

Tin-117m(4+)-DTPA for Palliation of Pain from Osseous Metastases: A Pilot Study

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The physical and biological attributes of $^{117m}\text{Sn}(4+)\text{-DTPA}$ indicate that it should be an effective agent for palliative therapy of painful bony metastatic disease. The aim of this study was to evaluate whether or not this agent could effectively reduce pain while sparing the hemopoietic marrow from adverse effects. **Methods:** Fifteen patients (10 males and 5 females) with painful bony metastases from various primary cancers were included in the study. Seven patients received 1.22 to 3.11 MBq/kg of ^{117m}Sn intravenously (Group 1) and eight patients received 4.85 to 5.77 MBq/kg (Group 2). All but one were treated as outpatients and followed for a minimum of 2 mo. **Results:** In the first group, pain relief was nonassessable in four patients because of death or additional treatment of soft-tissue disease by another modality. One patient had no relief of pain, one had complete relief of pain and one had transient relief of pain. No myelotoxicity was observed. For Group 2, three patients achieved complete relief of pain, two good relief, two partial relief and one began to experience pain relief when he suffered a pathological fracture 2 mo post-treatment. None of these patients had myelotoxicity. **Conclusion:** Tin-117m(4+)-DTPA can reduce pain from metastatic disease to bone without inducing adverse reactions related to bone marrow. Further studies are needed to assess tolerance levels for the bone marrow and to evaluate response rates and duration of effect.

Key Words: tin-117m-DTPA; pain palliation; bone metastases

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Biological and physical properties of stannic chelates, particularly $^{117m}\text{Sn}(4+)\text{-DTPA}$ (1), are useful treatment agents to relieve pain resulting from metastatic disease to bone. In contradistinction to other agents used for this purpose, ^{117m}Sn is not a beta emitter; it decays by isomeric transition with the emission of abundant (114%) conversion electrons of specific energy (127-129, 152 keV). These have a short, discrete range in tissue, approximately 0.3 mm, and therefore should result in reduced absorbed dose

to marrow. Is this range, however, sufficient to have an effect on tumor deposits in bone and thus relieve pain?

An earlier report discussed the biological distribution of $^{117m}\text{Sn}(4+)\text{-DTPA}$ in humans and provided dose estimates (2). The results of this study were a bone surface absorbed dose of approximately 54 mGy/MBq (200 rads/mCi) in men, a red marrow absorbed dose of about 5.94 mGy/MBq (22 rads/mCi) and all other tissues received no more than one-tenth the marrow absorbed dose. These results, however, were obtained from patients with advanced metastatic disease and not from normal individuals. Therefore, these dose estimates only provide a starting point from which to begin a clinical efficacy study and to evaluate adverse radiation effects. In this Phase II study, we attempt to answer the question asked earlier as well as evaluate the radiation effects on bone marrow.

METHODS

The production of $^{117m}\text{Sn}(4+)\text{-DTPA}$ used a previously described method (2). In short, ^{117m}Sn was produced with the neutron in elastic scattering reaction $^{117}\text{Sn}(n, n'\gamma)^{117m}\text{Sn}$. The enriched ^{117}Sn (84%) was obtained from Oak Ridge National Laboratory as oxide and was converted to metal by reduction at 600°C with hydrogen gas. The targets varied in mass between 26 and 83 mg, were encapsulated in quartz ampules and irradiated at either the High Flux Beam Reactor at Brookhaven National Laboratory for up to 28 days or at the High Flux Isotope Reactor at Oak Ridge National Laboratory for approximately 21 days. The end of bombardment specific activity averaged 2.2 mCi/mg from Brookhaven and 7.9 mCi/mg from Oak Ridge.

After irradiation, the sample was dissolved in concentrated HCl with heat and then added to a 20-fold molar excess (with respect to tin) of the acid salt of DTPA (pH 6). The pH was readjusted to 6 with NaOH and the solution was heated at 100°C for 30 min to insure complexation. A 2-fold equivalent excess of 30% H_2O_2 was added after cooling and the sample was reheated in a boiling water bath for 5 min. After cooling, an 80% molar amount of $\text{CaCl}_2\cdot 2\text{H}_2\text{O}$ (based on DTPA) was added and the preparation was sterile-filtered. Radiopharmaceutical quality was tested by paper chromatography, HPLC, and animal biodistribution studies, and it was checked for sterility and pyrogenicity (2).

Fifteen patients (10 men, 5 women) were enrolled in the study; the selection criteria are shown in Table 1. Five patients had primary breast carcinoma, six had prostate carcinoma and three

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TABLE 1
Patient Selection Criteria for Treatment with $^{117m}\text{Sn}(4+)\text{-DTPA}$

had primary lung carcinoma. One patient had an unknown primary carcinoma. The patients were divided into two groups, according to dose administration. Group 1 (seven patients) received approximately 2.64 MBq/kg body weight with a range of 1.22–3.11 MBq/kg (71.4 $\mu\text{Ci}/\text{kg}$, range 33–84 $\mu\text{Ci}/\text{kg}$). This level of radioactivity was calculated to be at half the threshold at which myelotoxicity would be expected based on our earlier study (2). Group 2 received 5.29 MBq/kg with a range 4.85–5.77 MBq/kg (143 $\mu\text{Ci}/\text{kg}$; range 131–156 $\mu\text{Ci}/\text{kg}$) when no myelotoxicity was encountered with the first group. The protocol was approved by the institutional review boards of each participating organization and the United States Food and Drug Administration. All subjects gave informed consent.

Prior to initiation of therapy, a ^{99m}Tc -MDP bone imaging study was obtained. Complete blood counts, including differential and platelet counts, electrolytes and blood chemistries were also obtained. No radiotherapy or chemotherapy had been administered in the prior month. Hormonal therapy was continued if the patient had been on therapy for more than 3 mo without improvement in their clinical status.

Tin-117m(4+)-DTPA was administered through an indwelling infusion line for 5–10 min. The patient was observed for 2 hr, during which time a urine specimen was obtained. A complete urine collection was obtained over 4 days as well as a blood specimen on the fourth day postinjection to calculate extracellular fluid concentration. This enabled estimation of bone uptake (2):

(percent bone uptake = % whole-body retention – % in extracellular fluid).

TABLE 2
Pain Scale

0 = No pain
1 = Slight pain controllable by anti-inflammatory drugs
2 = Moderate pain
3 = Intense pain, controllable by anti-inflammatory drugs, analgesics and steroids
4 = Excruciating persistent pain, partially controllable by a wide range of drugs including narcotics

To monitor ^{117m}Sn distribution, two imaging studies were obtained the first week as well as repeat chemistries. Complete blood counts were obtained weekly for at least 2 mo and less frequently thereafter. A repeat ^{99m}Tc -MDP bone imaging study was performed 2 mo later.

Patients were given forms to maintain daily records of medication, pain levels and sites for 2 wk. These records were then maintained biweekly for 6 wk. Pain was evaluated on a scale from 0 to 4 (Table 2).

RESULTS

Data for Group 1 patients are given in Table 3. Partial relief was achieved when the pain score dropped at least two levels. Good relief was achieved when no pain was evident, but the patient still was using narcotics. Complete relief was defined as no pain and no analgesia required. Although four patients were nonassessable because they died (two patients) or required treatment of soft-tissue disease by other modalities (two patients), we evaluated marrow effects in all the patients and no myelotoxicity was evident (ECOG level toxicity). Pain relief was observed in two patients, partial relief in one and nearly complete relief in another. One patient with carcinoma of the prostate obtained no relief.

Because no toxicity was seen in the Group 1 patients, the dose was increased by a factor of two for Group 2 patients (Table 4). In this group of patients, more definitive reduction of pain could be observed. All patients were followed for 2 mo, except for one patient who died at 6 wk because of brain metastases, despite rapid and complete relief of level four pain from metastatic carcinoma of the

TABLE 3
Palliation of Bone Pain with $^{117m}\text{Sn}(4+)\text{-DTPA}^*$

Patient no.	Primary Tumor	MBq/kg	Total MBq	% in Bone	Result	Follow-up at 2 mo
1	Breast	2.15	172	65.1	na	Died less than 1 mo due to brain metastases
2	Breast	1.22	65	—	na	Required chemotherapy for soft-tissue disease
3	Lung	2.63	146	40.9	na	Required chemotherapy for soft-tissue disease
4	Prostate	2.85	174	80.1	No relief	Required radiotherapy
5	Lung	2.59	155	52.2	na	Died in 5 days due to cardiac tamponade
6	Unknown	2.89	311	60.0	Partial relief	Renewed pain at 2 mo
7	Prostate	3.11	183	81.2	Good relief	Complete relief 2 mo

*1.22–3.11 MBq/kg; single administration.
na = not assessable.

TABLE 4
Palliation of Bone Pain with $^{117m}\text{Sn}(4+)\text{-DTPA}^*$

Patient no.	Primary tumor	MBq/kg	Total MBq	% in Bone	Result	Follow-up
1	Lung	5.40	331	—	Complete relief	Died in 6 wk due to brain metastases
2	Breast	5.25	311	72.1	Good relief	Pain recurred at 2 mo
3	Breast	5.00	296	59.2	Good relief	Decreased WBCs from chemotherapy 3 mo
4	Prostate	5.77	387	58.0	Partial relief	10 wk
5	Prostate	5.77	535	34.1	Complete relief	5 mo
6	Prostate	4.85	573	71.3	Complete relief	5 mo
7	Breast	5.59	279	69.2	Partial relief	Refused follow-up
8	Prostate	5.40	378	83.2	Improving	Path fx, 2 mo

*4.85–5.77 MBq/kg; single administration.

lung. In all, four patients had complete relief or at least a reduction of pain of two levels and three had partial relief of pain. An initial flare response in the first 7–10 days was noted in two patients with prostate cancer. Both patients subsequently had good relief of pain. A common response to treatment in a patient with prostate cancer is shown in Figure 1.

In one patient with metastatic carcinoma of the breast, low white blood cell counts were observed. The patient, however, had completed a chemotherapy course 2 mo before and had a diminished white blood cell count at the time of treatment. Her white cell count dropped from 3400/mm³ to 2000/mm³ (ECOG level 2, moderate toxicity) within 1 wk and remained at that level throughout the observation period. No change was noted in the platelet count, which always remained within normal limits. Platelet and white blood cell counts remained at normal levels in all other patients (Fig. 2).

Monitoring ^{117m}Sn distribution was readily accomplished by imaging the 158.6 keV gamma photon. The

pattern always followed that of the $^{99m}\text{Tc-MDP}$ images obtained prior to initiation of therapy (Fig. 3). One patient who had lung cancer died 5 days after dose administration because of a sudden pericardial tamponade. A 4-mm section of his spine was obtained for autoradiography which was performed by sandwiching the specimen between two sheets of x-ray film (Fig. 4). Interestingly, the images show some differences because of the shorter penetration of the conversion electrons through the thickness of the specimen.

DISCUSSION

Our earlier study gave favorable values for the use of $^{117m}\text{Sn}(4+)\text{-DTPA}$ as a therapeutic agent for pain palliation in patients with diffuse metastases to bone (2). The high bone surface-to-red marrow absorbed dose ratio suggests that this agent would be effective without resulting in marrow toxicity. The results in this study indicate that the dosage used is an effective range.

Studies with $^{153}\text{Sm-EDTMP}$ suggest that the theoretical marrow absorbed dose limit can be exceeded by a wide

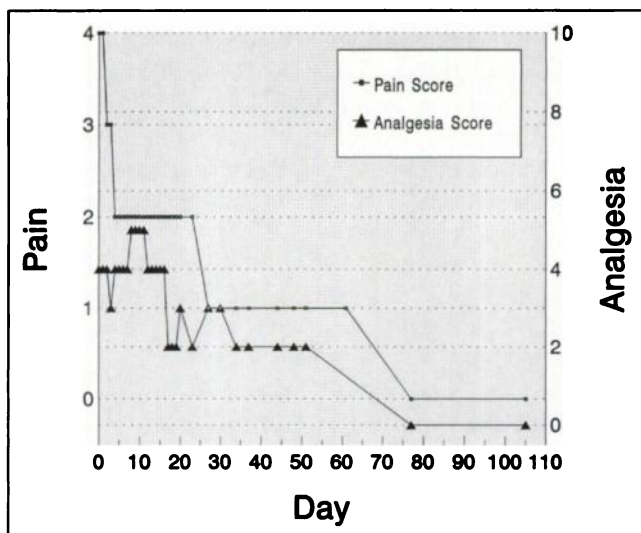


FIGURE 1. Response to $^{117m}\text{Sn}(4+)\text{-DTPA}$ in a patient with prostate carcinoma metastatic to bone. Analgesia score refers to number of doses required per day. See Table 2 for pain score.

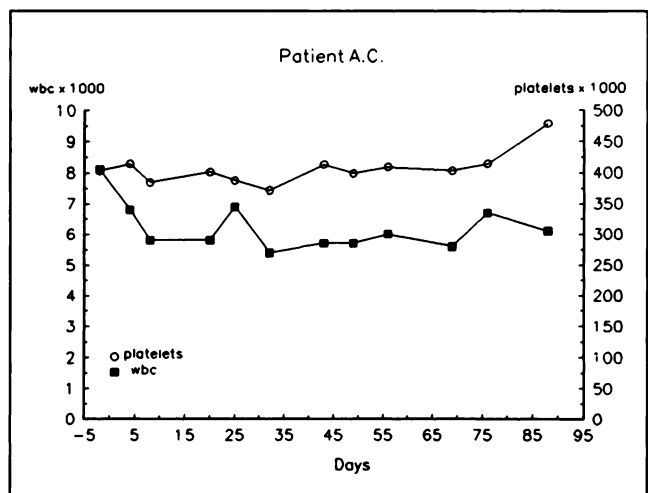


FIGURE 2. Time course of white blood cell and platelet counts in a patient with prostate carcinoma who received 387 MBq (5.77 MBq/kg) $^{117m}\text{Sn}(4+)\text{-DTPA}$.

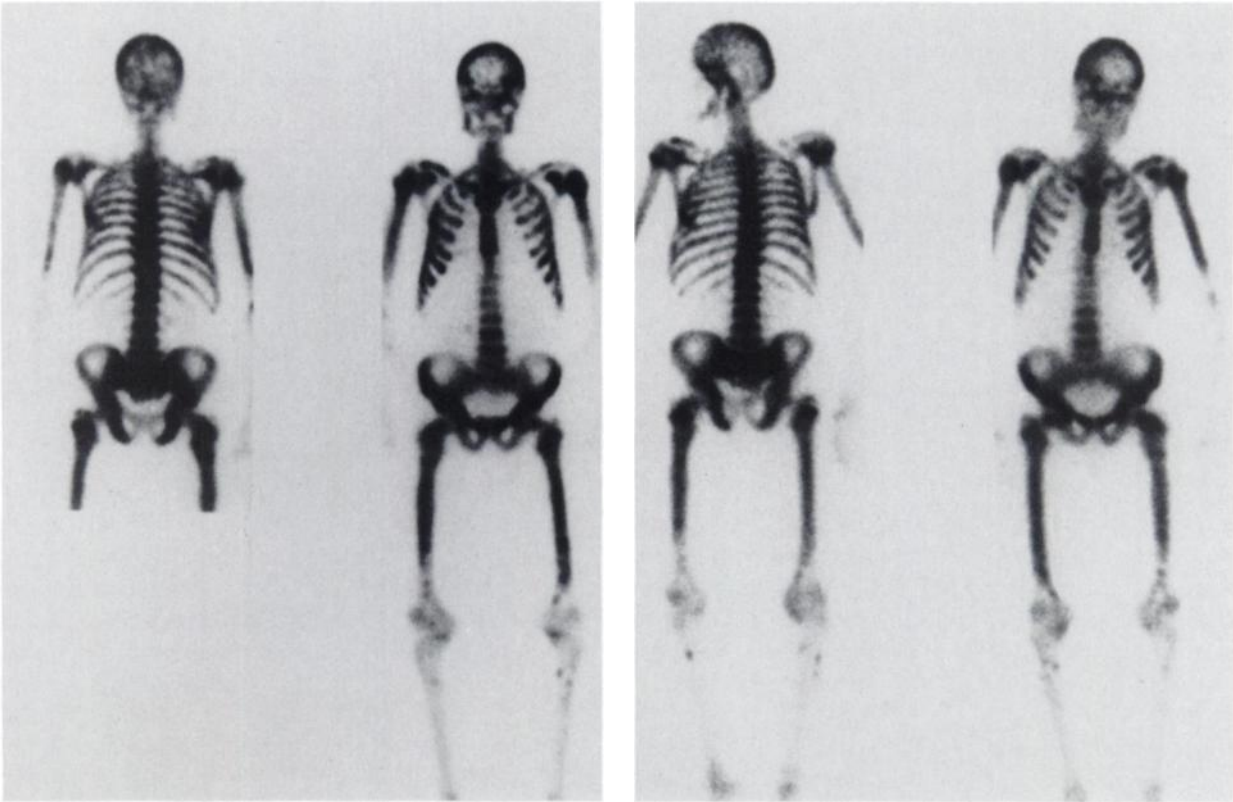


FIGURE 3. Bone scintigraphy of a patient with advanced osseous involvement of the skeleton with prostate carcinoma. The ^{99m}Tc -MDP examination (left) was performed just prior to treatment and the $^{117m}\text{Sn}(4+)\text{-DTPA}$ examination (right) was performed 8 days following administration with less than half the photon yield used in the ^{99m}Tc -MDP study. There is exact correlation of radioactivity distribution in these two "superscans."

margin before toxic effects are observed (3). The reason for this is probably twofold. First, distribution of radioactivity onto bone surfaces is nonuniform because it is a function of metastatic distribution, resulting in sparing large volumes of red marrow, which can then repopulate irradiated areas. Second, tolerance limits for effects from marrow irradiation are derived from acute doses of external radiation (4). The radiation absorbed dose from unsealed radionuclide sources is delivered with a dose rate that is relatively low and decreases exponentially over time, thereby resulting in lesser biological effects (5).

It is likely that much higher levels of radioactivity may be safely delivered. The successful palliation achieved in some of our patients encouraged us to proceed with further evaluation of this agent. Therefore, a dose escalation trial to examine the maximum tolerated dose is underway. Based on work with other agents, an increase in absorbed dose may not result in improved pain palliation beyond a certain point, even before toxicity is encountered (6). What is unknown is whether or not the duration of pain relief correlates with dose and whether higher doses delay the appearance of new metastases.

In this study, we have demonstrated that pain palliation can be achieved with $^{117m}\text{Sn}(4+)\text{-DTPA}$ without evidence of marrow toxicity, a common but undesirable toxic side effect with some bone pain palliation products. The excellent physical characteristics of ^{117m}Sn further support its

usefulness and extends the list of radiopharmaceuticals used for palliation. The physical half-life (13.6 days) is reasonable in terms of shelf life compared to the relatively short-lived ^{186}Re or ^{153}Sm and may be particularly useful in improving the target-to-nontarget ratio. This physical half-life is almost the same as that for ^{32}P , which has been used for 40 yr with good symptomatic response but with considerable myelotoxicity because of its energetic beta emission and concentration in hemopoietic cells.

The chemical stability of this agent is excellent, allowing unrefrigerated storage for at least 1 mo. The 158.6 keV gamma photon (86%) is also excellent for monitoring distribution and for comparison with standard bone imaging radiopharmaceuticals. The level of radioactivity required



FIGURE 4. Images of a spine specimen obtained at autopsy from a patient who died 5 days following administration of 155 MBq (2.59 MBq/kg) $^{117m}\text{Sn}(4+)\text{-DTPA}$. (Left) x-ray of the specimen. A region of radionecrosis from previous radiotherapy (arrowhead) does not take up the tracer. There are different areas of uptake in the two autoradiographs because of the limited penetration of the conversion electrons through the 4-mm thick specimen.

can be delivered simply without excessive dose to personnel or family members and does not require hospitalization or any unusual procedures. If the results from this study are confirmed in further clinical trials, $^{117m}\text{Sn}(4+)\text{-DTPA}$ may be the product of choice for bone pain palliation therapy. The reduced marrow toxicity will allow subsequent treatment options for the patient (including retreatment) that may not be possible following the use of other more toxic radiopharmaceuticals. It is estimated that therapeutic quantities of ^{117m}Sn can be produced at reasonable cost.

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