Rhenium-186(Sn)HEDP for Treatment of Painful Osseous Metastases: Results of a Double-Blind Crossover Comparison with Placebo

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Rhenium-186 (tin) hydroxyethylidene diphosphonate (HEDP) is a new radiopharmaceutical that simultaneously localizes in multiple skeletal metastases in patients wtih advanced cancer. A single intravenous administration of 30–35 mCi (1110–1295 MBq) is associated with a prompt, significant relief of osseous pain in about 80% of such patients. The efficacy of this new compound was evaluated further by utilizing a double-blind crossover comparison with ^{99m}Tc-methylene diphosphonate (MDP) as a radioactive placebo. The new rhenium compound resulted in a significantly ($p < 0.05$) greater decrease in pain than did treatment with the radioactive placebo. Rhenium-186(Sn)HEDP appears to be a useful new compound for the palliation of painful skeletal metastases.

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There are nearly 1 million new cases of cancer each year in the United States. Breast and prostate cancer account for about one-quarter of these new cases and, when advanced, metastasize to the skeleton about 80% of the time. These skeletal metastases often cause excruciating and debilitating pain.

Although external radiation therapy can provide significant palliation in about 80% of patients with osseous metastases, the amount of the body that can be subjected to such radiation is limited, even with regional or hemibody fields (*1,2*). Nausea, vomiting, or diarrhea occur in about half and hematopoietic toxicity in about one-third of patients treated with hemibody radiation.

Phosphorus-32-orthophosphate in intravenous administrations of 10 mCi (370 MBq) has been used over the last several decades as a palliative agent for painful skeletal metastases. The average marrow dose for this administered activity in normal man is about 240 rad (240 cGy) (*3*), so it is not surprising that some hematopoietic depression has been reported in up to 90% of patients so treated (*4*) with about 30% of the patients in some series requiring transfusion (*5*). In two recent series (*4,5*), about 75% of patients treated with ^{32}P-orthophosphate experienced relief of pain while 24% did not respond to treatment.

In the interest of decreasing marrow toxicity while providing relief of pain, strontium-89 as the lactate or, more commonly, as the chloride, has achieved some popularity over the last several decades. The average marrow dose appears to be about 70 rad/mCi (1.9 cGy/MBq) with a tumor/marrow dose ratio of about 10:1 (*6*). Thus, a typical administered activity of 2.8 mCi (104 MBq) to a 70-kg patient would result in a marrow dose of about 196 rad (196 cGy). At such dose levels, 80% of patients experienced a decrease in their total platelet count, although the decline in most cases (61%) was mild with the platelet count remaining in the normal range (*6*). Clinical relief of pain has been variable, ranging from 50% (*3*) to 82% (*6*) of patients in uncontrolled studies. Buchali and colleagues (*7*) noted pain relief in 7/19 (37%) patients treated with three monthly injections of 2.03 mCi (75 MBq) and in 11/22 (50%) patients who received a saline placebo. The differences were not significant. This raised the obvious question of whether the palliative response described by other workers was not simply a placebo response.

In 1988, we reported the development of a purified ^{186}Re(Sn) hydroxyethylidene diphosphonate (HEDP) compound that localizes in osteoblastic skeletal metastases and that emits beta particles with sufficient energy to be therapeutically useful (*8*). Initial human studies suggested that a 30–35-mCi (1110–1295 MBq) administration of this compound would result in relief of pain without significant bone marrow toxicity and with tumor/marrow dose ratios (median 15:1 and mean 22:1) that were higher than those achieved with ^{89}Sr-chloride (*9*). However, we could not be

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certain whether the apparent benefit that we were seeing was due to the ^{186}Re(Sn)HEDP or might be due to placebo effect. This report details the results of a double-blind crossover study in which the effects of ^{186}Re(Sn)HEDP were compared with those from a placebo.

MATERIALS AND METHODS

Study Design

The results of our initial uncontrolled trial of a single intravenous injection of about 33 mCi (1,221 MBq) of ^{186}Re(Sn)HEDP to each of 20 elderly men with advanced skeletal metastases have been published previously (*9*) and are summarized in Table 1. These preliminary findings suggest that 80% of our "typical" patients would respond favorably within 3 wk of the ^{186}Re(Sn)HEDP injection if they were going to respond at all, and that the duration of this response would be about 7 wk. Therefore, we designed a double-blind crossover study so that, if the patient responded to the initial injection within the first 3 wk, then follow-up would be extended to a full 8-wk period, at which time the patient would be crossed over to the second injection. If the patient did not respond within 3 wk, then at 4 wk crossover to the second injection would occur with follow-up for 8 wk thereafter. Thus, the total time in the study would be 12 wk, and no patient who might respond to the ^{186}Re(Sn)HEDP compound would be asked to wait more than 4 wk after receiving placebo. For the first 3 wk after the initial injection and prior to crossover, the two patient groups also would provide data for a parallel comparison of ^{186}Re(Sn)HEDP with placebo.

Calculation of Study Population Size

As would be expected in the initial trials of an investigational compound, the patients who were referred to us for entry into this study were very sick. Our prior experience (*9*) indicated that at least one-third of our patient population would require either additional cancer-specific therapy or would drop out or die during a 12-wk protocol period. Calculations of sample size revealed that nine evaluable subjects would be required to demonstrate a significant difference if the placebo response rate were 10% and the ^{186}Re(Sn)HEDP response rate were 80%. If the placebo response were 20% and the therapeutic response to ^{186}Re(Sn)HEDP were 60%, then 27 evaluable subjects would be required to detect a significant difference.

Based on these considerations, we decided to enter 20 subjects into the double-blind crossover comparison study with the anticipation that 10–15 of the subjects would provide evaluable data. If data from this initial group answered the question, then for ethical reasons the study would be terminated. If the data were equivocal, then an additional group of similar size would be studied with appropriate corrections being made in the statistical analysis.

TABLE 1
Rhenium-186(Sn)HEDP Palliation of Painful Skeletal Metastases (Reference *9*)

Patients:	20 men with advanced prostate cancer
Mean ^{186}Re(Sn)HEDP:	33.1 mCi (1,225 MBq) i.v.
Mean tumor dose:	4040 rad (4,040 cGy)
Mean marrow dose:	181 rad (181 cGy)
Pain relief:	Complete 5/20 (25%)
	Partial 11/20 (55%)
	None 4/20 (20%)
Duration of response:	7 wk
Time to onset:	1–3 wk

Patient Selection

From June 1989 to July 1990, 20 patients were entered into the study. The entry criteria were as follows:

A. Biopsy-proven carcinoma with standard ^{99m}Tc-diphosphonate bone scanning and radiographic evidence of osseous metastases.
B. Failure of prior conventional therapy.
C. A projected life expectancy of 4 mo without any additional tumor-specific therapy planned during that time.
D. A total white blood cell count of at least 4000/mm^3 (4.0 × 10^9/liter) with a total platelet count of at least 100,000/mm^3 (100 × 10^9/liter) and a serum creatinine concentration of 1.5 mg/dl (133 μmole/liter) or less.

All subjects had to be non-pregnant adults who were able to give informed consent according to the guidelines of the Institutional Review Board at the University of Cincinnati.

Assessment of Patient Characteristics at Entry

All patients underwent a review of their present illness, a physical examination, and routine laboratory examinations that included a complete blood cell count, total platelet count, renal and hepatic function studies, determination of serum calcium and phosphorus levels, and a urinalysis. A standard ^{99m}Tc-diphosphonate bone imaging study was used to document the extent of osteoblastic metastatic disease, and selected radiographs were obtained to confirm that the abnormal bone scan findings were reflective of metastatic disease.

Beginning at least 1 wk before the therapeutic administration, the patient was asked to keep daily logs that indicated analgesic intake and the level of pain both at rest and during activity. At the end of each week, the log sheets were turned in and average weekly pain and analgesic indices were calculated using methods previously developed by the National Radiation Therapy Oncology Group (*1,2*) for the evaluation of efficacy of external radiation therapy. The pain index was based on the patient's assessment of the severity of their pain at rest and during activity. The analgesic index was based on the number of doses and type of medication used for pain relief. The data obtained prior to the first injection were used as a baseline for the first injection, while the data from the last week prior to receiving the crossover injection were used as the baseline for the second injection.

Rhenium-186(Sn)HEDP Therapy

All patients were admitted to the General Clinical Research Center of the University of Cincinnati Hospital. The patients were randomized by the nuclear pharmacist to receive either ^{186}Re(Sn)HEDP or ^{99m}Tc-MDP (methylene diphosphonate). The ^{186}Re(Sn)HEDP radiopharmaceutical was prepared in our laboratory using methods described previously (*9*). The ^{99m}Tc-MDP was prepared using a routine, commercial formulation (Amerscan® MDP, Amersham Corporation, Arlington Heights, IL). The mean activity (± 1 s.d.) of ^{186}Re(Sn)HEDP administered per injection was 34.0 ± 0.8 mCi (1258 ± 29.6 MBq). The mean administered activity (± 1 s.d.) of the ^{99m}Tc-MDP placebo was 17.7 ± 1.5 mCi (654.9 ± 55.5 MBq).

Following injection of either agent, images were obtained in the nuclear medicine department. The ^{99m}Tc-MDP was selected

as a placebo because it would result in images visible to patients and to staff while not giving any therapeutic benefit. All physicians, nurses, and patients were kept blinded regarding which compound was administered at any time.

Follow-up

All patients were followed weekly for 12 wk after their initial administration or to the point of a major violation of protocol. At each weekly visit, the patients turned in their daily logs for assessment of the pain index and the analgesic index. At every other visit, the routine clinical laboratory tests obtained at entry into protocol were repeated.

Definition of End Points

The pain index was regarded as the primary end point for statistical analysis. However, for the purpose of determining crossover time, both the patient's and the physician's subjective impressions of the presence or absence of improvement were utilized.

All subjects were told they would receive a placebo as one of the two injections. They also were reassured that they could continue their analgesics as needed. They were encouraged to keep their analgesic intake relatively constant, unless an increase in analgesia were needed because of worsening pain or they became pain-free. The analgesic index was a secondary end point.

Statistical Analysis

The statistical analyses of the initial parallel groups and of the two-period crossover study data were performed using chi-square or t-tests as appropriate (*10*) on PC-SAS (Statistical Analysis System (*11*), and the University of Cincinnati Computer Center computer (Amdahl 5880; Amdahl, Sunnyvale, CA).

RESULTS

Completion of Protocol

Twenty patients were entered into the study. All had extensive metastatic disease on bone scans, and all had failed prior traditional therapy.

Thirteen of the 20 patients who were entered provided evaluable data. They consisted of 11 men and 2 women with a mean age of 65 ± 10 yr. Their primary cancer types included nine prostate, two lung, one thyroid, and one breast cancer. All of the patients had received prior external radiation therapy; 11 of 13 were receiving hormonal therapy; 4 had received prior chemotherapy; 3 had received prior ^{186}Re(Sn)HEDP radionuclide therapy. Ten of the 13 patients were taking narcotics regularly on a daily basis.

Ten of the 13 evaluable patients completed the 12-wk protocol without incident. Three of the 13 patients experienced protocol violations, all of which involved additional external radiation therapy for progressive, painful focal skeletal metastases. However, none of the protocol violations in this group of three patients occurred at such time that they could not be adequately evaluated after both injections.

Seven of the 20 subjects were excluded from analysis because we could not assess their pain or analgesic responses to both radionuclide administrations. Three of these seven individuals failed to receive both injections due to rapidly progressive cancer that required additional external radiation in two subjects and resulted in death in one. Three of the seven subjects received both injections, but two of them required additional specific anti-neoplastic therapy shortly after the second injection and one dropped out of the protocol 1 wk after the second injection, rendering data from the second injection unevaluable. One patient experienced the onset of shingles the afternoon that he received his initial injection; this severe neurogenic pain continued throughout the entire protocol period, rendering accurate assessment impossible. Three of the non-evaluable patients had been randomly assigned to receive the placebo first and four had been assigned to receive the ^{186}Re(Sn)HEDP at entry.

Randomization Into Treatment Groups

Six of the 13 evaluable patients were randomized to receive ^{186}Re(Sn)HEDP as their initial injection followed by the placebo injection, and 7 of these 13 patients were randomized to receive placebo initially followed by the ^{186}Re(Sn)HEDP injection.

Changes in Pain

Subjective improvement following ^{186}Re(Sn)HEDP was indicated by the observation that five of the six patients who initially received ^{186}Re(Sn)HEDP and their physicians thought that they had responded sufficiently that their crossover could be delayed to the 8-wk point, while only one of seven patients who initially received the placebo injection had such a response. These differences were significant ($p < 0.05$).

We also evaluated the response of each group to the initial injection [placebo versus ^{186}Re(Sn)HEDP] in parallel by comparing their average pain indices at 3-wk postinjection and prior to any crossover as a percent of baseline. The group initially receiving placebo experienced a 39% increase in pain while the parallel group initially treated with ^{186}Re(Sn)HEDP experienced a 22% decrease in pain ($p < 0.05$).

The mean changes (baseline-nadir) in pain index for the entire patient population following each treatment are shown in Table 2. While there was very little decrease in the pain index following placebo in either group, there was a definite decrease in the pain index following the ^{186}Re(Sn)HEDP injection in both groups. The differences were significant ($p < 0.05$).

TABLE 2
Mean (±1 s.d.) Decrease (Baseline-nadir) in Pain Index

	Treatment Sequence	
	^{186}ReHEDP→Placebo	Placebo→^{186}ReHEDP
Number of patients	6	7
Initial injection	2.6 ± 2.2	0.1 ± 1.8
Crossover injection	0.5 ± 2.2	2.8 ± 1.9
Initial—Crossover	2.1 ± 4.0	−2.7 ± 3.6
	$p < 0.05$	

TABLE 3
Average Percent Change In Pain Index

	Treatment sequence	
	^{186}ReHEDP→Placebo	Placebo→^{186}ReHEDP
Number of patients	6	7
Initial injection	43% ↓	3% ↑
Crossover injection	1% ↓	39% ↓

The magnitudes of the changes in pain index may be more easily appreciated by looking at the mean percent changes in the pain index following treatment (Table 3). The average percent overall decline in the pain index for all patients following the ^{186}Re(Sn)HEDP injection was about 40%, while there was essentially no change following the placebo.

An example of the changes that occurred in the pain index following each injection is shown in Figure 1. The patient is a 69-yr-old man with multiple skeletal metastases from cancer of the prostate. The images of the posterior lower thoracic and lumbar spine show an identical distribution of the ^{99m}Tc-MDP placebo and of the ^{186}Re(Sn)HEDP into multiple metastases. Following injection of placebo, his pain index increased. In contrast, the ^{186}Re(Sn)HEDP resulted in a mild initial increase in pain (flare reaction) followed by a dramatic decrease in pain beginning in the second week following the injection. For purposes of comparison, the pain indices are shown as a percent of baseline.

Changes in Analgesic Intake

Because an increase in oral analgesic intake might have occurred that could explain the apparent benefit in pain reduction following ^{186}Re(Sn)HEDP, we analyzed the treatment groups on the basis of maximal increases in analgesic index during each period. No significant differences were found between the two groups ($p = 0.2$). Thus differences in decreases in the pain index could not be explained by an increased analgesic intake in one of the two groups.

The mean decreases (baseline-nadir) in the analgesic index following each treatment were then evaluated (Table 4). In both treatment groups, there was a decrease in analgesic index after the first injection followed by an increase in analgesic index after the second injection. However, the decrease in the analgesic index was greater in the ^{186}Re(Sn)HEDP treated group than in the placebo-treated group ($p = 0.05$).

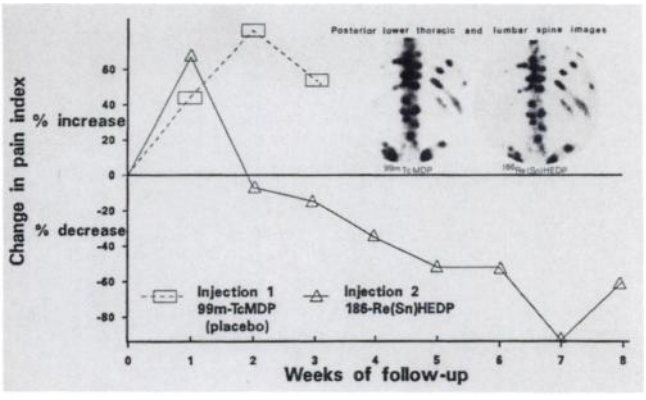

FIGURE 1. Posterior lower thoracic and lumbar spine images show identical distributions of the ^{99m}Tc-MDP placebo and ^{186}Re(Sn)HEDP therapeutic compound in a 69-yr-old man with extensive skeletal metastases from prostate cancer. His pain continued to increase following placebo, whereas it decreased rapidly and dramatically following the injection of a single dose of ^{186}Re(Sn)HEDP.

Toxicity

No patient experienced any appreciable change in blood pressure or pulse rate, and none had any clinically evident acute toxicity following injection of either compound.

Our initial studies (*9*) had indicated a clinically unimportant but statistically significant decline in both the total white blood cell count and in the total platelet count following the administration of ^{186}Re(Sn)HEDP. In the current population we were able to compare changes in total white blood cell count (WBC) and in total platelet count after ^{186}Re(Sn)HEDP with those observed following placebo (Table 5) and found that only the decline in the total WBC count was attributable to the ^{186}Re(Sn)HEDP injection ($p < 0.01$). There was no significant difference in the mean maximal decline in total platelet count between the placebo- and ^{186}Re(Sn)HEDP-treated groups, although the sample size was small. The absence of a significant decrease in total platelet counts following ^{186}Re(Sn)HEDP also reflects the progressive decline in platelets noted in the seven patients initially receiving placebo that presumably was due to the underlying malignancy (Table 5).

DISCUSSION

Initial trials with ^{186}Re(Sn)HEDP indicated that there were prompt, significant improvements in the quality of life in 80% of patients treated with a single intravenous injection (*9*). The time to response and overall response rates were similar to those that had been reported after hemibody external radiation (*2*). In contrast to external radiation or ^{32}P-orthophosphate therapy, no toxicity was evident other than a mild transient drop in the total platelet

TABLE 4
Mean (±1 s.d.) Decrease (Baseline-nadir) in Analgesic Index

	Treatment sequence	
	^{186}ReHEDP→Placebo	Placebo→^{186}ReHEDP
Number of patients	6	7
Initial injection	5.8 ± 5.3	0.6 ± 1.3
Crossover injection	−2.3 ± 2.9	−0.3 ± 2.2
Initial—Crossover	8.1 ± 7.0	0.9 ± 1.8
	p = 0.05	

TABLE 5
Mean (±1 s.d.) Decrease (Baseline-nadir) in Total White Blood Cell and Platelet Counts

	Treatment sequence			
	^{186}ReHEDP→Placebo		Placebo→^{186}ReHEDP	
	WBC × 10^3	Platelets × 10^3	WBC × 10^3	Platelets × 10^3
Number of patients	6	6	7	7
Post-initial injection	1.6 ± 1.3	94 ± 93	0.8 ± 0.7	62 ± 87
Post-crossover injection	−0.3 ± 0.5*	4 ± 59*	1.0 ± 0.7	64 ± 54
Initial—Crossover	2.2 ± 1.0*†	101 ± 111*‡	−0.2 ± 1.0†	−2 ± 64‡

* Number of patients = 5.
† $p < 0.01$.
‡ n.s.

and WBC counts that returned to baseline levels by the end of the 8-wk study period, and tumor/marrow dose ratios were about twice those reported for ^{89}Sr-chloride.

The current protocol compared responses to placebo with responses to ^{186}Re(Sn)HEDP. A significant advantage in pain reduction was associated with the ^{186}Re(Sn)HEDP treatment. This improvement was evident in spite of the fact that these were elderly, sick patients with advanced disease.

These combined results confirm that a single 30–35 mCi (1110–1295 MBq) intravenous injection of ^{186}Re(Sn)-HEDP can provide safe, predictable, symptomatic relief from painful osseous metastases in the majority of patients so treated and indicate that expanded clinical trials are warranted.

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