Bone Uptake Studies in Rabbits Before and After High-Dose Treatment with ^{153}Sm-EDTMP or ^{186}Re-HEDP

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The aim of this animal study was to measure the bone uptake of ^{99m}Tc-hydroxymethylene diphosphonate (HDP) before and after high-dose treatment with ^{153}Sm-ethylenediaminetetramethylenephosphonate (EDTMP) or ^{186}Re-(tin)1,1-hydroxyethylidene diphosphonate (HEDP) to prove or disprove post-therapeutic alterations of bone uptake of radiolabeled bisphosphonates. **Methods:** Quantitative bone scanning using 100 MBq ^{99m}Tc-HDP was performed on 12 rabbits before and 8 wk after radionuclide therapy with 1,000 MBq of either ^{153}Sm-EDTMP or ^{186}Re-HEDP. Whole-body images were acquired at 3 min, 3 h, and 24 h after injection, and the activities for the whole body, urinary bladder, and soft tissue were measured by region-of-interest technique. From these data, bone uptake was calculated as initial whole-body activity minus urinary excretion and remainder soft-tissue activity. **Results:** In animals treated with ^{153}Sm-EDTMP ($n = 6$), no differences could be proven for the bone uptake of ^{99m}Tc-HDP at 24 h after injection before and after therapy (51.1% ± 5.5% vs. 48.0% ± 6.1%, $P > 0.05$). There were also no significant differences for the remainder soft-tissue activities and the urinary excretion rates before and after therapy. Similar results were obtained in rabbits treated with ^{186}Re-HEDP: Bone uptake (44.8% ± 6.7% vs. 40.4% ± 4.9%, $P > 0.05$) and urinary excretion revealed no significant differences before and after treatment. **Conclusion:** No significant impairment of bone uptake of ^{99m}Tc-HDP could be observed 8 wk after high-dose radionuclide bone therapy. Because both the biokinetic data obtained for ^{186}Re-HEDP and ^{153}Sm-EDTMP and the myelotoxic effects were quite similar in rabbits to those in patients, it seems justifiable to expect the same result (i.e., no significant alteration of bone uptake of radiolabeled bisphosphonates) in patients undergoing a second radionuclide therapy within 2–3 mo after standard treatment with ^{186}Re-HEDP or ^{153}Sm-EDTMP.

Key Words: ^{99m}Tc-hydroxymethylene diphosphonate; ^{186}Re-(tin)1,1-hydroxyethylidene diphosphonate; ^{153}Sm-ethylenediaminetetramethylenephosphonate; bone uptake; post-therapeutic alterations

J Nucl Med 2003; 44:247–251

Treatment with ^{186}Re-(tin)1,1-hydroxyethylidene diphosphonate (HEDP) or ^{153}Sm-ethylenediaminetetramethylenephosphonate (EDTMP) for pain has been proven safe and successful in patients with widespread osseous metastases (*1–6*). Because the duration of pain relief is limited to a mean of 2–3 mo, subsequent therapy is recommended as long as blood cell counts, that is, leukocyte and platelet counts, are in the normal range. A drop in the level of platelets and leukocytes in the peripheral blood—the major side-effect of that treatment modality—is caused by irradiation of stem cells in the bone marrow by the β-particles of the skeleton-bound radiopharmaceutical (*3,7*). Thereby, it is known that higher activities of the radiopharmaceutical go along not only with higher grades of myelotoxicity but also with higher success rates for pain improvement (*4,8*). Consequently, skeletal uptake of administered activity is a main determinant of both radiation damage to bone marrow and the success of radionuclide therapy for bone pain. However, no data have been available on the skeletal uptake of radiolabeled bisphosphonates administered 2–3 mo after radionuclide bone therapy. The aim of this animal study, therefore, was to calculate bone uptake of ^{99m}Tc-hydroxymethylene diphosphonate (HDP) before and 8 wk after high-dose treatment with ^{153}Sm-EDTMP or ^{186}Re-HEDP to test whether bone uptake was impaired after therapy. We used a recently introduced method based on 3-phase bone scanning to quantify skeletal uptake of radiolabeled bisphosphonates (*9,10*).

MATERIALS AND METHODS

Animals and Study Design

Studies were performed on 12 female New Zealand White rabbits, 10–12 wk old and weighing a mean (±SD) of 2.5 ± 0.2 kg (Charles River, Kissleg, Germany). They were sufficiently large to undergo scintigraphic bone uptake measurements. For radionuclide bone therapy, we used ^{186}Re-HEDP (Mallinckrodt, Petten, The Netherlands) ($n = 6$) and ^{153}Sm-EDTMP (CIS, Gif-Sur-Yvette, France) ($n = 6$). Both tracers were administered intravenously at a standard activity of 400 MBq per kilogram of body weight. This dose has been proven myelotoxic in rabbits. It in-

Received Aug. 20, 2001; revision accepted Sep. 24, 2002.

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duces, in the platelet and leukocyte counts of their peripheral blood, a drop comparable to that in patients treated with standard activities as described recently (*11*). The main reason that higher activities are needed in rabbits than in patients is that, in rabbits, the bones are much smaller and the bone marrow much less, compared with the range of the β-particles. The result is lower irradiation of the bone marrow in rabbits than in patients, in whom a higher proportion of the β-rays is deposited in the bone marrow.

All animal studies were approved by the Ministerium für Umwelt, Natur und Forsten des Landes Schleswig-Holstein (X 252-72241.121-17 56-8/98) according to the German Law of the Protection of Animals.

One week before and 8 wk after radionuclide treatment, quantitative bone scanning was performed as described below after administration of 100 MBq of ^{99m}Tc-HDP (Mallinckrodt, Petten, The Netherlands). Furthermore, quantitative scanning was also performed after application of ^{186}Re-HEDP and ^{153}Sm-EDTMP to calculate the skeletal uptake of the respective radiopharmaceutical.

Scintigraphic Skeletal Uptake Measurement

Whole-body images were acquired simultaneously from anterior and posterior views at 3 min, 3 h, and 24 h after a bolus injection of the respective radiopharmaceutical (^{99m}Tc-HDP, ^{186}Re-HEDP, or ^{153}Sm-EDTMP). The acquisition time was 1 min in the blood-pool phase and 10 min for the later images. For each rabbit, images were obtained under the same conditions using a double-head gamma camera (Bodyscan; Siemens, Erlangen, Germany) equipped with high-resolution collimators for low energy. The energy windows were 140 keV ± 15%, 137 keV ± 15%, and 103 keV ± 15% for ^{99m}Tc, ^{186}Re, and ^{153}Sm, respectively.

For each image, the activities of the whole body, the urinary bladder, and the soft tissue of the flank were measured by region-of-interest (ROI) technique from both anterior and posterior views. Additionally, for uptake measurements of ^{186}Re-HEDP or ^{153}Sm-EDTMP, a rectangular ROI adjacent to the body was used to measure the bremsstrahlung of the β-particles of the radionuclide. An example of ROI positions is given in Figure 1. From these data, the geometric mean for each ROI was calculated after correction for different acquisition times; for radioactive decay; and, in cases of ^{186}Re-HEDP or ^{153}Sm-EDTMP, for bremsstrahlung. The initial whole-body activity of each rabbit was used as the reference value for further calculations of activity data, which are given as a percentage of initial whole-body activity. According to a simplified 3-compartment model, soft-tissue activity as compared with initial whole-body activity equals the activity of the flank as compared with the initial flank activity at 3 min after injection. Urinary excretion was determined by the difference of whole-body activities between the reference image at 3 min and the image of interest plus urinary bladder activity. From these data, bone uptake was calculated for 24 h after injection as 100% of initial whole-body activity minus both urinary excretion and soft-tissue retention as described in detail elsewhere (*9,10*).

Statistical Analysis

Data are given as mean ± 1 SD. A 2-tailed Student *t* test for unpaired data (including both the test of David, Pearson, and Stephens to prove normal distribution of the data and the F test) was used to evaluate statistical differences between rabbit subgroups, with $P < 0.05$ considered statistically significant (*12*).

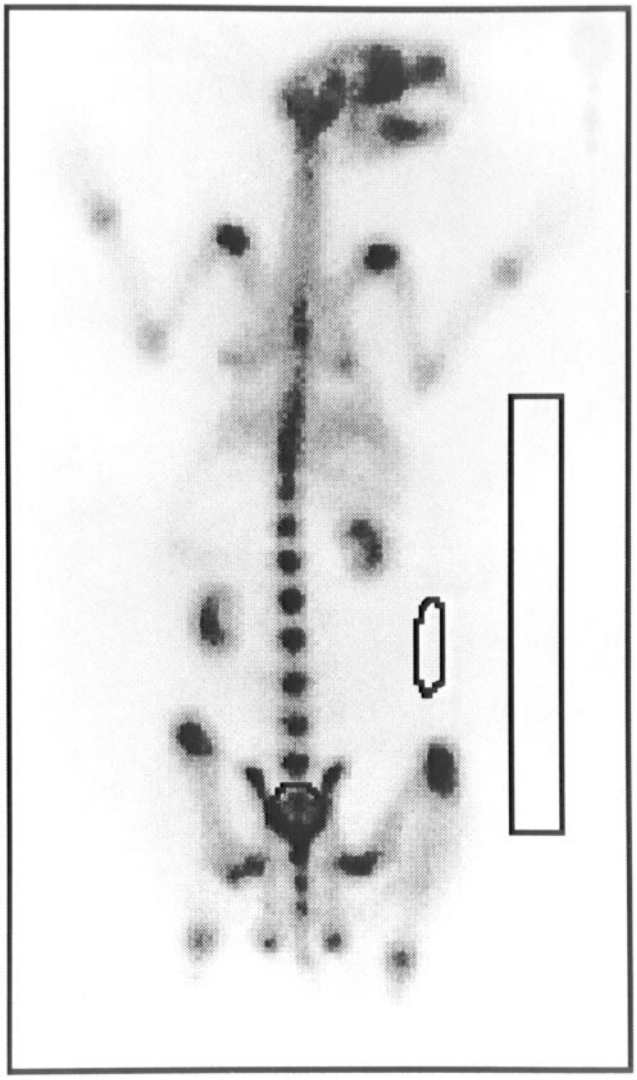

FIGURE 1. ROI positions on posterior whole-body scintigram of rabbit 3 h after injection of 1,000 MBq of ^{186}Re-HEDP.

RESULTS

The mean bone uptake of ^{99m}Tc-HDP at 24 h after injection before treatment with ^{153}Sm-EDTMP was 51.1% ± 5.5% of initial whole-body activity. Eight weeks after radionuclide therapy, the mean bone uptake value, 48.0% ± 6.1%, showed no significant difference ($P > 0.05$) from the pretreatment result (Table 1). Also, no significant differences between before- and after-therapy values could be proven for the remainder soft-tissue activities (16.4% ± 5.3% vs. 17.8% ± 3.5%) or for the urinary excretion rates at 24 h after injection (31.6% ± 3.0% vs. 34.2% ± 4.7%).

Similar results were obtained in rabbits treated with ^{186}Re-HEDP (Table 2). Both the mean bone uptake of ^{99m}Tc-HDP (44.8% ± 6.7% vs. 40.4% ± 4.9%) and the urinary excretion of ^{99m}Tc-HDP (37.0% ± 6.1% vs. 37.7% ± 4.9%) revealed no significant differences ($P > 0.05$ each) before and after treatment, although bone uptake values were lower in all animals after therapy. The remainder

TABLE 1
Bone Uptake, Soft-Tissue Retention, and Urinary Excretion of ^{99m}Tc-HDP in 6 Rabbits at 24 Hours After Injection Before and After Treatment with 1,000 MBq ^{153}Sm-EDTMP

	Before therapy			After therapy		
Rabbit no.	Bone	Soft tissue	Urine	Bone	Soft tissue	Urine
1	53.1	10.4	36.5	51.6	14.3	34.1
2	45.4	21.7	32.9	46.2	21.5	32.3
3	45.8	17.1	31.1	44.1	18.9	37.0
4	57.8	10.6	31.6	58.8	14.5	26.7
5	56.7	15.5	27.8	43.7	15.6	40.7
6	47.5	22.9	29.6	43.7	21.9	34.4
Mean ± SD	51.1 ± 5.5	16.4 ± 5.3	31.6 ± 3.0	48.0 ± 6.1	17.8 ± 3.5	34.2 ± 4.7

Data are percentage of initial whole-body activity.

soft-tissue activity was significantly higher ($P < 0.01$) after radionuclide therapy (22.0% ± 0.4%) than before (17.7% ± 1.6%).

Between the 2 rabbit groups treated with either ^{153}Sm-EDTMP or ^{186}Re-HEDP, no significant differences ($P > 0.05$ each) could be proven for the mean bone uptake, soft-tissue retention, and urinary excretion of ^{99m}Tc-HDP (Tables 1 and 2).

The mean bone uptake, soft-tissue retention, and urinary excretion of ^{153}Sm-EDTMP at 24 h after injection were 44.0% ± 6.5%, 9.8% ± 4.4%, and 46.3% ± 7.5%, respectively (Table 3). The corresponding results for ^{186}Re-HEDP were 31.2% ± 1.5%, 16.2% ± 2.7%, and 52.6% ± 3.4%. Thus, a significantly higher bone uptake was found for ^{153}Sm-EDTMP ($P < 0.001$), whereas soft-tissue retention was significantly lower for ^{153}Sm-EDTMP ($P < 0.02$). No differences were found between the urinary excretion rates for ^{186}Re-HEDP and ^{153}Sm-EDTMP ($P > 0.05$).

DISCUSSION

Because bone pain is relieved for only 2–3 mo in most patients undergoing radionuclide therapy with ^{186}Re-HEDP or ^{153}Sm-EDTMP, subsequent therapy is recommended as long as blood cell counts are in the normal range. The activity administered and the extent of radiopharmaceutical uptake by bone are known determinants of the success of this treatment (*4,8,13*). Radiation doses of up to 3 Gy to bone and bone marrow and of up to 140 Gy to metastatic sites have been reported (*3,7,8,14,15*), strongly suggesting at least alterations of the local bone metabolism and, thus, uptake of radiolabeled bisphosphonates by bone. For example, reduced bone uptake of radiolabeled bisphosphonates can be observed within the irradiation fields after external radiotherapy (*16*) that applies center doses of up to 40 Gy. Although comparably high local doses are achieved by radionuclide therapy only in single metastases and not in larger bone areas, most of the skeleton-bound activity of ^{186}Re-HEDP and ^{153}Sm-EDTMP, that is, 20%–50% of the total activity administered (*10*), is absorbed by nonmetastatic bone tissue. In contrast, in vitro experiments with rat osteoblastlike cells showed inhibitory effects at doses of as low as 100 cGy (*17*). Similar results, such as a dose-dependent decrease in cellular differentiation and proliferation and a decrease in the production of transforming growth factor β1 and vascular endothelial growth factor as markers for radiation-induced cytokine profile alterations,

TABLE 2
Bone Uptake, Soft-Tissue Retention, and Urinary Excretion of ^{99m}Tc-HDP in 6 Rabbits at 24 Hours After Injection Before and After Treatment with 1,000 MBq ^{186}Re-HEDP

	Before therapy			After therapy		
Rabbit no.	Bone	Soft tissue	Urine	Bone	Soft tissue	Urine
1	51.8	18.4	29.8	45.5	21.5	33.0
2	40.1	20.4	39.5	39.0	22.4	38.6
3	39.2	17.8	43.0	39.1	21.9	39.0
4	40.1	17.5	39.4	35.7	21.7	42.6
5	42.7	15.9	41.4	35.8	22.0	42.2
6	54.7	16.4	28.9	47.1	22.4	30.5
Mean ± SD	44.8 ± 6.7	17.7 ± 1.6	37.0 ± 6.1	40.4 ± 4.9	22.0 ± 0.4	37.7 ± 4.9

Data are percentage of initial whole-body activity.

TABLE 3
Bone Uptake, Soft-Tissue Retention, and Urinary Excretion of ^{153}Sm-EDTMP and ^{186}Re-HEDP in Rabbits at 24 Hours After Injection

Rabbit no.	^{153}Sm-EDTMP			^{186}Re-HEDP		
	Bone	Soft tissue	Urine	Bone	Soft tissue	Urine
1	42.9	6.2	50.9	30.6	11.3	58.1
2	45.3	16.2	38.5	31.1	16.5	52.4
3	31.6	9.8	58.6	33.9	17.1	49.0
4	49.0	4.1	46.9	29.9	15.1	55.0
5	49.3	9.4	41.3	30.0	18.8	51.2
6	45.7	13.0	41.3	31.9	18.4	49.7
Mean ± SD	44.0 ± 6.5	9.8 ± 4.4	46.3 ± 7.5	31.2 ± 1.5	16.2 ± 2.7	52.6 ± 3.4

Data are percentage of initial whole-body activity.

were found by Dudziak et al. (*18*) for dose levels of 40, 400, and 800 cGy. Thus, even the lower irradiation of the bones may have a general effect on bone metabolism and on bone uptake of bisphosphonates. Therefore, it seems important to know about changes in bone uptake some 2–3 mo after radionuclide therapy.

In this animal study, skeletal uptake of ^{99m}Tc-HDP was measured as an indicator of bone metabolism before and 8 wk after high-dose treatment with ^{153}Sm-EDTMP or ^{186}Re-HEDP to assess any post-therapeutic impairment of bone uptake. To measure skeletal uptake of the radiolabeled bisphosphonates used in this study, we used a recently introduced method that has been proven valid in patients in comparison with data from literature (*9,10*). This method is based on scintigraphic 3-phase whole-body imaging in combination with conventional ROI technique and allows calculation of kinetic data for the compartments assumed in this model: bone, soft tissue, and urinary excretion.

Significant alterations of ^{99m}Tc-HDP uptake by bone 8 wk after radionuclide therapy with ^{153}Sm-EDTMP or ^{186}Re-HEDP could be excluded in this study. In animals that received ^{153}Sm-EDTMP, uptake by bone was somewhat lower after radionuclide therapy in 4 of 6 rabbits, whereas in all animals treated with ^{186}Re-HEDP, uptake was lower, although not significantly so. On account of follow-up studies in nonmetastatic-tumor patients undergoing repeated bone scintigraphy, we know that variations of up to ±10% in bone uptake are observed within 6 mo in many cases (W. Brenner et al., unpublished data, 2000). These variations are due mainly to the error in measurement of this method rather than to real changes in bone uptake. In this study, in 4 of 6 rabbits treated with ^{186}Re-HEDP and in 1 of 6 rabbits treated with ^{153}Sm-EDTMP, bone uptake values were more than 10% lower after radionuclide therapy, whereas in only 1 of these cases was bone uptake reduced by more than 20%. According to a potential error of measurement of about 10%, these differences were statistically not significant, nor do changes within this range seem crucial from the clinical point of view. Furthermore, these findings have been observed after high-dose treatment, that is, 400 MBq of either ^{153}Sm-EDTMP or ^{186}Re-HEDP per kilogram of body weight: The activities usually applied in patients are 37 and 15–20 MBq per kilogram of body weight for ^{153}Sm-EDTMP and ^{186}Re-HEDP, respectively. Thus, a significant impairment of bone uptake of radiolabeled bisphosphonates in patients undergoing a second radionuclide therapy within 2–3 mo after standard treatment with ^{153}Sm-EDTMP or ^{186}Re-HEDP is not to be expected according to the data provided in this study. Also, no significant changes in urinary excretion and soft-tissue retention of ^{99m}Tc-HDP could be observed after administration of ^{153}Sm-EDTMP. Only the remainder soft-tissue activity of ^{99m}Tc-HDP was statistically increased after therapy with ^{186}Re-HEDP; urinary excretion rate remained unchanged. High-dose treatment with ^{186}Re-HEDP and ^{153}Sm-EDTMP therefore did not significantly alter the biodistribution of radiolabeled bisphosphonates, suggesting no major impairment of bone uptake in general because of this therapeutic modality.

To justify the transfer of such a conclusion to patients, it seems necessary to check the validity of the animal model for both ^{153}Sm-EDTMP and ^{186}Re-HEDP. At 24 h after injection, kinetic data similar to those reported in patients undergoing radionuclide bone therapy were observed (*5,8,10,19,20*). The bone uptake values in patients at 24 h after injection were 47.7% ± 11.2% for ^{153}Sm-EDTMP, soft-tissue retention was 12.7% ± 4.7%, and the urinary excretion rate was 39.5% ± 13.8% (*10*). The corresponding data in rabbits—44.0% ± 6.5% for bone uptake, 9.8% ± 4.4% for remainder soft-tissue activity, and 46.3% ± 7.5% for urinary excretion—showed no significant differences. Similar results were obtained for ^{186}Re-HEDP, although bone uptake values in rabbits, at 31.2% ± 1.5%, were somewhat higher than the 21.8% ± 9.0% observed in patients. Nevertheless, the bone uptake values in rabbits were significantly higher for ^{153}Sm-EDTMP than for ^{186}Re-HEDP, clearly reflecting the same differences between the biodistribution pattern of these radiopharmaceuticals as already observed in patients (*10*). One point to be addressed, however, is the problem of a solely local change and reduction of bone uptake in metastases or the adjacent bone

tissue, which may significantly hamper local-pain palliation in cases of retreatment. Because this point cannot be investigated by the model used in this study, a model with bone tumors or bone metastases is mandatory for further studies. For investigating the general effects of radionuclide bone therapy on bone uptake of bisphosphonates, however, the model used in this study—a normal nontumor model with animals large enough for scintigraphic bone scanning—seemed sufficient despite its limitations.

Furthermore, we could prove a transient decrease of about 50% and 60% in the leukocyte counts and platelet counts, respectively, of rabbits within 3 wk after radionuclide treatment. These findings are in line with the radiation-induced myelotoxic effects reported for patients treated with the activities recommended for clinical practice (*4*,*21*–*23*). Thus, the findings in rabbits concerning both the bone uptake and the biodistribution of ^{186}Re-HEDP and ^{153}Sm-EDTMP, as well as the radiation-induced myelotoxic effects, are comparable to the findings in patients. Therefore, one seems justified in expecting the same, that is, nonsignificant, effects on bone uptake in patients undergoing radionuclide therapy as are observed in rabbits.

CONCLUSION

In this study investigating the impact of radionuclide therapy with ^{186}Re-HEDP and ^{153}Sm-EDTMP on bone uptake of radiolabeled bisphosphonates in rabbits, no significant alterations of the bone uptake of ^{99m}Tc-HDP could be observed 8 wk after high-dose treatment. Because the biokinetic data obtained for ^{186}Re-HEDP and ^{153}Sm-EDTMP and the myelotoxic effects in rabbits were similar to those in patients, it seems justified to expect the same results on bone uptake in patients as in rabbits. Thus, significant impairment of the bone uptake of radiolabeled bisphosphonates in patients undergoing a second radionuclide therapy within 2–3 mo after standard treatment with ^{186}Re-HEDP or ^{153}Sm-EDTMP is not to be expected according to the data obtained from this animal study.

ACKNOWLEDGMENTS

The authors thank Dr. Hans-Ulrich Wottge and his team for providing perfect animal care service. The authors are grateful for financial support from Mallinckrodt GmbH, Hennef, Germany.

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