COMPARISON OF ^{99m}Tc-POLYPHOSPHATE AND ^{18}F. I. KINETICS

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In 12 patients with suspected bone lesions, the kinetics of intravenously injected ^{99m}Tc-polyphosphate (Tc-PP) were compared with those of ^{18}F. Both radiopharmaceuticals showed biexponential clearance from blood. With both agents, Exponent I clearance half-time is relatively shorter and represents uptake by bone. Exponent II clearance half-time is longer and represents mainly renal clearance. Both Exponent I and II clearances are longer with Tc-PP than with ^{18}F. The relatively slower blood clearance with Tc-PP is due to two major causes. The first is the relatively higher plasma protein binding associated with Tc-PP. About 80% of plasma radioactivity is protein-bound with Tc-PP, and only about 15% with ^{18}F. About 20% of total protein-bound Tc-PP radioactivity is bound to albumin; the remaining 80% is bound mainly to globulin fractions and, to a minor extent, to fibrinogen. Tc-PP protein binding is loose and seems to dissociate easily in vivo. The second major cause of slower Tc-PP blood clearance is red blood cell binding, which is firm and is not washed off completely with normal saline. About 28.2% of the injected dose of Tc-PP is excreted in urine in 4 hr. The genitourinary system is the major nonosseous structure to accumulate injected Tc-PP.

Until very recently, ^{18}F has been the most popular of the skeletal-imaging agents. Comparisons with ^{47}Ca, ^{85}Sr, ^{87m}Sr, and ^{68}Ga have shown ^{18}F to be the best bone-scanning agent (*1*). High production cost, however, and the necessity that the production center be near at hand make ^{18}F less than ideal. The high gamma photon energy associated with ^{18}F precludes wider use of the conventional scintillation camera, even with a special collimator (*2*).

With these objections in mind, Subramanian, et al introduced two ^{99m}Tc-labeled compounds for skeletal imaging—first, a tripolyphosphate (*3*) and, later, an improved synthetic linear long-chain polyphosphate (*4*). Technetium-99m-polyphosphate (Tc-PP) has been approved for clinical use and two commercial kits are currently available. In this paper, we report a clinical comparison of the kinetics of ^{18}F and Tc-PP.

MATERIALS AND METHODS

Twelve patients with suspected bone lesions were studied first with 2 to 4 mCi of ^{18}F, and a day or two later with 15 mCi of Tc-PP both given intravenously. Four milliliters of blood were drawn in test tubes containing anticoagulant at 10 min, 1, 2, 3, and 4 hr after injection of the radiopharmaceutical. An aliquot of the injected dose of ^{18}F and Tc-PP was diluted 1000 and 10,000 times, respectively, and 1 ml of this diluted sample was used as the standard. After the 4-hr blood sample was taken, 1 ml each of whole blood and plasma, and the red blood cells (RBC) in 1 ml of whole blood, along with 1 ml of the diluted standard, were counted in a well scintillation counter. The results were expressed as a percentage of the administered dose (standard) per liter of whole blood, plasma, or RBC. The RBC were washed three times with saline and the radioactivity remaining after each wash was measured.

After the radioactivity in 1 ml of plasma was determined, the proteins were precipitated with zinc sulfate and sodium hydroxide. The precipitate was washed once with saline and the radioactivity bound to protein in 1 ml of plasma was measured. The radioactivity free in the plasma, i.e., not bound to proteins, was determined by subtracting the precipitate radioactivity from the total plasma activity.

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A fraction of the plasma sample was subjected to standard microzone protein electrophoresis for the separation of several protein fractions. Each protein band was cut and counted separately to determine the percentage of total plasma protein radioactivity bound to each fraction. Urine was collected for 4 hr and the radioactivity thus excreted was measured. Skeletal images were obtained with a rectilinear scanner and scintillation camera.

RESULTS

Clearance of ^{18}F and Tc-PP from the blood was biexponential during the initial 4 hr: Exponent I and Exponent II (Fig. 1). Half-time clearance of Exponents I ($T_1^{1/2}$) and II ($T_2^{1/2}$) with ^{18}F was 24 min and 198 min, respectively. Ten minutes after injection, 3.8%/liter of the injected dose of ^{18}F was circulating in the blood. The blood radioactivity decreased to 0.73%/liter at 3 hr and did not change very much at 4 hr. Thus the 10-min-to-4-hr drop of blood activity was 84.7% (Fig. 2). In 1 to 3 hr, 13.8 to 16.0% of the ^{18}F plasma radioactivity was protein-bound; the remaining 86.2 to 84.0% was circulating free (not bound to protein) in plasma

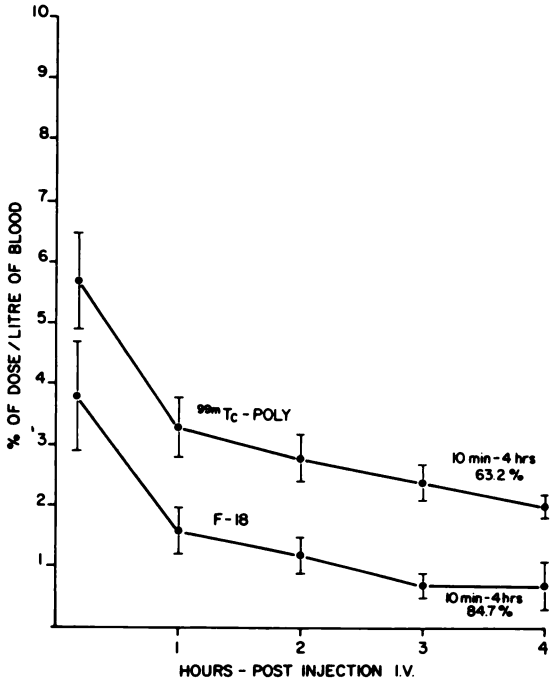

FIG. 2. Blood clearance of intravenously injected ^{18}F and Tc-PP (mean ± s.e. of 10 patients).

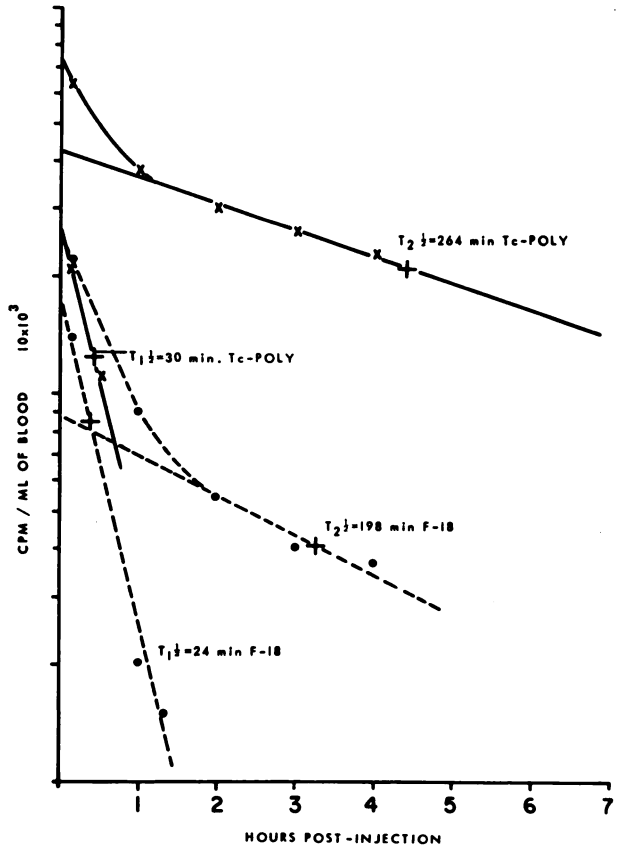

FIG. 1. Clearance of intravenously injected ^{18}F and ^{99m}Tc-polyphosphate from blood (mean of 10 patients). Exponent I represents uptake of radiopharmaceutical by bone. Exponent II represents mainly renal clearance.

(Table 1). There was no significant RBC binding with ^{18}F. The 3-hr postinjection period was the theoretical optimum time for scanning. However, clinically useful scans could be obtained as early as 1 to 2 hr after injection.

Half-time clearance of Exponent I ($T_1^{1/2}$) and Exponent II ($T_2^{1/2}$) with Tc-PP was 30 min and 264 min, respectively (Fig. 1). Ten minutes after injection, 5.7%/liter of the injected dose of Tc-PP was circulating in the blood. The blood radioactivity decreased to 2.4%/liter at 3 hr and to 2.03% at 4 hr postinjection. Thus the 10-min-to-4-hr drop in blood radioactivity was 63.2% (Fig. 2). Between the 10-min and 4-hr postinjection samples, 68.3 to 83.7% of the plasma radioactivity was protein-bound and the remaining 31.7 to 16.3% was circulating free, i.e., not bound to protein, in plasma (Table 1). By standard microzone protein electrophoresis, it was found that 21.7, 16.7, 18.5, 21.4, 15.5, and 6.2% of plasma-protein radioactivity was bound, respectively, to albumin, alpha-1, alpha-2, beta-globulins, fibrinogen, and gamma-globulin fraction (Fig. 3). At 10 min and at 4 hr, respectively, 1.14 and 2.7%/liter of the injected dose of Tc-PP was bound to RBC. After three washes with normal saline, 10-min RBC radioactivity decreased from 1.14 to 0.75%, and 4-hr radioactivity decreased slightly from 2.7 to 2.6%. As plasma radioactivity was decreasing, RBC radioactivity was simultaneously increasing; equilib-

TABLE 1. COMPARISON OF THE KINETICS OF ^{18}F AND ^{99m}Tc-POLYPHOSPHATE

Radiopharmaceutical	Blood clearance ($T_{1/2}$ min)		Plasma (% protein-bound)					4-hr urine excretion (% injected dose)
	Expo I	Expo II	10 min	1 hr	2 hr	3 hr	4 hr	
^{18}F	24	198	—	14.2	16.0	13.8	—	—
^{99m}Tc-PP	30	264	83.7	73.1	68.3	75.2	79.4	28.2

rium was reached at 4 hr (Fig. 4). With Tc-PP, the theoretical optimum time for imaging with the scintillation camera was beyond 4 hr postinjection. Camera studies obtained earlier than 4 hr had high background radioactivity, obscuring the bone detail seen in the later studies. However, clinically useful images could be obtained as early as 2½ to 3 hr using the rectilinear scanner.

Cumulative excretion of radioactivity in urine at 4 hr was about 28.2% of the injected dose of Tc-PP (Table 1).

Under the assumption that 50% of the injected dose is taken up by the bone within the first hour, a compartmental analysis was determined based on the measurement of intravascular, extravascular–extraosseous, and urine radioactivity (Fig. 5). Extravascular–extraosseous-compartment radioactivity was obtained by subtracting bone, intravascular, and urine-compartment radioactivity from the total injected dose. The results of 1- and 4-hr postinjection compartmental analysis are illustrated in Fig. 5.

DISCUSSION

Technetium-99m has a convenient physical half-life and its photon energy is ideal for present day equipment. The introduction of ^{99m}Tc-labeled phosphate compounds has signaled a breakthrough in skeletal imaging. Subramanian, et al showed that their second compound, a linear long-chain polyphosphate, was better than their first compound, tripolyphosphate (*3,4*). Much of the present knowledge about Tc-PP is based on these important studies, which were done in animals. In this paper, we have attempted to compare Tc-PP with ^{18}F clinically.

In rabbits, approximately 50% of the injected dose of Tc-PP is taken up by bone within 3 hr, 46.2% within the first hour. The radioactivity taken up by bone did not change appreciably at later hours (*4*). Urinary excretion in 1 to 3 hr in rabbits varied from 31.9 to 41.4% of the injected dose. The remaining 10 to 20% of radioactivity was distributed elsewhere.

After intravenous injection in humans, both Tc-PP and ^{18}F show biexponential (Exponents I and II) clearance from blood. As the blood samples were taken 10 min after injection, the exponent due to mixing of the radiopharmaceutical with the blood is not seen in Fig. 1. With both agents, Exponent I is relatively faster with a half-time clearance of 24 min for ^{18}F and 30 min for Tc-PP (Fig. 1). We suggest that Exponent I represents the uptake of Tc-PP by the bone. With both agents, Exponent II is relatively slower with a half-time clearance of 198 min with ^{18}F and 264 min with Tc-PP. This radioactivity represents mainly renal clearance. In rabbits it has been shown that most of the Tc-PP radioactivity enters the bone within the first hour; total bone radioactivity, when compared with the injected dose, did not change significantly in the later hours (*3,4*). These findings appear to confirm that Exponent I and Exponent II represent bone uptake and renal excretion, respectively. Extrarenal excretion of Tc-PP is negligible (*3,4*).

Clinically it has been shown that ^{18}F has a faster plasma and renal clearance than ^{85}Sr and ^{47}Ca (*1*). There is no RBC labeling with ^{18}F and radioactivity coating RBC is easily removed by a single washing with normal saline.

Tc-PP has a slower blood clearance than ^{18}F (Fig. 2). The 10-min-to-4-hr drop in blood radioactivity levels was 63.2% with Tc-PP, and 84.7% with ^{18}F. There are two major causes for the slower blood clearance with Tc-PP (Fig. 4 and Table 1). The first is RBC binding. It was found that as plasma radioactivity fell, there was a simultaneous rise of RBC radioactivity, indicating RBC labeling with Tc-PP (Fig. 4). Technetium-99m-polyphosphate–RBC radioactivity was not completely removable by washing with saline, indicating a firm binding. We have conducted in vitro RBC labeling studies; the preliminary results indicate that Tc-PP binds relatively firmly to RBC with an elution of 2% for each wash of the red blood cells with saline. All blood samples were kept at room temperature and centrifuged together after the 4-hr sample was taken; thus the rise in RBC radioactivity was not caused by a longer incubation period of any samples. Gradually rising RBC radioactivity seems to indicate that some breakdown product of Tc-PP is binding to the RBC in vivo. Four hours after injection, an aliquot of plasma and RBC had equal amounts of radioac-

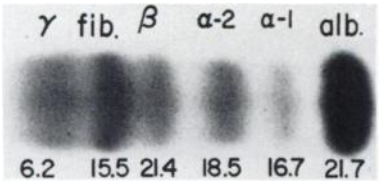

FIG. 3. Tc-PP in vivo protein-fraction labeling at 1 hr after administration.

tivity and total blood radioactivity was at its lowest point. Thus it seems that the theoretically ideal time for scanning is any time after 4 hr postinjection. Intravascular and presumably extravascular–extraosseous radioactivity is at a minimum; thus background radiation is low.

The second major cause of the relatively slower Tc-PP clearance from blood is increased protein binding. Only 13.8 to 16.0% of ^{18}F in plasma is protein-bound; the remaining 86.2 to 84% is free. In contrast, 68.3 to 83.7% of Tc-PP is protein-bound and only 31.7 to 16.3% is circulating free in plasma (Table 1). The difference in plasma protein binding between ^{18}F and Tc-PP was approximately 65% but the difference in 10-min-to-4-hr plasma clearance ratio was only 14.9%, suggesting that the Tc-PP was loosely bound to plasma protein.

Most of the Tc-PP was bound to globulin fractions of plasma protein, mainly alpha and beta globulins. Even though albumin usually makes up more than 50% by weight of total protein, only 21.7% of the Tc-PP was bound to albumin. Fibrinogen was associated with 15.5% of the total plasma protein radioactivity (Fig. 3).

Tc-PP radioactivity in several compartments could be calculated and analyzed. It was assumed (*4*) that 50% of the injected dose of Tc-PP enters the bone within the first hour and that this percentage does not change with time. In our study at 1-hr postinjection, 17% of the injected dose was in the intravascular compartment, 15% was excreted in urine, and the remaining 18% was distributed in the extravascular–extraosseous compartment (Fig. 5). At 4-hr postinjection, bone-compartment radioactivity remained unchanged (*4*), intravascular-compartment radioactivity decreased to 10%, urinary-excretion radioactivity increased to 28%, and the remaining 12% was distributed in the extravascular–extraosseous compartment. Thus the low background at 4 hr postinjection was due mainly to urinary excretion. Extravascular–extraosseous-compartment radioactivity was determined by subtracting the other three compartmental percentages from the total injected radioactivity. An almost equal amount of radioactivity was distributed between the intravascular and the extravascular–extraosseous compartments.

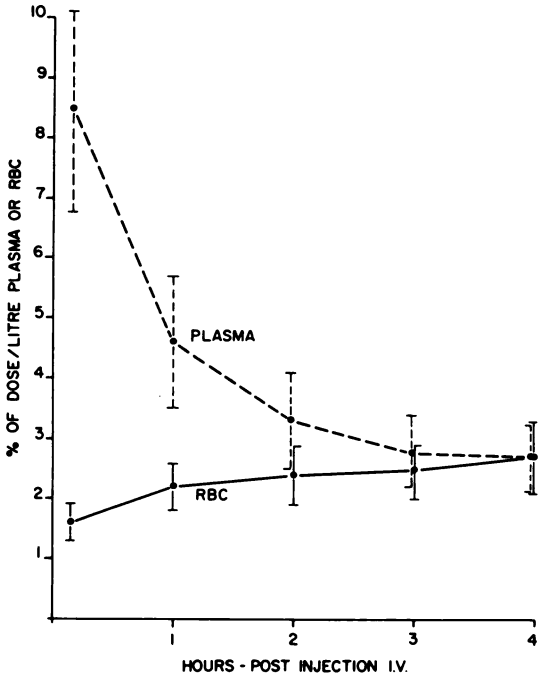

FIG. 4. Tc-PP clearance from plasma and red blood cells.

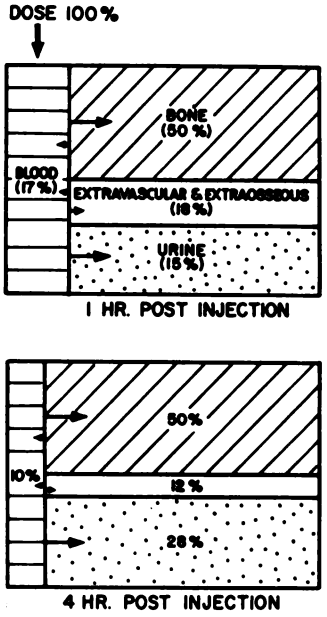

FIG. 5. Compartmental analysis of Tc-PP at 1 and 4 hr after administration.

Thus a delay of three additional hours did not seem to affect the net amount of radiopharmaceutical taken up by bone but it did reduce the background, mainly because of renal clearance. The question arises whether impaired renal function alters the net amount getting into bone. In one anephric patient, good bone images were still obtainable at 4 hr postinjection. Little background radioactivity obscured the skeletal image and there was no increase of

radioactivity in the soft tissues or in the bowel. This finding seems to indicate that kidneys are the major route of excretion and that in decreased or absent renal function, the net amount of tracer taken up by the bone may be increased, with background radioactivity remaining the same as in patients with good renal function. However, this finding must be confirmed by studies involving a large number of patients with impaired renal function.

The genitourinary system was the major nonosseous structure visualized with Tc-PP. The kidneys were seen in all patients with normal renal function. It appears that the radioactivity in the blood circulating through the renal parenchyma and in the urine present in the renal collecting system contributes to renal visualization. The heart and great vessels were not visualized. With Tc-PP, the slower renal clearance due to protein and RBC binding appears to facilitate kidney visualization.

The mechanism of localization of Tc-PP in bone is not definitely known. Skeletal localization appears to be similar to that experienced with other skeletal-seeking radionuclides and may be primarily a function of regional blood flow. Tc-PP is a complex (chelate) of tin, technetium, and polyphosphate. It is not clear how much of the polyphosphate will exchange with the phosphate moiety of calcium phosphate of bone matrix. It is possible that tin, which is present in the Tc-PP complex, may contribute to skeletal localization. A previous study showed that 30% of carrier-free tin localized in the skeleton (*5*).

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