PHYSICS AND RADIATION BIOLOGY

[^{32}P] Diphosphonate Dose Determination in Patients with Bone Metastases from Prostatic Carcinoma

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In an initial safety study, phosphorus-32 (as diphosphonate) was administered intravenously to five patients with painful bone metastases from prostatic carcinoma; two patients received 9 mCi and three were given 3 mCi. Hematological, biochemical, ECG, x-ray, bone-scan data, and clinical observation, were followed for 2 mo. At both dose levels, bone-marrow depression was noted. One of the patients, who received 9 mCi, had only a slight dip in the levels of circulating white blood cells and platelets. The other 9-mCi patient was the only one with discrete metastases by bone scan; he had bone-marrow depression, from which he recovered, and was the only one of the five who had relief of bone pain.

J Nucl Med 19: 98–104, 1978

Under various non-radiation forms of therapy, the relief of bone pain from metastatic carcinoma of the prostate has been disappointing; hormones and chemotherapeutic drugs have produced transient or inconstant benefits at best. Radiotherapy has been reserved mainly for selected cases of extreme pain; external beams have been used for discrete skeletal lesions and internal beta radiation for disseminated metastases.

Phosphorus-32 (as sodium orthophosphate) has been used therapeutically for many years in patients with skeletal metastases, especially those with tumor deposits from prostatic cancer (*1–5*). Because its effectiveness is unpredictable, [^{32}P] orthophosphate has been administered cautiously, usually in persons having refractory bone pain. Lack of success with this agent has been attributed to its relatively low concentration at tumor sites, in contrast to its wide distribution throughout the miscible phosphate pool of the body, in particular the bone marrow (*6,7*). From the beginning it has been apparent that depression of bone-marrow function was the most troublesome side effect of [^{32}P] orthophosphate therapy for bone metastases. Nearly all reports dealing with its use for this purpose have expressed a major concern about damage to the hematopoietic system.

The significant risk of bone-marrow depression and the uncertain control of tumor effects have led to trials of combined therapy in which [^{32}P] orthophosphate was given in conjunction with hormones, on the theory that hormonal stimulation would increase the concentration of radiophosphorus at the tumor sites. Initially the stimulating hormone was testosterone (*2,3,8–18*); more recently it has been parathormone (*18–23*). Neither combination has gained wide acceptance, and the hormone-radiopharmaceutical approach is still under investigation.

Because [^{32}P] orthophosphate has been shown to possess limited usefulness, investigators have searched for more specific radiopharmaceuticals for the treatment of bone metastases. There was an early attempt to enhance tumor radiation using polyphosphate containing P-32 (*24*). This molecule, how-

Received March 22, 1977; revision accepted Aug. 4, 1977.

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ever, is readily hydrolyzed to orthophosphate, thus reducing its effectiveness. With the observations of the strong absorption of phosphonates on hydroxyapatite (*25*), their stability and their specific bone-seeking properties (*26,27*), a stable molecule able to be randomly labeled with P-32 became available and was synthesized*. Phosphonates, with their enzyme-resistant P–C–P bonds, have a considerably longer effective half-life on bone mineral than phosphates with their P–O–P bonds, which are readily attacked by phosphatases (*27–29*).

Nonradioactive diphosphonate (disodium etidronate, HEDP) has been effective in the treatment of patients with symptomatic Paget's disease of bone (osteitis deformans) (*30–32*). Rationale for the trial of [^{32}P] diphosphonate as a therapeutic agent has also come from routine observations of primary and metastatic bone lesions markedly concentrating phosphonates labeled with Tc-99m (*33,34*) and from distribution studies of [^{32}P] HEDP in normal and tumor-bearing animals (*7,35*). A study of the comparative distribution of tracer doses of diphosphonates tagged with P-32 and Tc-99m in patients with osteogenic sarcoma has shown parallel tissue concentrations (*36*). Rat-tissue distribution of other [^{32}P] diphosphonate preparations has also been reported (*37*).

Before undertaking clinical trials of the bone-seeking agent, HEDP†, ethane-1-hydroxy-1, 1-diphosphonate, labeled with P-32, extensive quality-control and safety tests were conducted using normal rats and dogs, as well as dogs with spontaneous osteosarcomas (*7,35*). These studies found [^{32}P] HEDP to have excellent radiochemical purity and high specific activity. Tissue-distribution analyses at 24 hr showed [^{32}P] HEDP to be approximately 20 times more concentrated in the bone mineral, and about 20 times more dilute in the bone marrow, than [^{32}P] (*7*). In normal dogs, only the highest dose, 0.29 mCi/kg (equivalent to 20 mCi in a 70-kg patient) caused a significant reduction in peripheral blood lymphocytes and platelets, with maximum depression at 21 days and recovery by 42 days (*35*). Tumor-bearing dogs manifested therapeutic effects such as an increase in animal mobility, a decrease in serum alkaline phosphatase, and histologic evidence of tumor necrosis and liquefaction (*35*).

On the basis of the human and animal data, clinical studies were undertaken to establish levels of [^{32}P] HEDP for palliative therapy of painful bone metastases from cancer. In an abbreviated report we presented our experience with five patients who received [^{32}P] HEDP treatment for advanced (Stage D) prostatic carcinoma (*38*). That communication is a more detailed account of our findings.

MATERIALS AND METHODS

Criteria for the selection of patients were: (a) advanced, histologically proved adenocarcinoma of the prostate in relapse with symptomatic bone metastases, and (b) bone-scan evidence of metastases confirmed by either roentgen metastatic series and/or bone biopsy. These were patients in whom other modes of treatment had been tried and exhausted (e.g., hormone, castration, and chemotherapy).

Patients were not eligible if there was advanced renal failure, myocardial insufficiency or instability, low serum calcium, extensive prior external-beam radiation therapy, or if there was evidence of impending bone-marrow deficiency (e.g., low hematocrit, WBC, or platelet counts).

Laboratory data before, at the time of, and up to 8 wk following treatment included serum determinations of glucose, cholesterol, BUN, bilirubin, uric acid, calcium, phosphorus, proteins, SGOT, LDH, creatinine and acid and alkaline phosphatases, as well as determinations of peripheral blood WBC, RBC, hemoglobin, hematocrit, platelets, and WBC differential.

In addition to the hematologic and biochemical studies, the patients were followed with periodic Tc-99m HEDP‡ bone scans and roentgen skeletal surveys. To rule out cardiac effects as a result of HEDP binding of calcium, electrocardiographic tracings were obtained before therapy, during the 30-min i.v. infusion of the [^{32}P] HEDP, and following each treatment. The amount of stable diphosphonate administered per 3 mCi of P-32 was 6–12 mg.

The first two patients received a total of 9 mCi of [^{32}P] HEDP in three separate doses of 3 mCi each, given one week apart. Because the second patient showed a significant drop in peripheral leukocytes and platelets after the treatments, the remaining three patients received only a single dose of 3 mCi.

For clearance data, blood samples were obtained at ¼, ½, 1, 3, 6, and 24 hr after the end of the infusion. Information regarding urinary excretion was derived from 48-hr urine collections in four patients and from a 24-hr collection in one.

RESULTS

The responses of all five patients indicated that the [^{32}P] HEDP treatments had no appreciable effect on the serum levels of calcium, phosphorus, BUN, creatinine, glucose, proteins, uric acid, bilirubin, or cholesterol. Elevated serum-enzyme levels (alkaline and acid phosphatase, SGOT, and LDH) were not significantly lowered by the therapy. Two patients had a rise of their acid phosphatase levels during the period of study. No significant electrocardiographic changes were noted at any time. Skeletal roent-

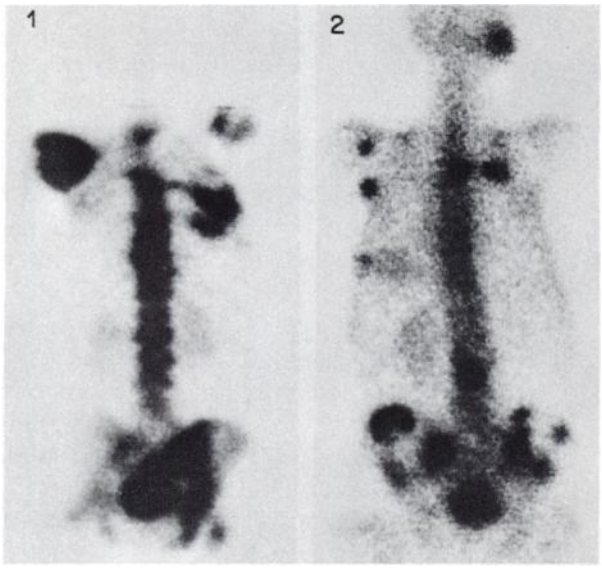

FIG. 1. Tc-99m HEDP bone scans (posterior views) of patients 1 and 2, who received a total of 9 mCi of [^{32}P] HEDP.

genography performed before and after the followup period remained unchanged. Slight changes were suggested in the bone scans, and these are covered in the descriptions of the cases.

Patient 1 was a 56-year-old man with a poorly differentiated prostatic adenocarcinoma with metastases diffusely and extensively seen by radiography and radionuclide bone scans (Fig. 1). He received three doses of 3 mCi each. From the start this patient had considerable bone pain, which was not significantly affected by the therapy. He continued a downhill course with the bone scan, suggesting an increase in the extent of the disease. He became less ambulatory and required more analgesics. There was a slight dip in the circulating leukocytes and platelets (Fig. 2). He died just before the laboratory, x-ray, and bone studies that were due 8 wk following the last dose of [^{32}P] diphosphonate. Death was attributed to a massive tumor burden.

Patient 2 was an 83-year-old man with an undifferentiated prostatic adenocarcinoma that metastasized focally to bone, and spread extensively into the soft tissues of the pelvis. This patient also received three doses of P-32 of 3 mCi each. The roentgenographic and bone-scan patterns of osseous metastases (Fig. 1) were significantly different from those observed in any of the other four patients, in that the lesions were more localized and discrete. This patient had a marked drop in the amount of circulating white blood cells and platelets, and this was considered a radiation effect. He required considerable support, including transfusions and antibiotics. He made a satisfactory recovery from his bone-marrow depression, with the WBC and platelet counts returning to well within normal levels (Fig. 2). Followup bone scans suggested less activity in some lesions. The radiographic metastatic survey detected no changes following treatment. The patient's bone pain decreased to the point where he no longer required analgesics. After what appeared to be effective therapy for his bone metastases, he had a rise in the level of serum acid phosphatase, presumably from extension of tumor into the soft tissues of the pelvis.

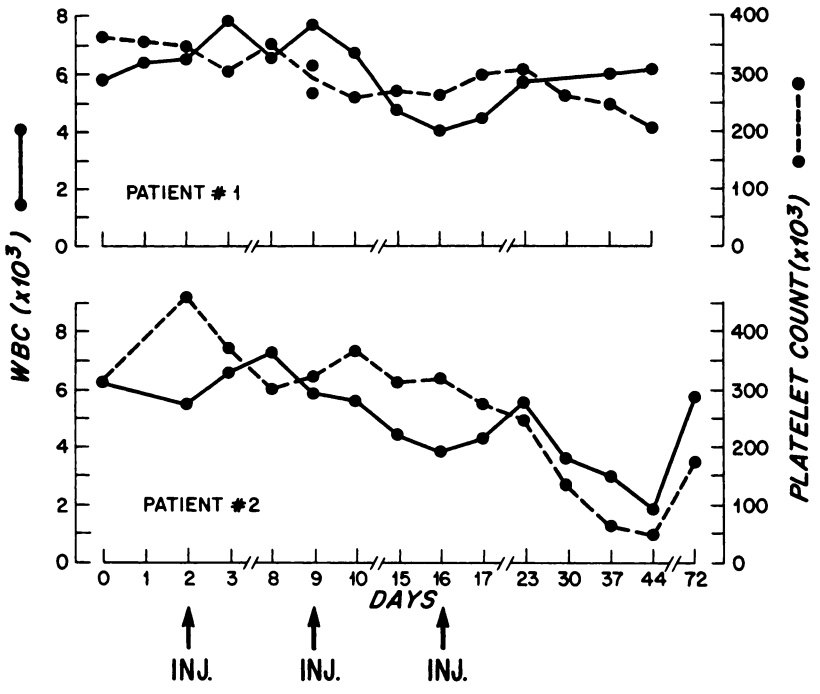

FIG. 2. Levels of WBCs and platelets in peripheral blood of the two patients who received a total of 9 mCi of [^{32}P] HEDP.

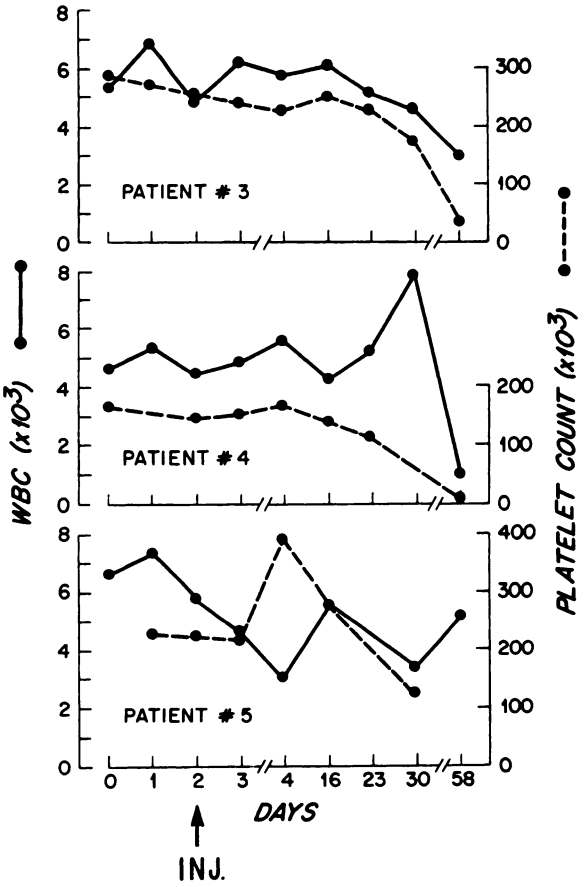

FIG. 3. Levels of WBCs and platelets in peripheral blood of three patients who received a single 3-mCi dose of [^{32}P] HEDP.

Patient 3 was a 79-year-old man with metastatic adenocarcinoma of the prostate. He received only a single dose of 3 mCi of [^{32}P] HEDP because of mild anemia (though his white blood cell and platelet counts were normal) (Fig. 3), and because of the bone-marrow depression noted in the second patient. After the P-32 therapy, this patient had a significant drop in the peripheral blood WBC and platelet counts, became more anemic, and required transfusions of packed red cells. From the start, this patient had diffuse and extensive involvement of the skeleton, as seen by roentgen skeletal survey and bone scan (Fig. 4), and no change was visible following therapy. The patient's pain continued to increase, and he required more analgesics. He had a slow downhill course.

Patient 4 was a 79-year-old man with adenocarcinoma of the prostate, who received only a single dose of 3 mCi of [^{32}P] HEDP. This man's peripheral blood picture was similar to that of Patient 3, though the platelet count was slightly depressed. He was on a steady downhill course before the P-32 therapy, and his deterioration continued. His pancytopenia was more profound than we anticipated, and he was considered to have been made worse by the treatment. He had marked drops in the peripheral WBC and platelet counts terminally (Fig. 3). As shown by the roentgenographic bone survey and the radionuclide bone scan (Fig. 4), this patient had diffuse and extensive osseous metastases. No significant change was noted in the roentgenographic studies before and after therapy, whereas the bone scan suggested a slight generalized increase in the activity. The patient's pain appeared to get worse during the period of study; he became totally bedridden and required substantial medication for relief of his discomfort. He died 8 wk following P-32 therapy.

Patient 5 was a 63-year-old man with moderately differentiated adenocarcinoma of the prostate. In many respects, this patient was similar to Patients 3 and 4 when he entered the study, and his course was similar. He too had a large tumor burden in-

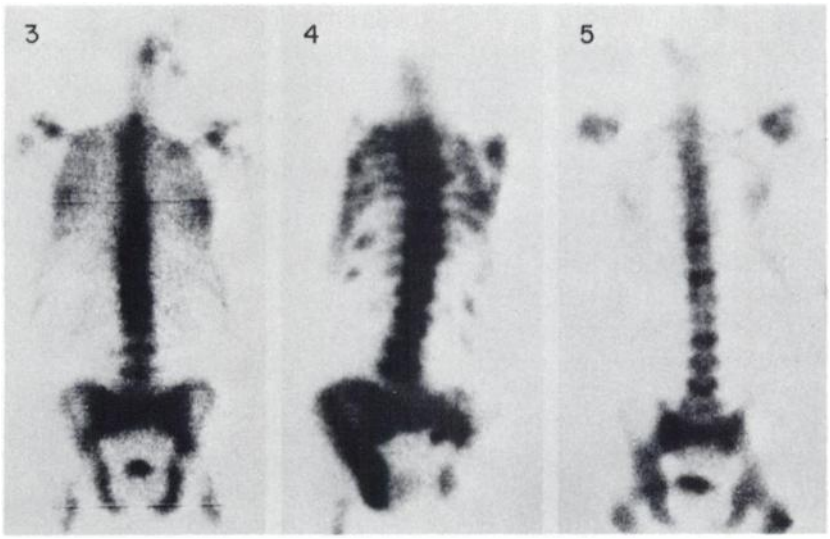

FIG. 4. Tc-99m HEDP bone scans (posterior views) of patients 3, 4, and 5, who each received one 3-mCi dose of [^{32}P] HEDP.

TABLE 1. P-32 ACTIVITY IN WHOLE BLOOD AFTER COMPLETION OF HALF-HOUR INFUSION OF RADIOPHOSPHONATE

Patient No.	Treatment No.	Percentage of dose in total blood volume (hr after end of infusion)					
		¼	½	1	3	6	24
1	1	4.4	3.4	2.0	0.6	0.4	0.3
	2	6.6	4.1	2.8	0.8	0.5	0.3
	3	—	—	—	—	—	—
2	1	11.3	9.2	6.5	2.0	1.2	0.5
	2	16.7	10.8	5.9	2.1	1.1	0.5
	3	13.0	8.6	4.8	2.4	1.2	0.7
3	1	7.9	—	3.1	0.7	0.5	0.2
4	*						
5	1	6.8	4.3	1.7	0.5	0.2	0.2

* No blood samples obtained.

volving the skeleton diffusely. After a single 3-mCi dose of P-32, there was a significant drop in the peripheral-blood WBCs and platelets, which occurred later than in Patient 4 (Fig. 3). He became anemic and was supported with transfusions. We considered this patient's hematologic changes to be primarily the result of extensive osseous metastases, and secondarily the result of P-32 therapy. By roentgenographic bone survey and by radionuclide bone scan (Fig. 4), he had extensive diffuse metastases. No significant change was noted in the x-ray studies. As his disease progressed, the bone scan suggested a slight increase in the Tc-99m diphosphonate concentration. With his continued deterioration, there was an increase in his bone pain and his need for analgesics. He became less ambulatory and was finally essentially bedridden. His course has not been significantly different from that expected in a patient with extensive neoplastic disease.

Blood clearance, expressed as percentage of administered dose in the total blood volume (the volume estimated from each patient's height and weight), is presented in Table 1. Urinary excretion, expressed as percentage of total administered dose, was determined by assaying aliquots of total urine collected for 24 hr in Patient 5 and for 48 hr in the other four patients (Table 2).

DISCUSSION

Even though the specific purpose of this study was a determination of radiation safety of [^{32}P] HEDP, and although the patients were in the end stages of disseminated prostatic carcinoma, there was a hope that definite benefits would ensue without significant depression of the bone marrow. Perhaps this was expecting too much in patients who were terminally ill, but the preliminary data generated hope.

Biologic systems usually show a range of responses, and patients with different degrees of disease broaden that spectrum, as this group has demonstrated. The main objective of establishing specific dose levels for therapy was not accomplished to the degree desired, but gross levels of dose were documented. Alleviation of pain was realized in one patient.

Bone scans may be giving a clue as to which patients would benefit from this mode of therapy. Patterns observed on the Tc-99m HEDP bone scans indicated that four of the men had extensive disease diffusely throughout the skeleton. The youngest of these four was given a total of 9 mCi of P-32 and showed no appreciable radiation effect on his bone marrow. The other three individuals in that group received only 3 mCi of P-32 and had varying degrees of bone-marrow depression. No relief of pain was achieved in any of these four patients. The patient who had discrete (localized) lesions by bone scan showed a different response. A total of 9 mCi of P-32 were administered to this man, who experienced severe bone-marrow depression, from which he made a satisfactory recovery after supportive therapy, including blood transfusions. His bone pain disappeared. His response may be suggesting that

TABLE 2. PERCENTAGE OF TOTAL P-32 DOSE IN POOLED URINE COLLECTED FOR 48 HR FOLLOWING I.V. [^{32}P] EHDP

Patient No.	Treatment No. 1	Treatment No. 2	Treatment No. 3
1	—	22.4	20.2
2	23.9	26.4	24.7
3	19.4		
4	9.0		
5*	21.1		

* 24-hr urine collection only.

the therapeutic index (ratio of radiation toxicity to benefit) of [^{32}P] HEDP, as treatment for bone metastases from prostatic carcinoma, may have a narrow range.

The bone-marrow reserve of prospective patients for [^{32}P] HEDP therapy may have to be determined more precisely, perhaps by a bone-marrow scan, because peripheral WBC and platelet counts appear to be unreliable determinations of bone-marrow reserve and/or bone-marrow involvement by tumor. It may be essential to select patients with a limited tumor burden involving the bone marrow, and careful tailoring of dose to the individual may be crucial. The selection process may rely heavily on the bone-scan pattern of the disease; patients with discrete lesions may be more receptive to [^{32}P] HEDP therapy. Quantitative bone scans that provide a more accurate measure of target-to-nontarget ratios may aid in this decision (*39*).

Before further assessments are made of radiophosphorus HEDP, certain statistical, biologic, and physical considerations are in order. From a statistical standpoint, a larger series of patients needs to be studied, if more accurate dose levels are to be established. From a biologic standpoint, patients with bone lesions from other neoplasms should be included—in particular breast carcinoma with osseous metastases—diseases that occur in younger patients with better bone-marrow reserves. From a purely physical standpoint, an isotope of phosphorus with less energetic beta radiation than P-32 might lower radiation toxicity to the bone marrow. P-33, with a physical half-life of 24 days, could fill the bill, since it has a maximum beta energy of 0.25 MeV, whereas P-32, with a physical half-life of 14 days, has a maximum beta energy of 1.71 MeV. The in vivo distribution characteristics are identical (*7*).

Ways of potentiating the radiation dose to the lesions should be considered at some point in the evaluation of [^{32}P] HEDP therapy for the bone metastases of prostatic carcinoma. Patients stimulated with testosterone and parathormone have received [^{32}P] orthophosphate with encouraging results (relief of pain), according to some reports. A combination of hormone and radiophosphorus HEDP may be worth trying.

It is difficult to synthesize and to control the quality of radiophosphorus-labeled disphosphonate, which makes it expensive and not readily available. A more practical approach would be the use of the stable diphosphonate molecule, to which has been attached a beta-emitting radionuclide. This would still permit the agent's deposition on bone mineral in a manner analogous to that of the technetium-99m-labeled radiopharmaceutical. Radionuclides having both beta and gamma emission should be considered, since this would permit therapy and whole-body imaging from the same dose.

Finally, it is conceivable that the observed bone-marrow depression, as evidenced by the drop in circulating leukocytes and platelets, is inherently so much a part of the approach to therapy by means of the bone-seeking radiopharmaceuticals that it poses an almost insurmountable obstacle. The problem becomes apparent when the difference in radiation dose to the bone marrow, as opposed to the bone proper, is calculated using the "S" method, which assumes that the cortical and trabecular bone are both uniformly labeled by the radionuclide (*40*). We have made two additional assumptions. The first was that 75% of the administered dose is deposited on bone. This is based on (a) data obtained with similar patients receiving Tc-99m diphosphonate (*41*), and (b) the equivalent concentrations of Tc-99m diphosphonate and [^{32}P] HEDP in normal bone and bone tumors in patients (*36*). The second assumption was that only 0.4% of the administered dose deposits within the bone marrow, as suggested by measurements of tissue distribution of [^{32}P] HEDP in animals (*7*). The biologic half-life was taken as 107 days, as is found in animals*.

With an administered dose of 3 mCi of [^{32}P] HEDP, the absorbed radiation doses are as follows:

1. Cortical bone to bone	114 rads
2. Trabecular bone to bone	73 rads
3. Cortical bone to bone marrow	7 rads
4. Trabecular bone to bone marrow	185 rads
5. Bone marrow to bone	7 rads
6. Bone marrow to bone marrow	56 rads

These calculated doses suggest that the basic idea of trying to treat bone metastases with a bone-seeking radiopharmaceutical has little merit because of the juxtaposition of bone marrow and bone mineral. With the enormous constraint of an adjacent radiosensitive marrow, it seems doubtful whether enough ionizing radiation can be delivered to bone metastases to retard tumor growth significantly, unless special measures can be taken to enhance selective concentration of the agent at the tumor sites.

FOOTNOTES

* Personal communication from Procter & Gamble Co., Cincinnati, Ohio.

† Procter & Gamble Co., Cincinnati, Ohio.

‡ Osteoscan, Procter & Gamble Co., Cincinnati, Ohio.

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