Diagnostic efficacy of technetium-99m pentavalent-dimercapto succinic acid versus gallium-67 citrate, imaging in patients with highly suspected acute bone and joint infections

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Abstract

The purpose of this study was to evaluate and compare the diagnostic efficacy of ^{99m}Tc(V) dimercaptosuccinic acid (^{99m}Tc(V)DMSA) with the ^{67}Ga-citrare (^{67}Ga-C) scintigraphy in patients with suspected bone and joint infection. Thirty one patients, 19 men and 12 women, aged 18-78 y with median age 56 y, with suspected acute bone infection, were enrolled in this study. Besides ^{67}Ga-C and ^{99m}Tc(V)DMSA scintigraphy, all patients underwent X-ray radiography and technetium-99m methylene disphosphonate (^{99m}Tc-MDP) bone scan for supporting the initial diagnosis. The ^{99m}Tc-MDP bone scan was considered positive for acute bone and joint infection when all its four scintigraphic phases were positive. Final diagnosis was based on needle aspiration and/or biopsy findings. Sensitivity, specificity, accuracy, positive and negative predictive values (PPV and NPV) were calculated. Our results have shown the following: Seventeen patients (17/31) had histologically confirmed acute bone and joint infections, while the remaining patients had no infection. ^{99m}Tc(V)DMSA diagnosed bone and joint infections in all positive (17/31) patients while ^{67}Ga-C in 16/31 patients. Discordant scintigraphic results were observed by ^{67}Ga-C in 2/31 cases: in one positive case of femur postoperative infection (false negative for ^{67}Ga-C) and in one case of clinicaly suspected infection in the femur while the patient had a preexisting fracture (false positive with ^{67}Ga-C). No false negative results were observed with ^{99m}Tc(V)DMSA. Sensitivity, specificity, PPV, NPV and accuracy were maximum for ^{99m}Tc(V)DMSA, while for ^{67}Ga-C were: 94.1%, 93%, 94.1%, 93%, and 93.5% respectively. It is concluded that considering the high sensitivity and specificity of ^{99m}Tc(V)DMSA in the detection of acute bone and joint infections, the lower radiation dose, the cost and the shorter time spent for the imaging procedure, as compared to ^{67}Ga-C, ^{99m}Tc(V)DMSA should be preferred to ^{67}Ga-C as a bone scan agent for the detection of acute bone and joint infections.

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Introduction

The accurate diagnosis of bone and joint infections remains an important clinical problem. Besides clinical evaluation, diagnosis is now based on laboratory findings such as leucocyte counts, and erythrocyte sedimentation rate, conventional and radionuclidic imaging modalities and pathology findings. Conventional radiographs have been reported to be of limited value [1]. Ultrasonography may not diagnose bone disease when located in depth. Computed tomography (CT) and magnetic resonance imaging (MRI) are used to guide needle biopsy [2,3], but may have artifacts even when several parameters of these tests are being considered. The sensitivity and specificity of CT and MRI, bone scintiscans and scans with labeled white blood cells [4-6] largely depend on preexisting bone disease, the so-called "unclean bone".

The three/four phase bone scan with technetium-99m (^{99m}Tc) labeled methylene diphosphonate (^{99m}Tc-MDP) is the routine nuclear medicine procedure for the diagnosis of bone and joint infection but is not specific, especially in cases of preexisting bone disease such as fractures. Combined ^{99m}Tc-MDP bone scan and ^{67}Ga-citrate (^{67}Ga-C) imaging was the first dual-tracer technique used to increase specificity in diagnosing bone infection reaching a diagnostic accuracy of 70%, with a high incidence of false positive results, especially in preexisting fractures, tumors and in inflammatory arthritis [7]. Indium-111 oxime (^{111}In-O) and technetium-99m hexamethyl-propylenamine oxime (^{99m}Tc-HMPAO) labeled leucocytes are

useful in the evaluation of bone infections, although this method is technically demanding, time consuming, and expensive [8]. Positron emission tomography (PET) for the diagnosis of infection has a sensitivity of 95%-100% and a specificity of 85%-95%, but its use in routine is limited because of the non availability of PET facilities in many departments and its high cost [9,10].

To overcome these problems, new agents are under investigation. Monoclonal anti-NCA-95 antigranulocyte antibody (BW 250/83) and murine anti-NCA-90 monoclonal antigranulocyte antibody Fab' fragments (MN3 Fab') labeled with ^{99m}Tc are recently used in imaging of bone and joint infections [11-14]. According to our knowledge there is only one other study using ^{99m}Tc pentavalent dimercaptosuccinic acid [^{99m}Tc(V)DMSA] for the diagnosis of bone and joint infections [15].

The purpose of this study was to evaluate ^{99m}Tc(V)DMSA for the diagnosis of bone and joint infections, as compared with the ^{67}Ga-C scan.

Patients and methods

Patients

Thirty one patients, 19 men and 12 women, aged 18-78 y with median age 56 y, were enrolled in this study. All of them were referred to our department for highly suspected acute bone and joint infections with no preexisting bone disease, except one patient with fracture of the femur and one with femoral head prothesis (Table 1, serial number of patients 15 and 1 respectively). All patients gave their written informed consent before the study. The study was approved by the scientific committee of the Board of our Hospital. All patients had positive clinical findings (localized pain and fever), X-rays findings and ^{99m}Tc-MDP bone scan suggestive of bone infection, high levels of leukocyte counts (more than 11x10^3 mm^3) and high erythrocyte sedimentation rate (for the first hour more than 20 mm for men and more than 25 mm for women). Final diagnosis was based on needle aspiration and/or bone biopsy. Patients' data and description of the sites of infection are shown in Table 1.

All patients underwent ^{99m}Tc(V)DMSA and ^{67}Ga-C scintigraphy. None of these patients had received antibiotic treatment before the study.

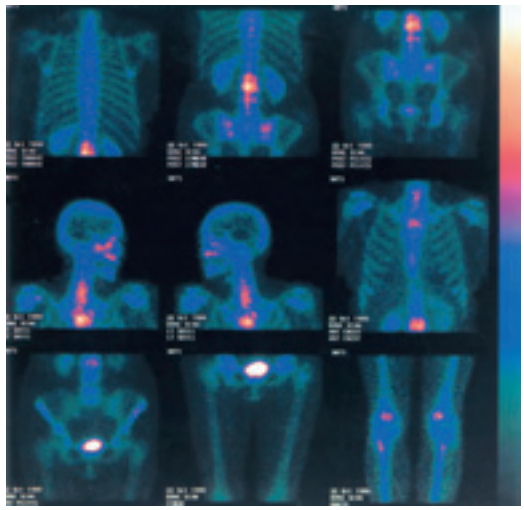
Radiopharmaceuticals and nuclear medicine imaging

Four phase bone scintigraphy was performed by the intravenous injection (i.v.) of 666-814 MBq of ^{99m}Tc-MDP in the form of a commercially provided radiopharmaceutical (Osteocis by CIS biointernational, affiliate with Schering S.A, Germany). A gamma camera (GE Millennium, Milwakee, USA) with a large field of view, equipped with a low energy parallel whole collimator, was used. The first phase (dynamic images) was performed immediately after the i.v injection of the radiotracer using a 68×68 matrix. The second phase (blood pool images) was obtained 5-10 min post injection (p.i.) Delayed images (static views, third and fourth phases) were performed at 3 and 24 h later using a 128x128 matrix. ^{99m}Tc(V)DMSA (Demoscan, Demokritus Greece) was also injected i.v., 48 h later in a dose of 740 MBq. ^{67}Ga-C in the form of a commercially provided radiopharmaceutical (provided by CIS biointernational, affiliated with Schering S.A.) was i.v. injected in a dose of 185 MBq immediately after the ^{99m}Tc(V)DMSA scintigraphy was completed. Static images were taken after 2-3 h. A medium energy parallel hole collimator was used. Images were performed 24 and 48 h p.i. The total calculated absorbed dose by each patient was 16.8 mSv.

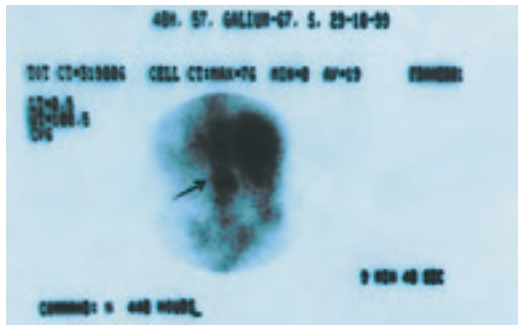
Table 1. *Patients' data and infection findings*

Patients no	Sex	Age (y)	Location of infection	Gallium imaging	^{99m}Tc (V)DMSA	Agent of infection
1	F	62	Femur (prothesis)	–	+	Staphylococcus epidermidis
2	F	80	Shoulder	+	+	Tuberculosis
3	F	57	L2-L3	+	+	Brucellosis
4	F	51	L1	+	+	Staphylococcus aureus
5	F	20	Ischium	–	–	–
6	F	36	Ischium	–	–	–
7	F	55	Ischium	–	–	–
8	F	80	L5	+	+	Staphylococcus aureus
9	F	40	Tibia	–	–	–
10	F	52	L1	–	–	–
11	F	68	L3	–	–	–
12	F	68	rib	+	+	Staphylococcus aureus
13	M	37	Ankle joint	+	+	Staphylococcus aureus
14	M	72	Ankle joint	+	+	"
15	M	65	Femur (fracture)	+	–	– (fracture)
16	M	31	Knee joint	+	+	Staphylococcus aureus
17	M	32	Tibia	–	–	–
18	M	18	Femur	–	–	–
19	M	47	Femur	–	–	–
20	M	52	Rib	–	–	–
21	M	62	L3	+	+	Staphylococcus aureus
22	M	67	L2	+	+	"
23	M	41	L1	+	+	"
24	M	78	Metatarsal	+	+	"
25	M	61	L2	–	–	–
26	M	36	Tibia	+	+	Klebsiella
27	M	43	Tibia	+	+	Staphylococcus epidermidis
28	M	56	Tibia	+	+	"
29	M	69	Sternum	–	–	–
30	M	71	Sternum	–	–	–
31	M	78	T8	+	+	E.coli

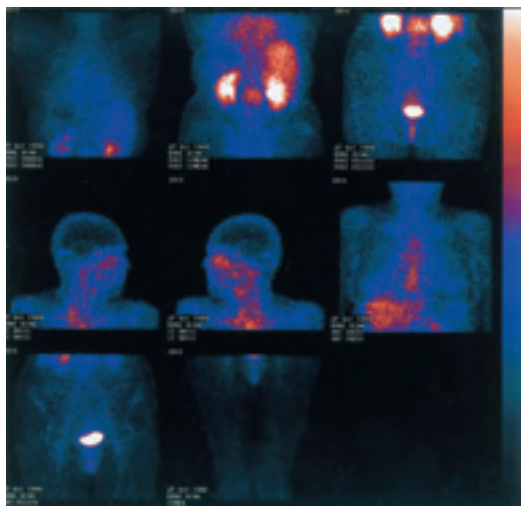
+: positive for infection, –: negative for infection



(a)

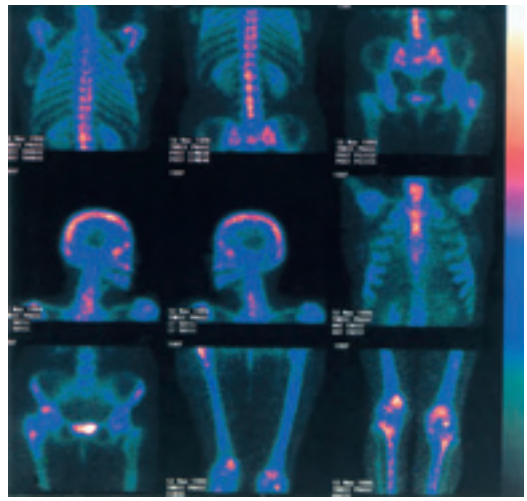


(b)

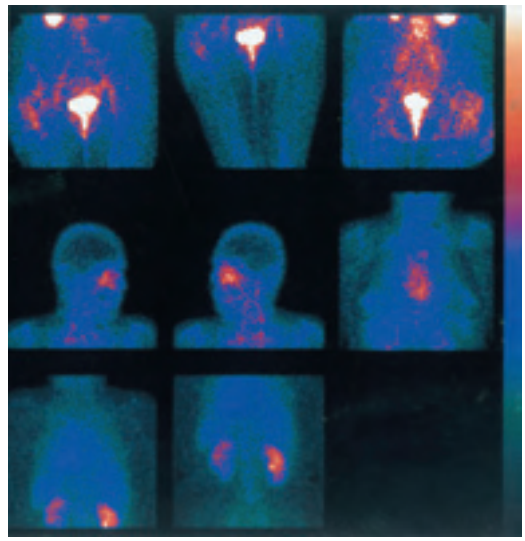


(c)

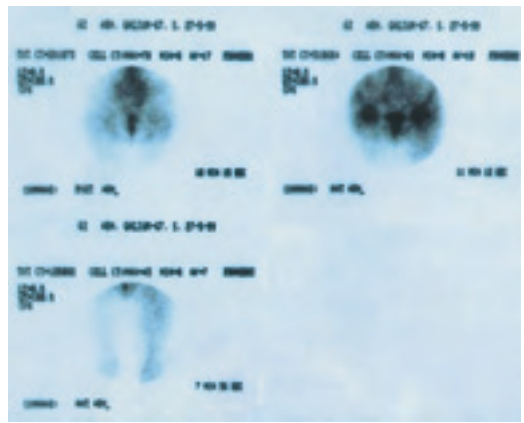
Figure 1. A patient with suspected infection of the lumbar L_2 and L_3 vertebrae. Bone scans: (a) with ^{99m}Tc-MDP, (b) with ^{67}Ga-citrate and (c) with ^{99m}Tc(V)DMSA showed enhanced uptake of the radiotracers in the suspected area of infection. True positive case of Brucellosis



(a)



(b)



(c)

Figure 2. A patient with suspected post-operative infection in the upper part of the right femur. (a) Bone scans with ^{99m}Tc-MDP and (b) with ^{99m}Tc(V)DMSA, showed an increased uptake in the upper part of the right femur, while (c) ^{67}Ga-citrate scintigraphy showed a slightly increased uptake (false negative case) Final diagnosis: osteomyelitis

Image interpretation

All scintigraphic images were evaluated by two nuclear medicine physicians blinded of the final diagnosis. The four phase bone scintigraphy was considered positive for bone infection when all its four phases were positive.

The ^{99m}Tc(V)DMSA and ^{67}Ga-C images were interpreted separately. Both ^{99m}Tc(V)DMSA and ^{67}Ga-C were classified as positive when a focally increased bone activity in the suspected area was identified and this activity was higher than in the ^{99m}Tc-MDP scan. ^{99m}Tc(V)DMSA and ^{67}Ga-C scans were interpreted as negative or doubtful if the uptake in the suspected area was low or rather diffused. Cases with uptake of ^{99m}Tc(V)DMSA or ^{67}Ga-C equal to the ^{99m}Tc-MDP uptake were not observed. The gold standard for the final diagnosis was the histological findings which were available after the scintiscans were performed. Results were considered false negative when there was no uptake of the radiopharmaceutical in the areas where clinical data and histological results were positive.

Data analysis

Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated for both ^{99m}Tc(V)DMSA and ^{67}Ga-C scans.

Results

Bone and joint infection were histologically confirmed in 17 patients while in 14 no bone infections were found. Both radiopharmaceuticals, ^{99m}Tc(V)DMSA and ^{67}Ga-C, were able to accurately diagnose bone and joint infections in all positive (17/31) patients. Discordant scintigraphic results between ^{67}Ga-C and ^{99m}Tc(V)DMSA were observed in 2/31 cases. One case of femur osteomyelitis due to staphylococcus epidermidis was false negative by the ^{67}Ga-C and another case with infection in the femur with preexisting fracture was false positive with ^{67}Ga-C. No false positive or/and false negative results were observed with the ^{99m}Tc(V)DMSA scan. In Figures 1 and 2 a true positive and a false negative case with ^{67}Ga-C are shown.

The scintiscan results of both scintigraphic procedures ^{99m}Tc(V)DMSA and ^{67}Ga-C, and the clinical data of these patients, are shown in Table 1. The sensitivity, specificity, accuracy, PPV and NPV of the ^{99m}Tc(V)DMSA was maximum while the relative figures for ^{67}Ga-C were: 94.1%, 93%, 93.5%, 94.1% and 93% respectively.

Discussion

^{99m}Tc(V)DMSA is a tumor seeking agent and has been used for the detection of medullary thyroid cancer, soft tissue, brain and lung tumors [16-18]. Uptake of this radiopharmaceutical by inflammatory tissues has also been reported [19] and is suggested to be due to increased capillary permeability and infiltration of the radiopharmaceutical into the interstitial space. Lee et al. (1997) described an incidentally uptake of ^{99m}Tc(V)DMSA in an abscess of the psoas muscle in a woman with systemic lupus erythematosus [20]. According to our knowledge there is only one reference on the application of ^{99m}Tc(V)DMSA for the diagnosis of bone and joint infections. Lee et al. (1998) studied 36 patients suspected to have bone and joint infections. In 16/36 patients, infection was excluded. ^{99m}Tc(V)DMSA was positive in 20/36 patients and ^{67}Ga-C was positive in 19/36 patients [15]. In our study ^{99m}Tc(V)DMSA had maximum sensitivity, specificity, accuracy, PPV and NPV (100% for all these parameters), while corresponding values for ^{67}Ga-C were lower (94.1%, 93%, 93.5%, 94.1% and 93% respectively).

The diagnostic value for ^{99m}Tc(V)DMSA was not dependent on the site of infection. Also ^{99m}Tc(V)DMSA did not accumulate in fractures without infection. On the contrary, ^{67}Ga-C in a case of preexisting fracture was false positive and in another case with a low grade infection was false negative. Imaging with ^{99m}Tc(V)DMSA as compared to ^{67}Ga-C and ^{111}In is a simpler procedure with a shorter investigation time, has a better image resolution and is cheaper. The price of 37 MBq of ^{67}Ga-C and of ^{111}In is 15 € and 30 € respectively, while for ^{99m}Tc(V)DMSA is less than 15 €. The higher sensitivity we have noticed for the ^{67}Ga-C scan (94%) as compared to the sensitivity noticed by others (70%) [5], may be due to the fact that all our patients except two had no other preexisting bone disease.

In conclusion, it is the opinion of the authors that ^{99m}Tc(V)DMSA may be used as a primary investigation for the detection of bone and joint infections, even when other bone diseases have preceded. More cases should be studied with this radiopharmaceutical.

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