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NUCLEAR, CHEMICAL, AND MECHANISTIC CONSIDERATIONS  
 IN THE USE OF  $^{117m}\text{Sn}(4+)$ -DTPA RELATIVE TO  $^{186}\text{Re}$ -HEDP  
 AND OTHER AGENTS FOR BONE PAIN THERAPY.

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INTRODUCTION

In previous studies designed to understand the mechanisms involved in the use of tin as a reducing agent for  $^{99m}\text{Tc}$ , it was discovered that  $\text{Sn}(4+)$ -DTPA is taken up almost exclusively by bone (1). Its biological distribution and uptake into normal as well as diseased bone are very similar to those of  $^{99m}\text{Tc}$ -MDP and other bone seeking radiopharmaceuticals in animals (2) and in humans (3). These observations, combined with the favorable nuclear and physical properties of  $^{117m}\text{Sn}$  compared to other bone localizing radiopharmaceuticals (Table 1) suggested the use of  $^{117m}\text{Sn}(4+)$ -DTPA for treating pain resulting

Table 1. Physical Characteristics of Radionuclides Useful for Bone Pain Therapy

Nuclide	Maximum $E\beta$ (MeV)	Weighted Average <sup>1</sup> $E\beta$ (MeV)	Average <sup>2</sup> Range (mm)	Half-Life (days)	Gamma Photons (MeV (%))
$^{89}\text{Sr}$	1.46	0.583	2.4	50.5	None
$^{186}\text{Re}$	1.08	0.329	1.05	3.71	0.137 (9.2)
$^{153}\text{Sm}$	0.81	0.225	0.55	1.93	0.103 (28)
$^{32}\text{P}$	1.71	0.695	3.0	14.3	None
$^{117m}\text{Sn}$	0.127 <sup>3</sup> 0.152 <sup>3</sup>		0.21 <sup>4</sup> 0.29 <sup>4</sup>	13.6	0.159 (86)

<sup>1</sup> MIRD: Radionuclide Data and Decay Schemes, Society of Nuclear Medicine, 1989.

<sup>2</sup> In water, Health Physics and Radiological Handbook, Nuclear Lectern Associates, 1984

<sup>3</sup> Monoenergetic conversion electron

<sup>4</sup> Discrete travel of emitted conversion electron (not an average)

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from metastatic disease to bone. In contradistinction to other agents, which are either available ( $^{89}\text{SrCl}_2$ ) or are being developed ( $^{186}\text{Re-HEDP}$ ,  $^{153}\text{Sm-EDTMP}$ ) for this purpose,  $^{117\text{m}}\text{Sn}$  is not a beta emitter. It decays by isomeric transition with the emission of monoenergetic conversion electrons (127, 129, 152, and 155 keV with a combined abundance of 110%). Because of their much limited and discrete range (0.2-0.3 mm) in tissue, these electrons should permit large bone radiation doses without excessive radiation to the bone marrow. In a human biodistribution study, the dose to bone surfaces was approximately 58 mGy/MBq, with a bone surface to marrow dose ratio of 10:1 (3). The  $t_{1/2}$  of 13.6 d provides intermediate dose rate and allows an adequate shelf life. A preliminary dose escalation therapy trial in patients has given very encouraging results. Of over twenty patients treated so far at the 2.5-8.5 MBq/kg levels, most experienced partial to good relief of pain without experiencing bone marrow suppression (Figure 1).

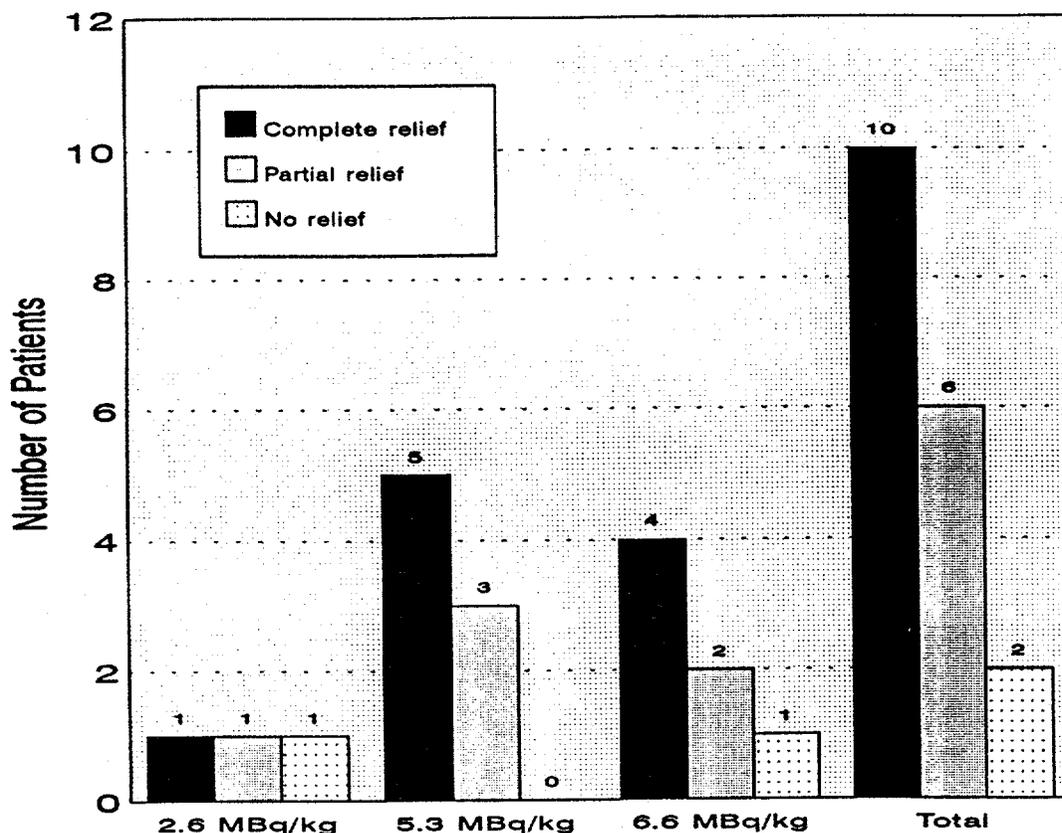


Figure 1. Bone pain palliation with  $^{117\text{m}}\text{Sn}(4+)$ -DTPA. Dose escalation results in patients following a single administration of an average of 2.6 MBq, 5.3 MBq, or 6.6 MBq/kg. Duration of relief lasted from 2 weeks to over 6 months, based on period of follow-up and other factors. None of the treated patients experienced marrow toxicity.

## **DISCLAIMER**

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This paper summarizes the results of our mechanistic studies on  $^{117m}\text{Sn}(4+)$ -DTPA to determine (i) the effect of oxidation state and specific activity of  $^{117m}\text{Sn}$ , (ii) effect of the addition of calcium, (iii) the nature of chemical species of tin in blood and urine, and (iv) kinetics of uptake and washout of radioactivity from bone relative to technetium, rhenium, and samarium bone agents.

## METHODS

Studies on the effect of the oxidation state were done using no-carrier-added  $^{113}\text{Sn}$  as well as  $^{117m}\text{Sn}$  produced either at the High Flux Beam Reactor at BNL or the High Flux Isotope Reactor at ORNL using the  $^{117}\text{Sn}(n,n'\gamma)^{117m}\text{Sn}$  reaction. Technetium-96 ( $t_{1/2}$  4.4d) was produced in the BLIP facility at BNL using the  $^{103}\text{Rh}(p,3p5n)^{96}\text{Tc}$  reaction (4). Technetium-96(Sn)-HEDP,  $^{186}\text{Re}(\text{Sn})$ -HEDP and  $^{153}\text{Sm}$ -EDTMP were either obtained or prepared as described earlier (5). Tin-117m(4+)-DTPA was prepared using the previously described method (3). Briefly, enriched  $^{117}\text{SnO}_2$  was reduced to  $^{117}\text{Sn}$  metal in a stream of  $\text{H}_2$  at  $650^\circ\text{C}$ . The  $^{117}\text{Sn}$  metal was transferred into a quartz ampule and sealed for irradiation. The irradiated tin was dissolved in conc. HCl inside a  $\text{N}_2$  filled glove box. A 20-fold molar excess of the acid salt of DTPA, adjusted to pH 6, was added and the pH of the mixture readjusted to 6 with NaOH. The solution was heated at  $100^\circ\text{C}$  in a boiling water bath for 5 min and then cooled. Two equivalents (over tin) of 30%  $\text{H}_2\text{O}_2$  were added and the solution was heated again for 5 min at  $100^\circ\text{C}$ . After cooling, an 80% molar amount (compared to DTPA) of  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  was added and the solution sterile filtered through a  $0.22 \mu\text{m}$  filter. HPLC methods were developed to characterize radiochemical purity and the oxidation state of tin in the administered radiopharmaceutical. Biodistribution studies were performed in normal mice and rats. In mice experiments, data were normalized to a 25 g body weight. Due to difference in the age group of the animals in various batches, concentration into bone was variable. Samples of blood and urine were obtained from patients undergoing the therapy trials.

## RESULTS AND DISCUSSION

Tin (4+)-DTPA gave higher bone uptake, and much faster blood and soft tissue clearance compared to Sn(2+)-DTPA in mice (Table 2). HPLC using C-18 columns with ion pairing (pH 4, 0.05M acetate, 0.002M  $\text{Bu}_4\text{NOH}$ , 5-10% MEOH after 8 min) or  $\mu\text{NH}_2$  columns (pH 4, 0.2M  $\rightarrow$  0.5M acetate after 6 min) gave a good separation of Sn(4+) ( $V_e/V_o = 1.75$  and 1.70 respectively for the two column systems). The stannous species, however, trailed in the C-18 column ( $V_e/V_o$  ranging from 1 to 5). The columns and the solvent systems need further optimization to provide simultaneous and more quantitative separations of the Sn(2+) and Sn(4+) species.

Table 2. Effect of Tin Oxidation State (Sn(4+) vs. Sn (2+)) on Biodistribution of <sup>117m</sup>Sn-DTPA in Normal Mice<sup>1</sup>

Bone to Tissue Ratio	Percent Sn(4+)-DTPA <sup>2</sup>			
	0	20	50	100
Blood	3	8	20	378
Spleen	12	16	22	36
Liver	4	6	15	13
Kidney	4	5	9	10
Muscle	91	120	108	128
Bone uptake (% Dose g <sup>-1</sup> )	8.0	8.4	9.7	10.2

<sup>1</sup>24h after injection, n=5; 2-3 mg/kg tin, 136-200 mg/kg DTPA.

<sup>2</sup>Synthetic mixtures of Sn(2+)- and Sn(4+)-DTPA were used.

The addition of up to 80% mole equivalent of calcium to tin-DTPA had no effect on the biodistribution but it rendered the radiopharmaceutical much less toxic (6). Studies on the effect of carrier tin and DTPA mass in mice at 24 h indicate that bone to blood, muscle, and kidney ratios are improved with increase in the amount of the carrier with no significant change in the absolute bone uptake (Table 3). Radioactivity excreted into the urine in patients was

Table 3. Effect of Carrier Tin on Biodistribution of <sup>117m</sup>Sn(4+)-DTPA in Mice<sup>1</sup>

Tissue	Bone to tissue Ratio			
	No-carrier-added <sup>2</sup>	Carrier tin present, mg/kg		
		0.072	0.338	1.61
Blood	48	675	746	1005
Spleen	46	88	98	124
Liver	14	20	21	27
Kidney	2	8	9	16
Muscle	54	185	231	316
Bone uptake (% Dose g <sup>-1</sup> )	11.0	11.6	11.8	11.1

<sup>1</sup> 24h after injection; n=5.

<sup>2</sup> <sup>113</sup>Sn used in this experiment.

shown to be intact Sn(4+)-DTPA by paper chromatography. When the urine was injected into mice, distribution corresponding to Sn(4+)-DTPA was observed (Table 4).

Table 4. Biodistribution (% ID/g) of  $^{117m}\text{Sn}(4+)\text{-DTPA}$  in Normal Mice

Organ	Original preparation	Patient urine
Bone	16.8 ± 2.0	17.9 ± 1.2
Blood	0.015 ± 0.003	0.017 ± 0.005
Liver	0.287 ± 0.029	0.756 ± 0.067
Kidney	0.729 ± 0.065	0.718 ± 0.079
Spleen	0.086 ± 0.024	0.662 ± 0.21
Stomach	0.062 ± 0.020	0.064 ± 0.015
Muscle	0.131 ± 0.082	0.078 ± 0.056
Whole Body	44.5 ± 3.1	43.6 ± 3.8
(% Remaining)		

The bone uptake and wash off of the various agents ( $^{96}\text{Tc}(\text{Sn})\text{-HEDP}$ ,  $^{117m}\text{Sn}(4+)\text{-DTPA}$ ,  $^{186}\text{Re}(\text{Sn})\text{-HEDP}$  and  $^{153}\text{Sm}\text{-EDTMP}$ ) in normal rats were monitored and compared for 192 h after injection (5). Bone wash off was calculated by dividing each bone uptake value by the maximum bone uptake value (reached at 3 h for all agents except for  $^{117m}\text{Sn}(4+)\text{-DTPA}$  in which case it took 24 h). Both the  $^{186}\text{Re}$  and  $^{96}\text{Tc}$  agents continued to wash off the normal bone (58% and 14% respectively at 192 h), whereas the  $^{153}\text{Sm}$  compound did not show detectable wash off. The  $^{117m}\text{Sn}$  agent did not show significant initial wash off (until 72 h) but at 192 hr, the wash off was 14%. These data are

Table 5. Bone Uptake and Retention of the Various Agents in Normal Rats<sup>1</sup>

Time (h)	$^{96}\text{Tc}(\text{Sn})\text{-HEDP}$	$^{186}\text{Re}(\text{Sn})\text{-HEDP}$	$^{153}\text{Sm}\text{-EDTMP}$	$^{117m}\text{Sn}(4+)\text{-DTPA}$
3	2.9 ± 0.1	1.9 ± 0.2	2.6 ± 0.1	2.8 ± 0.4
24	2.9 ± 0.2	1.6 ± 0.2	2.6 ± 0.1	3.6 ± 0.2
72	2.5 ± 0.2	1.2 ± 0.1	2.7 ± 0.2	3.5 ± 0.1
192	2.5 ± 0.2	0.8 ± 0.1	2.6 ± 0.1	3.1 ± 0.2

<sup>1</sup>Percent injected dose per g bone; n=4

explained satisfactorily on the basis of the redox chemistries of the various radiometal centers. The agents based on samarium and tin, which are relatively redox inactive metals, remain deposited longer on the bone presumably as insoluble oxides. However, technetium and rhenium agents continue to leach out due to the tendency of these redox-active d-block metals to undergo in-vivo oxidation to the permetallate forms. Higher rhenium wash off correlates well with the greater tendency (over technetium) for reduced rhenium complexes to undergo in-vivo oxidation.

Based on the above nuclear, chemical, mechanistic, and clinical considerations, we conclude that  $^{117m}\text{Sn}(4+)$ -DTPA is a useful agent for palliation of bone pain from osseous metastases in cancer patients and extends the list of radiopharmaceuticals being used or developed for this purpose. It is effective at about 5-8 MBq/kg levels without evidence of marrow toxicity which is a common but undesirable side effect with some bone pain palliation agents. The physical half-life of  $^{117m}\text{Sn}$  is reasonable in terms of shelf life and may be particularly advantageous in improving the therapeutic ratio over shorter lived agents. Stability of the radiopharmaceutical preparation is excellent (over 3 months storage at ambient temperature). The 158.6 keV gamma photon (86%) is ideal for monitoring distribution and gives images comparable to the  $^{99m}\text{Tc}$  bone agents. Patient hospitalization may not be required.

It is likely that much higher levels of radioactivity may be safely delivered. These studies and other mechanistic work, currently in progress, may provide information on whether or not the degree and duration of pain relief can be improved or if there is a delay in the development of new metastases and/or an improvement in patient survival at higher doses.

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