Technetium-99m Stannous Citrate Brain-Tumor Uptake in Mice: Concise Communication

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The pharmacodynamics of technetium-99m stannous citrate were studied in Yale–Swiss mice bearing a sarcoma-like transplantable brain tumor, and the renal kinetics were determined in normal mice. Using a rating system based on tumor uptake and tumor-to-brain, tumor-to-blood, and tumor-to-skin ratios, the data obtained with this compound were compared with similar data obtained previously in the same model with Tc-99m Fe-(ascorbic acid), Tc-99m Fe-(ascorbic acid)-DTPA, Tc-99m Sn-DTPA, [^{99m}Tc] pertechnetate, and [^{99m}Tc] pertechnetate with perchlorate predose. Technetium-99m stannous citrate does not appear to achieve tumor localization by a mode different from these other Tc-99m-labeled compounds, nor does it show any potential advantage as a scanning agent in this tumor model.

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Recently a new tumor-seeking agent, the technetium-99m citrate complex, has been described which, according to the information available, "has a rapid and high tumor uptake, making it especially useful for the visualization of brain tumors, bone tumors and metastases" (*1*). Over the past several years, we have been investigating and comparing potential scanning agents for brain tumors in a mouse model with a brain sarcoma (*2*) and the renal kinetics of many radiopharmaceuticals (*3*). The following investigations were undertaken in order to gain an understanding of the pharmacodynamics of this new compound and to compare it with other tumor-seeking agents in this model.

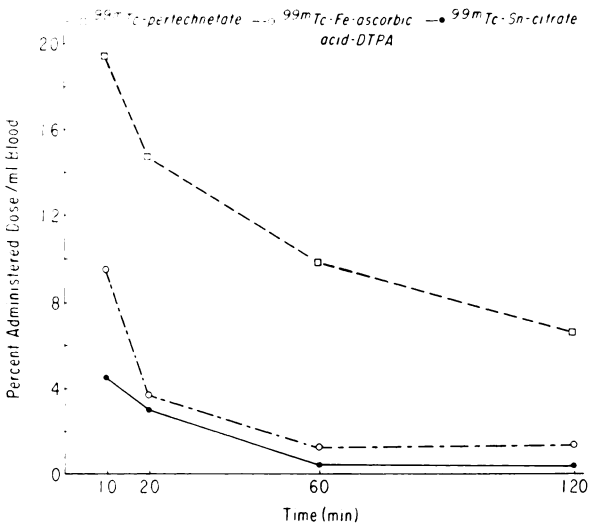

FIG. 1. Average percent dose per ml blood in tumor-bearing mice up to 2 hr after injection of [^{99m}Tc] pertechnetate, Tc-99m Fe-(ascorbic acid)-DTPA, and Tc-99m Sn-citrate. Student's t test shows significant differences ($p < 0.01$–$p < 0.001$) in blood concentrations for all comparisons at all time intervals except that for citrate and Fe-(ascorbic acid)-DTPA at 20 min ($p < 0.30$).

MATERIALS AND METHODS

Mouse tumor. The tumor is a methylcholanthrene-induced, cerebral sarcoma of mice, transplanted in situ, that has been described elsewhere (*4*).

Radiopharmaceutical. The Tc-99m Sn-citrate complex was prepared using a commercial kit*. The product was subjected to chromatographic analysis, which revealed less than 1% free pertechnetate. Other Tc-99m-labeled compounds were prepared from commercial kits.

Experimental technique. Distributional studies following tail-vein injection of the tracer were per-

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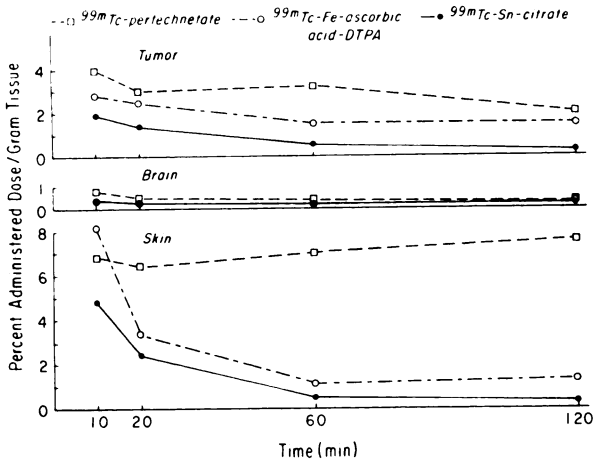

FIG. 2. Average percent dose per gram of mouse tumor, brain, and skin for varying time periods up to 2 hr after injection of [^{99m}Tc] pertechnetate, Tc-99m Fe-(ascorbic acid)-DTPA, and Tc-99m Sn-citrate. Student's t test shows significant differences in tumor uptake values ($p < 0.02$–$p < 0.001$) for all values at all time intervals. There are also significant differences in skin concentrations ($p < 0.05$–$p < 0.001$) for all values at all time intervals.

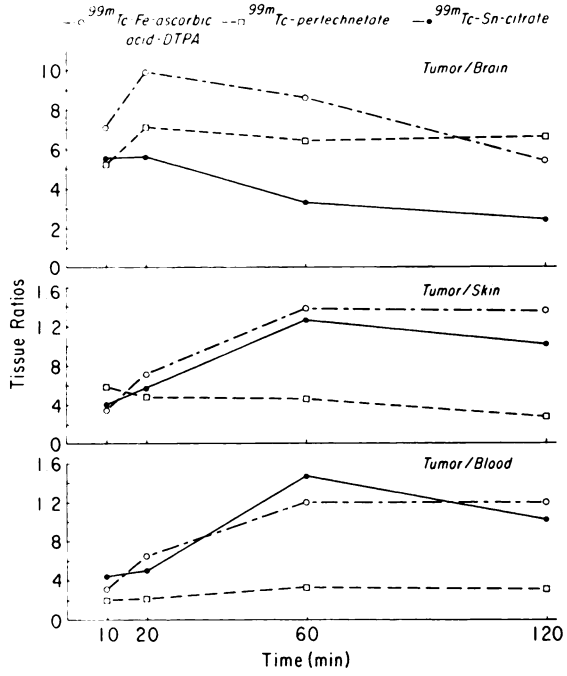

FIG. 3. Tumor-to-brain, tumor-to-muscle, and tumor-to-blood tissue ratios in mice at various times up to 2 hr after injection of [^{99m}Tc] pertechnetate, Tc-99m Fe-(ascorbic acid)-DTPA, and Tc-99m Sn-citrate.

formed in Yale–Swiss mice bearing the transplanted cerebral sarcoma. Tissues sampled included the tumor, brain, blood, and skin. Six mice were evaluated at each time period chosen for investigation.

Renal blood clearance studies. The methods for the measurement of renal blood and plasma clearance have been described previously (*3*). Classic clearance methods were used, except that quantitative urine collection was ensured by using normal male mice with penis ligation and intact bladder excision. Total remaining whole-body radiation burden for each time interval necessary to calculate percent retained dose per gram of tissue was obtained by subtracting activity excreted for that time interval from total radioactivity injected into each mouse.

RESULTS

Tumor and tissue uptake. In Figs. 1 and 2 the percent administered dose per gram of blood, transplanted brain tumor, normal brain, and skin are compared with results previously obtained in this model using [^{99m}Tc] pertechnetate (*5*) and the Tc-99m Fe-(ascorbic acid)-DTPA complex (*6*). The percent per gram tissue for the administered stannous citrate complex is the least of the three compounds in all tissues and at all time intervals up to 2 hr after injection. The level appears to parallel the technetium-DTPA complex quite well.

Tissue ratios. In Fig. 3 the tumor-to-brain, tumor-to-skin, and tumor-to-blood ratios are again compared with those found for pertechnetate and the Fe-(ascorbic acid)-DTPA complex. Stannous citrate shows again the least of the three in tumor-to-brain ratios. The tumor-to-skin and tumor-to-blood ratios of the stannous citrate and Fe-(ascorbic acid)-DTPA complex are virtually identical and are considerably higher than those for pertechnetate.

Renal excretion. The renal excretion rates for the same three Tc-99m compounds evaluated in the tissue study are compared in Fig. 4. Technetium-99m Sn-citrate was the most rapidly excreted, while the iron-(ascorbic acid)-DTPA was slightly slower and pertechnetate the slowest of the three. The time for 50% urinary excretion for Tc-99m Sn-citrate was 12.5 min. The ratio between red blood cells and plasma (RBC/P) at 5 min was 0.08 and at 60 min was 0.30. From the cumulative urinary excretion curve shown in Fig. 4, the classical UV value was obtained (U is urinary concentration, V is urinary volume). From a blood disappearance curve similar to that shown in Fig. 1, the corresponding blood concentration B was obtained. Renal blood clearance in the mouse (UV/B) for Tc-99m Sn-citrate was found to be 0.303 ml/min. When standardized to a 1.73-m^2 body surface area, the clearance was 62.5 ml/min. The corresponding renal plasma clearance values were 0.197 ml/min and 40.6 ml/min, respectively. For comparison, the renal blood clearances in the mouse for Tc-99m Fe-(ascorbic acid)-DTPA and [^{99m}Tc] pertechnetate were found to be 46.7 ml/min and 6.2 ml/min, respectively, when standardized to 1.73-m^2 body surface area (*6*). The

corresponding renal plasma clearances for the latter two compounds were 29.5 ml/min and 6.0 ml/min, respectively. The time for 50% urinary excretion of Tc-99m Fe-(ascorbic acid)-DTPA was 24 min; for [^{99m}Tc] pertechnetate it was 5.8 hr.

Relative rating system. In Table 1 six Tc-99m-labeled compounds used in brain scanning are compared using a rating system described previously (*2*) and averaging the data for 10–60 min after injection. The relative ratings were obtained for two methods of expressing tumor content: that of average percent administered dose per gram tumor, and that of percent retained dose per gram tumor. Technetium-99m Sn-citrate rated next to last (just above [^{99m}Tc] pertechnetate) using both methods.

Table 2 presents the same type of data for 2 hr after injection. Using tumor content expressed as percent administered dose per gram tumor, Tc-99m Sn-citrate ranks last. Using percent retained dose per gram tumor, Tc-99m Sn-citrate ranks next to last at 2 hr.

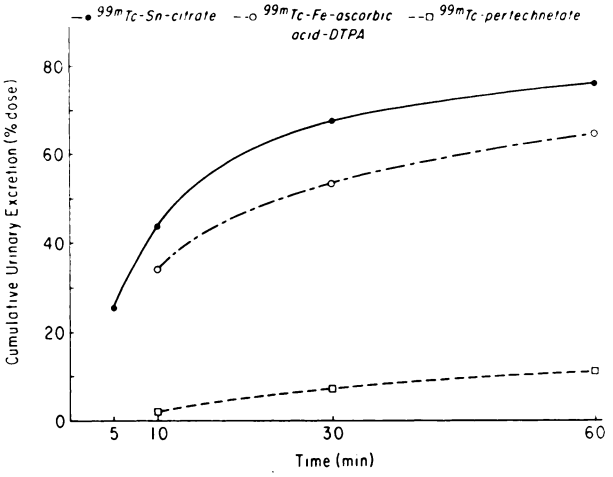

FIG. 4. Cumulative urinary excretion in mice after single intravenous injection in which percent injected dose is plotted against time for 2 hr after injection of Tc-99m Sn-citrate, Tc-99m Fe-(ascorbic acid)-DTPA, and [^{99m}Tc] pertechnetate.

DISCUSSION

Of the many ways of expressing tissue or organ concentration used in research studies with radionuclides, the most widely used expression has been that of percent administered dose per gram of tissue. Recently Woodard et al. (*7*) have suggested that tissue concentrations can also be expressed as microcuries per gram specimen over microcuries retained per gram body weight at the time the sample was obtained. We have used both methods of expression in this evaluation of Tc-99m Sn-citrate as a tumor-seeking agent. The expression of data in terms of percent administered dose per gram of tumor should give a better understanding of the avidity of the tumor for the radiopharmaceutical. The percent *retained* dose per gram tumor, on the other hand, should give a clearer understanding regarding relative retention of the tracer in the tumor in relation to other tissues of the body. In our experiments, neither method indicates high specificity of this Tc-99m compound for this tumor, and, in fact, both suggest lower specificity than for other compounds currently in use.

TABLE 1. RADIOPHARMACEUTICAL RATING IN MOUSE BRAIN SARCOMA*

Rating No.	Radiopharmaceutical	Average % administered dose/g tumor	Ratios		
			T/Br†	T/Bl†	T/Sk†
1	Tc-99m Fe-(ascorbic acid)	2.56	8.6	0.55	0.81
2	Tc-99m Fe-(ascorbic acid)-DTPA	2.13	8.6	0.69	0.77
3	Tc-99m Sn-DTPA	1.24	6.5	1.18	1.05
4	[^{99m}Tc] pertechnetate (perchlorate predose 3 μg/g)	4.50	7.7	0.28	0.63
5	Tc-99m Sn-citrate	1.27	4.8	0.80	0.74
6	[^{99m}Tc] pertechnetate	3.25	6.1	0.24	0.48

Rating No.	Radiopharmaceutical	Average % retained‡ dose/g tumor	Ratios		
			T/Br†	T/Bl†	T/Sk†
1	Tc-99m Fe-(ascorbic acid)	4.91	8.6	0.55	0.81
2	Tc-99m Sn-DTPA	4.44	6.5	1.18	1.05
3	Tc-99m Fe-(ascorbic acid)-DTPA	4.21	8.6	0.69	0.77
4	[^{99m}Tc] pertechnetate (perchlorate predose 3 μg/g)	4.90	7.7	0.28	0.63
5	Tc-99m Sn-citrate	3.14	4.8	0.80	0.74
6	[^{99m}Tc] pertechnetate	3.39	6.1	0.24	0.48

* 10–60 min after i.v. injection.
† Br = brain; Bl = blood; Sk = skin.
‡ Average % dose/g tumor calculated per retained body activity at given time.

TABLE 2. RADIOPHARMACEUTICAL RATING IN MOUSE BRAIN SARCOMA*

Rating No.	Radiopharmaceutical	Average % administered dose/g tumor	Ratios		
			T/Br†	T/Bl†	T/Sk†
1	Tc-99m Fe-(ascorbic acid)	1.75	7.7	0.77	1.21
2	Tc-99m Fe-(ascorbic acid)-DTPA	1.49	5.4	1.20	1.35
3	[^{99m}Tc] pertechnetate (perchlorate predose 3 μg/g)	5.14	8.3	0.33	0.84
4	Tc-99m Sn-DTPA	0.25	1.8	2.28	1.44
5	[^{99m}Tc] pertechnetate	2.03	6.6	0.38	0.27
6	Tc-99m Sn-citrate	0.31	2.3	1.07	1.09

Rating No.	Radiopharmaceutical	Average % retained‡ dose/g tumor	Ratios		
			T/Br†	T/Bl†	T/Sk†
1	Tc-99m Fe-(ascorbic acid)	6.97	7.7	0.77	1.21
2	Tc-99m Fe-(ascorbic acid)-DTPA	5.94	5.4	1.20	1.35
3	Tc-99m Sn-DTPA	4.72	1.8	2.28	1.44
4	[^{99m}Tc] pertechnetate (perchlorate predose 3 μg/g)	7.42	8.3	0.33	0.84
5	Tc-99m Sn-citrate	2.30	2.3	1.07	1.09
6	[^{99m}Tc] pertechnetate	2.86	6.6	0.38	0.27

* 2 hr after i.v. injection.
† Br = brain; Bl = blood; Sk = skin.
‡ Average % dose/g tumor calculated per retained body activity at given time.

The use of animal tumor models does not permit extrapolation to man without due caution. The clinical effectiveness of a tumor-scanning agent can be determined only by careful studies in man. In this mouse tumor model, however, our results indicate that Tc-99m stannous citrate does not appear to achieve tumor localization by a mode different from that of other technetium-99m compounds now in clinical use, nor does it show promise of any biologic advantage over these other compounds for brain tumor scanning. Of the extensive number of radionuclides that have been used for brain tumor scanning, because of favorable physical characteristics, technetium-99m has become the radionuclide of choice, administered as the pertechnetate ion or chelated with DTPA (*8*). Of the many radionuclides and compounds available, however, each may have some advantages and disadvantages, and the final choice will remain with the individual physician who matches the technical aspects of nuclear medicine procedures to specific clinical problems.

FOOTNOTE

* Solco Basle Ltd. of Switzerland.

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