BNL-83312-1999

1. Abstract

Project Title: **Tin-117m DTPA, A Radiopharmaceutical for the Treatment of Cancer-Related Bone Pain**

Objectives: The goal of this project at Brookhaven National Laboratory (BNL), in collaboration with the industrial partner Diatide (formerly Diatech), Inc., is to develop tin(Sn)-117m DTPA as a commercial radiopharmaceutical for the palliative therapy of cancer related bone pain. The invention, initial development, and preliminary Phase I/II clinical studies of Sn-117m DTPA for bone pain palliation have been accomplished at BNL. In contrast to competitive technologies, Sn-117m DTPA shows the potential for providing relief from bone pain without causing significant marrow toxicity which is a limitation of other radiopharmaceuticals either presently in use of those being developed for this application. An issued U.S. Patent and a second patent application on the tin-117m DTPA technology are assigned to the U.S. Department of Energy. Diatide, Inc., has obtained an exclusive license to this technology.

This project is designed to transfer the technology from BNL to Diatide, to identify the resources for and to establish the commercial manufacture of Sn-117m DTPA, and to complete the additional chemical, mechanistic, and Phase III clinical studies to support a New Drug Application (NDA). Specifically, BNL will conduct research and development studies to identify an optimal Sn-117m DTPA formulation and to characterize it chemically and biologically. The latter will include studies to determine how and in what form the dose is taken up by bone lesions. BNL will also participate in studies to develop a Sn-117 target suitable for commercial production of Sn-117m. BNL will transfer the technology to produce Sn-117m DTPA to Diatide, assist with the steps necessary to establish a commercial manufacturing operation, provide technical and scientific support during Phase III clinical trials, and assist with the preparation and submission of the NDA for FDA approval.

Project Performance Period: April 11, 1995 - April 10, 1998

Project Funding (by Fiscal Year) (DOE $): FY 95, 96, 97 @ $255K/yr.

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Principal Investigator(s) Organization: Brookhaven National Laboratory
Diatide, Inc.

2. Patentable or Potentially Patentable Inventions

"I am an owner, officer, or employee of a university, not-for-profit organization, or small business, and the information to be presented will contain information, data, or material pertaining to an invention, or inventions, made under a Government-funded contract grant that I believe is potentially patentable."

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RESEARCH SUMMARY

1. **Project Title:** **Tin-117m DTPA, A Radiopharmaceutical for the Treatment of Cancer-Related Bone Pain**

Principal Investigator: Suresh C. Srivastava

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2. **Principal Project Personnel**

BNL:

Suresh C. Srivastava, Ph.D., Principal Investigator; Time spent on project: 15%; See biosketch for additional information (Appendix 1)

George E. Meinken, M.S.
Thomas Martin, M.S.
Harold L. Atkins, M.D.

Diatide:

John Lister-James, Ph.D., Co-Principal Investigator
See biosketch for additional information (Appendix 1)

John E. Cyr, Ph.D.
Victor J. Becker, M.S.
Lorraine Baltzer-Cleri, M.S.

3. **Additional Information on BNL Project Personnel**

1. George E. Meinken, M.S.

Time spent on Project: 50%
Education: B.S. chemistry (RPI) 1968; M.S. Env. Science (NY Inst. Tech.), 1996.
Research expertise: Radiopharmaceutical chemistry, analytical methodology
Role: Carry out chemical and radiochemical investigations. In-vivo experimentation in mice. Provide technical support for the manufacture of tin-117m DTPA by the industrial partner.

2. Thomas Martin, M.S.

Time spent on project: 70%
Education: B.S. engineering chemistry (SUNY Stony Brook), 1987; M.S. chemistry (Adelphi Univ.), 1994.
Research expertise: Radiolabeling chemistry, quality control

Role: Carry out radiochemical and analytical experimentation using tin-117m DTPA. Assist with in-vivo work in mice.

3. Harold L. Atkins, M.D. (Collaborator)

Time spent on project: 40%
Education: B.S. (Yale Univ.), 1948; M.D. (Harvard Univ.), 1952.
Research expertise: Clinical nuclear medicine
Role: Carry out clinical work in patients. Prepare clinical protocols, assist Diatide with clinical issues.

4. Project Overview and Progress to Date

A. Specific Project Objectives

The goal of the project is to develop Sn-117m DTPA as a commercial radiopharmaceutical for the palliative therapy of cancer-related bone pain. The invention, initial development and preliminary phase I/II clinical studies of Sn-117m DTPA for bone pain palliation have been accomplished at BNL. In contrast to competitive technologies, Sn-117m DTPA provides relief from bone pain without causing bone marrow toxicity. An issued U.S. Patent and a second U.S. Patent Application on this technology are owned by Associated Universities, Inc. (AUI). Diatide, Inc (formerly Diatech) a company focused exclusively on radiopharmaceuticals, has obtained an exclusive license to this technology from AUI. This project is designed to transfer the technology from BNL to Diatide, Inc., to identify the resources for and to establish the commercial manufacture of Sn-117m DTPA, and to complete the additional chemical and mechanistic studies to permit Diatide to undertake the Phase III clinical studies needs to support a New Drug Application (NDA).

B. Technical Background/Industry Need:

Approximately 60-80% of patients with breast and prostate cancer and approximately 50% of patients with lung cancer will develop bone metastases. These three cancer types make up approximately 80% of 400,000 patients who develop bone metastases, per year, in the U.S. More than half of these patients experience severe, chronic pain, control of which is very important in clinical management. The pain results in immobility and a need for major narcotic analgesics. In many cases where cancer patients' survival time is relatively long, the quality of life progressively deteriorates to a very poor condition. A number of agents have been used for the palliation of bone pain from metastatic lesions primarily originating in breast and prostate cancers. Among these are phosphorus-32, strontium-89 chloride, samarium-153 EDTMP, rhenium-186 HEDP, and iodine-131 hydroxybenzylidene diphosphonate (HBDP). However, a limiting factor has been the absorbed dose to the red marrow which results in lower than desired bone to marrow dose ratios.

In previous studies at BNL designed to understand the mechanisms involved in the use of tin as a reducing agent for Tc-99m, it was discovered that Sn(4+)-DTPA is taken up almost exclusively by bone. Its biological distribution and uptake in normal as well as diseased bone are very similar to those of Tc-99m-MDP and other bone seeking radiopharmaceuticals in animals and humans. These observations, combined with the favorable nuclear and physical properties of Sn-117m suggested the use of Sn-117m(4+)-DTPA to treat pain resulting from metastatic bone disease. In contradistinction to other agents, which are either available (Sr-89 Cl_2; Metastron) or are being developed (Re-186-HEDP, Sm-153-EDTMP) for this purpose, Sn-117m is not a beta emitter. It decays by isomeric transition with the emission of monoenergetic conversion electrons (127, 129, and 152 keV with a combined abundance of 114%). Because of the much limited range (0.2-0.3 mm) in tissue, these electrons permit large bone radiation doses without excessive radiation to the bone marrow. The t½ of 13.6 d provides intermediate dose rate and allows a convenient shelf life. The 158.6 keV gamma photon (86%) is excellent for monitoring distribution and gives images comparable to the Tc-99m bone agents. In a human biodistribution study, the dose to bone surfaces (MIRDOSE 2) was approximately 215 rad/mCi, with a bone surface to marrow dose ratio of ~10:1.

Studies at BNL have continued to determine the effectiveness of Sn-117m-DTPA in a dose escalation therapy trial.

Preliminary Phase I/II clinical trials have confirmed that Sn-117m-DTPA in modest amounts (~140 μCi/kg) can provide palliative relief of pain from osseous metastases without resulting in myelosuppression. An agent such as Sn-117m(4+)DTPA, which irradiates bone metastases whilst sparing the radiosensitive bone marrow, is highly desirable. Development of this technology for commercialization is deemed very attractive.

C. Project Funding (FY 1995 through FY 1997)

Personnel	Year #1	Year #2	Year #3
S.C. Srivastava	0.15	0.20	0.15
G.E. Meinken	0.50	0.50	0.50
T. Martin	0.60	0.70	0.75
H. Atkins**	0.40	0.40	0.40
TOTAL FTEs	1.65	1.80	1.80
	Expenditures (in thousands)		
Direct & Allocated Costs	$175.0	$176.0	$176.0
Indirect costs - G&A	80.0	79.0	79.0
	$255.0	$255.0	$255.0
Funds - as provided	$255.0	$255.0	$255.0

**H. Atkins is a collaborator on the CRADA project. He does not receive salary for the effort reported above.
Total Participant Funds-in: $0
Total Participant In-Kind: $1,593K ($362K, 821K, and 410K, respectively, for years 1, 2, and 3).

D. Technical Approach:

(i) Define commercial dose (BNL and Diatide)

(ii) Develop a Sn-117 target to allow Sn-117m production scale-up (BNL and Diatide)

(iii) Establish manufacturing operation (Diatide, with help from BNL)

(iv) Prepare and submit New Drug Application (NDA) for FDA approval (Diatide)

BNL Role:

BNL will conduct research and development studies to identify an optimal Sn-117m DTPA formulation and to characterize it physically and biologically. The latter will include studies to determine how and in what form the dose is taken up by bone lesions. BNL will also participate in studies to develop a Sn-117 target suitable for commercial production of Sn-117m. BNL will transfer the technology of producing Sn-117m DTPA to Diatide, and assist Diatide with the steps necessary to establish a commercial manufacturing operation.

Partner Role:

Diatide will identify and secure a source of the enriched target isotope, Sn-117. With help from BNL, they will develop a Sn-117 target suitable for Sn-117m production scale-up to the commercial level. Primary and backup production sources (reactors) will be identified. Sn-117m target work-up and Sn-117m DTPA manufacturing operation will be established. Toxicology and dosimetry studies to support NDA filing will be undertaken. Phase III clinical trials will be conducted. An NDA will be prepared and submitted to the FDA.

E. Key Milestones:

FY 95	BNL: Define commercial dose
FY 95/96	Diatide: Establishment of manufacturing operation
FY 95/96	BNL: Completion of pharmacology studies
FY 97	Diatide: Completion of toxicology and clinical studies including dosimetry
FY 97	BNL: Complete mechanistic work, assess dosimetry information and clinical data
FY 98	Diatide: NDA submission

F. Progress To Date

(i) Summary

Diatide

Diatide has secured primary and back-up sources of Sn-117 target material, primary and back-up sites for irradiations and a sub-contractor, Golden Pharmaceuticals, Inc; (GPI) in Golden, Co. who will handle target work-up, final dose manufacture, QC and distribution. The manufacturing process has been established at the selected manufacturing site and qualified as producing final product which is equivalent to that prepared at BNL. Diatide has assumed responsibility for the IND, prepared an End-of-Phase II report/Phase III clinical protocol and conducted an End-of-Phase II/pre-Phase III meeting with the FDA. Clinical trials are expected to resume in September, 1996.

BNL

BNL has assisted Diatide in their efforts to initiate commercial manufacture of Sn-117m(4+)DTPA at GPI. A number of small scale production runs have been completed at GPI and the final products have been tested and validated at BNL for purity, homogeneity, and biodistribution. BNL will continue to provide scientific and technical support during scale up for Phase III clinical studies, planned to begin in September, 1996. Phase II clinical studies were completed at BNL and the VA Medical Center in Tucson, AZ. Based on the results of these studies in 47 patients and dosimetry calculations, the optimum dose range was chosen to be 10-20 mCi per 70 kg patient body weight.

Studies on the chemical composition and stability of the Sn-117m-DTPA have progressed. HPLC methods to analyze and separate Sn(4+) from Sn(2+), and to remove the bulk of the uncomplexed DTPA in the final product were developed. The effects of specific activity of Sn-117m and the oxidation state of tin on the biodistribution of Sn-117m(4+)DTPA were studied. Investigations have begun to elucidate the kinetics and the mechanisms of the bone uptake and excretion of tin-117m in mice.

(ii) Detailed Progress at BNL

a. Dose Selection

The optimum dose range for Phase III trials was determined to be 10-20 mCi per 70kg patient. We chose to suggest 10 mCi/70 kg to the FDA, based on a detailed analysis of the data from the

Phase I/II trials (Table 1) completed during FY 95, under BNL sponsorship. However, in response to comments from the FDA, during a meeting on February 7, 1996, Diatide will sponsor an extended Phase II/III trial in a total of about 400 patients. Three dose levels will be used: 5 mCi, 10 mCi and 20 mCi/70 kg. Strontium-89 chloride (Metastron) will be used as the fourth arm (control). These studies are expected to begin in September, 1996.

The optimum formulation of Sn-117m(4+)DTPA was established in collaboration with Diatide's manufacturing partner, GPI. Issues relating to specific activity, DTPA concentration, the addition of Ca^{++} ions, etc. were addressed.

GPI has carried out about 5 practice runs using stable tin as well as 4-100 mg quantities of HIFR (Oak Ridge) produced Sn-117m. BNL has provided continuous guidance for this work at GPI, and has evaluated the final product in terms of its quality and in-vivo performance (in mice). The streamlined GPI method to be used commercially was found to be practical, reliable, and reproducible. BNL will continue to work with Diatide/GPI to validate future clinical runs using ~>100 mg quantities of Sn-117, irradiated at Oak Ridge and at other places.

All preparations were assayed for Sn(4+)/Sn(2+) using a new HPLC procedure developed at BNL (Table 2). Chemical assays for Sn, Ca, and DTPA in the final product have not been carried out as yet. These will be done using future runs in collaboration with GPI.

b. Dose Characterization

Homogeneity of the Sn-117m(4+)DTPA was established using paper chromatography and HPLC (both reverse phase and ion exchange HPLC). Every sample prepared either at BNL or at GPI was studied at BNL using the optimized ion-exchange HPLC technique (see Table 2).

We have not yet isolated the tin-DTPA chelate out of solution in a form suitable for structural characterization. This task will be attempted during FY 97, probably in collaboration with an outside group with expertise in x-ray crystallographic studies.

c. Stability of the Dose

Stability of the various Sn-117m(4+)DTPA formulations at BNL as well as those carried at GPI have been investigated. Long-term studies of the material (3-6 month storage at 25°C) have been completed using several batches from BNL and two batches from GPI. The preparations were found to be completely stable as judged from the chromatographic analyses and mouse biodistribution data. Future commercial formulations (GPI) will also be evaluated for their stability against time, dilution, and other factors during FY 96/97. In-vitro methods (paper chromatography, HPLC, chemical assays) and biodistribution in mice will be utilized to determine the quality and the stability of the formulations.

Most of the formulations carried out at BNL and so far at GPI have been assayed for radionuclidic and radiochemical impurities. The optimum ranges based on these and other previous analyses have been established.

Assays for raw materials, and for chemical components, sterility, and apyrogenicity of the final product will be undertaken on GPI-prepared larger-scale clinical batches. These will be undertaken during FY 96 and 97 as the manufacturing operation proceeds at GPI.

d. Pharmacology

The kinetics of bone uptake and wash-off in mice and/or rats will be studied. Initial data were obtained earlier in a collaborative study with the University of Cincinnati (Table 3). Microautoradiographic studies will also be undertaken during FY 97.

In collaboration with the investigators at the VA Medical Center, Tucson, AZ, a pharmacokinetic analysis of the data from 17 prostate cancer patients was completed. These studies were done using the BNL-manufactured Sn-117m(4+)DTPA. This work has been accepted for publication in the *Journal of Nuclear Medicine*. Further studies are to continue.

e. Chemical and Mechanistic Investigations

We are initiating a dual-label study (using Sn-117m(4+)/C-14-DTPA in mice to determine the role of DTPA in the bone uptake and excretion of tin, and to possibly elucidate the mechanism of the binding of tin to bone. We will also study the chemical form of tin in blood (plasma and RBC) and in urine using ion-exchange HPLC. The effects of the tin oxidation state and carrier tin on biodistribution of tin in mice have been studied (Tables 4 and 5).

The chemical form of tin in 24-hour urine from patients appears unchanged from the original injected material. In one experiment, chromatographic analyses as well as mouse biodistribution data were essentially identical for the two samples of Sn-117m(4+)DTPA - the injectate and the material excreted in the urine (Table 6). These results attest to the high in-vivo stability of the tin-DTPA product.

A preliminary study on the role of the ratio of DTPA to tin in the biodistribution of Sn-117m(4+)DTPA in mice was completed (Table 7). It appears that it would be possible to remove the bulk of the DTPA from the final product prior to administration into patients without compromising the in-vivo distribution.

We will continue to provide scientific and technical support to Diatide and GPI during the Phase III clinical testing of commercially manufactured (at GPI) Sn-117m(4+) DTPA.

Table 1. Phase I/II Dose Escalation Trial with Sn-117m(4+)DTPA

Administered Activity	Patients Studied		Degree of Pain Relief*			
μCi/kg	Total	Not Assessable	Complete	Partial	None	Total % Response
71	9	4	0	3	2	60
143	10	2	4	3	1	88
179	10	2	3	3	2	75
229	10	1	1	4	4	56
286	11	1	4	5	1	90
Total	50	10	12	18	10	75

*Follow-up period ranging between 4 weeks to 14 months depending upon factors such as intervening death or being taken off protocol due to need for other therapy.

Table 2. HPLC Analysis of Tin-117m DTPA Samples*

Species	K' (Ve-Vo/Vo)
Ve	0
H_2O_2	0
Sn(4+)DTPA	1
Sn(2+)DTPA	3.8
DTPA	4.8

*DEAE 7.5x75 cm column; eluting buffer, pH 4.5 sodium phosphate, 0.05 M to 0.4 M gradient; flow rate 1.0 ml/min; uv (220 nm) and radioactivity detection.

Table 3. Bone Uptake and Retention of the Various Agents in Normal Rats[1]

Time (h)	^{96}Tc(Sn)-HEDP	^{186}Re(Sn)-HEDP	^{153}Sm-EDTMP	^{117m}Sn(4+)-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

[1]Percent injected dose per g bone; n=4. Studies done in collaboration with the University of Cincinnati.

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

Bone to Tissue Ratio	Percent Sn(4+)-DTPA[2]			
	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^{-1})	8.0	8.4	9.7	10.2

[1]24h after injection, n=5; 2-3 mg/kg tin, 136-200 mg/kg DTPA.
[2]Synthetic mixtures of Sn(2+)- and Sn(4+)-DTPA were used.

Table 5. Effect of Carrier Tin on Biodistribution of Sn-117m(4+)-DTPA in Mice[1]

Tissue	Bone to tissue Ratio			
	No-carrier-added[2]	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^{-1})	11.0	11.6	11.8	11.1

[1] 24h after injection; n = 5.
[2] Sn-113 used in this experiment.

Table 6. Biodistribution of tin-117m(4+)-DTPA in Normal Mice[1]

Organ	Material Injected	
	Original preparation	24 h 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 (% Remaining)	44.5 ± 3.1	43.6 ± 3.8

[1] 24h after injection; % injected dose per g tissue; n = 5

Table 7. Biodistribution of Sn-117m(4+)DTPA as a Function of the DTPA/tin ratio[1]

Ratio DTPA/Sn	Blood	Liver	Spleen	Kidneys	Bone	% Whole body Retention
1	0.013	4.00	1.27	0.87	10.2	33
3	0.011	0.79	0.23	0.78	8.9	27
20	0.02	0.41	0.14	0.81	9.8	27

[1]In mice at 24 hr, % injected dose per g tissue; n=5

5. Publications From Current Project

I. Original Research Articles

1. H.L. Atkins, L.F. Mausner, S.C. Srivastava, G.E. Meinken, R.F. Straub, C.J. Cabahug, D.A. Weber, C.T.C. Wong, D.F. Sacker, S. Madajewicz, T.L. Park, and A.G. Meek. Human biodistribution of Sn-117m(4+)DTPA: A new agent for palliative therapy of painful osseous metastases. Radiology 186, 279-283 (1993).

2. S.C. Srivastava, G.E. Meinken, L.F. Mausner, C. Cutler, H.L. Atkins, and E. Deutsch. Nuclear, chemical, and mechanistic considerations in the use of ^{117m}Sn(IV)-DTPA relative to ^{186}Re-HEDP and other agents for bone pain therapy. In: Technetium and Rhenium in Chemistry and Nuclear Medicine, M. Nicolini, et al, editors, SG Editoriali, Padova, 1994, pp. 287-292.

3. H.L. Atkins, L.F. Mausner, S.C. Srivastava, G.E. Meinken, C.J. Cabahug, and T. D'Alessandro. Tin-117m(4+)-DTPA for palliation of bone from osseous metastases: A pilot study. J. Nucl. Med. 36, 725-729 (1995).

4. H.L. Atkins and S.C. Srivastava. Radiolabeled bone seeking radiopharmaceuticals. The Quarterly J. Nucl. Med. 1996 (in press).

5. G.T. Krishnamurthy, F.M. Swailem, S.C. Srivastava, H.L. Atkins, L.J. Simpson, T.K. Walsh, F.R. Ahmann, G.E. Meinken, J.H. Shah. Sn-117m(4+)DTPA pharmacokinetics and imaging characteristics in patients with metastatic bone pain. J. Nucl. Med. 1996 (in press).

6. H.L. Atkins, S.C. Srivastava, L.F. Mausner, G. Meinken, G.T. Krishnamurthy, T. D'Alessandro, I. Zanzi, E. Silberstein, C.J. Cabahug, Y. Lau, T. Park, S. Madajewicz, F. Swailem. A dose escalation trial of Sn-117m(4+)DTPA; A new agent for palliation of painful bony metastases. Cancer, 1996 (submitted).

II. Published Abstracts

1. S.C. Srivastava, L.F. Mausner, H.L. Atkins, and G.E. Meinken. Treatment of metastatic bone pain with tin-117m(4+)-DTPA. WFNMB, 6th World Congress, Sydney, Australia, October, 1994.

2. S.C. Srivastava, G.E. Meinken, L.F. Mausner, C. Cutler, H.L. Atkins, and E. Deutsch. Nuclear chemical, and mechanistic considerations in the use of tin-117m-DTPA for bone pain therapy. J. Nucl. Biol. Med. 38, 465 (1994).

3. H. Atkins, G. Krishnamurthy, S. Srivastava, L. Mausner, G. Meinken, T. Walsh, F. Swailem, T. D'Alessandro, C. Cabahug, I. Zanzi, F. Ahmann, and J. Shah. A dose escalation trial of Sn-117m(4+)DTPA for bone pain palliation. J. Nucl. Med. 36, 31P (1995).

4. G.T. Krishnamurthy, F.M. Swailem, T.K. Walsh, F. Ahmann, C. Verdi, H. Garewal, J.H. Shah, H.L. Atkins, S.C. Srivastava, L.F. Mausner. Pharmaco-kinetics of Sn-117m(4+)DTPA in patients with multiple metastatic bone pain. J. Nucl. Med. 36, 30P (1995).

5. S.C. Srivastava. Tin-117m DTPA for therapy of bone pain due to cancer: Preliminary results. Indian J. Nucl. Med. 10, 222 (1995).

6. S.C. Srivastava. Radiopharmaceuticals for therapy of bone pain due to cancer. Abstract #1058, 1995 PACIFICHEM Congress, Honolulu, Hawaii, Dec. 17-22, 1995.

7. S.C. Srivastava, H.L. Atkins, G. Meinken, L.F. Mausner, G.T. Krishnamurthy and R.T. Dean. Tin-117m DTPA for therapy of bone pain due to cancer: Preliminary results. Diagnostic Oncology 4.5.94-95, 254 (1996).

8. G.T. Krishnamurthy, F.M. Swailem, S.C. Srivastava, H.L. Atkins, L.J. Simpson, T.K. Walsh, J.H. Shah, G.E. Meinken, and L.F. Mausner. Whole body and regional uptake and retention characteristics of Sn-117m(4+)DTPA by normal and metastatic bone in patients treated for bone pain palliation. J. Nucl. Med. 37, 72P (1996).

A DOSE ESCALATION TRIAL OF Sn-117m(4+)DTPA; A NEW AGENT FOR PALLIATION OF PAINFUL BONY METASTASES

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16 pages, 5 tables, 2 illustrations
Running Title: Dose escalation of Sn-117m(4+)DTPA

Précis

A dose escalation trial of Sn-117m(4+)DTPA was carried out in order to assess the myelotoxicity and efficacy of the radiopharmaceutical in the palliative therapy of painful bony metastases. Pain relief was obtained over a dose range of 2.64-19.58 MBq/kg administered activity, at a level comparable to other such agents with minimal effect on circulating platelets and white blood cells.

ABSTRACT

Background: The physical characteristics of Sn-117m combined with the biodistribution of the compound Sn-117m(4+)DTPA suggest that it should be an excellent agent for the palliation of pain from bony metastases. Prior work has established the dosimetry for the material in human beings. The presence of low energy conversion electrons should result in the relative sparing of the bone marrow while delivering a high radiation dose to sites of bony metastatic disease.

Methods: Forty-seven patients with painful bone metastases from various malignancies were treated with Sn-117m(4+)DTPA. The patients were assigned to 5 different dose levels ranging from 2.64 to 10.58 MBq/kg (71 to 286 μCi/kg) body weight. Follow up included review of pain diaries, medication requirements, blood chemistries, and hematological assessment. Three patients received a second treatment.

Results: There was an overall response rate for relief of pain of 70% (range:55.6-87.5%) in the 40 treatments which could be evaluated. No correlation was apparent between response rate and the five dose levels used. The relief was complete in 27.5%. Myelotoxicity was minimal with only one patient having grade 3 toxicity.

Conclusions: Sn-117m(4+)DTPA is an effective and safe radiopharmaceutical for palliation of painful bony metastases. A large scale trial should be carried out in order to evaluate it in comparison to other similar agents.

Key words: Sn-117m(4+)DTPA; Metastases; Radionuclide therapy; Bone pain; Palliation

A variety of radiopharmaceuticals have been examined for the relief of painful bony metastases. Among these are strontium-89 chloride[1] (FDA-approved; now available as "Metastron" from Amersham Healthcare, Arlington Heights, IL), samarium-153 EDTMP[2] and rhenium-186 EHDP[3] in addition to phosphorus-32 as sodium phosphate[4]. All are beta-emitting bone-seeking compounds which are taken up by bone with greater concentration at sites of metastasis. The only significant toxicity is bone marrow depression. We have investigated the potential of another agent, tin-117m(4+)DTPA, because of the premise that the limited range of the emitted conversion electrons from Sn-117m should be more sparing in radiation effects on the bone marrow. We have previously shown that Sn-117m(4+)DTPA is a bone-seeking compound with a distribution nearly identical to the diagnostic bone imaging radiopharmaceutical, Tc-99m MDP [5]. Our previous dose estimates based on the data obtained from the biodistribution study utilized the software program MIRDOSE2. A newer version, MIRDOSE3, is more sophisticated in its treatment of bone and bone marrow dosimetry. (MIRDOSE2 and MIRDOSE3 were supplied by Michael Stabin of the Radiation Internal Dose Information Center, Oak Ridge Institute for Science and Education, P.O. Box 117, Oak

Ridge, TN 37831.) We have recalculated the absorbed dose using the newer program.

An earlier publication detailed the results of a pilot study in ten patients that indicated that pain palliation could be obtained through administration of Sn-117m(4+)DTPA [6]. The present study was undertaken to evaluate the toxicity from escalating doses of Sn-117m and assess the dose response relative to efficacy.

Methods

A neutron inelastic scattering reaction was used to produce Sn-117m from an enriched (84%) Sn-117 target in the Oak Ridge National Laboratory High Flux Isotope Reactor (HFIR) or in the Brookhaven National Laboratory High Flux Beam Reactor (HFBR). Specific activity at end of bombardment averaged 81.4 MBq/mg (2.2 mCi/mg) from HFBR and 292.3 MBq/mg (7.9 mCi/mg) from HFIR.

The irradiated target was dissolved in concentrated HCl with heat and then added to a 20-fold molar excess of the acid salt of DTPA. The pH was adjusted to 6 with NaOH and the solution heated to 100°C for 30 minutes to insure complexation. After cooling a 2-fold molar excess of 30% H_2O_2 was added and the sample was reheated in a boiling water bath for 5 minutes. An 80% molar amount of $CaCl_2$-$2H_2O$ (based on DTPA) was added after cooling. The

preparation was then sterile-filtered. Radiopharmaceutical quality was tested by paper chromatography and HPLC [7]. Biodistribution studies in normal mice were performed on each batch as well as checking for sterility and pyrogenicity by standard methods.

A total of 47 patients with known metastatic disease to bone were enrolled in the study. These were 38 males and 9 females. Three patients (males) were treated twice. A variety of primary malignancies were studied and are listed in Table 1. All patients signed an approved informed consent form. All patients were over the age of 18 years and had histologically documented malignancy with metastases to bone with at least one painful lesion. Whole body bone scans with Tc-99m MDP had been performed within the prior month. There had been no new systemic chemotherapy or radiotherapy in the prior month and no new hormonal therapy in the prior 6 weeks. Other selection criteria included a Karnofsky performance status of $\geq 40\%$, serum creatinine of ≤ 2.0 mg/dL, a platelet count of $\geq 100{,}000/\mu L$, a granulocyte count $\geq 2000/\mu L$, and a normal bilirubin.

Complete blood counts, chemistries and electrolytes were obtained at time of treatment, one week later, and at intervals following treatment. The Sn-117m(4+)DTPA was administered through

an inlying infusion line. Blood samples and urine output were collected for at least 4 days and sometimes longer for radioactivity assay in order to calculate absorbed dose, as previously described[5]. Imaging of Sn-117m distribution with a gamma camera was carried out twice within the first eight days. In a few patients imaging of Sn-117m was also carried out at approximately 1 month and 3 months.

Patients were given forms which depicted an anatomical drawing of 13 body areas, checkpoints to describe the degree and the location of pain, space to provide information regarding sleep, descriptions of ability to sleep with or without analgesics, and doses of medications taken. Pain was recorded on a scale from 0 to 4 as previously described [6]. Patients were asked to complete these forms on a daily basis for at least two weeks and biweekly thereafter. Total pain score was obtained by adding the individual pain scores recorded for each of the 13 sites. Patients were followed until they died (22), or required other therapy, for a minimum of two months. Thirteen subjects could be followed for 6 months or more.

Five different levels of administered Sn-117m activity were used. These activities were 2.64 MBq/kg (71μCi/kg), 5.29 Mbq/kg (143 μCi/kg), 6.61 kg (229 μCi/kg),

and 10.58 MBq/kg (286 μCi/kg). These doses corresponded to a nominal dose of 5, 10, 12.5, 16 and 20 mCi for 70 kg men or 50 kg women.

Results

Only one patient experienced any untoward reaction to the administration of the Sn-117m(4+)DTPA. She had generalized itching the day following the administration readily relieved by antihistamine medication. Ten patients could not be evaluated for various reasons. These included the unanticipated need for chemotherapy for treatment of soft tissue disease, refusal to make follow-up visits or intervening death from disease progression.

A total of 11 treatments (27.5%) resulted in complete relief of pain for two weeks or more. An additional 17 treatments (42.5%) resulted a drop in the pain index of at least 50% for two weeks or more. Twelve treatment doses (30%) provided no or less than 50% relief of pain. The results related to the dose level are shown in Table 2. There is no clear trend of a response related to dosage or activity. Responses for the most part were long lasting, particularly in those who had complete relief of pain. Complete responses have lasted as follows: 5 weeks, 10

weeks, 13 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 12 months, 12 months, and 14 months.

Three of the patients with prostate cancer received a second dose of Sn-117m(4+)DTPA when symptoms recurred. Two of these patients had had a partial response from the first treatment. One of these patients experienced a complete response with the second treatment and the other again had a partial response. Another patient had a complete response lasting one year. He again had complete relief of pain for 5 months following the second therapy dose.

Toxicity was minimal. Although most patients experienced reductions in white blood cell and platelet counts, these were not of a serious nature. One patient with metastatic breast cancer had completed a course of chemotherapy approximately 6 weeks prior to Sn-117m administration and experienced a reduction in white blood cell count from 4500/μL prior to treatment to between 1900 and 2000/μL which persisted for several months. Her response is shown in Figure 1 along with two other women with breast cancer who also had received chemotherapy some time prior to their treatment with Sn-117m. The other breast cancer patients could not be evaluated because all required other therapy within weeks of the radiopharmaceutical administration. All patients had

normal levels of white cells and platelets prior to treatment. There were 8 patients who experienced level 1 toxicity and 2 had level 2 toxicity [Table 3]. All toxicities were related to reduction in white blood cell count, none to reduction in platelet count. Mean changes in white blood cell counts and platelets are shown in Table 4.

Recalculation of absorbed dose has resulted in a considerably lower value per unit activity to bone (17.6 mGy/MBq) and red marrow (2.65 mGy/MBq) when MIRDOSE3 is used. The results are shown in Table 5.

Discussion

The overall pain relief response of 70% is comparable to results with strontium-89 and other radiopharmaceuticals which have been investigated [1-4]. Among the five dose levels studied there was, however, no correlation of response to dose, an observation similar to the results obtained following the use of Sr-89 [8]. However, our series is too small for a definite conclusion regarding this. Our interest in studying Sn-117m is based upon the limited range (0.2-0.3 mm) of its conversion electrons which should result in reduced marrow toxicity as compared to strontium-89, in particular [1,8]. While a larger study needs to be performed in order to be definitive, the

results of this study would seem to be in agreement with this belief.

Despite the lower radiation absorbed dose to bone and marrow based on MIRDOSE3, there is still a very favorable ratio of bone:red marrow dose (~6.6). It should be recognized that these are average doses based on uniform distribution of the radioactivity in bone, approximately one-half in cortical bone and one-half in trabecular bone. In practice, it is likely that the patient with extensive bone metastases may experience a reduced radiation effect to the bone marrow than an individual with one or a few metastatic sites. In such cases the marrow adjacent to the areas of greatly increased activity would have very high absorbed dose but a major fraction of the marrow will be relatively spared.

The high ratio of bone surface dose to red marrow dose from Sn-117m, based on the limited range of its moderately low energy conversion electrons, is of particular advantage in patients with breast cancer. These patients have usually been subjected to considerable chemotherapy compromising the bone marrow and, as a consequence, have limited marrow reserve.

Other favorable characteristics of Sn-117m(4+)DTPA are 1) an excellent gamma photon (158.6 keV) in high abundance (86.4%)

suitable for imaging to monitor distribution (Figure 2), 2) an administered activity level that does not require hospitalization, 3) an intermediate physical half-life (13.61 days) which provides a reasonable shelf life for ease of manufacture and shipping 4) the preparations are stable chemically for over 3 months and do not require low temperature storage (9).

The high degree of efficacy and the lack of any significant toxicity warrant a large scale clinical trial to further evaluate Sn-117m(4+)DTPA as an agent for pain palliation in patients with bony metastases.

Acknowledgements

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Table 1

Primary Cancers of Patients Receiving Sn-117m(4+)DTPA

Primary	Number
Prostate	30*
Breast	7
Lung	7
Kidney	1
Pancreas	1
Unknown	1

* Three patients were treated twice.

TABLE 2

RESULTS OF DOSE ESCALATION TRIAL WITH Sn-117m(4+)DTPA

Administered Activity (μCi/kg)	Patients Studied		Degree of Pain Relief			Total % Response
	Total	Assessable	Complete	Partial	None	
71	9	5	0	3	2	60.0
143	10	8	4	3	1	87.5
179	10	8	3	2	3	62.5
229	10	9	1	4	4	55.6
286	11	10	3	5	2	80.0
Total	50	40	11	17	12	70.0

TABLE 3
ABSORBED DOSE TO MARROW AND MYELOTOXICITY

Administered Activity μCi (MBq)/kg	Absorbed Dose to Marrow, rad	Myelotoxicity Level* 0	1	2	3
33-84 (1.21-3.12)	33-81	3	1	1	0
97-156 (3.60-5.77)	61-164	7	1	0	1
179-204 (6.61-7.55)	100-202	7	1	0	0
228-229 (8.44-8.47)	180-205	5	3	0	0
285-320 (10.55-11.85)	110-235	7	2	1	0

MYELOTOXICITY CRITERIA

	0/WNL	1 (mild)	2 (moderate)	3 (severe)	4 (unacceptable)
WBC k/μL	≥4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	<1.0
Platelets k/μL	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.0	<25.0

* All toxicity observed was for white blood cells. No below normal level of platelets was seen.
WNL= within normal limits

TABLE 4

Effect of Sn-117m(4+)DTPA Therapy on White Blood Cells and Platelets

Nominal Dose	Max. %↓ WBC (Day)	Max. %↓ Platelets (Day)
5 mCi	12.0±8.9 (33±11)	22.2±18.5 (51±21)
10 mCi	27.9±19.4 (31±15)	27.1±12.6 (52±40)
12.5 mCi	20.6±7.5 (37±22)	12.4±6.6 (41±25)
16 mCi	34.1±17.6 (26±11)	26.1±24.5 (28±15)
20 mCi	28.3±15.8 (40±16)	33.2±21.4 (33±13)

Table 5

DOSE ESTIMATES FOR Sn-117m(4+)DTPA

	MIRDOSE2		MIRDOSE3	
	rad/mCi	mGy/MBq	rad/mCi	mGy/MBq
Adult Male				
Bone Surfaces	203	54.9	65.1	17.6
Red Marrow	22.6	6.1	9.8	2.65
Effective Dose Equiv.	7.74[1]	2.09[2]	2.30[1]	0.62[2]
Adult Female				
Bone Surfaces	265	71.7	63.2	17.1
Red Marrow	24.3	6.56	12.6	3.39
Effective Dose Equiv.	8.09[1]	2.18[2]	2.73[1]	0.74[2]

[1] rem/mCi
[2] mSv/MBq

Illustration

Figure 1. Response of total white blood count to Sn-117m(4+)DTPA therapy in 3 women who had metastatic breast cancer. Patient #1003 received 296 MBq (8 mCi). She had been receiving chemotherapy until 6 weeks prior to treatment. Patient #1002 received 311 Mbq (8.4 mCi) and Patient #2001 received 703 MBq (19mCi).

Figure 2. Image obtained 4 days following administration of 370 MBq (10 mCi) Sn-117m(4+)DTPA for palliation of painful bony metastases from a neuroendocrine pancreatic tumor. The pattern is identical to a Tc-99m HDP study obtained just prior to treatment.

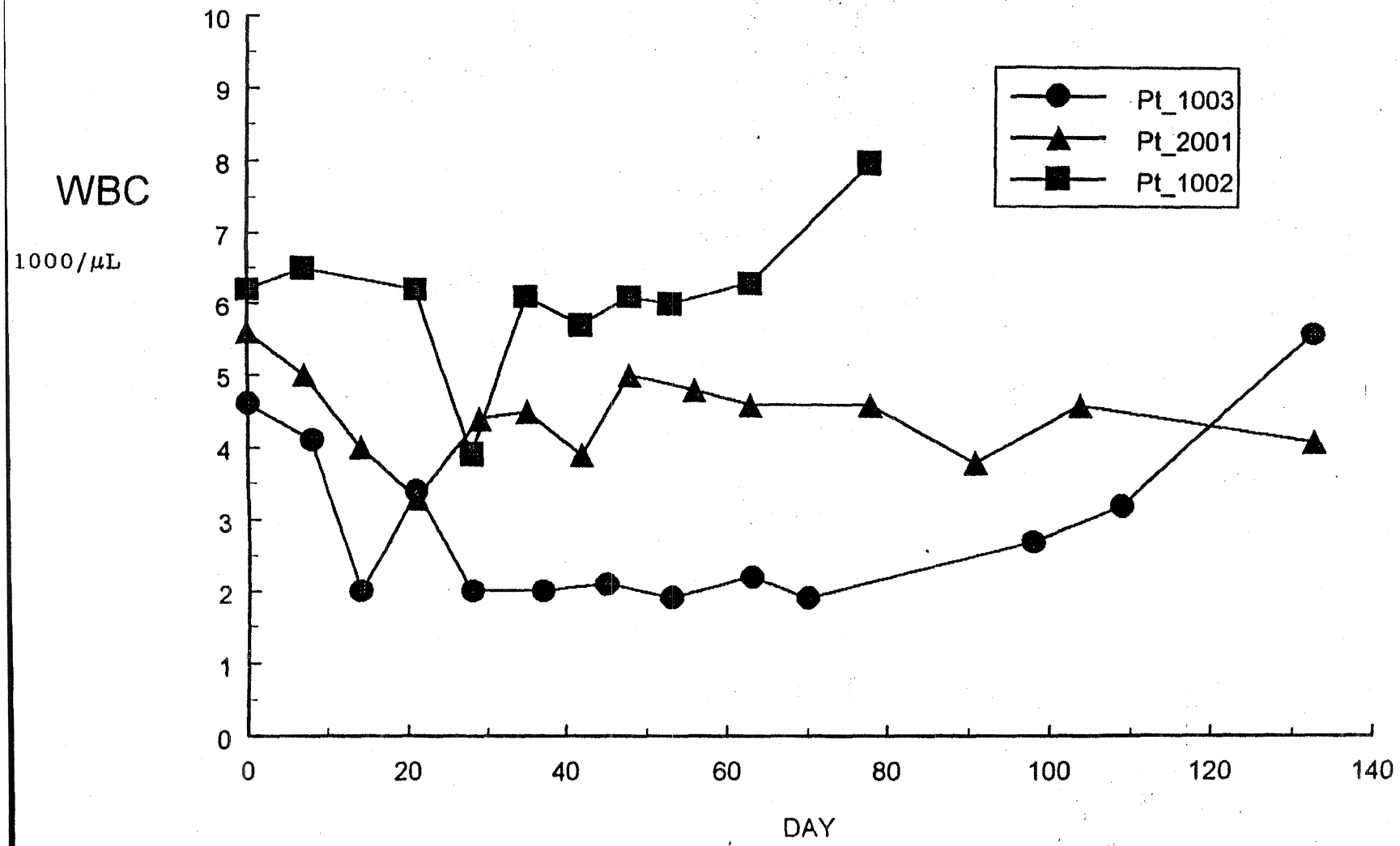
WBC
1000/μL
10
9
8
7
6
5
4
3
2
1
0
0
20
40
60
80
100
120
140
DAY
Pt_1003
Pt_2001
Pt_1002

Figure 1

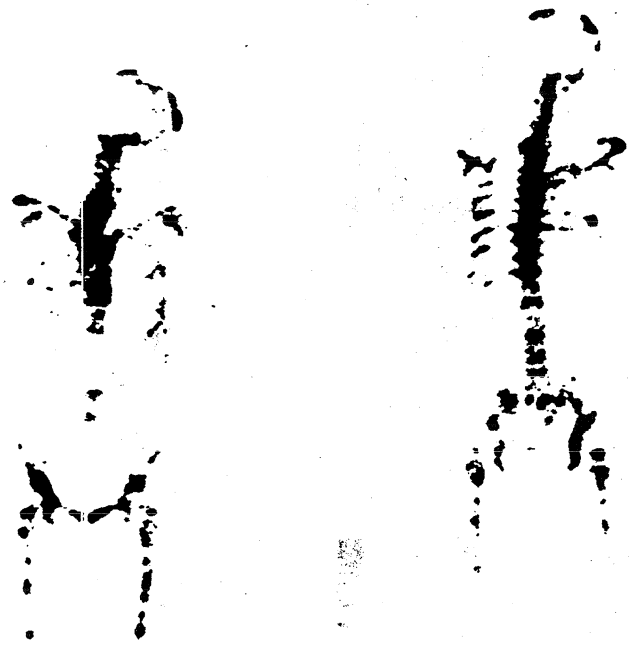

FIGURE 2.

J. Nucl. Medicine, 1996
(in press).

Sn-117m(4+) DTPA PHARMACO-KINETICS AND IMAGING CHARACTERISTICS IN PATIENTS WITH METASTATIC BONE PAIN

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Running head: Pharmacokinetics of Sn-117m(4+)DTPA

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ABSTRACT

Biokinetics and imaging characteristics of Sn-117m (4+) DTPA has been studied in 17 patients with metastatic bone pain using three dose levels; 180 μCi/kg (6.66MBq/kg), 229 μCi/kg (8.47MBq/kg) and 285 μCi/kg(10.55 MBq/kg) body weight. Following intravenous injection, the total body clearance of Sn-117m (4+)DTPA shows two components: a soft tissue component and a bone component. The soft tissue component accounts for 23% of the dose and consists of four sub-components with an average biologic clearance half-time of 1.45 days (range 0.1 to 3.2 days) The bone component accounting for the remaining 77% of the dose shows no biologic clearance. A mean 23% of the dose is excreted in urine in 14 days; 11.4% within 24 hours. The pattern of uptake appears similar to that of Tc-99m MDP. The peak uptake is noted in the normal bone by 24 hours and the metastatic lesions by 3-7 days. Pain palliation was noted with all three doses levels. Among the four potential bone pain palliation agents, Sn-117m (4+) DTPA shows the highest bone uptake and retention. Some biokinetic and radionuclidic features of Sn-117m(4+)DTPA are similar to other agents but many 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.

Sn-117m(4+) DTPA PHARMACO-KINETICS AND IMAGING CHARACTERISTICS IN PATIENTS WITH METASTATIC BONE PAIN

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Of the estimated 1.35 million people who would be diagnosed of some form of cancer in 1996 in the U.S.A. slightly more than half will develop metastasis (1). In patients whose primary 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; and a significant component of that strategy is proper management of pain (2). Five options are generally available for bone pain palliation from metastatic lesions. These options include: 1) non-steroidal anti-inflammatory agents, and opioids, 2) hormones, 3) cytotoxic chemotherapy, 4) external beam radiation, and 5) 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, the metastatic bone pain is usually severe, arises from multiple sites and may require large quantities of opiates. Given in 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 the therapy with these four options fail, pain palliation with radionuclides is considered (4,5,6). 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, P-32- orthophosphate is not currently used for metastatic bone pain palliation. At present, strontium-89 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 the 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. developed several Sn-117m based agents and demonstrated in mice bone uptake of Sn-117m in the stannic state (4+) complexed to pyrophosphate, EHDP, MDP, or DTPA. The highest uptake was noted with Sn-117m(4+)DTPA(15). The short range of the conversion electrons indicates potential bone marrow sparing features from therapeutic doses of Sn-117m (4+) DTPA (16). Pilot studies in humans by Atkins et al have shown promising results (17,18). Sn-117m with a monoenergetic gamma photon of 159 keV in 86% abundance serves as an excellent bone imaging agent enabling better quantification of total body uptake and retention as well as the uptake and retention by metastatic lesion and the normal bone.

The current project was undertaken to gather as complete a data set as possible under phase II studies to fully understand the biokinetics and the imaging characteristics of Sn-117m (4+) DTPA

prior to initiating a multicenter phase III clinical trial. Ideal physical characteristics of tin-117m described above combined with an intermediate physical half life of 13.9 days, provides an unique opportunity for studying long term biological behavior of the 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 communication we report the results of the biokinetic studies only.

MATERIALS AND METHODS:

This Sn-117m(4+)DTPA study was undertaken as a collaborative research project between the Veterans Administration Medical Center (VAMC) in Tucson, Arizona and the Brookhaven National Laboratory (BNL) in Upton, New York. 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. A total of seventeen patients with histologically confirmed primary malignancy with painful bone metastases was 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 six months 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 non-responders to these methods of pain control, before entering into Sn-117m(4+)DTPA therapy protocol. None of the patients

had received any radionuclide therapy within the last six months or chemotherapy within 3 months. Fifteen patients had extensive tumor spread to the bone, and two had limited spread as noted on a total body Tc-99m-MDP bone scan. Each subject was interviewed along with the spouse. The nature of the research study, its purpose, benefits and risks were explained to the patients, and the 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 had a recent assessment of their pain status. A whole body Tc-99m-MDP scan obtained within the last one month prior to entry had shown multiple metastatic bone lesions, many of which were painful. The patients were eligible to enter the study if they also had the following results: BUN<20mg%, creatinine <2mg%, bilirubin <2mg%, hemoglobin > 12mg%, WBC> 2000/uL, neutrophils> 1000/uL, and platelets> 100,000/uL. Karnofsky clinical score > 40.

Sn-117m (4+) DTPA preparation: Sn-117m (4+) DTPA was prepared at BNL as described earlier (15-18) and sent by air mail package for next day delivery to Tucson VAMC. Two to four patient doses were sent at a time for use within the next four weeks which was later extended to eight weeks shelf life. Briefly, the radionuclide Sn-117m was prepared using the Sn-117 (n, n,γ)Sn-117m reaction. Enriched Sn-117(84%) as the oxide or as the metal was used. The oxide when used was converted to metal by reduction at 600 degree C in a hydrogen flow for 2.5 hours prior to irradiation. Up to 100 mg Sn metal sealed in a quartz ampule was irradiated for 3-4

weeks using the BNL high flux beam reactor or the high flux isotope reactor at Oak Ridge National Laboratory. The specific activity of tin-117m at the end of the irradiation ranged from 2-8 mCi/mg (74-296 MBq/mg).

Sn-117m (4+) DTPA whole body scan: A few minutes before Sn-117m(4+)DTPA injection, the patient was asked to void in order to alleviate the need for void during the next two hours. 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 Sn-117m (4+) DTPA dose was infused slowly over a period of 2-4 minutes. 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 (Fig 1) received two doses, (six months interval between doses): 285 μCi/kg (10.55 MBq/kg) as the first and 180 μCi/kg (6.66 MBq/kg) as the second dose (This patient had received Sr-89 a year earlier and was considered a non-responder). 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 counting of the blood and urine samples. Another aliquot of the injected dose of known activity was kept next to the patient neck as standard during each Sn-117m bone scan obtained at intervals shown in Table 1. This known activity would enable the calculation of the exact microcurie concentration at the desired site.

The first, simultaneous anterior and posterior view whole body (WB) planar scan was started at

60 minutes after injection, before voiding (Fig. 1A). All of the subsequent WB scans (Fig. 1.B.C.D) 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 4- 6 weeks, 5 had 8-10 weeks and 4 had 12-14 weeks follow-up whole body images. In one patient, two additional images were taken: on day 99 (Fig. 1D) and day 133 (Fig. 1 E) post-therapy.

Scan parameters: Simultaneous planar anterior and posterior view WB images were obtained with a Picker. dual head Prism 2000, gamma camera fitted with low energy high resolution parallel hole collimator. The scan speed was set at 4.96 inches/minute and it usually took 18-20 minutes for the complete study depending upon the patient height. The spectrometer was set for Sn-117m gamma photon peak energy of 159 keV with a 20% window. The digital images were recorded on 256 x 1024 matrix. These parameters set for the first study (one hour after injection) 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.

Tc-99m-MDP bone scan: Simultaneous planar anterior and posterior view whole body bone scans were obtained with the same Picker, dual head Prism 2000 camera used for the Sn-117m study. Images were obtained at 2-3 hours after intravenous injection of 20mCi (740 MBq) Tc-99m-MDP using 140 keV photopeak and a 20% window setting. The first scan was obtained before Sn-117m (4+)DTPA therapy. Repeat Tc-99m-MDP bone scans were obtained at eight weeks and six months after injection of Sn-117m (4+) DTPA. The cross talk from 159 keV

gamma photon of Sn-117m during Tc-99m MDP bone scan at eight weeks was approximately 15%.

Blood and urine collection and counting; Blood samples (2-3ml) were drawn at intervals shown in Table 1. One ml 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 % injected dose in total blood. The height and weight based total blood volume for each patient was obtained from published tables. The blood samples for CBC, platelets, electrolytes, and chemistry were obtained both before injection, at weekly intervals for two months and at monthly intervals for the next four months after injection of Sn-117m (4+) DTPA (17).

The urine was collected at 2 hours, 24 hours and later as daily samples for 14 days. In the first six patients, we collected urine for only three days assuming that all of the radioactivity not taken up by the bone would be excreted in three 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. Daily urine volume was measured, and one ml of urine was counted from each daily sample in Canberra MCA Series 35 coupled to a NaI well counter using an off-set window setting of 130-220 keV for the 159 gamma photon. The results were expressed as % injected dose excreted in daily urine (Table 2)

Calculation of Sn-117m (4+) DTPA whole body (WB) retention. The geometric mean counts from the planar anterior and posterior view WB counts (including the standard) in the first scan (one hour after injection, prior to voiding) were obtained (as square root of Anterior x 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 WB 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 % injected dose retained (Fig. 4). All results are expressed as mean percent of injected dose $\pm$ 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 Sn-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 Sn-117m (4+) DTPA scans. Counts/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 Clearance: After intravenous injection, Sn-117m(4+) DTPA radioactivity remaining in whole blood at various times for up to 14 days post-injection is shown in Fig. 2. A mean (s.d) 14.7% $\pm$ 4.8 of the injected dose remained in the intravascular compartment at 15 minutes and the remaining 85.2% of the dose had already left the intravascular blood pool at this time (Fig. 2).

When the % dose in whole blood is plotted on the Y- axis and the time on the X-axis of a semilog scale, two clearance components, one rapid and the one slow, are readily evident from the curve. The fast component accounting for 20.8% of the blood radioactivity showed a clearance half time ($T_{\frac{1}{2}}$) of 58 minutes and the slow component accounting for the remaining 79.2% of the blood radioactivity showed a clearance $T_{\frac{1}{2}}$ of 6.9 days. Only 0.17% ± 0.08 of the dose remained in the blood compartment at 14 days post-injection (Fig. 2).

Urine clearance: 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 hrs post-injection. Daily and cumulative average excretion of Sn-117m (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 day one, two and three, respectively. The cumulative mean urinary excretion at the end of the first week was 19.5% and at the end of the second week 23% of the dose (Fig. 3).

Whole body(WB) retention of Sn-117m(4+)DTPA: The WB retention (WBR) curve shows two components, a soft tissue and a bone component (Fig. 4). The soft tissue component accounts for 23% of the dose and shows four subcomponents with biologic clearance half times ($T_{b\frac{1}{2}}$) of 0.04, 0.56, 2.0 and 3.2 days (average 1.45 days). The bone component accounts for the remaining 77 % of the dose and shows a $T_{b\frac{1}{2}}$ of infinity. We hypothesize that the faster component with $T_{b\frac{1}{2}}$ ranging from 0.1 to 3.2 days represents 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 Sn-117m. Since a cumulative mean 19.5% of the injected dose was excreted in urine at end of seven days, it can be assumed that the remaining 80.5% of the injected dose was retained in the whole body on the 7th day after injection. This value of 80,5% (Injected dose - Urine excretion method) WBR is very close to the value of 81.1% ± 5.5 obtained by the independent gamma camera geometric mean method. Because, the urine sample counting and the gamma camera WB 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 very simple yet a very reliable technique for long term follow-up. Mean (s.d) WBR of Sn-117m (4+) DTPA at the end of 35, 48, 63 and 93 days, post-dose 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% at 2 weeks(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% as the total body retention beyond two weeks(Table 4). In one patient, the scan of the pelvis (Fig. 1E) showing the lesion in the left hemipelvis was obtained 133 days post therapy (three days short of ten half lives). He had received 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 Sn-117m(4+) DTPA on the 133rd day from original 10 mCi (370 MBq) therapy dose (after accounting for urinary excretion and physical decay) approximately would be an equivalent of 8μCi (0.3 MBq) (Fig. 1E)

Metastatic and normal bone uptake and retention of Sn-117m (4+) DTPA: When decay corrected counts/pixel are plotted on the Y-axis against time on the X-axis, the curve for both the normal and abnormal (metastatic) pelvic bones show a different types of peak bone uptake. The normal bone reaches its peak uptake rapidly within 24 hrs where as the metastatic bone continues its uptake to reach the 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 post-injection (Fig. 4). The lesion/normal bone ratios varied greatly from patient to patient and from lesion to lesion within the same patient. The ratios ranged from a low of 2 to a high of 9.

Pattern of WB distribution of Sn-117m (4+) DTPA: Visually, the whole body distribution pattern of Sn-117m (4+) DTPA is similar to that of Tc-99m-MDP, both for normal bone and bone with metastatic involvement (Fig. 1). When the two bone studies are placed next to each other with the label covered, it is difficult to differentiate Sn-117m scan from Tc-99m bone scan.

Visually, the clarity of Sn-117m bone scans obtained at 24hrs, 72 hrs, 7 days and 6 week post therapy is equivalent to the 3 hr Tc-99m-MDP bone scan (Fig. 1). The urinary bladder is not seen beyond three days which enables assessment of the involvement of the pelvic bone metastasis much better in the Sn-117m (4+) DTPA scan than in the three hour Tc-99m-MDP scan where the bladder activity covers the pelvic bones. The pattern of bone uptake seen as early as one day post-injection of Sn-117m (+) DTPA remained the same for seven to ten physical half lives (91 to 133 days) as shown in Figure 1.

No soft tissue uptake was seen (other than kidney and bladder) in the scans obtained 72 hours and beyond with the sole exception of one patient where some liver uptake of Sn-117m (4+) DTPA was noted. This patient had a complicated medical course including a penetrating duodenal ulcer and mildly abnormal liver function tests. Spleen and other soft tissues did not show any uptake suggesting that Sn-117m (4+) DTPA was take up probably by the hepatocytes and not by R.E. cells. The exact cause for liver uptake could not be determined.

DISCUSSION

Requirement of an ideal bone pain palliation radiopharmaceutical: Management of intractable pain is a real challenge in Oncology. It becomes even a greater challenge when the pain is from bone due to multiple metastases, and when the physician's options are limited to either high doses of opiates or treatment with bone seeking radionuclides. Due to very energetic beta particles and incorporation into nuclear proteins of hematopoietic cells, P-32 orthophosphate is not considered ideal for bone pain palliation. At present, four radiopharmaceuticals (Table 4) are considered suitable for bone pain palliation. To be effective, a bone pain palliation radiopharmaceutical must be able to confront the basic behavior of the cancer spread to bone. Once the soft tissue cancer spreads to bone at one location, metastases tends to appear at

different locations at different times. An ideal bone pain palliation radiopharmaceutical (Table 5), therefore, must meet the following requisites: 1) Most of the administered dose should concentrate in the bone, predominantly at the site of bone metastases, 2) Once in the bone, it should not wash out to be taken up by soft tissues or excreted in urine where it can create a possible radiation contamination problem, 3) The total dose administered should be small to enable out-patient treatment and should not require any additional waiting or special monitoring before patient discharge, 4) The half life of the radionuclide should be long enough to allow a longer duration of action on all metastatic foci present at the time of injection; relieve pain from those currently painful, and prevent those currently painless ever becoming painful during ten physical half lives of the radionuclide, 5) The half life should be short enough to enable repeat pain palliation doses as new painful metastatic foci appear, without raising a concern for marrow suppression due to cumulative residual effect from the previous doses, 6) The production of the agent should be simple and the final product should have a sufficiently long "shelf-life" without requiring any special or expensive storage facilities, 7) The radioisotope should have particulate emission for therapeutic effect and should preferably emit gamma photons to enable imaging and quantification, 8) The treatment should not suppress the bone marrow, 9) Level of urinary excretion should be low enough not to raise concerns for radiation cystitis and, finally 10) The radiopharmaceutical should be readily available at low cost.

Relative bone uptake of pain palliation radiopharmaceuticals: The mean whole body Sn-117m(4-)DTPA retention of 81.1% on day 7 and 77% of the dose on day 14, is the highest

among the four bone pain therapy agents. 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 Sn-117m. We are unable to find similar data in the literature for the other three agents where the urine has been collected for a duration equal to at least one physical half life of the radionuclide. We would have over-estimated the WB retention level had we collected urine for only one 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 hrs and 46% in 24hrs has been reported for samarium-153 EDTMP (11,12,14). This leaves 54% of the administered dose for bone uptake at 24 hours (Table 3). Similarly, it has been reported that 45% of the dose as being excreted in urine at 5 hrs and 70 % in 3 days with rhenium-186 HEDP, leaving only 30% of the dose for bone uptake at 72 hours (9). Since the duration of urine collection was short (less than one physical half life of the radionuclide) with both Sm-153 EDTM and Re-186 HEDP, it is possible to over estimate their whole body retention. We were also unable to find in the published literature definitive urinary excretion values for strontium-89. Blake et al mentioned collecting urine in 14 patients for 96 hrs with strontium-85 and strontium 89, but the value for urine excretion as percent of the injected dose was not reported (19). The lack of an easily measurable gamma photon with Sr-89 or the very high gamma photon energy (514 keV) associated with Sr-85 make quantification imprecise for strontium. Firusian (6), based on rabbit data, made an assumption of 30 to 80% Strontium-89 uptake in to bone. The whole body retention curve for Sr- 85 and Sr-90 developed by Marshal, et al. in normal people shows an approximate 30% retention on day 10,

25% on day 30 and 18% on day 100 (20). This suggests that Sr-85 and Sr-89 are released from bone after the initial uptake. Sn-117m (4+) DTPA on the other hand, differs from Sr-89 in not showing any release from bone after the initial uptake (Fig. 4). It is not clear whether or not in patients Re-186 HEDP or Sm-153 EDTMP wash out from bone after the initial uptake.

Therapeutic doses of pain palliation radiopharmaceuticals: Our preliminary results indicate that a dose of 10 to 20 mCi (370-740 Mbq)per 70 kg body of Sn-117m (4+) DTPA may be sufficient to achieve pain palliation (21). For strontium-89, FDA has approved a dose of 4 mCi (148 Mbq) for adults. In clinical trials, doses ranging from 30 to 70 mCi with rhenium-186 HEDP, and 35 to 210 mCi with samarium-153 EDTMP have been used for pain palliation (9-13). Relatively-low level of administered dose along with low urine excretion of Sn-117m (4+) DTPA lessens the major concern for contamination when there is an accidental urine spill or incontinence. After noticing significant room contamination in two patients, all other patients were catheterized after treatment with Sm-153 EDTMP to avoid room contamination from urine spill (12). The 4 mCi (148 MBq) dose of Sr-89 does not seem to raise much concern for room contamination. Low administered doses with both Sr-89 and Sn-117m (4+) DTPA appear to have advantages over Re-186 HEDP and Sm-153 EDTMP which may require extra radiation monitoring because of the high levels of administered and excreted radioactivity. However, 50.5 days half of Sr-89 does pose a problem for long term storage of needles, syringes, and gloves used during injection.

Collection of urine daily for 14 days (a duration of one physical half life of Sn-117m) and WB measurement for up to 93 days (in one patient up to 133 days, almost up to ten physical half lives) have allowed us to measure the exact amount excreted in urine and that retained in the bone and the whole body. It is evident from the gamma camera results that Sn-117m (4+) DTPA shows seven day net bone uptake of 81.1% injected dose, a value exactly equal to 81.1% of injected dose obtained by the dose- urine excretion method (Tables 2,3). Urinary excretion of 23% of the dose in 14 days leaves the remaining 77% for bone uptake. The mean WB retention of 77% of the injected dose with Sn-117m (4+) DTPA is much higher than the value reported for Sm-153 EDTMP, Re-186 HEDP, and Sr-89 chloride (Table 4).

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 rhenium-186 EHDP bone uptake is thought to be similar to Tc-99m diphosphonates, by a process called chemisorption (9-13, 22). Tin(Sn) is a known bone seeker, and the uptake of Sn-117m(4+)DTPA is attributed mainly to tin and the role of DTPA being primarily to confer a very high in-vivo stability (15). Stannic (4+) status is very important to further enhance the net bone uptake without undergoing competitive side reactions(23). In mice, 53.8% of Sn-117m(4+)DTPA was taken up by the bone in contrast to only 30.8% uptake with Sn-117m(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 the therapeutic doses: The physical half life of 13.6 days and excellent chemical stability allow multiple doses of Sn-117m (4+) DTPA to be acquired and stored for up to 6-8 weeks, much like with Sr-89. Not much activity is lost due to decay if one has to wait several days to find another patient when the intended patient decides to decline treatment. Such is not the case with both samarium-153 and rhenium-186 which decays rapidly due to their short physical half lives (Table 4).

The duration of pain palliation with Sn-117m(4+)DTPA in the pilot studies has ranged from 3 months to 14 months following a single administration. In one of our patients (shown in Fig. 1), the pain palliation from each of two doses lasted for four months. The degree of the relief of pain post-therapy was 100% on both occasions. Partial to complete pain palliation has been noted in about 85% of 36 patients studied between Tucson VA and Brookhaven National Laboratory (21). We anticipate the total therapeutic dose to be between 10 to 20mCi (370-740 MBq) for a 70 kg patient. The biokinetic, nuclear physical and chemical characteristics combined with our preliminary pain palliation results with Sn-117m (4+) DTPA are very encouraging and appear to show that it may meet most of the requirements to qualify as an ideal bone pain palliation agent. Double blind studies comparing the results with the FDA approved Sr-89 chloride are required to pass any final judgement on this new agent. An application to the FDA to begin phase-III clinical trial is presently under preparation.

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LEGEND

Figure 1. Serial Sn-117m (4+) DTPA whole body images obtained under identical parameters. Note diffuse distribution at 1 hr and localization in bone by 5 hrs (A) in a prostate cancer patient with local metastasis in the left hemipelvis extending to right ischial tuberosity. Uptake in front of L_4-L_5 vertebra is due to low lying horseshoe kidney. By day 3 (B) most of the radioactivity localizes in bone. Seventh day images show minimal activity in the horseshoe kidney (C). Images on 70th and 99th day (D) show activity mostly in the left hemipelvic bone and the right ischial bone. The decrease in intensity in the later images is the effect of physical decay. The round activity to the right side of the neck is the external standard used to calculate regional uptake. The image on 133th day shows persistent uptake in the left hemipelvis (E). F is pre-therapy Tc-99m MDP scan showing a similar pattern of distribution.

Figure 2. Blood clearance of Sn-117m (4+) DTPA. About 14.4% of the injected dose remains in blood pool at 15 min post-injection. The remaining 85.15% has left the intravascular compartment. Notice biexponential type of clearance with differing T ½ clearance values.

Figure 3. Daily and cumulative urinary excretion of Sn-117m (4+) DTPA for 14 days. About 11.4% of the dose is excreted in 1 day and 11.6% in the next 13 days for a total of 23 % by 14 days.

Figure 4. Whole body clearance of Sn-117m (4+) DTPA measured by a dual head gamma camera method shows two compartments. The soft tissue accounting for 23% of the dose shows 4 compartments (mainly urinary excretion)with a biologic T ½ ranging from 0.1 to 3.2 days. The bone compartment accounts for the remaining 77% of the dose and shows no biologic clearance.

Figure 5. Uptake and retention of Sn-117m (4+) DTPA by normal (right pelvis) and metastatic bone (left pelvis) in a patient with prostate cancer. (shown in Fig.1). Note peak uptake by normal bone at 24 hrs. The metastatic bone shows continued uptake reaching peak at 7 days. No biologic excretion is seen from either bone.

TABLE 1: DATA COLLECTION SCHEME FOR BIOKINETIC STUDY OF Sn-117m (4+) DTPA

BLOOD SAMPLE COLLECTION TIME FOR

CLEARANCE	CELL COUNT	URINE COLLECTION AT
15 MIN	BASELINE	BASELINE
30 MINS	WEEKLY FOR	1 HR
45 MINS	8 WEEKS	2 HRS
1 HR	FOLLOWED BY	1 DAY
2 HRS	MONTHLY FOR	and
1st DAY	4 MONTHS	DAILY FOR
3rd DAY	(TOTAL 6 MONTHS)	14 DAYS
7th DAY		
14th DAY		

Tc-99m MDP BONE SCAN	Sn-117m (4+) DTPA BONE SCAN
PRE-Rx	1 HR
8 WEEK POST Rx	3.5 HR
6 MONTHS POST Rx	1 DAY
	3rd DAY
	7th DAY
	4th-6th WEEK
	8th-10th WEEK

TABLE 2 : DAILY AND CUMULATIVE URINARY EXCRETION (% DOSE) OF Sn-117m(4+)DTPA IN PATIENTS WITH METASTATIC BONE PAIN

Days	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Patient															
1- G.W.	0	7.7	2.9	2.6											
2- F.M.	0	5.8	1.4	1.3											
3- T.O.	0	20.5	3.9	2.3											
4- C.K.	0	18.6	5	6.2											
5- D.X.	0	8.7	2.3	1											
6- S.C.	0	10.5	1.9	1.4											
7- C.B.(1)	0	18.2	5.7	3	1.9	1.3	1.3	1.1							
8- A.H.	0	11.1	1.1	1.3	0.4	0.6	0.4	0.1							
9- F.K.	0	7.6	2	0.8	0.7	0.7	0.4	0.3							
10- R.M.	0	9.9	2.1	1.6	0.8	0.6	0.6	0.4	0.4	0.3	0.2				
11- M.S.	0	11.9	4.4	2.7	1.6	1.9	1.5	1.1	1.5	0.9	0.9	2.3	0.8	0.4	
12- J.D.	0	10.7	2.1	1.5	0.7	0.7	0.6	0.5	0.4	0.5	0.3	0.3	0.3	0.2	0.3
13- J.P.	0	12.2	3.3	2.5	1.1	0.3	0.3	0.7	0.7	0.7	0.3	0.6	0.3	0.2	0.2
14- C.B.(2)	0	9.6	2.2	1.1	1.3	1	0.7	0.5	0.6	0.4	0.5	0.5	0.4	0.4	
15- R.M.	0	9.2	1.4	1.1	0.7	0.5	0.1	0.2	0.6	0.3	0.4	0.4	0.2	0.2	
16- C.P.	0	15	2.7	1.4	1.5	1.2	1.4	0.9	0.8	0.3	0.9	0.6	0.4	0.4	0.4
17- R.B.	0	10.8	1.7	1.2	0.8	0.8	0.7	0.6	0.6	0.5	0.5	0.3	0.4	0.2	0.3
18- K.O.	0	7.2	2.4	3.3	1.6	1.5	1.2	1.3	0.4	0.6	0.6	0.9	0.4	0.9	0.3
Average(daily excretion)	0.0	11.4	2.7	2.0	1.1	0.9	0.8	0.6	0.7	0.5	0.5	0.7	0.4	0.4	0.3
ST. DEV.	0.0	4.1	1.3	1.3	0.5	0.5	0.5	0.4	0.3	0.2	0.3	0.7	0.2	0.2	0.1
Average (cumulative)	0	11.4	14.1	16.1	17.2	18.1	18.9	19.5	20.2	20.7	21.2	21.9	22.3	22.7	23
% WB Retention (Dose - Urine excretion)	100	88.6	85.9	83.9	82.8	81.9	81.1	80.5	79.8	79.3	78.8	78.1	77.7	77.3	77

Table 3. Percent Dose Urinary Excretion of Radiopharmaceuticals Suitable for Bone Pain Palliation

Agent	URINARY EXCRETION				
	5 hr	10 hr	24 hr	72 hr	14 days
Sn-117m (4+) DTPA Current Study			11.4%	16.1%	22.4%
Rhenium-186 HEDP	45% (9)*			70%(9,10)	
Samarium-153 EDTMP		36.8% (12)	46% (11,14)		

* References are shown within parenthesis

Table 4:Comparison of Percent Dose Whole Body Retention, and Nuclear and Physical Characteristics of Radiopharmaceuticals Suitable for Bone Pain Palliation

Percent Whole Body Retention (References)				
Days Post-Therapy	Sn-117m DTPA	Re-186 HEDP	Sm-153 EDTMP	Sr-89 Chloride
1 day	88.6		54 (11,12)	
3 days	83.9	30 (9,10)■		
7 days	81.1			31 (20)
14 days	77.0			25 (20)
100 days	77.0			18 (20)
Nuclear and Physical Characteristics				
Half Life	13.6 days	90.6 hr	46.3 hr	50.5 days
γ 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

Whole Body Retention = (Dose - urine excretion). *Conversion electrons with discrete energy, NA = Not Applicable. ■=References with in parenthesis.

Table 5: An ideal bone pain palliation radiopharmaceutical.

1. Should deposit with high concentration in bone, mostly at the metastatic sites
2. Should not wash out from bone.
3. Dose should be small, yet relieve pain.
4. Have intermediate physical half life (1-2 weeks, and good shelf- life.
5. Simple method of production and storage.
6. Allow frequent repeat dose when new metastases appear.
7. Have particulate emission for therapy and gamma photons for imaging.
8. Should not suppress bone marrow.
9. Should not cause radiation cystitis.
10. Should be readily available at low cost.

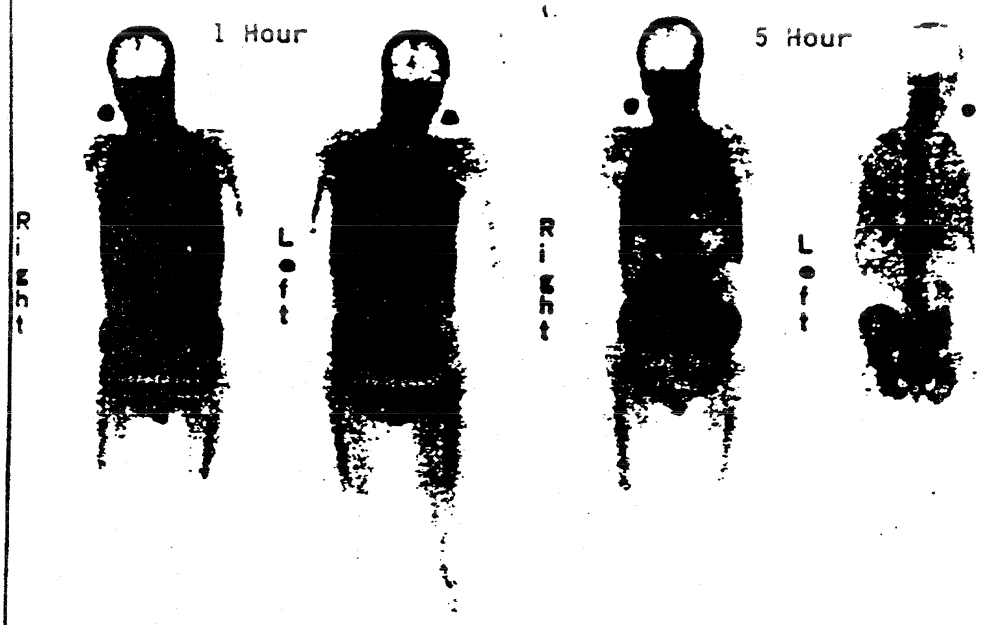

1 Hour
5 Hour
Right
Left
Right
Left

Fig 1A

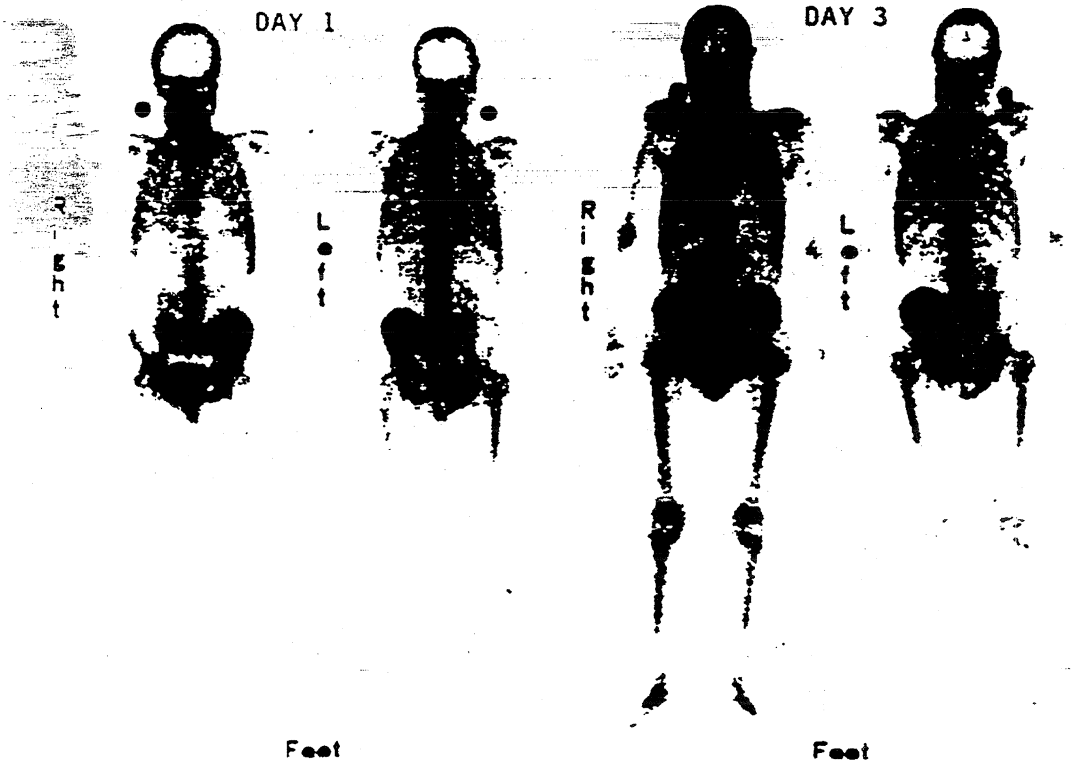

DAY 1
DAY 3
Right
Left
Right
Left
Feet
Feet

Fig 1B

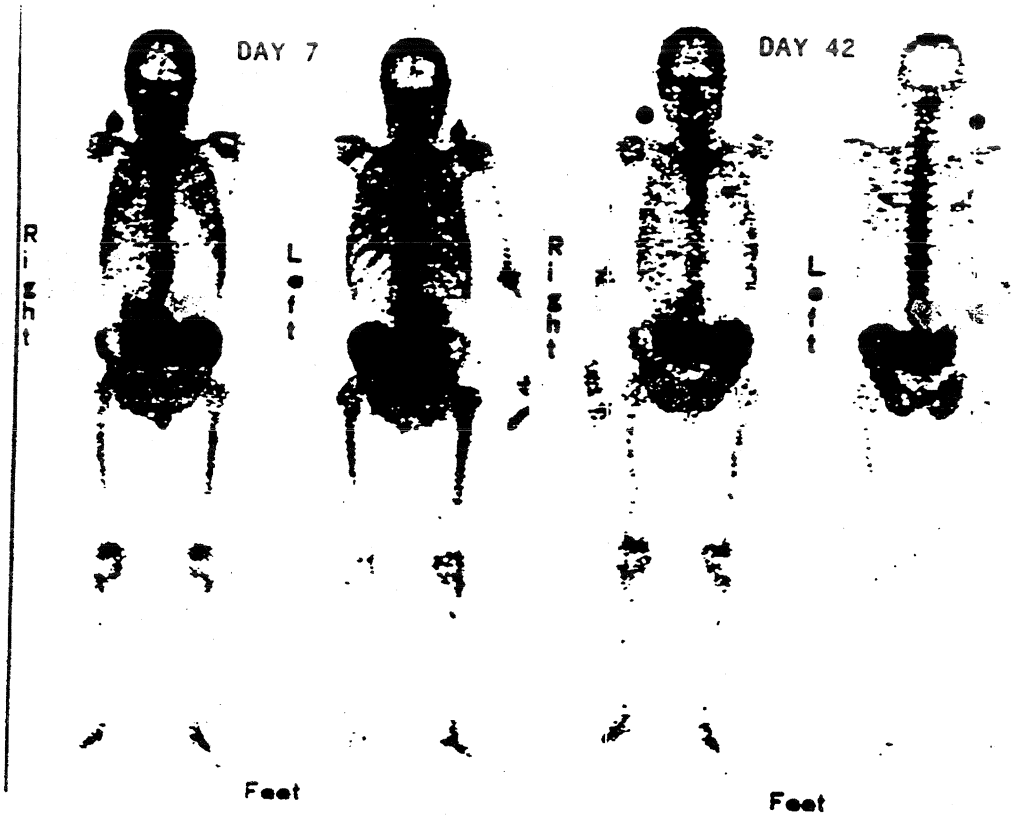

DAY 7
DAY 42
Right
Left
Right
Left
Feet
Feet

Fig 1C

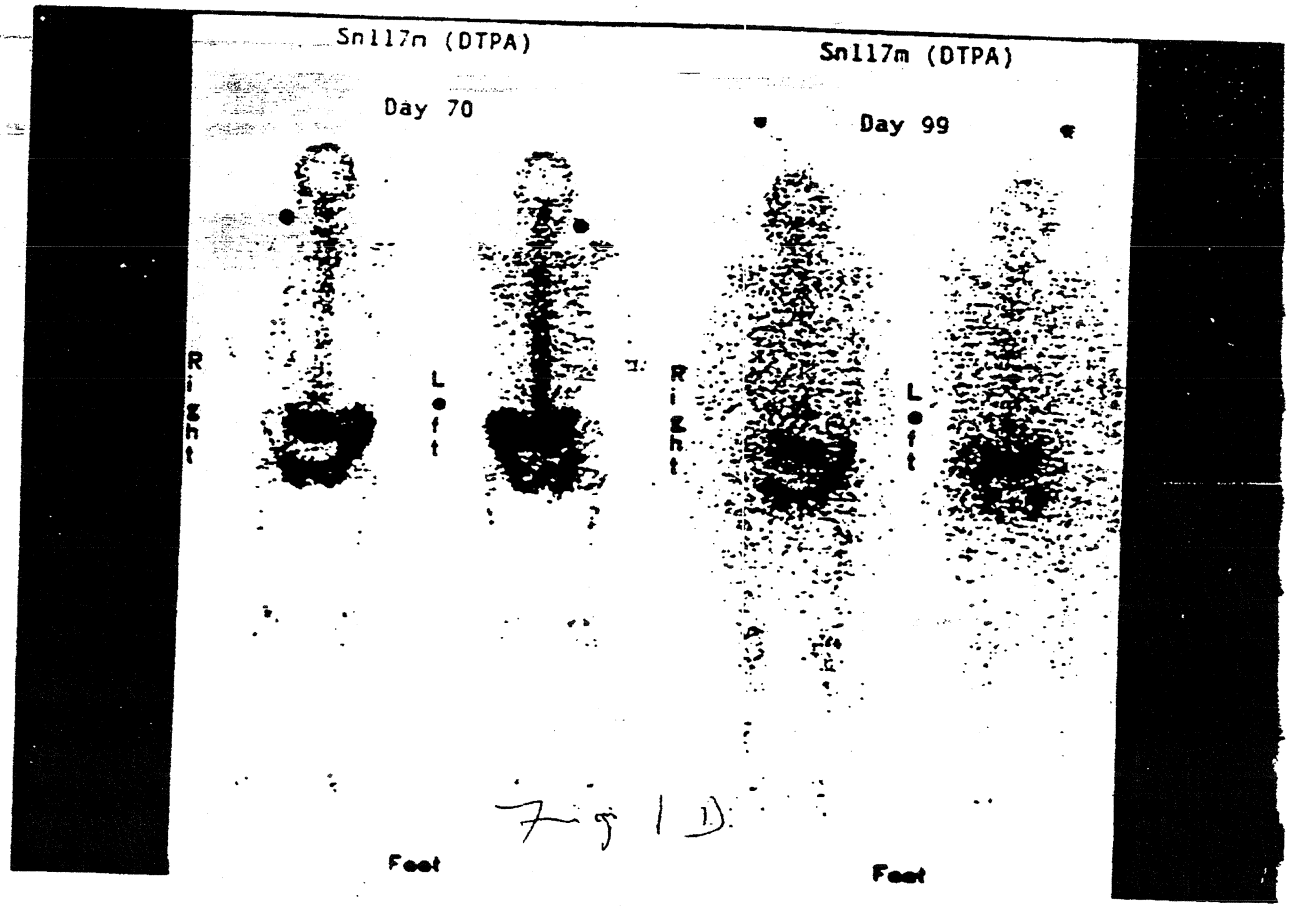

Sn117m (DTPA)
Day 70
Sn117m (DTPA)
Day 99
Right
Left
Right
Left
Feet
Feet

Fig 1D

Sn-117m(4+)DTPA

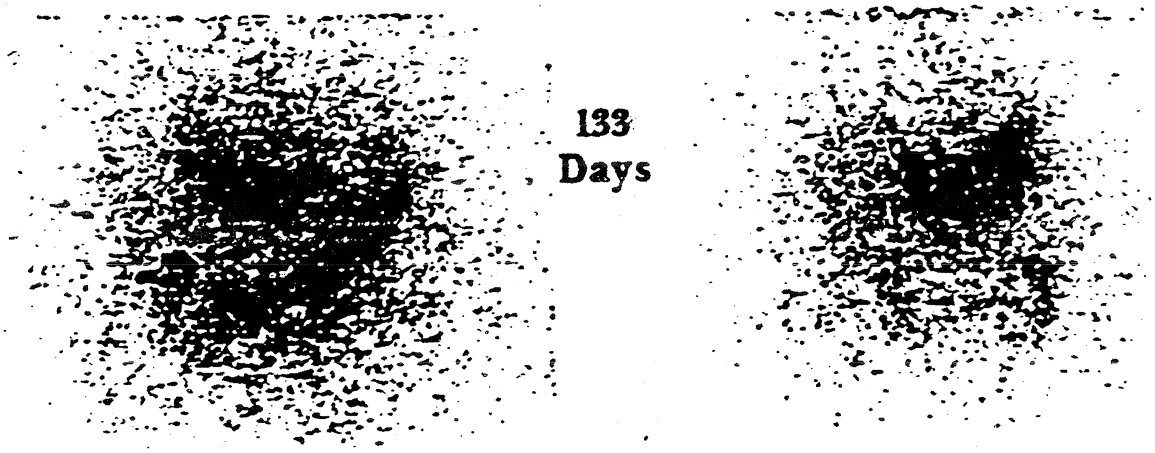
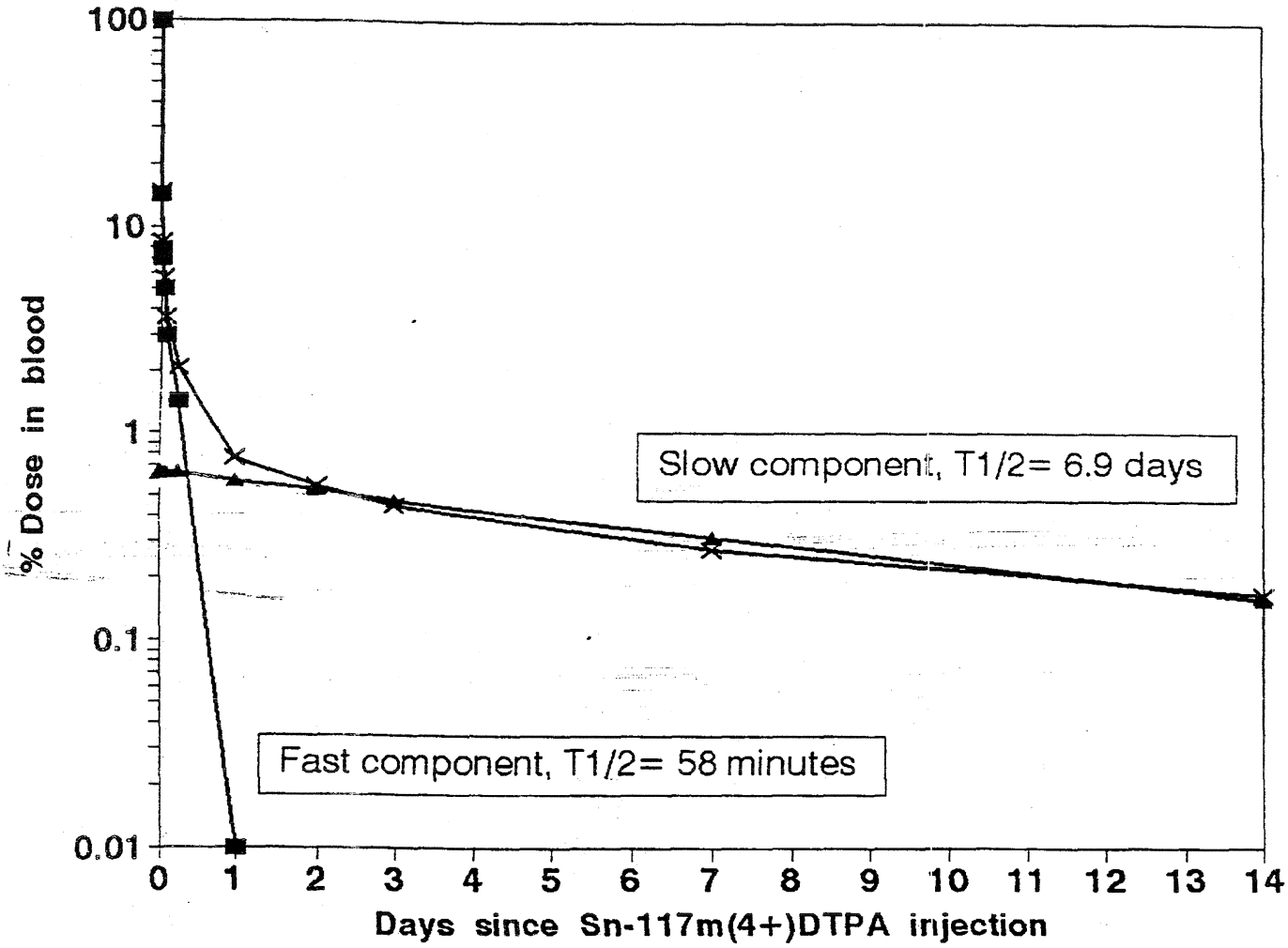
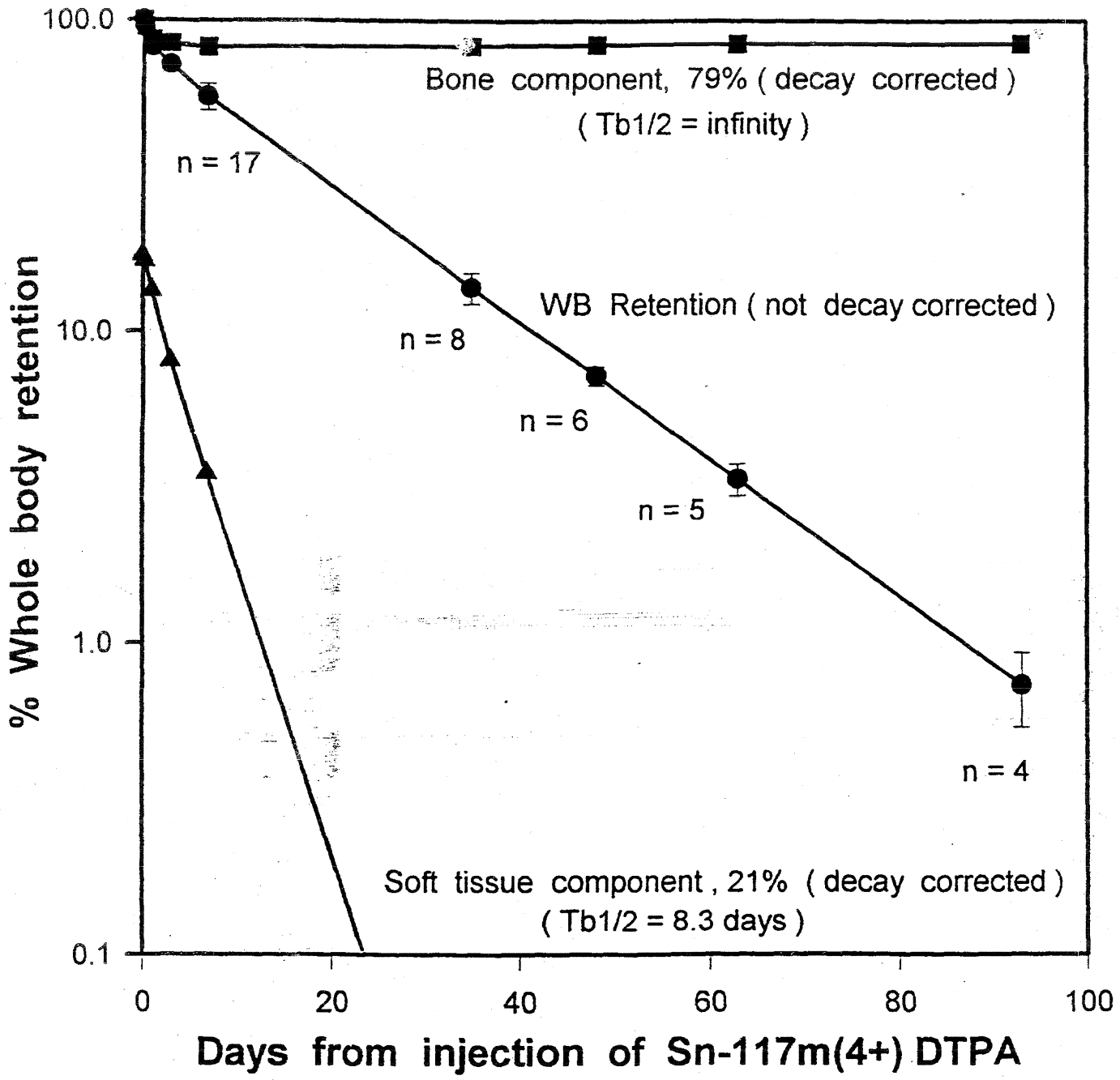
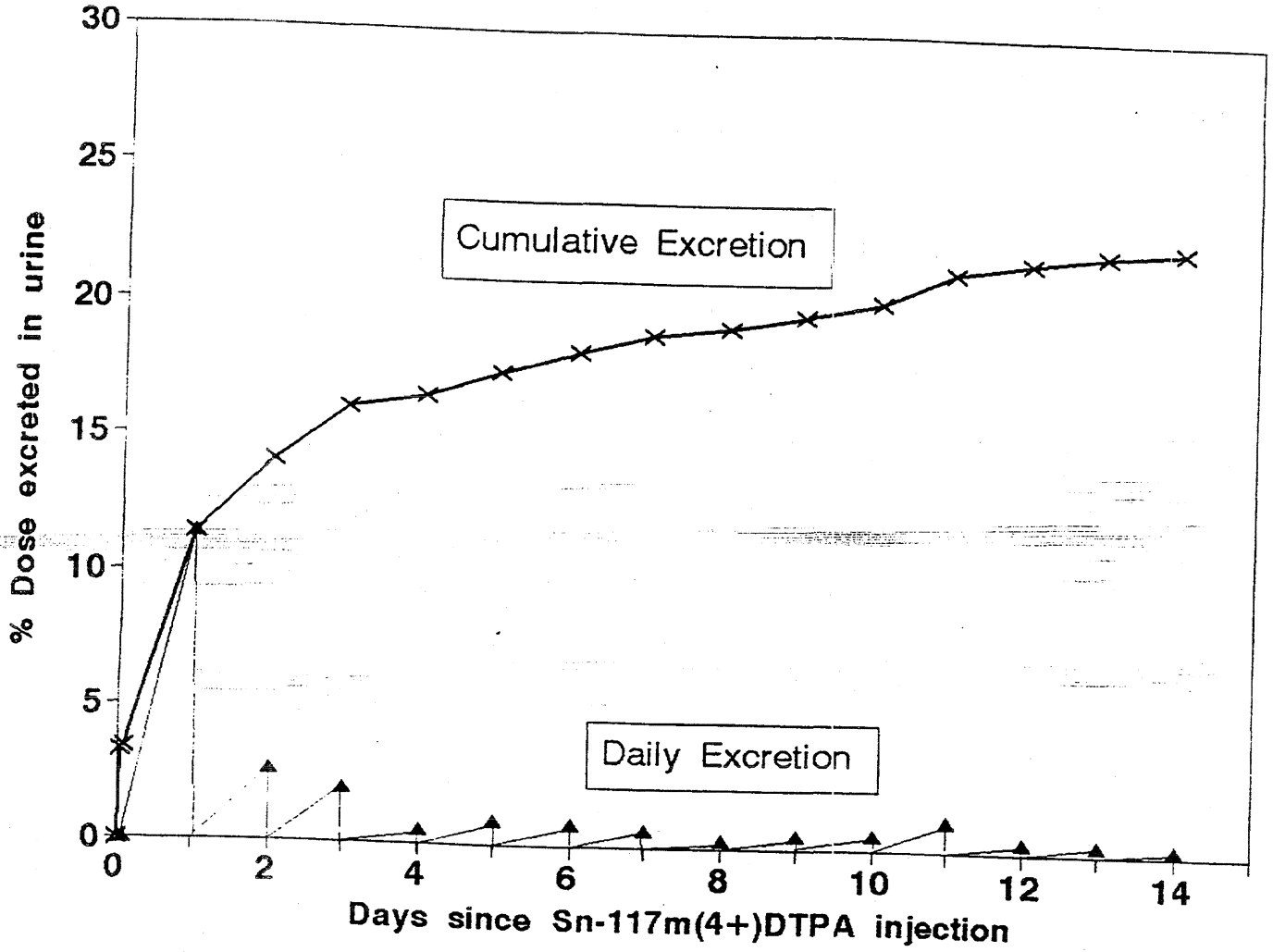


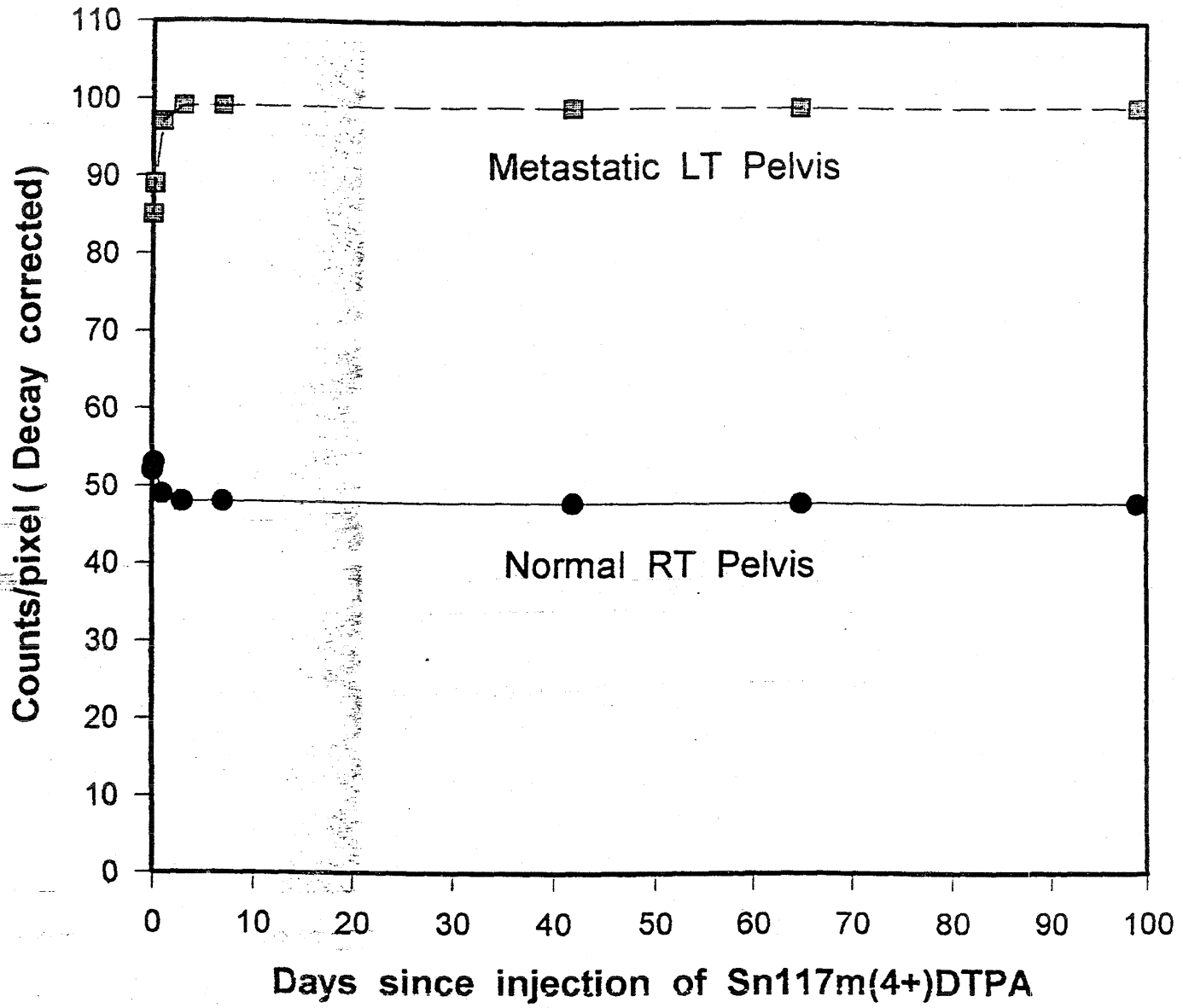
Fig 1E

Fig 1F (MDP Scan)
will be shown


100
10
1
0.1
0.01
% Dose in blood
Slow component, T1/2= 6.9 days
Fast component, T1/2= 58 minutes
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Days since Sn-117m(4+)DTPA injection


100.0
10.0
1.0
0.1
% Whole body retention
Bone component, 79% (decay corrected)
(Tb1/2 = infinity)
n = 17
WB Retention (not decay corrected)
n = 8
n = 6
n = 5
n = 4
Soft tissue component , 21% (decay corrected)
(Tb1/2 = 8.3 days)
0
20
40
60
80
100
Days from injection of Sn-117m(4+) DTPA


30
25
20
15
10
5
0
% Dose excreted in urine
Cumulative Excretion
Daily Excretion
0
2
4
6
8
10
12
14
Days since Sn-117m(4+)DTPA injection


110
100
90
80
70
60
50
40
30
20
10
0
Counts/pixel (Decay corrected)
Metastatic LT Pelvis
Normal RT Pelvis
0
10
20
30
40
50
60
70
80
90
100
Days since injection of Sn117m(4+)DTPA