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TECHNETIUM-99m-LABELED STANNOUS IMIDODIPHOSPHATE, A NEW RADIODIAGNOSTIC AGENT FOR BONE SCANNING: COMPARISON WITH OTHER ^{99m}Tc COMPLEXES

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Imidodiphosphate (IDP) is an analog of pyrophosphate and diphosphonate, with a P–N–P bond instead of P–O–P or P–C–P. We have labeled IDP with ^{99m}Tc quantitatively (98%) using stannous ions as the reducing/complexing agent in a freeze-dried kit form. Radiobioassay of this compound was carried out in rabbits and the results were compared with those of eight other Tc-labeled bone-imaging agents, using the performance of simultaneously administered ^{85}Sr as a reference standard. The ^{99m}Tc-IDP concentrated 20% higher in the bone, and its soft-tissue and blood levels were lower than with ^{85}Sr. By comparison, the concentrations in the bone of the other ^{99m}Tc agents were 20% less than that of ^{85}Sr. Regarding blood levels, Tc-IDP performed worse than the Tc-diphosphonate but better than the pyrophosphate and the other technetium complexes. Scintillation camera images of ^{99m}Tc-IDP in both rabbits and dogs showed excellent details of the skeleton. In a preliminary human study, images with ^{99m}Tc-IDP were somewhat inferior to those comparably procured with ^{99m}Tc-methylene diphosphonate, but count rates with the IDP complex were about twice those with the MDP compound. Because of its better bone uptake, however, it is suggested that ^{99m}Tc-IDP may be clinically useful in spite of its relatively slow blood clearance.

Technetium-99m, with its excellent physical characteristics and easy availability from a generator, has become the most important nuclide for organ imaging in nuclear medicine. In the past few years several ^{99m}Tc-labeled phosphate compounds have been developed for skeletal imaging, including pyrophosphate (*1*), polyphosphates (*2,3*), and diphosphonates (*4–8*). These agents have proven useful in bone imaging and have replaced the previously used ^{85}Sr and ^{87m}Sr. Compared with ^{18}F, however, the above phosphate compounds have lower bone uptake and relatively slow blood clearance, with the possible exception of ^{99m}Tc-MDP (*8*).

In a continuing effort to find better bone-imaging agents, we have studied a wide variety of phosphate compounds labeled with ^{99m}Tc, using stannous chloride as the reducing/complexing agent in freeze-dried kit forms. These new compounds include two diphosphonates (AEDP, MDP), a series of polyfunctional phosphonates (NTMP, EDTMP, HMDTP, and DATHTP), and several cyclic and linear phosphates. Biologic distribution of these compounds and their evaluation are already available elsewhere (*9*). They were developed from the concept that phosphate compounds with P–O–P linkages, and diphosphonates with P–C–P bonds, have affinity for hydroxyapatite crystals (*10–12*), and that stannous chelates of these compounds form stable complexes with ^{99m}Tc (*1–7*). We have recently labeled with ^{99m}Tc an analog of both pyrophosphate and diphosphonate called imidodiphosphate (IDP). It has P–N–P bonds instead of a P–O–P or a P–C–P structure (Fig. 1) and has been shown to have simi-

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Abbreviations used in text:
IDP, imidodiphosphate
MDP, methylene diphosphonate
HEDP, ethylenehydroxydiphosphonate
AEDP, aminoethylenediphosphonate
HMDTMP, hexamethylenediaminotetra(methylene phosphonate)
EDTMP, ethylenediaminotetra(methylene phosphonate)
DTPMP, diethylenetriaminopenta(methylene phosphonate)

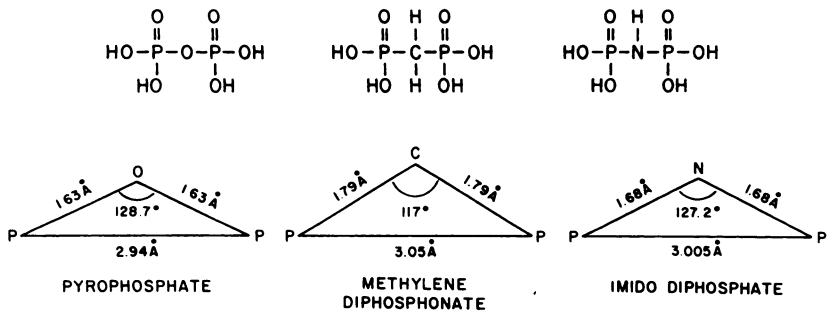

FIG. 1. Structural formulas (shown in acid form) for pyrophosphate, methylenediphosphonate, and imidodiphosphate along with interatomic distances and bond angles of central atoms. Notice similarity between pyrophosphate and IDP.

lar chemical and biologic behavior (*12–14*). Like the pyrophosphate and the diphosphonates, the imidophosphate exerts an inhibitory effect on the crystallization of calcium phosphate in vitro. Because of these and other chelating and biologic properties (*15–19*) we considered ^{99m}Tc-IDP as a candidate for bone imaging. We have also studied a new polyfunctional phosphonate compound, DTPMP, because of its similar chemical properties (*20*) and because it showed promise as a bone-seeking chelate for short-lived trivalent radionuclides such as ^{113m}In and ^{111}In (*21*).

In this report a method is presented for labeling imidodiphosphate with ^{99m}Tc in an "instant kit" form, and data are presented on the biologic distribution of this compound in experimental animals, with preliminary evaluation in a patient. DTPMP (an analog of DTPA) was also labeled with ^{99m}Tc and is compared with other ^{99m}Tc-labeled complexes for bone imaging.

MATERIALS AND METHODS

Imidodiphosphate 99% pure was obtained as the tetrasodium salt from Boehringer–Mannheim and was used without any further purification. If desired, this compound can be synthesized in the laboratory by methods already available in the literature (*15*). The DTPMP was obtained as a sodium salt solution from Calgon and was recrystallized before use. Other chemicals used in the preparations are standard laboratory reagents of analytical grade.

After preliminary experiments, freeze-dried "instant" labeling kits were prepared containing 5 mg of tetrasodium imidodiphosphate and 100 μg of $SnCl_2 \cdot 2H_2O$; 25 mg DTPMP and 500 μg of $SnCl_2 \cdot 2H_2O$ were used for the other kit. Methods similar to those previously described for other ^{99m}Tc compounds (*8,9*) were used including the freeze-drying equipment. These kits were prepared under sterile conditions and the final pH of the preparation was adjusted to 6.5 for imidodiphosphate and 7.2 for DTPMP before freeze-drying. Kit preparation methods for other compounds referred to in this article have already been reported (*8,9*). For labeling with ^{99m}Tc one simply adds to the kit vial the desired activity of $^{99m}TcO_4$ in 2–5 ml of volume and mixes well. The labeling yield is better than 98% for both the compounds and very little free TcO_4 is detected by paper chromatography in 85% methanol in water. After labeling, the final range of the pH of ^{99m}Tc-imidodiphosphate compound was 6.2–6.5, and for ^{99m}Tc-DTPMP it was 7.0–7.2. Both compounds were found to be stable for at least 4 hr after preparation as determined by paper chromatography and imaging studies in rabbits.

The organ distribution of the ^{99m}Tc-imidodiphosphate was studied in New Zealand adult albino rabbits weighing 3.5–5 kg. Data were collected after i.v. injection of 50–200 μCi containing 0.1–0.2 mg of IDP per animal, and the IDP was compared with 10–20 μCi of ^{85}Sr administered simultaneously as a biologic standard. The methods of tissue assay used were similar to those described elsewhere (*2–4*). These animals were sacrificed at various time intervals from 15 min to 24 hr after injection. A similar study was performed with ^{99m}Tc-DTPMP at 2 hr, using 50–200 μCi of ^{99m}Tc and 1–2 mg of DTPMP per rabbit. Because of the excellent skeletal uptake of ^{99m}Tc IDP in rabbits, a dog weighing 25 kg was also imaged to evaluate the biologic behavior of this compound in a mammal higher than the rabbit. A whole-body image of the dog was obtained in the right lateral projection 4 hr after intravenous injection of 5 mCi of ^{99m}Tc-IDP. The instrument used was an Ohio-Nuclear model 100 camera fitted with a 140-keV high-sensitivity parallel-hole collimator with a data-density setting of 200.

A toxicologic study was conducted in both mice and rabbits by serial injection of graduated doses. The acute toxicity of imidodiphosphate ($LD_{50/30}$) was determined to be 45–50 mg imidodiphosphonic acid per kilogram body weight; this is comparable to toxicities determined for the diphosphonates HEDP and MDP (*8,9*).

An imaging study was performed in an adult albino rabbit weighing 4.2 kg after i.v. administration of 5 mCi of ^{99m}Tc-IDP, using the Searle Radiographics Pho/Gamma HP camera fitted with a 140-keV, high-resolution, parallel-hole collimator. Images in the posterior projection were obtained from

TABLE 1. TECHNETIUM-99m-LABELED STANNOUS IMIDODIPHOSPHATE IN RABBITS. SIMULTANEOUS STUDY WITH ^{85}Sr

Organ	15 min (6)		1 hr (6)		2 hr (9)		4 hr (9)		24 hr (7)	
	^{99m}Tc	^{85}Sr	^{99m}Tc	^{85}Sr	^{99m}Tc	^{85}Sr	^{99m}Tc	^{85}Sr	^{99m}Tc	^{85}Sr
	Percent dose in whole organ									
Blood	15.4	16.1	5.90	8.17	2.92	5.19	1.69	2.72	0.734	0.250
Liver	4.24	2.13	2.08	1.58	2.00	0.947	1.58	0.576	0.661	0.004
Muscle	9.32	15.6	4.47	9.55	3.01	7.96	1.53	4.80	0.599	0.628
Kidney	5.52	1.27	4.75	0.938	4.39	0.638	2.90	0.267	2.19	0.022
Marrow	1.07	0.903	0.646	0.817	0.643	0.499	0.447	0.300	0.331	0.070
Urine	13.3	4.94	37.6	8.96	47.4	16.6	49.5	26.2	—	—
Whole femur	0.782	0.741	1.46	1.27	2.06	1.67	1.81	1.84	1.67	1.55
Whole tibia	0.561	0.540	1.12	1.03	1.63	1.34	1.57	1.57	1.09	1.38
	Percent dose/1% body weight*									
Blood	2.20	2.29	0.843	1.17	0.420	0.742	0.242	0.388	0.105	0.331
Liver	1.40	0.692	0.674	0.489	0.734	0.357	0.491	0.168	0.225	0.016
Muscle	0.217	0.363	0.104	0.222	0.070	0.186	0.035	0.125	0.014	0.015
Kidney	11.8	2.68	8.14	1.54	8.02	1.14	5.41	0.488	4.63	0.067
Marrow	0.489	0.410	0.294	0.382	0.291	0.227	0.203	0.137	0.150	0.032
Large intestine	1.03	1.79	0.491	0.961	0.331	0.762	0.142	0.421	0.049	0.088
Small intestine	0.732	1.23	0.406	0.654	0.323	0.669	0.245	0.300	0.069	0.042
Femur	3.60	3.41	5.70	5.23	8.40	6.84	7.71	7.87	6.75	6.39
Tibia	3.14	3.02	5.26	4.67	7.94	6.60	7.59	7.64	6.64	6.58
Pelvis	6.03	5.06	7.15	5.47	9.66	7.35	11.0	9.83	8.97	8.13
Spine	3.63	3.76	6.23	5.82	9.25	8.05	8.97	9.57	6.96	6.96
Average bone	4.10	3.82	6.08	5.30	8.81	7.21	8.83	9.16	7.32	6.93
	Ratios									
Bone/blood	1.86	1.71	7.75	4.53	24.8	10.5	39.8	23.6	69.4	20.9
Bone/muscle	18.7	10.6	68	23.9	177	44	288	73.3	528	462
Bone/marrow	8.92	9.84	23	13.9	37	36	50	66.9	59	217

* Percent dose/1% body weight = (percent dose in organ or sample) $\Big/ \left(\frac{\text{weight of organ or sample}}{\text{body weight}}\right) \times 100$.

TABLE 2. COMPARATIVE RESULTS OF ^{99m}Tc-LABELED BONE-IMAGING AGENTS IN RABBITS. SIMULTANEOUS STUDY WITH ^{85}Sr AT 2 HR

Organ	$^{99m}Tc/^{85}Sr$ ratios calculated from specific concentrations*								
	IDP (9)	MDP (12)	HEDP (12)	Pyro-phosphate (12)	Poly-phosphate (12)	AEDP (6)	HMDTMP (6)	EDTMP (6)	DTPMP (6)
Blood	0.552	0.371	0.362	0.703	1.48	0.416	0.703	0.881	0.461
Liver	2.12	0.568	0.954	0.779	2.61	0.766	0.855	1.78	0.544
Muscle	0.350	0.192	0.172	0.365	0.623	0.135	0.407	0.438	0.221
Kidney	7.27	3.93	3.53	2.81	9.46	3.71	7.06	8.44	3.82
Marrow	1.24	0.617	0.814	0.726	2.95	0.852	0.713	1.22	0.547
Femur	1.23	0.820	0.796	0.710	0.826	0.641	0.434	0.677	0.419
Tibia	1.20	0.730	0.798	0.694	0.66	0.641	0.437	0.684	0.384
Pelvis	1.34	0.920	0.913	0.918	1.01	0.693	0.516	0.720	0.627
Spine	1.17	0.826	0.801	0.827	0.82	0.618	0.428	0.572	0.415
Average bone	1.24	0.833	0.832	0.812	0.87	0.648	0.456	0.662	0.467

* Numbers in parentheses under each compound indicate number of animals studied for that compound.

1 to 24 hr after injection in three separate views collecting 300,000 counts for each. No attempts were made to remove the urine from the bladder during this study. Similarly, another adult rabbit was imaged with 5 mCi of ^{99m}Tc-DTPMP.

Because of the insignificant toxicologic problems and high bone uptake of ^{99m}Tc-IDP, a volunteer patient who had previously had a ^{99m}Tc-MDP bone scan was studied with IDP after informed consent was obtained. This 33-year-old woman with a recent left radical mastectomy was intravenously injected with 15 mCi of ^{99m}Tc-IDP containing 1.5 mg of tetrasodium imidodiphosphate (equivalent to 1 mg of the acid). Whole-body images with the pa-

tient in both anterior and posterior projections were obtained 3 hr after injection using an Ohio-Nuclear series 100 camera with a high-sensitivity, low-energy, parallel-hole collimator. The equipment used, the data-density setting, and the time of imaging were the same as those used for the previous ^{99m}Tc-MDP bone scan.

RESULTS

In order to compensate for biologic variation, bone-seeking agents are best studied by comparing the quantitative uptake of the new compound with that of simultaneously administered ^{85}Sr for purposes of normalization. One should compare not only the whole-organ uptakes but also the concentration ratios, especially in the case of the bone seekers. Whole-organ uptake for the skeleton is difficult to estimate because of the wide variations from one bone to another. Nevertheless, the data for single bones are useful.

Table 1 contains distribution data for ^{99m}Tc-IDP in rabbits, with ^{85}Sr used simultaneously. The number shown in parentheses after the time of study is the number of animals used for that time interval. The values for each organ shown are the averages for each group of animals. The figures shown under "percent dose/1% body weight" were determined by the formula given under Table 1. In the case of bone the values tabulated were determined as follows. For a given animal the concentrations for the femur, tibia, spine, and pelvis were averaged. These individual averages for the four types of bone were then averaged for all the animals in that time-of-study group to give the figure in the table. The mean values for bone-to-organ ratios were calculated similarly for each group.

Table 1 illustrates the wide variation of concentrations in various bones. By comparison, however, ^{99m}Tc-IDP has approximately 25% more uptake than ^{85}Sr at time intervals up to 2 hr and equivalent uptake at later times. This concentration change with time may be due to the metabolic breakdown of the compound at the bone mineral surface, with the ^{99m}Tc complex being more labile; also we know that the biologic half-life of ^{85}Sr is prolonged. Even at time intervals later than 2 hr, ^{99m}Tc-IDP concentration in bone is at least 20–25% higher than for the other Tc complexes (Table 2). From the standpoint of imaging, another important factor is the blood concentration of ^{99m}Tc-IDP. Even though it is lower than ^{85}Sr at all times, it is not quite as low as some of the other ^{99m}Tc compounds shown in Table 2. Certainly this may represent a disadvantage, since bone/blood concentrations may not be higher than those of the earlier ^{99m}Tc complexes—notably those of MDP and HEDP. Of further interest is the lower blood level of ^{99m}Tc-IDP at 2 hr than that of the pyrophosphate complex.

Table 2 compares a variety of ^{99m}Tc compounds with ^{85}Sr, the data being taken (at 2 hr in rabbits) from the present and previous distribution studies. The number in parentheses under each compound indicates the number of animals used for that compound. The total-organ distribution data are available elsewhere (*8,9*). The values shown here have been derived from the earlier data except for the new complexes IDP and DTPMP. Only the mean values of the ^{99m}Tc/^{85}Sr ratios for each organ are shown.

Figure 2 shows a series of composite whole-body images of a 4.2-kg adult rabbit, the dose being 5 mCi of ^{99m}Tc-IDP. Times after dose are indicated. Each whole-body image is a composite of three separate images for each of which 300,000 counts were collected.

The rabbit images shown in Fig. 2 clearly demonstrate the high skeletal localization of ^{99m}Tc-IDP at 1–24 hr after injection of the compound. This

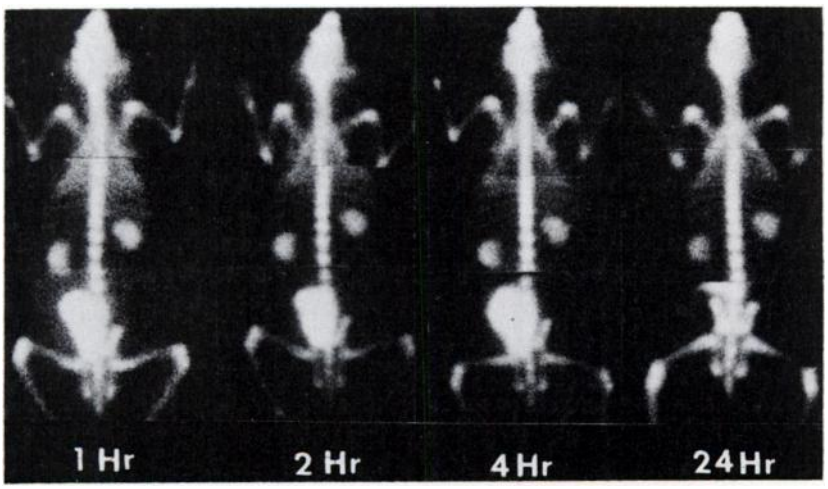

FIG. 2. Serial composite whole-body images of 4.2-kg adult albino rabbit intravenously injected with 5 mCi of ^{99m}Tc-IDP; times after dose are shown. Searle Radiographics Pho/Gamma HP camera with 140-keV, high-resolution, parallel-hole collimator was used and 300,000 counts were collected for each view.

FIG. 3. Whole-body right lateral image of 25-kg mongrel dog at 4 hr after injection with 5 mCi of ^{99m}Tc-IDP. Ohio-Nuclear series 100 area scan scintillation camera fitted with 140-keV, high-sensitivity, parallel-hole collimator was used.

compares very favorably with the images obtained with ^{99m}Tc-diphosphonates. The details of all skeletal structures are very clearly seen.

Imaging studies conducted with ^{99m}Tc-DTPMP also showed good delineation of the skeleton in the rabbit but not as good as those obtained with ^{99m}Tc-IDP. We noted that the concentration of the DTPMP complex at 24 hr was minimal and urinary excretion of the complex was higher at earlier time intervals. DTPMP's lower bone uptake may be due to its rapid urinary excretion as well as lower affinity for bone mineral. Because of its poor imaging characteristics, DTPMP images are not shown here.

Figure 3 shows the whole-body image of a dog in the right lateral position at 4 hr after injection of 5 mCi of ^{99m}Tc-IDP. The vertebral column and all the ribs are clearly delineated. The large accumulation of the activity in the pelvic area is bladder urine.

Figure 4 illustrates comparative whole-body images in a 33-year-old female patient obtained with both ^{99m}Tc-MDP and ^{99m}Tc-IDP performed within a 10-day interval. These images were obtained with 15 mCi of each of the compounds and using an Ohio-Nuclear whole-body imaging camera as previously described. The count rates obtained with ^{99m}Tc-IDP were approximately twice that of the MDP compound. Due to the higher bone concentration and count rates, the anterior image was obtained in 8.6 min with IDP versus 15.6 min using a data density of 200 for both. Similarly, the posterior view took 8.2 min for IDP and 13.0 min for MDP.

DISCUSSION

Imidodiphosphate is an analog of pyrophosphate and diphosphonate and has been found to be present in biologic systems. Correl (*22*) first proved that P–N–P linkages are present in algal "polyphosphate." This new compound is more clearly analogous to pyrophosphate than to the diphosphonates (*13,16,17*). The P–X–P bond angles and P–X bond distances of pyrophosphate, imidodiphosphate, and the methylene diphosphonate (in acid form) are shown in Fig. 1. The bond angles and distances are remarkably similar for P–N–P and P–O–P, but the P–C–P bond angle is more acute: 117° versus 127° and 129° for the other two (*13*). Because of the longer P–C bond length, however, the interphosphorous P–P distances are approximately the same in all three compounds. It was therefore expected that the geometry and stability of the metal and ion complexes would be similar, as would biochemical

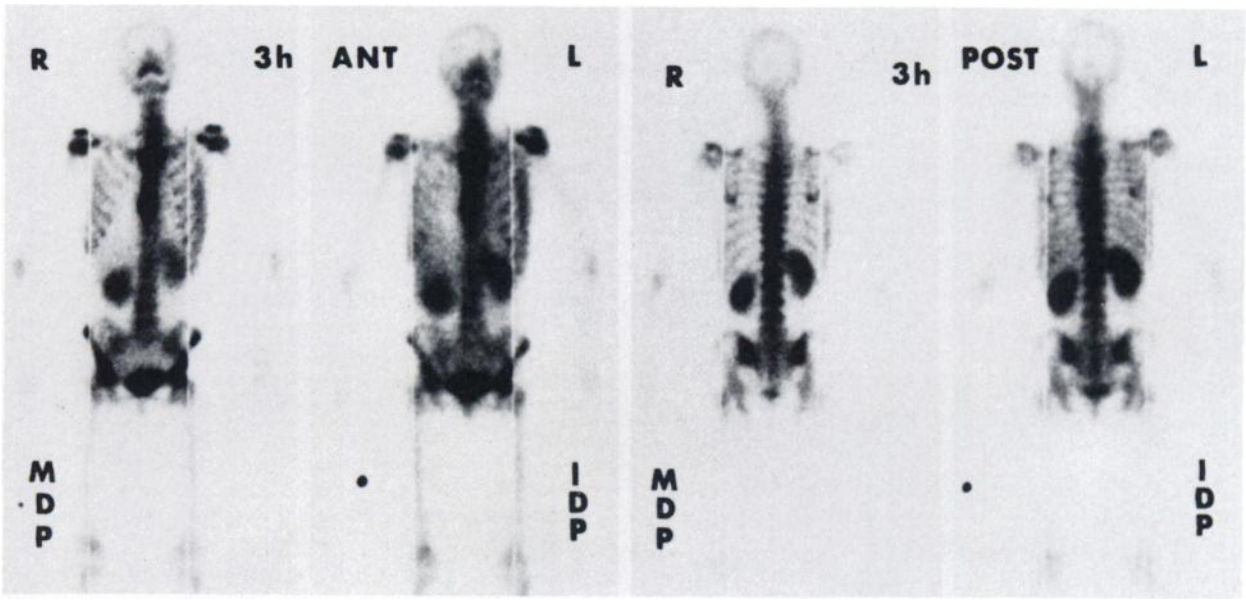

FIG. 4. Whole-body images of 33-year-old woman with recent modified left radical mastectomy after 15 mCi each of ^{99m}Tc-MDP and ^{99m}Tc-IDP, done 10 days apart under identical conditions. Ohio-Nuclear series 100 area scan scintillation camera with 140-keV, high-sensitivity, parallel-hole collimator was used with the same data-density setting for both (see text for other details).

behavior, and this has been confirmed by the success of ^{99m}Tc bone-imaging agents formulated with these compounds using divalent tin. Yount and others (*16,17*) have also found during their study of ATP analogs, with P–C–P and P–N–P bonds for the last two phosphorus atoms in ATP, that in high ionic strength solutions AMP–PNP forms stronger chelates with divalent cations of calcium, magnesium, and manganese, and the PNP analog is biologically more active than the P–C–P analog of ATP. Other workers (*18,19*) have shown that compounds containing imidodiphosphate structures are good chelating agents for tin. Imidodiphosphate has more chelating capacity for calcium than pyrophosphate (*15*). Moreover, Robertson and Fleish (*14*) showed that imidodiphosphate inhibits the precipitation of calcium phosphate and the dissolution of preformed calcium phosphate in vitro, characteristics similar to pyroprosphate, polyphosphate, and diphosphonate; criteria useful in developing bone-imaging agents. These factors prompted us to develop ^{99m}Tc-IDP for use in bone imaging. The compound DTPMP was also studied because of its recent availability and the ability of its analogs to inhibit calcium phosphate precipitation in vitro (*20*). Because the chemical structures of these multidentate ligands resemble those of the well-known trivalent metal chelators DTPA and EDTA, short-lived indium radionuclides (^{113m}In and ^{111}In) have also been labeled with EDTMP and DTPMP and have potential for skeletal imaging (*21*).

The DTPMP complex definitely has a lower blood level than IDP and a few other complexes shown in Table 2. However, the bone concentration is considerably lower with DTPMP than with other compounds and is equivalent to that of HMDTMP. The soft-tissue concentrations with all these complexes are lower than with ^{85}Sr especially in the case of muscle. The liver concentration for some ^{99m}Tc complexes is somewhat higher than that of ^{85}Sr. This should not be a problem because the total liver concentration is relatively low. Overall, from the distribution studies in rabbits it may be inferred that the ^{99m}Tc-IDP complex has the highest bone uptake of all the compounds reported here, but its blood clearance is somewhat slower than with either ^{99m}Tc-MDP or ^{99m}Tc-HEDP and slightly faster than with the pyrophosphate complex.

The dog image in Fig. 3 is also included to show the high quality of bone image that can be obtained with ^{99m}Tc-IDP in a higher mammal than a rabbit. This bone scan of the dog suggests the new compound may behave similarly in humans. This type of evaluation, including tissue radioassay and imaging in a higher mammalian species, is useful and necessary before clinical trials can be performed with any new radiodiagnostic agent.

In the patient scans (Fig. 4) visual comparisons are possible because identical conditions were used for the MDP and IDP tracers. Clearly the ^{99m}Tc-MDP images are superior. In the anterior and posterior views the ribs and vertebrae are better defined with MDP than with the IDP complex. The latter does show these, to be sure, but the increased body background due to blood activity slightly obscures the skeleton. Perhaps at a later time interval the IDP images might be as good as or better than the MDP scans.

Fluorine-18 is the ideal agent for bone imaging from a biologic behavior standpoint, due to its fast blood clearance and high skeletal uptake. The ^{99m}Tc-MDP complex has been shown to have a blood clearance similar to that of ^{18}F but a lower bone uptake. Our new complex of technetium (^{99m}Tc-IDP) seems to be a good bone-localizing agent, with high concentrations in the skeleton comparable to those of ^{18}F and certainly much higher than ^{99m}Tc-MDP. But its blood clearance seems to be slower than ^{99m}Tc-MDP (and also slower than ^{18}F) although faster than ^{99m}Tc-pyrophosphate. Further quantitative studies will be necessary to assess its clinical value.

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