Rhenium-188(Sn)HEDP for Treatment of Osseous Metastases

Harry R. Maxon, III, Louis E. Schroder, Lee C. Washburn, Stephen R. Thomas, Ranasinghage C. Samaratunga, Danuta Biniakiewicz, Jonathan S. Moulton, Dwight Cummings, Gary J. Ehrhardt and Victoria Morris

Department of Radiology, Divisions of Nuclear Medicine, Medical Physics and Diagnostic Radiology; Department of Internal Medicine, Division of Hematology-Oncology, and Radiation Safety Office, University of Cincinnati Medical Center, Cincinnati, Ohio; and University of Missouri Research Reactor, Columbia, Missouri

Rhenium-188 (tin) hydroxyethylidine diphosphonate [^{188}Re(Sn)HEDP] is a new radiopharmaceutical that localizes in skeletal metastases and emits beta particles that may be therapeutically beneficial. **Methods:** It was evaluated by in vitro and in vivo testing in the laboratory, in animals and in humans using ^{188}Re from a variety of sources. It may be produced by a desk-top method developed previously for ^{186}Re(Sn)HEDP using ^{188}Re produced through neutron irradiation of either enriched ^{187}Re or naturally occurring rhenium targets or the use of a ^{188}W/^{188}Re generator. **Results:** So long as the mass of rhenium in the ^{188}Re-perrhenate to be processed into ^{188}Re(Sn)HEDP is at least 100 μg, satisfactory radiochemical yields and purity may be obtained by all methods. The ^{188}Re(Sn)HEDP has biodistribution and radiation dosimetry characteristics that are similar to those noted previously for ^{186}Re(Sn)HEDP and appears to result in similar benefits and toxicities in patients with skeletal metastases. External radiation exposure monitoring indicates that, only 4 hr after a therapeutic administration of 1110 MBq (30 mCi) of ^{188}Re(Sn)HEDP, average exposure rates at 1 meter from the patient would be only 0.5 mR/hr. **Conclusion:** Same-day, on-demand, outpatient therapy of disseminated skeletal metastases appears to be feasible with ^{188}Re(Sn)HEDP.

Key Words: rhenium-188-diphosphonate; osseous metastases

J Nucl Med 1998; 39:659–663

Over the last two decades, a variety of radiopharmaceuticals have been developed that have the potential to deliver therapeutic doses of ionizing radiation to sites of metastatic cancer in bone (*1*). Unfortunately, the only two that have been widely used to date are relatively long-lived beta emitters that have no gamma emissions suitable for high-resolution nuclear medicine imaging: ^{32}P with a physical half-life of 343 hr and a maximum beta energy of 1.71 MeV and ^{89}Sr with a physical half-life of 1212 hr and a maximum beta energy of 1.46 MeV. The relatively long half-lives in particular make these radiopharmaceuticals widely accessible but can present a problem in countries where radiation safety regulations require protracted patient isolation in the hospital. Although the U.S. Food and Drug Administration has recently approved ^{153}Sm-EDTMP for use as a palliative agent, it must be produced in a reactor and, with a physical half-life of about 46 hr, may not be readily available in many countries.

Rhenium-188 has beta emissions with a maximum energy of 2.12 MeV and an average penetration in soft tissue of 3 mm that are sufficient for therapy. It has a relatively short physical half-life of only 17 hr and can be produced either by neutron irradiation in a nuclear reactor or by an on-site ^{188}W/^{188}Re generator. The resulting ^{188}Re-perrhenate then can be converted to the bone-seeking radiopharmaceutical, ^{188}Re(Sn)HEDP, using desk-top methods developed previously at the University of Cincinnati (*2*). This radionuclide also has a 10% abundant, 155-keV gamma emission suitable for nuclear medicine imaging and in vivo biodistribution studies.

This study was undertaken to determine:

1. The feasibility of using ^{188}Re obtained from neutron irradiation of relatively inexpensive natural rhenium targets or from a potentially more widely available ^{188}W generator.
2. The biodistribution and radiation dosimetry to normal organs from ^{188}Re(Sn)HEDP compared to previously established values for ^{186}Re(Sn)HEDP.
3. Potential benefits and toxicity of ^{188}Re(Sn)HEDP in a limited number of patients with extensive skeletal metastases from prostate cancer.
4. The feasibility of outpatient therapy with ^{188}Re(Sn)HEDP based on potential radiation exposures to people coming into contact with the patients.

All animal studies were approved by the Institutional Animal Care and Use Committee of the University of Cincinnati. All human studies were performed and informed consent was obtained in accordance with the Institutional Review Board of the University of Cincinnati. All uses of radioactivity were performed in compliance with the Radiation Safety Committee of the University of Cincinnati.

MATERIALS AND METHODS

Preparation of Rhenium-188(Sn)HEDP for Human Use

Enriched (98.8% ^{187}Re and 1.2% ^{185}Re) targets were provided by NeoRx Corp. (Seattle, WA). They underwent neutron irradiation in the University of Missouri Research Reactor Facility (Columbia, MO) resulting in ^{188}Re-perrhenate with a small amount of ^{186}Re-perrhenate. This mixture was shipped to the University of Cincinnati Medical Center where it was processed as described previously for ^{186}Re(Sn)HEDP (*2*). The preparation took place under an Investigational New Drug exemption obtained for this purpose from the U.S. Food and Drug Administration. This product was used in all administrations to patients.

The ^{188}Re-perrhenate solution was diluted to 4 ml with nitrogen-purged water and added to a sterile, lyophilized kit containing 75 mg Na_2HEDP, 20.9 mg $SnCl_2$ and 10 mg ascorbic acid. The mixture was heated in a boiling water bath for 10 min and then diluted to 20 ml with 3 m*M* ascorbic acid. An Accell QMA anion-exchange Sep-Pak cartridge (Waters Associates, Milford, MA) was prewashed with 10 ml of 3 m*M* ascorbic acid, and the diluted radiopharmaceutical preparation was loaded onto the cartridge, which was then washed with 10 ml of 3 m*M* ascorbic acid and eluted with a 0.3 *M* NaCl/0.01 *M* Na_2HEDP/3 m*M* ascorbic acid (pH 7.0) solution. The first 1 ml of eluate was discarded, the next

Received Mar. 14, 1997; revision accepted Jun. 24, 1997.

For correspondence or reprints contact: Harry R. Maxon, III, MD, Saenger Professor of Radiological Sciences, Division of Nuclear Medicine, University of Cincinnati Medical Center, Cincinnati, OH 45267-0577.

3 ml were collected as the product, and the remainder was discarded. The 3 ml of product solution was passed through a 0.22-μ filter into a nitrogen-purged vial and then diluted with 3 ml of 0.01 *M* Na_2HEDP. This final product was assayed for ^{188}Re and ^{186}Re content using a calibrated intrinsic germanium detector, and the levels of ReO_4^- and ReO_2 impurities were determined by paper chromatographic analyses using acetone and 0.9% NaCl/0.01 *M* Na_2HEDP, respectively, as solvents. Data from sterility and pyrogen tests were available after administration to patients.

During these studies, 12 separate batches of ^{188}Re(Sn)HEDP were prepared for human use. At the time of injection, the average radiochemical purity was 97.3%, and the average radionuclidic purity was 98.7%. Specific contaminants were (mean ± 1 s.d.): ReO_4^- 2.23% ± 1.35%; ReO_2 0.42% ± 0.14%; and ^{186}Re 1.27% ± 0.71%.

In the process of developing a method for the preparation of ^{188}Re(Sn)HEDP, it became evident that the total mass of rhenium in the product received from the University of Missouri Research Reactor Facility had to be at least 100 μg or yields would be very low and would contain as yet unidentified chemical complexes that altered the biodistribution. The ^{188}Re targets used in the human radiopharmaceutical preparations contained a mean (± 1 s.d.) mass of 1298 ± 426 μg of rhenium. The final patient preparations of ^{188}Re(Sn) HEDP contained 7.21 ± 0.28 μg of rhenium per 37 MBq (1 mCi) administered, and the total mass of rhenium administered to each individual patient ranged between 238 and 360 μg.

The problems with low rhenium mass were not encountered in the preparation of ^{186}Re(Sn)HEDP, because that procedure always used a rhenium mass of approximately 500 μg. The recovered radiochemical yields for both ^{186}Re(Sn)HEDP and ^{188}Re(Sn)HEDP (made with higher levels of rhenium) were generally in the 40%–50% range. We have not performed a detailed study of the precise rhenium mass levels at which problems occur, but we have found that the preparation appears to behave normally when the rhenium mass is approximately 100 ug or higher, whereas problems occur when the rhenium mass is appreciably lower than 100 μg. Little is known about the exact nature of rhenium complexes with HEDP, and we have not investigated the differences in chemical composition of the complexes formed with high versus low rhenium mass.

Evaluation of Alternative Sources of Rhenium-188

Generator-Produced Rhenium-188. Workers at Oak Ridge National Laboratory (Oak Ridge, TN) developed a tungsten-$^{188}/^{188}Re$ alumina-based generator that produces high yields of carrier-free ^{188}Re (*3*). Gary Griffiths of Immunomedics, Inc. (Warren, NJ) in collaboration with F.F. Knapp, Jr., at Oak Ridge National Laboratory, provided 7.7 ml of the center fraction obtained with 20 ml of 0.9% NaCl eluant and containing 1295 MBq (35 mCi) of ^{188}Re as perrhenate at the time of shipment according to their protocol for human preparations. This was divided into two batches and converted to ^{188}Re-(Sn)HEDP using our protocol for human preparations.

The first batch contained no-added-carrier and yielded only 7.3% ^{188}Re-(Sn)HEDP. Images obtained about 3 hr after injection into a New Zealand white rabbit revealed unusually high soft-tissue activity. In contrast, when 132 μg of nonradioactive NH_4ReO_4 carrier containing 91.6 μg of Re were added to the second batch before processing, the resultant radiochemical yield of 43.2% ^{188}Re(Sn)HEDP was no different from that obtained using reactor produced ^{188}Re. When the carrier-added product was injected into rabbits, imaging 3–4 hr later (Fig. 1A) revealed a biodistribution very similar to that seen in a man with metastatic prostate cancer who received reactor-produced ^{188}Re(Sn)HEDP (Fig. 1B).

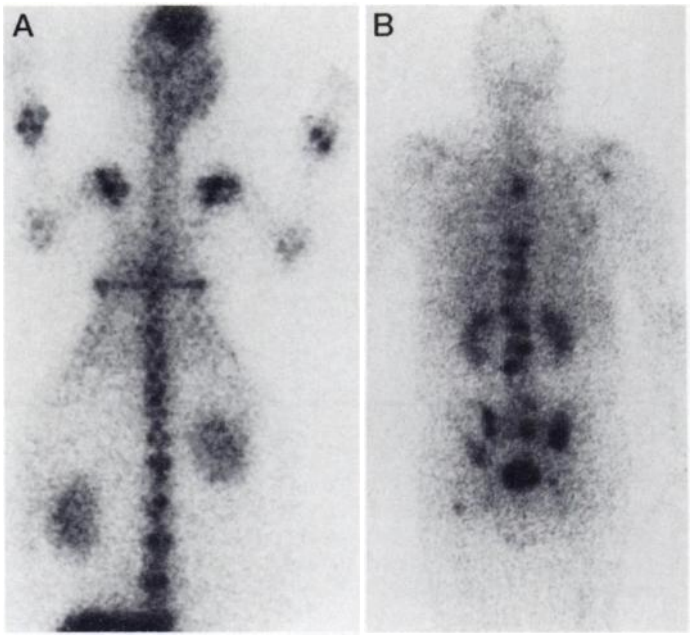

FIGURE 1. Biodistribution of ^{188}Re(Sn)HEDP about 3 hr after injection. (A) New Zealand white rabbit: carrier-added, generator-produced perrhenate. (B) Human patient with prostate cancer: reactor-produced perrhenate from enriched ^{187}Re targets.

Natural, Nonenriched Rhenium Targets for Neutron Irradiation

Because both ^{188}Re and ^{186}Re are potential therapeutic radionuclides, and because the requisite enriched ^{187}Re and ^{185}Re targets for their preparation are expensive and of limited availability, a preliminary evaluation was undertaken of the use of nonenriched, naturally occurring rhenium targets.

NeoRx Corp. (Seattle, WA) provided natural rhenium targets. After neutron irradiation in the University of Missouri Research Reactor Facility, the resulting $^{186}Re/^{188}Re$-perrhenate was shipped to the University of Cincinnati Medical Center for processing on two occasions.

The first batch was prepared without added rhenium carrier, and the total mass of rhenium was lower than the 100 μg required, being estimated at about 35 μg. The resultant radiochemical yield was only 20.7%.

The second batch was prepared after adding sufficient carrier as NH_4ReO_4 to increase the total mass of rhenium to 116 μg. The resultant radiochemical yield was 41.6%, which is the same as that achieved using enriched targets.

The radiochemical purity of the first batch was 92.4% Re(Sn)HEDP, and it contained unacceptable amounts of ReO_2. The second batch was 96.4% Re(Sn)HEDP and met radiochemical purity requirements for human studies. Using a calibrated intrinsic germanium detector, the final preparations for injection were found to contain 29% ^{188}Re and 71% ^{186}Re in the first batch and 38% ^{188}Re and 62% ^{186}Re in the second batch. Preparation of the first batch was completed 29.5 hr and the second batch 33.3 hr after removal of the targets from the reactor. After injection of 89 MBq (2.4 mCi) of batch 2 into a New Zealand white rabbit, the 24-hr images revealed the expected, normal biodistribution of Re(Sn)HEDP (Fig. 2A). For comparison, Figure 2B shows the biodistribution at 24 hr of 1,909 MBq (51.6 mCi) of ^{188}Re(Sn)HEDP, prepared using enriched ^{187}Re targets, in a man with skeletal metastases from prostate cancer.

Radiation Dosimetry

Based on prior work at the University of Cincinnati (*2,4*) and subsequent organ dose calculations based on biokinetic data for

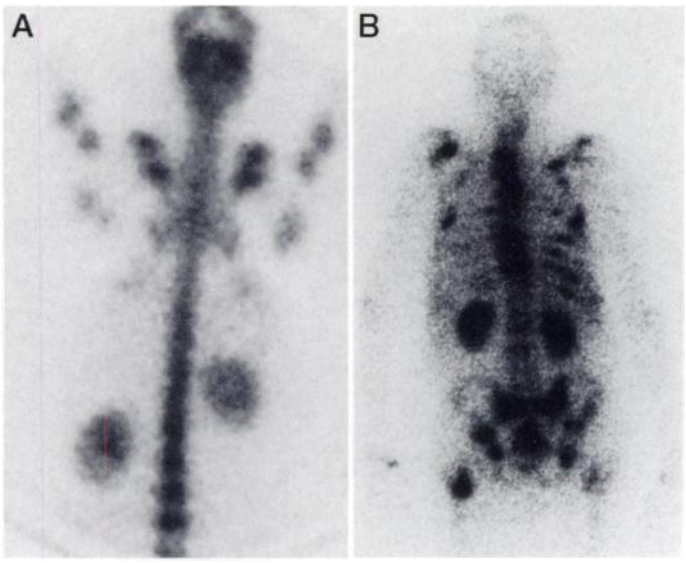

FIGURE 2. Biodistributions 24 hr postinjection of (A) ^{188}Re-/^{186}Re-(Sn)HEDP mixture from naturally occurring rhenium targets in a New Zealand white rabbit and (B) ^{188}Re(Sn)HEDP from purified ^{187}Re targets in a man with prostate cancer metastatic to bone.

^{186}Re(Sn)HEDP from 65 administrations to 38 patients with cancer metastatic to bone, it was possible to project potential radiation doses for ^{188}Re(Sn)HEDP in man (Table 1). Although biodistribution studies of ^{188}Re(Sn)HEDP in two dogs revealed findings similar to those observed in humans who had received ^{186}Re(Sn)HEDP, an additional evaluation was undertaken in rats before human trials.

A total of 10 rats were injected with ^{186}Re(Sn)HEDP and 10 were injected with ^{188}Re(Sn)HEDP. Five from each group were killed at 3 and at 24 hr postinjection. Decay-corrected percent uptakes were calculated for all major organ systems, including normal bone, the kidneys, testes, bladder wall and whole body. The only significant differences occurred in kidneys and bone (Table 2). The potential impact of the biodistribution observed in rats on human dosimetry was evaluated by extrapolating the rat data to humans. For ^{188}Re(Sn)HEDP, three human biodistribution models were used:

1. An unadjusted model assuming the same biodistribution for both radiopharmaceuticals.
2. A model assuming a 48% increase in uptake by the kidneys and an 18% decrease in uptake by normal bone.
3. A model assuming a 26% increase in uptake by the kidneys and a 15% decrease in uptake by normal bone.

The resulting radiation doses did not differ appreciably from those originally projected, regardless of model.

It should be noted that, given a biological half-time in bone of Re(Sn)HEDP of 60 hr and physical half-times of about 91 hr for ^{186}Re and of about 17 hr for ^{188}Re, the residence times for equal administered activities would be about 2.7 times longer for ^{186}Re(Sn)HEDP than for ^{188}Re(Sn)HEDP. However, the ratios of S-values from various sources to targets for ^{188}Re-(Sn)HEDP versus ^{186}Re(Sn)HEDP ranged from 1.7–2.3. Thus, for ^{188}Re(Sn)HEDP, as compared to ^{188}Re(Sn)HEDP, the residence time was reduced, but the S-value increased by almost the same factor. The net effect of these differences on the radiation dose was one of essentially no change.

Five patient volunteers then were injected intravenously with diagnostic administrations of 178–185 MBq (4.8–5.0 mCi) of ^{188}Re(Sn)HEDP. All five were men with prostate cancer, and their ages ranged between 54 and 77 yr. No acute reactions or toxicity were evident. Based on observed biokinetic data from these five men, radiation doses were calculated as described earlier (*2,4*). The resulting radiation doses are shown in Table 3 and are, as expected, very similar to those projected from earlier experience with ^{186}Re(Sn)HEDP (Table 1). Although the ratio of the calculated radiation doses in normal bone as compared to red bone marrow was about 0.9 for ^{188}Re(Sn)HEDP (Table 3) in these five patients, the same ratio previously observed for ^{186}Re(Sn)HEDP in five similar but different patients was about 1.2 (*4*). These differences appear to reflect the increase in kidney uptake and decrease in bone uptake of ^{188}Re(Sn)HEDP as compared with ^{186}Re(Sn)HEDP as shown in Table 2.

As noted previously (*2,4*), we have used two models for calculating radiation dose to the skeleton and to the bone marrow. Both use standard MIRD schema and an ICRP model that assumes a uniform surface deposition of HEDP in bone where 50% deposits in cortical bone and 50% deposits in trabecular bone. The two models differ in the manner in which residence times are calculated for the total skeleton.

In the "fixed" model, the peak activity of Re(Sn)HEDP in "normal skeleton" is held constant at 22% of the administered activity based on data from ^{99m}Tc-HEDP (*2*), and the residence time is calculated using actual measurements of Re(Sn)HEDP kinetics in normal bone. In the "variable" model it is assumed that all activity not shown to be in the urine, blood or kidneys at each point in time is distributed evenly throughout the skeleton, and the residence time is derived accordingly.

TABLE 1
Projected Radiation Doses from Rhenium-188-(Sn)HEDP Based on Prior Human Experience with Rhenium-186-(Sn)HEDP

Organ	Calculated (^{186}Re) and extrapolated (^{188}Re) dose in rad/mCi or cGy/37 MBq (mean ± 1 s.d.)	
	^{186}Re(Sn)HEDP	^{188}Re(Sn)HEDP
Kidneys	3.7 ± 2.4	4.4 ± 0.01
Gonads	0.5 ± 0.2	0.3 ± 0.1
Red marrow	5.4 ± 1.4	3.2 ± 0.6
Total body	0.6 ± 0.2	0.4 ± 0.1

TABLE 2
Decay-Corrected Biological Uptakes of Rhenium-186-(Sn)HEDP and Rhenium-188-(Sn)HEDP in Kidneys and Bone in Normal Rats

	% at 3 hr		% at 24 hr		%Difference ^{188}Re vs. ^{186}Re	
	^{186}Re	^{188}Re	^{186}Re	^{188}Re	3 hr	24 hr
Average both kidneys	0.69	1.02	0.42	0.53	48 ↑	26 ↑
Average both femurs	0.90	0.74	0.66	0.56	18 ↓	15 ↓

The differences are significant ($p \leq 0.001$) in both organs at both 3 and 24 hr.

TABLE 3
Radiation Doses to Normal Organs in Five Male Patients with Prostate Cancer from Rhenium-188-(Sn)HEDP

Organ	Calculated dose (rad/mCi or cGy/37 MBq)		
	Mean ± 1 s.d.	Median	Range
Kidneys	5.2 ± 1.2	4.7	3.9–6.9
Bladder wall*	3.6 ± 1.1	3.4	2.0–5.4
Red marrow	3.5 ± 0.7	3.6	2.7–4.5
Normal skeleton	3.2 ± 0.5	3.2	2.4–4.0
Testes	0.14 ± 0.03	0.15	0.13–0.99
Total body	0.37 ± 0.06	0.37	0.29–0.47

*Assuming voiding every 4.8 hr.

The fixed model would seem to be most applicable to patients with only a few metastases and tends to give a lower bound estimate. The variable model, in general, provides an upper bound estimate compatible with more extensive disease, although it still might underestimate the dose when the marrow is extensively replaced by tumor.

Therapeutic Administrations

Patient Selection and Evaluation. Patients were interviewed to ascertain their eligibility for participation, and informed consent was obtained. They were required to have biopsy-proven cancer of the prostate with scintigraphic (^{99m}Tc-MDP) and radiographic evidence of skeletal metastases that had failed hormonal therapy. Their white blood cell counts had to be at least 4.0×10^9/liter with a total platelet count of at least 100×10^9/liter and a serum creatinine of 133 μmol/liter (1.5 mg/dl) or less. Exclusion criteria included prior whole-body or hemibody irradiation, prior bone marrow transplant, or clinical evidence of impending spinal cord compression, pathologic fracture, or disseminated intravascular coagulopathy. Their clinical responses to therapy and toxicity were assessed using indices of daily pain and of daily analgesic intake and weekly laboratory testing for 8 wk after treatment as described previously (*5*).

Patients

Eight men with progressive, painful and extensive skeletal metastases from prostatic cancer volunteered for the therapeutic protocol. Their mean (± 1 s.d.) age was 72.6 ± 5.1 yr. Seven had undergone prior surgical orchiectomies, and the eighth had received hormonal therapy. Three had received prior local external radiation therapy for skeletal metastases: one to a single hip; one to the mid-dorsal and lumbar spine and hemipelvis; and one to the lower lumbar spine and pelvis. Five of the eight patients were receiving daily narcotic therapy.

RESULTS AND DISCUSSION

Pain Relief

The first five men received a single intravenous injection of 1262 ± 33.3 MBq (34.1 ± 0.9 mCi) of ^{188}Re(Sn)HEDP. Two of the five did not obtain pain relief; both required urgent external radiation therapy for spinal cord compression: one at 3 wk and one at 8 wk postinjection. The other three patients experienced marked pain relief, achieving nadir pain indices that were less than 15% of their baseline values. In all three, pain relief continued at the final 8-wk follow-up visit. Two of the three responders also had a reduction in their pain medications of at least 50%; in the other, analgesic requirements did not change. None of the five men had any acute reactions.

Three men received a single intravenous injection of 1817 ± 85 (49.1 ± 2.3 mCi) of ^{188}Re(Sn)HEDP. One experienced a transient increase in pain shortly thereafter (so called "flare" reaction); no other acute reactions occurred. Only one of three experienced a decrease in his pain index, to 36% of baseline, and he also was able to decrease his analgesic intake to 28% of baseline. The second patient had no decrease in his pain index but was able to decrease his analgesic intake to 22% of baseline. The third subject had no response to treatment. By 8 wk postinjection, all three had ceased to respond.

Thus, a positive response, as indicated by at least a 50% reduction in pain and/or analgesic usage, was seen in 5/8 (63%) patients, which is consistent with earlier, more extensive experience with ^{186}Re(Sn)HEDP.

Toxicity

Hematopoietic. Thrombocytopenia was found only in one patient who received 1247 MBq (33.7 mCi) ^{188}Re(Sn)HEDP. From a baseline platelet count of 218×10^9/liter (normal: 150–375), he declined to a nadir value of 146×10^9/liter.

Leukopenia was noted in three patients. One man with a baseline white blood cell count of 4.8×10^9/liter (normal: 4.8–10.8) experienced a transient decline to a value of 3.6×10^9/liter 1 wk after receiving 1265 MBq (34.2 mCi) of ^{188}Re(Sn)HEDP. A second patient experienced a decline from a baseline value of 5.8×10^9/liter to a nadir value of 3.8×10^9/liter 8 wk after receiving 1247 MBq (33.7 mCi) of ^{188}Re(Sn)HEDP, and he was the same patient who experienced thrombocytopenia. A third patient had a decline in his white blood cell count from a baseline value of 5.4×10^9/liter to a nadir value of 2.9×10^9/liter that persisted, beginning week 5 after the administration of 1909 MBq (51.6 mCi) of ^{188}Re(Sn)HEDP.

All but one patient were anemic at entry, with a mean (± 1 s.d.) baseline hemoglobin concentration in those seven patients of 11.4 ± 1.3 g/dl (normal: 14–18). Applying common toxicity criteria for hemoglobin (Class I = Hgb 10.1–13.9 g/dl; Class II = Hgb 8.0–10.0 g/dl; Class III = Hgb 6.5–7.9 g/dl) to both baseline and nadir values, an increase in grade of anemia by one class was seen in four patients: in two who received 1288 and 1909 MBq (or 34.8 and 51.6 mCi) of ^{188}Re(Sn)HEDP) Class I → Class II; in one receiving 1265 MBq (34.2 mCi) of ^{188}Re(Sn)HEDP normal → Class I; in one man who received 1247 MBq (33.7 mCi) of ^{188}Re(Sn)HEDP (and who also experienced both thrombocytopenia and leukopenia) Class II → Class III. All but one of the four patients who experienced worsening of their anemia had returned to their baseline category by 8 wk after injection, and the fourth was improving.

Based on these limited data, hematopoietic toxicity after 35 mCi of ^{188}Re(Sn)HEDP appears to be mild and consistent with earlier, more extensive experience with similar activities of ^{186}Re(Sn)HEDP.

Renal. Two patients experienced mild renal toxicity with serum creatinine concentrations greater than 133 μmol/liter (1.5 mg/dl). Both experienced transient, minimal increases in their serum creatinine concentrations to a peak value of 142 μmol/liter (1.6 mg/dl), at 1–2 wk postinjection that returned to normal by 8 wk postinjection. At the same time, both went from a normal baseline urine analysis to trace proteinuria. One of the patients, who received 1909 MBq (51.6 mCi) of ^{188}Re(Sn)HEDP, returned to a normal urinalysis, while the other, who received 1288 MBq (34.8 mCi) of ^{188}Re(Sn)HEDP, continued to have trace proteinuria. Urinalyses in other subjects were variable, as often is the case in patients with prostate cancer, but none developed elevated serum creatinine levels.

Radiation Safety Considerations

External monitoring of four patients was performed by Radiation Safety personnel using a calibrated Bicron RSO-5 (Bicron Corp., Newbury, OH) survey meter. Measurements were obtained at 46 cm and 1 m from the central axis of the patient immediately after injection (four patients), and 4 (three patients) and 24 hr (three patients) later. All four patients had measurements at least two different times. Their average administered activity was 1,413 MBq (38.2 mCi) of ^{188}Re(Sn)HEDP (range 1265–1798 MBq or 34.2–48.6 mCi). The results shown in Table 4 suggest that these patients may be treated as outpatients without undue radiation exposures to their families or to the public, depending on the activity administered.

CONCLUSION

Given the caveat that particular attention must be paid to the amount of carrier rhenium in the ^{188}Re-perrhenate that is to be processed into ^{188}Re(Sn)HEDP, satisfactory radiochemical

TABLE 4
Potential Radiation Exposures to the Public from Four Men with Skeletal Metastases from Prostate Cancer Treated with Rhenium-188-(Sn)HEDP

Time postinjection	Radiation exposures (mean ± 1 s.d.) in mR/hr/10 mCi*	
	Distance from the patient axis	
	46 cm	1 m
0 hr	0.77 ± 0.22	0.24 ± 0.07
4 hr	0.42 ± 0.25	0.17 ± 0.08
24 hr	0.08 ± 0.06	<0.06

*1 mR/hr/10 mCi = 7×10^{-10} coul/kg/hr/MBq.

yields and purity of ^{188}Re(Sn)HEDP may be obtained using ^{188}Re from neutron irradiation in a nuclear reactor of either enriched ^{187}Re or naturally occurring rhenium targets or from perrhenate obtained from a ^{188}W/^{188}Re generator system. The generator would have the advantages of onsite availability in large cancer centers or in countries where nuclear reactors are not readily accessible. The use of naturally occurring rhenium targets would eliminate the cost of obtaining enriched target material but would require therapy with a combination of ^{188}Re and ^{186}Re(Sn)HEDP, both of which may be useful agents.

The biodistribution and radiation dosimetry of ^{188}Re(Sn)HEDP are quite similar to those found with ^{186}Re(Sn)HEDP, and the limited data in this study suggest similar benefits and toxicities of the two compounds. Moreover, the short physical half-life of ^{188}Re combined with the rapid renal clearance of HEDP results in such low potential radiation exposures to other people from patients treated with ^{188}Re(Sn)HEDP that same-day outpatient therapy may be feasible.

These considerations indicate an appealing flexibility in the production and use of ^{188}Re(Sn)HEDP for treatment of skeletal metastases that warrant further investigation.

ACKNOWLEDGMENTS

This work was supported by the National Cancer Institute, National Institutes of Health Grant CA-32863, by a grant from the Department of Energy for the production of ^{188}Re by the University of Missouri Research Reactor Facility and by NeoRx Corp., Seattle, WA, which prepared the material used in the targets for ^{188}Re production.

REFERENCES

1. Hosain F, Spencer RP. Radiopharmaceuticals for palliation of metastatic osseous lesions. Biologic and physical background. *Semin Nucl Med* 1992;22:11–16.
2. Maxon HR, Schroder LE, Thomas SR, et al. Rhenium-186-(Sn)HEDP for treatment of painful osseous metastases: initial clinical experience in 20 patients with hormone-resistant prostate cancer. *Radiology* 1990;176:155–159.
3. Callahan AP, Rice DE, Knapp FF Jr. Rhenium-188 for therapeutic applications from an alumina-based tungsten-188/rhenium-188 radionuclide generator. *NucCompact-Eur/Am Commun Nucl Med* 1989;20:3–6.
4. Maxon HR, Deutsch EA, Thomas SR, et al. Rhenium-186(Sn)HEDP for treatment of multiple metastatic foci in bone: human biodistribution and dosimetric studies. *Radiology* 1988;166:501–507.
5. Maxon HR, Schroder LE, Hertzberg VS, et al. Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo. *J Nucl Med* 1991;32:1877–1881.

Biodistribution Studies on L-3-[Fluorine-18]Fluoro-α-Methyl Tyrosine: A Potential Tumor-Detecting Agent

Tomio Inoue, Katsumi Tomiyoshi, Tetsuya Higuichi, Khalil Ahmed, Muhammad Sarwar, Keiko Aoyagi, Shigeko Amano, Saleh Alyafei, Hong Zhang and Keigo Endo

Department of Nuclear Medicine, Gunma University School of Medicine, Gunma, Japan

Iodine-123-α-methyl tyrosine has proven to be a promising SPECT agent for imaging amino acid uptake in tumors. We developed L-[3-^{18}F]-α-methyl tyrosine (FMT) for PET studies. The aim of this study was to investigate its potential use as a tumor-detecting agent by using tumor-bearing mice. **Methods:** We investigated the biodistribution in normal BALB/C mice and BALB/cA nude mice bearing human rectal cancer cell line (LS180) until 120 min postinjection. FMT tumor uptake at 60 min postinjection in mice with LS180 rectal cancer, RPMI1788 B-cell lymphoma and MCF7 mammary cell carcinoma was assessed, and the results were compared with ^{18}F-fluoro-2-deoxy-D-glucose (FDG) tumor uptake. The effect of competitive inhibition of large neutral amino acid transport system using unlabeled L-alanine was also investigated. **Results:** The amount of FMT in blood fell to 1.05%ID/20 g at 60 min postinjection, whereas that in the pancreas was 15.2%ID/20 g, resulting in a high pancreas-to-blood ratio of 14.5. In other organs, initial uptake peaked at 5 min postinjection and then declined with time. In LS180 tumor-bearing mice, peak FMT uptake in tumor was observed at 60 min postinjection. Tumor-to-blood and tumor-to-muscle ratios ranged from 1.60 to 2.94 and from 2.79 to 3.25 over the 120-min observation period. Tumor uptake of FMT was clearly reduced by inhibition of the amino acid transport system. In mice with LS180 and MCF7 tumors, FMT tumor uptake at 60 min postinjection was significantly higher than FDG tumor uptake, whereas in RPMI1788 lymphoma, uptake of FDG was significantly higher than FMT tumor uptake. Tumor-to-blood ratios of FMT in mice with LS180, RPMI1788 and MCF7 tumor at 60 min postinjection were 1.82, 5.88 and 3.56, respectively. **Conclusion:** FMT, like other fluorinated amino acids, may become a promising tumor-detecting agent for PET, assuming that efficient methods of radiosynthesis are developed.

Key words: fluorine-18-methyl tyrosine; biodistribution studies; PET

J Nucl Med 1998; 39:663–667

A glucose analog, ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG), has been widely used for tumor imaging with PET, and its usefulness for detecting various malignant tumors, such as

Received Mar. 1., 1997; revision accepted Jun. 12, 1997.

For correspondence or reprints contact: Tomio Inoue, MD, Department of Nuclear Medicine, Gunma University School of Medicine, 3-39-22 Showa-machi Maebashi, Gunma 371, Japan.