Iodine-131-Labeled Diphosphonates for Palliative Treatment of Bone Metastases: II. Preliminary Clinical Results with Iodine-131 BDP3

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The kinetics, dosimetry, and response of iodine-131 α-amino-(4-hydroxybenzylidene)-diphosphonate ([^{131}I]BDP3) treatment were investigated with patients who had pain symptoms from bone metastases of various primary carcinoma. The blood clearance of [^{131}I] BDP3 was rapid. More than 90% disappeared from the blood pool at 2 hr after injection. The excretion of the activity occurred solely through the kidneys and mean total-body retention at 48 hr was 48.6%. The urinary activity showed a metabolite which must be formed by an in vivo cleavage reaction of a phosphorus-carbon bond. The uptake of in vivo cleaved [^{131}I] iodide in the unblocked thyroid was ~0.5%. The effective half-life of [^{131}I]BDP3 in metastatic bone (median 182 hr; range 177–205 hr) proved to be longer than in unaffected areas (145 hr; 140–165 hr). Palliative therapies were performed with 18 patients. They received doses ranging between 6 and 48 mCi [^{131}I]BDP3. The response was 44% complete pain relief, 6% substantial pain relief, 22% minimal improvement, and 28% no change. The duration of response ranged between 1 and 8 wk.

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Iodine-131- (^{131}I) labeled α-amino-(4-hydroxybenzylidene)-diphosphonate (BDP3) was recently suggested as a radiopharmaceutical for the treatment of pain syndromes originating from disseminated bone metastases (*1*). This suggestion was supported by the high bone affinity, low uptake in the residual organs and other favorable biokinetic characteristics which were received from animal experiments. First scintigraphic results revealed high uptake of [^{131}I]BDP3 in bone metastases which encouraged us for a clinical phase I trial. This paper describes biokinetic characteristics, dosimetric calculations, and preliminary clinical results of palliative therapy of bone metastases with [^{131}I]BDP3.

MATERIALS AND METHODS

α-Amino - (4-hydroxybenzylidene)- diphosphonate (BDP3) was labeled with ^{131}I according to a procedure recently described in the literature (*1*). The specific activity of the radiopharmaceutical was generally ~35 mCi ^{131}I/mg BDP3.

The quality of labeling and the analysis of renal excreted activity was performed by radio thin layer chromatography (RTLC) on silica-gel plates.* The solvent consisted of acetone (65%), n-butanol (20%), H_2O (5%), and 25% aqueous ammonia (10%). Activity profiles were measured with a RTLC scanning device.†

Twenty-four hours after the injection of [^{131}I]BDP3—the patients received between 6 and 48 mCi (Table 1)—bone scintigrams were performed in order to monitor metastatic bone uptake. Additionally, serial scintigraphic images of three patients were taken over a time period of up to 500 hr and stored by computer.‡ Identical positioning of the patients and co-measurement of the physical decay of a standard activity guaranteed reproducible results. The physical half-life of the standard activities deviated by 0.6%. Those patients who received [^{131}I]BDP3 doses above 15 mCi were imaged with a pinhole collimator. The evaluation of the kinetics of [^{131}I]BDP3 in metastatic and normal bone was subsequently analyzed by selecting regions of interest (ROIs) over the respective areas in the skeleton. ROIs

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TABLE 1
Individual Results of [^{131}I]BDP3 Therapy

Patient no.	Primary tumor	Site of bone met.	[^{131}I]BDP3 (mCi)	48-hr retention (%)	Response*	Duration
1	Prostate	Ribs Pelvis	1. 17.5 2. 20 (+5 wk) 3. 10 ^{89}Sr (+5 mo)	— 52.3 —	+++ – –	1 wk
2	Prostate	Diffuse	48	—	++	6 wk
3	Prostate	Pelvis	1. 17.5 2. 20 (+4 wk) 3. 10 ^{89}Sr (+6 mo)	47.6 — —	+++ – –	2 wk
4	Prostate	Diffuse	1. 40 2. 10 ^{89}Sr (+10 wk)	29.7 —	+ +	1 wk
5	Prostate	Diffuse	40	52.3	+	
6	Prostate	Diffuse	1. 30 2. 30 (+12 wk)	64.2 51.1	+++ +	6 wk
7	Prostate	Vertebrae Sacrum	6.35	48.4	+	3 wk†
8	Prostate	Multiple	15	—	+++	2 wk
9	Breast	Diffuse	11.4	45.5	+++	5 wk
10	Breast	Multiple	20	—	–	
11	Breast	Multiple	18.9	42.3	–	
12	Breast	Vertebrae	18.2	39.0	+++	3 wk†
13	Breast + thyroid	Diffuse (Breast)	40	58.3	–	
14	Bronchus	Vertebrae	40	39.2	+	2 wk†
15	Diff. thyr.	Pelvis	1. 30 2. 10 ^{89}Sr (+14 days)	51.1 —	– –	
16	Rectum	Sacrum	1. 40 2. 10 ^{89}Sr (+4 wk)	36.9 —	– –	
17	Hypernephroma	Ribs	12	52.3	+++	8 wk
18	Plasmocytoma	Sternum Pelvis	15	—	+++	2 wk†

* (–) No change; (+) Minimal improvement; (++) Substantial pain relief; (+++) Complete pain relief.
† Duration of indicated response could no longer be observed.

of scintigrams which were taken with a pinhole collimator were corrected for their position (*2*). The effective half-lives of [^{131}I]BDP3 in normal bone and bone metastases could finally be obtained from linear regression fitting of the ROI time data to a straight line in a semilogarithmic plot.

In order to evaluate the blood clearance, blood samples were collected from three patients over a time period of 50 hr. They were counted in a gamma counter, corrected in respect to physical decay and calculated as percent total activity in whole blood (Fig. 1).

The excretion of [^{131}I]BDP3 into the urine as a function of time was monitored by serial collection of urine over a time period of ~50 hr. Data were complete for analysis for three patients. The results were depicted as percent of the injected activity (Fig. 2).

Where it was possible, the 48-hr retention of the injected activity was measured either by the evaluation of the excreted urinary activity (four patients) or by total-body counting (ten patients) with a dose rate meter at 1 hr (100%) and 48 hr. The device was positioned 2 m from the sitting patient. Standard measurements revealed sufficient accuracy for this purpose.

Within the last two years, 18 patients were selected for radionuclide therapy with [^{131}I]BDP3 in order to achieve palliation of metastatic bone disease. Two prerequisites were connected with their selection: (a) the pain must have originated from metastatic bone lesions, and (b) there was positive uptake of a preceding technetium-99m methylene diphosphonate (MDP) scan. Eight patients had primary carcinoma of the prostate. All of them had transurethral prostatectomy, bilateral orchidectomy, estrogen, and where necessary palliative external radiotherapy before they were treated with [^{131}I]BDP3. Five patients had bone metastases from carcinoma of the breast. They were treated by radical mastectomy, hormone therapy, chemotherapy, diphosphonate therapy against hypercalcemia, and palliative external radiation therapy before [^{131}I]BDP3 treatment. The remaining five patients had primary carcinoma at various sites as indicated in Table 1. They were also pretreated by chemo- and external radiotherapy as well in two cases by ^{131}I iodide-therapy against bone metastases from primary thyroid carcinoma. Table 1 summarizes all treatment data in detail including therapy repetitions with [^{131}I]BDP3 (three cases) and strontium-89 (^{89}Sr) (five cases).

The therapeutic response after ^{131}I treatment was

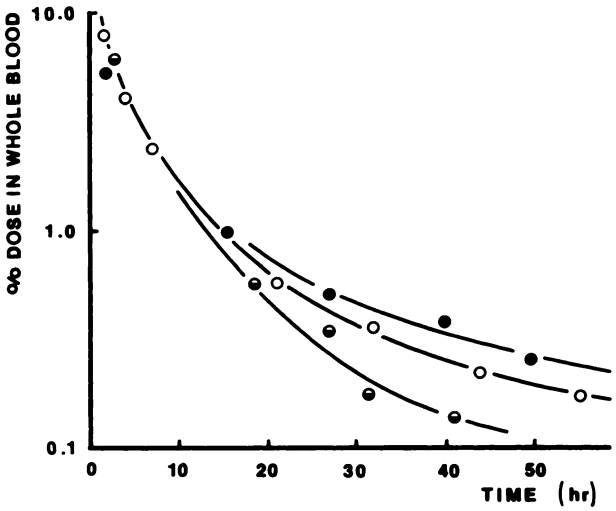

FIGURE 1
(-●-) = Patient 9; (-○-) = Patient 7; (-◒-) = Patient 12. Disappearance of [^{131}I]BDP3 from whole blood of three patients as function of time

monitored according to subjective pain alleviation, analgesic requirements, and the degree of rehabilitation. In reference to studies with analgesic drugs and cancer pain (*3*) the patients rated their improvements on a scale ranging from no pain at all to unbearable pain. Parallel to patients' rating, comments of ward doctors and nurses served as an additional monitor for pain reduction. The duration of any therapy response was defined as the period of time during which the patient maintained pain relief. Unfortunately, the time of pain reduction could not always be determined exactly because the follow-up was interrupted in four cases before pain recurrence occurred.

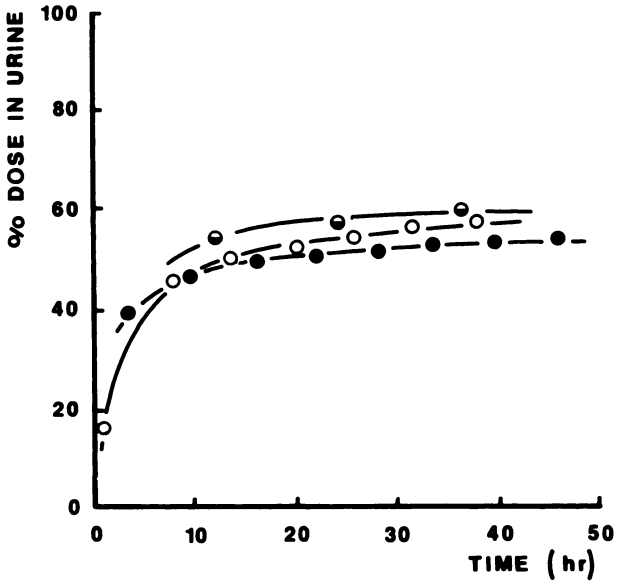

FIGURE 2
(-◒-) = Patient 11; (-○-) = Patient 9; (-●-) = Patient 7. Appearance of renal excreted activity in three patients as function of time

Dosimetric calculations referred to the MIRD concept (*4*) and pharmacokinetics of [^{131}I]BDP3 in man. This concept assumes that the distribution of activity in bone is homogeneous and that the skeleton consists of 80% cortical and 20% trabecular bone.

RESULTS

Blood Clearance

Figure 1 shows the disappearance of [^{131}I]BDP3 from whole blood of three patients as a function of time. The course of the blood-clearance curves are at least triexponential. The half-lives of the individual phases were estimated to $T_1 = <2$ hr, $T_2 = 3$ hr, and $T_3 = 19$ hr.

The disappearance of [^{131}I]BDP3 from whole blood as depicted in Fig. 1 occurred rapidly. Within 2 hr after application, >90% of the injected activity was either deposited in bone tissue or excreted by the kidneys. The blood-clearance of the residual activity (1%) occurred with enhanced effective half-lives which can be explained with protein binding and intravascular redistribution of nonspecific bound [^{131}I]BDP3. The blood-clearance of [^{131}I]BDP3 proceeded very similarly to that of [^{99m}Tc]diphosphonate complexes (*5*). Because of these characteristics, an overall effective half-life of 2 hr was assumed for the calculation of the total-body dose.

Urinary Excretion

The urinary excretion of [^{131}I]BDP3 proceeded rapidly. Figure 2 shows the activity which appeared in the urine of three patients with time. The urinary excreted activities approached the 50% injected dose level at about 10–24 hr. The increase of urinary excreted activity beyond that point was very small. Due to the fast blood clearance and lack of kidney parenchyma fixation, the appearance of radioactivity in the urine was rapid (Fig. 2). At 24 hr a plateau was attained so that at 48 hr after application a mean 56.2% of the injected activity was found in the patients' urine.

The total-body retention values which were obtained by total-body counting correlated very well with the retention values estimated by urinary excreted activities. Table 1 shows the 48-hr retention values, which were measured by both methods. Almost no radioactivity passed through the intestine. Therefore, total-body retention measurements matched the renal excretion. For absorbed dose calculations an extrapolated total-body retention of 50% at the time of injection was assumed. The mean 48-hr total-body retentions are (± s.d.):

Calculated from 48-hr urine	43.8 ± 4.1%;
Measured with dose-rate meter	48.6 ± 9.8%.

The urinary excreted activity was analyzed by thin layer chromatography in order to establish the in vivo stability of [^{131}I]BDP3. Surprisingly, a metabolite was detected in the urine of all patients (five) subjected to

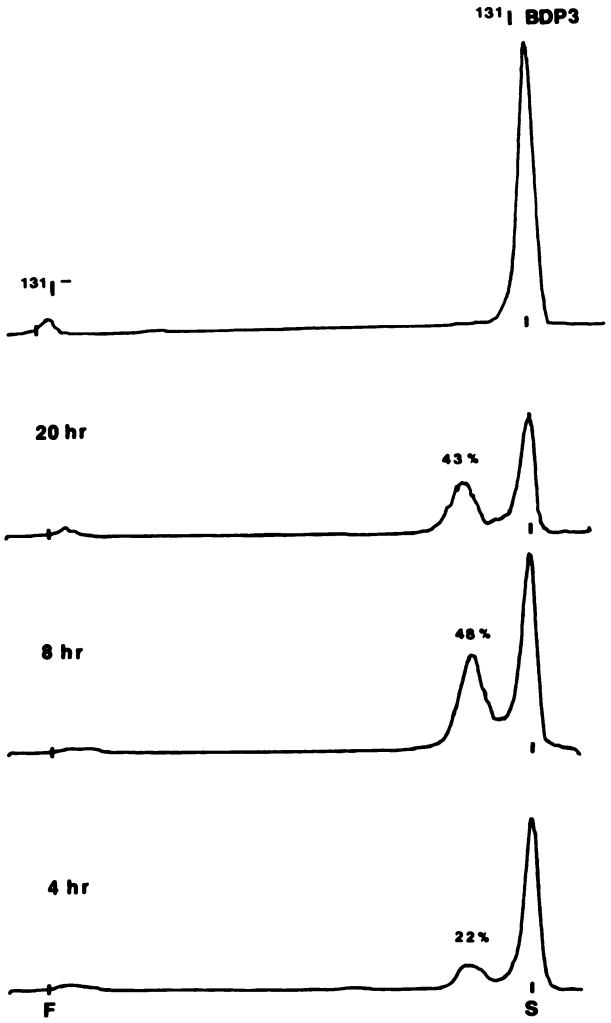

FIGURE 3
RTLC-activity profiles of urine samples (Patient 11) at various times after injection of [^{131}I]BDP3. Upper profile originated from 24-hr urine of rat with osteosarcoma

urine analysis. Figure 3 shows the activity profiles of RTLC scans at various times after [^{131}I]BDP3 application. The proportionate amount of metabolized [^{131}I] BDP3 increased with time. By comparison, the 24-hr urine of rats which had intratibially transplanted osteosarcoma did not show [^{131}I]BDP3 metabolism.

TABLE 2
Parameters of [^{131}I]BDP3 Kinetics in Bone and Bone Metastases

Patient	Site of bone met.	$t_{½}$	Site of normal bone	$t_{½}$	Ratio*
7	Thoracic v.	182 hr	Lumbar v.	145 hr	7.4
	Lumbar v.	187 hr			5.2
8	Thoracic v.	205 hr	Thoracic v.	140 hr	2.5
18	Sternum	177 hr	Lumbar v.	164 hr	—†
	R. pelvis	180 hr			—

* Ratio of bone met./normal bone at time 0 hr (extrapolated).
† Bone sites are not comparable because of different bone masses.

Kinetics in Bone and Bone Metastases

For dosimetric calculations it was necessary to estimate the effective half-lives of [^{131}I]BDP3 in bone and bone metastases. Figure 4 shows three examples of the decrease of dose in metastatic and normal bone tissue as a function of time. The normalized scintigrams which were received at the beginning and at the end of the series of measurements also indicate the faster decrease of activity from normal bone than from bone metastases by contrast enhancement on the late image.

The scintigraphic images revealed no specific uptake by organs other than bone. The ratios of bone metastases/normal bone ranged just after application of [^{131}I] BDP3 between 2.5 and 7.4 (Table 2). Figure 4 shows the decay of ^{131}I activity with time in ROIs over metastatic and nonmetastatic bone areas of three patients. Curves diverging with time indicate prolonged retention of [^{131}I]BDP3 in bone metastases as compared with normal bone. Thus, because of longer effective half-lives in metastatic bone tissue, ratios of metastatic bone/normal bone increased with time. Table 2 summarizes ratios of bone metastases and normal bone together with the uptake ratios at 24 hr after injection.

Uptake in Other Organs

No other organs showed positive contrast on the scintigrams from 4 hr on after [^{131}I]BDP3 was injected. In order to prevent thyroid uptake—~0.5% of the injected dose was liberated as free radioiodide during the distribution phase—all patients were blocked with Lugol's solution. Radioiodide cleavage was not observed after [^{131}I]BDP3 was bound to bone.

Dosimetry

According to the results described above, the following pharmacokinetic parameters were used for dosimetric calculations: Approximately 50% of injected [^{131}I]BDP3 was retained by the patient; the remaining activity was released from the total body with an effective half-life of ~2 hr; the retained activity was homogeneously distributed in the skeleton; the bone metastases accumulated more [^{131}I]BDP3; and the effective half-life was enhanced. These data and the tabulated "S" values yielded absorbed doses in bone, bone marrow, total body, and bone metastases which are summarized in Table 3.

According to the kinetics in and affinity to bone metastases, radiation doses of 1,200 to >3,000 rad can be achieved in bone metastases with 40 mCi [^{131}I]BDP3. Fifty percent is liberated after ~7.5 days (one effective half-life). Similar radiation doses were obtained with ^{89}Sr (*8,9*). However, dose rates were considerably lower with ^{89}Sr; therefore, the time of response was extended with ^{89}Sr (9 days (*9*), compared with [^{131}I]BDP3, 1–3 days).

The absorbed doses in bone metastases of Patient 18 could not be obtained since there was no comparable bone tissue, i.e., metastatic vertebra compared with normal vertebra.

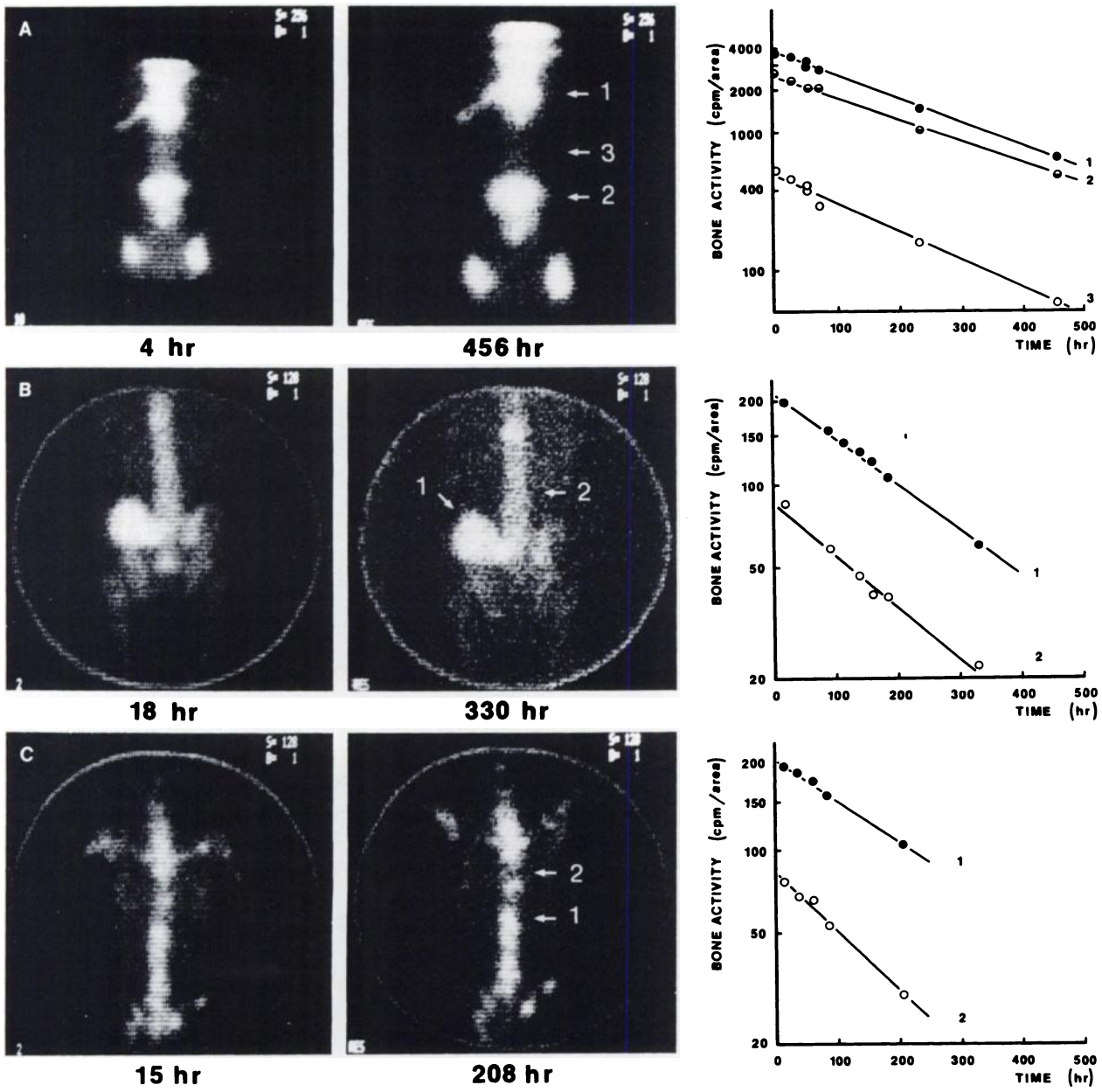

FIGURE 4
A–C: Normalized scintigrams and activity-time curves of indicated ROIs over metastatic and normal bone tissue of three patients (A = Patient 7; B = Patient 18; C = Patient 8). Effective half-lives are summarized in Table 2

Therapy Results

The patients received single doses ranging from 6 to 48 mCi [^{131}I]BDP3. Three patients who primarily showed very good response and subsequently perceived pain recurrence were treated with an additional [^{131}I] BDP3 dose. Since no improvement was observed with [^{131}I]BDP3, ^{89}Sr was applied for a second respectively third retreatment (Table 1). Strontium-89 emits higher energetic beta-radiation and has been successfully used for this kind of treatment (*8–11*). In all cases, however, no improvement of the patients' condition was achieved. This result may rule out the necessity of high energy beta-particles in order to get a palliative effect. In our opinion, the dose determining affinity and kinetics of the radiopharmaceutical in the neoplastic bone area are solely responsible for response.

The clinical results of Table 1 were set in the order corresponding with the primary tumor site and re-

TABLE 3
Absorbed Radiation Dose Achieved with [^{131}I]BDP3

Item	rad/mCi	(Gy/GBq)
Bone	9.07	(2.45)
Bone marrow	2.94	(0.79)
Total body	1.05	(0.28)
Bone metastasis 1, Patient 7	61.7	(16.7)
Bone metastasis 2, Patient 7	86.2	(23.2)
Bone metastasis, Patient 8	33.2	(8.97)

sponse. Table 4 shows that best results were achieved with prostate carcinoma patients. Patients with breast carcinoma and carcinoma of other sites showed less frequent pain reduction. Of all patients, 72% experienced pain reduction. The frequency of response was similar to a [^{32}P]phosphate study (*13*). However, the duration of response, 1 to 8 wk for any degree of response, appeared to be somewhat short. This was partially due to the interruption of the follow-up of four patients.

Table 1 shows the individual responses of [^{131}I]BDP3 therapy with respect to the grade of pain reduction and duration. Table 4 summarizes the results according to the site of primary tumor, degree of palliative response and range of duration. The overall results were 44% complete pain relief, 6% substantial pain relief, 22% minimal improvement, and 28% no change.

The peripheral blood count (erythrocytes, leukocytes and platelets) were measured routinely just before and 4–6 wk after the treatment. No changes were observed which could be related to the [^{131}I]BDP3 treatment.

DISCUSSION

The pharmacokinetics, dosimetry, and palliative efficacy of [^{131}I]BDP3 were evaluated with patients who developed pain from disseminated bone metastases. Since this study also includes patients who were treated at the beginning with probably insufficient doses of [^{131}I]BDP3, the therapeutic efficacy must be considered as preliminary.

TABLE 4
Iodine-131 BDP3 Response with Respect to Site of Primary Tumor

Primary tumor	Response*	Patients†	Duration (range)‡
Prostate	–	0	—
	+	3	1–3
	++	1	6
	+++	4	1–6
Breast	–	3	–
	+	0	–
	++	0	–
	+++	2	3–5
Other	–	2	–
	+	1	1
	++	0	–
	+++	2	2–8
Sum	–	5 (28%)	–
	+	4 (22%)	1–3
	++	1 (6%)	6
	+++	8 (44%)	1–8

* See Table 1.
† Number of patients.
‡ Weeks.

The chromatographic analysis of the renal excreted activity revealed an unexpected [^{131}I]BDP3 metabolite. The metabolite has not yet been identified. However, in respect to the data received with RTLC it must be formed by an oxidative P-C-bond cleavage reaction, since diphosphonates do not migrate on silica-gel plates under the described conditions. Due to chromatographic comparison of possible metabolites which may be formed by this reaction we have strong evidence for a benzylidene(mono)phosphonate derivative.

This finding may be helpful for the interpretation of the surprising strong bone marrow response observed during phosphorus-32 hydroxyethylidene diphosphonate ([^{32}P]HEDP) therapy (*6*). If [^{32}P]HEDP is similarly susceptible to an in vivo P-C cleavage reaction [^{32}P] phosphate would have been formed which, after DNA incorporation into bone-marrow cells, adds to the absorbed dose therein. By comparison, no [^{131}I]BDP3 metabolism was observed with normal and osteosarcoma-bearing SD-rats (Fig. 3). Another small peak which moved close to the solvent front refers to in vivo cleaved [^{131}I]iodide.

The reason for the enhanced retention of activity in neoplastic bone tissue was related to the liberation and/or formation of hydroxyapatite binding sites—mediated by the enhanced osteoclastic and/or osteoblastic activity that accompanies enhanced bone turnover (*1,7*). Thus, from normal bone, remobilized [^{131}I]BDP3 can be reutilized by higher affinity metastatic regions. Therefore, an effective half-life greater than the physical half-life is possible. This effect is considered to be favorable for the palliative purpose. The effective half-lives are summarized in Table 2. The values indicate enhanced [^{131}I]BDP3 retention in all metastatic areas.

The results of therapy demonstrate that only rather small radiation doses are required for a palliative effect. Retrospective studies on external radiotherapy support this finding; they reported that there is no evidence of a dose-related response above 400 rad (*12*).

Forty millicuries of BDP3 represents a sufficiently safe dose in respect to bone marrow depression. According to the absorbed dose calculations this would yield 120 rad to the bone marrow. Peripheral blood count changes which can surely be related to the [^{131}I] BDP3 treatment were not observed within a time period of ~6 wk. Due to other pretreatment modalities such as chemotherapy and the mostly advanced status of disease several patients were already blood cell deficient. Even with those patients no dramatic changes occurred. An explanation for the observed bone-marrow tolerance may be connected with the rather short beta-particle range of ^{131}I. Bone surface bound [^{131}I]BDP3 irradiates less bone marrow volume than higher energetic beta-emitters such as ^{89}Sr and ^{32}P.

The rather low doses at the beginning of our trial must also be considered for a statistical impairment—

at that time we did not know the proper [^{131}I]BDP3 dose including its effect on pain reduction and bone marrow response. Additionally, as it was demonstrated by repeated treatments with [^{131}I]BDP3 and ^{89}Sr, the progression of bone metastases and less tolerance in pain perception indicated an end point for this kind of treatment.

A correlation of those patients who perceived pain remission with the degree of [^{131}I]BDP3 uptake or any other parameter could not be evaluated. The only prerequisite for pain reduction seemed to be the liberation of absorbed doses around 1,000 rad in areas of stimulated nociceptors. It is still unknown by what mechanism energetic electrons such as beta-particles affect the depolarization rate of involved nerve endings.

The phase I clinical results indicate clinical efficacy of [^{131}I]BDP3 for the palliative therapy of pain syndromes associated with disseminated bone metastases. Iodine-131 proved to exhibit several favorable features as a beta-source for an osteotropic diphosphonate derivative. Gamma-radiation for scintigraphic measurements and an appropriate physical half-life for the storage tanks in radionuclide therapy wards make this a simple labeling procedure. Our presently performed [^{131}I]BDP3 therapies are standardized to 21.6 mCi/m^2 body surface. This is necessary in order to receive results which are comparable to other radiopharmaceuticals.

FOOTNOTES

* Merck, Darmstadt, FRG.
† Berthold, Wildbad, FRG.
‡ Dycom 80, Elscint, Haifa, Israel.

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