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Abstract

Mice bearing Ehrlich tumor were administered 97Ru-chloride or 103Ru-chloride intravenously. Examinations of various tissues indicated similar distributions by the two radionuclides. The levels were higher in the lung, liver and kidney than in the tumor tissue. Rats bearing AH-130 tumor were administered 103Ru-chloride intravenously. The 103Ru distribution in rats was highest in the spleen, followed by the liver and kidney; however, the radioactive distribution in the tumor tissue exceeded the muscle level by about 5-fold. Tumors were delineated in rats by scintigraphy. The findings indicate that ruthenium radionuclides may be a useful clinical agent in the delineation of some types of tumors. Ruthenium-97 would be favored in possible clinical usage due to its shorter physical half-life and lower levels of gamma energy.

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TISSUE DISTRIBUTIONS OF ^{97}RU AND ^{103}RU IN SUBCUTANEOUS TUMOR OF RODENTS

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Abstract: Mice bearing Ehrlich tumor were administered ^{97}Ru-chloride or ^{103}Ru-chloride intravenously. Examinations of various tissues indicated similar distributions by the two radionuclides. The levels were higher in the lung, liver and kidney than in the tumor tissue. Rats bearing AH-130 tumor were administered ^{103}Ru-chloride intravenously. The ^{103}Ru distribution in rats was highest in the spleen, followed by the liver and kidney; however, the radioactive distribution in the tumor tissue exceeded the muscle level by about 5-fold. Tumors were delineated in rats by scintigraphy. The findings indicate that ruthenium radionuclides may be a useful clinical agent in the delineation of some types of tumors. Ruthenium-97 would be favored in possible clinical usage due to its shorter physical half-life and lower levels of gamma energy.

Several effective radionuclides are currently available in clinical scintigraphy (1–6) but the availability of other radionuclides would be useful in some situations. Ruthenium red is known to have a selective affinity to glycoproteins and polysaccaharides of organellas, cells and tissues (7–9). Transformed cancer cells are stained more intensely with ruthenium red than normal cells (10). The mechanism of this binding affinity has not yet been clarified, but the possibility of binding by the ruthenium ion itself cannot be ruled out. The present study examines the tissue distributions of ^{103}Ru in tumor-bearing mice and rats and ^{97}Ru in tumor-bearing mice. A subsequent report will cover clinical trials with these radionuclides.

MATERIALS AND METHODS

Ruthenium-97 and ^{103}Ru as chloride in hydrochloride solution (manufactured by New England Nuclear Laboratories and the Radiochemical Center, respectively) were purchased from the Japanese Isotope Society. Ruthenium-103 had a carrier which contained 1.1 mg of Ru per ml and ^{97}Ru was carrier free. Each radionuclide in hydrochloride was adjusted to a pH of 1.5–2.0 with sodium hydroxide, since precipitation occurs at higher pH. The solution was passed through a Millipore filter for sterilization prior to use.

Animals used were 20 male mice of the ddy strain weighing about 20 g and 4 male rats of the Donryu strain weighing about 200 g. Each experimental group

consisted of 4 animals.

Ehrlich ascites tumor cells were transplanted subcutaneously in the lower thigh of mice. AH-130 ascites tumor cells were transplanted subcutaneously in the lower thigh of rats. These tumor cells were previously cultured over a long period of time in our laboratories. The experiment was initiated when the tumors grew to about 2 cm in diameter. Inflammation was induced artificially with croton oil injected subcutaneously in the lower thigh. In mice, ^{97}Ru-chloride solution or ^{103}Ru-chloride solution was administered intravenously in the tail vein at a dose of 1 μCi per g of body weight. In rats, ^{103}Ru-chloride solution was administered in the same manner, at a dose of 0.5 μCi per g of body weight. The animals were sacrificed by severing the carotid artery. Mice treated with ^{103}Ru were killed at 1, 24 and 72 hours after radionuclide injection; mice treated with ^{97}Ru were killed at 24 and 72 hours after injection. Rats were killed at 48 hours after ^{103}Ru injection. Blood and 0.2 to 0.5 g of spleen, liver, kidney, lung, and muscle (lower thigh) were collected from all animals and weighed wet. In addition, 0.2 to 0.5 g of rat bone (femur with bone marrow), heart, small intestine, testicle, subcutaneous fat (abdominal wall) and inflammatory tissue (lower thigh) were collected and weighed wet. The radioactivity of each tissue was measured with an auto-well scintillation counter (Aloka). The residual body radioactivity after radionuclide injection was measured with a scinticamera (Pho/Gamma III, Nuclear Chicago Laboratories) at 1, 2, 6 and 11 days in the ^{103}Ru group and at 1, 3, 6 and 10 days in the ^{97}Ru group, under fixed geometical conditions. The biological half-life was calculated. Scinticamera was connected with a Toshiba data processor (DAP-5000) for scintigraphy.

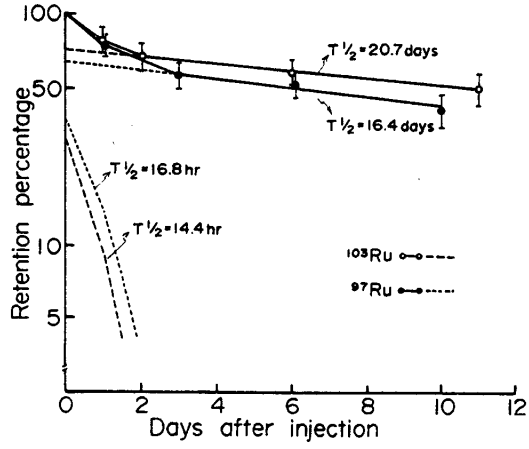

Fig. 1. Whole body ruthenium radionuclide retention percentages at various time periods in mice bearing Ehrlich tumor. Dotted lines indicate the biological half-life components calculated from whole body counts. The linear sections of the solid lines show the long-life phase. The short-life phase was calculated by subtracting the extrapolation of the long-life phase from the solid line.

RESULTS

Fig. 1 shows the radioactive retention percentages of ^{103}Ru and ^{97}Ru in mice. The short-life phase of biological half-life in ^{103}Ru was estimated to be about 14 hours and the long-life phase was about 20 days; in ^{97}Ru, the short-life phase was estimated to be about 16 hours and the long-life phase was about 16 days.

TABLE 1. TUMOR-TO-TISSUE RATIOS FOR ^{97}Ru AND ^{103}Ru IN MICE BEARING EHRLICH SUBCUTANEOUS TUMOR

Radionuclide	Time (hr) after i.v. injection	Tissue					
		Blood	Lung	Liver	Spleen	Kidney	Muscle
^{103}Ru-chloride	1	0.18±0.02	0.41±0.05	0.53±0.11	1.29±0.28	0.49±0.07	2.27±0.45
	24	0.46±0.06	0.53±0.06	0.29±0.04	0.90±0.14	0.29±0.05	1.85±0.46
	72	1.21±0.17	0.70±0.12	0.27±0.02	0.90±0.15	0.30±0.02	1.93±0.50
^{97}Ru-chloride	24	0.86±0.01	0.39±0.05	0.26±0.04	1.47±0.18	0.19±0.02	1.35±0.25
	72	1.48±0.28	0.48±0.02	0.19±0.02	1.20±0.27	0.14±0.01	1.12±0.05

The tissue ratios are presented as mean ± S. D. in 4 animals per group.

Table 1 shows the radioactive ratios of tumor-to-tissue in mice at three times periods after injection. Both ^{97}Ru and ^{103}Ru indicated similar distributions. The radioactivity (count/g wet weight) in blood decreased gradually to a value lower than in the tumor at 72 hours after injection. The radioactivity of the lung, liver and kidney was higher than in the tumor. Tumor radioactivity was higher than in the spleen and muscle.

TABLE 2. TUMOR-TO-TISSUE RATIOS FOR ^{103}Ru IN RATS BEARING SOLID TUMOR (AH-130) 48 HOURS AFTER I. V. INJECTION

Tissue	Ratio*
Spleen	0.36±0.10
Liver	0.52±0.12
Kidney	0.81±0.23
Lung	1.28±0.24
Blood	1.72±0.58
Bone (femur with bone marrow)	2.02
Inflammatory tissue (lower thigh)	2.46
Heart	3.17±0.74
Small intestine	3.78±0.91
Testicle	4.17±0.79
Muscle (lower thigh)	5.82±3.21
Subcutaneous fat (abdominal wall)	10.42±2.68

* The tissue values are presented as mean I. S. D. in 4 animals, except for the bone and inflammatory tissue that are based on one case each.

Table 2 shows the ^{103}Ru radioactive ratios of tumor-to-tissue in rats at 48 hours after injection of ^{103}Ru-chloride. The ratio of tumor-to-muscle was 5.82. Positive-delineation of the AH-130 tumor was obtained by scintigraphy (Fig. 2).

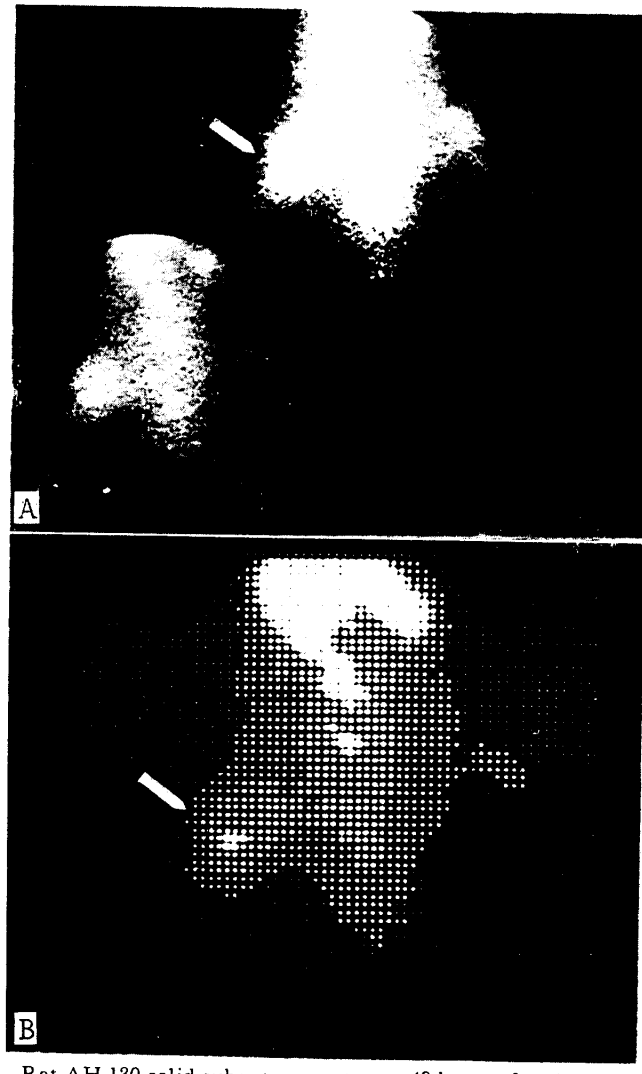

Fig. 2. Rat AH-130 solid subcutaneous tumor 48 hours after injection of ^{103}Ru-chloride. A, Scintigram showing positive-delineation of tumor in the lower right thigh (arrow). B, Digital scintigraphy of the same areas shown in Fig. 2A. Density of over 50% (white areas), density between 35% to 50% (light gray areas) and density less than 35% (dark gray areas).

DISCUSSION

Ruthenium-97, ^{103}Ru and ^{105}Ru are among ruthenium radionuclides those gamma emissions can be measured externally. Ruthenium-103 has a physical half-life of 39.5 days, undergoes beta decay and emits gamma rays at 0.497 Mev (88%) and at 0.61 MeV. Ruthenium-97 has a physical half-life of 2.9 days, decays by electron capture and emits gamma rays at 0.018 MeV, 0.215 MeV (91%) and 0.32 MeV. Ruthenium-97 is, therefore, more suitable for clinical practice.

Other data is available on the biological behavior of radioactive ruthenium (11-18). In clinical applications of radionuclides the biological half-life is an extremely important factor. The short-life phase of biological half-life following injection in chloride form was about 16 hours for ^{97}Ru and about 14 hours for ^{103}Ru. The long-life phase was about 16 days for ^{97}Ru and about 20 days for ^{103}Ru. The reasons for these differences are unclear, but the presence or absence of a carrier may be an important factor (19).

As the radioactive clearance of Rn-radionuclide from the blood is slow, the tumor is likely to be surrounded with a blood pcol during scintigraphy. The initiation of scanning should be determined by conditions of blood clearance. From our experimental results with Rn-radionuclides, the optimal starting period appears to be from 3 to 6 days after the administration of the nuclide.

The presence of abundant radioactivity in the liver and spleen indicates the difficulty of scanning for abdominal tumors. Furthermore, variations in uptake were present in the spleens of mice and rats. It is possible that splenic hematopoietic differences of mice and rats may be a factor contributing to this variation (20).

In the present investigation, rats bearing AH-130 tumors showed a ^{103}Ru uptake that was about five times higher than muscle, and the tumor was delineated by scintigraphy. Although further investigations on Ru-radionuclides are required, especially on the complex forms for injection, the results of this study suggest on preliminary basis that ^{97}Ru may be clinically useful for delineating certain kinds of tumors.

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