TIME COURSE OF ^{99m}Tc(Sn)-TETRACYCLINE UPTAKE IN EXPERIMENTAL ACUTE MYOCARDIAL INFARCTION

B. Leonard Holman and Franklin G. Zweiman

Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts

The relative concentration of ^{99m}Tc(Sn)-tetracycline in infarcted myocardium was determined as a function of time after coronary artery occlusion in mongrel dogs. The concentration ratio (infarct-to-normal myocardium) was highest within the first 2 days after occlusion (6.7 ± 0.5 at 1 day and 8.0 ± 1.6 at 2 days). By 1 week after occlusion the ratio had fallen to 1.9 ± 0.2. In the region of infarction, the concentration of ^{99m}Tc(Sn)-tetracycline was homogeneously distributed across the inner three-quarters of the myocardial wall; the outer quarter of the wall had substantially lower concentrations during the first 5 days after infarction. The present study confirms the observation suggested in initial investigations in man that scintigraphy performed with ^{99m}Tc(Sn)-tetracycline will distinguish between acute and chronic myocardial infarctions.

Technetium-99m-(Sn)-tetracycline is sequestered by acutely infarcted myocardium (*1*). Initial clinical studies (*2*) indicate high accuracy in detecting the acute infarct using external imaging after intravenous injection of this radiotracer. An advantage of this technique over scintigraphic techniques that assess regional myocardial perfusion is its ability to differentiate between acute and chronic infarction. Although clinical studies indicated that maximal uptake occurred early in the course of infarction, it was difficult to determine the time course exactly since the number of sequential studies that could be performed was limited. To estimate the relative ^{99m}Tc(Sn)-tetracycline concentration in older infarcts, we determined the time course of the tracer's uptake as a function of time after coronary artery occlusion in dogs.

In addition, there has been some question regarding the distribution of the labeled tetracycline across the myocardial wall in regions of infarction. Studies with unlabeled tetracycline suggested that the pharmaceutical concentrated primarily along the borders of the infarct (*3*). On the other hand, acute myocardial infarct scintigraphy performed with ^{99m}Tc(Sn)-tetracycline indicated a more uniform uptake of the radiotracer throughout the infarct (*2*). To resolve this question, we determined the concentration gradient of this tracer across the myocardial wall.

METHODS

Technetium-99m-(Sn)-tetracycline was prepared by New England Nuclear Corp. There were 10–20 mg of tetracycline in the final dose administered to each animal.

Twenty-four mongrel dogs (15–22 kg) were anesthetized with phenobarbital (30 mg/kg). The right carotid artery was exposed. A catheter guidewire system, with 5 mm of occluded catheter material placed on the tip of the guidewire, was introduced into the artery. Under fluoroscopic control, the left coronary ostium was selectively entered. After the 5-mm plug was positioned in the left main coronary, the guidewire was pulled back, leaving the plug in the artery.

Technetium-99m-(Sn)-tetracycline (10–15 mCi) was injected intravenously at various times after occlusion: 1 hr (six dogs), 24 hr (four dogs), 3–5 days (five dogs), 7–9 days (three dogs), and 13–14 days (four dogs).

The animals were killed by injecting concentrated potassium chloride solution intravenously 24 hr after administration of the radiopharmaceutical. The hearts were excised and sections (1–2 gm) were obtained from the tissue distal to the coronary occlusion and from tissue distal to a patent coronary

Received April 30, 1975; revision accepted June 7, 1975.

For reprints contact: B. Leonard Holman, Dept. of Radiology, Harvard Medical School, 25 Shattuck St., Boston, Mass. 02115.

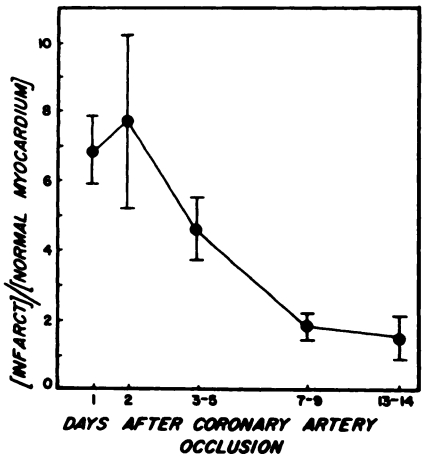

FIG. 1. Concentration ratio of ^{99m}Tc(Sn)-tetracycline between infarcted and normal myocardium as function of time after coronary artery occlusion (± s.e.m.).

artery branch. Each full-thickness tissue section was cut into four sections (endocardial I, endocardial II, epicardial II, and epicardial I), so that endocardial I was the innermost quarter of the myocardial wall and epicardial I was the outermost quarter. A portion of each tissue specimen was set aside for histologic examination. The remainder of the specimen was assayed in a gamma well counter and the counting rate per gram of tissue was determined.

Optical microscopy of the histologic sections following staining with hematoxylin and eosin was performed to confirm the presence of myocardial infarction in the tissue distal to the occlusion and to confirm that tissue distal to the patent vessel showed no evidence of pathologic changes.

RESULTS

The relative concentration of ^{99m}Tc(Sn)-tetracycline in infarcted myocardium as a function of time is shown in Fig. 1. The highest concentration ratio between infarcted and normal myocardium was seen within the first 2 days after coronary artery occlusion: 6.7 ± 0.5 s.e.m. (range, 5.1–8.4) 1 day, and 8.0 ± 1.6 s.e.m. (range, 4.7–12.2) 2 days after occlusion. The concentration ratio fell 43% by 3–5 days after occlusion [4.5 ± 0.7 s.e.m. (range, 2.0–7.0)] compared to the second day. By 1 week after occlusion, the ratio had fallen to 1.9 ± 0.2 s.e.m. (range, 1.4–2.1) and, by 2 weeks, to 1.5 ± 0.2 s.e.m. (range, 0.9–2.0).

The distribution of the radiotracer was relatively evenly divided within the two endocardial (I and II) and inner epicardial (II) sections (Fig. 2). The concentration of the outer epicardial section was 53.8% of the mean of the inner three fractions at 2 days after occlusion, but this approached the concentration of the inner three-quarters of the wall as time progressed (64.1% at 3–5 days, 72.4% at 7–9 days, and 96.3% at 13–14 days).

DISCUSSION

There is a very rapid decrease in the concentration ratio of ^{99m}Tc(Sn)-tetracycline between infarcted and normal myocardium as a function of time after coronary artery occlusion in the dog. As a result, infarct detection after the administration of this radiotracer should be most sensitive within the first 2 days following occlusion. At 3–5 days the concentration ratio may not be sufficiently high to

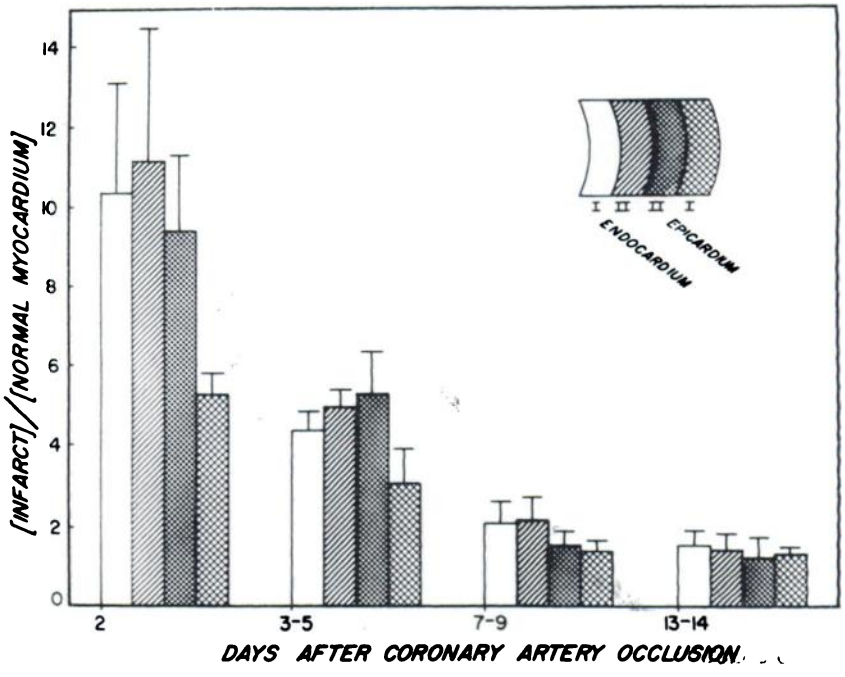

FIG. 2. Gradient of ^{99m}Tc(Sn)-tetracycline concentration ratio across myocardial wall as function of time after coronary artery occlusion (± s.e.m.).

result in an abnormal scintiscan. By 1 week following coronary artery occlusion, the infarct-to-normal ratio was less than 2:1.

This study would suggest that uncomplicated infarcts older than 6 days should have insufficient concentration ratios between infarcted and normal myocardium to result in abnormal scintigraphy. Thus, an abnormal scintiscan obtained 7 days or more following onset of symptoms would indicate either reinfarction or further extension of the infarct. Since some infarcts have concentration ratios of 7:1 as late as 3–5 days after occlusion, an abnormal scan at this time does not necessarily indicate reinfarction.

The radiopharmaceutical is fairly uniformly distributed throughout the inner three-quarters of the myocardial wall. A number of investigators have found a disproportionate reduction in subendocardial flow in ischemic regions (*4–6*). This results from redistribution of blood from the endocardial layers that are most necrotic to the surviving epicardial ones (*7*). Thus, the greatest concentration of ^{99m}Tc(Sn)-tetracycline is found in that portion of the wall with the greatest degree of tissue necrosis.

Initial studies of unlabeled tetracycline distribution in cases of acute infarction indicated fluorescence primarily around the borders of the infarct (*3*). The present study showed that distribution of the tetracycline is uniform throughout the inner three-quarters of the myocardial wall. This discrepancy results either because unlabeled and ^{99m}Tc(Sn)-tetracycline distribute differently in the infarcted myocardium or because the binding of tetracycline in the region of infarction alters its ability to fluoresce. The mechanism by which ^{99m}Tc(Sn)-tetracycline is sequestered in the infarcted myocardium is unknown, as is the chemical form of the radiolabel after it becomes fixed to the damaged tissue.

ACKNOWLEDGMENT

This work was supported in part by USPHS Grants HL 17739, HL 11668, GM 01910, and GM 18674.

REFERENCES

1. HOLMAN BL, DEWANJEE MK, FLIEGEL CP, et al: Detection and localization of experimental myocardial infarction with ^{99m}Tc-tetracycline. *J Nucl Med* 14: 595–599, 1973

2. HOLMAN BL, LESCH M, ZWEIMAN FG, et al: Detection and sizing of acute myocardial infarcts with ^{99m}Tc(Sn)-tetracycline. *N Engl J Med* 291: 159–163, 1974

3. MÁLEK P, KOLC J, ZÁSTAVA VL, et al: Fluorescence of tetracycline analogues fixed in myocardial infarction. *Cardiologia* 42: 303–318, 1963

4. BECKER LC, FERREIRA R, THOMAS M: Mapping of left ventricular blood flow with radioactive microspheres in experimental coronary artery occlusion. *Cardiovasc Res* 7: 391–400, 1973

5. BECKER LC, FORTUIN NJ, PITT B: Effect of ischemia and antianginal drugs on the distribution of radioactive microspheres in the canine left ventricle. *Circ Res* 28: 263–269, 1971

6. MOIR TW, DEBRA DW: Effect of left ventricular hypertension, ischemia, and vasoactive drugs on the myocardial distribution of coronary flow. *Circ Res* 21: 65–74, 1967

7. HIRZEL HO, NELSON GR, SONNENBLICK EH, et al: Redistribution of collateral blood flow from necrotic and surviving myocardium within 24 hours following acute coronary occlusion. *Clin Res* 23: 187, 1975

NOTICE OF NEXT ABNM CERTIFYING EXAMINATION

The American Board of Nuclear Medicine announces that its Fourth Certifying Examination in Nuclear Medicine will be held on Saturday, September 18, 1976.

The 1976 examination will be the last given under the present requirements of a combination of training and experience. Beginning with the 1977 examination, it will be necessary for candidates to have had two years of creditable performance in an accredited nuclear medicine residency.

Applications for the 1976 examination are available from:

The American Board of Nuclear Medicine
475 Park Avenue South
New York, New York 10016
Telephone (212) 889-0717

Applications should be accompanied by an application fee of $400 and submitted by the deadline of June 1st, 1976.