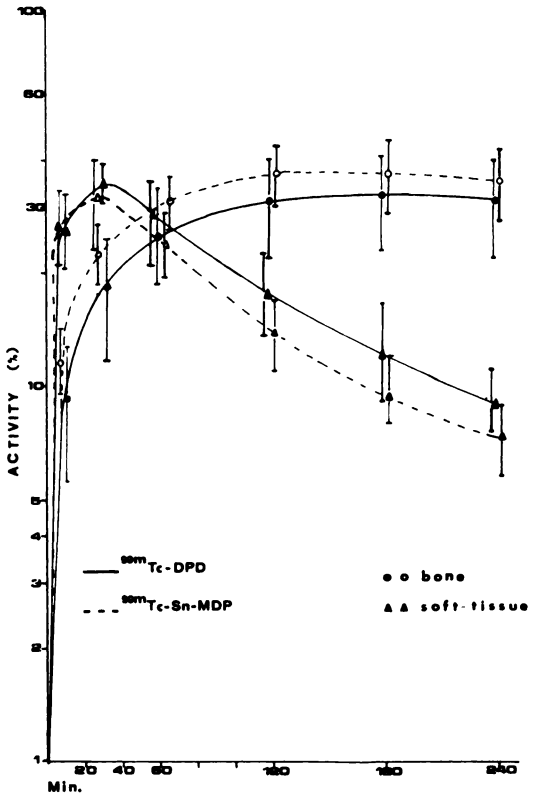


FIG. 5. Computer-generated average curves for compartmental model of bone and soft tissue.

The average ratio for bone uptake to soft-tissue retention ($\alpha/\beta$) is 3.95 (100%) for Tc-99m(Sn)MDP and 2.94 (74%) for Tc-99m DPD, but the apparent difference of 26% is not statistically significant.

In conclusion, our study indicates that MDP yields bone images comparable to those obtained with DPD, but data derived from compartmental analysis, suggest that MDP has a higher bone uptake and lower soft-tissue retention in comparison with DPD.

## FOOTNOTES

* Byk-Mallinckrodt.
† Behring Institute.

## REFERENCES


1. D'ADDABBO A, FRATELLO A, GRASSO G, et al: $^{99m}$Tc-pyrophosphate kinetics in man. *La Ricerca Clin Lab* 8: 100-111, 1978
2. GARCIA DA, TOW DE, KAPUR KK, et al: Relative accretion of $^{99m}$Tc-polyphosphate by forming and resorbing bone system in rats: Its significance in the pathologic basis of bone scanning. *J Nucl Med* 17:93-97, 1976
3. JONES AG, FRANCIS MD, DAVIS MA: Bone imaging: Radionuclide reaction mechanisms. *Semin Nucl Med* 6:3-18, 1976
4. KRISHNAMURTHY GT, BRICKMAN AS, BLAHD WH: Technetium 99m-Sn-pyrophosphate pharmaco-kinetics and bone image changes in parathyroid disease. *J Nucl Med* 18: 236-242, 1977
5. ROSENTHALL L, KAYE M: Technetium-99m-pyrophosphate kinetics and imaging in metabolic bone disease. *J Nucl Med* 16:33-39, 1975
6. ROSENTHALL L, KAYE M: Observations on the mechanism of $^{99m}$Tc-labeled pyrophosphate complex uptake in metabolic bone disease. *Semin Nucl Med* 6:59-67, 1976
7. HOSAIN P: Tc-99m labelled pyrophosphate: Simple and reproducible bone scanning agent. *Br J Rad* 46:724-755, 1973
8. SUBRAMANIAN G, MC AFEE JG, BLAIR RJ, et al: Technetium-99m-methylene diphosphonate, a superior agent for skeletal imaging: Comparison with other Technetium complexes. *J Nucl Med* 16:744-755, 1975
9. FOGELMAN I, BESSENT RG, TURNER JG, et al: The use of whole body retention of $^{99m}$Tc diphosphonate in the diagnosis of metabolic disease. *J Nucl Med* 19:270-275, 1978
10. CANIGGIA A, VATTIMO A: Kinetics of $^{99m}$Technetium-Tin-Diphosphonate in normal subjects and pathological conditions: A simple index of bone metabolism. *Calcif Tissue Int* 30:5-13, 1980
11. FOGELMAN I, BESSENT RG, BEASTALL G, et al: Estimation of skeletal involvement in primary hyperparathyroidism. Use of 24-hour whole-body retention of technetium-99m-diphosphonate. *Ann Int Med* 92:65-67, 1980
12. FOGELMAN I, BESSENT RG, COHEN HN, et al: Skeletal uptake of diphosphonate. Method for prediction of postmenopausal osteoporosis. *Lancet* 2:667-670, 1980
13. MACFARLANE JD, KHAIRI MRA, RICCIARDONE M, et al: Renal excretion of $^{99m}$Tc-diphosphonate in osteomalacia. *Ann Int Med* 90:350-351, 1979
14. MAKLER PT JR, CHARKES ND: Studies of skeletal tracer kinetics IV. Optimum time delay for Tc-99m(Sn)-methylene-diphosphonate bone imaging. *J Nucl Med* 21:641-645, 1980
15. D'ADDABBO A, CONTE E, FANFANI G, et al: Bone turnover functional scintigraphy and computer analysis of $^{99m}$Tc-Sn-MDP kinetics in normal subjects and patients with chronic renal failure. *J Nucl Med All Sci* 25:204-205, 1981
16. HALE TI, JUCKER A, VGENOPOULOS K, et al: Clinical experience with a new bone seeking $^{99m}$Tc radiopharmaceutical. Sonderdruk aus Nuc. Compact. G-I-T Verlag Ernst Giebeler. *Darmstad* 12:54-55, 1981
17. WACHEK W, SEIDEL L, HOECHST AG: Results of a multicenter study of a new bone-seeking $^{99m}$Tc-labelled phosphate complex (DPD Hoechst—Teceos). *J Nucl Med All Sci* 25: 210-215, 1981
18. COBELLI C, LEPSCHY A, JACUR GR: Identifiability results on some—Constrained compartmental system. *Mathematical Biosciences* 47:173-195, 1979
19. CONTE E, PIERALICE M, D'ADDABBO A: Parameter and structural identifiability of linear kinetic models by the quantitative analysis of gamma-camera dynamic studies. *J Nucl Med All Sci* 25:203-204, 1981
20. JAMES F, ROOS M: MINUIT, A system for function minimization and analysis of the parameter errors and correlations. *Comput Phys Comm* 10:343-346, 1975
21. NELDER J, MEAD R: A simplex method for function minimization. *Comput J* 7:308-312, 1965
22. BUELL U, KLEINHANS E, ZORN-BOPP E, et al: A comparison of bone imaging with Tc-99m DPD and Tc-99m MDP: Concise communication. *J Nucl Med* 23:214-217, 1982
23. BERMAN M, WEISS ME, SHAHN E: The routine fitting of kinetic data to models. A mathematical formalism for digital computer. *Biophys J* 2:275-287, 1962
24. BERMAN M, WEISS MC, SHAHN E: Some formal approaches to the analysis of kinetic data in terms of linear compartmental systems. *Biophys J* 2:289-316, 1962 (b)
25. HADLEY G: Linear programming. Addison Wesley, Reading, MA 1961
26. LEVIN MJ: Optimum estimation of impulse response in presence of noise. *IRE Trans Circuit Theory*, C T-7, No. 1, 1960
27. NAGUMO J, NODA A: A learning method for system identification. *IEEE Trans Automatic Control*, A C-12, 282-286, 1967