^{99m}Tc-Imidodiphosphonate: a superior radio-pharmaceutical for *in vivo* positive myocardial infarct imaging

II: Clinical data

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SUMMARY ^{99m}Tc-Imidodiphosphonate was investigated as a new myocardial infarct imaging agent. In the acute phase, 50 patients admitted to the coronary care unit were serially scanned over a period of 7 days. A mobile gamma camera linked on line to a remote data processor was used. Because of higher uptake in infarcted myocardium and faster blood clearance, superior images than those recorded with ^{99m}Tc-pyrophosphate were obtained. Its ease of preparation, low cost, and favourable dosimetry (because of its label with conventional ^{99m}Tc) transforms this agent into the present radiopharmaceutical of choice for acute infarct imaging in particular if sizing and follow-up is intended versus time and type of treatment. In this series, no false positive cases were seen. The sensitivity of the method in the detection of full thickness myocardial infarction was 95 per cent. It dropped to 70 per cent in the detection of subendocardial infarction. However, some of these apparent false negative cases may reflect severe ischaemia without infarction. It is postulated that this discrimination may not always be realistic.

Bed-side diagnosis with radionuclide investigations is one of the aims of the physician using diagnostic nuclear medicine imaging techniques in the hospital environment. Effective non-invasive imaging techniques to investigate bed-ridden patients require, however, mobile gamma cameras—these have been developed in the past 2 years. The clinical data which are the subject of this paper have been obtained with such a new mobile gamma camera placed in the coronary care unit and linked on line to data processing equipment of the Department of Nuclear Medicine. It is the first time that this particular equipment has been used in the United Kingdom in the coronary care unit, and for the first time it has been linked on line to a remote computer system (Brown *et al.*, 1977).

Early recognition of myocardial infarction is not always easy. Other clinical conditions may obscure or mimic the clinical picture and all available traditional means of diagnosis (clinical, electrocardiographic, and serum enzyme measurements)

are sometimes insufficient to allow a definite appraisal. The cardinal and classical symptom of cardiac chest pain is often absent (Papp, 1952) and atypical chest pain, so often present, only underlines the practical difficulties of differentiating the pain arising from acute myocardial necrosis from other non-cardiac conditions. Entities known to give rise to uninterpretable electrocardiographic traces include the presence of previous myocardial damage caused by infarction or surgery, or abnormal ventricular activation such as bundle-branch block, paced rhythms, or pre-excitation. In addition, serum enzyme measurements are often unreliable and false positive readings occur frequently (Savranoglu *et al.*, 1959; Sobel and Shell, 1972); borderline results may maintain rather than eliminate the diagnostic problem.

The value of another specific and diagnostic technique in the early diagnosis of this condition is thus evident. Such a test, which should be safe, reproducible, repeatable, and non-invasive, will find a place in the diagnosis and management of patients suspected of acute myocardial infarction. This paper describes experience with ^{99m}Tc-IDP imaging (Ell

Fig. 1 The Searle Radiographics Low Energy Mobile gamma camera used in this investigation. Dimensions in inches: height 89, width 30½, length 73.

et al., 1978) not previously available in the context of infarct scanning, and its purpose is to clarify to what extent this test fulfils the above-mentioned criteria.

Subjects and methods

Fifty unselected patients admitted to the coronary care unit with suspected or proven myocardial infarction were investigated using a Searle Radiographic Low Energy Mobile gamma camera (Fig. 1). Standard parallel hole low energy and high resolution collimation was used. The mobile gamma camera was linked on line to a Varian 620 i data processing system 500 metres away. Each patient was imaged as soon as possible after the acute event and thereafter at daily intervals for 7 days whenever feasible or until the image became negative. Each scan was performed 1 hour after intravenous injection of 8 to 10 mCi ^{99m}Tc-IDP and routine anterior, left anterior oblique, and left lateral projections were recorded. For each view 400 000 counts were collected. In addition, every patient underwent daily 12 lead electrocardiograms and daily estimation of creatine kinase (CK), aspartate transaminase (AsT), and hydroxybutyric dihydrogenase (HBD).

^{99m}Tc-IDP is the new and now routine radiopharmaceutical used for whole body bone scanning in this hospital. To investigate the possibility of false positive myocardial imaging, 30 patients referred for whole body bone scanning with a variety of non-cardiac conditions also underwent myocardial imaging 1 hour after intravenous injection of the same dose of ^{99m}Tc-IDP. From 10 such

patients, after informed consent, blood samples were taken at 5 minutes, 1, 2, and 3 hours after intravenous administration of the radiopharmaceutical to obtain blood clearance data for comparison with other similar data recorded for other ^{99m}Tc-labelled phosphates (Ell, 1975).

Results

Two hundred and seven scans were obtained on 50 patients, and all scans were rated with criteria of positivity 1+ to 4+, as previously described (Parkey *et al.*, 1977). In the following results, scans rated 1+ are considered *negative*; those rated 2+ to 4+ are *positive*.

Twenty-two patients (44% of all admissions) were diagnosed on the basis of the electrocardiogram to have full thickness myocardial infarction (McConahay *et al.*, 1970). Of these, 21 patients had a positive scan and one patient had a negative scan: sensitivity of detection—95 per cent (Table 1). The patient with the negative scan was imaged on one occasion only at 48 hours after infarction, and it is possible that further imaging would have been positive. Ten patients (20% of admissions) were judged on the electrocardiographic criteria (Friedberg, 1966) to have subendocardial infarction (Table 1). Of these, 7 had positive and 3 had negative ^{99m}Tc-IDP scans: sensitivity of detection—70 per cent. Of the 7 patients with positive scans, 3 showed no rise in serum CK, AsT, or HBD levels. Further analysis of these results is presented in Table 2.

The remaining 18 patients (36% of admissions) presented with doubtful diagnoses. Of these 18, 13 had abnormal electrocardiograms resulting from conduction defects or previous ischaemic damage rendering electrocardiographic diagnosis impossible. All 5 patients with negative scans and 1 of the 8 with a positive scan showed no rise in serum enzymes. The remaining 5 patients with doubtful diagnoses had normal electrocardiograms and none of the patients in this group had a positive scan. Four of these patients had negative or borderline enzyme rises.

Table 3 summarises the blood clearance data obtained for ^{99m}Tc-IDP and compares it with

Table 1 ^{99m}Tc-IDP scan results from 50 investigated patients

Diagnosis	No. of cases	Positive scan	Sensitivity
Transmural infarction	22 (44%)	21	95%
Subendocardial infarction	10 (20%)	7	70%
Doubtful diagnosis	18 (36%)	8	—
Patients Total	50 (100%)		

Table 2 Analysis of the ^{99m}Tc -IDP scans and enzyme results in patients with subendocardial infarction and in patients with non-contributory electrocardiograms

Diagnosis	^{99m}Tc -IDP scan	No. of cases	Positive enzymes	Borderline enzymes	Negative enzymes
Subendocardial infarction	+ve scan	7	3	1	3
	-ve scan	3	2	1	0
Previously abnormal electrocardiogram	+ve scan	8	5	2	1
	-ve scan	5	0	0	5
Normal electrocardiogram	+ve scan	0			
	-ve scan	5	1	1	3

Table 3 Human blood clearance of ^{99m}Tc -labelled phosphates

Agent	% of 5-minute post inj. sample at:		
	1 hour	2 hours	3 hours
Polyphosphate	54	38	29
Monofluorophosphate	44	35	33
Pyrophosphate	39	30	26
Ethyl hydroxydiphosphonate	28	21	14
Methylene diphosphonate	25	16	12
Imidodiphosphonate	30	20	14

similar data of other ^{99m}Tc -labelled phosphates. Fig. 2 to 8 are representative of the spectrum of images obtained with this technique in this series of patients. Fig. 9 shows a graph where the percentage of total of each type of a positive scan (from 1+ to 4+ positive) is plotted against time (days after infarction). Table 4 shows the results obtained with the group of 30 patients referred for whole body bone scanning for a variety of reasons but mainly for the detection of bony metastases and also

images 60 minutes after the intravenous administration of ^{99m}Tc -IDP.

Discussion

Imaging for acute myocardial infarction is generally performed 1 hour after intravenous injection when ^{99m}Tc -phosphates are used as radiopharmaceuticals. In order to achieve images of high technical quality it is always important to ensure that the best signal to noise ratio is obtained. It is, therefore, desirable to maximise the information coming from the organ or area of interest (myocardium and infarcted area) and to minimise interfering information coming from neighbouring structures (blood pool or neighbouring organs). In the particular case of ^{99m}Tc -IDP this has been achieved to a larger extent than has been possible with other ^{99m}Tc -labelled phosphates. Maximum information coming from the area of interest to be imaged has been achieved with the very high uptake in infarcted myocardium (normal to abnormal ratio of 1:20) of

Fig. 2 The distribution of ^{99m}Tc -IDP to be expected in an anterior infarct (in red) and in an inferior infarct (in yellow)

Fig. 3 Normal ^{99m}Tc-IDP scan taken 60 minutes after intravenous injection. Note excellent definition of sternum and ribs with little blood background activity.

^{99m}Tc-IDP (Ell *et al.*, 1978). Minimum interfering information from the blood pool has been achieved also with ^{99m}Tc-IDP, particularly when compared with ^{99m}Tc-pyrophosphate the standard phosphate so far in use for acute infarct imaging (see Table 3). The images obtained with this radiopharmaceutical are of high quality and reproducibility. High uptake in bone and in infarcted myocardium is obtained with little radioactive blood background activity seen at 60 minutes after injection. Fig. 2 to 8 clearly

underline this point. High uptake in normal bone is not considered a disadvantage. It allows exact location of the sternum and xyphoid and the rib arches, this being an excellent anatomical reference system for the interpreting observer. It was consistently felt throughout this investigation that both for the cardiologist and the nuclear medicine physician the interpretation of these images, particularly when compared with ²⁰¹Tl imaging, is much easier and perhaps, therefore, more accurate.

Fig. 4 A typical ^{99m}Tc-IDP scan of a patient with an extensive anterior myocardial infarction. 9 point smoothed image shown on the right. Note large area of abnormal uptake in the heart (anterior image).

Fig. 5 A typical ^{99m}Tc -IDP scan of a patient with an inferior myocardial infarction. Abnormal uptake well seen in 3 projections (from left to right, in the anterior, the left anterior oblique, and the left lateral images).

Fig. 6 Serial ^{99m}Tc -IDP scans (left anterior projections) obtained from day 1 until day 7 after admission. Note negative image by day 7 in a patient with an inferior-posterior infarct.

Fig. 7 Serial ^{99m}Tc -IDP scans (anterior projections) obtained from day 1 until day 5 after admission. Note progressive diminished activity in the heart by day 5 in a patient with an anterior infarct.

Fig. 8 Typical image of a subendocardial infarct. Note generalised and diffuse uptake of ^{99m}Tc-IDP in the heart. Note excellent definition of sternum and ribs and little blood background activity (image recorded 60 minutes after intravenous injection).

A point concerning cost and dosimetry. ²⁰¹Tl imaging may cost up to £50 per individual scan. This factor excludes serial imaging of patients on a cost effective basis. It, therefore, prevents any attempt at serial sizing of acute infarction and monitoring its change with time or treatment. In addition the dosimetry to the patient from ²⁰¹Tl

Fig. 9 Distribution of positive ^{99m}Tc-IDP scans.

Table 4 30 patients with non-cardiac acute pathology (outpatients referred for whole body bone scanning)

No. of patients	4+ Positive image	3+ Positive image	2+ Positive image	1+ Positive image
30	0	0	1	29

and ^{99m}Tc-IDP is different (70 mRad against 15 mRad/mCi whole body), again favouring the choice towards ^{99m}Tc-phosphate imaging if serial investigations are to be undertaken. In summary ^{99m}Tc-IDP offers the distinct advantages of high uptake in the infarcted myocardium (positive rather than negative image), fast clearance from the blood, lower dosimetry to the patient, and negligible cost (50 pence per individual scan). This in turn allows for serial imaging and for quantification and sizing of the infarct against time or treatment.

If high sensitivity of detection of myocardial infarction is to be achieved with this technique serial scanning is mandatory. Two patients not included in this series underline this fact. They had clinical and electrocardiographic evidence of infarction (one transmural and one subendocardial infarct) and negative ^{99m}Tc-IDP scans. Both patients, however, were scanned only once and, at 4 days after the acute event, clearly too late. With the experience gained subsequently it was felt that these two cases should not be counted as true false negatives. Fig. 9 indicates why ^{99m}Tc-IDP scanning, in contrast to ²⁰¹Tl imaging, allows the distinction of old from recent myocardial necrosis. By 7 days, only one patient retained a 3+ positive image. Though late positive images have been described (Parkey *et al.*, 1977) they occur infrequently. This is a most useful feature of positive myocardial infarct imaging.

In the majority of patients, the diagnosis of myocardial infarction could be made on the basis of well-established criteria. A high sensitivity (95%) was achieved with ^{99m}Tc-IDP scanning in patients judged to have transmural myocardial infarction. Seventy per cent of those patients judged to have subendocardial necrosis had positive ^{99m}Tc-IDP scans. Three patients may thus be considered to represent false negatives. However, one of these had borderline serum enzyme increases which may represent the hinterland between infarction and ischaemia without infarction. However, of the 7 subendocardial infarctions with a positive ^{99m}Tc-IDP scan, 3 had no enzyme rise. The distinction between infarction and ischaemia in these cases may be unrealistic; the use of ^{99m}Tc-IDP being sufficiently sensitive to show myocardial damage undetected by enzyme elevation. In these 4 cases quoted above, the ^{99m}Tc-IDP scan was considered to be of special diagnostic value.

Eighteen patients (36%) presented with a doubtful diagnosis either because of previous abnormal and uninterpretable electrocardiograms or because of normal electrocardiograms (Table 2). Of the patients with abnormal electrocardiograms, 3 patients with positive scans had borderline or normal enzyme levels. It was considered justifiable to classify these patients as infarcted or having severe ischaemia. None of the 5 patients with abnormal electrocardiograms and a negative ^{99m}Tc -IDP scan had enzyme rises. Thus in all these cases the ^{99m}Tc -IDP scan was of considerable diagnostic value. It was of equal value in excluding infarction in 4 out of the 5 patients with normal electrocardiograms who had little or no rises in serum enzyme levels. The fifth patient who had enzyme increase may represent a false negative ^{99m}Tc -IDP scan. The value of the ^{99m}Tc -IDP scan in the diagnosis of myocardial infarction is exemplified in the following 2 cases:

Case 1: A 60-year-old man with an 8-year history of coronary heart disease had 2 previous myocardial infarctions. He underwent resection of left ventricular aneurysm and mitral valve replacement for ischaemic mitral regurgitation at the age of 55. Since that time he had been admitted to hospital 5 times with angina. He was admitted on this occasion with a 35-minute episode of chest pain and clinical evidence of left ventricular failure. The electrocardiogram was unhelpful because of previous infarctions and the resected left ventricular aneurysm. Serum CK was raised to a borderline level of 127 I.U. An initially negative ^{99m}Tc -IDP scan became 3+ positive on serial imaging, confirming myocardial infarction which had otherwise been in doubt.

Case 2: A 58-year-old man without previous history was admitted with a short episode of central chest pain, followed by syncope. By the time of admission the only clinical abnormality was systemic hypertension. The electrocardiogram showed sinus rhythm, left bundle-branch block, first degree heart block, and ventricular premature beats; this pattern did not change during the course of his hospital admission. A serum enzyme level was borderline but the ^{99m}Tc -IDP serial scans were negative. Thus a diagnosis of Adams-Stokes attack secondary to conduction disease was made, and the negative scan supported an atypical history in deciding against infarction.

False positive imaging may occur and has been described (Ell, 1976; Parkey *et al.*, 1977). However, in our group of 30 patients with non-cardiac acute pathology only one patient presented with a 2+ positive image (Table 4). This was a 63-year-old man referred for Ca bronchus and whole body bone

scanning (scanning for secondary deposits). Though he had no symptoms myocardial ischaemia was possible.

The ultimate validation of myocardial scanning with ^{99m}Tc -labelled phosphate will require further investigation. However, some points already deserve comment. Animal experiments show quite clearly that positive uptake of ^{99m}Tc -labelled phosphates occurs in those hearts where cells have died or are severely damaged (Ell *et al.*, 1978; Grossmann *et al.*, 1977; Parkey *et al.*, 1977). There is, therefore, evidence available pointing at the correlation between a positive myocardial infarct scan and the existence of severe or irreversible cellular destruction. It is interesting to note that a diagnosis of subendocardial infarction is an electrocardiographic one and can be made in the presence of normal or borderline serum enzyme levels (5 out of 10 cases in our series). The same lack of correlation is observed in relation to ^{99m}Tc -IDP uptake (3 out of 10 patients had an electrocardiographic diagnosis of subendocardial infarction with a negative scan). It is possible that ischaemia without infarction is responsible for some of the cases of electrocardiographic diagnosis of subendocardial necrosis with negative serum enzymes and negative scans (1 out of 10 in our series).

Conclusion

^{99m}Tc -IDP is the phosphate of choice for positive acute myocardial infarct imaging. In this series of 50 patients it contributed to diagnosis and, therefore, to management in 36 per cent of the cases. With serial imaging no false positive cases were found. The sensitivity of the technique for the detection of full thickness infarction is 95 per cent. Though it drops to 70 per cent when subendocardial infarctions are judged by standard electrocardiographic criteria, some of these apparent false negatives may represent severe ischaemia without infarction.

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