Relative Distribution of Diphosphonate Between Bone and Soft Tissue at 4 and 24 Hours: Concise Communication

Marie L. Smith, William Martin, Ignac Fogelman, and Rodney G. Bessent

Royal Infirmary, and Department of Clinical Physics and Bio-Engineering, Glasgow, Scotland

Digital bone scintigrams were obtained in 19 patients using Tc-99m hydroxyethylidene diphosphonate (HEDP). These were quantitated for skeletal, soft-tissue and renal uptake of tracer using a contrast-enhancement technique to define the regions of interest. Twenty-four hr whole-body retention (WBR) of HEDP was also measured. It was found that approximately 70% of retained diphosphonate was localized in the skeleton at 24 hr, with 26% in soft tissue and 4% in kidneys. However, we have shown that over a wide spectrum of whole-body retention measurements (18 to 70%) the 24-hr soft-tissue component, as a percentage of administered dose, remained relatively constant whereas skeletal tracer accumulation mirrored WBR ($r = 0.98$, $p < 0.001$). The present study indicates that, despite a significant but essentially stable soft-tissue component, measurement of 24-hr WBR of HEDP accurately reflects skeletal metabolism.

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Bone scintigraphy, using the technetium-99m-labeled diphosphonates, now has an established role in the investigation of skeletal disease. If pathology is focal, as in metastatic disease (*1*) and Paget's disease (*2*), it is easy to differentiate normal from abnormal. In contrast, in the metabolic bone disorders, which usually result in a generalized alteration of skeletal metabolism, scintigraphic diagnosis tends to rely upon a subjective impression of altered tracer uptake throughout the whole skeleton, which may be difficult to appreciate (*3*). In such a situation, quantitation of tracer uptake by bone could be of diagnostic value. However, the early quantitative and semiquantitative techniques used [e.g., measurement of ratios between bone and soft-tissue (*4*,*5*) and the Metabolic Index (*6*)] have proved disappointing, largely because of their inability to differentiate altered skeletal metabolism in individual subjects (*7*). This has led to increasing interest in methods of quantifying total tracer uptake by the skeleton in an attempt to recognize subtle alterations in skeletal function.

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For reprints contact: Marie L. Smith, Royal Infirmary and Dept. of Clinical Physics and Bio-Engineering, Glasgow, G4 0SF, Scotland.

One such technique, the 24-hr whole-body retention (WBR) of hydroxyethylidene diphosphonate (HEDP) provides a quantitative measure of diphosphonate retention in the body 24 hr after an intravenous dose of Tc-99m HEDP and, in the presence of normal renal function (*8*), has proved to be a sensitive means of identifying patients with increased bone turnover (*9*,*10*).

However, while 24-hr WBR is believed to be primarily a measure of bone uptake of tracer, the relative distribution of diphosphonate between bone and soft tissue has not been investigated. The present study was undertaken to repair this omission. In addition, the distribution of diphosphonate in the body 24 hr after injection was studied to determine whether it differs substantially from that at 4 hr, the time interval used in conventional bone scanning (*11*).

METHODS

Nineteen patients undergoing routine bone scanning were studied using 15 mCi of Tc-99m hydroxyethylidene diphosphonate (HEDP) (Table 1). Ten standard bone-scan views were obtained from each patient at both 4 and 24 hr after injection, using a wide-field gamma camera

TABLE 1. STUDY POPULATION (CLINICAL/ SCAN DIAGNOSIS)

Diagnosis	Number
Negative bone scan	5
Primary hyperparathyroidism	4
Paget's disease	3
Thyrotoxicosis	2
Osteoporosis (with vertebral collapse)	2
Osteoporosis (without vertebral collapse)	2
Hypothyroidism	1

with low-energy parallel collimator, interfaced to a minicomputer. Images were stored on magnetic tape for subsequent analysis. An image of room background was also stored on each occasion. In addition, 24-hr whole-body retention of HEDP was measured in each patient using the same gamma camera with a fishtail collimator as previously described (*12*).

The relative percentages of diphosphonate in bone at 4 and 24 hr were calculated in individual patients using the following method. All images were standardized to 100 sec acquisition time. Each of the ten computer images was contrast-enhanced until the "hot areas" (i.e., the bones) were above the upper display threshold (Fig. 1); the areas of these regions and the counts within them were then obtained from the computer. Areas of overlap and known areas of high soft-tissue uptake (i.e., bladder and kidneys) were excluded by drawing conventional regions of interest.

The high count rates obtained at 4 hr made background correction unnecessary. At 24 hr, however, the count rate is approximately 1/20th of that at 4 hr, and background activity and "edge effect" (counts around the periphery of the image) become important. Twenty-four/hr images were therefore corrected by subtracting the appropriate bone background and "edge" counts. Edge background was standardized by averaging edge counts over all the images. The percentage of activity in bone was then calculated by summing the bone counts and total counts for all the views.

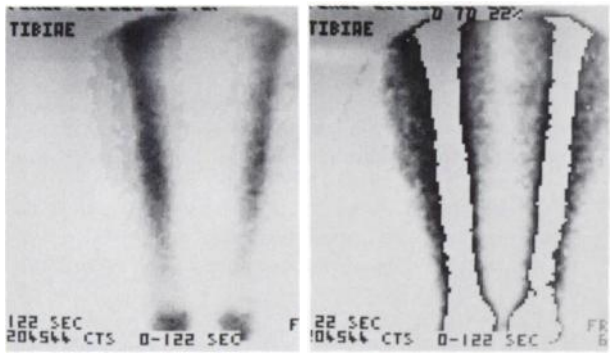

FIG. 1. Four-hour bone scintigram (Tc-99m HEDP) of tibiae before contrast enhancement (right). Same, after contrast enhancement (left).

TABLE 2. RELATIVE PERCENTAGES IN BONE AND SOFT TISSUE

	4 hr	24 hr	
Bone	65.7 ± 5.2	72.1 ± 8.4	$p < 0.002$
Kidneys	2.94 ± 0.94	4.11 ± 1.6	$p < 0.002$
Soft tissue	34.3 ± 5.2	27.9 ± 8.4	$p < 0.002$

n = 19

One potential source of error in this method is an apparently increased soft-tissue count rate as a result of scattered photons from the hotter bone, but phantom studies showed that this effect is not significant, and correction was not required.

Statistical analysis of the results was performed using the Wilcoxon test for paired samples and the Wilcoxon test for groups.

RESULTS

Whole-body retention results (ranging from 18 to 70%) fell within the established normal range of 12.21–26.13% (*13*) in seven patients (mean 21.3% ± 3, s.d.) and were elevated in 12 (mean 34.6% ± 13.2). The relative percentages of activity in bone and soft tissue at 4 hr and 24 hr in all 19 patients are shown in Table 2. At 24 hr after injection there was relatively more activity in bone than at 4 hr ($p < 0.002$). This was coupled with a relative decrease in 24-hr soft-tissue activity, but there was an increase in 24-hr renal activity relative to the 4-hr levels ($p < 0.002$, $p < 0.002$).

Since the 24-hr WBR of each patient was measured, it is possible to calculate the absolute percentage of administered dose in bone and soft tissue at 24 hr. These results, separating the patients with normal WBR from those with an elevated WBR, are shown in Table 3. Patients with an elevated WBR had a significantly higher percentage of the initial dose in bone at 24 hr, compared with those with a normal WBR ($p < 0.001$). However, there was no significant difference in the 24-hr soft-tissue component between the two groups.

In all 19 patients there was good correlation between WBR and percentage of initial dose in bone at 24 hr ($r = 0.98$, $p < 0.001$; Fig. 2). Even excluding the top two points (since they may unduly influence the correlation) the r value remains significant at 0.89, $p < 0.001$. There was no significant correlation between WBR and 24-hr soft-tissue activity (Fig. 3).

DISCUSSION

In the past, the techniques available for quantitation of technetium-labeled diphosphonate in the skeleton

TABLE 3. PERCENTAGES OF INITIAL DOSE IN BONE AND SOFT TISSUE

	Normal WBR group	Elevated WBR group	
% Dose in bone at 24 hr	14.6 ± 2.4	26.2 ± 13.0	$p < .001$
% Dose in soft tissue (including kidneys) at 24 hr	6.7 ± 1.3	8.4 ± 3.0	N.S.
	n = 7	n = 12	

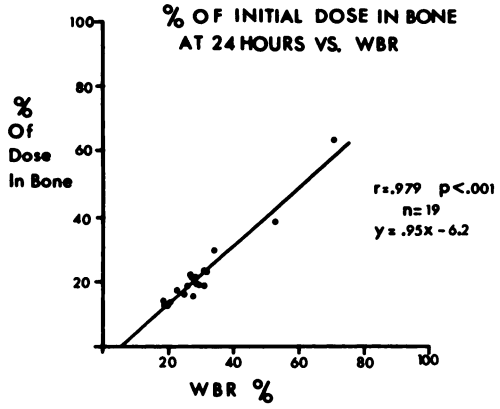

FIG. 2. Good correlation (r = 0.979) between WBR and percentage of initial dose in bone at 24 hr.

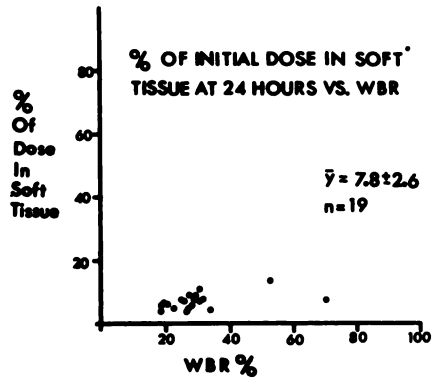

FIG. 3. No correlation between WBR and percentage of initial dose in soft tissue at 24 hr.

from routine computerized bone scans have relied largely on the use of conventional regions of interest drawn around individual bones (*14*), a tedious and time-consuming exercise. The method of quantifying total skeletal uptake of tracer used in the present study is simple and allows rapid analysis of bone scintigrams using a few easily defined regions of interest.

We have found that relative tracer activity in the skeleton is greater at 24 hr than at 4 hr. It is unclear, however, whether this reflects a true increase in osseous localization, or a more rapid clearance of diphosphonate from soft tissue than from bone in the intervening 20 hr. We have also shown that renal accumulation of tracer is relatively higher at 24 hr than at 4 hr, which may be a consequence of renal tubular excretion of diphosphonate (*15*).

Analysis of bone scans performed 24 hr after the intraveous administration of technetium-labeled hydroxyethylidene diphosphonate (HEDP) has shown that approximately 70% of retained activity is localized in bone, and 30% is in soft tissue (including kidneys). This results in a significant soft-tissue contribution to 24-hr whole-body retention (WBR) of HEDP. Nevertheless, when the absolute percentage of administered dose in bone and soft tissue was calculated, it was found that the soft-tissue component remained essentially constant over a wide range of WBR measurements (18 to 70%), whereas absolute skeletal uptake of diphosphonate appeared to increase in parallel with WBR. Indeed there was no correlation between soft-tissue activity and WBR, but a very strong positive correlation between skeletal uptake of diphosphonate and WBR. It may thus be concluded that although there is a significant soft-tissue contribution to WBR, this remains relatively constant, and WBR does indeed provide a reliable measure of osseous uptake of diphosphonate, an index of skeletal metabolism.

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Announcement

Howard Parker, M.D., Program Chairman, announces plans for a Western Regional Hawaii Spring Conference to take place April 10-14, 1983 at the Waiohai Hotel on Kauai and April 14-15, 1983 at the Hawaiian Regent in Honolulu. The program will feature invited speakers covering topics of current interest, including cardiology, instrumentation, computers, NMR, and interesting clinical case studies. The meeting is sponsored by the Pacific Northwest, Southern California, Northern California, and Hawaii Chapters of the Society of Nuclear Medicine.

For further information, contact: Jean Parker, P.O. Box 40279, San Francisco, CA 94140. Tel: (415)647-0722.

Western Regional Chapters
Society of Nuclear Medicine
Hawaii Spring Conference

April 10-14, 1983 | **Waiohai Hotel** | **Poipou Beach, Kauai**
April 14-15, 1983 | **Hawaiian Regent Hotel** | **Honolulu, Oahu**

Topics	Speakers	Topics	Speakers
Bone	Hirsch Handmaker Philip Matin	Cardiovascular Nuclear Medicine	William Ashburn Elias Botvinick Heinz Schelbert
Gallium & Indium-111	Naomi Alazraki-Taylor	NMR Computers & Instrumentation	Catherine Mills L. Stephen Graham Michael Graham Tom Lewellen Ernie Garcia Wes Wooten Joe Areeda David Williams
Gastric Emptying	Andrew Taylor		
Gastroesophageal Reflux	Ralph Gorten		
G.I. Bleeding	Robert Lull		
Monoclonal Antibodies	Sally DeNardo Sam Halpern		
SPECT Imaging	Richard Wasnich Paul Garver	Emergency Nuclear Medicine	Fred Gilbert Robert Nordyke

There will be a Keynote Address on Sunday evening, April 10, 1983. Speaker to be announced.

Dr. O.A. Bushnell will be a featured guest speaker on Friday morning, April 15, 1983, for "The Two Saints of Kalaupapa" (A history of the leper colony on Molokai).

Programs and registration materials may be obtained by contacting Jean Parker, PO Box 40279, San Francisco, CA 94140. Tel: (415)647-0722 or 647-1668.