Radionuclide bone scanning

Helen Carty

Radionuclide bone scanning is the second most frequently performed radionuclide study in childhood. There are a wide variety of indications, many advantages, and few disadvantages. Functional as well as anatomical information is obtained. Bone scanning is particularly valuable in the diagnosis of inflammatory conditions, trauma, and in the investigation of occult bone pain and vascular insult as well as malignant disease.

Radiopharmaceuticals

Bone scanning in children became a practical investigation after the introduction of technetium labelled polyphosphonate compounds in 1971. The compound now in universal use as a pharmaceutical for routine bone scanning is methylene diposphonate labelled with technetium: $^{99m}$Tc MDP. This compound has a rapid clearance from blood, 40% of the administered activity being in the urine by one hour, and a high affinity for bone with fast uptake. Thus, injected radioactivity is relatively low. The combination of rapid blood and soft tissue clearance with a high affinity for bone uptake means that scans can be performed within an acceptable time from injection, two hours being the favoured scanning time. Photon activity at this point is mainly from bone with little soft tissue contribution. Thus bone detail is high and images easy to interpret.

Technetium is a satisfactory radionuclide, having the advantages of being freely available, stable, relatively cheap, a photon energy of 140 kev that is readily detectable by the crystals in the gamma camera, and a half life of six hours that is long enough to enable easy and flexible planning of a day's imaging but short enough so that radiation is not unduly prolonged once imaging has been achieved.

The precise mechanism of MDP uptake by bone is not known but it is a function of osteoblastic activity. A positive scan, usually manifest as an area of increased activity or 'hot' spot, is dependent on increased osteoblastic activity at the pathological site and an intact blood supply to ensure that the radionuclide reaches the lesion. Areas of decreased photon activity will appear as 'cold' spots on images and may be due to reduction in blood supply to the lesion, as occurs with avascular necrosis, or extensive destruction occasionally seen in metastatic disease and osteomyelitis. In the latter, a subperiosteal abscess will also produce a cold spot.

A positive $^{99m}$Tc MDP bone scan indicates pathology in the region of the increased activity but does not indicate the aetiology of the lesion, although this can usually be inferred from the clinical presentation.

Scanning with labelled white cells is now possible, a positive scan being specific for infection. White cells may be labelled by two methods, either with $^{111}$indium or with $^{99m}$Tc hexamethylpropyleneamine-oxine (HMPAO).

As HMPAO is technetium labelled, it is more freely available than indium and is generally favoured in acute infection. Labelling may be achieved with as little as 5 ml of blood (J Gordon, personal communication) but is more satisfactory with a minimum of 20 ml. The child's blood is withdrawn into an acid citrate dextrose syringe, through a needle of 23G or larger to prevent damaging the cells. The blood is then centrifuged in the radiopharmacy to elute the white cells, which after labelling, are reinjected into the child.

The choice of $^{111}$indium or $^{99m}$Tc HMPAO for imaging infection depends primarily on two factors, the chronicity and site of the suspected lesion. As white cell turnover is generally slower in chronic foci the ability to image over a longer time period, more than 24 hours, is an advantage. The physical half life of $^{111}$indium, which is 2-8 days, as compared with $^{99m}$Tc of six hours, provides this facility.

$^{99m}$Tc HMPAO cells are cleared from the bloodstream by the spleen and degradation products are excreted by bowel and kidney and thus are less suitable for thoracolumbar bone sepsis imaging than $^{111}$indium labelled cells, should this region be the area of main interest. In the limbs, $^{99m}$Tc HMPAO should be used because of a lower radiation dose.

Gallium citrate accumulates in both inflammatory and neoplastic lesions and is on occasion helpful in the diagnosis of chronic inflammation, but has been superseded by white cell labelled scans in acute disease. It is no longer indicated for the diagnosis of bone neoplasia as the combination of the clinical presentation and other imaging techniques have rendered its use obsolete. Disadvantages of gallium are a high radiation dose, delayed imaging times — lesion to background ratio is best at about 48 hours after injection — and a high excretion into the gastrointestinal tract that necessitates bowel preparation with cathartics if the suspected lesion is in the abdomen. The dosimetry of these compounds is shown in table 1.
In practice, the combination of the clinical picture, 99mTc MDP scanning and ultrasound will enable a diagnosis of osteomyelitis to be made in most children, the white cell labelled scans being used mainly in the investigation of persistent pyrexia of unknown origin without localising signs.

Metaiodobenzylguanidine, MIBG, a precursor of vanillylmandelic acid, may be labelled with 123I for diagnostic purposes or 131I for diagnosis if 123I is not available, and for radio nuclide treatment in children with neuroblastoma.21-23 MIBG uptake is specific for bone marrow metastases in children with neuroblastoma. It is also taken up in many, though not all, primary tumours, and in general is negative in non-catecholamine secreting tumours. The sensitivity for the detection of lesions may in part be dose related.24 A positive MIBG scan with bone disease indicates a stage IV tumour. There are conflicting reports about the sensitivity and specificity of MIBG and MDP scanning in the detection of metastases in these children, some children with MIBG negative scans having positive MDP scans and vice versa.21,22,24 A positive MIBG scan is specific for bone marrow disease while a positive MDP scan could indicate some other bone pathology. Comparison with the radiographs of the scintigraphic abnormality will resolve the cause of the positive scan and eliminate benign disease. In practice, if either scan is positive, this should be regarded as an indication of continuing bone disease in these children and therefore stage IV disease.

Advantages of bone scanning
After an injection of a bone seeking radiopharmaceutical the whole body may be imaged without an increase in radiation dose and provides confirmation that a suspected lesion is solitary. The investigation is non-invasive – apart from the injection and sedation for small children before scanning, as it is imperative that the child remains still so that high quality images are obtained. Scans are positive many days before radiographic changes in both infection and trauma.26-31 The localisation of a lesion on bone scintigraphy helps to focus attention on radiographic changes which may have been initially overlooked and localises a lesion for further investigation by computed tomography or magnetic resonance imaging where indicated.

Disadvantages of bone scanning
There are few disadvantages. There is a radiation dose from a bone scan. The effective dose equivalent of a 99mTc MDP bone scan using the Advisory Committee maximum recommended administered doses is 5.0 mSv based on an injected dose of 600 MBq, but the injected dose in children is based on an adult dose of 400 MBq and therefore the effective dose equivalent is proportionately lower, as compared with 1.2 mSv from a pelvic radiograph,26 but this dose must be kept in perspective in relation to the information gained. A positive scan lacks diagnostic specificity if looked at in isolation but when reviewed in the context of the clinical history and radiographic changes, a specific diagnosis is usually possible. Bone scans must never be interpreted in isolation.

The biodistribution of MDP in children is different to adults with higher activity in the growth plates26 but the dose rate remains within acceptable limits. The radiation dose is also affected by the body's ability to excrete the radiopharmaceutical, for MDP this is the kidneys. The dose rises in renal failure. Gonadal dose may be reduced by a regimen of high fluid intake, bladder emptying, or frequent nappy changing in the appropriate age groups.

Indications
The main indications for bone scintigraphy in children are summarised in table 2.

OSTEOMYELITIS, CELLULITIS, AND SEPTIC ARTHRITIS
At the time of clinical presentation of acute osteomyelitis radiographs are usually normal. Most osteomyelitis foci in the long bones in children are in the metaphyseal region of the bones, and in children with a typical clinical presentation, positive radiographs or ultrasonic examination, further imaging is not always necessary. When there is doubt about the localisation of the focus or about the clinical diagnosis, bone scintigraphy with MDP should be undertaken before exploratory surgery. The scintigram will localise the lesion within the bone, show whether it is anterior or posterior, and exclude or confirm associated septic arthritis. It will also confirm that the focus is solitary. The technique of scanning is important.1 Limbs must be imaged separately from the axial skeleton so that count rates from affected regions are adequate for diagnosis. 'Babygram' scans will lead to false negative results. Ideally, three phase bone scans should be used in children with suspected infection. A three phase scan is composed of time activity curves generated over the region of interest during the injection and compared with the normal side: 'a radionuclide

<table>
<thead>
<tr>
<th>Radionuclide bone scanning</th>
<th></th>
</tr>
</thead>
</table>

Table 1 Dosimetry

<table>
<thead>
<tr>
<th>Product</th>
<th>Injected dose (MBq)</th>
<th>Critical organ dose (mSv)</th>
<th>Whole body dose (mSv)</th>
<th>Effective dose equivalent (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>111In white blood cells</td>
<td>12-16</td>
<td>(Spleen) 98</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>99mTc white blood cells</td>
<td>200</td>
<td>(Spleen) 32</td>
<td>3-4</td>
<td>4-0</td>
</tr>
<tr>
<td>67Ga</td>
<td>80</td>
<td>(Bone) 47</td>
<td>9-6</td>
<td>18-0</td>
</tr>
</tbody>
</table>

Figures quoted are from Amersham International.
angiogram, an image of the affected region during the 'blood pool' phase taken within five minutes of injection, and delayed high resolution images at two to four hours after injection. The distribution of MDP reflects regional blood flow and is increased in inflammation. Imaging by this technique is said to increase the sensitivity for the detection of osteomyelitis. In practice, in small infants a two phase scan is usually performed as imaging during injection is sometimes difficult, and experience has shown that two phase scanning is adequate for reliable diagnosis.

In osteomyelitis, all three phases of the bone scan are positive. In cellulitis, the first two phases are positive but no focus of bone infection is seen on the late images. Scintigraphic findings in septic arthritis will usually show increased activity on all three phases, but unless there is concomitant osteomyelitis, no focus of activity is visible in the bone on the static images. In all children, the hyperaemia of infection will cause increased uptake in the growth plates distal to a lesion. This must not be mistaken with other infective foci. The normal growth plate has a linear appearance on scintigraphy with a sharply demarcated transition to the shaft uptake. In metaphyseal infection there is a loss of this sharp transition with a flare of increased activity into the shaft. Foci of infection in the diaphysis usually appear as hot spots, though where there is tamponade of the vascular supply to a region of bone, usually from a high pressure subperiosteal abscess or tamponade of the blood supply to the joint, most frequently seen in the hip joint, a positive scan may be indicated by photopenia. Photopenia of a portion of the bone or of the hip joint carries a poor prognosis with almost inevitable development of avascular necrosis of the femoral head. Bone scanning is particularly helpful in the diagnosis of saccroiliac infections which often present clinically as hip or leg pain with poorly localised signs. The radio-0

graphs are usually normal, the focus being identified by scintigraphy. Osteomyelitis of flat bones is also difficult to diagnose clinically but can be identified early with scintigraphy. Similarly, bone scans in juvenile discitis and axial skeletal osteomyelitis will be positive before radiographic changes are visible.

The reliability of 99mTc MDP scanning in osteomyelitis has been the subject of many reports with false positive and false negative scans occurring in these reports. The accuracy rate is generally reported as 75% or better but in one report it is reported as low as 33% in neonates with a range of 33 to 100%. A consensus view for the role of MDP scintigraphy in infection is that when a positive scan is reported the diagnosis is confirmed, and antibiotic treatment and surgical drainage should be instituted as appropriate. A negative MDP scan does not exclude osteomyelitis and other imaging, either with white cell scanning, ultrasound or magnetic resonance, should be employed and antibiotic treatment instituted.

The specificity of MDP scintigraphy in septic arthritis and cellulitis is reported as high as 93% and 100% when reviewed together with the clinical parameters but blind reading of bone scans will reduce the specificity of interpretation as the scan in isolation cannot distinguish infective from other forms of arthritis.

White cell scanning should be undertaken in MDP negative scans when there is a strong suspicion of infection, in pyrexia of unknown origin clinically suspected to be of bony origin, and in suspected reactivation of old osteomyelitis. It may be used for the primary diagnosis before an invasive procedure than MDP scintigraphy. When positive, the scan is specific for infection. In sickle cell disease, scintigraphy with MDP is not reliable in distinguishing osteomyelitis from bone infarction.

INVESTIGATION OF OCCULT BONE OR JOINT PAIN AND TRAUMA

The first imaging investigation in children presenting thus is plain radiography and, increasingly, ultrasound, which is particularly useful in the appendicular skeleton but has little role in the tubular bone. If there is a positive scan and ultrasound negative bone pain, the next investigation is scintigraphy with MDP, which should include images of the whole of the skeleton with localising anterior, posterior, and lateral views of a region of abnormality. Once the lesion is thus localised, review of the radiographs will often then reveal an abnormality and further investigation can be instituted. Lesions that are commonly diagnosed in this way are spiral and calcaneal fractures in toddlers, stress fractures and compartment syndromes especially in young athletes, spondylolysis, carpal trauma, sacrosili-tis, osteomyelitis, spinal infection, osteochondrildes, congenital abnormalities, osteoid osteoma, other benign and occasionally malignant bone tumours, tarsal coalition, and occasionally vascular malformations. While the scintigraphic appearances of these lesions are often non-specific, the combination of the clinical presentation, the location of the lesion in the skeleton and in the individual portion of the bone, and the age of the child, often indicates a specific diagnosis. Many regions of the immature skeleton have increased uptake normally such as growth plates and synchondroses and are often misinterpreted as areas of pathology.

Children who present with radiographically negative bone trauma fall commonly into two age groups – the toddler and the adolescent. The toddler usually presents with pseudoparesis of arm or leg. When radiographs are negative the decision to undertake scintigraphy usually depends on associated constitutional symptoms and concern about early osteomyelitis or parental anxiety. Most of these children will recover if a wait and see policy is adopted as the lesions are seldom serious but they may well have unnecessary hospitalisation or antibiotics. An early bone scan will not resolve the clinical dilemma and avoid these problems. Good communication between paediatrician, orthopaedic surgeon, and radiologist will encourage appropriate selection of patients and avoid overuse of scintigraphy.

In the older child, most radiographically negative trauma relates to the wrist or spine. Early
Radionuclide bone scanning

Scintigraphy will select those patients with fractures, distinguish a fracture from a bad joint sprain and in patients with a spondylolysis even if radiographically evident will show those in whom active repair efforts are present, as these are usually hot on scanning. Scintigraphically negative spondylolysis that is painful may require surgical intervention.

ATHLETIC INJURY

The growing interest in sports with intensive training schedules for children has led to an increase in overuse related injury as well as acute trauma. The main overuse injuries are stress fractures, chronic avulsion injuries at the site of muscle insertion, shin splints, and compartment syndromes with occasional patients presenting with reflex sympathetic dystrophy after minor injury.61-63 Scintigraphy has a major role in the investigation of all these lesions and should be carried out early after onset of symptoms if radiographs are negative. It is possible to grade stress fractures by scintigraphy. Resumption of training is in part based on grading. Too early a return to activity may lead to long term complications.

HIP PAIN

Hip pain in the young child has three main causes, most frequently idiopathic synovitis (the irritable hip syndrome), Perthes’ disease, and rarely septic or traumatic arthritis.64-66 The presenting complaint may be leg pain.67 The initial imaging approach should be radiographs and ultrasound of the hip. If an effusion is demonstrated it is then aspirated to exclude infection. If both these investigations are normal, scintigraphy should be undertaken. Pinhole views of the hips and anterior and posterior views of the lumbar spine and pelvis must be done routinely to exclude spinal, sacroiliac, or pelvic pathology causing referred hip pain.68 Scintigraphy is a highly sensitive method of distinguishing Perthes’ disease from other conditions. In the acute phase of Perthes’ disease, the femoral head is photopenic in its lateral two thirds. Reactive increased uptake is often present in the metaphysis, mirroring the metaphyseal changes seen on radiographs. The scintigram mirrors the physiological state of vascular supply to the femoral head and is a much more sensitive indicator of the repair process than radiographs and will anticipate radiographic changes by some months. Until magnetic resonance imaging becomes freely available and cheaper, scintigraphy will remain an important and cheap method of resolving the cause of hip pain.

CHILD ABUSE

The skeletal survey is the most convenient, best understood imaging method in children suspected of child abuse. When lesions are found on the skeletal survey, no other skeletal imaging is usually employed. A bone scan is in general a more sensitive method of detecting fractures, with the exception of the skull vault and intra-capsular metaphyseal fractures, than radiographs67 but is seldom undertaken, usually because of logistical reasons and a reluctance to increase radiation to the child who already has positive radiographs. The main indications for scintigraphy in a child suspected as the victim of abuse are a radiographically negative survey with strong suspicion of abuse, to resolve the nature of a doubtful lesion on radiographs, and the detection of additional rib fractures, particularly at the necks of the ribs in children in whom one mid-shaft fracture has been detected. Detection of further fractures will resolve any doubt that may exist about the nature of the one fracture.

High resolution, straight images, with limbs imaged separately and images of adequate size presented for reporting must be done if scanning is to be undertaken.

Occasionally, unsuspected extraskeletal injuries may be detected during scintigraphy in these children – mainly visceral and soft tissue lesions.72

PRIMARY AND METASTATIC BONE DISEASE

With the advent of magnetic resonance, scintigraphy is no longer indicated to assess the extent of a primary tumour, the soft tissue component, narrow infiltration, and skip lesions being better appreciated by magnetic resonance.73 Scintigraphy is still indicated to confirm that a presenting lesion is solitary in all primary malignant bone tumours, as metastatic disease or a multifocal origin on presentation alters management and affects prognosis.77 In children on treatment who develop focal bone pain, even if radiographs show a lesion, a bone scan should be done to identify further areas of silent disease and the extent of spread, so that management decisions can be made. In radiographically negative bone pain in a child with malignant disease, a bone scan is mandatory. The role of MDP and MIBG bone scanning in the management of children with neuroblastoma has already been discussed.

Children with cancer are mostly treated as part of a multicentre trial. Protocols for initial and follow up investigation are sometimes drawn up without seeking advice from radiologists as to the most sensitive imaging indications of disease and the most appropriate time of the investigations. A little early advice will avoid unnecessary investigations.

Other applications

In monoarticular or polyarticular arthritis, bone scanning has been shown to be of value in the evaluation of monoarticular and non-rheumatic polyarticular disorders, but while it will show disease activity in children with connective tissue diseases and juvenile chronic arthritis, it seldom is indicated as clinical assessment and biochemical parameters provide the relevant information and management is not altered.78

Marked radionuclide uptake is present in lesions of active fibrous dysplasia79 and in the growing edges of exostoses,80 but imaging is not routinely indicated and should only be done when assessing complications of these diseases.
such as fractures or the assessment of femoral head vascularity after a fracture through an area of fibrous dysplasia in the femoral neck.

Finally, scintigraphy has a major role in the assessment of mandibular growth and asymmetry. Surgery for these conditions is determined in part by the activity shown on scintigraphy. The optimum time for surgery is when growth has ceased – as evident by low or normal activity on the bone scan.

Bone scanning in paediatric practice contributes a great deal to identifying the cause and location of pathological conditions in children and must be technically of a very high quality and interpreted by doctors familiar with paediatric disease, together with the clinical information and other imaging procedures, if the maximum benefit is to be gained.

Radionuclide bone scanning