CLINICAL COMPARISON OF THE KINETICS OF ^{99m}Tc-LABELED POLYPHOSPHATE AND DIPHOSPHONATE

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Kinetics of ^{99m}Tc-labeled polyphosphate and diphosphonate (disodium ethane-1-hydroxy-1, 1-diphosphonate) are studied and compared clinically in ten patients in a paired study. Four hours after injection, both agents show a bi-exponential type of blood clearance. The Exponent I represents bone uptake and the Exponent II, mainly the renal excretion. The clearance of diphosphonate is relatively faster than that of polyphosphate resulting in significantly lower blood background radioactivity. Both agents show identical plasma protein fraction binding and 4-hr urinary excretion. The kidneys are well visualized with both agents, consistently better with polyphosphate. The sensitivity for the detection of lesions is similar for both. At the end of 4 hr, 10% of the dose of ^{99m}Tc-polyphosphate is circulating in the blood, 33.3% is excreted in urine, and the remaining 56.3% is taken up by bone and other tissues. The corresponding values with ^{99m}Tc-diphosphonate are: 7.0% in blood, 33.8% in urine, and 59.2% in bone and other tissues. It is concluded that both ^{99m}Tc-labeled polyphosphate and diphosphonate are excellent skeletal-imaging agents and have equal sensitivity. No toxic reactions are noted with either agent.

Since its introduction, ^{99m}Tc-labeled polyphosphate (*1,2*) has become the radiopharmaceutical of choice for skeletal imaging. In our laboratory (at Wadsworth VAH), ^{99m}Tc-labeled polyphosphate (Tc-poly) has totally replaced sodium fluoride (^{18}F) for skeletal imaging. Both animal and clinical (*2–4*) studies have demonstrated its superiority over ^{18}F. The ideal physical characteristics of the gamma photon of ^{99m}Tc and the low cost of production of Tc-poly have contributed mainly to this change. Lately, diphosphonates labeled with ^{99m}Tc have been used for skeletal imaging (*5–7*). In previous comparative studies of the kinetics of Tc-poly and ^{18}F (*3*), we have shown that Tc-poly is far superior for bone imaging. In this communication, we report the results of a comparative clinical investigation of the kinetics of ^{99m}Tc-labeled disodium ethane-1-hydroxy-1, 1-diphosphonate (Tc-dip), and sodium polyphosphate (Tc-poly).

MATERIALS AND METHODS

Ten patients with suspected bone lesions were studied. The nature of the study was explained and written informed consent was obtained from each patient. The kinetic studies were done with 15 mCi each of ^{99m}Tc-sodium polyphosphate and ^{99m}Tc-disodium ethane-1-hydroxy-1, 1-diphosphonate. MPI bone Scintigraphin Reagent™ (disodium ethane-1-hydroxy-1, 1-diphosphonate) kits were supplied through the courtesy of Medi-Physics, Inc., Emeryville, Calif. Polyphosphate kits were bought from New England Nuclear, North Billerica, Mass. An interval of a minimum of 2 days and up to a maximum of 15 days was allowed between the two studies. The radiopharmaceutical that was prepared according to the manufacturer's instructions was used within 3 hr of its preparation. No special patient preparation measures were taken before the injection and they were allowed ad libitum fluid intake. The urinary bladder was emptied before the injection.

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Four-milliliter blood samples were drawn and placed in test tubes containing anticoagulants at 10 and 30 min and at 1, 2, 3, and 4 hr after intravenous injection of the radiopharmaceuticals. An aliquot of the injected agent was diluted 1000 times and used as the standard. A milliliter of whole blood and plasma from each sample was pipetted on the same day and counted the next day along with the standard in a well counter. The results were expressed as percentage of the administered dose per liter of blood or plasma. From the 1-hr blood sample the red blood cells were separated and washed three times with normal saline and the radioactivity remaining with the cells after each wash was determined. The radioactivity remaining with the cells after the first wash was considered as a reference level of 100% and the reduced radioactivity following subsequent washes was expressed as a percentage lost after each wash.

After measuring the radioactivity in 1 ml of the 1-hr plasma sample, the proteins were precipitated with zinc sulfate and sodium hydroxide. The radioactivity bound to protein in the 1-ml plasma sample was determined and subtracted from total plasma radioactivity, the resultant indicating the free or unbound radioactivity. The radioactivity bound to each protein fraction was determined by Microzone electrophoresis; the details of this technique are given elsewhere (*3*).

Urine was collected as hourly samples for 4 hr. The volume of each sample was measured, a milliliter of urine was counted with the standard, and the results were expressed as a percentage of the administered dose excreted per hour. The 4-hr cumulative excretion was calculated.

In addition to these ten comparative studies skeletal images were obtained of 500 patients with Tc-poly and of 50 patients with Tc-dip.

RESULTS

The blood clearances of Tc-poly and Tc-dip are biexponential (Fig. 1). As with ^{18}F (*3*), the clearance time of Exponent I is relatively faster than that of Exponent II. The blood clearance half-time of Exponent I is 18 min with Tc-dip and 30 min with Tc-poly. Exponent II has a blood clearance half-time of 168 min with Tc-dip and 294 min with Tc-poly. We suggest that Exponent I represents mainly bone uptake and Exponent II merely urinary excretion. The faster blood clearance of Tc-dip results in significantly ($p < 0.02$) lower blood background radioactivity (Fig. 2 and Table 2). A similar type of biexponential blood clearance was noted in our study comparing Tc-poly with ^{18}F (*3*).

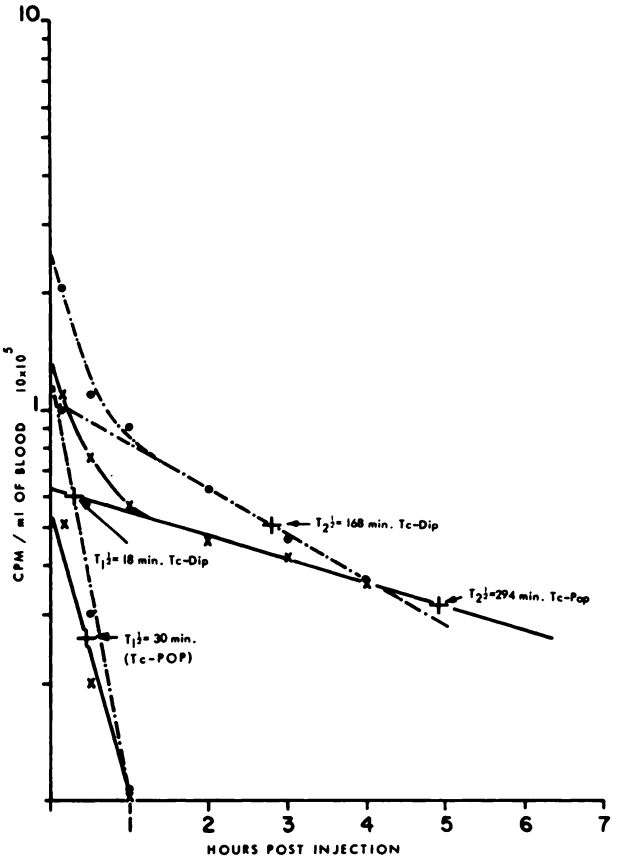


FIG. 1. Clearance of ^{99m}Tc-labeled polyphosphate (Tc-poly) and diphosphonate (Tc-dip) from blood. Note the biexponential (Exponent I represented by $T_1^{1/2}$ and Exponent II represented by $T_2^{1/2}$) type of clearance. Both components ($T_1^{1/2}$ and $T_2^{1/2}$) are faster with Tc-dip.

Hour-to-hour urinary excretion of both radiopharmaceuticals was nearly identical. During the first hour 11.5% of Tc-poly and 13.3% of Tc-dip were excreted. The total 4-hr urinary excretion was 33.3% of the injected dose with Tc-poly (Fig. 3), and 33.8% with Tc-dip.

At 1 hr, 75.4% of plasma radioactivity was protein-bound with Tc-poly and 84.2% was protein-bound with Tc-dip. The remaining plasma radioactivity was free (Table 1). Figure 4 shows the percentage of total plasma-protein radioactivity bound to each fraction with both agents at 1 hr after injection. Only 24% of plasma protein radioactivity was bound to albumin; the rest was bound mainly to globulin fractions and to a minor extent, to fibrinogen.

Figure 5 shows the skeletal images obtained at 4 hr with Tc-poly and Tc-dip. There was no disparity in the sensitivity of lesion detection between the two radiopharmaceuticals. All the lesions seen with one agent were also seen with the other. Of a total of 50 patients studied with Tc-dip, three showed evidence of poor in vitro labeling or in vivo instability;

TABLE 1. KINETICS OF ^{99m}Tc-LABELED POLYPHOSPHATE AND DIPHOSPHONATE

Radiopharmaceutical	Blood clearance half-time (min)		Plasma (1 hr)		4-hr urinary excretion (% injected dose)
	Exponent I	Exponent II	% Protein-bound	% free	
^{99m}Tc-polyphosphate	30	294	75.4	24.6	33.3
^{99m}Tc-diphosphonate	18	168	84.2	15.8	33.8

none of a total of 500 patients studied with Tc-poly showed any evidence of in vivo instability or poor in vitro labeling (Fig. 6). Skeletal images obtained with both agents showed all the lesions detected on a skeletal roentgenogram as well as additional lesions not seen on the roentgenogram.

A significant amount of Tc-poly radioactivity was bound to red blood cells (*3*). The Tc-poly RBC binding was quite firm with an elution of only 2% by each wash. In contrast, Tc-dip was not bound to red cells and all the RBC radioactivity was completely removed with two to three saline washes.

Table 2 shows the blood and plasma clearance of Tc-poly and Tc-dip in man. Table 3 shows the total body distribution of Tc-poly, Tc-dip, and ^{18}F at 4-hr postinjection. Table 4 shows the percentage of bone uptake and urinary excretion of ^{18}F, ^{85}Sr, Tc-poly, and Tc-dip in different species of animals and in man, as reported in the literature. Figure 7 shows the comparative chemical structure of polyphosphate and diphosphonate.

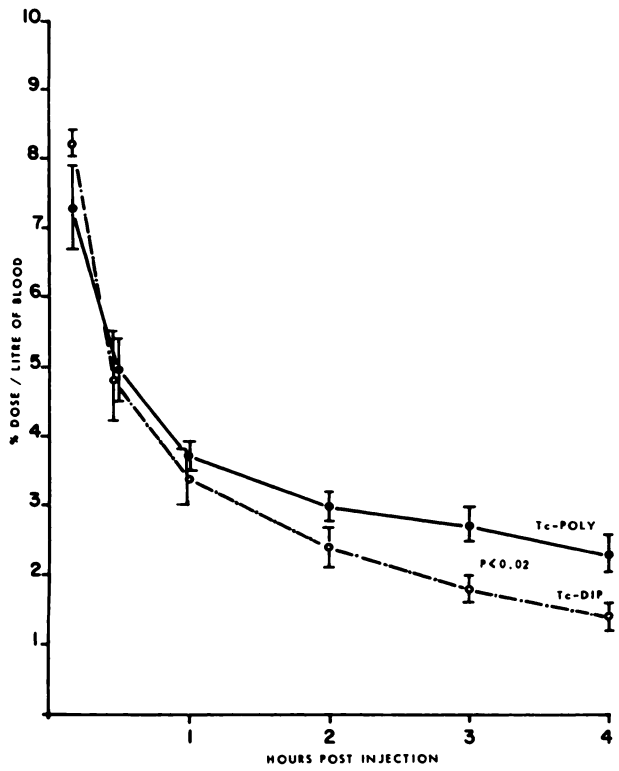


FIG. 2. Blood clearance of ^{99m}Tc-labeled polyphosphate (Tc-poly) and diphosphonate (Tc-dip) in man. Tc-dip clears at a slightly faster rate, giving lower blood background radioactivity ($p < 0.02$).

DISCUSSION

The introduction of ^{99m}Tc-labeled phosphate complexes has revolutionized skeletal imaging in nuclear medicine. The first polyphosphate compound labeled with ^{99m}Tc was sodium tripolyphosphate, prepared in 1971 by Subramanian and McAfee (*1*). The following year, Subramanian, et al introduced ^{99m}Tc-labeled polyphosphate, which was found to be useful for skeletal imaging in both animals (*2*) and man (*3,4*). Today in most laboratories, including ours, ^{99m}Tc-labeled complexes have totally replaced ^{18}F for skeletal imaging. Recently, ^{99m}Tc-labeled diphosphonates have been introduced for skeletal imaging (*5–7*). It is not clear at present whether any real difference exists between ^{99m}Tc-labeled polyphosphates and diphosphonates although chemically, Tc-poly and Tc-dip differ in their phosphorus, oxygen, and carbon atom linkages, polyphosphates showing P–O–P linkage and diphosphonates showing P–C–P linkage (Fig. 7). This study was undertaken to study and compare the kinetics of ^{99m}Tc-labeled polyphosphate and diphosphonate (disodium ethane-1-hydroxy-1, 1-diphosphonate) in man.

During 4-hr periods the blood clearance of Tc-poly and Tc-dip is biexponential. We hypothesize that Exponent I represents blood clearance due to bone uptake of these radiopharmaceuticals. The blood clearance half-time of 30 min with Tc-poly and 18 min with Tc-dip suggests that the bone uptake is a rapid biologic process. The Exponent I accounts for 50% of the radioactivity cleared from the blood, most of which is taken up by the bone. The clearance half-time of Exponent I is influenced very little by urinary excretion. Less than 6.5% of Tc-poly is cleared in the urine during this 30 min and less than 3.5% of Tc-dip is cleared in the urine during 18 min (13.3% in 1 hr).

In mice (*5*), rats (*7*), and rabbits (*6*) the maximum range bone uptake of diphosphonates reached 44.4 to 49.6% of the dose at 1 hr postinjection and did not increase further to any significant level at 3,

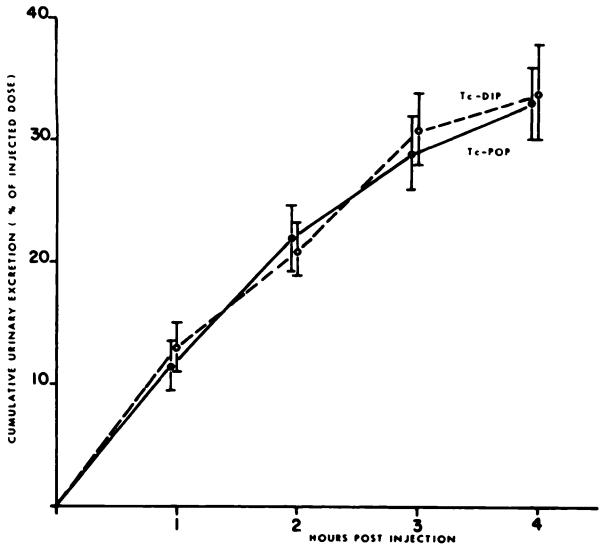


FIG. 3. Urinary excretion of ^{99m}Tc-labeled polyphosphate (Tc-poly) and diphosphonate (Tc-dip) in man. Note nearly identical hour-to-hour and cumulative 4-hr excretion with both agents.

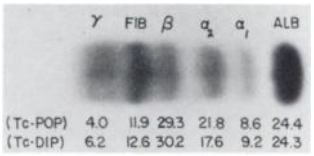


FIG. 4. In vivo plasma protein binding of ^{99m}Tc-labeled polyphosphate (Tc-poly) and diphosphonate (Tc-dip) in man. Note that most radioactivity is bound to globulin fractions and only 25% to albumin.

6, or 24 hr. A similar type of bone uptake results was seen with Tc-poly when injected into the rabbits (*1,2*). This strongly supports our hypothesis that the bone uptake is a very rapid biologic process and is represented in man by Exponent I of the blood clearance curve. However, the animals were not sacrificed in these experiments (*1,2,5–7*) at shorter intervals than 1 hr to test whether the maximum bone uptake occurs sooner. Our clinical studies do suggest that Tc-poly and Tc-dip enter the bone more rapidly, reaching the maximum probably within 30 min.

We hypothesize that the clearance half-time of Exponent II represents the clearance of blood radioactivity due primarily to urinary excretion. The clearance of Tc-poly is relatively slower than that of Tc-dip and hence results in higher blood background radioactivity. Two factors may contribute to this difference. The polyphosphates are larger molecules (mol wt 300–4000) than diphosphonates (mol wt 250). The smaller size of the diphosphonate molecule may facilitate rapid bone uptake during Exponent I, resulting in shorter clearance half-time (18 min). The other cause of difference in blood clearance between Tc-poly and Tc-dip may be the red cell binding. It was shown in our previous study (*3*) that Tc-poly was bound to red cells rather firmly; no such firm red cell binding was noticed with Tc-dip. The more rapid blood clearance of Tc-dip might allow greater flexibility by permitting earlier imaging.

The length of the molecule plays an important part of the net bone uptake. It has been shown that shorter chain-length polyphosphates yield highest bone concentration; with increasing chain length, bone uptake decreases. The high bone uptake associated with long-chain polyphosphates has been attributed to the degradation of the longer chain-length into shorter-chain polyphosphates (*8*). It is not clear from our study whether the chain length of the polyphosphate played any part in the prolongation of the clearance half-time of both exponents. In any given batch of polyphosphate kits the exact chain length is not known. Usually it is a mixture of both short and long chains.

Both Tc-poly and Tc-dip show almost identical plasma-protein fraction binding (Fig. 4). Even though albumin forms more than 50% of plasma protein by weight, only 24% of the plasma ^{99m}Tc

TABLE 2. CLEARANCE OF ^{99m}Tc-LABELED POLYPHOSPHATE AND DIPHOSPHONATE (EHDP) FROM BLOOD AND PLASMA (PERCENT DOSE PER LITER)*

Radiopharmaceutical	Time, postinjection											
	10 min		30 min		1 hr		2 hr		3 hr		4 hr	
	B	p	B	p	B	p	B	p	B	p	B	p
Tc-polyphosphate												
mean (N = 10)	7.3	11.8	4.9	7.6	3.7	5.5	3.0	4.1	2.7	3.3	2.3	2.8
s.e.	0.5	0.9	0.4	0.6	0.3	0.4	0.2	0.3	0.2	0.2	0.2	0.2
Tc-diphosphonate (EHDP)												
mean (N = 10)	8.2	12.9	4.8	7.7	3.4	5.5	2.4	3.9	1.8	2.9	1.4	2.2
s.e.	1.1	1.6	0.6	1.0	0.3	0.6	0.3	0.5	0.2	0.3	0.1	0.3

* B = blood; p = plasma.

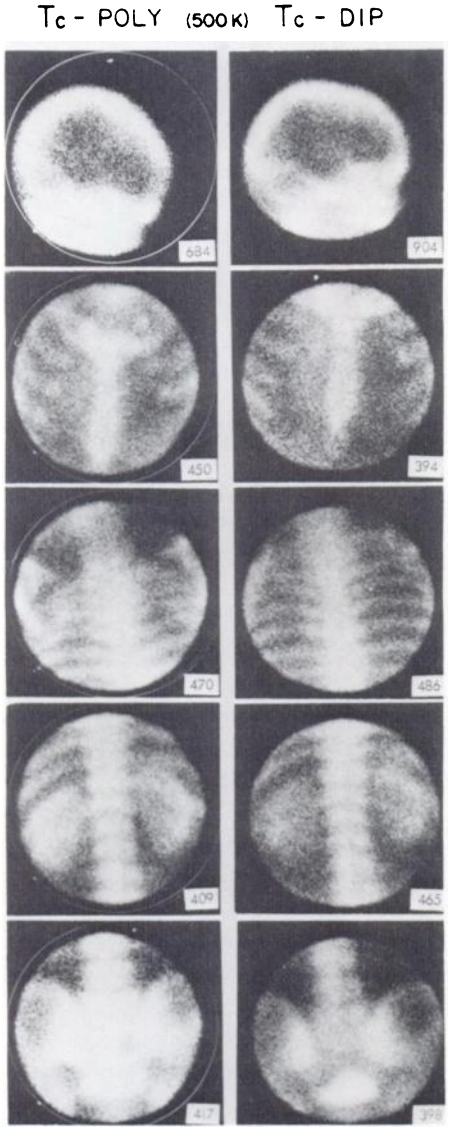


FIG. 5. Skeletal images obtained with ^{99m}Tc-labeled polyphosphate (Tc-poly) and diphosphonate (Tc-dip). Images were obtained 4 hr postinjection. Number at bottom of each image denotes time in seconds required to accumulate count of 500,000. Kidneys are visualized with both agents, but consistently better with Tc-poly.

radioactivity was bound to albumin. The rest was bound to fibrinogen and globulin fractions.

Hour-to-hour and 4-hr cumulative urinary excretions of Tc-poly and Tc-dip were nearly identical. About 33% of the injected dose of both agents was excreted during the 4-hr interval (Fig. 3). The total urinary excretion being the same as that of Tc-poly, the cause of relatively lower Tc-dip blood radioactivity is not clear from our study. It may suggest bone and soft tissue uptake during Exponent II; if it does, the amount of Tc-dip entering bone and other tissues during Exponent II appears to be very small (less than 3%). Figure 5 illustrates normal skeletal images obtained with Tc-poly and Tc-dip. The quality of the image appears satisfactory with both agents. The time taken to obtain an identical number of counts for each view with both agents is shown under each scintiphoto and it appears that the time required to obtain identical images was almost the same with both agents.

Table 3 summarizes the body distribution of ^{18}F, Tc-poly, and Tc-dip. In our previous study comparing ^{18}F and Tc-poly (*3*), it was shown that the kidneys were poorly visualized with ^{18}F and that the kidney images obtained with the ^{18}F scan did not correlate with kidney function tests. Similar re-

TABLE 3. BODY DISTRIBUTION OF BONE-SEEKING RADIONUCLIDES IN MAN AT 4 HR POSTINJECTION (% INJECTED DOSE)

Organ	Radiopharmaceutical		
	^{18}F	Tc-poly	Tc-dip
Blood	3.5	10.0	7.0
Urine	19.2*	33.3	33.8
Bone and other tissues	77.3	56.7	59.2

* *J Nucl Med* 10: 8–17, 1969 (Ref. 14).

TABLE 4. 3- TO 4-HR UPTAKE AND URINARY EXCRETION OF BONE-SEEKING RADIOPHARMACEUTICALS (% OF ADMINISTERED DOSE)

Radiopharmaceutical	Rat		Rabbit		Man	
	Bone	Urine	Bone	Urine	Bone	Urine
	75.2*	19.0*	—	—	77.3	19.2†
^{18}F	—	—	49.1‡	22.7‖	—	—
^{85}Sr			to 68.1‖			
^{99m}Tc-polyphosphate	—	—	41.4‡	45.8‡	56.7	33.3
^{99m}Tc-diphosphonate	44.2*	49.3*	47.2	53.4	59.2	33.8

* *J Nucl Med* 14: 73–78, 1973 (Ref. 7).
† *J Nucl Med* 10: 8–17, 1969.
‡ *Radiology* 102: 701–704, 1972 (Ref. 2).
‖ *J Nucl Med* 13: 947–950, 1972 (Ref. 4).

sults with ^{18}F were reported by Sharma and Quinn (*9*). In contrast, excellent kidney images were obtained during skeletal imaging with Tc-poly (*4,10*). The reason for the better kidney images obtained with Tc-poly appears to be the greater renal uptake and excretion of that radiopharmaceutical. In 4 hr, an average of only 19.2% of the dose of ^{18}F is cleared through the kidneys. In contrast, 33.3% of Tc-poly is cleared through the kidneys in the same interval (Table 3). The increased amounts of Tc-poly radioactivity retained and cleared through the kidneys probably results in a superior kidney image. Although satisfactory renal images were also obtained with Tc-dip, the Tc-poly kidney images were consistently superior. The superior renal images obtained with Tc-poly in man can be attributed to its relatively increased kidney retention. This inference is also supported by the fact that the adult rabbit kidney retained 4.3% of the dose per 1% body weight of Tc-poly at 3 hr (*2*) as against a retention of only 1.9% dose per 1% body weight of Tc-dip at 4 hr (*6*).

Tc-poly demonstrated greater stability than Tc-dip. None of the 500 patients who had skeletal images with Tc-poly had evidence of significant in vivo breakdown or poor in vitro labeling of the radiopharmaceutical whereas three of 50 patients who had skeletal images with Tc-dip showed in vivo breakdown or poor in vitro labeling. In a patient who had a well-functioning cadaver kidney transplant (Fig. 6), Tc-dip showed marked uptake by the gastrointestinal tract, resulting in no bone uptake. Three days later, a Tc-poly study showed excellent skeletal images and an area of abnormal osteoblastic activity adjacent to the third dorsal spine (Fig. 6). Different types of diphosphonates labeled with ^{99m}Tc are available for skeletal imaging. We have studied only one of them. Each of our ampules contains 1.0 mg of the sodium salt of ethane-1-hydroxy-1, 1-diphosphonate and 0.3 mg of stannous chloride. In the case of polyphosphate, each vial contains 40.0 mg of sodium polyphosphate and 1.0 mg of stannous chloride. It has been shown that diphosphonate or the polyphosphate/stannous chloride ratio may influence the biologic distribution (*7*).

The sensitivity of detection of the pathological lesion was the same for both agents. All the lesions noted on bone roentgenograms were detected also by skeletal images obtained with Tc-poly and Tc-dip. In the routine bone imaging, two lateral views of the skull were included. The time taken to obtain 500, 000 counts for each lateral view of the skull was two to three times greater than that required to obtain the identical number of counts over other bones (Fig. 5). The longer time taken over the skull probably indicates a slower metabolic activity of the skull bone.

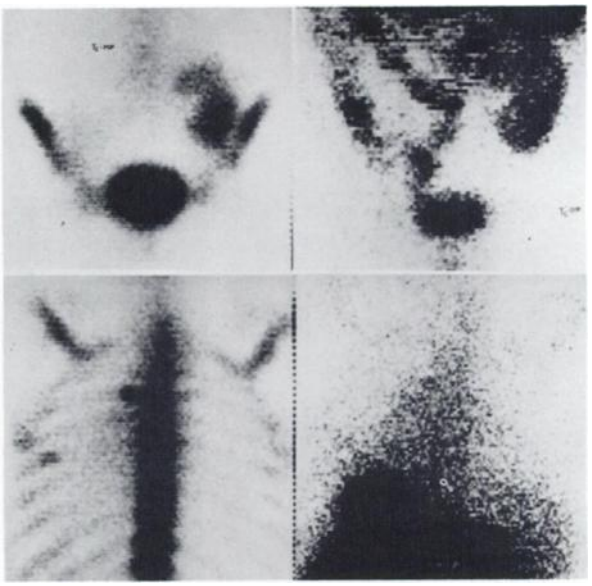
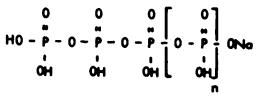
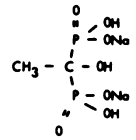


FIG. 6. Patient with well-functioning cadaver kidney transplant, showing poor labeling or in vivo breakdown of ^{99m}Tc-labeled diphosphonate (right). No uptake is seen in bone and material is concentrated in gastrointestinal tract. Bone images with ^{99m}Tc-polyphosphate (left) are excellent, showing increased uptake over third dorsal vertebra and fourth rib on left side. Transplanted kidney is in left iliac fossa. (Top row) anterior; (bottom row) posterior.



POLYPHOSPHATE (MONO-SODIUM POLYPHOSPHATE)
HYDROLYZABLE, NON-DISCRETE CHAIN LENGTH



DIPHOSPHONATE (DISODIUM ETHANE - 1 - HYDROXY - 1, 1 - DIPHOSPHONATE)
NON-HYDROLYZABLE, DISCRETE CHAIN LENGTH

FIG. 7. Comparative chemical structure of polyphosphate and diphosphonate (EHDP).

In addition to skull metastatic lesions, several intracerebral metastatic lesions were detected during bone imaging with Tc-poly and Tc-dip (Fig. 8). In some instances the intracerebral lesions detected with Tc-poly and Tc-dip were clinically unsuspected. However, it is not clear at this time whether all intracerebral lesions are detected with Tc-poly or Tc-dip. If the sensitivity for detection of intracerebral lesion with Tc-poly and Tc-dip is the same as TcO_1, then these radiopharmaceuticals may serve as both skeletal and intracerebral tumor-detecting agents. Figure 8

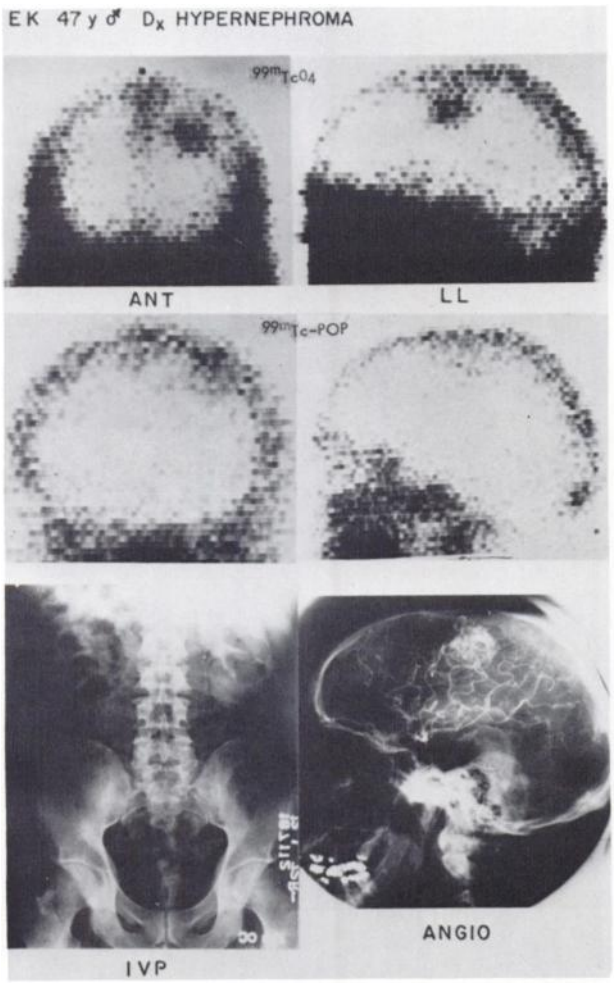


FIG. 8. Detection of intracerebral metastasis with ^{99m}Tc-polyphosphate (Tc-poly). Patient with right nephrectomy (IVP) for hypernephroma, showing intracerebral metastasis with both ^{99m}Tc-pertechnetate (top) and polyphosphate (middle). Cerebral angiogram (angio) confirmed findings of ^{99m}Tc-polyphosphate image.

shows a cerebral metastatic lesion from a right kidney hypernephroma.

The body distribution at 4 hr of ^{18}F, Tc-poly, and Tc-dip is summarized in Table 3. In terms of biologic activity ^{18}F is still the best available bone-seeking agent. It shows relatively high bone uptake (Table 3), low renal clearance, and low blood background activity. However, its high cost of production and high gamma photon energy make ^{18}F less than ideal for skeletal imaging.

The net bone uptake of ^{18}F, ^{85}Sr, Tc-poly, and Tc-dip varies in different species of animals and in man (Table 4). In rats more than 75% of the dose of ^{18}F is concentrated in bone at 4 hr. Strontium-85 concentration in rabbit bone varies from 49.1 to 68.1% of the dose, depending upon the age of the animal. The bone in younger animals with increased biologic activity concentrates radioactivity more readily than the bone in older animals (*2*). At 4 hr, 41.4% of the dose of Tc-poly was taken up by bone in rabbits, and 44.2% of Tc-dip was taken up by bone in rats (Table 4). More than 45% of the dose of both radiopharmaceuticals was excreted in urine in 4–5 hr. In man, 33.3% of Tc-poly and 33.8% of Tc-dip are excreted in urine in 4 hr, leaving 56.7% and 59.2%, respectively, for bone and other tissue uptake. The remaining radioactivity, 10% of Tc-poly and 7% of Tc-dip, circulates in blood (Table 3).

The mechanism of deposition of diphosphonates is by a process called "chemisorption" occurring on the surface of the bone (*11,12*). A similar mechanism of bone uptake is associated with polyphosphates (*6*). These agents localize in bone wherever there is active transport of calcium and phosphorus. Diphosphonates are stable and resistant to hydrolysis by enzymes whereas polyphosphates are biodegradable into smaller chain lengths by serum phosphatase enzymes. Controversy as to the importance of biodegradability has been expressed in the literature (*6*). In one study of over 1000 patients (*13*) and in our studies of 50 patients, none showed any evidence of toxicity with Tc-dip. We feel at this time that no need for such concern exists with reference to either Tc-poly or Tc-dip.

ACKNOWLEDGMENT

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