values. Technetium-99m-sestamibi scanning is more sensitive than CT for localizing soft-tissue disease, especially in the mediastinum, although liver metastases should be assessed on CT scans. Bone metastases from MTC are best assessed on bone scans.

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Tin-117m(4+)DTPA: Pharmacokinetics and Imaging Characteristics in Patients with Metastatic Bone Pain

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Biokinetics and imaging characteristics of ^{117m}Sn(4+)DTPA have been studied in patients with metastatic bone pain. **Methods:** Seventeen patients with bone pain due to metastasis were given three dose levels: 180 μCi/kg (6.66 MBq/kg), 229 μCi/kg (8.47 MBq/kg) and 285 μCi/kg (10.55 MBq/kg) body weight. Periodic blood and daily urine samples were collected for 14 days to measure percent injected activity retained in blood and that excreted in urine. Simultaneous anterior and posterior view whole-body images were obtained under identical scan settings at 1, 3.5 and 24 hr and on Days 3 and 7 and between 4–6 and 8–10 wk postinjection. The total body retention was calculated using the geometric mean counts. **Results:** After intravenous injection, the total body clearance of ^{117m}Sn(4+)DTPA shows two components: a soft-tissue component and a bone component. The soft-tissue component accounts for 22.4% of the dose and consists of four subcomponents with an average biologic clearance half-time of 1.45 days (range 0.1–3.2 days). The bone component accounting for the remaining 77.6% of the dose shows no biologic clearance. A mean 22.4% of the dose is excreted in urine in 14 days; 11.4% within 24 hr. The uptake pattern appears similar to that of ^{99m}Tc-MDP. Peak uptake is observed in normal bone by 24 hr and metastatic lesions by 3–7 days. Pain palliation was observed with all three doses levels. **Conclusion:** Among the four potential bone pain palliation radionuclides, ^{117m}Sn(4+)DTPA demonstrates the highest bone uptake and retention. Some biokinetic and radionuclidic features of ^{117m}Sn(4+)DTPA are similar to other agents, but many features are different and unique and may make it an ideal bone pain palliation agent. Double-blind comparative studies are needed to determine its exact role in bone pain palliation.

Key Words: bone pain palliation; pharmacokinetics; tin-117m(4+)DTPA

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Of the estimated 1.35 million people in the U.S. who would be diagnosed of some form of cancer in 1996, slightly more than half will develop metastasis (*1*). In patients whose primary

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cancer site is the prostate, breast and lung, about 75%–80% develop bone pain due to bone metastasis in the near terminal stages requiring some form of pain palliation. The strategy for treatment of terminal cancer patients is to improve their quality of life; a significant component of that strategy is proper management of pain (*2*). Five options are generally available for bone pain palliation from metastatic lesions: (a) nonsteroidal anti-inflammatory agents and opioids, (b) hormones, (c) cytotoxic chemotherapy, (d) external beam radiation and (e) internal radiation through radionuclides. The first three options work effectively in the initial stages and the fourth, external radiation, is suitable for a single site of painful metastasis. In the terminal stages, metastatic bone pain is usually severe, arises from multiple sites and may require large quantities of opiates. Given in the high doses required to control pain, opiates diminish the quality of life through their many side effects, of which sedation and constipation are the two most important (*3*). When therapy with these four options fail, pain palliation with radionuclides is considered (*4–6*). Four radionuclides that have been used for pain control include: phosphorus-32, strontium-89, samarium-153 and rhenium-186.

Because of frequent and severe bone marrow suppression, phosphorus-32-orthophosphate is not currently used for metastatic bone pain palliation. At present, ^{89}Sr is the only radionuclide that has undergone extensive clinical trials and has received FDA approval for bone pain palliation (*7,8*). Rhenium-186-HEDP (*9,10*) and samarium-153-EDTMP (*11,12*) are two other agents whose biokinetic studies have shown potential for bone pain palliation. Early results with rhenium-186-HEDP (*13*) and samarium-153-EDTMP (*14*) in humans have shown optimistic results. Phase III human trials have been completed and both of these agents are pending FDA approval.

Tin(Sn)-117m(4+)DTPA is a new agent with unique physical and biological characteristics that may make it an ideal agent for the treatment of metastatic bone pain. Srivastava et al. (*15*) developed several ^{117m}Sn based agents and demonstrated bone uptake of ^{117m}Sn in the stannic state (4+) complexed to pyrophosphate, EHDP, MDP or DTPA in mice. The highest uptake was seen with ^{117m}Sn(4+)DTPA. The short range of the conversion electrons indicates potential bone marrow sparing features from therapeutic doses of ^{117m}Sn(4+)DTPA (*16*). Pilot studies in humans by Atkins et al. (*17,18*) have shown promising results. Tin-117m with a monoenergetic gamma photon of 159 keV in 86% abundance serves as an excellent bone imaging agent, enabling accurate quantification of total-body uptake and retention as well as uptake and retention by metastatic lesion and normal bone.

The current project was undertaken to gather as complete a dataset as possible under Phase II studies to fully understand the biokinetics and imaging characteristics of ^{117m}Sn(4+)DTPA before initiating a multicenter Phase III clinical trial. Ideal physical characteristics of ^{117m}Sn described above combined with an intermediate physical half-life of 13.9 days provides a unique opportunity for studying the long-term biological behavior of this bone pain palliation agent. Biokinetics is the study of what the body does to the injected radiotracer and biodynamics is the study of what the tracer does to the body. In this article, we report the results of the biokinetic studies only.

MATERIALS AND METHODS

This study was undertaken as a collaborative research project between the Veterans Administration Medical Center (VAMC) in Tucson, AZ and the Brookhaven National Laboratory (BNL) in Upton, NY. Human studies were initiated first at BNL after obtaining FDA approval under a physician-sponsored Investigational New Drug. The project was approved by the VAMC and University of Arizona Human Subjects Committee as a collaborative research project with BNL. Seventeen male patients (age range 45–81 yr) with histologically confirmed primary malignancy with painful bone metastases were studied. Fourteen patients had primary malignancy in the prostate, two in the lung and one in the kidney. One patient with prostate cancer received two doses with an interval of 6 mo between the doses, thus making a total of 18 studies. All patients had received, at various times, prior radiation therapy, chemotherapy, hormonal therapy or opioids for pain palliation and were considered, recently, as nonresponders to these methods of pain control, before entering into the ^{117m}Sn(4+)DTPA therapy protocol. None of the patients had received any bisphosphanates or radionuclide therapy within the last 6 mo or chemotherapy within 3 mo. Fifteen patients had extensive tumor spread to the bone, and two had limited spread as demonstrated on a total-body ^{99m}Tc-MDP bone scan. Each subject was interviewed along with the spouse to elicit full cooperation by both for rigid data collection. The nature of the research study, its purpose, benefits and risks were explained to the patients, and informed written consent was obtained on a form approved by the Human Subjects Committee.

Subject Selection

All subjects were referred for therapy by their primary physician after they underwent recent assessment of their pain status. A whole-body ^{99m}Tc-MDP scan obtained within the last month prior to entry in the study demonstrated metastatic bone lesions, many of which were painful. The patients were eligible to enter the study if they also had the following results: BUN <20 mg/dl, creatinine <2 mg/dl, total bilirubin <2 mg/dl, hemoglobin >12 g/dl, WBC >2000/μl, neutrophils >1000/μl, and platelets >100,000/μl. Karnofsky clinical score >40.

Tin-(4+)DTPA Preparation

Tin-117m(4+)DTPA was prepared at BNL as described earlier (*18*) and sent by air mail for next day delivery to Tucson VAMC. Two to four patient doses were sent at a time for use within the next 4 wk, which was later extended to 8 wk shelf life. Briefly, ^{117m}Sn was prepared using the ^{117}Sn (n, n, γ) ^{117m}Sn reaction. Enriched ^{117}Sn (84%) as the oxide or metal was used. The oxide, when used, was converted to metal by reduction at 600°C in a hydrogen flow for 2.5 hr prior to irradiation. Up to 100 mg Sn metal-sealed in a quartz ampule were irradiated for 3–4 wk using the BNL high-flux beam reactor or the high-flux isotope reactor at Oak Ridge National Laboratory. The specific activity of ^{117m}Sn at the end of the irradiation ranged from 2 to 8 mCi/mg (74–296 MBq/mg).

Tin-117m(4+)DTPA Whole-Body Scan

A few minutes before ^{117m}Sn(4+)DTPA injection, the patient was asked to void to alleviate the need for voiding during the next 2 hr. An indwelling catheter was placed in the antecubital vein in each arm, one for injection of the radiopharmaceutical and the other for blood withdrawal at frequencies shown in Table 1. The weight-based ^{117m}Sn(4+)DTPA dose was infused slowly over 2–4 min. Three dose levels were used. Four patients received 180 μCi/kg (6.66 MBq/kg), five received 229 μCi/kg (8.47 MBq/kg) and nine received 285 μCi/kg (10.55 MBq/kg) body weight. One patient (shown in Fig. 1) received two doses (6-mo interval between doses): 285 μCi/kg (10.55 MBq/kg) as the first dose and 180 μCi/kg (6.66 MBq/kg) as the second (This patient had received ^{89}Sr 1 yr earlier and was considered to be a nonresponder. His pain had worsened recently and he wanted to try the new experimental agent). The total individual dose injected into patients ranged from a low of 10 mCi (370 MBq) to a high of 25.9 mCi (958.3 MBq). An aliquot of the injected dose was kept as a standard for later

TABLE 1
Data Collection Schema for Biokinetic Study of Tin-117m(4+)DTPA

Blood sample collection time for				
Blood clearance	Cell count	Urine collection at	^{99m}Tc-MDP bone scan	^{117m}Sn(4+)DTPA bone scan
15 min	Baseline	Baseline	Pre-Rx	1 hr
30 min	Weekly for 8 wk followed	1 hr	8 wk post-Rx	3.5 hr
45 min	by monthly for 4 mo	2 hr	6 mo post-Rx	day 1
1 hr	(total 6 mo)	1 day and daily for		Day 3
2 hr		14 days		Day 7
Day 1				Weeks 4–5
Day 3				
Day 7				
Day 14				

counting of the blood and urine samples. Another aliquot of the injected dose of known activity was kept next to the patient's neck as a standard during each ^{117m}Sn bone scan obtained at intervals shown in Table 1. This known activity would enable calculation of the exact microcurie concentration at the desired site.

The first, simultaneous anterior and posterior view whole-body planar scan was started 60 min after injection before voiding. All subsequent whole-body scans (Fig. 1A, 1B) were obtained using the same camera under identical scan parameters used for the first scan. The scan intervals are shown in Table 1. Eight patients had follow-up whole-body images at 4–6 wk, 5 at 8–10 wk and 4 at 12–14 wk. In one patient, two additional images were taken; on Days 99 (Fig. 1B) and 133 (Fig. 1C) post-therapy.

Scan Parameters

Simultaneous planar anterior and posterior view whole-body images were obtained with a dual-head gamma camera fitted with low-energy, high-resolution parallel-hole collimators. The scan speed was set at 4.96 inches/minute and it usually took 18–20 min for the complete study, depending on the patient height. The spectrometer was set for ^{117m}Sn gamma photon peak energy of 159 keV with a 20% window. The digital images were recorded on a 256 × 1024 matrix. These parameters set for the first study (1 hr postinjection) were used for all of the subsequent imaging studies. An aliquot of the standard was kept, next to the neck, in all of the scans (Fig. 1) for quantification of tissue uptake.

Technetium-99m-MDP Bone Scan

Simultaneous planar anterior and posterior view whole-body bone scans were obtained with the same camera used in the ^{117m}Sn study. Images were obtained 2–3 hr after intravenous injection of 20 mCi (740 MBq) ^{99m}Tc-MDP using the 140 keV photopeak and a 20% window setting. The first scan was obtained before ^{117m}Sn(4+)DTPA therapy (Fig. 1D). Repeat ^{99m}Tc-MDP bone scans were obtained 8 wk and 6 mo after injection of ^{117m}Sn(4+)DTPA. The crosstalk from the 159 keV gamma photon of ^{117m}Sn during the ^{99m}Tc-MDP bone scan at 8 wk was approximately 15%.

Blood and Urine Collection and Counting

Blood samples (2–3 ml) were drawn at the intervals shown in Table 1. One milliliter of anticoagulated blood (EDTA) was counted in an NaI well counter along with the standard. The counts in 1 ml of blood were multiplied by the total blood volume, and the results were expressed as the percent injected dose in total blood. The height- and weight-based total blood volume for each patient was obtained from published tables (*19*). The blood samples for CBC, platelets, electrolytes and chemistry were obtained both before injection, at weekly intervals for 8 wk and at monthly intervals for the next 4 mo after injection of ^{117m}Sn(4+)DTPA (*17*). The urine was collected at 2 hr, 24 hr and later as daily samples for 14 days. In the first six patients, we collected urine for only 3 days, assuming that all of the radioactivity not taken up by the bone would be excreted in 3 days. When we found out otherwise, we extended urine collection for 7 days in three, 10 days in one and 14 days in eight patients. After collecting the last sample, all urine samples were counted at one time along with the standard. One milliliter of urine was counted from each daily sample in a dl NaI well counter using an offset window setting of 130–220 keV for the 159 gamma photon. The results were expressed as the percent injected dose excreted in daily urine (Table 2).

Calculation of Tin-117m(4+)DTPA Whole-Body Retention

The geometric mean counts from the planar anterior and posterior view whole-body counts (including the standard) in the first scan (1 hr postinjection prior to voiding) were obtained (as the square root of anterior × posterior counts). The geometric mean counts of the standard kept next to the neck were subtracted from the total counts in the image, and the net counts were considered as 100% of the injected dose. The net whole-body counts from later scans were corrected for physical decay. The geometric mean counts were divided by the counts from the first study, and the results were expressed as the percent injected dose retained (Fig. 4). All results are expressed as mean percent of injected dose ± s.d. and the mean values were tested by Student t test for statistical significance.

Calculation of Normal and Metastatic Bone Uptake and Retention of Tin-117m(4+)DTPA

Regions of interest were drawn over normal bone and metastatic foci, and decay-corrected counts of pixels were drawn from all seven ^{117m}Sn(4+)DTPA scans. Counts per pixels were plotted against time (Fig. 5). Time to peak was noted for both normal and metastatic bone lesions. The slope of the curve was watched for any evidence of washout.

RESULTS

Blood Radioactivity

After intravenous injection, ^{117m}Sn(4+)DTPA radioactivity remaining in whole blood at various times for up to 14 days postinjection is shown in Figure 2. A mean (s.d.) 14.8% ± 4.8% of the injected dose remained in the intravascular compartment at 15 min, and the remaining 85.2% of the dose had already left the intravascular blood pool at this time. When the percent injected radioactivity in blood is plotted on the y-axis and time on the x-axis of a semilog scale, three clearance components are readily evident from the curve with a clearance half-time ($T_{1/2}$) of 10.1 ± 1.4 min, 10.8 ± 0.3 hr and 6.59 ± days. Only 0.17% ± 0.08% of the dose remained in the blood compartment at 14 days postinjection.

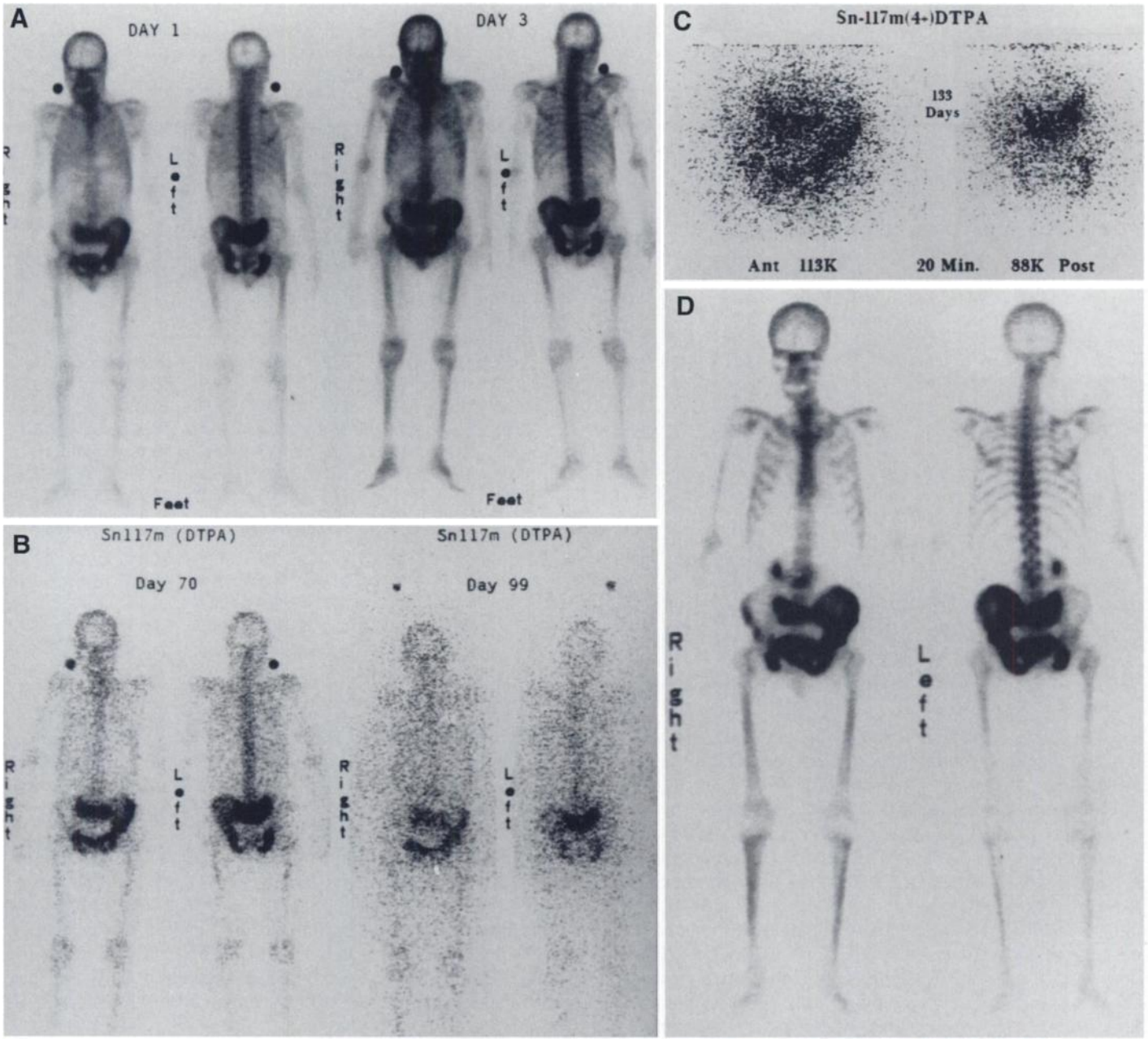

FIGURE 1. Serial ^{117m}Sn(4+)DTPA whole-body images obtained under identical parameters. There is excellent localization in bone by 24 hr (A) in a prostate cancer patient with local metastasis in the left hemipelvis extending to the right ischial tuberosity. Uptake in front of L4–L5 vertebra is due to low-lying horseshoe kidney. By Day 3, almost all of the radioactivity localizes in the bone. Images on Days 70 and 99 (B) show radioactivity mostly in the left hemipelvic bone and right ischial bone. The decrease in intensity in the later images is the effect of physical decay. Round activity on the right side of the neck is the external standard kept for calculation of regional uptake. At 133 days, the image shows persistent uptake in the left hemipelvis (C). Pre-therapy ^{99m}Tc-MDP scan (D) shows a pattern of distribution similar to ^{117m}Sn(4+)DTPA (A). Horse-shoe kidney is prominent in front of L4–L5 vertebra.

Urinary Excretion

A mean (s.d.) 3.5% ± 1.7% of the injected dose was excreted in urine in the first urine sample collected at 2.0 hr postinjection. Daily and cumulative average excretion of ^{117m}Sn(4+)DTPA in urine is shown in Table 2. A cumulative mean 11.4%, 14.1% and 16.1% of the injected dose was excreted in urine by Days 1, 2 and 3, respectively. The cumulative mean urinary excretion at the end of the first week was 19.5% of the dose and 22.4% at the end of the second week (Fig. 3).

Whole-body Clearance and Retention of Tin-117m(4+)DTPA

The whole-body clearance curve shows two components: soft-tissue and bone (Fig. 4). The soft-tissue component accounts for 22.4% of the dose and has four subcomponents with biologic clearance half-times ($Tb_{1/2}$) of 0.04, 0.56, 2.0 and 3.2 days (average 1.45 days). The bone component accounts for the remaining 77.6% of the dose with a $Tb_{1/2}$ of infinity. We hypothesize that the smaller components with $Tb_{1/2}$ ranging from 0.1 to 3.2 days represent urinary excretion. We also hypothesize that the larger component primarily represents bone uptake with no biologic clearance at all when this component is corrected for the physical decay of ^{117m}Sn. Since a cumulative mean 18.9% of the injected dose was excreted in urine at end of 7 days, it can be assumed that the remaining 81.1% of the injected dose was retained in the whole body 7 days postinjection. This value of 81.1% (Injected dose − Urine excretion method) whole-body retention is equal to the value of 81.1% ± 5.5% obtained by the independent gamma camera geometric mean method. Because the urine sample counting

TABLE 2
Daily and Cumulative Urinary Excretion (%ID) of Tin-117m(4+)DTPA in Patients with Metastatic Bone Pain

Patient no.	Age	Sex	Days (postinjection) 0.0	0.1	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	63	M	0.0	0.8	7.7	10.6	13.2											
2	69	M	0.0	1.1	5.8	7.2	8.5											
3	53	M	0.0	4.3	20.5	24.4	26.7											
4	76	M	0.0	5.0	18.6	23.6	29.8											
5	77	M	0.0	1.9	8.7	11.0	12.0											
6	51	M	0.0	5.4	10.5	12.4	13.8											
7	70	M	0.0	3.6	18.2	23.9	26.9	28.8	30.1	31.4	32.5							
8	72	M	0.0	2.9	11.1	12.2	13.5	13.9	14.5	14.9	15.0							
9	71	M	0.0	2.3	7.6	9.6	10.4	11.1	11.8	12.2	12.5							
10	79	M	0.0	6.7	9.9	12.0	13.6	14.4	15.0	15.6	16.0	16.4	16.7	16.9				
11	45	M	0.0	1.7	11.9	16.3	19.0	20.6	22.5	24.0	25.1	26.6	27.5	28.4	30.7	31.5	31.9	31.9
12	70	M	0.0	5.4	10.7	12.8	14.3	15.0	15.7	16.3	16.8	17.2	17.7	18.0	18.3	18.6	18.8	19.1
13	65	M	0.0	3.8	12.2	15.5	18.0	19.1	19.4	19.7	20.4	21.1	21.8	22.1	22.7	23.0	23.2	23.4
14	70	M	0.0		9.6	11.8	12.9	14.2	15.2	15.9	16.4	17.0	17.4	17.9	18.4	18.8	19.2	19.2
15	80	M	0.0	3.9	9.2	10.6	11.7	12.4	12.9	13.0	13.2	13.8	14.1	14.5	14.9	15.1	15.3	15.3
16	63	M	0.0		15.0	17.7	19.1	20.6	21.8	23.2	24.1	24.9	15.5	26.1	26.7	27.1	27.5	27.9
17	67	M	0.0	4.2	10.8	12.5	13.7	14.5	15.3	16.0	16.6	17.2	17.7	18.2	18.5	18.9	19.1	19.4
18	81	M	0.0	2.3	7.2	9.6	12.9	14.5	16.0	17.2	18.5	18.9	19.5	20.1	21.0	21.4	22.3	22.6
Average (cumulative)			0.0	3.5	11.4	14.1	16.1	16.6	17.5	18.3	18.9	19.2	19.7	20.2	21.4	21.8	22.2	22.4
s.d.			0.0	1.7	4.1	5.2	6.0	4.9	5.1	5.5	5.8	4.2	4.0	4.5	5.1	5.3	5.4	5.4
Daily excretion			0.0	0.0	11.4	2.7	2.0	0.5	0.9	0.8	0.6	0.3	0.5	0.5	1.2	0.4	0.4	0.2
% Whole-body retention (Dose − urine excretion)			100	96.5	88.6	85.9	83.9	83.4	82.5	81.7	81.1	80.8	80.3	79.8	78.6	78.2	77.8	77.6

and the gamma camera whole-body counting methods are two independent techniques, the closeness of the values between the two methods during the first week assures us that the gamma camera method alone, used in the subsequent weeks and months, is a simple, yet reliable technique for long-term follow-up (*20*). Mean (s.d.) whole-body retention of ^{117m}Sn(4+)DTPA at the end of 35, 48, 63 and 93 days postdose was 82.9% ± 8.6%, 83.8% ± 5.2%, 84.3% ± 9.1% and 84.3% ± 10.1%, respectively. These mean values, which are slightly higher than the value of 77.6% at 2 wk (Dose − Urine), were not statistically different and probably reflect the effect of small sample size. To be on the conservative side, we have chosen the lower value of 77.6% as the total body retention beyond 2 wk (Table 3). In one patient, the scan of the pelvis (Fig. 1C) showing the lesion in the left hemipelvis was obtained 133 days post-therapy (3 days short of 10 half-lives). He had received a 10-mCi (370 MBq) dose and had excreted in urine a cumulative 19.2% of the dose in 13 days. The estimated whole-body retention of ^{117m}Sn(4+)DTPA on the 133rd day from the original 10-mCi (370 MBq) therapy dose (after accounting for urinary excretion and physical decay) approximately would be an equivalent of 8 μCi (0.3 MBq).

Metastatic and Normal Bone Uptake and Retention of Tin-117m(4+)DTPA

When decay-corrected counts per pixel are plotted on the y-axis against time on the x-axis, the curve for both the normal and abnormal (metastatic) pelvic bones shows different types of peak bone uptake. The normal bone reaches its peak uptake rapidly within 24 hr, whereas uptake in metastatic bone may peak in 3–7 days. After the peak uptake, both normal and metastatic bone do not show any biological clearance when followed for 99 days postinjection (Fig. 5). The lesion-to-normal bone ratios ranged from a low of 2 to a high of 9 and varied from patient to patient and within the same patient.

Pattern of Whole-Body Distribution of Tin-117m(4+)DTPA

Visually, the whole-body distribution pattern of ^{117m}Sn(4+)DTPA is similar to that of ^{99m}Tc-MDP for normal bone and bone with metastatic involvement (Fig. 1). Visually, the clarity of ^{117m}Sn bone scans obtained at 24 and 72 hr and on Day 7 Week 6 post-therapy is equivalent to the 3-hr ^{99m}Tc-MDP bone scan (Fig. 1). The urinary bladder is not seen beyond 3 days, which enables assessment of the involvement of the pelvic bone metastasis much better on the ^{117m}Sn(4+)DTPA scan than on the 3-hr ^{99m}Tc-MDP scan where the bladder activity covers the pelvic bones. The pattern of bone uptake seen as early as 1 day postinjection of ^{117m}Sn(+)DTPA remained the same for 7–10

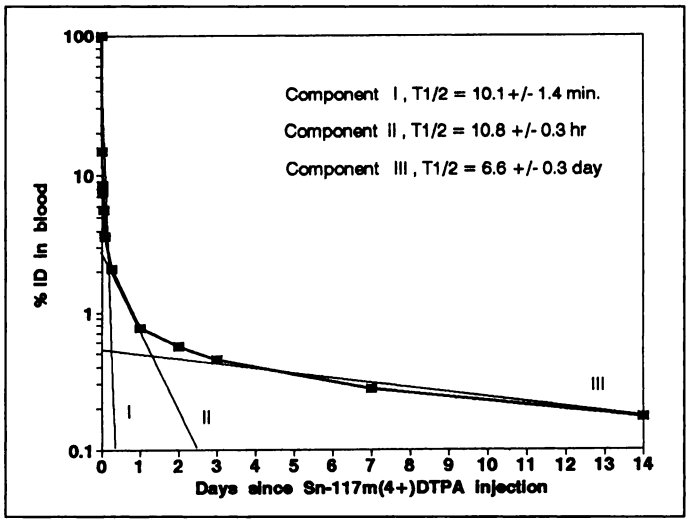

FIGURE 2. Blood clearance of ^{117m}Sn(4+)DTPA. About 14.4% of the injected dose remains in the blood pool at 15 min postinjection. The remaining 85.15% has left the intravascular compartment. Notice triexponential type of clearance with differing $T_{1/2}$ clearance values.

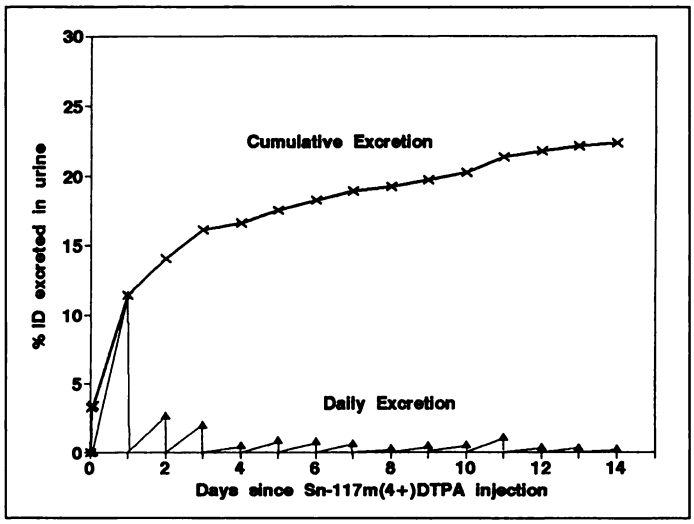

FIGURE 3. Daily and cumulative urinary excretion of ^{117m}Sn(4+)DTPA. About 11.4% of the injected dose is excreted on the Day 1 and 11.6% in the next 13 days for a total of 22.4% by 14 days.

physical half-lives (91–133 days) as shown in Figure 1. No soft-tissue uptake was seen (other than kidney and bladder) in the scans obtained 72 hr and beyond, with the sole exception of one patient in whom some liver uptake of ^{117m}Sn(4+)DTPA was noted. The spleen and other soft tissues did not demonstrate any uptake, suggesting ^{117m}Sn(4+)DTPA uptake by hepatocytes and not by reticuloendothelial cells. The exact cause for liver uptake could not be determined.

DISCUSSION

Management of intractable bone pain is a real challenge in oncology. The physicians' options get limited to large doses of opiates or radionuclide therapy when the pain is from multiple bone metastasis. Quality of life often deteriorates due to sedation and constipation when large doses of opiates, necessary for pain relief, are used. Currently, radionuclides are an optimal choice. To be effective, bone pain palliation radiopharmaceuticals must be able to confront the basic behavior of cancer spread to bone. Bone metastases tend to appear at different locations at different times. An ideal bone pain palliation radiopharmaceutical should therefore satisfy the following requisites:

1. Most of the administered radioactivity should concentrate in bone, preferably at the metastatic site.

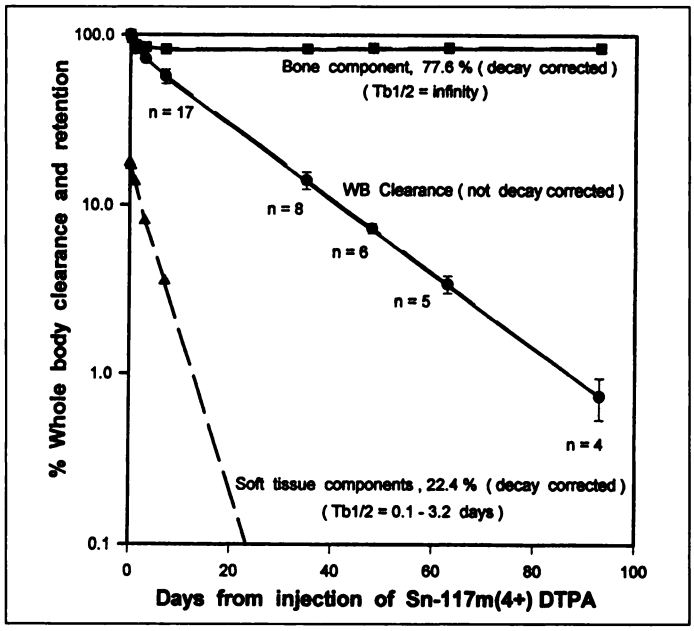

FIGURE 4. Whole-body clearance and retention of ^{117m}Sn(4+)DTPA measured by the dual-head gamma camera method shows two components. The soft-tissue component, accounting for 22.4% of the dose, shows four compartments (mainly urinary excretion) with a biologic half-life ranging from 0.1 to 3.2 days. The bone component accounts for the remaining 77.6% of the dose and shows no biologic excretion.

TABLE 3
Comparison of Percent Dose Whole-Body Retention and Nuclear and Physical Characteristics of Radiopharmaceuticals Suitable for Bone Pain Palliation

Percent whole-body retention				
Days post-therapy	^{117m}Sn-DTPA	^{186}Re-HEDP	^{153}Sm-EDTMP	^{89}Sr-chloride
1	88.6		54 (*11,12*)	
3	83.9	30 (*9,10*)		
7	81.1			31 (22)
14	77.6			25 (22)
100	77.6			18 (22)
Nuclear and physical characteristics				
Half-life	13.6 days	90.6 hr	46.3 hr	50.5 days
Gamma photon keV (%)	159 (86%)	137 (9.2%)	103 (28%)	909 (0.0002%)
Maximum E_β (MeV)	NA	1.09	0.81	1.46
Average E_β (keV)	127* 152*	329	224	58
Range (mm)	0.2, 0.3	1.05	0.55	2.4

*Conversion electrons with discrete energy.
Whole-Body retention = (Dose − Urine excretion). NA = not applicable.

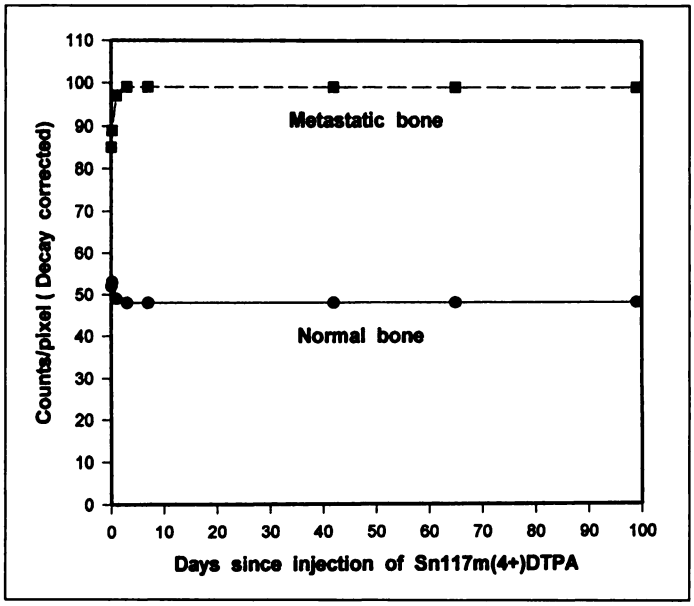

FIGURE 5. Uptake and retention of ^{117m}Sn(4+)DTPA by normal and metastatic bone in the same patient depicted in Figure 1. Note peak uptake by normal bone at 24 hr. The metastatic bone shows continued uptake, which reaches peak at 7 days. No biologic excretion is seen from either bone.

2. Once in the bone, it should not wash out of the bone to be taken up by soft tissue, resulting in unnecessary radiation or activity excretion in urine creating contamination problems.
3. Total administered activity should be small to enable outpatient treatment without requiring special monitoring or having the patient wait before discharge from the clinic.
4. Tracer half-life should be sufficiently lengthy to allow longer duration of action on all metastatic foci present at the time of injection and relieve pain from those that are currently painful, and prevent those that are currently painless from becoming painful during the 10 physical half-life of the radionuclide.
5. The half-life should be short enough to enable repeat pain palliation doses as and when new painful metastatic foci appear without raising concern for marrow suppression due to cumulative residual activity from previous doses.
6. The radiopharmaceutical should have particulate emission for therapy and a gamma photon for imaging and quantification.
7. It should not suppress bone marrow.
8. The amount excreted in the urine should be low enough so that radiation cystitis does not occur.

Relative Bone Uptake of Pain Palliation Radiopharmaceuticals

The mean whole-body ^{117m}Sn(4+)DTPA retention of 81.1% on Day 7 and 77.6% of the dose on Day 14 is the highest among the four bone pain therapy agents (Table 3). The high degree of bone uptake is also reflected in its low urinary excretion monitored for 14 days, a duration equal to one physical half-life of ^{117m}Sn. We could not find similar data in the literature for the other three agents, in which the urine has been collected for a duration equal to at least one physical half-life of the radionuclide. We would have overestimated the whole-body retention level had we collected urine for only 1 day (when 11.4% of the dose was excreted) and assumed that the rest was retained in the whole body. An additional 11.6% of the dose was excreted during the next 13 days.

A mean urinary excretion of 36.8% in 10 hr and 46% in 24 hr has been reported for ^{153}Sm-EDTMP (*11,12,14*). This leaves 54% of the administered dose for bone uptake at 24 hr (Table 3). Similarly, it has been reported that 45% of the dose is excreted in the urine at 5 hr and 70% in 3 days with ^{186}Re-HEDP, leaving only 30% of the dose for bone uptake at 72 hr (*9*). Since the duration of urine collection was short (less than one physical half-life of the radionuclide) with both ^{153}Sm-EDTMP and ^{186}Re-HEDP, it is not known how much is excreted in the urine during one physical half-life of the agent. We were also unable to find definitive urinary excretion values for ^{89}Sr in the published literature. Blake et al. (*21*) reported collecting urine in 14 patients for 96 hr with ^{85}Sr and ^{89}Sr, but the value for urine excretion as the percent of the injected dose was not reported. The lack of an easily measurable gamma photon with ^{89}Sr or a high gamma photon energy (514 keV) associated with ^{85}Sr make quantification imprecise for strontium. Firusian et al. (*6*), based on rabbit data, made an assumption of 30%–80% of ^{89}Sr uptake into bone. The whole-body retention curve for ^{85}Sr and ^{90}Sr developed by Marshal et al. (*22*) in normal subjects shows an approximate 30% retention on Day 10, 25% on Day 30 and 18% on Day 100. This suggests that ^{85}Sr and ^{89}Sr are released from the bone after the initial uptake. Tin-117m(4+)DTPA, on the other hand, differs from ^{89}Sr in not showing any release from bone after the initial uptake (Fig. 4). The nonrelease from normal bone could be a disadvantage if it causes bone marrow suppression with the therapeutic dose. Our preliminary results have not shown bone marrow suppression with ^{117m}Sn(4+)DTPA. Further follow-up is needed to exclude such a possibility. It is not clear whether ^{186}Re-HEDP or ^{153}Sm-EDTMP washes out from bone after the initial uptake.

Therapeutic Doses of Pain Palliation Radiopharmaceuticals

Our preliminary results indicate that a dose of 10–20 mCi (370–740 MBq) per 70 kg body of ^{117m}Sn(4+)DTPA may be sufficient to achieve pain palliation (*23*). For ^{89}Sr, the FDA has approved a dose of 4 mCi (148 MBq) for adults. In clinical trials, doses ranging from 30 to 70 mCi with ^{186}Re-HEDP and 35 to 210 mCi with ^{153}Sm-EDTMP have been used for pain palliation (*9–13*). Relatively low levels of the administered dose along with low urine excretion of ^{117m}Sn(4+)DTPA lessens concerns about room contamination if there is an accidental urine spill or incontinence. After noticing significant room contamination in two patients, Eary et al. (*12*) had the remaining patients catheterized after treatment with ^{153}Sm-EDTMP to avoid room contamination from urine spill. The 4-mCi (148 MBq) dose of ^{89}Sr does not seem to raise much concern for room contamination. Low administered activity with both ^{89}Sr and ^{117m}Sn(4+)DTPA appear to have advantages over ^{186}Re-HEDP and ^{153}Sm-EDTMP, which may require additional radiation monitoring because of the high levels of administered and excreted radioactivity. However, the 50.5-day half-life of ^{89}Sr does pose a problem for long-term storage of needles, syringes and gloves used during injection.

Mechanism of Uptake of Bone Pain Palliation Radiopharmaceuticals

Strontium-89 uptake is attributed to an exchange mechanism with calcium of the hydroxyapatite crystal in the bone mineral matrix (*6*). Samarium-153-EDTMP and ^{186}Re-HEDP bone uptake is thought to be similar to that of ^{99m}Tc-diphosphonates through a process called chemisorption (*9–13,24*). Tin is a known bone seeker, and bone uptake of ^{117m}Sn(4+)DTPA is attributed mainly to tin and the role of DTPA being primarily to confer high in vivo stability (*15*). Stannic (4+) status is very important to further enhance net bone uptake without undergoing competitive side reactions (*25*). In mice, 53.8% of ^{117m}Sn(4+)DTPA was taken up by the bone in contrast to only 30.8% uptake with ^{117m}Sn(2+)DTPA (*15,16*). In addition, the blood and soft-tissue clearances of the stannic chelates were much faster than those of the stannous chelates (*15,16*).

Acquisition and Storage of Therapeutic Doses

A physical half-life of 13.6 days and excellent chemical stability allow multiple doses of ^{117m}Sn(4+)DTPA to be acquired and stored for up to 6–8 wk, characteristics quite similar to ^{89}Sr. Not much activity is lost due to decay if one has to wait several days to administer the dose to another patient when the intended patient declines treatment. Such is not the case with ^{153}Sm and ^{186}Re, which decays rapidly due to their short physical half-lives (Table 3).

CONCLUSION

The duration of pain palliation with ^{117m}Sn(4+)DTPA in the pilot studies has ranged from 3 to 14 mo following a single administration. In one of our patients (Fig. 1), who had not responded to a single dose of ^{89}Sr a year earlier, pain palliation from each of two ^{117m}Sn(4+)DTPA doses lasted for 4 mo. The degree of pain relief post-therapy was 100% on both occasions. Partial to complete pain palliation has been observed in about 85%

of 36 patients studied at VAMC and BNL (*23*). We anticipate the total therapeutic dose to be between 10–20 mCi (370–740 MBq) for a 70-kg patient. Favorable biokinetic, nuclear physical and chemical characteristics combined with our preliminary pain palliation results suggest that ^{117m}Sn(4+)DTPA meets most of the requirements for an ideal bone pain palliation agent (Table 3). Double-blind studies comparing the results with a placebo or the FDA-approved ^{89}Sr-chloride are required before final judgments are made on this new agent. An application to the FDA to begin Phase III clinical trials is under preparation.

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Scintigraphic Assessment of Therapeutic Success in Aldosteronomas Treated by Transcatheter Arterial Embolization Using Absolute Ethanol

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Adrenocortical scintigraphy was examined as an indicator of therapeutic success in aldosteronomas treated by transcatheter arterial embolization (TAE) with absolute ethanol (AE). **Methods:** Adrenocortical scintigraphy was performed 7 days after intravenous injection of 37 MBq ^{131}I-6-β-iodomethyl-19-norcholesterol before and after TAE. Complete or incomplete therapeutic success was determined by periodic measurements of the levels of plasma aldosterone and correlated with the scintigraphic results. **Results:** The aldosteronoma was visualized as a hot nodule in nine patients and a warm nodule in one patient before TAE. Scintigraphy showed a hot, residual hot or warm nodule on seven occasions (six occasions after the first TAE and one occasion after the second TAE) when the techniques were incompletely successful and disappearance on seven occasions when success was achieved (three occasions after the first TAE and one occasion after the second TAE). Of the seven occasions when TAE was unsuccessful, four patients received the second or third TAE to result in complete destruction of the aldosteronoma; three patients underwent unilateral adrenalectomy. **Conclusion:** Adrenocortical scintigraphy can correctly predict the effect of TAE on aldosteronomas and is a valuable indicator for decisions on the necessity of repeated TAE or adrenalectomy.

Key Words: adrenal gland; primary aldosteronism; transcatheter arterial embolization; absolute ethanol

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Primary aldosteronism is one of the causes of secondary hypertension. Its incidence is assumed to be <2% of hyperten-