Value of a 24-Hour Image (Four-Phase Bone Scan) in Assessing Osteomyelitis in Patients with Peripheral Vascular Disease

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The delayed images of the four-phase ^{99m}Tc phosphonate bone scan are compared with the delayed images of the three-phase study in patients with diabetes mellitus and/or peripheral vascular disease and suspected osteomyelitis. Three-phase bone imaging includes an immediate postinjection radionuclide angiogram, a blood-pool image, and delayed static images to 7 hr. The four-phase study adds a 24-hr static image. The scan is positive for osteomyelitis if images show progressively increasing lesion to background activity ratios over time. The results of analyzing 21 three- and four-phase bone scans in 17 patients were correlated with clinical course, cultures, and/or x-rays, gallium scans, and CT scans. The accuracy of four-phase bone imaging for diagnosing osteomyelitis was 85%; for three phase, 80%. Sensitivity for four phase was 80%; specificity was 87%. Sensitivity for three phase was 100%; specificity was 73%. Since overall accuracy of the four-phase study is slightly better than three phase, in these patients with diabetes mellitus and/or peripheral vascular disease, the addition of a 24-hr image, creating a four-phase bone scan, is recommended.

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steomyelitis, particularly in patients with diabetes or atherosclerotic vascular disease, is associated with a high rate of serious morbidity, including limb loss (1). Radionuclide skeletal scintigraphy has been proposed as a superior technique to skeletal radiography for early diagnosis (2,3). Three-phase radionuclide bone imaging comprised of a postinjection radionuclide angiogram, followed by a "blood-pool" image, and delayed static imaging at 2-3 hr and/or 5-7 hr has been proposed as a means to increase specificity of skeletal scintigraphy (3,4). This report reviews our initial experience with a four-phase technetium-99m (^{99m}Tc) labeled phosphate bone scan protocol and compares it to the three-phase study for evaluating adults with suspected osteomyelitis. The four-phase bone scan differs from the three-phase scan method by the addition of a static 24-hr image.

MATERIALS AND METHODS

Patients with lower extremity ulcers, underlying diabetes mellitus, and/or peripheral vascular disease, who were referred to our institution for bone scans because of suspected osteomyelitis between January 1982 and December 1983, were identified. Twenty-one scans in 17 patients had all four phases of the bone scan, including the radionuclide angiogram, blood-pool image, delayed 2-4-hr, 5-7-hr, and 24-hr static images.

Bone scans were performed using 20 mCi of $[^{99m}Tc]$ methylene diphosphonate (MDP) or hydroxymethylene diphosphonate (HDP). All scans were obtained using a 37 photomultiplier tube scintillation camera with a low-energy, all-purpose, parallel-hole collimator. The first phase of the bone scan consisted of the radionuclide angiogram, comprised of sequential images at 2-3 sec per frame over the involved region of suspected osteomyelitis and the opposite presumed normal anatomic region, if possible. The radionuclide angiogram was carried out for ~60 sec, followed by a

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Three- and four-phase bone scan over feet in patient with nonhealing ulcer over left great toe with complicating osteomyelitis. A: Shows radionuclide angiogram at 2 sec per frame. Brisk hypervascular response to region of left great toe is evident. B: Shows hypervascularity of left foot and particularly region of left great toe. Sequential images at 2, 5 $\frac{1}{2}$, and 24 hr show increasing activity in toe relative to activity in normal background. This pattern is consistent with underlying osteomyelitis, for both three and four phases of bone scan



Blood-pool and sequential bone scan images over left foot taken from medial and lateral aspects of ankle in patient with nonhealing ulcer over heel. Right leg has been amputated due to peripheral vascular disease. Images show small hypervascular region in heel on blood-pool image corresponding to nonhealing ulcer. Sequential images at 2, 4, and 24 hr show markedly increased activity in region of calcaneus. Between 4 and 24 hr, calcaneus activity does not seem to decrease relative to background activity, but neither does it seem to increase. Therefore, based on 24-hr image, scan was interpreted as indeterminate for osteomyelitis. Up to 4 hr, however, scan would have been interpreted as compatible with osteomyelitis. Based on clinical course, patient was thought not to have had osteomyelitis

blood-pool image at 1-2 min postintravenous injection of the radiopharmaceutical. The second, third, and fourth phases of the bone scan were the delayed static images at 2-4 hr, 5-8 hr, and 24 hr, respectively, obtained in frontal and lateral projections, if possible, for at least 200,000 counts. Images of the opposite presumed normal anatomic region were obtained whenever possible. Because of the sparsity of counts at 24 hr, due to physical decay of the ^{99m}Tc, 100,000-count images were obtained at that time, and for comparison, a 100,000-count image was also obtained at 5-8 hr. Scintillation camera intensity settings were carefully monitored so that images of comparable counts and intensities were available for interpretation.

BONE SCAN INTERPRETATION

Scan criteria for osteomyelitis were presence of an increasing lesion to background activity ratio (a) from 2-24 hr of the four-phase study and (b) from 2 to 5-8 hr of the three-phase study (see Fig. 1) assessed by visual inspection of the images. If lesion-to-background activity ratio remained abnormal and unchanged on the images, it was interpreted as indeterminate for osteomyelitis (see Fig. 2); if lesion to background activity ratio decreased over the three- or four-phase scanning intervals, it was interpreted as no osteomyelitis (see Fig. 3). Thus, we omitted the radionuclide angiogram and blood-pool images from consideration in assessing presence or absence of osteomyelitis. All image interpretations were made by two experienced nuclear medicine physicians. Interpretations of no osteomyelitis, osteomyelitis, or indeterminate for osteomyelitis were made for three-phase and four-phase studies independently. Patients were categorized as actually having had osteomyelitis or not based on clinical course, cultures obtained at surgery in those patients who went to surgery, and correlation with other diagnostic tests including xrays, gallium scans, and CT scans.

RESULTS

The results are presented in Table 1. There were 21 three- and four-phase bone scans performed on 17 patients which could be correlated with surgical pathology and/or clinical course. The patients had underlying peripheral vascular disease and/or diabetes mellitus with soft-tissue ulcers and were being evaluated for suspected osteomyelitis.

There was agreement of no osteomyelitis with surgical pathology and/or clinical course for both three- and four-phase bone imaging studies in 11 scans (Table 1). In two cases of proven "no osteomyelitis," three-phase studies were false positive, while the 24-hr image supported a diagnosis of "no osteomyelitis" (Fig. 3). In two other cases of no osteomyelitis, the three-phase study was falsely positive, while the four phase was indeterminate (Fig. 2). In five proven osteomyelitis patients, four scans were positive by three- and four-phase studies (Fig. 1), and one was false negative for four phase, but positive for three phase. Thus, in four of 21 scans, the 24-hr image favorably influenced the interpretation of

Sequential blood-pool, 2, 6, and 24-hr images over feet in patient with nonhealing ulcer over left great toe. Blood-pool image shows hypervascular response to region of ulceration (arrow). Sequential images up to 6 hr would be compatible with osteomyelitis involving left great toe. However, 24-hr image shows evidence for decreasing activity in left great toe relative to background. Tarsal bones and distal tibia on left also show augmented activity, probably related to degenerative disease and generalized hypervascular response stimulated by soft-tissue ulceration. Based on 24-hr image, scan was interpreted as indicating no osteomyelitis. First three phases of bone scan were compatible with osteomyelitis. Clinically, patient's course indicated no osteomyelitis



the study; in one scan the 24-hr image was unfavorable. There was agreement between three- and four-phase bone scans on 16 of 21 scans. Accuracy, sensitivity, and specificity vary depending upon how one considers the indeterminate scan results. Omitting the one scan which was indeterminate for three-phase, four-phase, and clin/path results, and considering the two fourphase indeterminate scans whose clin/path results were negative as false positives, the accuracy for four phase was 85%; the accuracy for three phase was 80%. Sensitivity for four phase was 80%; specificity was 87%. Sensitivity for three phase was 100%; specificity was 73% (Table 2). If we omit all indeterminate scan results from the calculations, the accuracy for four phase increases to 94%; sensitivity remains 80%; specificity increases to 100%. If we arbitrarily choose to consider the two indeterminate four-phase scans as false negatives, accuracy remains 85%; sensitivity falls to 57%; specificity remains 87%.

Although this study does not purport to evaluate

	Seen 41		Sees -t		Scan		Tetolo	
Item	Four Phase	Three Phase	Four Phase	n — Three Phase	Four Phase	Three Phase	Four Phase	Three Phase
Path/clin +	4	5	1			_	5	5
Path/clin —	_	4	13	11	2		15	15
Path/clin indeterminate	_	_	-		1	1	1	1
Totals four phase	4	_	14		3	_	21	_
Totals three phase	_	9	_	11	_	1	_	21
 Indicates osteomyelitis. Indicates no osteomyeliti 	S .							

 TABLE 1

 Four-Phase Compared with Three-Phase Bone Scan Correlation with Surgical Pathology and/or Clinical Course

Osteomyelitis							
	Sensitivity <u>TP</u> TP+FN						
Three phase	5	= 100%					
Four phase	$\frac{4}{4+1}$	= 80%					
	Specificity <u>TN</u> TN+FP						
Three phase		= 73%					
Four phase	11+4 13 13+2	= 87%					
	Accuracy <u>TP+TN</u> TP+FP+TN+FN						
Three phase	5+11	= 80%					
Four phase	5+4+11+0 	= 85%					
	4+2+13+1						

 TABLE 2*

 Sensitivity, Specificity, and Accuracy of Four Phase

 Compared with Three Phase for Diagnosis of

 Osteomyelitis

 These calculations omit one scan which was indeterminate for three-phase, four-phase, and clin/path results and classify two indeterminate four-phase scans which had positive clin/path results as false-positive scans.

gallium scans in these subjects, coincidentally, there were six gallium scans done on five of the patients studied. For five of six scans, there was excellent agreement between gallium and delayed [^{99m}Tc]phosphonate bone image assessment for osteomyelitis. There was one case of disagreement, where three-phase delayed bone images were false positive and four-phase was indeterminate, while gallium was negative for osteomyelitis. Surgical pathology revealed no active bone infection at that time.

DISCUSSION

Osteomyelitis associated with vascular insufficiency particularly in the presence of diabetes mellitus presents special diagnostic and treatment problems. Most patients are in the sixth to ninth decades and note few systemic manifestations of infection. Pain, swelling, and long-standing indolent ulcers are common in this population. Progression to osteomyelitis, thus, is always possible and difficult to diagnose, particularly in the presence of diabetic neuropathy. Progression of osteomyelitis in this unfortunate population culminates fre-

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quently in amputation despite initial trials of conservative surgical or medical therapy. Fifty percent of patients with osteomyelitis and nonhealing ulcers reported in another study (5) required amputation; the other 50% were successfully treated for their osteomyelitis and eventually healed their ulcers.

Scintigraphic imaging of bone is considered the optimal diagnostic technique for assessment of osteomyelitis (2-4). Pediatric bone scanning is complicated by the normal augmented uptake characteristic of the rapid growth regions of the metaphyseal-epiphyseal areas of bones. Many reports of false-negative bone scans in young children have been documented (6-8). Technetium-99m-labeled phosphate bone scans in adults, particularly those afflicted with ulcers, cellulitis, and edema commonly associated with peripheral vascular disease present different problems. Technetium-99m phosphate or phosphonate uptake in bone is associated with bone blood flow (9) and osteogenic activity. Blood flow is obviously a critical variable in vascular disease patients, and the effect of compromised peripheral blood flow on the bone scan in these patients is not defined (see Fig. 4). In this group of patients a major cause of false-positive results appears to be degenerative disease. Figure 4 shows a region of increasing lesion-to-background activity in degenerative disease which was not an area of suspected osteomyelitis clinically. Thus, in the presence of degenerative findings, superimposed osteomyelitis would be difficult to diagnose or exclude by sequential bone images. Degenerative disease is a cause of false-positive three- or fourphase bone imaging for osteomyelitis.

Gallium-67 imaging has been proposed as a valuable alternative diagnostic imaging technique allowing improved differentiation of cellulitis from osteomyelitis and distinction between remote and persistent active osteomyelitis (8, 10). We have noted isolated instances of slightly increased activity on gallium scans in the presence of noninfective bony reactive lesions, such as osteoarthritic degenerative disease, but data to document the capability or unreliability of gallium to differentiate between degenerative disease and osteomyelitis is lacking. For infants and young children, the increased radiation exposure from gallium compared with [99mTc]phosphate, gives rise to appropriate reluctance to use gallium freely. Nonetheless, because of the documented failures of [99mTc]phosphate imaging in this age group, some physicians prefer gallium as a first-line imaging tool to diagnose osteomyelitis, because of its demonstrated higher sensitivity (6,8); others recommend that gallium be used when [99mTc]phosphate scans are inconclusive (7). In chronic osteomyelitis, gallium imaging has been recommended as the preferred imaging agent for following response to therapy and evaluating activity of an infectious process (11,12). This is consistent with other reports showing

This patient has gangrene of 4th and 5th toes. 1st and 2nd distal phalanges have been amputed previously. Radionuclide angiogram shows marked hypervascular response to 1st left toe at level of metacarpal phalangeal joint. There is markedly decreased activity to distal phalanges in 3rd and 4th toes. Sequential imaging shows increasing activity in 1st left digit compatible with osteomyelitis. This patient has severe peripheral vascular disease. Note augmented activity in right tarsal bones, probably related to degenerative disease. Differentiation between osteomyelitis and degenerative disease in presence of peripheral vascular disease may be very problematic



higher sensitivity for gallium imaging to define chronic soft-tissue infections over indium-111 leukocyte imaging which is preferred for acute soft-tissue infectious processes (13). Only five of the patients studied here also had gallium scans. Thus, we do not have sufficient data to draw conclusions on the value of gallium scans in peripheral vascular disease patients with skin ulcers and suspected osteomyelitis. We believe, however, that the four-phase bone scan provides much valuable information in these patients. In addition to assessment of osteomyelitis based on the delayed 2-24 hr images, the radionuclide angiogram and blood-pool images, performed as part of the four-phase bone scan, reveal presence or absence of the hypervascular response which has been shown to accurately predict potential for healing or nonhealing of the ulcer (5). In this study, we have shown that the delayed static images of the four-phase bone scan are reasonably accurate for assessing osteomyelitis. The value of adjunctive gallium scanning in these patients remains to be clarified.

Maurer et al. have demonstrated increased diagnostic efficacy of "blood-pool" imaging and radionuclide angiography in addition to 2-3 hr delayed images in evaluation of patients with suspected osteomyelitis in both the adult and pediatric age groups (4). Among their criteria for osteomyelitis, they included hyperemia imaged on the radionuclide angiogram and bloodpool phases. Because most of the patients studied here had cellulitis, ulcers, and edema, most had a hyperemic vascular response on the radionuclide angiogram or blood-pool image, even though there was underlying peripheral vascular disease. Although there was variability, i.e., some of the patients showed a brisk, marked hypervascular response, while others showed a slightly delayed and less intense pattern of increased activity on the radionuclide angiogram and blood-pool images, there were no characteristics of these early images to differentiate between those who had osteomyelitis and those who only had cellulitis (see Fig. 3). Even among those patients who did not have a hypervascular response on radionuclide angiogram or blood-pool images because of severe underlying peripheral vascular disease, osteomyelitis was found in one case. Nonetheless, augmented lesion to background activity was apparent on delayed images and followed the pattern of increasing with time from 2-24 hr, despite the lack of hypervascular activity on the first phase of the study. Thus, we did not use the presence or absence of the hypervascular response on the first phase of the three- or fourphase bone scan as a criterion for osteomyelitis. In the presence of peripheral vascular disease, the radionuclide angiogram and blood-pool images have proved useful in predicting healing of "nonhealing" skin ulcers, but can be misleading in assessing osteomyelitis.

Specific benefit of three-phase bone scanning in the diabetic foot has been reported by Park et al. (14). Our experience suggests that additional diagnostic information, in the form of increased specificity, may be gathered without additional radiation exposure for the patient by obtaining a 24-hr static image, creating a fourphase bone scan. In light of the severe consequences of osteomyelitis in adults with vascular disease, a tech-

nique such as the four-phase bone scan, which offers the possibility of more accurate diagnosis, warrants clinical consideration.

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REFERENCES

- 1. Waldvogel FA, Medoff G, Swartz MN: Osteomyelitis: A review of clinical features, therapeutic considerations and unusual aspects. *N Engl J Med* 282:316-322, 1970
- 2. Nelson HT, Taylor A: Bone scanning in the diagnosis of acute osteomyelitis. *Eur J Nucl Med* 5, 267-269, 1980
- 3. Handmaker H, Leonards R: The bone scan in inflammatory osseous disease. Semin Nucl Med 6:95, 1976
- 4. Maurer AH, Chan DPC, Camargo EE: Utility of threephase skeletal scintigraphy in suspected osteomyelitis: Concise communication. J Nucl Med 22:941-949, 1981
- 5. Alazraki N, Lawrence P, Syverud J: Radionuclide angiography and blood pool imaging to assess skin ulcer healing prognosis in patients with peripheral vascular disease. J Nucl Med 25:P47, 1984 (abstr)
- 6. Ash JM, Gilday DL: The futility of bone scanning in neonatal osteomyelitis: Concise communication. J Nucl

Med 21:417-420, 1980

- 7. Handmaker H: Acute hematogenous osteomyelitis: Has the bone scan betrayed us? *Radiology* 135:787-789, 1980
- Lisbona R, Rosenthall L: Observations on the sequential use of 99m-Tc phosphate complex and 67-Ga imaging in osteomyelitis, cellulitis and septic arthritis. *Radiology* 123:123-129, 1977
- 9. Charkes ND: Skeletal blood flow. Implications for bone-scan interpretation. J Nucl Med 21:91-98, 1980
- Howie DW, Savage JP, Wilson TG, et al: The technetium phosphate bone scan in the diagnosis of osteomyelitis in childhood. J Bone Joint Surg 65A:433-437, 1983
- Graham GD, Lundy MM, Frederick RJ, et al: Scintigraphic detection of osteomyelitis with Tc-99m MDP and Ga-67 citrate: Concise communication. J Nucl Med 24:1019-1022, 1983
- 12. Alazraki N, Fierer J, Resnick D: The role of technetium-99m-phosphate and gallium-67-citrate scans in monitoring of patients with chronic osteomyelitis. *Am J Roentgenol*: in press
- Sfakianakis GN, Al-Sheikh W, Heal A, et al: Comparisons of scintigraphy with In-111 leukocytes and Ga-67 in the diagnosis of occult sepsis. J Nucl Med 23:618-626, 1982
- 14. Park H, Wheat J, Siddiqui AR, et al: Scintigraphic evaluation of diabetic osteomyelitis: Concise communication. J Nucl Med 23:569-573, 1982