ACCUMULATION OF ^{99m}Tc-GLUCOHEPTONATE IN ACUTELY INFARCTED MYOCARDIUM

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The distribution of ^{99m}Tc-glucoheptonate in normal mice and its accumulation in acutely infarcted myocardium were studied in animals. Rapid blood clearance and low concentration of the tracer in normal myocardium were found in tissue distribution studies performed in mice. Experimental myocardial infarction was performed in nine dogs. Four hours after the intravenous injection of ^{99m}Tc-glucoheptonate the uptake ratio of the myocardial infarcted area to normal myocardium was 20:1; to blood, 9:1; and to lung, 6:1. The greatest concentration of radiopharmaceutical in the infarcted tissue was noted in areas that had 20–40% of normal perfusion. Regions of infarction were clearly defined by external gamma scintigraphy. Clinical investigation of this tracer in humans appears warranted.

Several radioactive tracer techniques have been advocated for the diagnosis of acute myocardial infarction: (A) gated blood-pool studies detect myocardial infarctions by demonstrating them as areas of akinesis or dyskineses (*1,2*); (B) radiopotassium and its analogs, which concentrate in the myocardium in proportion to blood flow, demonstrate infarcts as areas of reduced tracer uptake (*3–6*); and (C) radioactive tracers such as ^{99m}Tc-tetracycline (*7,8*) and ^{99m}Tc-pyrophosphate, which accumulate in the acutely infarcted myocardial tissue, show the infarct as an area of increased activity (*9,10*). Camin observed that ^{99m}Tc-glucoheptonate, a ^{99m}Tc complex of seven-carbon organic acids, concentrated in heat-damaged myocardia of rats (*11*). Studies in our laboratory and that of Fink/Bennett showed accumulation of ^{99m}Tc-glucoheptonate in the myocardium after ligation of a coronary artery (*12,13*). The present report describes the biologic behavior of this tracer in normal mice, its accumulation in dog myocardium after coronary artery ligation, and the relation of tracer concentration to regional perfusion.

METHODS

Mouse tissue distribution. Twenty-four laboratory mice were injected with 2 μCi of ^{99m}Tc-glucoheptonate and then sacrificed at 2, 5, 10, and 30 min and 1, 4, 6, and 24 hr. Three mice were sacrificed at each interval. The heart, lungs, liver, stomach, spleen, kidneys, gastrointestinal tract, carcass, muscle, and blood were counted in a well counter against known standard solutions of comparable volume. Correction of the carcass count was made for activity remaining in the tail.

Dogs with acute myocardial infarction. Nine mongrel dogs weighing from 30 to 40 lb were anesthetized with sodium pentobarbital, intubated, and placed on a respirator. A left lateral thoracotomy was performed. The pericardium was retracted and the anterior descending coronary artery was firmly tied off. Distal to the ligature a localized area of persistent ventricular akinesis and discoloration was seen, indicating severe persistent myocardial ischemia and presumably subsequent infarction. Two hours after ligation, 5 mCi of ^{99m}Tc-glucoheptonate was injected intravenously. In four of the nine dogs, a catheter was placed in the left atrium and 30 min after the glucoheptonate injection 50 μCi of ^{85}Sr-labeled carbonized microspheres was injected through the catheter to determine the relative perfusion to various areas of the myocardium. All nine dogs were sacrificed and the hearts were removed 4 hr after glucoheptonate injection. Samples (1–2 gm) were obtained at the center and edge of the infarcted area along with representative portions of normal right and left ventricular tissue and samples of blood, lung, liver, and stomach. These samples were weighed and then assayed in a well counter to determine the concentration of each tracer. Concentrations of ^{99m}Tc-glucoheptonate (expressed as counts/min/gm of tissue) were calculated for in-

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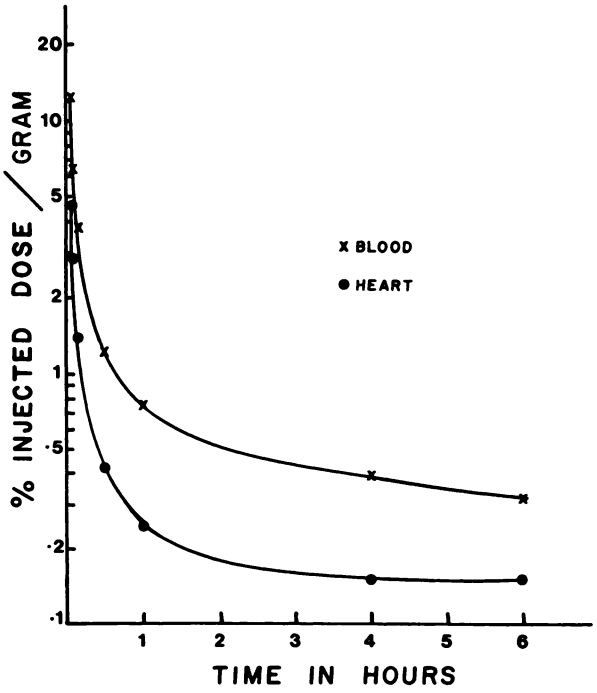

FIG. 1. Percent injected dose of ^{99m}Tc-glucoheptonate as function of time after intravenous injection in heart and blood.

TABLE 1. RATIOS OF MAXIMAL ^{99m}Tc-GLUCOHEPTONATE UPTAKE IN THE INFARCT TO UPTAKE IN NORMAL TISSUES

Dog	Infarct to normal left ventricle	Infarct to blood	Infarct to lung
A	16:1	7:1	4:1
B	19:1	8:1	3:1
C	9:1	2:1	3:1
D	32:1	17:1	9:1
E	10:1	4:1	3:1
F	32:1	15:1	11:1
G	9:1	4:1	3:1
H	28:1	10:1	9:1
I	25:1	10:1	11:1
Average	20:1	9:1	6:1

TABLE 2. AVERAGE PERCENT DOSE $\times 10^{-3}$ OF ^{99m}Tc-GLUCOHEPTONATE PER GRAM OF TISSUE

Dog	Maximum myocardial infarct	Normal left ventricle	Blood	Lung
C	2.8	0.3	1.4	1.0
D	8.3	0.3	0.5	1.0
E	2.7	0.3	0.7	0.8
F	16.4	0.5	1.1	1.5
G	4.4	0.5	1.1	1.7
H	10.9	0.4	1.1	1.2
I	8.7	0.4	0.9	0.8
Average	7.7	0.38	1.0	1.1

farcted left ventricle, normal left ventricle, blood, and lungs. Concentration ratios of infarct-to-normal left ventricle, infarct-to-blood, and infarct-to-lung were calculated. The ratio of infarct-to-normal left ventricle, determined by glucoheptonate, was compared with the corresponding blood flow determined by microsphere distribution.

In two additional mongrel dogs, closed-chest coronary embolism was produced by the introduction of 0.1–0.2 ml of elemental mercury under fluoroscopic guidance. Two hours later, 5 mCi of ^{99m}Tc-glucoheptonate was injected intravenously. Images of the chest were obtained in the left lateral position at 4 and 24 hr after injection on a Searle Radiographics Pho/Gamma III scintillation camera using a 4,096-hole, high-sensitivity, parallel-hole collimator. Images (4 and 24 hr) were also obtained on a control dog without a myocardial infarction.

RESULTS

Mouse distribution data. The initial half-time for blood disappearance of the glucoheptonate was less than 2 min. At 1 hr after intravenous injection, less than 0.3% glucoheptonate was concentrated in the myocardium (Fig. 1). At this time the greatest concentrations were in the gastrointestinal tract (8.43%), kidneys (4.59%), and liver (2.22%).

Concentration of ^{99m}Tc-glucoheptonate in infarcted myocardium in dogs. From the glucoheptonate tissue-assay results the maximum concentrations for the infarcted left ventricle were picked out; ratios were then determined between these infarcted values and normal left ventricle, blood, and lung. Averaging each type of ratio for the nine dogs, the results were as follows: infarct-to-ventricle, 20:1 (range, 9:1–32:1, see Table 1); infarct-to-blood, 9:1 (range, 2:1–17:1); and infarct-to-lung, 6:1 (range, 3:1–11:1).

The average maximum activity per gram of infarcted myocardium was 7.7×10^{-3}% of the injected dose with a range of 2.2×10^{-3} to 16.4×10^{-3}%. The average injected activity per gram of normal left ventricle was 0.3×10^{-3}%; of blood, 1.0×10^{-3}%; and of lung, 1.1×10^{-3} % (Table 2).

In the four dogs receiving left atrial injections of ^{85}Sr-labeled carbonized microspheres, capillary perfusion of 1–2 gm sections of infarcted tissue was compared with perfusion of the normal left ventricle. The perfusion for the normal left ventricle was taken as 100%. Almost zero perfusion was noted at the infarct center in two of the dogs. The other two dogs had perfusions of 8% and 27% of normal left ventricle at the infarct center. Ratios of the concentration of ^{99m}Tc-glucoheptonate in infarcted myocardium to

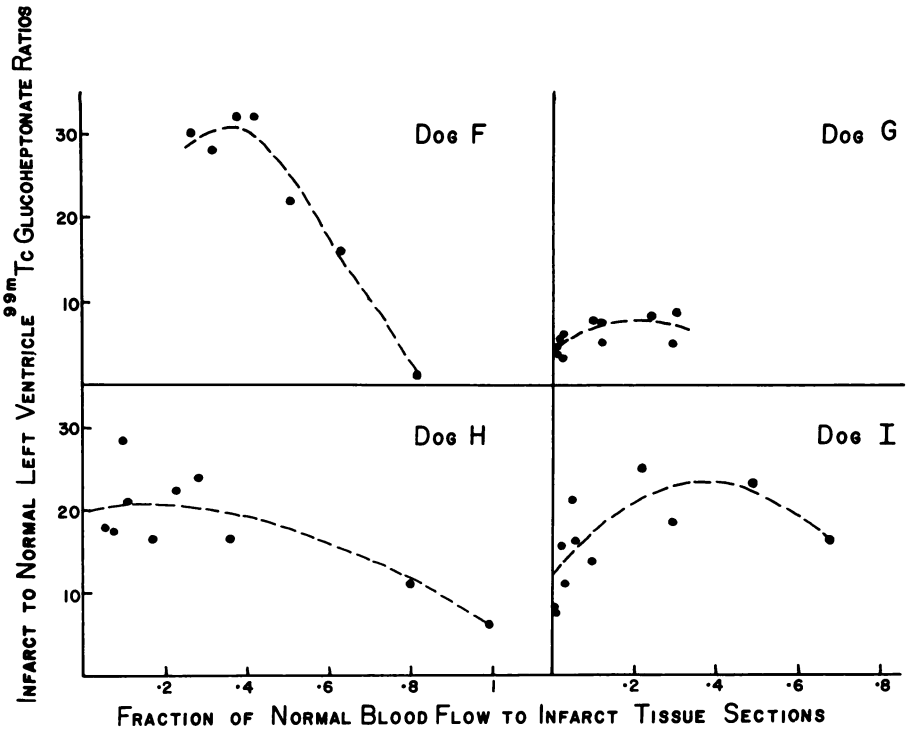

FIG. 2. Infarct-to-normal left ventricle ^{99m}Tc-glucoheptonate uptake ratios as function of fraction of normal blood flow to damaged area for four dogs.

that in normal myocardium were plotted as a function of the fraction of normal blood flow (Fig. 2). In each of the four dogs, maximum ^{99m}Tc-glucoheptonate uptake was noted in sections that received from 20–40% of normal flow. Outside these areas there was less accumulation of the tracer.

External imaging. The area of infarction could be discerned at 6 hr by external gamma scintigraphy but was better defined on the image obtained at 24 hr. Figure 3 shows left lateral scintigrams of the chest obtained 24 hr after ^{99m}Tc-glucoheptonate injections in the control dog and in the two dogs with closed-chest infarctions. The dome of the liver is noted in all three scintigrams. The two dogs with infarction show tracer uptake above the liver corresponding to the areas of infarction. No such activity is seen in the control dog.

Toxicity. The acute LD_{50} of stannous glucoheptonate administered intravenously in mice is 1,500 mg/kg. Daily intravenous injections of 800, 400, and 80 mg/kg for 15 days produced no ill effects (data supplied by New England Nuclear Corp.). Since the average dose of glucoheptonate is less than 100 mg/70-kg man, it appears that this agent will be safe for repetitive studies in patients.

DISCUSSION

This study has demonstrated that ^{99m}Tc-glucoheptonate accumulates in acutely infarcted and ischemic

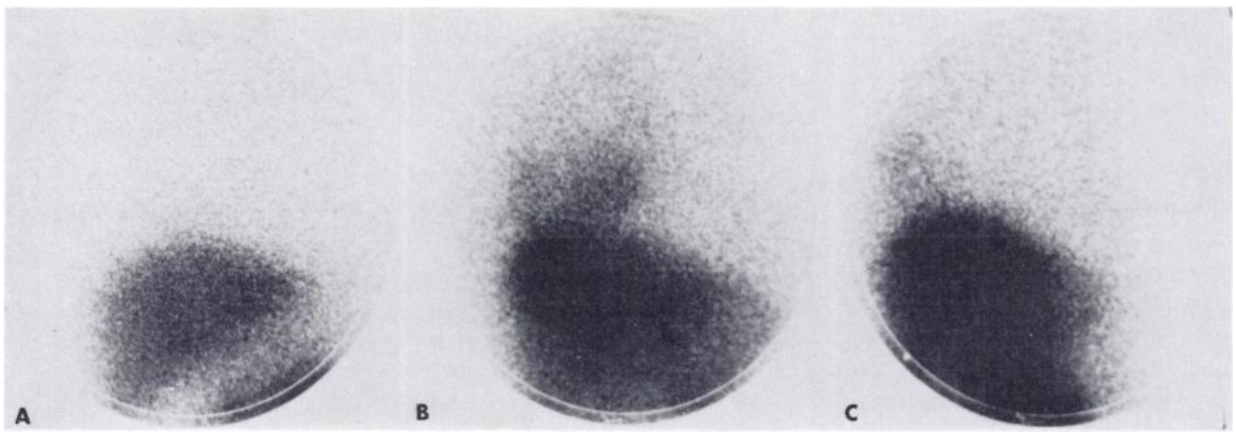

FIG. 3. Left lateral view scintigraphs 24 hr after injection of one control dog (A) and two dogs with experimental myocardial infarction (B and C). Areas of increased tracer uptake corresponding to areas of myocardial infarction are noted above dome of liver.

myocardium in higher concentrations than in normal myocardium and blood. Maximal tracer concentration in myocardium occurred distal to the coronary artery ligature, especially in areas that still had small amounts of blood flow. Myocardium with essentially no flow showed a somewhat lower, although substantial, relative uptake of ^{99m}Tc-glucoheptonate. This finding was unexpected since the mechanisms for concentration of ^{99m}Tc-tetracycline suggest that the tracer binds to the irreversibly damaged tissue that occurs in zones of lower flow (*14*). Similarly, the mechanism postulated for ^{99m}Tc-pyrophosphate uptake suggests that the tracer binds to irreversibly damaged mitochondria (*9*). These proposed mechanisms raise the possibility that the highest concentration of tracer would occur in regions of greatest flow reduction. On the other hand, ^{99m}Tc-glucoheptonate achieved its peak concentration in regions with some remaining flow, suggesting that delivery of the tracer is best accomplished by the vascular system rather than by diffusion. Two factors appear to play a synergistic role in causing ^{99m}Tc-glucoheptonate to concentrate in tissue: there must be sufficient residual or collateral flow to the affected region to present the tracer to the tissue, and there must be an alteration in the myocardial cell that either makes it permeable to the tracer or causes the tracer to be actively transported across the membrane.

Technetium-99m-glucoheptonate compares favorably with other recently introduced radioactive tracers that localize in myocardial infarction. The ratios of infarct-to-normal left ventricle and infarct-to-blood are superior to those noted with ^{99m}Tc-tetracycline and are approximately equal to those noted with ^{99m}Tc-pyrophosphate (*7,9*). The absence of overlying skeletal activity avoids the potential problem often seen when ^{99m}Tc-pyrophosphate is used as an infarct-imaging agent (*9,10*).

The peak concentration of the tracer in the infarct, compared with surrounding structures, appears to occur earlier with glucoheptonate than with either pyrophosphate or tetracycline. Although tetracycline concentrates in the infarct fairly rapidly, about 24 hr are required for sufficient blood clearance to permit satisfactory imaging. Pyrophosphate can be imaged within 1 hr after tracer administration although the best images are not obtained until 24–48 hr after infarction. In a study on ^{99m}Tc-glucoheptonate for infarct imaging by Fink/Bennett, et al (*13*), peak infarct-to-normal myocardial ratios of 21:1 and 16:1 were found at 24 hr that compare with the average ratio of 21:1 that we observed 6 hr after infarction (4 hr after the tracer injection). The images obtained at 22 hr after injection possessed target-to-background ratios superior to those obtained at 4 hr. Imaging time, however, was quite long when imaging was performed 22 hr after tracer injection. Preliminary data in patients with acute myocardial infarction indicate that an interval of 2–5 hr between injection and imaging gives target-to-background ratios adequate for external scanning. From these data it appears that for imaging acute myocardial infarction ^{99m}Tc-labeled glucoheptonate may offer an advantage over other tracers currently under clinical investigation.

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