THE KINETICS OF ^{99m}Tc-, ^{113m}In-, AND ^{169}Yb-DTPA COMPOUNDS IN BRAIN SARCOMA AND KIDNEYS OF MICE

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During the past several years, diethylenetriaminepentaacetic acid (DTPA) compounds complexed with ^{113m}In, ^{169}Yb, and ^{99m}Tc have been introduced as new radiopharmaceuticals for brain tumor scintigraphy (*1–4*). The compounds have been reported to have several advantages over routine brain scanning agents such as ^{99m}Tc-pertechnetate, including a more rapid kidney excretion and higher tumor-to-brain ratios.

Because we have available in our laboratory a transplantable brain tumor in mice for studies of the pharmacokinetics of brain scanning agents (*5,6*), we have compared the tumor localization properties of these three DTPA compounds. In addition, using the same strain of mice as was used in the brain tumor studies, we have devised a method to measure renal clearance of radiopharmaceuticals (*7*). Renal clearance in mice of the three DTPA compounds has been established by this method and has been correlated with brain tumor localizing properties.

MATERIAL AND METHOD

Mouse brain tumor. The mice were males of the Yale-Swiss strain. The tumor is a methylcholanthrene-induced, transplantable brain tumor obtained initially in 1951 (*8*). The technique of transplantation has been described in detail previously (*5,6,8*). The experimental technique may be summarized as follows. Mice were studied one week after transplantation when the tumor had grown to a size of approximately 4 mm^3. Aqueous solutions of radionuclides were injected through the tail vein, care being taken to avoid infiltration. Mice were left undisturbed between the time of injection and the time of tissue sampling. At the appropriate time the animals were quickly euthanized. Samples of blood, tumor, brain, skin, and muscle tissue were removed, weighed, and placed in counting vials.

Renal clearance procedure. The method for determining renal clearance has been described in detail in a previous publication (*7*). In summary, Yale-Swiss mice of the same age and sex which had no brain tumors were used. The mouse was induced to urinate, the penis was then ligated, and injections were made through the tail vein. At the end of the experimental time period, the animals were sacrificed, a heart blood sample was obtained, and urine was quantitatively collected by intact bladder removal. A standard curve of blood concentration was used to correlate blood levels with urine content of radioactivity, and the renal clearance was calculated by the classical technique (UV/B). The results are normalized to 1.73 m^2 surface area so that comparison could be made to humans. The clearance of inulin in the mice expressed in this way is approximately 100 ml/min which correlates nicely with the known inulin clearance in man.

Radiopharmaceuticals. Technetium-99m-DTPA complex (Tc-DTPA) was prepared in our laboratory using a commercially available kit (Renotec, Squibb Radiopharmaceutical Div., New Brunswick, N.J.). Preparations of Tc-DTPA, prepared according to the directions provided, normally have 90–100% of the activity in the bound form, as determined by thin-layer radiochromatographic technique. The Tc-DTPA has been tested for acute intravenous toxicity in mice and found to be nontoxic at a dose level of 20 ml/kg (*9*).

Indium-113m-DTPA (In-DTPA) was prepared in our laboratory using the method of Clements, et al (*1*). Indium-113m was eluted from a generator (New England Nuclear Corp., Cambridge, Mass.) with

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TABLE 1. DISTRIBUTION OF RADIOPHARMACEUTICALS IN MICE OF VARIOUS TISSUES (PERCENT DOSE PER GRAM)

Time post-injection (min)	Tumor			Brain			Blood			Skin			Muscle		
	^{99m}Tc-DTPA	^{169}Yb-DTPA	^{113m}In-DTPA	Tc	Yb	In	Tc	Yb	In	Tc	Yb	In	Tc	Yb	In
10	2.32 ±0.85	2.05 ±0.70	2.18 ±0.52	0.36 ±0.06	0.32 ±0.09	0.25 ±0.07	8.18 ±1.24	4.46 ±0.09	5.16 ±0.83	5.95 ±1.54	3.89 ±0.97	5.37 ±1.07	2.36 ±0.56	1.58 ±0.36	2.13 ±0.89
20	2.03 0.74	1.25 0.42	1.86 1.06	0.22 0.08	0.14 0.07	0.37 0.15	4.06 1.53	1.61 0.40	4.94 4.12	3.20 2.09	1.84 0.88	3.61 2.50	1.28 0.73	0.67 0.42	2.07 1.74
30	2.31 1.21	0.65 0.18	1.20 0.51	0.31 0.26	0.09 0.04	0.21 0.09	2.93 0.77	0.79 0.33	1.31 0.59	2.06 0.58	0.88 0.42	1.47 0.38	0.74 0.21	0.29 0.15	0.47 0.23
60	1.52 0.44	0.42 0.15	0.33 0.08	0.12 0.02	0.11 0.08	0.11 0.04	1.38 0.18	0.12 0.05	0.24 0.14	0.76 0.12	0.28 0.14	0.21 0.17	0.40 0.16	0.09 0.03	0.09 0.05
90	1.44 0.50	0.17 0.03	0.23 0.09	0.13 0.06	0.07 0.02	0.11 0.07	0.91 0.22	0.03 0.01	0.12 0.03	0.45 0.12	0.10 0.05	0.12 0.03	0.21 0.04	0.03 0.01	0.06 0.01
120	1.04 0.46	0.15 0.03	0.21 0.09	0.18 0.12	0.09 0.01	0.10 0.04	0.79 0.17	0.04 0.006	0.11 0.03	0.51 0.22	0.09 0.01	0.08 0.02	0.22 0.09	0.03 0.01	0.05 0.02
180	1.02 0.46	0.09 0.04	0.14 0.04	0.19 0.08	0.08 0.04	0.11 0.03	0.74 0.24	0.01 0.003	0.06 0.02	0.49 0.15	0.06 0.03	0.09 0.05	0.22 0.06	0.02 0.01	0.04 0.03
240	1.01 0.21	0.08 0.03	—	0.12 0.02	0.08 0.03	—	0.91 0.19	0.01 0.002	—	0.72 0.36	0.08 0.04	—	0.34 0.19	0.02 0.01	—

Each data point shows the standard of deviation $[(\Sigma d^2)n]^{1/2}$ of at least six observations.

0.05 *N* HCl. Fe^{3+} (200 μg in 0.2 cc) 0.05 *N* HCl, was added to the carrier-free ^{113m}In, followed by an excess of DTPA (1.6 mg). The mixture was titrated to pH 7–7.5 with dilute NaOH and finally sterilized by autoclaving.

Ytterbium-169-DTPA chelate (Yb-DTPA) was obtained as an investigational drug (Minnesota Mining and Manufacturing Co., St. Paul, Minn.). The specific activity was 0.2 mCi/ml (0.255 mg DTPA) as of date of assay. The injected solution contained 0.4 mCi/0.51 μg/DTPA per 0.01 ml.

Evaluation of results. Activities were expressed as percent injected dose per gram of tumor, and tissue ratios were determined for each time interval. For each experimental point, the standard deviation was calculated $[(\Sigma d^2)n]^{1/2}$. Each data point was made up of at least six independent observations. Student t-test of significance was used to evaluate differences between groups of animals with an arbitrary level of significance, chosen as $p < 0.05$. In skin, where an average of 30% of skin weight is fur, we corrected the observed concentration to 100% skin by multiplying by 100/70.

RESULTS

Tissue localization of radioactivity. In Table 1, the data for each of the three compounds in tumor, brain, blood, skin, and muscle at 10, 20, 30, 60, 90, 120, 180, and 240 min after injection are seen. Significant differences are present between Tc-DTPA and the other two compounds in tumor, blood, skin, and muscle after the 30-min time interval. In general, no significant differences were detected between Yb-DTPA and In-DTPA although several observations were of marginal significance.

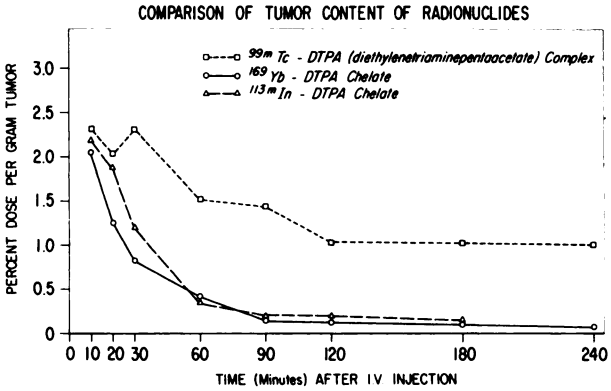

FIG. 1. Time-course plot of % dose/gm tissue of labeled DTPA compounds. There is marked divergence of ^{99m}Tc-DTPA complex after 30-min point.

Figure 1 shows the mean percent dose per gram of tumor content. For Tc-DTPA, beginning at the 30-min point, there is marked deviation in tumor content from those of the other nuclides. Figure 2 shows the significantly higher tumor-to-brain ratio with Tc-DTPA, beginning at the 60-min observation. Tumor-to-brain ratios with Yb-DTPA and In-DTPA, somewhat below Tc-DTPA during the first 30 min, were markedly reduced after 30 min.

Renal clearance. Table 2 shows the renal clearance evaluation indices for the three DTPA compounds compared to the standards (^{14}C-inulin and ^{131}I-o-iodohippurate). These data, expressed as

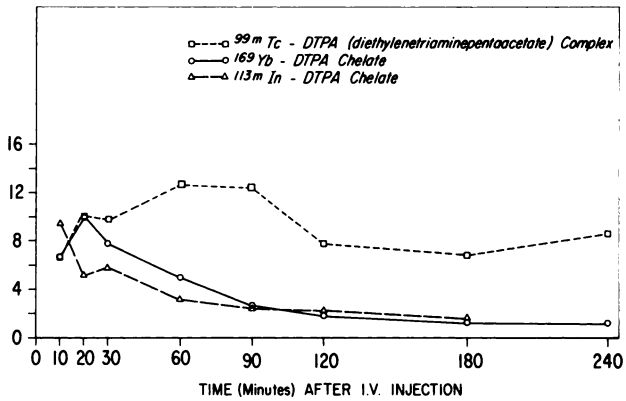

FIG. 2. Tumor-to-brain ratios of labeled DTPA compounds plotted against time. ^{99m}Tc-DTPA complex tumor-to-brain ratios are elevated after 30-min point.

plasma clearance, are presented in detail in a separate publication (*10*). For Yb-DTPA the blood clearance was 356.6 ml/min at low blood levels and 134.6 ml/min at high blood levels per 1.73 m^2 surface area. The point of 50% urinary excretion occurred at 9.5 min. When standardized to 1.73 m^2 surface area, the average In-DTPA clearance was 169.8 ml/min at low blood concentration and 109.0 ml/min at high blood concentration. The point of 50% urinary excretion occurred at 11.5 min. For Tc-DTPA the clearance was 36.1 ml/min per 1.73 m^2 surface area. Because of its low clearance rate only high blood concentrations were observed during the period of study. The point of 50% urinary excretion occurred at 25 min.

Comparison with pertechnetate and chlormerodrin results. Figure 3 compares mean tumor content of Tc-DTPA and Yb-DTPA with values obtained previously for ^{99m}Tc-pertechnetate (pertechnetate) (*5*), and ^{197}Hg-chlormerodrin (chlormerodrin) (*6*). Because Yb- and In-DTPA parallel closely, only one is shown. Compared with chlormerodrin and pertechnetate, both DTPA compounds have significantly less tumor content of radionuclide. Tc-DTPA is intermediate between the more rapidly excreted compounds and the standard agents. Figure 4 compares tumor-to-brain ratios for the two DTPA compounds and pertechnetate and chlormerodrin. Chlormerodrin shows a slow, progressively rising tumor-to-brain ratio to peak at approximately 4 hr. Pertechnetate rises slowly and plateaus. Yb-DTPA and In-DTPA peak early and then decline. Tc-DTPA has a more prolonged and higher tumor-to-brain ratio curve than the other DTPA compounds.

Relationship between renal clearance and tumor localization. Table 3 shows the relationship between renal clearance and tumor content of radioactivity obtained with different brain tumor scanning agents. Only the overall average clearance of blood is shown. Pertechnetate is shown both with and without perchlorate blocking, and chlormerodrin is shown with and without meralluride blocking. The slowest cleared (only 3.7 ml/min) is pertechnetate with

TABLE 2. RADIOPHARMACEUTICAL EVALUATION INDICES

Compound	Labeled compound or carrier*		Average blood concentration and range/ml		UV/B clearance (ml/min)†	
	Body dose (μg)	Dose (μg/gm BW)	cpm%	μg%	L	H
^{14}C-inulin	254.0	12.7	1.26 0.41–3.26	3.20 1.04–8.29	101.2	
^{131}I-o-iodohippurate* (OIH)	20.0	1.0	L 0.38 0.20–0.83 H 2.38 1.46–3.30	0.08 0.04–0.17 0.48 0.29–0.66	221.1	190.0
^{169}Yb-DTPA*	10.2	0.51	L 0.33 0.07–0.87 H 3.62 1.42–6.67	0.03 0.01–0.09 0.37 0.15–0.68	356.6	134.6
^{113m}In-DTPA*	40.0	2.0	L 0.50 0.27–0.84 H 3.20 1.17–6.50	0.20 0.11–0.34 1.28 0.47–2.60	169.8	109.0
^{99m}Tc-DTPA*	142.0	7.1	3.98 2.85–6.25	5.65 4.05–8.88	—	36.1

* The substance calculated.
† Extrapolated to a 1.73 m^2 surface area UV/B · 1.73/0.114 $W^{2/3}$ F = 206.0 for a 20-gm mouse.
L Low concentration of substance in blood/ml : : 0.1–1.0% dose.
H High concentration of substance in blood/ml : : 1.0 and over % dose.

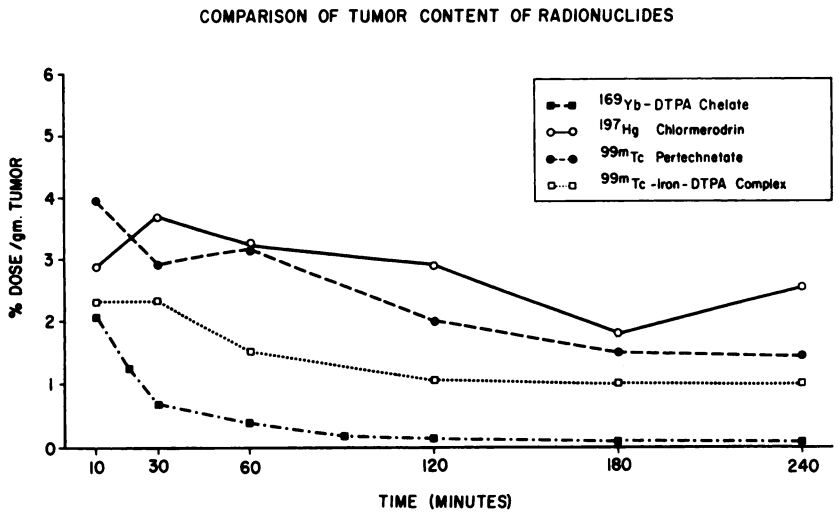

FIG. 3. Time-course plots of % dose/gm tumor of labeled DTPA compounds compared with ^{197}Hg-chlormerodrin and ^{99m}Tc-pertechnetate. Because of similarity of ^{169}Yb-DTPA and of ^{113m}In-DTPA curves, only ^{169}Yb-DTPA curve is shown.

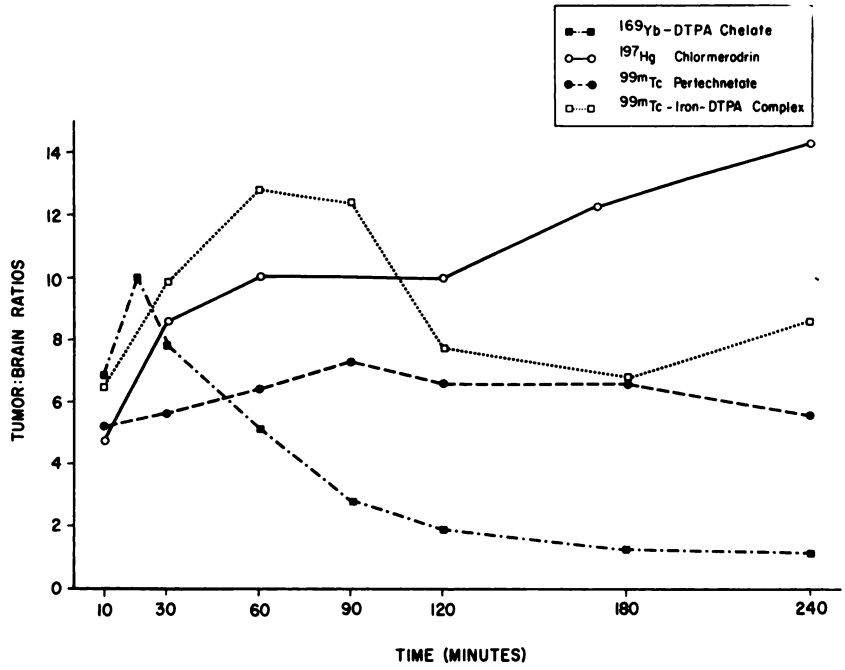

FIG. 4. Tumor-to-brain ratios of labeled DTPA compounds plotted against time compared with those of ^{197}Hg-chlormerodrin and ^{99m}Tc-pertechnetate. Because of similarity of ^{169}Yb-DTPA and of ^{113m}In-DTPA curves, only ^{169}Yb curve is shown.

perchlorate administered prior to dosing, and it was associated with the highest tumor content of radioactivity. The most rapid is Yb-DTPA (275.9 ml/min), and here the tumor content is least. Tumor-to-brain ratios, although more variable, showed some tendency to be highest when renal clearance is intermediate to slow. Figure 5 shows graphically the relationship on a semilog scale for tumor content and blood clearance. The fit of the curve to the data points is striking.

DISCUSSION

The tumor-to-brain ratios reported here are somewhat at variance with those reported by others. Clements, et al (*1*) reported tumor-to-brain ratios for In-DTPA in a transplantable mouse ependymoma of 25:1, 30 min after injection, and 24:1, 60 min after injection. In the same tumor model, Gilday, et al (*3*) reported maximum tumor-to-brain ratios for Yb-DTPA of 19:1 at 30 min and 18:1 at 60 min following injection. O'Mara, et al (*11*), working with a mouse ependymoblastoma, found maximum ratios of 30:1 with In-DTPA 1 hr after injection. All of these studies were performed with the experimental tumor implanted subcutaneously, rather than in the brain, as is the case with our study. Differences in blood supply and pressure relationships may account for the differences in tumor-to-brain ratios. Burdine, et al (*12*), working with a viral-induced in situ brain tumor in hamsters, found maximum tumor-to-brain ratios on the order of 11:1, 30 min after injection. It is of some interest that in all studies

comparing In-DTPA with pertechnetate, the ratio of DTPA to pertechnetate has been between 1.4 and 2.0.

No reports of experimental brain tumor localization of Tc-DTPA could be found in the literature with which these data could be compared; however, a report by Atkins, et al (*13*) suggests considerable differences in renal clearance of several Tc-DTPA preparations which differed in technique of formulation. The Tc-DTPA compound used in these experiments was excreted more slowly than ^{99m}Tc-DTPA(Fe) and ^{99m}Tc-DTPA(Sn). As Tc-DTPA clearance was only about one third that of inulin, significant tubular reabsorption is indicated, possibly because the Tc-DTPA bond is not firm. Indeed, the Squibb Tc-DTPA has been shown to have clearance closer to Tc-iron ascorbic acid complex than to Tc-DTPA (*13*). In-DTPA and Yb-DTPA clearances are above inulin, indicating possible tubular secretion of these chelates in mice.

TABLE 3. RELATION OF BRAIN TUMOR UPTAKE TO RENAL BLOOD CLEARANCE IN MICE

Tumor scanning agents	UV/B clearance (ml/min)*	Highest % dose/gm tumor	Maximum tumor: brain ratios
^{99m}Tc (perchlorate predose 3.0 μg/gm BW)	3.7	5.14	9.7
^{99m}Tc	6.2	3.93	7.3
^{197}Hg-chlormerodrin	8.2	3.67	14.5
^{197}Hg-chlormerodrin (meralluride predose 0.56 μg/gm BW)	11.6	3.24	14.2
^{99m}Tc-iron-ascorbic acid-DTPA	36.1	2.32	12.8
^{113m}In-DTPA	136.6	2.18	10.0
^{169}Yb-DTPA	275.9	2.05	9.4

* Extrapolated to 1.73 m^2 surface area.

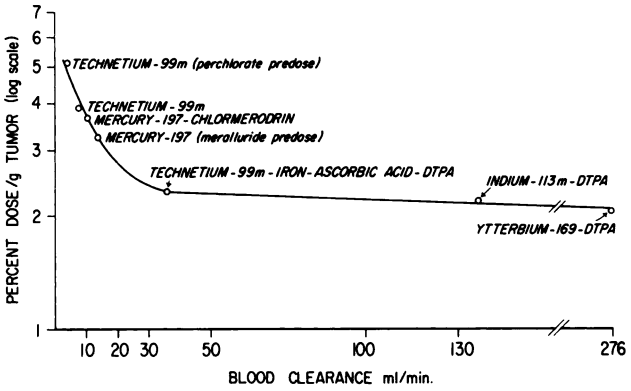

FIG. 5. Relationship of tumor uptake to renal clearance in mice. Maximum % dose/gm tumor (irrespective of time, log scale) is plotted against average renal blood clearance, UV/B, in ml/min, standardized to body surface area of 1.73 m^2.

Comparative clinical trials of the three DTPA compounds evaluated in this report with pertechnetate have been reported. In-DTPA brain scans were found by Clements, et al (*1*) to be comparable with pertechnetate in the detection and characterization of intracranial lesions. Gilday, et al (*3*) found that scan and camera images in 50 paired-patient studies performed with pertechnetate and Yb-DTPA were comparable. Brookeman and Williams (*14*) performed paired brain images with pertechnetate and Squibb Tc-DTPA 2 days apart in 14 patients with a variety of intracranial lesions and found that all lesions were visualized equally well with both scanning agents. We have performed comparative studies in patients (*15*) and find several advantages for Tc-DTPA complex over pertechnetate, including clearer delineation of some metastatic brain tumors, earlier optimum dose-to-scan interval, and less interference from salivary gland and choroid plexus concentration.

We are planning studies of the relationship of tumor uptake and renal clearance in patients with brain tumors to establish whether findings in this study can be confirmed in man. Such studies should constitute a useful standard by which these and other radiopharmaceuticals for brain tumor scanning can be judged.

SUMMARY

Studies of experimental tumor localization and renal clearance in mice of DTPA preparations labeled with ^{99m}Tc, ^{113m}In, and ^{169}Yb revealed significant differences between the technetium compound and the indium and ytterbium chelates. These were (A) slower renal clearance and (B) higher radionuclide tumor content and tumor-to-brain ratios with the technetium compound. These findings support the contention that the Tc-DTPA preparation used in these experiments is not a true chelate and is biologically more like the iron-ascorbic acid complex of technetium than a DTPA chelate. The results also suggest that there may be some advantages for this technetium compound for tumor localization studies over the true DTPA chelates.

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