Pharmacokinetics of Technetium-99m Diphosphonate

Frank P. Castronovo,* Milton J. Guiberteau,† Gerald Berg,‡
Kenneth A. McKusick,* Ronald J. Callahan,* and Majic S. Potsaid*

Massachusetts General Hospital, Boston, Massachusetts
and Waterbury Hospital, Waterbury, Connecticut

Increased diagnostic information may be derived with Tc-99m diphosphonate from a detailed kinetic analysis of blood disappearance, urinary excretion, and quantitative assessment of skeletal uptake. Blood and urine determinations were studied in three populations: normal volunteers, patients with negative bone scans, and patients with positive bone scans. Quantitative imaging studies were performed in normal volunteers and patients with a scintillation camera interfaced to a computer. All subjects were scanned in the lower lumbar region up to 1 hr after Tc-99m diphosphonate administration. Blood levels exhibited a triexponential clearance pattern. Significant ($p < 0.05$) differences were observed for the 5-min blood and 0–1 hr urine values among the various groups. The computer-generated images showed an initial early uptake in bone, kidneys and soft tissue. Thereafter, a parallel fall-off in activity was observed in kidney and soft tissue, with a concomitant increase in bone. Skeletal uptake was different for normal and diseased bone.

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Based on animal and human data, it is generally agreed that approximately 50% of a bone-seeking radiopharmaceutical such as technetium-99m diphosphonate is deposited on the skeleton of normal individuals, while the other half is excreted through the urinary tract (*1–4*). It is also recognized that this distribution can vary as a result of certain diseased states, in particular with bone or renal abnormalities (*5,6*). To study such distribution differences, in vitro quantitative measurements have been made of blood clearance and urinary excretion (*7–9*). Additional studies employing a computer-assisted scintillation camera system determined the rate of accumulation of this agent in bone as an in vivo procedure (*10–13*).

With the use of these methods of analysis, this report presents the pharmacokinetics of Tc-99m diphosphonate in normal volunteers and patients, with the patient population subdivided into those with normal and those with abnormal bone scans.

MATERIALS AND METHODS

Male volunteers (N = 5) served as normal control subjects. They were 31–42 years of age, had normal renal function as measured by BUN, and had no clinical evidence of systemic or localized bone disease. This group was subjected to both the in vitro and in vivo studies.

A total of 37 patients with normal BUN values had in vitro determinations of blood clearance and urinary excretion. Twenty-three of these patients had bone scans that were interpreted as normal, while the remaining 14 had bone scans that were interpreted as showing metastases or metabolic bone disease.

For the in vivo scintillation camera–computer analyses of subjects with negative bone scans (4 volunteers, 2 patients), they were positioned supine and remained immobile. The detector head of the scintillation camera, interfaced with a laboratory computer, was positioned over the lower lumbar region using a parallel-hole collimator. After ad-

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For reprints contact: Frank P. Castronovo, Dept. of Radiology, Massachusetts General Hospital, Boston MA 02114.

* Department of Radiology, Massachusetts General Hospital, Boston, Mass.

† Active Duty, US Army.

‡ Department of Radiology, Waterbury Hospital, Waterbury, Conn.

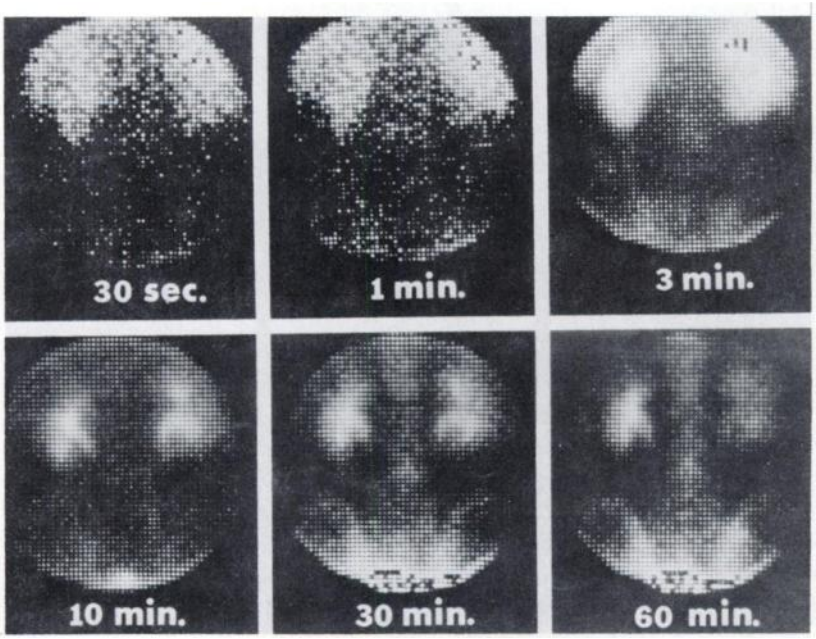

FIG. 1. Serial computer-generated posterior views of Tc-99m diphosphonate distribution in lower back region of normal volunteer, showing initial soft-tissue uptake followed by rapid renal concentration and late accumulation in bone as soft-tissue background decreases.

ministration of the Tc-99m diphosphonate, the following data sequences were stored on disc: 3-sec intervals for 60 sec; 1-min intervals for the next 9 min; and 5- or 10-min intervals up to 60 min. These data were framed and regions of interest were selected to include kidney, spine, and soft tissue, and were corrected for decay and background. The "net count per cell" at 1 hr was arbitrarily assigned a value of 100%. A graph was then constructed relating "percent of the 1-hr count per cell" compared with "time after administration." A similar study was done with two abnormal patients; one with Paget's disease and the other with metastases in vertebrae from carcinoma of the prostate.

Blood clearance and urinary excretion data were obtained on the 5 volunteers and the 37 patients. Blood specimens were collected by serial venous puncture at selected time periods up to 7.5 hr after Tc-99m diphosphonate administration. The urine was collected for the intervals: 0–1, 1–4, and 4–7 hr. All samples collected were analyzed in a well gamma counter and their radioactivity expressed as percent of administered dose per whole-blood volume or as percent of dose in total urine volume excreted.

RESULTS

Figure 1 illustrates a qualitative study of normal Tc-99m diphosphonate distribution in the lower lumbar region at several intervals after administration. There was an initial rapid soft-tissue and renal accumulation of the tracer followed by gradual clearance from these tissues with a concomitant increase in the bones. The skeletal components were best resolved at 1 hr.

Figure 2 shows the computer-generated quantitative data, plotted as the percentage of counts per cell at 1 hr ($\bar{m}$, N = 6) against time: for the lumbar spine. This normal pattern shows a rapid early peak to 60% at 15 sec followed by a series of less definite peaks and valleys up to 10 min (75–60%). Thereafter, a gradual increase in bony uptake was observed until the termination of the study at 1 hr. The arbitrary 100% value at this time was greater than the highest value observed during the early vascular phase of the study.

The Tc-99m diphosphonate uptake results for a spine involved with Paget's disease are shown in Fig. 3. The early vascular phase was much greater than that observed in the normal bone scans, and maximum skeletal uptake was observed at this early time.

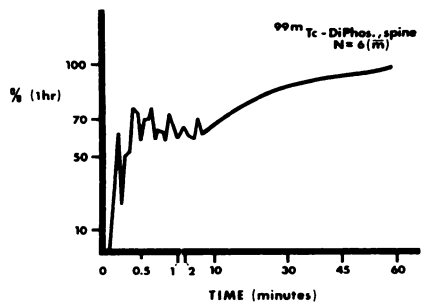

FIG. 2. Dynamic uptake pattern of Tc-99m diphosphonate in the normal spine expressed as percent of the 1-hr uptake value vs. time. Note dual time scale in seconds (0–60 sec) and minutes (2–60 min). Early vascular-related phase is less prominent than bony uptake at 1 hr.

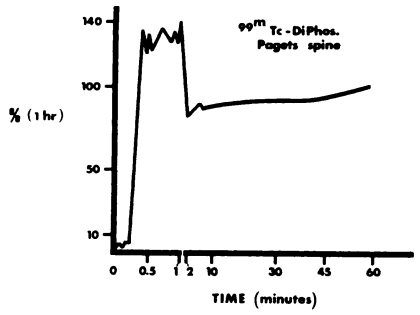

FIG. 3. Dynamic uptake pattern of Tc-99m diphosphonate in a Pagetoid spine expressed as percent of the 1-hr uptake value vs. time. Note dual time scale in seconds (0–60 sec) and minutes (2–60 min). The early, predominantly vascular phase is followed by rapid bone uptake of the tracer.

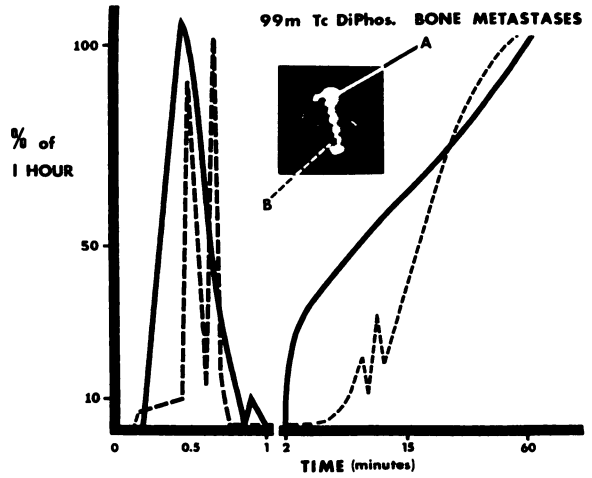

FIG. 4. Dynamic uptake pattern of Tc-99m diphosphonate in vertebral metastases from carcinoma of the prostate, expressed as percent of the 1-hr uptake value vs. time. Note dual time scale in seconds (0–60 sec) and minutes (2–60 min). A = hot lesion, B = colder lesion. Early vascular phase followed by rapid uptake is characteristic of both lesions. At 1 hr the ratio of A/B in counts per cell = 6.57.

Figure 4 illustrates the uptake patterns for a "hot" lesion (A) and a "colder" lesion (B) in a spine involved with metastases. Of particular interest are the initial peaks at 0–1 min for both lesions, which return to baseline values at 1–2 min before rising to their 1-hr levels. Relative to the normal pattern of uptake (Fig. 2), both these lesions indicate greater initial vascularity (0–1 min) with an increased rate of uptake later (2–60 min). However, the Paget's pattern (Fig. 3) shows greater initial vascularity and rate of uptake relative to metastatic and normal bone.

A triexponential blood-clearance pattern was observed in individuals with negative scans (volunteer plus patient) and is illustrated in Fig. 5. The mean half-times and corresponding percentages attributable to each compartment are also included in the figure. Urinary excretion was more rapid in volunteers ($t_{1/2}$ = 75 min) than in patients ($t_{1/2}$ = 108 min).

Tables 1–3 list the results for blood clearance and urinary excretion at certain time periods for all subjects. As shown in Table 1, during the first hour following injection, urinary excretion was significantly greater ($p < 0.01$) in normal volunteers than in patients without bone disease. Thereafter, the urinary excretion patterns were similar, as was the tracer content in the blood at 5 min, 1 hr, and 4 hr. Table 2 shows a significantly greater tracer concentration ($0.02 < p > 0.01$) in the blood at 5 min for volunteers, relative to those patients with positive bone scans. Also, the urinary excretion pattern at 0–1 hr is significantly greater for volunteers ($p < 0.01$). When patients with positive bone scans are compared with those with negative scans (Table 3), the Tc-99m diphosphonate content in the blood at 5 min was significantly greater in the negative scan group. No significant difference in urinary excretion was found between patients with and without bone disease as detected by the scan.

DISCUSSION

The pattern of the lumbar vertebral uptake of Tc-99m diphosphonate was similar in volunteers and patients with normal bone scans (N = 6, Fig. 2). Soon after the intravenous injection of the diphosphonate, the initial component of activity over the spine was believed to be aortic as measured by this

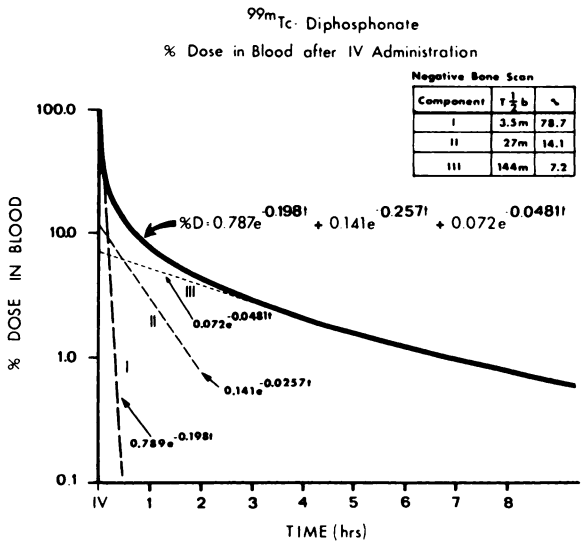

FIG. 5. Determination of rate constants for phases 1, 2, and 3 of blood content of Tc-99m diphosphonate after iv administration. The mean blood levels in 5–7 subjects were used, from 2 min to 7.5 hr after injection.

technique; but thereafter gradual uptake was observed in the lumbar spine, apparently reaching an equilibrium by 1 hr. Initial activity in the early vascular phase was never greater than the levels measured at 1 hr. However, in the Paget's and metastatic lesions, atypical uptake patterns were found, as illustrated in Figs. 3 and 4. The early dominant peak, at least in Paget's disease, is thought to be due to increased vascularity in the diseased bone. This increased regional blood flow in Pagetoid bone was investigated by Rhodes and co-workers with Tc-99m-labeled albumin microspheres, and they concluded that the phenomenon results from an extensive capillary bed and not from arteriovenous shunts (*14*). Concomitant with the increased regional blood flow we find an almost immediate accumulation of the diphosphonate in the bone with Paget's disease (Fig. 3).

TABLE 1. TECHNETIUM-99m Sn-DIPHOSPHONATE: BLOOD CLEARANCE AND URINARY EXCRETION

Population	Measurement	N	m ± s.d.	p Values
NV	5 min blood	5	25.90 ± 6.73	>0.1
NP	5 min blood	23	21.23 ± 6.84	<0.2
NV	1 hr blood	5	8.43 ± 2.57	>0.1
NP	1 hr blood	23	6.74 ± 2.08	<0.2
NV	4 hr blood	5	2.44 ± 1.14	>0.6
NP	4 hr blood	8	2.14 ± 1.39	<0.7
NV	0–1 hr urine	5	32.16 ± 13.27	<0.01
NP	0–1 hr urine	10	13.18 ± 5.86	
NV	1–4 hr urine	5	19.98 ± 4.87	>0.1
NP	1–4 hr urine	4	11.61 ± 10.14	<0.2
NV	4–7 hr urine	5	9.65 ± 5.77	>0.2
NP	4–7 hr urine	4	5.63 ± 4.98	<0.3

NV: Normal volunteers: NP: Patients with normal bone scans.

TABLE 2. TECHNETIUM-99m Sn-DIPHOSPHONATE: BLOOD CLEARANCE AND URINARY EXCRETION

Population	Measurement	N	m ± s.d.	p Values
NV	5 min blood	5	25.90 ± 6.73	>0.01
NP	5 min blood	14	16.68 ± 6.39	<0.02
NV	1 hr blood	5	8.43 ± 2.57	>0.1
NP	1 hr blood	13	5.99 ± 3.22	<0.2
NV	0–1 hr urine	5	32.16 ± 13.27	<0.01
NP	0–1 hr urine	7	13.74 ± 6.27	
NV	1–4 hr urine	5	19.98 ± 4.87	>0.09
NP	1–4 hr urine	6	20.15 ± 9.67	

NV: Normal volunteers: NP: Patients with normal bone scans.

TABLE 3. TECHNETIUM-99m Sn-DIPHOSPHONATE: BLOOD CLEARANCE AND URINARY EXCRETION

Population	Measurement	N	m ± s.d.	p Values
NP	5 min blood	23	21.23 ± 6.84	>0.05
PP	5 min blood	14	16.86 ± 6.39	<0.1
NP	1 hr blood	23	6.74 ± 2.08	>0.4
PP	1 hr blood	13	5.99 ± 3.22	<0.5
NP	0–1 hr urine	10	13.18 ± 5.86	>0.8
PP	0–1 hr urine	7	13.74 ± 6.27	<0.9
NP	1–4 hr urine	4	11.61 ± 10.14	>0.2
PP	1–4 hr urine	6	20.15 ± 9.67	<0.3

NP: Patients with normal bone scans. PP: Patients with positive bone scans.

The metastatic lesions in Fig. 4 illustrate an uptake pattern profoundly different from that observed in subjects with negative bone scans (Fig. 2) and in Paget's disease (Fig. 3). The initial vascular phase up to one minute exhibits itself as a dual peak for the colder lesion (Fr. 4B), and a single peak for the hot lesion (A). Thereafter, the hot lesion accumulates the tracer quite rapidly, whereas in the colder lesion uptake is most rapid after a 10-min delay. The comparative qualitative uptake in each lesion is apparent from Fig. 4, and quantitatively the counts per cell in the hot area is some 6.5 times that in the colder area. From the pattern of uptake of the colder lesion, it is suggested that sluggishness of tracer accumulation may be partially the result of an arrest of intraosseous blood flow secondary to osteolytic metastases, as has been reported for similar lesions (*15,16*). The hot lesion accumulates the tracer more rapidly, suggesting greater extraction of the tracer per unit time. Increased "extraction" efficiency has been reported to influence the accumulation of bone-seeking agents (*17*). This rapid uptake of the diphosphonate by bone may also be due partially to increased transcapillary migration secondary to disease, as suggested by Hughes and co-workers (*18*). Although the patterns of uptake observed for Paget's and metastatic bone involve one patient each, we feel that the difference in uptake patterns of Tc-99m diphosphonate between normal and diseased bone suggests that more specific diagnostic information may be possible using initial skeletal-uptake data.

The multiexponential blood-clearance pattern for Tc-99m diphosphonate in subjects with normal bone scans has been reported by other investigators for various Tc-99m-labeled bone agents (*19,20*). Our observed clearance pattern (Fig. 5) shows an initial rapid fall in Tc-99m diphosphonate concentration in the blood with a half-time of 3.5 min, followed by medium ($t_{1/2}$ = 27 min) and slow $t_{1/2}$ = 144 min) components. We conclude that the initial

rapid blood clearance represents the relatively rapid movement of Tc-99m diphosphonate from the vascular compartment to other compartments. The latter are believed to be both cellular and extracellular, with glomerular filtration predominating. After this initial disappearance a slower phase is observed, ($t_{1/2}$ = 27 min) which represents primarily bony uptake, with a lesser fraction going to the kidneys. The very slow disappearance of diphosphonate from the blood compartment ($t_{1/2}$ = 144 min) may be associated with protein binding of the tracer.

The possibility of an extravascular compartment as a primary determinant for skeletal accumulation was proposed by Charkes and co-workers for F-18, where bony uptake was assumed to be dependent on the establishment of a high concentration of tracer in the extracellular fluid (ECF) (*21*). According to Jones and co-workers, the pure dilution effect of the blood component by the ECF for a 70-kg person would result in a blood concentration of 19–20% of the administered Tc-99m diphosphonate by 2 to 3 min (*22*). This is in close agreement with our data (Fig. 5) showing 78.7% of the administered dose to be eliminated from the vascular compartment with a half-time of 3.5 min, with approximately 20% remaining in the blood at 5 min (Tables 1–3).

Of interest is the significant difference in the Tc-99m diphosphonate blood concentration at 5 min between patients with positive bone scans (16.86% ± 6.39), and those with normal bone scans—including patients (21.23% ± 6.84) and volunteers (25.90% ± 6.73), as shown in Tables 1–3. The more rapid early vascular disappearance of the tracer in those patients showing positive bone scans may be related to an increase in ECF secondary to skeletal disease. Citrin and co-workers compared blood levels at 6 hr between normals and patients for a variety of Tc-99m-labeled skeletal agents (*23*). In this study the Tc-99m diphosphonate concentration in the vascular system showed a difference between patients (0.59% ± 0.07) and normals (0.77% ± 0.06).

The urinary clearance data for both volunteers and patients (Tables 1–3) show a major portion of the Tc-99m diphosphonate to be excreted within 4 hr. This agrees with the work of Citrin (*23*). The volunteers, however, excreted a significantly greater total amount of the administered dose relative to patients with positive or negative bone scan. This observed difference may be related to an increased bony uptake of the Tc-99m diphosphonate by patients with positive scans relative to normal volunteers. Conversely, the similar pattern of tracer excretion between the volunteers and patients with negative scans suggests that other physiological factors such as inactivity, degree of hydration, and the illness itself may account for the observed differences relative to the positive-scan group.

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