

Accumulation of ^{99m}Tc -MIBI in bone marrow

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^{99m}Tc -MIBI (Sestamibi) was originally developed for myocardial perfusion studies. The agent also may be used for the depiction and characterization of tumors. Performing such examinations has shown uptake in skeletal structures in several patients suggesting bone engagement of the disease which later was excluded. Retrospective evaluation of 44 examinations with ^{99m}Tc -MIBI performed in order to localize diseased parathyroid in patients with suspected hyperparathyroidism showed skeletal activity in 21 (48%) patients. Although these patients represent a selected group, the observation indicates a mechanism for skeletal accumulation of this radiopharmaceutical. Evaluation of another 13 normocalcemic patients undergoing whole-body registration for malignancy staging or to assess lower extremity ischemia with ^{99m}Tc -MIBI showed skeletal activity in 6 (46%) patients. Complementary mouse experiments confirmed skeletal uptake of ^{99m}Tc -MIBI, where most of the activity is taken up by the red bone marrow. It is concluded that homogeneous, diffuse weak skeletal activity at examination with ^{99m}Tc -MIBI is a normal finding and does not indicate malignancy.

Key words: mouse experimentation, skeletal activity, ^{99m}Tc -MIBI (Sestamibi), tumor detection

INTRODUCTION

TUMOR DETECTION and characterization promises a challenging future for nuclear medicine. A number of radiopharmaceuticals have also been utilized for this purpose. ^{99m}Tc -hexakis-2-methoxyisobutyl isonitrile (^{99m}Tc -MIBI, ^{99m}Tc -Sestamibi, RP-30, Cardiolite®) was originally developed for myocardial perfusion studies.^{1,2} Following the incidental finding of a lung metastasis at cardiac imaging,³ several case reports describing uptake in various tumors appeared^{4–8} and, later, a series of different tumors depicted by this radiopharmaceutical have been published.^{9–13} In addition, there are indications that ^{99m}Tc -MIBI may be used to predict multidrug resistance at chemotherapy of tumors.¹⁴ Though non-specific, ^{99m}Tc -MIBI must today be considered an established agent for

tumor detection. Consequently, its anatomical distribution including normal variations also outside the heart has to be established in order to make the detection and evaluation of neoplastic lesions as accurate as possible.

One early non-cardiac application of ^{99m}Tc -MIBI was for the detection of parathyroid adenomas.¹⁵ Routinely performing such investigations as double-phase studies solely using this radiopharmaceutical,¹⁶ we have noted diffuse weak activity in the skeletal structures in a number of the patients examined. In the present report the incidence of skeletal activity at examination with ^{99m}Tc -MIBI has been analyzed by reviewing these examinations as well as a number of whole-body examinations performed in patients in order to stage malignant disease or to assess arterial leg ischemia. In addition, a few experiments were performed in mouse with ^{99m}Tc -MIBI and ^{99m}Tc -HDP to assess the distribution between bone and bone marrow.

MATERIALS AND METHODS

Patients

Forty-four consecutive examinations in 31 patients with suspected primary and in 13 patients with suspected

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Table 1 Clinical data and findings in 13 whole-body examinations with ^{99m}Tc -MIBI. Two patients are illustrated in Figure 3

Patient No.	Age (yrs)	Gender (M/F)	Diagnosis/Question at issue	Skeletal activity (vertebrae and pelvis) (+/-)
1	38	M	Hodgkin's lymphoma	+
2	42	F	Hodgkin's lymphoma	+
3	45	M	Hodgkin's lymphoma	-
4	46	M	Malignant thymoma	-
5	48	F	Ectopic Cushing	-
6	51	M	Hodgkin's lymphoma	+
7	67	M	Hodgkin's lymphoma	+
8	67	M	Tumor of unknown origin	-
9	70	M	Tonsillar carcinoma	+
10	74	M	Leg circulation	-
11	75	M	Leg circulation	-
12	78	F	Hodgkin's lymphoma	-
13	80	M	Leg circulation	+
60 (mean)		10M/3F		6+/7-

secondary or tertiary hyperparathyroidism were reviewed in retrospect. There were 36 women and 8 men. The mean age was 61 years, ranging between 33 and 85. Evaluation was also performed of whole-body examinations in 10 patients investigated for staging of malignancy and in 3 patients investigated to assess the severity of peripheral arterial disease.¹⁷ The tumor patients also underwent whole-body bone scintigraphy which excluded malignant affection of the skeleton. All these 13 patients were normocalcemic. Details of the patients are presented in Table 1.

Imaging procedure

500 MBq ^{99m}Tc -MIBI (Cardiolite, Du Pont Ltd., Stevenage, UK) was administered in an antecubital vein. The hyperparathyroid patients were examined with one head of a Biad or Triad XLT gammacamera (Trionix Research Laboratory Inc., Twinsburg, OH, USA). Ten-minutes frontal acquisitions in a 128×128 or 256×256 matrix of an area from the submandibular glands to the heart, including shoulders, were performed 15 minutes, 1, 2 and 3 hours after administration of the activity. The early registration, after 15 minutes, was used for evaluation of skeletal uptake. Whole body anterior and posterior scans were acquired in a 256×1024 matrix at 7.5 cm/min using both heads of the Biad XLT camera, starting 10 minutes after administration of the activity.

Radiopharmaceuticals for mouse experimentation

^{99m}Tc -MIBI and hydroxymethylene diphosphonate (HDP, Osteoscan, Mallinckrodt Medical, Petten, Netherlands) were prepared with $^{99m}\text{TcO}_4^-$ for the specific activity used in clinical practice and thereafter diluted with physiologic saline. 0.1 MBq was injected in a volume of 0.2 ml via a tail vein.

Organ distribution of activity in mouse

Outbred NMRI female mice aged 8 weeks (young) or 6 months (old) were used (B&K Universal, Sollentuna, Sweden). The study was approved by the local committee for animal experimentation. The mice were killed by cervical dislocation. The hind legs were removed and bones dissected free from soft tissue. The experiment assessing the distribution of activity between bone and bone marrow was performed in young animals using both femora. The ends were cut away and their activity assessed. The marrow was thereafter flushed out with a hypodermic needle and physiologic saline, the bones were rinsed and their activity reassessed. The remaining osseous activity was calculated as a percentage for each pair of femora. In the experiment studying the age influence on the activity distribution, heart, submandibular glands and liver were assessed in addition to both femora and tibiae. The activity of the organs was expressed as a percentage of the injected inoculum. The organ activity was measured with a well-type gamma-counter (1282 Compugamma, LKB-Wallac, Bromma, Sweden). Correction was made for decay of ^{99m}Tc during the measuring time, background activity and counter dead-time. All samples were measured for a sufficient time to obtain a maximal statistical uncertainty of 3%, indicated as one standard deviation.

Statistics

Statistical analysis was performed by Student's *t*-test. $P < 0.05$ was considered significant.

RESULTS

Hyperparathyroid patients

The findings on reviewing the hypercalcemic patients are

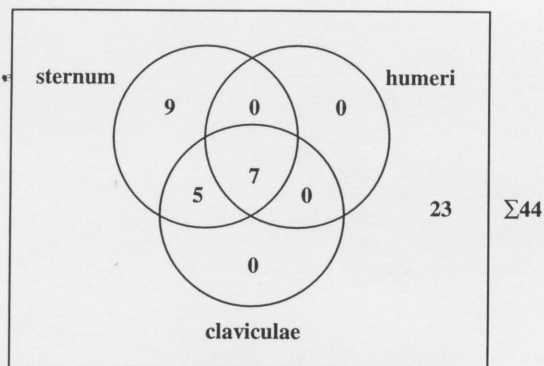


Fig. 1 Venn-diagram showing the frequency of detectable sternal, clavicular and humeral activity in 44 patients with hyperparathyroidism examined with ^{99m}Tc -MIBI to detect parathyroid adenoma or hyperplasia.



Fig. 3 Posterior whole-body scans with 500 MBq ^{99m}Tc -MIBI in two of the patients presented in Table 1. Patient No. 5 shows no skeletal activity (A). Patient No. 7 shows activity in the vertebral column and pelvis (B).

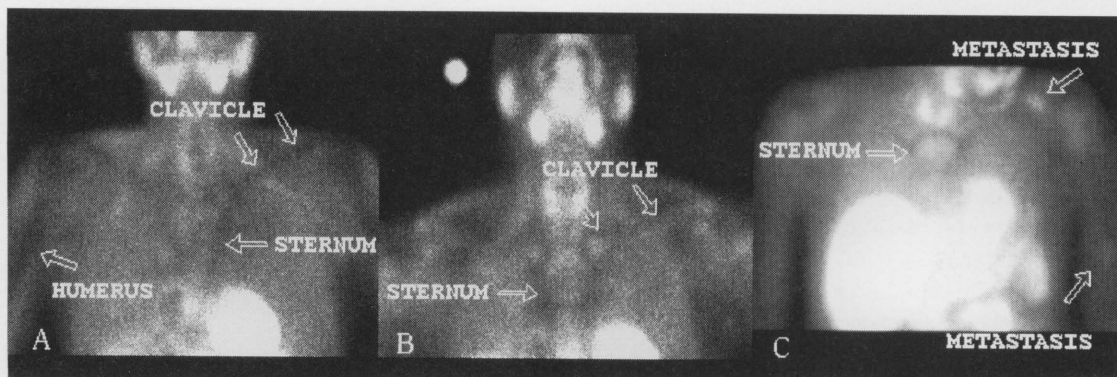


Fig. 2 Frontal acquisitions of 3 patients examined 15 minutes after administration of 500 MBq ^{99m}Tc -MIBI to detect parathyroid disease. There is regular activity in sternum but clavicles and humeri appear as defects in (A). There is sternal and clavicular activity in (B). (C) shows regular activity in sternum but focal activity in the left shoulder and left arm caused by bone metastases of renal carcinoma.

shown in Figure 1. The examinations were analyzed with regard to detectable activity in the sternum, clavicular and humeri. There was activity of varying intensity of the skeletal structures in 21 (48%) of the 44 patients. Activity in clavicular or humeri was always symmetric. The activity always extended in the centrifugal direction, i.e. there was never isolated activity in clavicular and/or humeri. The mean age of the patients showing skeletal activity was 59 years (\pm SD 14) and the mean age of the patients not showing this was 65 years (\pm SD 12). The difference between these two figures is not significant. Two patients with skeletal activity and one with focal uptakes caused by metastases are shown in Figure 2.

Whole-body examinations

The findings at the whole-body examinations together with clinical data are presented in Table 1. The examinations were analyzed with regard to detectable activity in the dorsal and lumbar vertebral column and pelvis. There was either activity in all these structures or not. The intensity varied considerably, and 6 (46%) of the 13 patients showed skeletal activity. The mean age of these patients was 58 years (\pm SD 17) and that of the patients not showing skeletal activity was 62 years (\pm SD 15). The difference between these two figures is not significant. One patient without and one patient with skeletal activity are shown in Figure 3.

Table 2 ^{99m}Tc -MIBI or ^{99m}Tc -HDP activity of femoral diaphyses in young mice before and after flushing the marrow (n = 20)

Radiopharmaceutical	Time to sacrifice	Activity in femora before flushing (percentage of inoculum)		Remaining activity after flushing (percentage)	
		mean	\pm SD	mean	\pm SD
^{99m}Tc -MIBI	15 min	0.38	0.16	20.5	7.3
^{99m}Tc -HDP	4 hrs	0.75	0.21	96.3	2.4

Table 3 Percentage of administered ^{99m}Tc -MIBI activity in different organs of young and old mice sacrificed 15 minutes after injection of activity (n = 20)

	Hind legs		Heart		Submandibular glands		Liver	
	mean	\pm SD	mean	\pm SD	mean	\pm SD	mean	\pm SD
Young animals	0.62	0.12	0.89	0.23	0.99	0.25	17.5	1.75
Old animals	0.57	0.14	0.82	0.10	1.48	0.55	18.5	1.93
Significance	Not significant		Not significant		p < 0.001		Not significant	

Animal experiments

The recovered activity of the femoral diaphyses after injection of ^{99m}Tc -HDP, which is a bisphosphonate commonly used for bone scintigraphy, was twice that after ^{99m}Tc -MIBI injection. About 80% of the ^{99m}Tc -MIBI activity was removed from the femoral diaphyses by flushing the marrow cavity and rinsing the bones. In contrast to this, less than 5% of the bone-seeking activity was removed by the same procedure (Table 2).

There was a non-significant reduction in the uptake of ^{99m}Tc -MIBI in the hind legs with age. For comparison, the age influence on the uptake in heart, submandibular glands and liver, which also concentrate ^{99m}Tc -MIBI, was also studied.¹⁸ The only significant effect with age was a strongly increasing uptake in the submandibular glands (Table 3).

DISCUSSION

^{99m}Tc -MIBI is incorporated in metabolically active tissues and organs, and retained in the mitochondria by a specific mechanism.¹⁹ Although this, in practice, makes the distribution non-specific, aberrant accumulation of the agent may add considerable information at a given clinical situation in a tumor patient. The normal distribution of ^{99m}Tc -MIBI, as well as uptake in various pathological conditions, has recently been reviewed.¹⁸ No accumulation in bone or bone marrow has been reported.

The study was initiated by the finding of skeletal activity in several malignancy investigations with ^{99m}Tc -MIBI. This suggested widespread skeletal engagement which was ruled out by complementary examinations and an obvious clinical course. For apparent reasons, the possibility to perform nuclear medicine examinations in

normal volunteers is restricted and information on normal activity distribution sometimes has to be acquired from patient examinations or from animal experiments. The hyperparathyroid patients were a group readily available at our institution, but represented a selection in which the skeletal uptake theoretically may be promoted by the disease. Conclusions drawn from these patients must therefore be restricted, but the findings show that there is a mechanism for skeletal accumulation of this radiopharmaceutical and at least in these patients there is visible skeletal activity in approximately half of the examinations. This may also be of particular interest, since investigation with ^{99m}Tc -MIBI in tumor patients is today a reality, and hypercalcemia in malignancy is a well known finding. Despite this, the findings made in the hypercalcemic patients were confirmed in the normocalcemic patients undergoing whole-body examination, approximately half of them showing skeletal activity.

It is essential to find out if the skeletal activity at ^{99m}Tc -MIBI scintigraphy is caused by accumulation in osseous tissue or in bone marrow. As the extension and metabolism of the red bone-marrow continuously decreases with age, the centrifugal activity distribution in the patients in Figure 1 indicates uptake in the marrow. A coupling to this is also indicated by the difference in age, though not significant, between the patients with and without skeletal activity in both clinical groups. The findings in the animal experiment in Table 2 also confirm there is an uptake of ^{99m}Tc -MIBI in the diaphysis which, in these rather young animals, is about half of what is acquired at bone scintigraphy. The fact that most of the activity was removed by flushing the marrow cavity, whereas very little was removed in the animals given the bone-seeking agent, confirms that most of the ^{99m}Tc -MIBI is accumulated in

the marrow but the findings indicate that some of this activity is retained also in normal metabolically active bone tissue. It is not known if this is increased at hyperparathyroidism.

There is a non-significant decrease in the accumulation of ^{99m}Tc -MIBI in the skeleton with age. This may be explained by the fact that both young and old animals had macroscopically red marrow in femora and tibiae. Consequently, the difference in the age of the animals, 8 weeks and 6 months, may not have been sufficient to demonstrate a difference due to ageing of the bone marrow, and animals older than 6 months should have been used. It was, however, not possible to obtain an homogeneous group of animals older than this.

Figure 2C illustrates the importance of differentiating between normal bone and bone marrow activity, and activity caused by malignancy at investigation with ^{99m}Tc -MIBI. It is finally concluded that homogeneous, diffuse weak skeletal activity at examination with ^{99m}Tc -MIBI is a normal finding and does not indicate malignancy.

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