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COMPARISON OF UPTAKE OF ^{67}Ga-CITRATE AND ^{57}Co-BLEOMYCIN IN TUMOR USING A SEMICONDUCTOR DETECTOR

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Distribution studies in Ehrlich's tumor-bearing mice were performed with ^{67}Ga-citrate and ^{57}Co-bleomycin. The tumor-to-nontumor ratios for ^{57}Co-bleomycin were always superior to those of ^{67}Ga-citrate. However, the absolute uptake in tumor of ^{67}Ga-citrate was greater than that of ^{57}Co-bleomycin. Similar results were obtained in bone, muscle, intestine, and liver. The accumulation of ^{67}Ga-citrate and ^{57}Co-bleomycin in tumor was greater than in inflammatory lesions.

In 1969 Edwards and Hayes reported that carrier-free ^{67}Ga-citrate exhibited marked uptake in malignant tumors (*1*). Since then, many tumor-scanning agents have been proposed for the scintigraphic detection of cancer. However, as yet, success has been limited. Cobalt-57-bleomycin (^{57}Co-BLM) has recently been introduced by Nouel and Maeda for detecting the localization and extent of tumors in humans (*2,3*). Grove and Hisada have compared the uptake of ^{57}Co, ^{111}In, and ^{67}Ga-labeled bleomycin in tumors and concluded that ^{57}Co-bleomycin is far superior to ^{111}In and ^{67}Ga-labeled bleomycin (*4,5*).

The purpose of this communication is to report the comparison of uptake of ^{67}Ga-citrate and ^{57}Co-bleomycin in Ehrlich's tumor. The method used in this study is a previously reported one using a Ge(Li) semiconductor detector (*6*).

MATERIALS AND METHODS

The experimental animals were mice (DDN-strain) 10 days after transplantation of Ehrlich's tumor cells into the femoral region. The ^{67}Ga-citrate (carrier-free) used in this investigation was supplied by the Philips-Duphar Cyclotron and Isotope Laboratory and the ^{57}Co-bleomycin was supplied by the Daiich Radioisotope Laboratory of Japan.

Standard solutions were produced by mixing 10 μCi of each of the two radiopharmaceuticals (^{67}Ga-citrate and ^{57}Co-bleomycin). The standard solution (0.2 ml) was injected into the tail vein of mice. Four mice were sacrificed at 3, 6, 24, 48, 72, and 120 hr post-injection. The tumor, liver, bone (vertebra), muscle, kidney, small intestine, and blood (0.2 ml) were analyzed. The average percent dose per gram of tissue for the four mice was reported.

Yoshida sarcoma cells were injected into the right femoral region of a rat (Donryu strain). Ten days later croton oil (0.1 ml) was injected intramuscularly into the left paraspinous muscles of the same rat to produce the experimental inflammatory condition. Acute inflammation was simulated by taking measurements of uptake 5 hr after injection of croton oil whereas for subacute inflammation measurements at 48 hr were used. A mixture of ^{67}Ga-citrate and ^{57}Co-bleomycin (0.2 ml) was injected intraperitoneally into the experimental animals 24 hr before they were sacrificed. Samples of inflammatory and tumor lesion were analyzed at necropsy for ^{67}Ga-citrate and ^{57}Co-bleomycin content.

The photopeaks of the ^{67}Ga and ^{57}Co radioisotopes in each organ were measured with a 4,000-channel multianalyzer attached to a Ge(Li) semiconductor detector. The semiconductor detector used here is manufactured by the ORTEC Company and has a capacity of 50 cc with a full width at half-maximum (FWHM) of 4.5 keV for the ^{60}Co gamma

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ray (1.33 MeV). The photopeaks of the radionuclides were measured at 92 keV, 184 keV, and 300 keV in ^{67}Ga, and at 121 keV in ^{57}Co. The uptake of ^{67}Ga and ^{57}Co by each organ was measured by comparing the activity of the photopeaks of standard solutions with that of the corresponding photopeaks in the organs.

RESULTS

The distribution of ^{67}Ga-citrate and ^{57}Co-bleomycin into the different organs at 3, 6, 24, 48, 72, and 120 hr after injection is shown in Table 1. Figure 1 was obtained from the data in Table 1. The tumor uptake of ^{67}Ga-citrate reached a maximum at 24 hr after injection and then the activity gradually decreased. Cobalt-57-bleomycin, on the other hand, reached a maximum at 6 hr after injection and then the activity decreased rapidly. The accumulation of ^{67}Ga-citrate in tumor is always higher than that of ^{57}Co-bleomycin. Similar results were obtained in bone, muscle, intestine, and kidney (Fig. 1). The rapid decrease in activity of ^{57}Co-bleomycin is a result of its more rapid excretion through the kidney than that of ^{67}Ga-citrate.

The tumor-to-nontumor ratios for the ^{57}Co-bleomycin were always superior to those of ^{67}Ga-citrate as seen in Table 2.

Table 3 shows the uptake of ^{67}Ga-citrate and ^{57}Co-bleomycin in experimental inflammatory lesions compared with tumor lesions. In acute and subacute inflammatory lesions, ^{67}Ga-citrate always accumulates to a greater extent than ^{57}Co-bleomycin. With both agents mentioned above, the uptake in tumor was greater than in inflammatory lesions.

DISCUSSION AND CONCLUSIONS

In this experiment the authors could detect ^{67}Ga-citrate and ^{57}Co-bleomycin in organs at the same time with a Ge(Li) semiconductor detector, which has a high resolution for gamma rays. This method made it possible to detect ^{67}Ga and ^{57}Co simultaneously and to estimate their relative uptakes and thus minimize the differences caused by individual variations in experimental animals as well as decrease the number of animals needed.

From these results, it was postulated that ^{57}Co-bleomycin was more specific than ^{67}Ga-citrate for the detection of tumors. Cobalt-57-bleomycin disappears rapidly from blood and is excreted mainly through the kidneys so high tumor-to-nontumor ratios are obtained shortly after injection. This must be the best characteristic of this radiopharmaceutical. Recently, Grove and Tanaka reported similar results (*4,7*).

Although the mechanism of accumulation into the tumor cell is still unknown, the authors postulate that the gallium ion might pass through the tumor cell membrane much more easily than the other elements because the ionic radius of gallium (0.62 Å) is similar to that of magnesium (0.66 Å), which is abundant in the tumor cell membrane. Intracellular localization of ^{67}Ga-citrate in the cytoplasm was greater than in the nuclei. In the cytoplasm, most of the ^{67}Ga was seen in mitochondrial and microsomal fractions (*8*). Nelson, et al, using an electron-microscopic autoradiogram, reported that ^{67}Ga localizes in the lysosomes in tumor cells (*9*). On the contrary, twice as much ^{57}Co-bleomycin was found in the nuclei as in the cytoplasm with the ^{57}Co-

TABLE 1. COMPARISON OF UPTAKES OF ^{67}Ga-CITRATE AND ^{57}Co-BLM IN EHRLICH'S TUMOR-BEARING MICE TISSUES (% DOSE/GM)*

	Tumor		Liver		Kidney		Intestine		Bone		Blood		Muscle	
Time (hr)	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM
3	2.61 ±0.45	1.52 ±0.31	1.76 ±0.58	0.59 ±0.18	3.59 ±1.44	1.37 ±1.02	4.25 ±1.21	0.07 ±0.02	3.48 ±1.37	0.12 ±0.10	7.177 ±2.800	0.029 ±0.020	1.11 ±0.37	0.05 ±0.02
6	3.39 0.59	2.34 0.68	4.72 1.21	0.81 0.23	7.78 2.21	2.06 1.16	5.29 3.01	0.10 0.08	5.40 2.61	0.09 0.03	7.005 3.100	0.013 0.006	1.12 0.40	0.05 0.04
24	3.79 1.01	0.71 0.41	7.32 1.87	0.21 0.08	6.69 2.90	0.91 0.68	2.02 0.80	0.04 0.03	3.83 1.98	0.07 0.04	0.813 0.420	0.015 0.008	0.22 0.10	0.02 0.008
48	2.55 0.57	0.34 0.22	6.30 1.91	0.22 0.12	6.82 2.38	0.46 0.33	1.35 0.56	0.03 0.01	2.62 0.65	0.03 0.02	0.507 0.310	0.015 0.003	0.28 0.08	0.02 0.01
72	1.83 0.34	0.21 0.13	6.88 2.50	0.16 0.15	5.82 1.02	0.34 0.10	0.21 0.12	0.01 0.008	2.62 1.02	0.02 0.01	— —	— —	0.22 0.12	0.018 0.006
120	1.73 0.62	0.16 0.08	4.98 1.17	0.09 0.04	1.52 0.84	0.05 0.02	0.15 0.08	0.003 0.001	0.43 0.21	0.003 0.002	— —	— —	0.043 0.020	0.001 0.0006

* Values are given ± s.e. (no. of animals is 4).

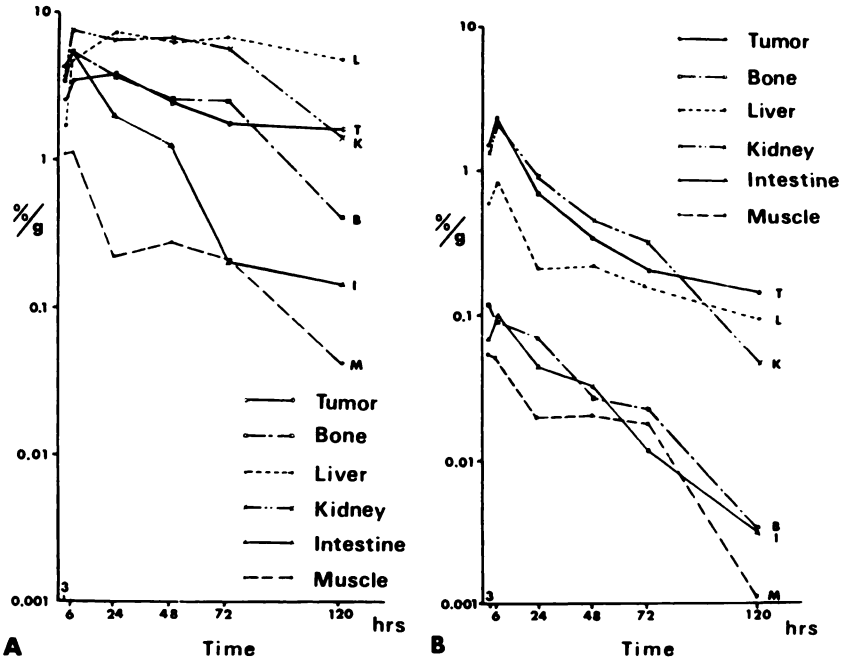

FIG. 1. Gallium-67-citrate (A) and ^{57}Co-bleomycin (B) were injected simultaneously into Ehrlich's tumor-bearing mice. Ordinate is retention value of radionuclide expressed as percent of administered dose per gram tissue weight in various tissues and tumor. Abscissa is time interval after administration of ^{67}Ga-citrate and ^{57}Co-bleomycin. Note difference in distribution in organs with two scanning agents.

TABLE 2. RELATION OF TUMOR UPTAKE TO OTHER TISSUES IN EHRLICH'S TUMOR-BEARING MICE

	T/M		T/B		T/L		T/K		T/Bo.		T/In.	
Time (hr)	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM	^{67}Ga-cit.	^{57}Co-BLM
3	2.35	30.4	0.36	52.4	1.48	2.58	0.73	1.11	0.75	12.7	0.61	21.7
6	3.03	46.8	0.48	18.0	0.72	2.89	0.44	1.14	0.63	26.0	0.64	23.4
24	17.20	35.5	4.66	54.6	0.52	3.38	0.57	0.78	0.99	10.1	1.88	17.8
48	9.11	17.0	5.03	22.7	0.40	1.55	0.37	0.74	0.97	11.3	1.89	11.3
72	8.32	11.7	—	—	0.27	1.40	0.31	0.62	0.70	10.5	8.71	21.0
120	40.20	160.0	—	—	0.35	1.77	1.14	3.20	4.02	53.3	11.50	53.3

T:Tumor, M:Muscle, L:Liver, B:Blood, K:Kidney, Bo:Bone, In:Intestine.

bleomycin being strongly attached to DNA molecules in the studies of Kono (*10*). According to the above information, it is logical to propose that the different rates of uptake and excretion of ^{57}Co-bleomycin and ^{67}Ga-citrate are explainable by their different sites of localization within the cell.

It is obvious that both agents have advantages and disadvantages that must be weighed before their application to an individual case. Further investigations of the clinical applications of ^{57}Co-bleomycin are in progress and will be reported in the near future.

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TABLE 3. COMPARISON OF UPTAKE OF ^{67}Ga-CITRATE AND ^{57}Co-BLM IN INFLAMMATORY AND TUMOR LESIONS OF YOSHIDA SARCOMA-BEARING RATS 24 HR AFTER INTRAPERITONEAL INJECTION (% DOSE/GM)*

Lesions	^{67}Ga-citrate	^{57}Co-BLM	$\frac{^{67}\text{Ga-citrate}}{^{57}\text{Co-BLM}}$
Inflammation (acute stage)	0.244 ± 0.079	0.009 ± 0.002	25.4
Tumor	0.530 ± 0.156	0.114 ± 0.052	4.6
Inflammation (subacute stage)	0.114 ± 0.034	0.004 ± 0.001	29.2
Tumor	0.935 ± 0.196	0.081 ± 0.025	11.5

* Values are given ± s.e. (no. of animals is 3).

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