Effect of Clodronate Treatment on Bone Scintigraphy in Metastatic Breast Cancer

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Because of their high affinity for bone, bisphosphonates are used both in the treatment of benign and malignant bone disease and in radiopharmaceutical bone imaging. A prospective study was undertaken to evaluate whether intravenous clodronate (dichloromethylene bisphosphonate) therapy might affect the results of bone scintigraphy with ^{99m}Tc-labeled methylene diphosphonate (MDP). In 11 female patients with breast cancer and metastatic bone disease, quantitative bone scans were obtained using a region of interest (ROI) method on Days 0 and 22. After intravenous clodronate therapy from Day 1 to Day 21, all metastatic bone lesions were still detectable, and median ROI ratios did not differ to a statistically significant extent from baseline values. Serum calcium levels decreased (p = 0.0449), whereas parathyroid hormone concentrations showed an increase (p = 0.0053). Mean serum levels of creatinine, inorganic phosphorus, osteocalcin, gamma glutaminyl-transpeptidase and alkaline phosphatase remained unchanged. However, a more than twofold rise in the serum activity of alkaline phosphatase was measured in three patients. We conclude that 3 wk of intravenous clodronate treatment did not impair the sensitivity of ^{99m}Tc-MDP bone scintigraphy in detecting bone lesions in patients with metastatic breast cancer.

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Bisphosphonates have become important as therapy for Paget's disease of bone (1,2) and tumor-associated hypercalcemia which has persisted after fluid repletion (3–7). In clinical trials, they have also proved to be effective in the prevention of glucocorticoid-induced bone loss (8) as well as in the treatment of metastatic bone disease (9–11) and postmenopausal osteoporosis (12,13).

Bisphosphonates are characterized by a central phosphorus-carbon-phosphorus structure. They are tightly bound to calcified bone matrix and are powerful inhibitors of osteoclast-mediated bone resorption (14). A direct cytotoxic effect on mature osteoclasts, an inhibition of oste-

oclast precursor access to the bone matrix and an impairment of the differentiation of osteoclast precursors are hypothesized as the mode of action (15).

In the diagnostic field, bisphosphonates are used as bone-avid carriers for ^{99m}Tc in bone scintigraphy, in which increased tracer uptake when compared to the normal skeleton is found in regions of active bone formation (16). Radiopharmaceutical bone imaging is of proven value in preoperative tumor staging as well as in the initial assessment and follow-up of neoplastic bone destruction (16).

There is, however, conflicting data as to what extent the affinity of radiolabeled bisphosphonate for bone is altered in the presence of therapeutically administered bisphosphonates. The aim of this study was to evaluate whether previous bisphosphonate treatment for metastatic bone disease might give rise to false-negative bone scans and might therefore reduce the diagnostic efficiency of radiopharmaceutical bone imaging.

MATERIAL AND METHODS

Patient Population

Eleven female patients (aged 49–80 yr, mean age 58 yr) with advanced breast cancer were enrolled in the study since November 1989. Inclusion criteria were histologically verified breast cancer, radiological evidence of sclerotic or mixed bone metastases, skeletal pain and no previous therapy with bisphosphonates. Patients with purely osteolytic bone metastases were excluded from the trial since there have frequently been false-negative bone scans in this variant of neoplastic bone destruction (16). Patient characteristics are shown in Table 1.

Basic cancer treatment consisted of hormonal therapy and/or cytostatic drugs (Table 1). Dosage and mode of application remained unchanged within 2 mo prior to and during the investigation.

Treatment

Clodronate (dichloromethylene-1,1-bisphosphonic acid; Boehringer Mannheim, Vienna, Austria) was administered intravenously at a dose of 300 mg per day from Day 1 to Day 21. The drug was diluted in 500 ml 0.9% saline solution and was infused over 2 hr.

The protocol was approved by the Ethics Committee of the Lainz Hospital, Vienna. Written informed consent was obtained from each patient.

TABLE 1
Patient Characteristics

Patient no.	Age	Metastasis	Chemotherapy*	Endocrine therapy	Initial calcium (mmol/liter)	No.†	Median ratio Day 0	Median ratio Day 22
						Regions of interest		
1	49‡	Bone, liver	CMF	None	2.30	2	2.775	5.180
2	49‡	Bone, liver	DI	None	2.54	9	2.390	2.650
3	49‡	Bone, lung	None	Goserelin	2.32	7	3.930	3.940
4	50	Bone	DI	None	2.21	12	5.085	2.165
5	57	Bone	None	Tamoxifen	2.27	2	1.900	1.965
6	58	Bone	None	4-OH Andro	2.52	3	1.975	2.200
7	58	Bone, lung	DI	None	2.38	5	4.320	2.730
8	65	Bone	DI	None	2.56	6	2.890	1.890
9	67	Bone, lung	DI	Tamoxifen	2.55	6	1.805	1.830
10	69	Bone, liver	CMF	None	2.48	3	2.380	2.190
11	80	Bone, lung	CMF	Tamoxifen	2.63	5	2.230	1.830

*DI = doxorubicin (Adriamycin) plus ifosfamide; CMF = cyclophosphamide plus methotrexate plus 5-fluorouracil and 4-OH Andro 4-hydroxyandrostendione.
†Number of ROIs selected for measurement.
‡Premenopausal hormonal status.

Laboratory Monitoring

Serum levels of total calcium, inorganic phosphorus, creatinine, blood urea nitrogen (BUN), total protein and the serum activities of alkaline phosphatase and gamma-glutaminyl transpeptidase were measured three times a week with standard automated methods. Since Ladenson et al. did not find an improvement in the correlation between total calcium and ionized calcium by correcting serum calcium levels for the effects of protein, albumin or pH, we used uncorrected serum calcium levels (17).

Serum concentrations of intact parathyroid hormone (PTH) and total osteocalcin were determined on Days 0, 7, 14 and 22 with immunoradiometric assays (Allegro PTH kit, Nichols Institute, San Juan Capistrano, CA; Elsa-Osteo kit, CIS International, Gif sur Yvette, France). The osteocalcin kit used the sandwich technique and a human standard.

Bone Scans

On Days 0 and 22, quantitative bone scans were obtained from all patients by a region of interest (ROI) technique (18). Three hours after the intravenous injection of 15 mCi of ^{99m}Tc-methylene diphosphonate (MDP), the entire skeleton was imaged. To enable quantitative evaluation of scintigrams, analog images were digitized by a computer interfaced to a gamma camera (19). Computer images were acquired using a 128 × 128 mode. All bone metastases were analyzed. A ratio of the activity measured in these ROIs and of the activity determined in corresponding sites of unaffected bone was calculated after subtraction of background activity. If the contralateral site was also involved in the metastatic bone disease or if the skull or the spine were selected as the site to be counted, an arbitrary area of normal bone was chosen for comparison. The activity was expressed as average counts per pixel because of the different sizes of the lesions.

Statistical Analysis

The median of the ROI ratios was determined for each patient. A Wilcoxon matched pairs signed rank test was applied to determine the statistical significance of the medians of the ROI ratios on Days 0 and 22. A multivariate analysis of variance (MANOVA) was performed to calculate significances of the changes in serum

parameters. We used the SAS software system (SAS Institute Inc., Cary, NC). Probability of values less than 0.05 were considered to indicate significance.

RESULTS

Activity ratios for a total of 60 ROIs were selected for comparison in serial bone scintigrams. The number of osseous metastases varied interindividually from 2 to 12 (Table 1) and remained unchanged from the first to the second bone scan. There was no significant difference observed in the scintigraphic detection of osseous metastases when the medians of the activity ratios on Days 0 and 22 were compared with the Wilcoxon matched pairs signed rank test (p = 0.5937). In two patients, a more than 10% rise in the medians was found. In five patients, the median remained unchanged within the 10% limit. In four patients, it decreased when compared to the first evaluation (Table 1). Intravenous treatment with clodronate for 21 days did not interfere with radiopharmaceutical bone scanning sensitivity (Fig. 1).

Clodronate treatment induced a fall of serum calcium (p = 0.0449) and an increase of serum parathyroid hormone (p = 0.0053, Fig. 2). The course of laboratory parameters is listed in Table 2). Initially, a slightly elevated serum calcium (2.63 mmol/liter; normal range of serum calcium 2.1–2.6 mmol/liter) was measured in one patient (Patient 11). Under clodronate therapy, she showed a transient, asymptomatic hypocalcemia (nadir of serum calcium 1.85 mmol/liter on Day 22). Without any specific treatment, the patient became normocalcemic 3 days after discontinuation of intravenous bisphosphonate administration.

There was no significant change in the mean serum levels of creatinine, inorganic phosphorus, osteocalcin, gamma glutamyl-transpeptidase or alkaline phosphatase (Table 2).

In three patients, serum levels of alkaline phosphatase increased more than twofold during clodronate treatment (Fig. 3). The alkaline phosphatase activity returned to baseline levels within 3 mo. All three patients also exhibited a rise in osteocalcin levels. In two of these patients (Patients 6 and 11), gamma glutamyltrans-peptidase remained unchanged. The third patient (Patient 1) showed an increase in gamma glutamyltranspeptidase (132 U/liter on Day 0 as compared to 193 U/liter on Day 22).

DISCUSSION

Recent clinical investigations evaluating the effect of bisphosphonate therapy on the sensitivity of bone scans have focused on Paget's disease (20–22). In these studies, bisphosphonates were administered orally for 3–6 mo until bone scintigraphy was repeated. The long period of bisphosphonate administration resulted in problems in interpreting the scintigraphic changes. The decreased uptake of the radiolabeled bisphosphonate might have been both a sign of a reduced activity of disease or a sign of bone saturation with bisphosphonates. Since bone pain was also ameliorated in the patients studied and biochemical serum and urinary parameters revealed an impressive reduction of bone turnover, the changes in bone scans were obviously the desired effects for therapy. However, the reduced activity of Paget's disease following successful treatment with bisphosphonates may also conceal a coincident interference with the sensitivity of the scintigraphic method used.

In metastatic bone disease, two case reports concerning interactions between bisphosphonate therapy and bone scan reliability have been published so far. In both reports,

FIGURE 2. Change of the serum levels of calcium and PTH (mean ± s.e.m.). Clodronate therapy induced a decrease in calcium (p = 0.0449) accompanied by an increase in PTH (p = 0.00553). To convert picomoles of intact PTH per liter to picograms per milliliter multiply by 9.5.

severe impairment of radiopharmaceutical bone imaging was demonstrated during or immediately after treatment with etidronate (1-hydroxy-ethylidene-1,1-bisphosphonate) (23,24).

Sandler et al. observed bisphosphonate-induced artifacts in serial bone scintigraphy. The bone scans were obtained 24 and 96 hr after administration of a single dose of etidronate for treatment of hypercalcemia (serum calcium: 3.94 mmol/liter) in a patient with milk-alkali syndrome (25). Another bone scan obtained 2 wk later revealed normal biodistribution of ^{99m}Tc-MDP.

In our prospective study, we did not find that clodronate therapy for 21 days interfered with the sensitivity of radiopharmaceutical bone imaging. The intravenous route of application was chosen due to poor gastrointestinal absorption of bisphosphonates. Each patient received a cumula-
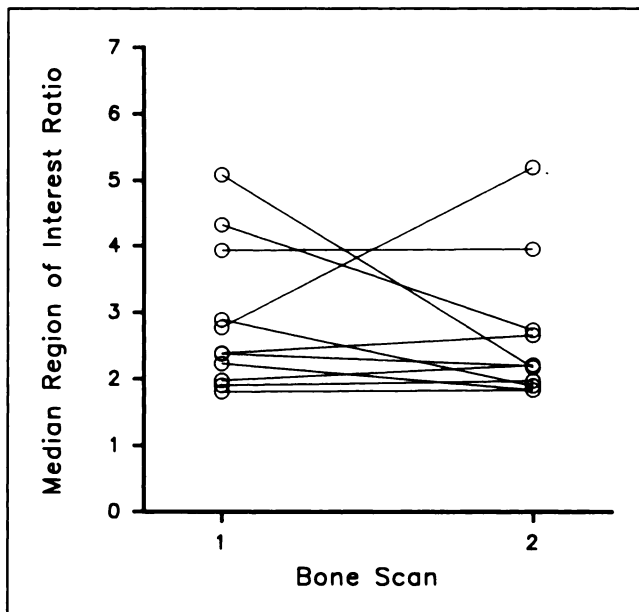

FIGURE 1. Change in ROI ratio. No statistically significant differences were found when the median ROI ratio of each patient was compared in the first and second bone scans obtained before and after intravenous administration of clodronate for 21 days (p = 0.5937).
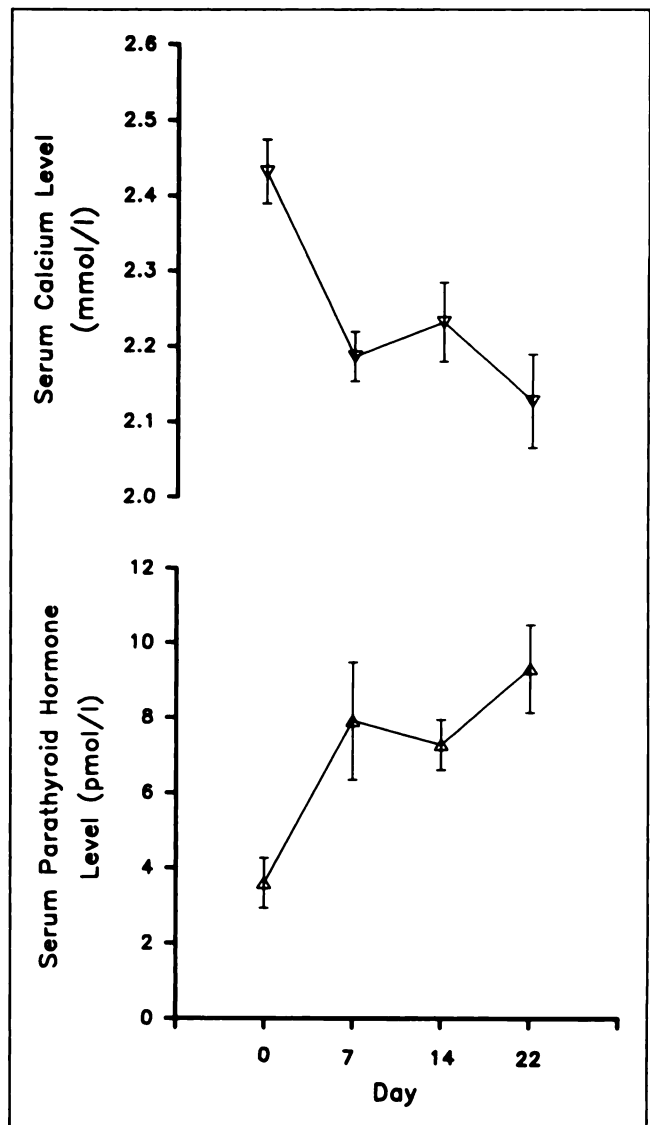
TABLE 2
Laboratory Findings (mean ± s.e.m.) Before and After Treatment with Clodronate

	Day 0	Day 7	Day 14	Day 22
Calcium (mmol/liter)	2.43 ± 0.04	2.18 ± 0.03*	2.23 ± 0.05*	2.12 ± 0.06*
Phosphate (mmol/liter)	1.08 ± 0.05	1.13 ± 0.04	1.06 ± 0.06	1.11 ± 0.05
Creatinine (μmol/liter)	77.79 ± 6.18	76.90 ± 7.07	77.79 ± 6.18	76.90 ± 7.95
Alkaline phosphatase (U/liter)	252 ± 48	288 ± 57	377 ± 100	416 ± 113
Gamma-GT (U/liter)	52 ± 15	53 ± 18	70 ± 22	49 ± 17
Parathyroid hormone (pmol/liter)	3.60 ± 0.65	7.92 ± 1.56*	7.28 ± 0.66*	9.32 ± 1.18*
Osteocalcin (pmole/liter)	3338 ± 598	3424 ± 621	3641 ± 521	3702 ± 622

*$p < 0.05$ when compared to values determined on Day 0.

Gamma-GT = gamma glutamyltranspeptidase. The normal range of parathyroid hormone is 1.0–6.0 pmole/liter. To convert picomole parathyroid hormone per liter to picograms per milliliter, multiply by 9.5. The normal range of osteocalcin is 1200–5300 pmole/liter. To convert picomoles osteocalcin per liter to nanograms per milliliter, multiply by 0.0058.

tive dose of 6300 mg of clodronate equivalent to an oral treatment ranging from 196 to 393 days, if the oral dose of clodronate is 1600 mg per day and the absolute bioavailibility is 1%–2% (26,27). By limiting the intervals between scintiscans to 3 wk, we intended to reduce changes in serial bone scintigraphy to pure osseous saturation with bisphosphonates and to exclude effects of bone healing as much as possible. Our findings confirm the observations of Kanis et al., who reported unaltered whole-body retention of labeled bisphosphonates after 5 days of intravenous clodronate therapy for Paget's disease (28).

Etidronate, which was obviously responsible for impaired radiopharmaceutical bone imaging, binds twice as strongly to the surface of hydroxyapatite crystals than clodronate (29). About 75% of the intravenously administered clodronate dose in vivo is excreted within 24 hr in the urine, whereas about 50% of an equal etidronate dose is chemisorbed to the bone (17,30,31). In our trial, potential effects of differences in the pharmacokinetic properties of clodronate and etidronate were blunted by the extensive, intravenous treatment with clodronate and the resulting relatively high concentrations of the bisphosphonate on bone surface. Therefore, divergences between our results and the case reports mentioned above might not be attributed to variant pharmacokinetic characteristics of the bisphosphonates used.

In two of the patients with disturbed biodistribution of radiotracer, etidronate was administered for treatment of hypercalcemia (24,25). In patients with calcium concentrations as high as that reported by Sandler et al. (25), formation of complexes between the labeled bisphosphonate and calcium ions might occur in blood. The time required for normalization of serum calcium was not mentioned in the paper. Due to the delayed onset of the hypocalcemic response of bisphosphonates and the single low dose of etidronate (450 mg), serum calcium could also have been in the hypercalcemic range 96 hr after the bisphosphonate application at the time of the second impaired bone scan.

Clodronate therapy led to a decrease in serum calcium, which stimulated PTH secretion in a counter-regulatory way. This mechanism prevents development of symptomatic hypocalcemia even after high dose bisphosphonate administration (32). Serum activity of alkaline phosphatase increased in three patients. A concurrent rise in serum osteocalcin, a protein produced only by bone-forming and teeth-forming cells, indicates an osteoblastic origin of the enzyme (33). In one of these patients, a rise in serum gamma glutaminyltranspeptidase levels was also determined. Thus, a contribution of the hepatic isoenzyme of alkaline phosphatase to the rise in total serum enzyme activity seems probable in this case. Moreover, a clodronate-induced deterioration of hepatobiliary function cannot be ruled out in this woman with extensive liver metastases.

The rise in alkaline phosphatase and osteocalcin, both markers of enhanced bone remodeling, might indicate progression of tumor and of sclerotic bone destruction or the initiation of bone healing (34,35). In patients with osteolytic bone metastases responding to hormonal or cytostatic treatment, Coleman et al. found a maximum increase in both serum parameters between the first and second month following the start of successful therapy (35). A comparable effect induced by clodronate was reported by Chapuy et al. (36). In mixed and sclerotic bone metastases, which are generally characterized by enhanced bone turnover, bone repair and tumor progression cannot be validly differentiated on the bases of changes of biochemical, radiographic or radioisotopic parameters within the first 6 mo (37). In none of the three patients with transiently increasing alkaline phosphatase levels did further follow-up examinations reveal an objective response according to the criteria of the International Union Against Cancer (data not shown) (38).

In summary, our findings indicate that even intravenous treatment with 300 mg of clodronate for 3 wk did not saturate bone to such an extent that further bisphosphonate is not chemisorbed to the bone surface. Moreover, it appears that previous clodronate therapy does not impair the sensitivity of radiopharmaceutical bone imaging in patients with metastatic breast cancer.
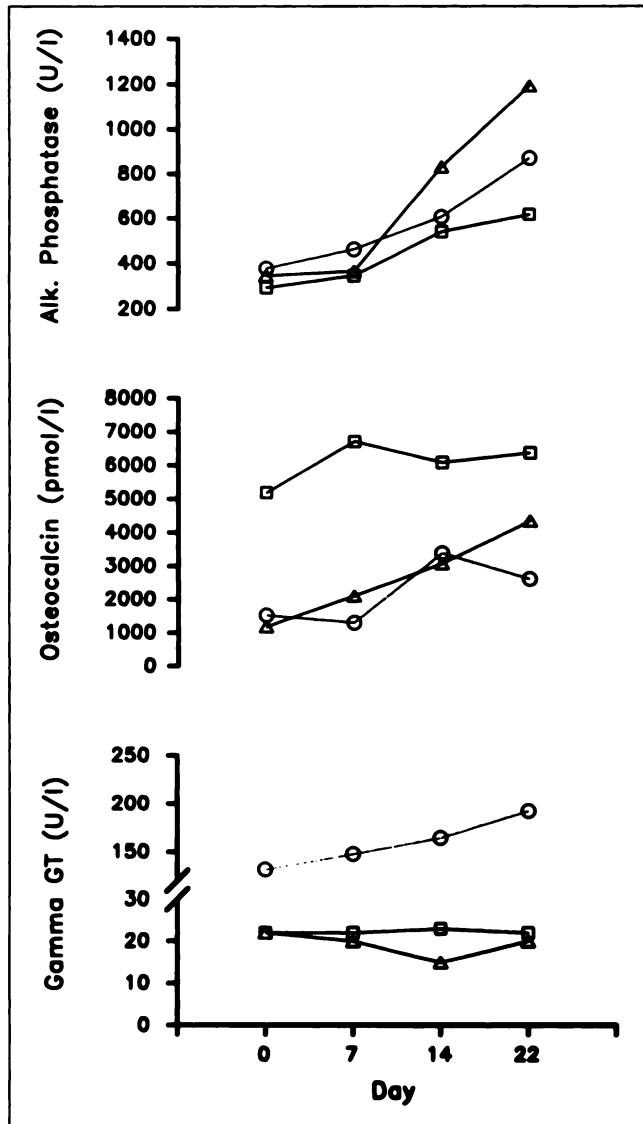
FIGURE 3. Course of serum levels of alkaline phosphatase, osteocalcin and gamma glutamyltranspeptidase in three patients with increasing serum activity of alkaline phosphatase during clodronate therapy. The solid lines represent patients without an increase in gamma glutamyltranspeptidase activity: the squares denote Patient 6, the triangles denote Patient 11. The broken line and the circles represent the course of the three parameters in Patient 1. To convert picomoles osteocalcin per liter to nanograms per liter multiply by 0.0058.

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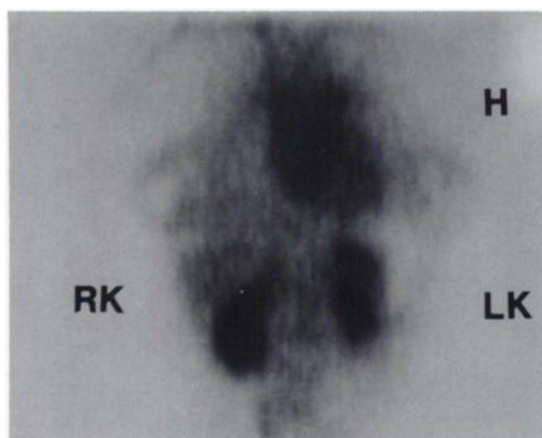
FIRST IMPRESSIONS

FIGURE 1.

FIGURE 2.

PURPOSE

A 28-yr-old woman who takes oral contraceptives was admitted for bone scanning due to increasing back pain. Static images showed bilateral "oval formed" increased activity above the kidneys. Clinical investigation was negative. This unexpected finding needed further investigation. The patient then underwent dynamic bone scanning followed by static scanning at 5 min, 8 min and after 3 hr. The dynamic study did not show increased activity anywhere in the thorax. After 5 and 8 min, the static scan showed diffuse increased activity bilaterally, with a central photopenic area level with the 6-7 costa. The 3-hr scan reproduced the same results as the previous scintigrams described above. The area with reduced blood supply was subsequently identified as the papilla mammae and areola. There was no activity in the thorax or elsewhere in the soft tissue of the mammae. Scintigrams were registered 2 days prior to her regular menstruation. Static views after 5 min are seen in Figure 1 (H = heart; RK = right kidney; LK = left kidney) and static views after 3 hr are seen in Figure 2. Both kidneys are also visible on the bone scan.

TRACER

Technetium-99m-MDP.

ROUTE OF ADMINISTRATION

Intravenous injection.

TIME AFTER INJECTION

Immediately, 5 min, 8 min and 3 hr.

INSTRUMENTATION

SOPHY gamma camera.

CONTRIBUTORS

Bob Dugal and Martha Henriksen.

INSTITUTION

Vest Adgar Central Hospital, Christiansen, Norway.