Bone Marrow Absorbed Dose of Rhenium-186-HEDP and the Relationship with Decreased Platelet Counts

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Rhenium-186(Sn)-1,1-hydroxyethylidene diphosphonate (^{186}Re-HEDP) has been used for palliation of metastatic bone pain. The purpose of this study was to find a relationship between the bone marrow absorbed dose and the toxicity, expressed as the percentage decrease in the peripheral blood platelet count. **Methods:** The bone marrow absorbed dose was calculated according to the MIRD model using data obtained from ten treatments of patients suffering from metastatic prostate cancer; noninvasive and pharmacokinetic methods were used. The bone marrow doses were related to toxicity using the pharmacodynamic sigmoid E_{max} model. **Results:** The mean bone marrow absorbed doses using the noninvasive and pharmacokinetic methods were in a close range to each other (1.07 mGy/MBq and 1.02 mGy/MBq, respectively). There was a good relationship between the toxicity and the bone marrow absorbed dose ($r = 0.80$). Furthermore, the $EDrm_{50}$ (i.e., the bone marrow absorbed dose producing a 50% platelet decrease) to bone marrow for ^{186}Re-HEDP was on the order of 2 Gy. **Conclusion:** Although the function of normal bone marrow is affected by metastases in patients with metastatic bone disease, the MIRD model can be used to relate toxicity to the bone marrow absorbed dose after a therapeutic dosage of ^{186}Re-HEDP.

Key Words: bone metastases; rhenium-186-HEDP; dosimetry; toxicity

J Nucl Med 1996; 37:38–41

Prostate cancer is the second most common malignancy in men in the Netherlands. The incidence is 55 per 100,000 men per year (crude rate; i.e., the total number of new cases per 100,000 male individuals of the total population), increasing to 795 per 100,000 at age 85 yr (*1*). Bone metastases frequently occur in these patients. These metastases are a major cause of serious morbidity from cancer, resulting in pain, loss of function due to pathologic fracture and neurological symptoms from nerve compression (*2,3*). Therapy usually includes analgesics, systemic therapy with hormonal or cytotoxic agents, palliative surgery and external beam radiotherapy. External beam radiotherapy plays an important role in the treatment of patients with bone pain, particularly in the prevention of impending pathologic fracture, the treatment of localized painful bone metastases as well as the treatment or prevention of spinal cord compression (*4,5*).

Recently, intravenously administered bone-seeking radiopharmaceuticals have re-emerged as a palliative treatment modality for osteoblastic bone metastases, especially when originating from prostate cancer (*6,7*). The clinical development of bone-seeking radiopharmaceuticals is based on the rationale that medium-to high-energy beta particle radiation, targeted and delivered to bone metastases, can potentially result in more effective antitumor activity, while normal tissues are relatively spared from the damaging effects of radiation.

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 (*8–11*). Rhenium-186 has a relatively short physical half-life ($T_{1/2}$ = 89.3 hr). It has a beta emission suitable for therapy (E_{max} = 1.07 MeV) and a gamma emission (yield of 9%) suitable for external imaging (E_γ = 137 keV). Side effects of ^{186}Re-HEDP appear to be mainly limited to thrombocytopenia, while leukopenia plays a minor role (*12*). Since use of radionuclide therapy in the clinical setting is usually limited by the most radiosensitive organ, assesment of bone marrow toxicity has been identified as a key issue to the success of the therapeutic use of bone-seeking radiopharmaceuticals.

Most dosimetric studies in patients with bone metastases are based on the calculation of the bone marrow absorbed dose according to the Society of Nuclear Medicine's Medical Internal Radionuclide Dosimetry (MIRD) committee formalism (*13*). Calculation of the bone marrow absorbed dose, however, from radionuclides deposited on bone surfaces is a difficult problem due to the complex geometry of the soft tissue and bone intermixture (*14*). This problem is even more prominent in patients with bone metastases, in which the normal bone marrow distribution is disturbed by the metastases.

In this article, we calculated the bone marrow absorbed doses using the MIRD formalism after therapeutic administration of ^{186}Re-HEDP in 10 patients with metastatic prostatic cancer. These doses were related to the percentage of decrease in peripheral blood platelet count.

MATERIALS AND METHODS

Patients

The ten patients were derived from two separate studies. Their ages ranged from 59 to 78 yr (mean 68 ± 6.6 yr). Eight patients with histologically confirmed prostatic cancer entered a ^{186}Re-HEDP dosage escalation study (*12*). Two patients were studied after receiving a fixed administered activity of 1295 MBq ^{186}Re-HEDP. The study was approved by the hospital review board and all patients gave written informed consent.

All patients were suffering from metastatic bone pain and failed prior hormonal therapy. No patient had received prior chemotherapy. All patients had scintigraphic and radiological evidence of at least four bone metastases.

Each patient had adequate hematological function with a leukocyte count $>4.0 \times 10^9$/liter and a platelet count $>150 \times 10^9$/liter. The patients who entered the fixed dosage protocol received prior local external beam radiotherapy to limited parts of the skeleton, but this did not influence platelet suppression (*15*).

Tracer Preparation

We previously reported the preparation of ^{186}Re-HEDP (*16,17*). The radiopharmaceutical was administered as a bolus injection

Received Nov. 29, 1994; revision accepted Apr. 3, 1995.

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through a running intravenous saline drip. The administered doses ranged from 1163 to 2914 MBq. Blood activity concentration and urinary excretion of ^{186}Re-HEDP were monitored up to 72 hr (*16,17*).

Dosimetric Calculations

All dosimetry calculations were performed using the MIRD formalism. The absorbed dose $D(r_k)$ in the target organ r_k (the red marrow) is calculated according to Equation 1.

$$D(r_k) = \sum_h \tilde{A}(r_h) * S(r_k \leftarrow r_h). \quad \text{Eq. 1}$$

$$\tilde{A}(r_h) = \int_0^\infty A(r_h)\, dt. \quad \text{Eq. 2}$$

$$S(r_k \leftarrow r_h) = \frac{\sum_i \delta_i * \phi_i(r_k \leftarrow r_h)}{M_{r_k}}. \quad \text{Eq. 3}$$

In Equations 1 and 2, $\tilde{A}(r_h)$ and $A(r_h)$ represent the cumulated and instantaneous activities, respectively. $S(r_k \leftarrow r_h)$ indicates the absorbed dose in organ r_k per nuclear transition in organ r_h. The S-factor is comprised of the energy emission per nuclear transition δ_i, the absorbed fractions $\phi_i(r_k \leftarrow r_h)$ and the mass of the target organ M_{r_k}.

For red marrow absorbed dose calculation of a bone seeking radiopharmaceutical like ^{186}Re-HEDP, the most relevant source organ is the trabecular bone, which is close to the red marrow (*18–20*). Other relevant source organs are the cortical bone, red marrow (*20*) and remainder of the body (*21*).

S-Value Calculation

In this study, the S-value from trabecular bone to red marrow for beta particles has been calculated for ^{186}Re using the results and the tabulations reported by Heggie et al. [Table 1, (*22*)]. ICRP-38 (*23*) was used for the emission characteristics of ^{186}Re. For the Auger and conversion electrons of ^{186}Re, an absorbed fraction of 1/2 may be assumed (*22*). For the photon emissions of ^{186}Re, we used the MIRDOSE2 computer program (*24*). Since this program is not able to calculate S-values for ^{186}Re photon emissions, the source code and the decay data files were modified. MIRDOSE2 was also used to calculate S-values for red bone marrow, cortical bone and the remainder of the body to the red marrow. The MIRDOSE2 software assumes a red marrow mass of 1.12 kg (*24,25*), whereas other references assume a mass of 1.5 kg, which seems more correct (*19,26*). In this study, we modified the source code so that the marrow mass equals 1.5 kg. In addition, the bone marrow mass for each individual patient was corrected, assuming that a patient with a greater body surface area has a greater bone marrow mass. Body surface area was calculated from the lean body mass (instead of actual body mass).

TABLE 1
Data Used to Calculate S(RM ← TrB) for Healthy Adults

	∂(kg * mGy/MBqh)	ϕ_i
Beta-particles	0.1896	0.364
Auger and conversion electrons	0.0082	0.5
Photons	0.0069	0.0616
S(RM ← TrB) = 0.0491 mGy/MBq h		

ϕ_i is calculated using the method presented by Heggie et al. (22) and the emission spectrum of ^{186}Re as obtained from ICRP-38. A bone marrow weight of 1.5 kg was used (*19,26*).

Calculation of Cumulated Activities

The cumulated activity in the total body $\tilde{A}_{TB}$ is calculated by collection and measurement of activity excreted in the urine. This total body activity is the sum of the activity in the bone marrow, in the skeleton and in the remainder of the body.

It is assumed that the activity in the skeleton is distributed equally over the trabecular and the cortical bone, since ^{186}Re has a half-life of less than 15 days (*23,27*). In addition, it is assumed that the radioactivity in the remainder of the body is merely distributed in the blood.

The cumulated activities in the source organs were calculated using two different calculation methods: the noninvasive and the pharmacokinetic method.

Noninvasive Method. Estimates are based on urinary excretion data only. The amount of activity in the total body ($\tilde{A}_{TB}$) is the difference between the injected dose and the excreted activity. The amount of activity in the blood and bone marrow is neglected. This assumption implies that the cumulated activity in the trabecular bone $\tilde{A}_{TrB}$ and the cortical bone $\tilde{A}_{CrB}$ is half the cumulated activity in the total body $\tilde{A}_{TB}$ (Eq. 4).

$$\tilde{A}_{TrB} = \tilde{A}_{CrB} = 0.5 * \tilde{A}_{TB}. \quad \text{Eq. 4}$$

Pharmacokinetic Method. In this method, the cumulated activity calculated using the noninvasive method is corrected for the cumulated activity in the blood ($\tilde{A}_{Bl}$) and the cumulative activity in the red bone marrow ($\tilde{A}_{RM}$) (Eq. 5A). The activity concentration in the bone marrow is assumed to be equal to 30% of the activity concentration in the blood (*20*). A blood content of 6 liters and a red marrow mass of 1.5 kg are assumed (*27*) (Eq. 5B).

$$\tilde{A}_{TrB} = 0.5 * (\tilde{A}_{TB} - \tilde{A}_{Bl} - \tilde{A}_{RM}). \quad \text{Eq. 5A}$$

$$\tilde{A}_{RM} = 0.3 * 1.5 * \tilde{A}_{Bl}/6. \quad \text{Eq. 5B}$$

The calculated bone marrow doses are related to the percentage of decrease in peripheral platelet count at the lowest point. This point is used as a reference for toxicity (*15*). We used the pharmacodynamic sigmoid E_{max} model to describe this relationship. This model is the simplest model which adequately describes drug effect over the whole range of concentrations (*28*). This model is defined as:

$$E = \frac{E_{max} * C^N}{C^N + EC_{50}^N}, \quad \text{Eq. 6}$$

where E is effect, C is concentration, N is a number influencing the slope of the curve, E_{max} is the maximum effect attributable to the drug and EC_{50} is the concentration producing 50% of E_{max}.

For this study, Equation 6 can be rearranged into:

$$\%DEC = \frac{100 * Drm^N}{Drm^N + EDrm_{50}^N}, \quad \text{Eq. 7}$$

in which %DEC is the percentage of decrease in peripheral platelet count, 100 is the maximum effect and $EDrm_{50}$ is the absorbed bone marrow dose producing 50% platelet decrease.

RESULTS

The bone marrow absorbed doses for each patient are listed in Table 2. The mean bone marrow absorbed dose calculated according to the noninvasive method equals 1.07 ± 0.19 mGy/MBq (mean ± s.d.) and 1.02 ± 0.19 mGy/MBq (mean ± s.d.) according to the pharmacokinetic method.

There is a minimal difference in absorbed doses between the two methods (a mean decrease in calculated bone marrow dose

TABLE 2
Patients, Administered Dosages, Percentage of Platelet Decrease and Results of Absorbed Bone Marrow Doses (Gy) Calculations Using a Noninvasive (Drm 1) and Pharmacokinetic Approach (Drm 2)

Patient no.	Dosage (MBq)	% platelet decrease	Drm (1)	Drm (2)
03P330	1252	33	1.11	1.06
05P330	1834	61	2.61	2.53
07P330	1865	69	2.08	2.01
11P330	2353	34	2.09	1.93
12P330	2339	64	1.86	1.80
14P330	2373	64	2.38	2.19
15P330	2914	68	3.08	2.95
16P330	2911	46	3.55	3.41
03P341	1310	22	1.49	1.43
04P341	1163	28	1.35	1.29

of 0.05 mGy/MBq). Therefore, the noninvasive method was used to describe the dose toxicity effect.

The relationship between percentage decrease of platelet count (%DEC) and the calculated bone marrow absorbed dose (Drm) according to the noninvasive method can be described by the following formula:

$$\%DEC = \frac{100 * Drm^{1.29}}{Drm^{1.29} + 2.09^{1.29}}. \quad (r = 0.80) \quad \text{Eq. 8}$$

In this equation, 2.09 is the 50% effective bone marrow absorbed dose ($EDrm_{50}$) in Gy. This means that with ^{186}Re-HEDP an absorbed dose of 2.09 Gy to the bone marrow will lead to 50% decrease of peripheral platelet count. Figure 1 shows a graphic representation of this relationship. When the bone marrow mass is adjusted for each individual patient using the lean body mass, the relationship improves slightly (r = 0.84). Table 3 shows the statistic variables of the two methods used. It can be seen that the $EDrm_{50}$ remains in the same order of magnitude (1.95 Gy).

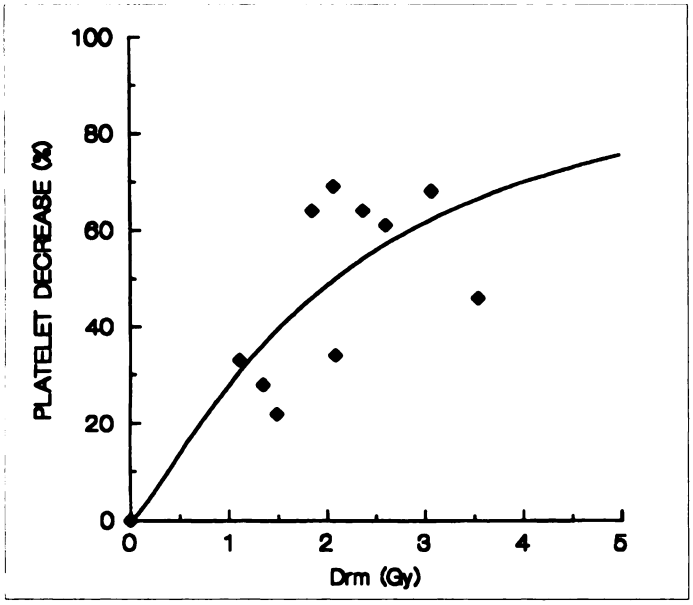

FIGURE 1. Relationship between the bone marrow absorbed dose (Drm) and the percentage of decrease in peripheral platelet count (%DEC).

DISCUSSION

The bone marrow is the dose-limiting organ when bone-seeking radiopharmaceuticals are used (*6*). Therefore, when these radiopharmaceuticals are used for the treatment of metastatic bone pain, accurate bone marrow absorbed dose estimates adequately predicting myelotoxicity, are necessary. The bone marrow absorbed dose of ^{186}Re-HEDP depends on the early distribution, kinetics in the body, particularly in the red marrow and on the physical characteristics of ^{186}Re. Most investigators use the MIRD schema for calculation of bone marrow absorbed doses, which provides a comprehensive method for the estimation of absorbed doses. In this model, normal marrow and bone masses associated with a 70-kg man are assumed. Furthermore, the model is based on the assumption of a uniform distribution of radiopharmaceuticals in tissues and cells and a homogeneous deposition of energy. It is becoming increasingly clear that heterogeneity will be an important factor in both radiation protection dosimetry and therapeutic application (*29–31*).

In this study, we evaluated the relationship between the bone marrow absorbed doses, calculated according to the MIRD scheme and the percentage of decrease in peripheral blood platelet count to predict toxicity after systemic administration of the bone-seeking radiopharmaceutical ^{186}Re-HEDP in patients with metastatic bone cancer.

Both noninvasive and pharmacokinetic methods were used to calculate the bone marrow absorbed dose. Calculations made with the noninvasive approach were in the same range as those calculated with the pharmacokinetic method. This can be explained by the fact that almost all ^{186}Re, which is not excreted into the urine, will be taken up by the skeleton and the circulating activity is rapidly cleared from the blood (*16*). Therefore, the contribution to the total bone marrow absorbed dose by the blood is low. Consequently, the noninvasive approach gives an adequate estimation of the bone marrow absorbed dose. This noninvasive approach is based on the amount of ^{186}Re, which is excreted into the urine. We previously described the excellent relationship between the amount of ^{186}Re excreted into the urine and the so-called bone scan index (*16,32*), as a measure for metastatic involvement of the skeleton. This means, assuming that all ^{186}Re not excreted into the urine will be taken up by the skeleton, that one can predict the amount of ^{186}Re in the skeleton and subsequently the platelet toxicity with this (*15*). This is a relatively simple clinical tool to predict ^{186}Re-HEDP toxicity.

The calculated bone marrow absorbed doses are in agreement with published bone marrow absorbed dose calculations by Maxon et al. (*33*), who reported an average marrow dose of 0.92 mGy/MBq. They used a fixed model designed for standard man and a variable model in which it is assumed that all activity not shown to be in the urine, kidney or blood at each time point is evenly distributed throughout the skeleton. They found, however, a significant but poor relationship ($p < 0.05$, r =

TABLE 3
Parameters Describing the Relationship between Calculated Bone Marrow Absorbed Doses and Percentage of Platelet Decrease Using the Standard Bone Marrow Mass (1.5 kg) (Model 1) and the Bone Marrow Mass Adjusted to Individual Body Surface (Model 2)

Model	F-value	Correlation coefficient (r)	$EDrm_{50}$ (Gy)	95% confidence interval $EDrm_{50}$	Variation unexplained (%) $(1 - r^2)$
1	61	0.80	2.09	1.39–2.80	36
2	77	0.84	1.95	1.41–2.49	29

0.35) between the total marrow dose received from the ^{186}Re-HEDP and the nadir in platelet count (*33*).

Radiobiologic data have demonstrated that dose-effect relationships cannot often be described by a simple linear model. Therefore, we used an accepted pharmacodynamic model to describe the relationship of the bone marrow absorbed dose and the percentage of the platelet decrease. The results show that dose calculation with the MIRD model makes it possible to relate toxicity to the bone marrow absorbed dose. The dose-effect curve can be adequately described by the sigmoid E_{max} model, which is a known pharmacodynamic model. Besides assesment of the relationship between bone marrow absorbed dose and platelet decrease ($r = 0.80$), this model enables us to determine the 50% effective dose ($EDrm_{50}$) to the bone marrow for ^{186}Re-HEDP, which is on the order of 2 Gy.

CONCLUSION

Our results show that the MIRD model can be used to describe the bone marrow absorbed dose and the subsequent percentage decrease in peripheral platelet counts after treatment with ^{186}Re-HEDP. We also calculated the $EDrm_{50}$ to be approximately 2 Gy. A more convenient, simpler a priori method for predicting platelet toxicity is possible using the previous reported relationship between decrease of peripheral platelet count versus the administered dose of ^{186}Re-HEDP and the extent of bone metastasis (*15*).

ACKNOWLEDGMENTS

The authors thank Ruth van der Wijngaart and Ron Jonk for their assistance and data management and Jan de Groot for the illustration. This investigation was supported by Mallinckrodt Medical Inc., St. Louis, MO, and Mallinckrodt Medical B.V., Petten, The Netherlands.

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