INVESTIGATIVE NUCLEAR MEDICINE

The Effects of Deferoxamine Mesylate on Gallium-67 Distribution in Normal and Abscess-Bearing Animals: Concise Communication

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Deferoxamine mesylate (DFO), given to rabbits 20 min after gallium-67 citrate, induces prompt and rapid urinary excretion of Ga-67 activity with concommitant decrease in blood and muscle activity. When DFO is given after 2 hr or later, the effect is smaller (15% decrease in blood activity compared with 50%). In abscess-bearing rats the same effect was observed: DFO accelerated the Ga-67 blood clearance by increasing urinary excretion. Tissue-distribution studies and direct counting of abscesses showed that DFO lowers Ga-67 activity in all organs as well as in the abscess if given 2 or 4 hr after Ga-67 citrate, but the abscess-to-blood ratio increases. At 24 hr after Ga-67 citrate, DFO administration causes an improvement in the ratios of abscess-to-blood and abscess-to-normal tissue. Thus, DFO could be used to decrease the radiation burden from Ga-67 citrate after imaging has been performed, and also to increase the target-to-nontarget ratio.

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The use of Ga-67 citrate for tumor and abscess detection is hindered by the slow blood clearance, high soft-tissue activity, masking by large-bowel excretion, and relatively high radiation dose (*1*). It has been shown that the administration of iron dextran to the experimental animal lowers blood and soft-tissue activity, increases abscess-to-muscle ratio, and increases gallium excretion (*2*). This effect is probably due to displacement of gallium from its transferrin-bound complex, thus making gallium available for excretion. This method, however, is not applicable to patients because of the large amount of iron needed to attain the effect. Deferoxamine mesylate (DFO), isolated from microorganisms of the Actinomycetes group, is a highly potent and specific iron-chelating agent (*3*), which can be used for treatment of iron overload (*4,5*) in doses of up to 425 mg/kg without significant untoward effect (*4,7*). After our preliminary report on the effect of DFO on Ga-67 distribution (*7*), this substance was further investigated in tumor-bearing animals (*8,9*). Its possible effect on Ga-67 distribution was studied in rabbits and in abscess-bearing rats.

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MATERIALS AND METHODS

Tissue-distribution studies were performed in 12 random-bred female rabbits weighing 1.2–1.5 kg. Ga-67 citrate, 0.3 mCi/kg body weight, was injected intravenously. Twenty minutes later, 50 mg deferoxamine mesylate* in 1 ml 0.9% saline was injected intravenously into six of the 12 animals. The other six animals, serving as controls, were given 1 ml saline instead of DFO. Four hours after radiogallium administration, the animals were killed by an overdose of pentothal; and samples of blood, liver, spleen, kidney, muscle, and bone were obtained. Ga-67 activity in samples was measured in a well counter and values were expressed as percentage of injected dose/gram of tissue.

In vivo distribution studies were carried out in 1.0–1.2 kg female random-bred rabbits using ketamine HCl/promazine HCl anesthesia. Butterfly needles were placed into ear veins of a pair of rabbits positioned side-by-side

under a 37-PM-tube gamma camera, equipped with medium-energy collimator. The 93- and 184-keV peaks were used, with 20% and 30% windows, respectively. A simultaneous bolus injection of Ga-67 citrate (0.3 mCi/kg) was given to the two animals and acquisition was started on the magnetic disc of a dedicated minicomputer system. A 128 × 128 matrix was used, at a rate of two frames per minute. After a 30-min baseline acquisition, 50 mg DFO in 1 ml saline were injected into the experimental animals, while the controls received 1 ml of saline only. In the first experiments, acquisition was continued for 180 min, but later a 30-min period was found adequate to observe the DFO action. Small-sized animals were used so that the heart, kidneys, and bladder of both animals could be included in the field of view. Regions of interest over the heart, left kidney, bladder, and background were drawn and time/activity curves were generated. The right kidney was not included because of liver superposition. A background area was selected in the right flank between liver and bony structures of pelvis. In addition, three paired experiments each were carried out by varying the time intervals between the injection of radiogallium and DFO as follows: 2, 4, 5, and 24 hr.

Ga-67 whole-body retention studies were performed in six rabbits using the same doses of Ga-67 citrate and DFO as in the previous experiments. The DFO was injected into the experimental animals 20 min after Ga-67-citrate, and an equivalent volume of saline was given to the controls. Whole-body counting was performed with a gamma camera using a medium-energy collimator and the same spectrometer settings as for imaging. The animals were placed 160 cm from the crystal face of the camera. Counts were obtained from experimental and control animals as well as for room background at 24, 48, 72, 96, 192, and 216 hr after Ga-67 injection. Sufficient time was allowed to collect 100–300 kilocounts from the animals after background subtraction. Results were expressed as the ratio of counts in the DFO-treated animals over counts in control animals.

Abscesses were produced by injecting 0.1 ml turpentine into the thigh of 36 albino female rats weighing 250–300 g. Seventy-two hours after the turpentine injection, swelling of the whole thigh was observed. Ga-67 citrate (0.05 mCi) was injected intravenously. Six rats each were given 25 mg DFO intravenously at 2, 4, and 24 hr after Ga-67 citrate, and were killed 1 hr later along with six control animals receiving only the gallium. Samples were obtained from blood, spleen, muscle, kidneys, liver, and gut. The turpentine-injected thigh from the hip to the knee—including skin, muscle, and bone—was excised as well as the contralateral control thigh. Samples were weighed and Ga-67 activity determined in a well counter. Results were calculated as percentage of injected dose per gram and per whole organ.

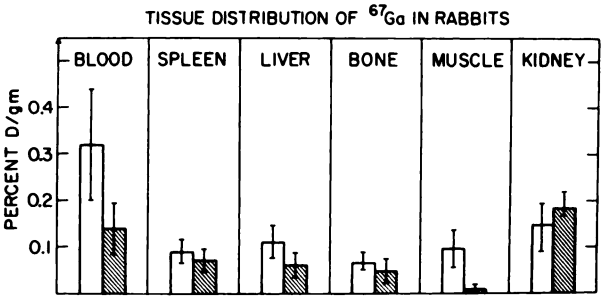

FIG. 1. Ga-67 tissue distribution in control (open bars) and DFO rabbits (hatched bars), at 4 hr after Ga-67 citrate (220 min after DFO).

RESULTS

The tissue-distribution studies at 4 hr (Fig. 1) showed that the blood level in DFO treated rabbits (20 min after Ga-67 administration) was 50% of the blood levels in the control animals ($0.001 < P < 0.01$) and muscle activity also decreased significantly ($P < 0.001$). Renal radioactivity at 4 hr after Ga-67 administration and 220 min after DFO did not differ significantly; in fact it tended to be higher in the experimental than in control animals

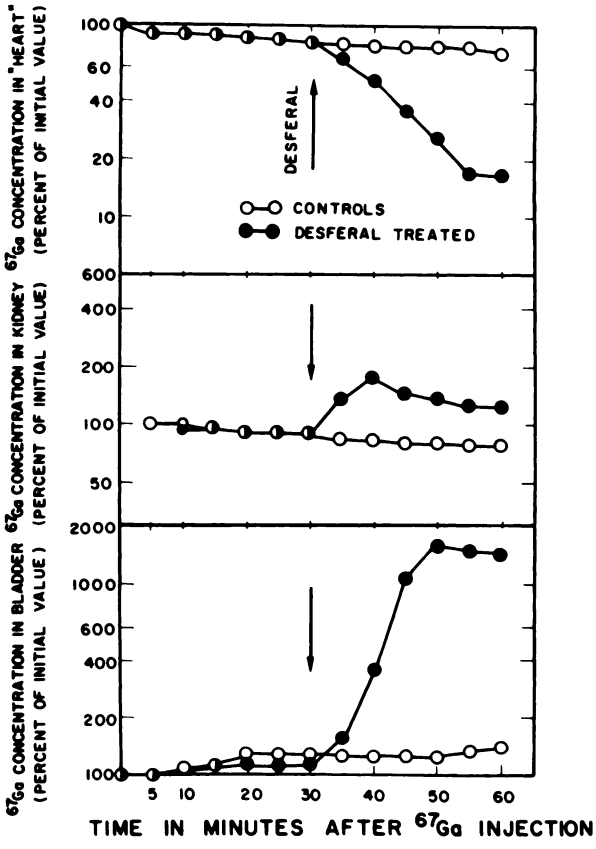

FIG. 2. Ga-67 time-activity curves (semilog) for heart (blood), kidney, and bladder of control rabbits (n = 3) and DFO-treated rabbits (n = 3). DFO was injected 30 min after radiogallium (arrow). Note marked decrease in blood and increase in kidney and bladder activity in DFO-treated rabbits.

($P > 0.05$). Subsequent in vivo experiments showed that by this time most of the activity had been excreted through the kidneys into the bladder. The differences in spleen, liver, and bone activity were not statistically significant ($P > 0.05$). Results of three paired experiments in rabbits injected with DFO 20 min after Ga-67 citrate are shown in Fig. 2. The decrease in blood activity and increase in kidney and bladder activity started 2–3 min after the DFO injection, and this effect continued for 20–30 min. The differences in blood, kidney, and bladder activity between the experimental and control animals were highly significant ($P < 0.001$), and could be observed visually even when frames were replayed sequentially on the computer display at high speed. In the experimental animals the activity was seen to move from the heart to the kidneys and bladder, whereas in the controls seen alongside, no change could be observed (Fig. 3).

The effect of varying the time of DFO administration on the blood levels of Ga-67 is shown in Fig. 4. When DFO is given 20–30 min after radiogallium, a decrease of 50% is observed; DFO given at 2 hr or later causes a decrease of only 17% ± 5% below the blood levels of the controls. This effect is also statistically significant ($P < 0.001$). Ga-67 total-body retention in DFO-treated and controls is shown in Fig. 5. At 24 hr the experimental animals retained 50% of the activity of the controls; at 48 hr it was 10% of control, it continued to decrease up to 216 hr. These differences were also significant ($P < 0.001$).

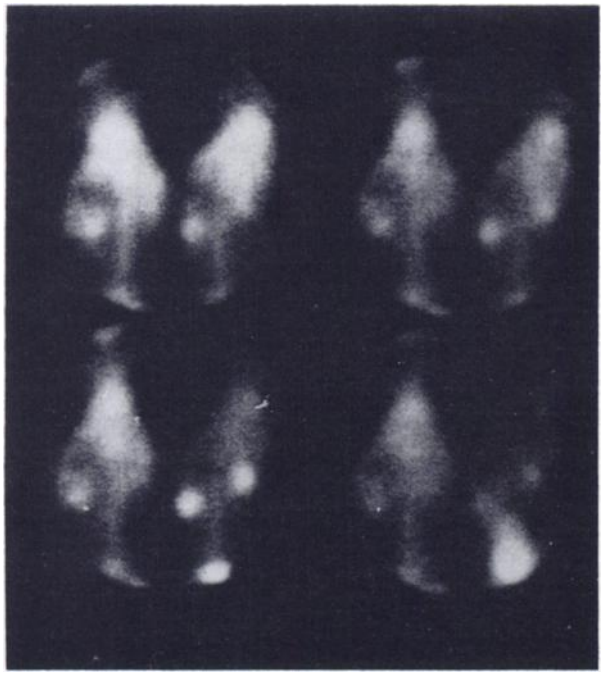

FIG. 3. Images of control and DFO-treated rabbits 20 (top left), 35 (top right), 45 (bottom left) and 55 min (bottom right) after radiogallium injection. In each pair animal on the left is control and one on right received 50 mg DFO i.v. 30 min after radiogallium. Note decrease in heart and increase in kidney and bladder activity in experimental animal.

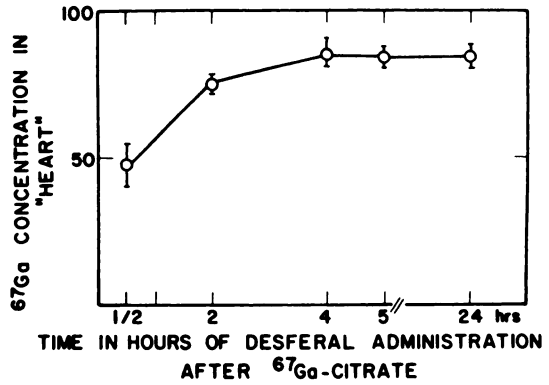

FIG. 4. Effects of time delay between injections of radiogallium and DFO. Blood Ga-67 concentration is expressed as ratio of control-to-experimental values. Note decrease in DFO effect when injected 2 hr or more after radiogallium.

In abscess-bearing rats (Table 1) DFO given 2 hr after Ga-67 showed a 90% decrease in the blood activity. Four hours after Ga-67 administration, DFO lowered Ga-67 blood levels by a factor of 6.7, and when given 24 hr after radiogallium the activity decreased by a factor of 5.1. These changes are highly significant, the P values being much less than 0.001 for all groups.

Gallium-67 activity in the control rats was found to be twice as high as in the DFO-treated animals at 2 hr after administration of DFO. The abscessed-to-normal thigh ratio was higher in control animals at 2 hr (2.20 against 1.05), but at 4 and 24 hr the ratio was higher in the treated animals (1.61/1.32 and 2.77/2.36, respectively). The total amount of activity, however, was higher in the abscessed thigh of the controls at 2, 4, and 24 hr. The ratio in DFO-treated to controls was maximal (0.84) at 24 hr. The abscess-to-blood ratio was considerably higher in the DFO-treated animals at all times, being 2.54 times control at 2 hr and about four times control animal at 4 and 24 hr.

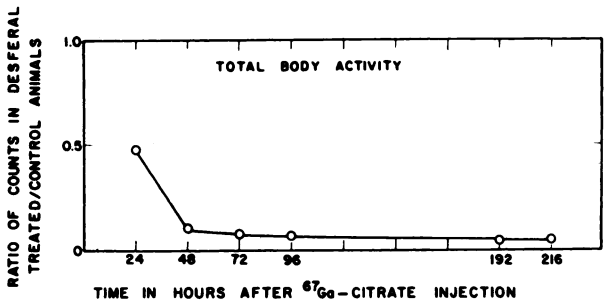

FIG. 5. Ratios (control vs. experimental rabbits) of Ga-67 total-body activity. DFO was injected 20 min after Ga-67. Values were expressed as percentages of 24-hr total-body count in control group. Note marked decrease in activity in DFO-treated animals.

TABLE 1. EFFECT OF DFO IN ABSCESS-BEARING RATS

	Time after Ga-67 citrate injection (hr)					
	2		4		24	
Ratios (cpm/g)	DFO	Control	DFO	Control	DFO	Control
Abs/normal thigh	1.05*	2.20	1.61	1.32	2.77	2.36
Abs/blood	1.17	0.46	2.47	0.65	12.50	3.11
Thigh abscess (DFO) / Thigh abcess (control)	0.50		0.56		0.84	
Blood (% Dose/g)	0.2 ± 0.01	1.7 ± 0.05	0.2 ± 0.05	1.2 ± 0.06	0.04 ± 0.00	0.2 ± 0.02

* Each point represents mean for six animals.

DISCUSSION

It is well known that gallium and iron both have an affinity for the same metal-binding plasma proteins—for transferrin in particular (*10–12*). An additional similarity is presented in this paper; that is, the formation of a chelate complex of gallium with deferoxamine mesylate, which is excreted by the kidneys in the same way as iron-DFO. In the rabbit, DFO showed a maximum "galliuretic" effect when given within 20 min after radiogallium; if given later the effect decreased. In abscess-bearing rats, DFO was seen to decrease blood activity by 90% when given 2 hr after radiogallium. In these animals the "galliuretic" effect also faded as the time interval between radiogallium and DFO was increased. It is possible that the decrease in the DFO effect with time after radiogallium injection is due to gallium being partially cleared from the plasma and shifted into cells where it forms more stable complexes not susceptible to DFO displacement. It seems unlikely that this decrease in the effect of DFO has to do with permeability, since DFO is a compound of low molecular weight, with distribution in the intracellular volume (*3*).

Whole-body counting in the rabbit indicated that, for the same dose, DFO-treated animals retain less Ga-67 activity than controls. This marked difference between DFO-treated animals and controls—observed for up to 8 days—indicates that DFO administration will result in reduction of the radiation dose from radiogallium. Since the "galliuretic" effect was observed even when DFO was given 24 hr after radiogallium, the possibility exists that DFO may be used even after obtaining the 24-hr images and still achieve a reduction in the radiation dose. DFO lowers Ga-67 concentration in all organs as well as in the abscess, but its most marked effect is on Ga-67 blood levels. A 90% decrease in blood levels was shown to occur when DFO is given 2 hr after radiogallium, and although it also lowers the absolute Ga-67 concentration in the abscess, the abscess-to-blood ratio remains higher in the DFO-treated animals. As the interval between the DFO and radiogallium is lengthened, the decrease in gallium concentration in the abscess is less evident, until at 24 hr the concentration is similar to that in the control animals. We conclude from our data that the best time for DFO administration to optimize target to nontarget ratio and to decrease radiation burden is between 8 and 24 hr.

FOOTNOTE

* Desferal, Ciba Pharmaceutical Co., Summit, NJ.

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