RADIONUCLIDE IMAGING IN INFLAMMATORY SKELETAL DISEASE

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A b s t r a c t

Skeletal scintigraphy is, in addition to plain radiography, the most important method for diagnosing inflammatory skeletal disease. It is important for the localisation of inflammation as well as for its highly negative, predictive value. The patients reported in this study were examined by three-phase scintigraphy by which the inflammatory process was detected in soft tissue (hyperaemia) in the first and second phases and in bone tissue (local increase in radioactivity) in the third, delayed phase. A comparison with other scintigraphic methods is discussed.

K e y w o r d s

skeletal scintigraphy, three-phase scintigraphy, osteomyelitis.

INTRODUCTION

Antibiotic therapy has brought about many changes in the occurrence and form of inflammatory skeletal diseases. It has dramatically reduced the incidence of haematogenous osteomyelitis particularly at infancy (*1*) but the incidence of hypodermic infections still shows an increasing tendency. Early diagnosis, therefore, is the key factor for successful therapy.

Osteomyelitis is a disease that affects both bones and marrow. The disease either can arise in marrow and propagate into bone or inflammation of periosteal (soft) tissue may affect bones. The manifestation and course of osteomyelitis depend on the patient's age, location of the lesion, patient's immunological status, infectious agent and original location of inflammation. The course may be acute and can heal without any residual signs. If the disease is not recognized in time and is not treated properly, it may result in chronic osteomyelitis. This happens in 4 % of all cases (1).

MATERIALS ANS METHODS

Trauma, articular replacements, immunological and haematological diseases are indicated as predisposition factors that may result in chronic osteomyelitis.
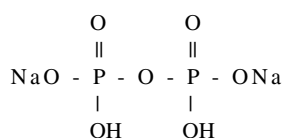
Osteomyelitis can be induced by three basic mechanisms:
1. haematogenous dissemination
2. environmental contamination
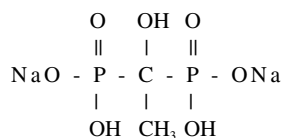3. implantation, for example, during penetrating injury

The metaphysis of long bones is very frequently affected by the above-mentioned haematogenous dissemination. The slowest blood stream is observed in marrow capillaries in locations adjacent to the growth plate. Pathological processes resulting from infection are well known. There is a rapid onset of inflammation manifested by oedema, exudate production, change in local blood supply, etc., followed, after some time, by a reaction of the bone to the development of inflammation.

Radionuclide diagnosis of osteomyelitis. Any osseous infection results in changes in hyperaemia, capillary permeability and osteoblastic reactions of bones to inflammation. All these changes lead to an increased accumulation of radiopharmaceuticals that are used in skeletal scintigraphy.
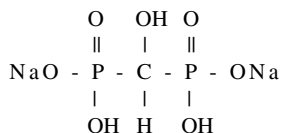
Skeletal scintigraphy is the most frequently performed scintigraphy at nuclear medicine departments, it is used in about 50% of all patients examined *(2)*. *Subramanian* and *McAffe* introduced ^{99m}Tc polyphosphates into clinical practice for the first time in 1971 *(8)*. These compounds are based on a P-O-P bond with the simplest molecule - pyrophosphate *(Fig. 1)*. Several years later, diphosphonates, i.e., organic analogues of pyrophosphate, were developed. These compounds are based on a P-C-P bond and are more stable than pyrophosphate. The substance that is now most frequently used in skeletal scintigraphy is ^{99m}Tc-labelled hydroxymethylene diphosphonate (^{99m}Tc-MDP).

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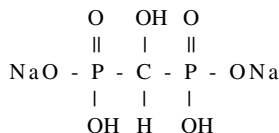O & & O \\
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Disodium pyrophosphate (PYP)

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Disodium hydroxyethylene diphosphonate (HEDP)

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Disodium methylene diphosphonate (MDP)

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Disodium hydroxymethylene diphosphonate (HMDP)

Fig. 1
Pharmaceuticals used in skeletal scintigraphy

Radiopharmaceuticals and the techniques used. Mechanisms responsible for incorporation of labelled phosphonates into bone are not yet fully understood. Phosphonates absorbed by the skeleton are hydrolysed and linked to bone.

Recently, positron emitters have been introduced; they are most often ^{18}F-labelled compounds.

After intravenous application, half-life of radionuclide elimination from vascular into extravascular space is 2 to 4 min. During 3 h under normal circumstances, the skeleton binds 30% to 40% radioactivity, of which 35% is excreted by the kidneys and 5% to 10% remains in blood. Three phases of radiopharmaceutical uptake can be distinguished.

1) 1- to 2-minute blood pool when the labelled compound is present intravascularly

2) the compound is present both intra- and extra-vascularly, but extravascular presence predominates

3) the compound is largely bound to the skeleton.

The maximum activity of ^{99m}Tc-MDP in the skeleton is achieved at 65 min., the maximum contrast (bone vs. background) is obtained within 6 h of application. Hence, optimum scanning is achieved during 2 to 3 h after radioisotope administration.

The quantity of radioactivity and its distribution in the skeleton is affected by two factors: blood flow and metabolic osseous turnover.

Examination Techniques. Generally, we can distinguish three main types of radioactivity scanning in skeletal scintigraphy: planar, single photon emission computed tomography (SPECT), three-phase scintigraphy.

In planar scanning, the patient is lying below a gamma camera and a static radiograph of the area covered by the gamma camera detection system is taken. If we want to scan another area, we must move the patient and take another radiograph. Planar scanning is similar to plain radiography. The main disadvantage of this technique is an overlapping of structures. For more precise spatial determination, we need at least two images (anterior and lateral).

SPECT is a technique which, by its principle and evaluation, is very similar to computed tomography. Scanning is performed with a SPECT gamma camera, the patient is lying and one, two or three gamma camera heads are rotating around him. The gamma camera takes one radiograph and turns by 2 degrees to take another radiograph. After scanning, the reconstruction of all images is carried out and transversal, coronal and sagittal sections are displayed. This method eliminates an overlapping of individual structures which can be distinguished in the patient's body.
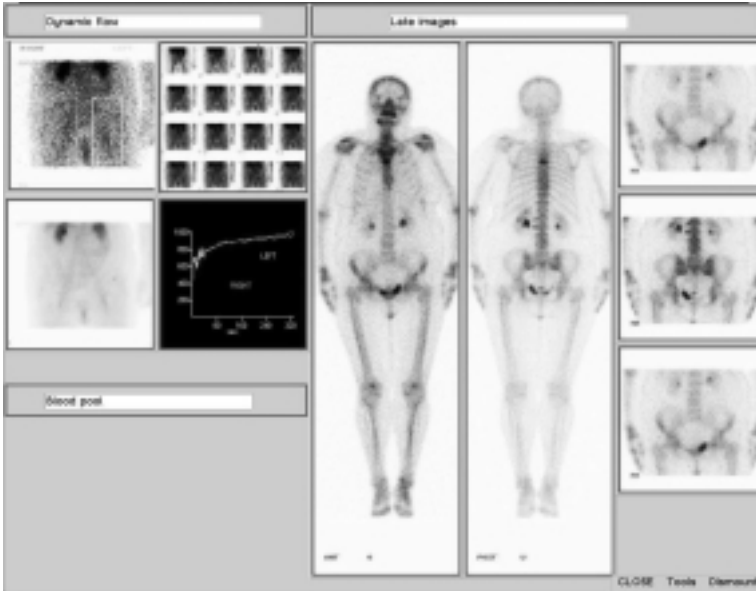
Three-phase scintigraphy is based on three phases of the metabolism of radiopharmaceuticals, i.e., the presence of a radionuclide first in blood, then in soft tissue and finally in bone. In many cases, this procedure also allows us to distinguish between an inflammatory process in soft tissue and that in bone tissue.
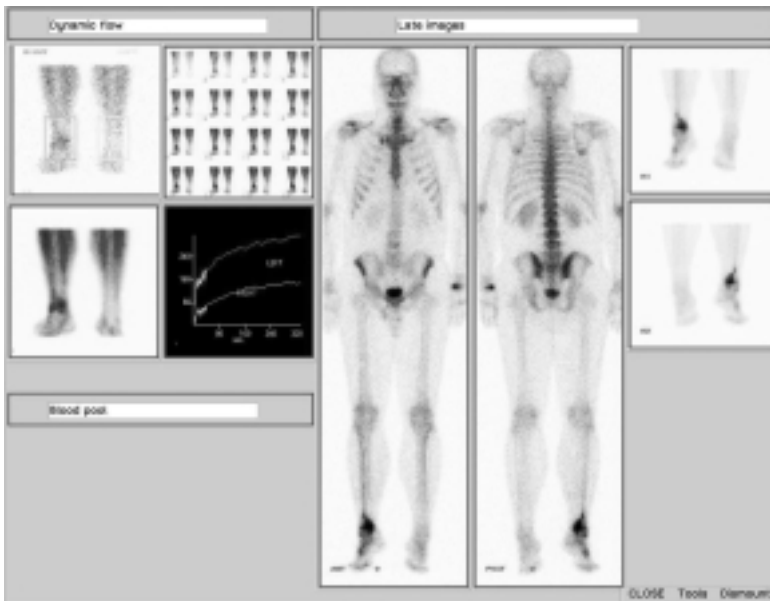
RESULTS

The results of three-phase skeletal scintigraphy in a 45-year woman are shown in *Fig. 2*. After injury, osteomyelitis was suspected in the proximal part of the femur. However, the finding in a radiograph was negative. The left part shows fully symmetrical hyperaemia in the first phase of examination (dynamic flow) during the first 320 sec. In the second phase, the finding is also symmetrical and the radioactivity curves above both areas of distal femoral sections are nearly identical. In the third phase of examination, i.e. in late images, no asymmetry was found. This finding eliminates osteomyelitis.

The results of three-phase skeletal scintigraphy in a 30-year patient with suspected osteomyelitis in the distal tibia of the left lower extremity, also after injury, are shown in *Fig. 3*. The examination was performed after intravenous application of 700 MBq ^{99m}Tc-MDP. The first phase of examination (dynamic flow) was monitored within 320 sec of application. The radioactivity curves show a big difference in hyperaemia between the distal tibia regions of the right and the left leg. A significant difference in ^{99m}Tc-MDP accumulation can also be seen between the right and the left tibia in late images. This finding is typical of acute osteomyelitis.
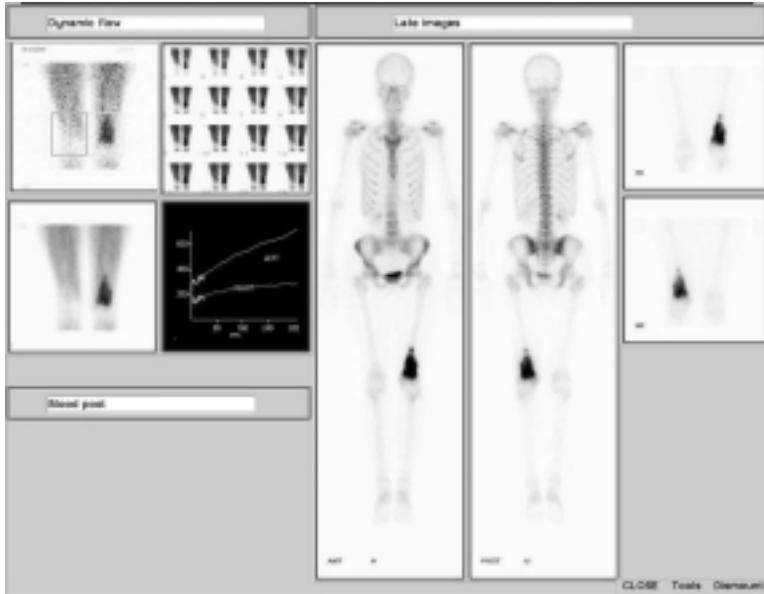
The result of three-phase skeletal scintigraphy after intravenous application of 700 MBq ^{99m}Tc-MDP is shown in *Fig. 4*. A 21-year woman with a painful lesion in the distal metaphysis of the left femur was examined. A radiograph showed a slight periosteal reaction. For several months, the patient had problems which gradually increased. Examinations by three-phase scintigraphy revealed, in its

Fig. 2
Normal three-phase skeletal scintigraphy

Fig. 3
Pathological findings – increased hyperaemia and radioactivity accumulation in the distal region
of the right tibia during three-phase skeletal scintigraphy

Fig. 4
Pathological findings –increased hyperaemia and radioactivity accumulation in the distal region
of the left femur during three-phase skeletal scintigraphy

Fig. 5
Pathological findings – slightly increased hyperaemia and radioactivity accumulation in the left
hip joint during three-phase skeletal scintigraphy

first and second phase, significant hyperaemia in the distal region of the left femur. In the third phase, high radioactivity accumulation can be seen in this region. The finding is typical of osteomyelitis.

Fig. 5 shows the result of three-phase skeletal scintigraphy in a 69-year-old patient with a total replacement of the left hip joint. He complained of pain that had increased progressively during several months prior to examination. An increase in vascularisation with hyperaemia was seen in the area of the prosthesis in the first phase and an increase in radioactivity was also evident in the third phase (late images). These findings indicate the presence of infection.

DISCUSSION

Tuberculous osteomyelitis is often present (30 – 50 % of the cases) in scintigrams in the form of multiple foci of increased radioactivity *(9)*. This condition very often affects vertebrae, and clinical findings can easily be confused with metastases. *Salomon (4)* has stated that the occurrence of tuberculous osteomyelitis in the US population has reached about 3 % in the patients suffering from tuberculosis. Tuberculous spondylitis is the most frequent form of osseous tuberculosis.

Bone inflammation can be diagnosed with the use of [67]Gallium citrate, [111]Indium chloride, labelled leukocytes or monoclonal antibodies.

[67]Ga accumulates in inflammatory lesions but the mechanism of its localisation is not well understood. Opinions on the sensitivity and specificity of this method for the diagnosis of osteomyelitis vary. The values usually reported are 22 % for sensitivity and about 90 % for specificity *(6)*. *Schauwecker (7)* reports 81 % for sensitivity and 69 % for specificity in osteomyelitis but, for skeletal scintigraphy in uncomplicated cases, the values are 94 % for sensitivity and 95 % for specificity. It is recommended to scan 24 h after ^{67}Ga administration. The use of [111]Indium chloride is not recommended because the radionuclide is not taken up by fractured bone. In this method, the reported sensitivity and specificity are 60 – 80 % and 92 – 95 %, respectively *(7)*.

Leukocytes can be visualised with the use of ^{99m}Tc-labelled hexamethyl para-amino-oxim (^{99m}Tc-HMPAO). However, the preparation of radiopharmaceuticals is time consuming. It involves collection of blood from the patient, separation of leukocytes, and their reaction with ^{99m}Tc-HMPAO. The labelled leukocytes are then administered to the patient. Studies have shown that, in an infection older than 6 weeks, labelled leukocytes fail to accumulate. *Schauwecker (7)* reports 87% and 81% for sensitivity and specificity, respectively, but some other authors give values for specificity below 60 % *(3)*. The low specificity of this method can be explained by leukocyte uptake by non-inflammatory, injured tissues in fractures and surgical interventions.

Monoclonal antibodies are the most advanced radiopharmaceuticals that are used in the diagnosis of inflammation. Their sensitivity of about 83 – 100 % and

specificity of 100 % are the great advantage of this technique *(5)*. When vertebrae are affected, both sensitivity and specificity are lower. However, the method has also some disadvantages: the cost of one examination is high and monoclonal antibodies, as foreign proteins, may induce the production of antibodies in the patient. Elevated titres of these antibodies can interfere with the results of scintigraphic examination.

It can be concluded that, in diagnosing bone inflammation, the most important technique is three-phase scintigraphy after a plain roentgenogram of the skeleton has been taken.

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DIAGNOSTIKA KOSTNÍCH ZÁNĚTŮ POMOCÍ RADIONUKLIDŮ

S o u h r n

Scintigrafie skeletu zůstává po prostém rentgenovém snímku nejdůležitější diagnostickou technikou v diagnostice kostních zánětů. V současné době je stále častěji scintigrafie ⁶⁷Ga nahrazována scintigrafií značenými leukocyty jako další radionuklidová zobrazovací technika. Scintigrafie skeletu zůstává nezbytnou jednak pro vlastní lokalizaci zánětu a dále pro vysokou negativní prediktivní hodnotu. Jako typický nález u třífázové scintigrafie skeletu vidíme lokální překrvení v první a druhé fázi vyšetření a ložiskové zvýšení radioaktivity ve třetí fázi.

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