Tissue Distribution Studies with Radioactive Manganese: A Potential Agent for Myocardial Imaging

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Manganese, a trace metal, is known to localize in mitochondria. Because mitochondria are abundant in heart muscle, the possible utility of radioactive manganese as a myocardial imaging agent was examined in 25 rats and six dogs. Myocardial uptake of Mn-54 in rats was found to exceed that of thallium-201; myocardium-to-blood ratios averaged 306:1 versus 48:1 for Tl-201. In the dog, uptake of Mn-54 by ischemic myocardium was reduced by 17–75% compared with normal myocardium. Thus, radioactive manganese appears promising as an intravenous myocardial imaging agent, and might be useful in studying the function of myocardial mitochondria by external imaging.

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Manganese is a trace metal whose normal concentrations in whole blood range from 8–9 μg per liter (*1*). It is primarily an intracellular ion (*2*), located mainly in the mitochondria (*3–5*). Distribution studies in a rat tumor model have suggested high heart uptake (*6,7*). Accordingly, an investigation of manganese as a potential myocardial imaging agent was initiated.

METHODS

Twenty-five Sprague-Dawley rats, each weighing approximately 250 g, were injected with 10 μCi carrier-free $^{54}MnCl_2$. Groups of five rats each were sacrificed at 0.5, 1, 2, 4, and 6 hr. The heart, liver, and one kidney were immediately excised, washed once in water and once in 10% formaldehyde solution, blotted dry, weighed, and the activity of Mn-54 measured in an autogamma well counter. For comparison, 10 μCi of carrier-free $^{201}TlCl$* was administered intravenously to each of 34 rats and its uptake and distribution studied in a similar manner.

In addition, the myocardial uptake and organ distribution of Mn-54 was examined in six dogs that ranged in weight from 21 to 35 kg (mean 27 kg). Each animal was injected intravenously with an average of 9.2 μCi/kg. Two dogs were sacrificed 30 min following the intravenous administration of Mn-54 and four dogs at 4 hr. In two of the dogs sacrificed at 4 hr, ligation of the middle third of the left anterior descending coronary artery had been performed three days before injection. The organs to be counted were weighed and tissue samples (approximately 1 g) removed for counting. The hearts of the two dogs with experimentally induced coronary occlusion were sliced into several cross sections about 1 cm thick. Infarcted myocardium was readily visible grossly. Each slice was then divided into segments weighing about 1 g each (Fig. 1) and the uptake of Mn-54 determined.

RESULTS

In rats, the initial organ distribution of Mn-54 and Tl-201 and their respective redistribution with

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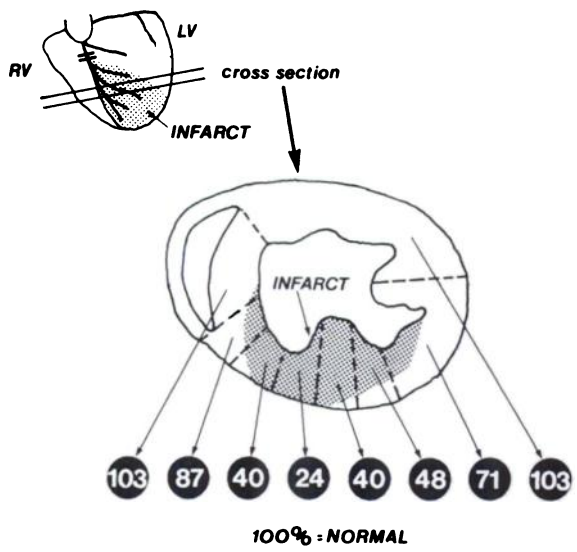

FIG. 1. Cross section of dog heart showing regional concentrations of Mn-54 in normal and infarcted myocardium 4 hr after administration of Mn-54. Shaded area indicates region of infarct. Concentration of Mn-54 in normal myocardium is normalized to 100%. Concentration of Mn-54 in center of infarct is only 24% of normal.

time are compared in Table 1. Thirty minutes after injection, myocardial concentrations of Mn-54 averaged 1.86 ± 0.1% (SEM) of injected dose/g and of Tl-201, 1.43 ± 0.12% dose/g. Within the next 5.5 hr, myocardial concentrations of Tl-201 decreased by 67% whereas those of Mn-54 decreased only by 45%. This resulted in markedly higher myocardium-to-blood ratios for Mn-54 (306:1) than for Tl-201 (26:1) at 4 hr after administration.

While both ions achieved similar concentrations in the kidney, they differed markedly with respect to uptake by the liver. Hepatic concentrations for Tl-201 ranged from 0.21 ± 0.03 to 0.40 ± 0.03% injected dose/g or 4.2–4.0% dose in the whole liver during the study period. The hepatic uptake of Mn-54 was significantly higher, ranging from 2.98 ± 0.16 to 3.74 ± 0.24% injected dose/g liver or from 22 to 28% injected dose/total liver.

In the experiments with dogs, the distribution of Mn-54 was similar to that observed in the rats and is shown in Table 2. The uptake of Mn-54 by the heart averaged 2.5% at 30 min and 2.1% at 4 hr after injection. Blood levels in the dogs decreased much as in the rats, and myocardium-to-blood ratios in the four dogs sacrificed at 4 hr averaged 74.6:1.

Figure 1 shows the regional myocardial distribution of Mn-54 in a cross section through the left ventricle obtained from a dog with an experimentally induced myocardial infarction. Manganese-54 concentrations within the infarcted myocardium were markedly reduced. In the two dogs with experimental myocardial infarctions, concentrations of Mn-54 in the ischemic zone were reduced by an average of 47% (ranging from 17 to 75%) compared with normal myocardium.

DISCUSSION

The results of this study demonstrate a high affinity of manganese for myocardium and suggest the potential usefulness of radioactive manganese as a myocardial imaging agent. In rats, the amount of manganese accumulated by the myocardium and the myocardium-to-blood ratios, markedly exceeded the analogous values obtained for Tl-201, the current myocardial imaging agent of choice. Myocardium-to-blood ratios averaged 306:1 at 4 hr after administration. At this time, blood levels for Mn-54 had significantly decreased, whereas no significant change in myocardial concentrations had occurred, compared with the 2-hr values. The underlying mecha-

TABLE 1. TISSUE CONCENTRATIONS* OF Mn-54 AND Tl-201 IN RATS

Time after injection (hr)		0.5	1.0	2.0	4.0	6.0
Blood conc.	Mn-54	0.043 ± 0.002	0.020 ± 0.001	0.013 ± 0.002	0.005 ± 0.001	0.006 ± 0.001
(±1 SEM)	Tl-201	0.030 ± 0.001	0.027 ± 0.002	0.022 ± 0.002	0.022 ± 0.003	0.018 ± 0.001
Myocardial conc.	Mn-54	1.86 ± 0.10	1.92 ± 0.13	1.43 ± 0.11	1.53 ± 0.07	1.02 ± 0.09
(±1 SEM)	Tl-201	1.43 ± 0.12	1.13 ± 0.07	0.87 ± 0.08	0.56 ± 0.02	0.47 ± 0.04
Liver conc.	Mn-54	3.74 ± 0.24	2.98 ± 0.16	3.75 ± 0.28	3.51 ± 0.42	3.01 ± 0.24
(±1 SEM)	Tl-201	0.34 ± 0.03	0.40 ± 0.03	0.33 ± 0.03	0.28 ± 0.02	0.21 ± 0.02
Kidney conc.	Mn-54	4.23 ± 0.24	4.36 ± 0.24	3.78 ± 0.15	3.88 ± 0.06	3.31 ± 0.33
(±1 SEM)	Tl-201	3.21 ± 0.24	3.33 ± 0.29	4.17 ± 0.35	4.25 ± 0.26	4.90 ± 0.80
Myocardium/blood	Mn-54	43.3	96.0	110.0	306.0	170.0
	Tl-201	47.7	41.9	39.5	25.5	26.1
Myocardium/liver	Mn-54	0.50	0.64	0.38	0.44	0.34
	Tl-201	4.21	2.83	2.64	2.00	2.24

* Expressed as percentages of the total dose/g tissue.

TABLE 2. UPTAKE OF Mn-54 IN DOGS

	Blood sample	Total	Myocardium RV	Myocardium Septum	Myocardium LV	Lung	Liver	Kidney	Muscle
30 min after injection (two dogs)									
% Dose/organ	—	2.50	—	—	—	—	—	—	—
% Dose/g tissue	—		0.013	0.015	0.017	—	—	—	—
4 hr after injection (four dogs)									
% Dose/organ (±1 SEM)	—	2.07 ±0.08				2.12 0.01	41.35 ±6.43	8.49 4.20	
% Dose/g tissue (±1 SEM)	0.00017 ±0.00003		0.012 ±0.002	0.014 ±0.003	0.012 ±0.002	0.009 ±0.001	0.054 ±0.012	0.135 ±0.015	0.0010 ±0.0002

nism for this late "plateau" is not clear but may be at least in part related to individual variations. Even if Mn-54 concentrations had shown a continuous fall from 2 to 6 hr, however, myocardium-to-blood ratios at 4 hr would still have been greater than 200:1, and thus significantly higher than similar ratios observed for Tl-201, which averaged 51:1 at 10 min (*8*), and 47.7:1 and 25.5:1 at 30 min and 4 hr, respectively. Myocardium-to-blood ratios were somewhat lower in the dogs but still exceeded those reported previously for Tl-201 (*8*). In the four dogs, myocardium-to-lung ratios averaged 1.33 on a per gram basis. Assuming a specific gravity of 1.00 for myocardium and 0.33 for lung tissue (*9*), however, these ratios become 4:1 on a per unit volume basis and should be sufficient for proper delineation of the myocardium by clinical imaging. Clearly the imaging possibilities should be carefully explored.

As mentioned previously, manganese is considered a trace metal, with amounts of 12–20 mg present in man (*10*). In humans, the highest concentrations of manganese have been observed in the liver, kidney, and pituitary gland (*2,11*). In our study, total uptake of manganese by the liver ranged from 30% to 50% of the total injected dose. Because of the proximity of this organ to the heart, the high liver uptake could limit the use of radioactive manganese for conventional two-dimensional imaging. Similarly, the relatively high radiation dose to the liver could represent a serious disadvantage for the use of radioactive manganese. Absorption of manganese usually occurs through the small intestine and excretion through the gastrointestinal mucosa, biliary tract, and, to some degree, through pancreatic secretions (*12–15*). The presence of an enterohepatic circulation has been postulated. The elimination of manganese is accomplished almost exclusively through the gastrointestinal tract, with virtually none excreted through the kidney (*16,17*).

The average daily dietary intake of manganese in the United States is about 2.4 mg (*18*). It is present largely in organic form and its absorption, therefore, is variable. In the plasma, manganese is bound to a specific globulin, transmanganin (*19*) which becomes involved in metabolic pathways (*20,21*).

The data suggest manganese as a potentially useful heart imaging agent, provided a suitable isotope of the element is available. Obviously, the Mn-54 used in this study is not suitable for clinical imaging because of its long physical half-life (300 days) and high-energy gamma photons (835 keV). But other radioisotopes of manganese may be useful. For example, Mn-52, a positron emitter, could permit three-dimensional myocardial imaging by means of emission tomography, including a quantitative assessment of in vivo myocardial metabolism. This manganese isotope has a half-life of 5.7 days. The abundance of high-energy photons together with the relatively long physical half-life, however, make Mn-52 unsuitable for clinical studies. On the other hand, Mn-52m, although it emits high-energy gammas, gives a greater abundance of 511-keV annihilation photons (193%). Because of its rather short physical half-life of 22 min, the radiation dose should be small with this isotope, which might well be useful for clinical studies. We believe, therefore, that manganese merits further study as a diagnostic myocardial imaging agent.

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FOOTNOTE

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