POSSIBLE ENHANCEMENT OF ^{67}Ga-CITRATE IMAGING BY IRON DEXTRAN

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The whole-body retention of ^{67}Ga-citrate was studied in intact and in abscess-bearing rabbits. The abscess-to-muscle ratio was obtained using a data processor. Administration of iron dextran lowers the whole-body retention in both the intact and abscess-bearing animals. The optimum time for administering the iron dextran was 24 hr after the ^{67}Ga-citrate injection. At this time, the abscess-to-muscle ratio was highest and the cathode-ray screen images showed lowered background activity and much better definition of the lesion.

The use of ^{67}Ga-citrate for the detection and localization of neoplasms and abscesses is hindered by (A) poor-quality images due to low target-to-nontarget ratio, (B) the long delay after injection (48 hr) required for optimal imaging, and (C) failure to accumulate tracer in all tumors.

Despite these drawbacks, ^{67}Ga-citrate may be of great help in certain clinical situations. Previous studies indicated that gallium is bound to plasma proteins and possibly to transferrin (*1*), although this point has been challenged (*2*). Tracer concentrations of gallium in animals can be displaced from soft tissues by administering scandium simultaneously (*3*). Hill, Merz, and Wagner report that gallium uptake by leukocytes in tissue culture can be increased by increasing the Fe^{+2} concentration in the culture medium (*4*).

This paper describes the results of iron administration on whole-body gallium retention and abscess-to-muscle ratios in rabbits.

MATERIALS AND METHODS

Experimental animals. Female rabbits, about 3 kg, were used. Food and water were provided ad libitum throughout the procedure.

Abscess production. Commercially available turpentine (0.2 ml) was injected into the muscles of one thigh. Forty-eight hours after injection an abscess containing necrotic material and fluid could be detected.

Dosing. One millicurie of ^{67}Ga-citrate (Medi-Physics, Emeryville, Calif.) was administered through an ear vein, and iron dextran (Imferon®) was then given intravenously (15 mg Fe^{+2}/kg). The intravenous route was preferred since intramuscular injection causes tracer to accumulate at the site of injection.

Standard. One millicurie of ^{67}Ga-citrate was placed in a water-filled 2-liter plastic bottle and counted from the same distance and the same intervals as the animals.

Whole-body counting. A 2-in. uncollimated NaI crystal probe, connected to a pulse-height analyzer with a 100–300-keV window, was used. The animal was sedated and placed on a board at 150 cm from the probe.

The whole-body retention was calculated by first determining the following correction factor f at 5 min after injection:

$$f = \frac{\text{net counts from rabbit at 5 min}}{\text{net counts from standard at 5 min}} \times 100\%.$$

The correction factor for the difference in geometry was 92 ± 6%, indicating a good correlation. The whole-body retentions (%) at 24 and 48 hr were expressed as follows:

$$\frac{\text{net counts from rabbit}}{\text{net counts from standard}} \times \frac{100\%}{f}.$$

By using this equation, the physical-decay factor does not have to be considered separately.

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Abscess-to-muscle ratio. These activity ratios were calculated using a scintillation camera interfaced to an image display and analysis system; 35-mm images were taken from the camera's display screen. Areas of interest over the abscess and the normal thigh were flagged, the background was subtracted, counts were normalized for area, and the abscess-to-muscle ratio was calculated.

PROCEDURE

Forty-eight hours after the turpentine injection, 1 mCi of ^{67}Ga-citrate was given, and 5 min later the baseline (100% dose) for the whole-body retention was determined. The animal was counted again at 24 and 48 hr. Sufficient counts were collected to ensure that the relative standard deviation did not exceed 1%.

Six "untreated" control animals did not receive iron dextran: in two no turpentine was injected, and in four abscesses were produced. Five animals with no turpentine injections were treated with iron dextran: in three the iron was injected 24 hr before the gallium, and in two 24 hr after the gallium.

Thirteen abscess-bearing animals were treated with iron dextran: seven received the intravenous iron 24 hr before the gallium, and six were given iron 24 hr after the gallium. The image display and analysis studies were only done in the animals with abscesses at 48 hr.

RESULTS

Whole-body retention and abscess-to-muscle ratio in "untreated" animals. Table 1 shows the differences in whole-body retention between the abscess-bearing and intact animals. The abscess-to-muscle ratio in four animals was found to be 2.72 ± 0.33.

Whole-body retention and abscess-to-muscle ratio in animals pretreated with iron dextran. Table 2 shows that the abscess-bearing group has a higher whole-body retention. The greater variation observed may be explained by differences in abscess size and location (deep-seated or superficial, focal or cellulitis-like lesion). After administration of iron dextran, retention is considerably decreased in both abscess-bearing and intact animals at 24 hr ($p = 0.05$, $t = 2.262$) and at 48 hr ($p = 0.005$, $t = 3.690$). The abscess-to-muscle ratio is lower than in the untreated group.

Whole-body retention and abscess-to-muscle ratio in animals treated with iron dextran after gallium administration. As seen in Table 3, the whole-body values at 24 hr are in the range of the untreated group, with the abscess-bearing animals showing a slightly higher value. At 48 hr after gallium injection and 24 hr after iron dextran treatment, the values dropped to the same level in both the abscessed animals and in the intact animals. The abscess-to-muscle

TABLE 1. INTACT AND ABSCESS-BEARING RABBITS

	Whole-body retention (%)		Abscess-to-muscle ratio
	24 hr	48 hr	
Intact animals (n = 2)	77.0 ± 0.1	73.0 ± 0.5	—
Animals with abscesses (n = 4)	85.0 ± 5.56	75.0 ± 4.83	2.72 ± 0.33

TABLE 2. ANIMALS PRETREATED WITH IRON DEXTRAN

	Whole-body retention (%)		Abscess-to-muscle ratio
	24 hr	48 hr	
Intact animals (n = 3)	67.3 ± 1.15	55.3 ± 1.15	—
Animals with abscesses (n = 7)	76.42 ± 4.32	65.85 ± 2.10	1.99 ± 0.31

TABLE 3. ANIMALS TREATED WITH IRON DEXTRAN 24 HR AFTER GALLIUM ADMINISTRATION

	Whole-body retention (%)		Abscess-to-muscle ratio
	24 hr	48 hr	
Intact animals (n = 3)	78.5 ± 2.13	67.0 ± 1.0	—
Animals with abscesses (n = 6)	84.66 ± 5.71	68.34 ± 0.57	5.58 ± 0.50

TABLE 4. ANIMALS TREATED WITH IRON DEXTRAN AND ^{67}Ga-CITRATE SIMULTANEOUSLY

	Whole-body retention (%)		Abscess-to-muscle ratio
	24 hr	48 hr	
Abscess-bearing animals (n = 3)	75.54 ± 0.64	67.98 ± 2.04	2.02 ± 0.28

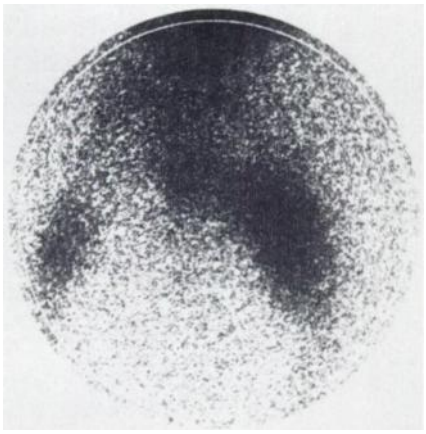

FIG. 1. Abscess-bearing rabbit without iron dextran administration.

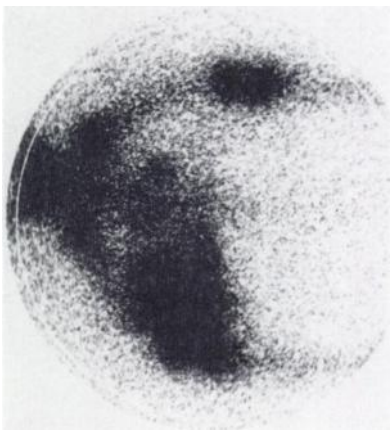

FIG. 2. Abscess-bearing rabbit with iron dextran administered 24 hr after injection of ^{67}Ga.

ratio of these animals is twice that of the untreated group at 24 hr ($p = 0.05$, $t = 2.306$) and at 48 hr ($p = 0.001$, $t = 5.041$) and almost three times that of the pretreated group.

Whole-body retention and abscess-to-muscle ratio in animals treated with iron dextran and ^{67}Ga-citrate simultaneously. The effect of administering iron dextran simultaneously with the gallium is shown in Table 4. In these abscess-bearing animals, the values obtained at 24 and 48 hr are similar to those observed in the pretreated animals ($p = 0.05$, $t = 2.571$).

DISCUSSION

These experiments support the view that the distribution of gallium in tracer concentration is influenced by iron dextran loading. Moreover, more activity is retained in the abscess-bearing animals than in the intact animals. The observations in intact untreated animals are very similar to previously published data (*5*). Administration of iron dextran before or simultaneously with the gallium has less effect than injecting the iron 24 hr after. This observation may help to decrease the radiation dose in patients.

The striking difference in the abscess-to-muscle ratios can be clearly seen from the scintillation camera images (Figs. 1 and 2), which show that iron dextran administration, 24 hr after the tracer, decreases the background activity, making the distinct features within the lesion become apparent. It would be instructive to obtain similar data in humans in order to determine the clinical value of this procedure. The kinetics of ^{67}Ga distribution in the intact rabbit can be remarkably altered by pharmacologic doses of iron. In an experimental model of abscess, iron administration 24 hr after radiogallium greatly improved both the abscess-to-muscle ratio and the quality of the images. These results are consistent with the hypothesis that binding of gallium to transferrin or other proteins is important to the initial deposition of ^{67}Ga in an abscess. Thereafter, displacing these proteins with iron enhances the clearance of gallium from the body and increases the abscess-to-nontarget ratio.

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