Pharmacokinetics of Rhenium-186 After Administration of Rhenium-186-HEDP to Patients with Bone Metastases

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The pharmacokinetics of ^{186}Re-HEDP, a radiopharmaceutical for palliative treatment of metastatic bone pain, was investigated in 11 patients (17 studies) who suffered from metastatic breast or prostate cancer. Half-life times of ^{186}Re in three blood fractions (whole blood, plasma and plasma water) were 40.1 ± 5.0, 41.0 ± 6.0 and 29.5 ± 6.4 hr, respectively. Time-dependent increase in plasma-protein binding was observed, probably caused by in vivo decomposition of ^{186}Re-HEDP. Total urinary ^{186}Re excretion was 69% ± 15%, of which 71% ± 6% was excreted in the first 24 hr after injection. The BSI (i.e., fraction of the skeleton showing scintigraphic evidence of metastatic disease) closely correlated with the fraction of dose non-renally cleared (r = 0.98). This implies that the amount of radioactivity taken up by the skeleton and hence the bone marrow absorbed dose can be predicted from a diagnostic pre-therapy ^{99m}Tc-HDP scintigram. The pharmacokinetic behavior indicates that ^{186}Re-HEDP has suitable properties to justify its application.

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Metastatic involvement of the skeleton is common in patients with breast or prostate cancer (*1*). A prominent symptom caused by these metastases is pain. The standard therapy for bone metastases is local external beam radiotherapy (*2,3*), but due to the large number of lesions in many patients, radionuclide therapy using specifically localized internal beta emitters is preferable. Several bone-seeking agents in radionuclide therapy have been used for palliative purposes (*4*) without achieving widespread clinical acceptance. Phosphorus-32-sodium phosphate was the first and most widely employed radionuclide for palliative treatment of bone metastases (*5*). Because of undesirable myelosuppression, its use for this purpose has been abandoned. Robinson et al. described favorable responses with ^{89}Sr in patients with carcinoma of the prostate or breast (*6*). Unfortunately, this radionuclide has a relatively long physical half-life (50 days) and does not emit gamma-rays for post-therapy quantitative imaging. Recently, rhenium-186(Sn)-1,1-hydroxyethylidene diphosphonate (^{186}Re-HEDP) has been proposed for palliation of pain resulting from metastatic bone lesions of various tumor types. Initial results showed that ^{186}Re-HEDP is able to reduce pain caused by multiple bone metastases (*7–11*).

Rhenium-186 has a relatively short physical half-life ($t_{½}$ = 89.3 hr). It has both beta emissions suitable for therapy (E_{max} = 1.07 MeV) and gamma emissions suitable for external imaging (E_{γ} = 137 keV), with an external photon yield of 9%. The short physical half-life of ^{186}Re accounts for relatively high dose rates and allows for repeated treatments at timed intervals. Moreover, problems of radioactive waste handling and storage are reduced.

As part of an ongoing dose-escalation study of ^{186}Re-HEDP, its pharmacokinetic behavior was investigated. Urine and blood samples were collected and analyzed for total ^{186}Re. From the analytical results, relevant pharmacokinetic variables were calculated and judged on their clinical implications.

METHODS

Patients

Eleven patients who suffered from metastatic bone pain were studied. All patients had histopathologically proven breast (two patients, mean age: 47 yr) or prostate cancer (nine patients, mean age: 65 yr). Six patients (04P330/331; 05P330/331; 02P341 I/341 II; 07P330/331; 03P341 I/341 II; 04P341 I/341 II) underwent two pharmacokinetic investigations, resulting in a total of seventeen studies. All patients failed prior hormonal and/or chemotherapy and had scintigraphic and radiological evidence of bone metastases. The study was approved by the hospital review board and all patients gave witnessed informed consent.

Preparation of ^{186}Re-HEDP

Enriched ^{186}Re was irradiated at the reactor of the University of Missouri, St. Louis, MO to produce ^{186}Re. The ^{186}Re(Sn)HEDP complex was prepared by reconstitution of a lyophilized mixture of Na_2/H_2-HEDP (10 mg), $SnCl_2 \cdot 2H_2O$ (3.85 mg) and gentisic acid (3 mg) with 1 ml of a radioactive solution of $Na^{186}ReO_4$ (2000–2800 MBq per 0.005–0.1 mg Re) in saline. The

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^{186}Re(Sn)HEDP complex was formed by reduction of the RE(VII) with stannous ion and brief heating (10 min at 98–100°C). The pH of the resulting solution was adjusted to 5–6 by addition of 1 ml sodium acetate solution (39 mg of sodium acetate trihydrate/ml). Radiochemical purity of the ^{186}Re(Sn)HEDP-complex was checked using Whatman 3 MM chromatography paper. Free perrhenate and reduced hydrolyzed rhenium ($^{186}ReO_2$) were determined in two separate systems using acetone and 0.01 *M* Na_2/H_2-HEDP in 0.9% (w/v) saline as the solvent, respectively. The radiochemical purity of ^{186}Re-HEDP prior to injection proved to be consistently over 97%.

All components originated from Mallinckrodt Medical Inc., St. Louis, MO and were manufactured according to GMP procedures.

Radiopharmaceutical Administration

Patients were hospitalized in an isolated room in the nuclear medicine ward for 24 hr. Thirteen patients received a 1262 ± 63 MBq dose, three a dose of 1828 ± 40 MBq, and one a dose of 2353 MBq ^{186}Re-HEDP. The appropriate dose was measured by a radioactivity calibration system (VDC-101, Veenstra Instruments, Joure, The Netherlands) and administered as a bolus injection via a running intravenous saline drip.

Blood Sampling and Urine Collection

Following injection, blood samples were drawn from an antecubital vein opposite to the injection side at timed intervals (2, 4, 6, 8, 10, 20, 30, 60 min and 2, 3, 4, 10, 18, 24, 48, 72 hr postinjection) and centrifuged immediately after collection (10 min, 700 × g). Total urine was collected by spontaneous voiding or catheterization during 72 hr postinjection at intervals of 4 hr. Adequate diuresis was ensured by regular fluid intake (at least 2 liters per 24 hr).

Measurements

Radioactivity measurement of the blood (0.25 ml), plasma (0.25 ml), plasma water (0.1 ml) and urine (0.1 ml) samples was performed in duplicate in a Packard Minaxi gamma counter. Appropriate corrections were made for decay with time of injection as reference time. Plasma-protein binding was determined immediately upon collection of plasma samples by centrifugal ultrafiltration (60 min, 950 × g) with the Amicon Centrifree micropartition system (No. 4104). Similarly, protein binding was determined in vitro after incubation (10 min, 37°C) of ^{186}Re-HEDP or $^{186}ReO_4^-$ in 3 ml plasma.

Pharmacokinetic Calculations

Curve Fitting: Blood, Plasma and Plasma Water. Time-concentration curves for total ^{186}Re in whole blood, plasma and plasma water (=free ^{186}Re) were described with the equation:

$$C(t) = \sum_{i=1}^{3} A_i \cdot e^{(-k_i \cdot t)},$$

in which A_i (i = 1...3) are the intersections with the y-axis (cpm/ml) and k_i (i = 1...3) are the disposition constants in h^{-1}. The terminal phase rate constant is k_3. The program MKMODEL (*12*) was used for calculation of the A_i and k_i values.

Urine

Urine was collected at timed intervals. Total ^{186}Re excretion in MBq/hr was plotted against the midpoint of an appropriate collection interval. Time-excretion curves were described, using the iterative nonlinear least squares program MKMODEL, according to:

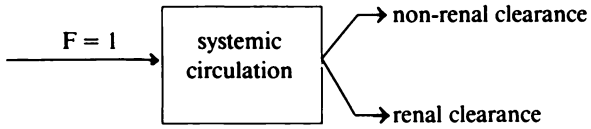
$$U(t) = \sum_{i=1}^{2} U_i \cdot e^{(-k_i \cdot t)},$$

in which U(t) is excretion in MBq/hr at midpoint of collection interval and U_i and k_i are variables comparable to A_i and k_i. By integrating the equation from zero to infinity, which represents the area under the curve, the total amount excreted up to infinity was obtained according to:

$$\sum_{i=1}^{2} \frac{U_i}{k_i}.$$

Fraction Renally Cleared and Fraction Non-renally Cleared

When ^{186}Re-HEDP has entered the systemic circulation by intravenous bolus administration, the bioavailable fraction is defined as F = 1. Total-body clearance (TBC) of ^{186}Re-HEDP is divided into renal clearance and non-renal clearance, in which TBC is clearance of whole blood, plasma or plasma water, depending on the blood fraction investigated. This is represented schematically by:



Elimination from the systemic circulation can be described by the fraction of dose renally cleared (frac ren) and the fraction of dose non-renally cleared (frac non-ren). The frac non-ren represents the fraction of the dose cleared by organs other than the kidneys.

Since it is evident from scintigraphic studies that ^{186}Re-HEDP is mainly taken up by bone, frac non-ren will be considered as the fraction of administered dose entering the bone pool. Frac ren was calculated as (dose totally excreted in urine/dose administered) and frac non-ren was calculated as (1 − frac ren).

Area Under the Curve and Terminal Half-life

The area under the curve (AUC) and half-life (terminal) were calculated from the A_i and k_i values by:

$$AUC_{0-\infty} = \sum_{i=1}^{3} \frac{A_i}{k_i} \text{ and } T_{1/2} = \frac{0.693}{k_3}.$$

Clearance

TBC_x was calculated for each blood fraction as:

$$TBC_x = \frac{\text{dose}}{AUC_{0-\infty,x}} \text{(ml/min)}$$

and renal clearance was obtained from:

$$Cl_{x,ren} = \frac{\text{amount excreted in urine}_{0-\infty}}{AUC_{0-\infty,x}} \text{(ml/min)},$$

in which x represents the blood fraction under investigation. Non-renal clearance originated from $Cl_{x,non\text{-}ren} = TBC_x - Cl_{x,ren}$.

Volume of Distribution at Steady-State ($V_{d,ss}$)

Volume of distribution at steady-state ($V_{d,ss}$) was calculated from the coefficients and exponents of the three exponential

TABLE 1
Patient Survey

Patient no.	BSI	Dose (MBq)	Creatinine clearance* (ml/min)	Fraction of dose renally cleared 0-∞	% Total urine excretion in 24 hr urine
03P330	20	1252	89	0.81	75
04P330	65	1104	66	0.57	68
04P331	80	1313	74	0.47	68
05P330	63	1834	123	0.66	71
05P331	85	1272	116	0.51	73
07P330	43	1865	88	0.80	69
01B330	47	1300	108	0.68	73
01B341	25	1247	72	0.99	82
02P341 I	90	1316	82	0.47	67
02P341 II	90	1269	77	0.54	62
03P341	40	1310	79	0.73	72
04P341	68	1163	73	0.65	76
10P331	45	1786	100	0.75	59
11P330	20	2353	110	0.76	82
07P331	43	1305	59	0.90	75
03P341 II	50	1263	69	0.79	77
04P341 II	68	1289	76	0.59	65
Mean			86	0.69	71
s.d.			19	0.15	6

* Calculated according to Cockroft and Gault (*18*).

curve fit. Plasma data were used for determination of all $V_{d,ss}$ values according to:

$$V_{d,ss} = \frac{\text{dose} \cdot \sum_{i=1}^{3} A_i/k_i^2}{(\sum_{i=1}^{3} A_i/k_i)^2}.$$

This formula calculates $V_{d,ss}$ from a single injection without the assumption of any model (*13*). Prior to calculation, A_i (cpm/ml) values were converted to MBq/ml. The conversion factor was determined using standard solutions of ^{186}Re.

Scintigraphy and Bone Scan Index

At least 2 wk prior to therapy, a diagnostic whole-body scintigram was obtained using ^{99m}Tc-HDP (Osteoscan-HDP, Mallinckrodt Medical, Petten, The Netherlands). From these scintigrams, the bone scan index (BSI) as described by Blake et al. (*14*) was determined in order to provide an index of the extent of metastatic disease and relate it to pharmacokinetic variables. In brief, this method divides the skeleton into four anatomical regions: (1) spine, (2) pelvis, (3) shoulder girdle and ribs and (4) extremities. Each region is scored visually on a scale of 0 to 10 for the apparent proportion of skeleton involved. Scores for each region are summed, and the sum renormalized to a scale of 0 to 100 as an index for the extent of skeletal involvement. Post-therapy scintigrams were obtained using the 137 keV gamma emission of ^{186}Re.

Statistical Analysis

Data were analyzed with the SYSTAT 5.0 program (SYSTAT, Inc., Evanston, IL). Friedman two-way analysis of variance was used to test for differences between renal clearance of plasma water and creatinine clearance. Linear regression analysis was applied to calculate the correlation between BSI and frac nonren or $V_{d,ss}$.

RESULTS

Pharmacokinetic Variables

Characteristics of patients are summarized in Table 1. In Figure 1, typical decay curves are shown for blood,

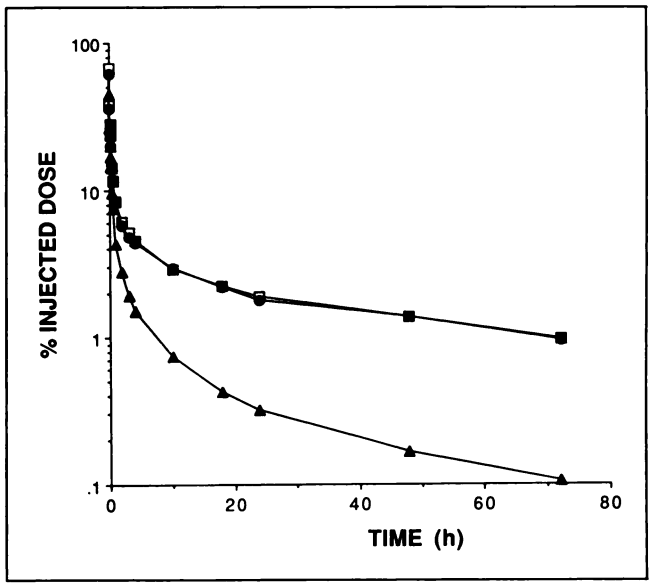


FIGURE 1. Representative disappearance curves of ^{186}Re for blood (□—□), plasma (●—●) and plasma water (▲—▲) as function of time postinjection (Patient 05P331).

plasma and plasma-water of patient No. 05P331. The terminal half-life of ^{186}Re for plasma water (29.5 ± 6.4 hr) is quite different from those for blood (40.1 ± 5.0 hr) and plasma (41.0 ± 6.0 hr). The resulting pharmacokinetic variables are presented in Table 2.

Protein Binding

An increase with time for plasma-protein binding was observed in all patients (Fig. 2, Patient 05P331). The binding increased from 51% ± 6% to 89% ± 5%. In vitro, the binding to proteins in plasma was found to be 52% ± 1% (n = 8) for ^{186}Re-HEDP and 80% ± 1% (n = 8) for $^{186}ReO_4^-$.

Urinary Excretion and Renally and Non-renally Cleared Fractions

Data for urinary excretion and the fraction renally cleared are presented in Table 1. The percentage of the injected ^{186}Re dose totally excreted was 69 ± 15 (s.d.). The percentage of total urinary excretion voided within the first 24 hr showed a narrow range of 71 ± 6 (s.d.)

Bone Scan Index

BSI values, determined from the diagnostic pre-therapy ^{99m}Tc-HDP scintigram, varied from 20 to 90 (Table 1). An excellent correlation was found between BSI and frac non-ren (Fig. 3), which can be described as frac non-ren = 0.006 (± 0.000 s.e.) × BSI with a s.e.e. of 0.074 and a r^2 of 0.957. This regression equation only holds for the interval 20 < BSI < 90. For BSI values <20, a deviation from linearity may occur.

Analogously, a good correlation was found between BSI and the volume of distribution in steady state ($V_{d,ss}$) normalized to body weight: $V_{d,ss}$ = 0.019 (±0.002, s.e.) × BSI with a s.e.e. of 0.403 and a r^2 of 0.892.

Ratio of Plasma Water Clearance Versus Creatinine Clearance

Renal clearance of plasma water (96 ± 21 ml/min) appeared to be significantly different from the creatinine clearance (86 ± 19 ml/min) upon comparison of these parameters in each patient (p = 0.03), resulting in a ratio slightly exceeding 1 (1.1 ± 0.2).

TABLE 2
Pharmacolkinetic Variables

Variable		Blood*		Plasma		Plasma water	
Half-life	(h)	40.1	(5.0)	41.0	(6.0)	29.5	(6.4)
Total Cl	(ml/min)	40	(13)	28	(9)	145	(38)
Renal Cl	(ml/min)	26	(6)	18	(4)	96	(21)
Non-renal Cl	(ml/min)	14	(10)	10	(7)	48	(31)
$V_{d,ss}$	(l/kg)			1.1	(0.5)		

* Numbers in parentheses = s.d. values.
Cl = clearance; V_d = volume of distribution; and ss = steady-state.

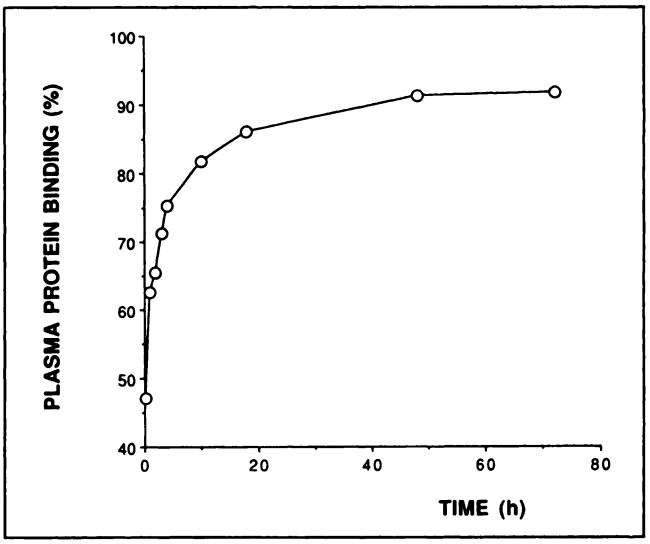


FIGURE 2. Plasma-protein binding (%) of ^{186}Re at different time points postinjection (Patient 05P331).

Post-therapy ^{186}Re-HEDP Scintigraphy

The post-therapy ^{186}Re-HEDP scintigram showed no uptake in organs other than the skeleton and kidneys. The ^{186}Re-HEDP images were identical to the ^{99m}Tc-HDP scintigram, showing the same number and localization of the metastases (Fig. 4). This indicates that the two radiopharmaceuticals concentrate in metastatic bone lesions by a similar mechanism.

DISCUSSION

Rhenium-186-HEDP is a bone-seeking agent suitable for palliative treatment of bone metastases whose most relevant pharmacokinetic variables are described in this study. Whole blood half-life time is 40.1 ± 5.0 hr, which implies that repeated doses may be administered after a

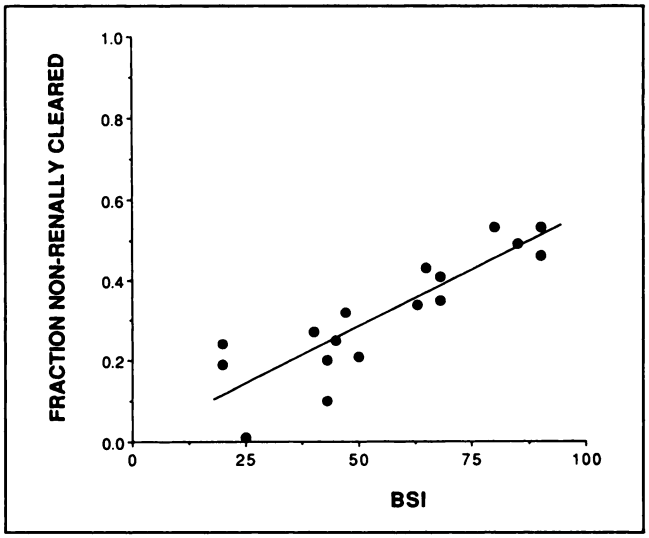


FIGURE 3. Correlation between fraction of dose non-renally cleared and BSI.

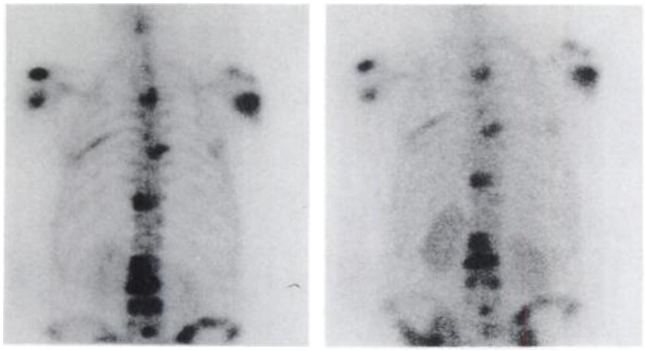


FIGURE 4. (Left) ^{99m}Tc-HDP scintigram: 400 MBq, 2 hr post-injection; (Right) ^{186}Re-HEDP scintigram: 1786 MBq, 3 hr post-injection (Patient 10P331).

theoretical interval of 200 hr (elimination of a drug is over 96% after five half-lives). However, the optimal interval time between two doses will also depend on the overall clinical condition of the patient. Actual thrombocyte and leukocyte counts, reflecting bone marrow function, are better parameters for establishing a time interval for a repeated dose. Initial clinical experience indicates a suitable time interval of about 6–8 wk (*10*). As for the plasma water (free) half-life time, this value is quite different from whole blood and plasma half-life times. This phenomenon is explained by nonconstant protein binding.

The renal excretion of a drug depends not only upon its physicochemical properties and the physiology of the kidney, but also upon its binding to plasma proteins. The plasma-protein binding of ^{186}Re shows a conspicuous increase with time. It is attractive to speculate that this is caused by in vivo decomposition of ^{186}Re-HEDP leading to compounds having a different plasma-protein binding. This is supported by data from our control experiments in which ^{186}Re-HEDP and $^{186}ReO_4^-$ were found to differ in their in vitro binding to proteins in plasma with values of 52% ± 1% (n = 8) and 80% ± 1% (n = 8), respectively, as well as by the work of Roodt et al. (*15*) who observed the in vivo formation of $^{186}ReO_4^-$ from ^{186}Re-HEDP in five patients with bone metastases treated with ^{186}Re-HEDP. No final explanation for the observed increase in plasma-protein binding and its underlying mechanism now exists, and further studies are needed to clarify this phenomenon.

The clearance of ^{186}Re is different for each of the three blood fractions. Obviously, plasma water (free) clearance is highest because only non-protein-bound substances are cleared by the kidney. By using the calculated creatinine clearance (Table 1) as an estimate of the glomerular filtration rate (GFR), it is possible to assess the excretion ratio of ^{186}Re, which is defined as renal clearance of plasma water divided by the GFR and appears to be close to 1. An excretion ratio >1 indicates a substance predominantly secreted by the kidney, while a ratio <1 indicates that it is predominantly reabsorbed (*16*). When the excretion ratio of a compound is equal to or close to 1 (as is the case for ^{186}Re), it is either predominantly filtered by the glomeruli, or tubular secretion and reabsorption contribute equally to renal clearance (*16*). Separate studies are necessary to discriminate between the two mechanisms of renal handling. Anyhow, the main determinant for the renal excretion rate will be GFR, which can not be influenced by enhancing diuresis. In cases of diminished GFR due to an obstructive nephropathy and subsequently renal dysfunction, which frequently occurs in patients with prostatic cancer, the excretion of ^{186}Re will decrease accordingly. This implies that application in cases of renal dysfunction needs further consideration.

Rhenium-186 is primarily excreted into the urine (69% ± 15%). The percentage excreted is closely correlated with the BSI (r = 0.98). Consequently, the BSI is a good predictor for the amount of ^{186}Re excreted into the urine. Assuming that the radioactivity seen in the kidneys is excreted into the urine (frac ren), the frac non-ren approaches the total ^{186}Re-HEDP uptake in the skeleton. This is not only important for the prediction of the bone marrow absorbed dose, but also implies that the more extensive the metastatic disease (high BSI) the smaller the amount of ^{186}Re excreted in the urine. The existence of more lesions (i.e., a higher BSI) gives rise to a greater value of the $V_{d,ss}$, which is further evidence that ^{186}Re-HEDP binds preferentially to metastatic lesions, producing an increased lesion-to-normal bone ratio. Since the ^{186}Re agent continuously washes off from normal bone (*15*), the frac non-ren could theoretically approach zero in patients with a very low BSI. In such cases, in spite of a good initial uptake in normal bone, almost all the ^{186}Re-HEDP is washed off eventually within the time period over which the frac non-ren is calculated (from zero to infinity, decay-corrected).

Preliminary results (*10*) have shown that the limiting factor of ^{186}Re-HEDP therapy is mainly confined to the bone marrow toxicity. Therefore, it would be clinically relevant to predict this toxicity on the strength of pre-therapy scintigraphy. The BSI can play an important role in this, because it predicts the percentage of uptake in the skeleton, from which the bone marrow absorbed dose can be estimated according to Turner et al. (*17*), resulting in a more individualized dosage and hence to an improvement of the efficacy of ^{186}Re-HEDP.

In conclusion, the pharmacokinetic behavior of ^{186}Re-HEDP in metastatic lesions makes it a suitable radiopharmaceutical for the palliation of metastatic bone pain. This study provides the basis for calculating a better estimate of dosimetry for patients receiving ^{186}Re-HEDP therapy and warrants further controlled clinical trials to define optimum dosing levels and schedules.

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REFERENCES

1. Scher HI, Yagoda A. Bone Metastases: pathogenesis, treatment and rationale for use of resorption inhibitors. *Am J Med* 1987;82(suppl 2A):6–28.
2. Hendrickson FR, Shehata WM, Kirchner AB. Radiation therapy for osseous metastasis. *Int J Radiat Oncol Biol Phys* 1976;1:275–278.
3. Gilbert HA, Kagan AR, Nussbaum H, et al. Evaluation of radiation therapy for bone metastases: pain relief and quality of life. *Am J Roentgenol* 1977;129:1095–1096.
4. Kim SI, Chen DCP, Muggia FM. A new look at radionuclides therapy in metastatic disease of bone (review and prospects). *Anticancer Res* 1988;8:681–684.
5. Harbert JC. Radionuclide therapy of bone pain. In: Harbert JC, ed. *Nuclear medicine therapy.* New York: Thieme Medical Publishers, Inc.; 1987:208–219.
6. Robinson RG, Spicer JA, Preston DF, Wegst AV, Martin NL. Treatment of metastatic bone pain with strontium-89. *Nucl Med Biol* 1987;14:219–222.
7. Ketring AR. Sm-153-EDTMP and ^{186}Re-HEDP as bone therapeutic radiopharmaceuticals. *Nucl Med Biol* 1987;14:223–232.
8. Maxon HR, Deutsch EA, Thomas SR, et al. Re-186(Sn)HEDP for treatment of multiple metastatic foci in bone: human biodistribution and dosimetric studies. *Radiology* 1988;166:501–507.
9. Maxon HR, Schroder LE, Thomas SR, et al. Re-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.
10. Zonnenberg BA, de Klerk JMH, van Rijk PP, et al. Re-186-HEDP for treatment of painful bone metastases in patients with metastatic prostate or breast cancer. Preliminary results [Abstract]. *J Nucl Med* 1991;32:1082.
11. 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.
12. Holford N. An extended least squares modelling program. Version 3.13, October 1986. Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand.
13. Gibaldi M, Perrier D. Pharmacokinetics. In: Gibaldi M, Perrier D, eds. *Pharmacokinetics*, second edition. New York: Marcel Dekker Inc.; 1982:319–355.
14. Blake GM, Zivanovic MA, McEwan AJ, Ackery DM. Sr-89 therapy: strontium kinetics in disseminated carcinoma of the prostate. *Eur J Nucl Med* 1986;12:447–454.
15. Roodt A, Libson K, Cutler C, Deutsch E, Thomas SR, Maxon HR. Studies on the mechanism of action of 186-Re(Sn)-HEDP, a new agent for the treatment of painful skeletal metastases [Abstract]. *J Nucl Med* 1989;30:732.
16. Diers Caviness M, MacKichan J, Bottorff M, Taylor W. Renal clearance. In: Diers Caviness M, MacKichan J, Bottorff M, Taylor W, eds. *Therapeutic drug monitoring: a guide to clinical application.* Irving, TX: Abbott Laboratories, Diagnostics Division; 1987:107–129.
17. Turner JH, Martindale AA, Sorby P, et al. Samarium-153-EDTMP therapy of disseminated skeletal metastasis. *Eur J Nucl Med* 1989;15:784–795.
18. Cockroft DW, Gault NH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.