BRAIN TUMOR-SCANNING AGENTS COMPARED IN AN ANIMAL MODEL

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Sixteen radiopharmaceuticals for brain tumor localization have been compared in a mouse brain tumor model. A rating system is presented for such intercomparison. The results indicate that ^{111}In-chloride injected at pH 1.5 has the most favorable biologic characteristics for brain tumor imaging.

Radiopharmaceuticals for the diagnostic delineation of tumors have been selected rather empirically based on availability of radionuclide and chemical form and on the physical properties of the radionuclide. Recent publications have attempted to review and organize experimental results using various animal tumor systems and radiopharmaceuticals (*1–6*). However, these studies deal with a limited number of compounds, use diverse techniques and animal tumor systems for measurements, and, therefore, exacting intercomparison of the numerous labeled compounds may not be possible. The search for a better scanning agent to detect and localize brain tumors continues with the resultant addition or suggestion of new compounds. DiChiro's question, "Which radioisotope for brain scanning?" (*6*), is just as timely now as when first proposed.

This paper reports on a controlled intercomparative study of 16 radiopharmaceutical preparations using as a model a well-established transplantable in situ mouse brain tumor technique. Time-course tissue distribution studies of tumor, brain, blood, and skin are reported as are tumor-to-tissue ratios, estimated total-body radiation dose, and the relationship between maximum tumor uptake and renal blood clearance. When an attempt was made to intercompare the results obtained from this series of compounds, the need for a relative rating system became apparent. The rating system reported here takes into consideration (A) the amount of radioactivity in the tumor at the time of scanning and (B) the background activity in brain, blood, and skin at the time of scanning. Skull bone determinations, although important, were not done because of technical difficulties encountered in working with mice at this age. Physical and radiobiologic properties including radiation energy, physical half-life, and absorbed radiation dose, also important, will be considered separately.

MATERIALS AND METHODS

Radiopharmaceuticals. Radiopharmaceuticals used in this study were: ^{111}In-chloride (pH 1.5), ^{99m}Tc-Fe-ascorbic acid, ^{67}Ga-lactate, ^{197}Hg-chlormerodrin, ^{99m}Tc-Sn-DTPA, ^{111}In-bleomycin, ^{131}I-human serum albumin, ^{169}Yb-DTPA, ^{99m}Tc-Fe-ascorbic acid-DTPA, ^{113m}In-DTPA, ^{67}Ga-chloride, ^{67}Ga-citrate, ^{67}Ga-Fe-DTPA, and ^{99m}Tc-pertechnetate. In addition, ^{99m}Tc-pertechnetate with perchlorate predose and ^{197}Hg-chloromerodrin with meralluride predose were studied. When possible, the radiopharmaceuticals were purchased from commercial suppliers; otherwise, the material was prepared from commercial kits or prepared in our laboratory using accepted manufacturing and quality-control procedures.

Mouse distributional studies. The mouse brain tumor system (*7*) used was a methylcholanthrene-induced, transplanted cerebral sarcoma. The exact technique followed and some of the specific data relating to these compounds have appeared previously (*8–12*). To summarize, following tail vein injection of the radiopharmaceutical, time-course distributional studies were performed in Yale-Swiss mice at 10, 20, and 30 min and at 1, 2, 3, 4, 6, 24, and 48 hr. Tissues sampled were tumor, brain, blood, and skin. Six mice were used for each point. Tissue samples were weighed, dissolved in nitric acid, counted for gamma activity in a scintillation well

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counter, and compared with a standard representative of the total dose injected. Tumor-to-brain, tumor-to-blood, and tumor-to-skin ratios were calculated. Results were averaged for the 10–30 min and the 1–2 and 3–4 or 3–6-hr intervals. The 24- and 48-hr values were listed independently.

Renal blood clearance data. The method for measurement of renal blood clearance and most of the values reported have been described previously in detail (*10–16*) as special research projects have been completed. Classic clearance methods were used with the exception that quantitated urine collection was assured by penis ligation and intact bladder dissection.

Radiation dose calculations. The estimated radiation doses to the total human body from radioactivity throughout the body for the various radiopharmaceuticals were calculated using the methods proposed by the Medical Internal Radiation Dose Committee (MIRD) of the Society of Nuclear Medicine (*17–19*). The activity-time integrals used in the dose calculations for human beings were those calculated for mice, using radioactive excretion measurements for the 2–4-hr period after injection and total-body radioactivity retention measurements for subsequent time. Abundance and mean energies of emissions from radionuclides (*20*) and absorbed fractions (*21*) were taken from the MIRD pamphlets and from Dillman (*22*).

RESULTS

Evaluation of results. The average value of data obtained from at least six mice was used for each data point. On the basis of tissue distribution data, a rating number was assigned for each radiopharmaceutical for the 10–30 min, the 1–2, the 3–4 or 3–6, 24-, and 48-hr time intervals. The compound having the average highest dose percent per gram tumor was assigned a value of one, with each one of the other compounds being assigned a sequentially higher number depending on its relative percent dose per gram tumor value. In a similar manner, the compound having the highest tumor-to-brain ratio was assigned a value of one, with each one of the other compounds being assigned a sequentially higher number as its tumor-to-brain ratio decreased. Relative values were assigned to tumor-to-blood and tumor-to-skin ratios in a like manner. The sum of the four sequential numbers then was used to determine the final distributional rating number. The compound with the lowest total sum was assigned the best final rating number, one, and the compound with the highest sum was given the poorest rating, 16. To remain in a time-interval grouping, a compound had to localize at least to the extent of 1% dose/gm tumor; otherwise it was dropped from that group.

Table 1 gives the average percent dose per gram tumor and the tumor-to-brain, tumor-to-blood, and tumor-to-skin ratios 10–30 min after intravenous injection of the 16 radiopharmaceuticals. The values listed are the average of measurements made on 18 mice. Standard deviations were determined for each point (10, 20, and 30 min), but are not given in Table 1 since the data in this table represent an average of the three points. Based on the relative sequential number system described, the compounds

TABLE 1. RADIOPHARMACEUTICAL RATING IN MOUSE BRAIN SARCOMA*

Rating No.	Radiopharmaceutical	Average (% dose/gm tumor)	Ratios		
			T/Br	T/Bl	T/Sk
1	^{111}In-chloride (pH 1.5)	9.02	7.5	0.19	2.08
2	^{99m}Tc-Fe-ascorbic acid	2.78	9.1	0.49	0.74
3	^{67}Ga-lactate	5.58	6.1	0.27	0.79
4	^{197}Hg-chlormerodrin	3.04	6.8	0.25	1.13
5	^{99m}Tc-Sn-DTPA	1.49	7.4	0.84	0.75
6	^{111}In-bleomycin (pH 6.5)	2.71	11.8	0.63	0.54
7	^{131}I-human serum albumin	7.03	6.3	0.13	2.81
8	^{169}Yb-DTPA	1.32	8.2	0.72	0.69
9	^{99m}Tc-Fe-ascorbic acid-DTPA	2.34	8.6	0.52	0.57
10	^{113m}In-DTPA	1.75	6.8	0.61	0.59
11	^{67}Ga-chloride	5.32	5.6	0.22	0.67
12	^{67}Ga-citrate	4.53	5.7	0.18	1.02
13	^{67}Ga-Fe-DTPA	1.94	7.6	0.36	0.51
14	^{99m}Tc-pertechnetate (perchlorate predose 3 μg/gm BW)	4.74	5.6	0.24	0.64
15	^{197}Hg-chlormerodrin (meralluride predose 0.56 μg Hg/gm)	2.80	6.6	0.21	0.56
16	^{99m}Tc-pertechnetate	3.28	6.0	0.21	0.49

* Ten to 30 min after i.v. injection.

are presented in order of increasing biologic distribution rating number. The compounds with better imaging distributional patterns (lower sequential numbers) appear in the upper part of the table whereas those with poorer distributional patterns (higher sequential numbers) appear near the bottom.

For the 10–30-min postinjection period, the best biologic distribution for brain scanning is exhibited by ^{111}In-chloride (pH 1.5) and the worst rating is obtained by the widely used ^{99m}Tc-pertechnetate. The ^{99m}Tc-Fe-ascorbic acid complex, as suggested by Stapleton, Odell, and McKamey (*23*) and by Konikowski, et al (*11*), ranks a surprising second rating, with ^{67}Ga-lactate third, and ^{197}Hg-chlormerodrin fourth. Predosing with perchlorate moves ^{99m}Tc-pertechnetate only from 16th to 14th position whereas predosing with meralluride moves ^{197}Hg-chlormerodrin from 4th to 15th rank. The other rankings are: 5th, ^{99m}Tc-Sn-DTPA; 8th, ^{169}Yb-DTPA; 9th, ^{99m}Tc-Fe-ascorbic acid-DTPA; 10th, ^{113m}In-DTPA; and 13th, ^{67}Ga-Fe-DTPA.

Table 2 gives the average percent dose per gram tumor and the tumor-to-brain, tumor-to-blood, and tumor-to-skin ratios for 13 radiopharmaceuticals 1–2 hr postinjection. These 13 compounds gave an average tumor uptake in excess of 1% dose/gm tumor for this time interval. Again, the compounds are listed in order of increasing distributional rating number with those having the best imaging properties being represented by the smaller rating numbers. Each value represents the average results from 12 animals.

For the 1–2-hr postinjection period ^{111}In-chloride (pH 1.5) and ^{99m}Tc-pertechnetate still rank first and last, respectively, in our distributional rating system. The use of perchlorate predose elevates ^{99m}Tc-pertechnetate to the tenth place whereas the use of meralluride predose increases the rating of ^{197}Hg-chlormerodrin from fifth to second.

In Table 3 are presented the average percent dose per gram tumor and the tumor-to-brain, tumor-to-blood, and tumor-to-skin ratios for the radiopharmaceuticals 3–4 or 3–6 hr postinjection. The average values resulting from 12 or 18 animals were used for each point. As with previous tables, the substances are listed in order of increasing distributional rating number.

For the 3–4 or 3–6 hr postinjection interval, again ^{111}In-chloride (pH 1.5) occupies the first rating position and ^{99m}Tc-pertechnetate is found last. Predosing with perchlorate elevates pertechnetate to the tenth spot whereas ^{197}Hg-chlormerodrin with and without meralluride predose occupies the second and third rating positions, respectively. During the first three time intervals, ^{131}I-human serum albumin is found in positions seven, four, and five.

Table 4 gives the average percent dose per gram tumor and the tissue ratios for the remaining radiopharmaceuticals at 24 and 48 hr. Each value is the average obtained from six mice. At 24 hr, only five compounds are found in tumor concentration greater than 1% dose/gm tumor; at 48 hr, only four compounds have an average tumor concentration in excess of 1% dose/gm tumor. As in previous tables, the compounds are listed in order of increasing distributional rating number.

At 24 hr, ^{67}Ga-lactate gives the best tissue distributional pattern for brain scanning. Indium-111-chloride is second. In third rank is found ^{131}I-human serum albumin followed by ^{67}Ga-chloride and ^{67}Ga-citrate.

TABLE 2. RADIOPHARMACEUTICAL RATING IN MOUSE BRAIN SARCOMA*

Rating No.	Radiopharmaceutical	Average (% dose/gm tumor)	Ratios		
			T/Br	T/Bl	T/Sk
1	^{111}In-chloride (pH 1.5)	14.56	11.4	0.46	2.22
2	^{197}Hg-chlormerodrin (meralluride predose 0.56 μg Hg/gm)	2.70	13.6	0.59	2.41
3	^{67}Ga-lactate	6.08	8.8	0.89	0.66
4	^{131}I-human serum albumin	11.24	7.8	0.24	3.34
5	^{197}Hg-chlormerodrin	3.06	9.9	0.55	1.60
6	^{67}Ga-chloride	6.51	7.5	0.67	0.82
7	^{67}Ga-citrate	4.78	8.2	0.66	0.54
8	^{99m}Tc-Fe ascorbic acid	1.82	7.4	0.74	1.11
9	^{99m}Tc-Fe-ascorbic acid-DTPA	1.48	7.0	1.20	1.37
10	^{99m}Tc-pertechnetate (perchlorate predose 3 μg/gm BW)	4.70	9.0	0.32	0.73
11	^{113}In-bleomycin (pH 6.5)	1.63	7.1	0.84	0.94
12	^{67}Ga-Fe-DTPA	1.43	5.1	0.61	0.69
13	^{99m}Tc-pertechnetate	2.43	6.8	0.33	0.34

* One to 2 hr after i.v. injection.

TABLE 3. RADIOPHARMACEUTICAL RATING IN MOUSE BRAIN SARCOMA*

Rating No.	Radiopharmaceutical	Average (% dose/gm tumor)	Ratios		
			T/Br	T/Bl	T/Sk
1	^{111}In-chloride (pH 1.5)*	15.70	14.0	0.89	1.85
2	^{197}Hg-chlormerodrin*	2.20	12.5	0.92	3.64
3	^{197}Hg-chlormerodrin* (meralluride predose 0.56 μg Hg/gm)	1.78	8.7	0.95	3.75
4	^{67}Ga-lactate*	6.55	9.1	0.96	0.88
5	^{131}I-human serum albumin*	15.69	8.0	0.39	3.33
6	^{67}Ga-citrate*	5.76	11.1	0.93	0.80
7	^{67}Ga-chloride*	7.31	8.4	0.79	1.21
8	^{99m}Tc-Fe-ascorbic acid	1.40	8.0	1.41	1.42
9	^{99m}Tc-Fe-ascorbic acid-DTPA	1.16	5.8	1.83	1.68
10	^{99m}Tc-pertechnetate (perchlorate predose 3 μg/gm BW)	4.02	7.7	0.30	0.83
11	^{67}Ga-Fe-DTPA*	1.66	7.6	0.78	0.78
12	^{111}In-bleomycin (pH 6.5)	1.03	7.1	0.90	0.74
13	^{99m}Tc-pertechnetate*	1.46	6.5	0.28	0.25

* Three to 4 or 3 to 6 hr after i.v. injection.

TABLE 4. RADIOPHARMACEUTICAL RATING IN MOUSE BRAIN SARCOMA

Rating No.	Radiopharmaceutical	Average (% dose/gm tumor)	Ratios		
			T/Br	T/Bl	T/Sk
		24 hr after iv injection			
1	^{67}Ga-lactate	3.87	5.0	7.3	1.6
2	^{111}In-chloride (pH 1.5)	10.82	8.1	4.4	0.8
3	^{131}I-human serum albumin	6.45	5.5	0.4	1.2
4	^{67}Ga-chloride	1.85	4.9	7.0	1.9
5	^{67}Ga-citrate	2.32	4.8	3.5	1.1
		48 hr after iv injection			
1	^{111}In-chloride (pH 1.5)	4.02	6.6	4.3	0.3
2	^{131}I-human serum albumin	3.53	5.0	0.4	1.1
3	^{67}Ga-citrate	1.52	3.7	5.7	0.9
4	^{67}Ga-lactate	1.27	4.9	4.0	0.5

Four compounds remain for evaluation at 48 hr. In order of preferred distributional rating, these are ^{111}In-chloride, ^{131}I-human serum albumin, ^{67}Ga-citrate, and ^{67}Ga-lactate.

Table 5 gives the highest percent dose per gram tumor uptake irrespective of time, the renal blood clearance in milliliters per minute, and the maximum tumor-to-brain ratios of the 16 radiopharmaceuticals. The renal blood clearance data are standardized by calculation to a uniform body surface area of 1.73 m^2. The compounds are listed in order of decreasing maximum tumor uptake.

In Fig. 1, the highest percent dose per gram tumor of each radiopharmaceutical is plotted on a log scale against the average renal blood clearance in milliliters per minute standardized to a uniform body surface area of 1.73 m^2.

Table 6 lists the estimated absorbed radiation dose to the total human body based on biologic data generated in these mouse studies. The absorbed total-body dose is given in units of millirads per millicurie injected.

DISCUSSION

There are a number of ways in which the relative merits of radiopharmaceuticals as scanning agents may be assessed. Ideally, they should be intercompared clinically in patients. They may be compared by lumping together large numbers of cases from different investigators obtained from the literature, or a single investigator can evaluate several tracers in different groups of patients. A third approach to comparison is to perform repeated scans in the same patient using a different substance for each scan before the tumor has undergone significant change. A modification of this last approach is to

TABLE 5. RELATION OF BRAIN TUMOR UPTAKE TO RENAL BLOOD CLEARANCE IN MICE

Tumor-scanning agents	Highest (% dose/gm tumor)	UV/B* clearance (ml/min)	Maximum tumor:brain ratios
^{111}In-chloride (pH 1.5)	18.64	0.45	17.2
^{131}I-human serum albumin	14.92	0.14	9.8
^{67}Ga-lactate	7.90	3.8	10.6
^{67}Ga-chloride (pH 3.0)	7.86	6.1	9.9
^{67}Ga-citrate	5.92	0.7	12.5
^{99m}Tc-pertechnetate (perchlorate predose 3 μg/gm BW)	5.14	3.7	9.7
^{99m}Tc-pertechnetate	3.93	6.2	7.3
^{197}Hg-chlormerodrin	3.67	8.2	14.5
^{197}Hg-chlormerodrin (meralluride predose 0.56 μg Hg/gm BW)	3.24	11.6	14.2
^{99m}Tc-Fe-ascorbic acid†	3.19	31.0	9.8
^{111}In-bleomycin	2.95	52.4	13.5
^{99m}Tc-Fe-ascorbic acid-DTPA†	2.79	46.7	9.9
^{67}Ga-Fe-DTPA	2.42	33.8	8.7
^{113m}In-DTPA	2.18	136.6	10.0
^{99m}Tc-Sn-DTPA	2.09	171.6	10.1
^{169}Yb-DTPA	2.05	275.9	9.4

* Extrapolated to 1.73 m^2 surface area.
† Commercial kit, the same batch.

use multiple tracers for each scan depending on instrumentation and data handling to differentiate results. All of these clinical approaches have obvious shortcomings.

The surgical biopsy approach to the intercomparison of radiopharmaceuticals is relatively unreliable, particularly in the case of brain tumors. When biopsy samples of tumor and brain are obtained at the time of surgery, a number of techniques and clinical conditions must be accepted. Hepatic and renal function and alterations in the blood-brain barrier may be caused by intravenous infusions, cerebral angiography, prolonged anesthesia, operative procedures, and other necessary conditions. The biopsy samples of normal brain must of necessity be minute and located immediately adjacent to the tumor. These small brain samples show large statistical and distributional variations and may be infiltrated with tumor.

The use of autopsy specimens for the intercomparison of radiopharmaceuticals is also open to serious questions. The number of samples available is limited. In addition, the dying process, particularly in patients with cancer, may be prolonged over a period of time, leading to unusual distributional patterns caused by a failing heart and by drastic changes in liver and kidney function.

Although the process is also subject to limitations, there is a need for carefully controlled laboratory intercomparison studies of radiopharmaceuticals in the same biosystem. The suitability of tumor-bearing mice for predicting relative usefulness of radionuclides in brain tumors has been discussed and evaluated by Locksley, et al (*24*). The fact that the brain tumor in our system is an in situ intracerebral tumor, thus subject to the normal vasculature and pressures of a brain tumor, dispels some of the questions previously raised as to validity of results due to tumor location (*3,4*).

A very important relationship in organ imaging

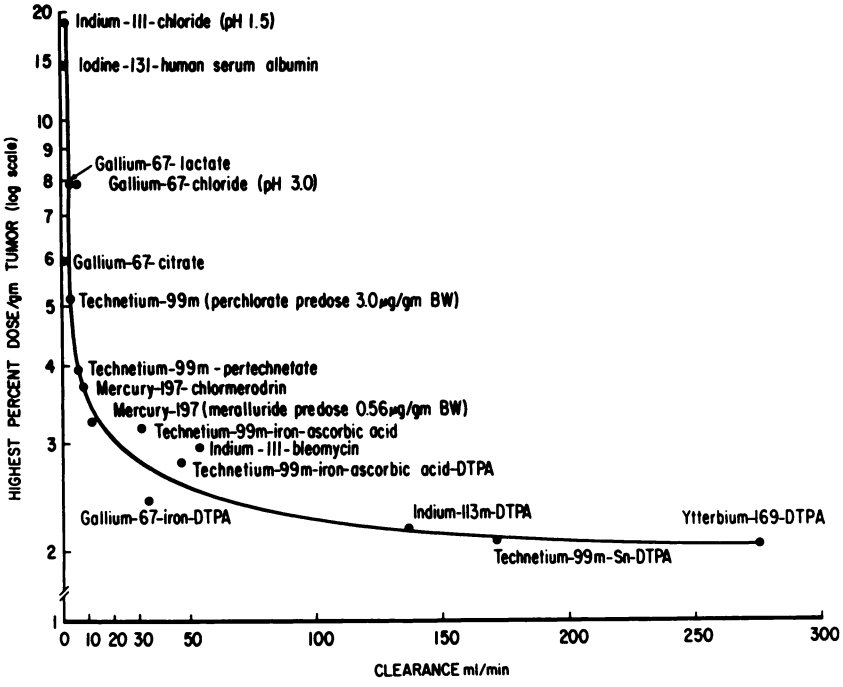

FIG. 1. Tumor uptake of 16 radiopharmaceuticals in highest percent dose per gram tumor (log scale) plotted against renal blood clearance in milliliters per minute standardized to body surface area of 1.73 m^2. Inverse relationship is noted.

TABLE 6. ABSORBED DOSES OF VARIOUS RADIOPHARMACEUTICALS TO TOTAL BODY RANKED IN ORDER OF DECREASED DOSE RATE

Scanning agents	Absorbed dose (mrad/mCi)
^{111}In-chloride (pH 1.5)	395
^{131}I-human serum albumin	329
^{67}Ga-citrate	209
^{67}Ga-lactate	180
^{67}Ga-chloride	112
^{67}Ga-Fe-DTPA	82
^{111}In-bleomycin	74
^{197}Hg-chlormerodrin	38
^{169}Yb-DTPA	34
^{197}Hg-chlormerodrin (meralluride predose 0.56 μg Hg/gm BW)	33
$^{99m}TcO_4^-$	8.2
$^{99m}TcO_4^-$ (perchlorate predose 3 μg/gm BW)	7.5
^{99m}Tc-Fe-ascorbic acid	4.5
^{99m}Tc-Fe-ascorbic acid-DTPA	4.2
^{113m}In-DTPA	2.5
^{99m}Tc-Sn DTPA	1.1

is the time-course of the radiopharmaceutical in the target organ compared with that of the adjacent nontarget activity. The simple target-to-nontarget activity ratio would be a useful criterion if measurements were precise and not distorted by statistical variation. If the ratio of target-to-nontarget activity is high, then the activity in both the target and nontarget areas can be small and amplification of the target activity to any desired level can be made. However, this is seldom the case and statistical variations of lower count levels become very important. The investigator must therefore be concerned with the absolute values of target and nontarget activity. We have thus set an arbitrary lower limit of 1% dose/gm tumor as the lower concentration limit for including the radiopharmaceutical in our evaluation system even though this limitation may not be necessary in certain cases of high target-to-nontarget ratios.

The radiopharmaceutical figure of merit has been introduced in various forms as a means of evaluating and intercomparing scanning agents (*25–28*). The figure of merit is usually expressed as a ratio $(T - NT)^n/(T + NT)^{1/2}$ where $n = 1$ or 2, and T and NT are the target and nontarget activity values, respectively. The figure of merit seeks to maximize the difference between target and nontarget activity and to minimize the error of difference. It takes into account both the absolute and the relative counting rate in the target and nontarget areas.

It is difficult to develop meaningful nontarget activity values from animal studies when the nontarget data are segmented into compartments such as brain, blood, skin, and others. Although blood and brain are generally considered the most important background activity areas contributing to nontarget activity in brain scanning, skin cannot be overlooked (*29*). In an intercomparison of eight tumor-scanning radiopharmaceuticals using the transplantable Yoshida sarcoma, Emrich, et al (*2*) emphasize the importance of blood background in the use of their relative tumor index, which multiplies the percent dose per gram tumor by the tumor-to-blood ratio. They state that other biologic and radiologic factors can be used as additional multipliers to develop expanded comparative tumor index values but limit their use to the tumor-to-blood ratio. We have chosen a different approach to comparative rating by using a sequential numbering summation of four factors for various time intervals. These four factors are the target tumor concentration in percent dose per gram tumor and the nontarget concentration as evidenced by tumor-to-brain, tumor-to-blood, and tumor-to-skin ratios. The substances are rated for various time periods to help determine the optimum time of scanning for each.

Of the eight radiopharmaceuticals studied in the transplantable Yoshida sarcoma by Emrich, et al (*2*), four are common to our studies at 6, 24, and 48 hr. When their tumor index is used (tumor uptake times tumor-to-blood ratio), the ratings secured at 6 hr, in order of decreasing effectiveness, were ^{67}Ga-citrate, ^{131}I-human serum albumin, ^{203}Hg-chlormerodrin, and ^{99m}Tc-pertechnetate. Our rating system using the additional parameters of tumor-to-brain and tumor-to-skin ratios gives an order of preferred biologic distribution for the 3–6-hr period for these compounds of labeled chlormerodrin, ^{131}I-albumin, ^{67}Ga-citrate, and ^{99m}Tc-pertechnetate. At 24 hr, their rating system gives a compound order of ^{67}Ga-citrate, chlormerodrin, and ^{131}I-albumin; our order is ^{131}I-albumin and ^{67}Ga-citrate. At 48 hr, their relative distributional order for brain-scanning effectiveness does not change; neither does ours.

Attempts have been made by other investigators to relate tumor uptake to blood supply. Emrich, et al (*2*) have plotted their tumor uptake after 24 hr against the blood biologic half-life for their eight compounds and observed a straight line relationship for the radiopharmaceuticals with the exception of ^{67}Ga-citrate and ^{75}Se-selenite. This they attribute to the intracellular deposition of the two compounds. The extracellular deposition of the other radiopharmaceuticals would account for the observation that the longer the substances remain in the blood, the greater the tumor uptake. Matthews and Molinaro (*4*), in their brain tumor localization studies with seven intracellular, ten extracellular, and four arsenic formulations, also noted that tumor concentration independent of blood level suggested mainly intra-

cellular deposition. In our studies, we have chosen to relate tumor uptake to renal blood clearance since the physiologic "presence" of a radioactive substance cleared principally by renal function is dependent both on blood concentration and urinary excretion. We have also chosen to use the highest tumor concentration, regardless of time, rather than limit data interpretation to one specific time period. When the log of the maximum tumor uptake is plotted against the renal blood clearance, as shown in Fig. 1, a rather remarkable inverse relationship is noted. Gallium-67-citrate does diverge from this curve.

For relative comparison only, the estimated absorbed radiation dose to the total human body was calculated using mouse biologic data and human absorbed fractions. Radiation dose is affected by both clearance and radiation decay characteristics. In general, the slower the clearance and the more unfavorable the radiation decay characteristics, the greater will be the total-body radiation dose. The estimated absorbed total-body radiation doses range from a high of 395 mrad/mCi injected, for ^{111}In-chloride, to a low of 1.1 mrad/mCi injected, for ^{99m}Tc-Sn-DTPA. Although there can be no valid direct comparison between the estimated relative values reported here and the true human absorbed total-body radiation dose, it is interesting to compare the estimated 0.21 rad/mCi injected value obtained here with the 0.26 rad/mCi injected value for humans for ^{67}Ga-citrate, as reported in a recent MIRD publication (*30*).

Proper tissue distribution is essential for any organ- or tumor-imaging compound. Other parameters such as biologic clearance and radiation decay characteristics that affect radiation dose to the patient must be considered in any type of product comparison. Frequently the product having good radiation and clearance characteristics, i.e., ^{99m}Tc-pertechnetate, has poor tissue distribution and the substance having the best distribution pattern, i.e., ^{111}In-chloride, has other unfavorable properties. Studies relating to these parameters in a mouse biosystem cannot be conclusive regarding a choice of a clinical imaging agent. Nonetheless, if one were to use this information as a guide to choosing agents for clinical investigation, ^{111}In-chloride injected at pH 1.5 would appear to have the most favorable biologic characteristics for brain tumor imaging. We are continuing pharmacologic studies with this compound.

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REFERENCES

1. HAYES RL, EDWARDS CL: New applications of tumor-localizing radiopharmaceuticals. In *Medical Radioisotope Scintigraphy*, vol 2, Vienna, IAEA, 1972, pp 531–552

2. EMRICH D, VON ZUR MUHLEN A, WILLGEROTH F, et al: Comparison of tumor uptake and kinetics of different radiopharmaceuticals under experimental conditions. *Acta Radiol [Ther] (Stockh)* 11: 566–576, 1972

3. LONG RG, MCAFEE JG, WINKELMAN J: Evaluation of radioactive compounds for the external detection of cerebral tumors. *Cancer Res* 23: 98–108, 1963

4. MATTHEWS CME, MOLINARO G: A study of the relative value of radioactive substances used for brain tumor localization and of the mechanism of tumor: Brain concentration. Uptake in transplantable fibrosarcoma, brain and other organs in the rat. *Br J Exp Pathol* 44: 260–277, 1963

5. SOLOWAY AH, ARONOW S, KAUFMAN C, et al: Penetration of brain and brain tumor. VI. Radioactive scanning agents. *J Nucl Med* 8: 792–799, 1967

6. DICHIRO G, ASHBURN WL, GROVE AS: Which radioisotope for brain scanning? *Neurology* 18: 225–236, 1968

7. FARR LE, KONIKOWSKI T: The effect of regional thermal-neutron exposure upon the growth and transplantability of a malignant tumor in the mouse. In *Biological Effects of Neutron and Proton Irradiations*, vol 2, Vienna, IAEA, 1964, pp 159–160

8. KONIKOWSKI T, HAYNIE TP: The effect of perchlorate on the localization of ^{99m}Tc-pertechnetate in a mouse brain sarcoma. *J Nucl Med* 11: 443–448, 1970

9. KONIKOWSKI T, HAYNIE TP: The effect of meralluride blocking on localization of radiochlormerodrin in a mouse brain tumor (sarcoma). *Int J Appl Radiat Isot* 21: 711–718, 1970

10. HAYNIE TP, KONIKOWSKI T, GLENN HJ: The kinetics of ^{99m}Tc-, ^{113m}In-, and ^{169}Yb-DTPA compounds in brain sarcoma and kidneys of mice. *J Nucl Med* 13: 205–210, 1972

11. KONIKOWSKI T, GLENN HJ, HAYNIE TP: Renal clearance and brain tumor localization in mice of ^{99m}Tc compounds of (Sn) DTPA, (iron-ascorbic acid) DTPA, and iron-ascorbic acid. *J Nucl Med* 13: 834–842, 1972

12. KONIKOWSKI T, GLENN HJ, HAYNIE TP: Kinetics of ^{67}Ga compounds in brain sarcoma and kidneys of mice. *J Nucl Med* 14: 164–171, 1973

13. KONIKOWSKI T, HAYNIE TP, FARR LE: Inulin clearance in mice as a standard for radiopharmaceutical assay. *Proc Soc Exp Biol Med* 135: 320–324, 1970

14. KONIKOWSKI T, HAYNIE TP, GLENN HJ, et al: Iodohippurate sodium ^{131}I (OIH) clearance in mice. Bioassay of radiopharmaceuticals. *Proc Soc Exp Biol Med* 137: 1343–1351, 1971

15. KONIKOWSKI T, GLENN HJ, HAYNIE TP, et al: Renal clearance in mice as a bioassay for radiopharmaceutical intercomparison of commercial sources of iodohippurate sodium ^{131}I (OIH). *Int J Nucl Med Biol* 1: 23–30, 1973

16. KONIKOWSKI T, GLENN HJ, HAYNIE TP, et al: An intercomparison of radiopharmaceutical kinetics in the mouse. *J Nucl Med* 14: 417, 1973

17. LOEVINGER R, BERMAN M: A schema for absorbed dose calculations for biologically distributed radionuclides. MIRD Pamphlet No 1, *J Nucl Med* 9: Suppl No 1, 7–14, 1968

18. BERGER MJ: Energy deposition in water by photons from point isotropic sources. MIRD Pamphlet No 2, *J Nucl Med* 9: Suppl No 1, 15–25, 1968

19. BROWNELL GL, ELLETT WH, REDDY AR: Absorbed fractions for photon dosimetry. MIRD Pamphlet No 1, *J Nucl Med* 9: Suppl No 1, 27–39, 1968

20. DILLMAN LT: Radionuclide decay schemes and nuclear parameters for use in radiation-dose estimation. MIRD Pamphlet No 4, *J Nucl Med* 10: Suppl No 2, 5–32, 1969

21. SNYDER WS, FORD MR, WARNER GG, et al: Estimates of absorbed fractions for monoenergetic photon sources uniformly distributed in various organs of a heterogenous phantom. MIRD Pamphlet No 5, *J Nucl Med* 10: Suppl No 3, 5–52, 1969

22. DILLMAN LT: Personal communication, Delaware, Ohio, Ohio Wesleyan University

23. STAPLETON JE, ODELL RW, MCKAMEY MR: Technetium/iron/ascorbic acid complex: A good brain scanning agent. *Am J Roentgenol Radium Ther Nucl Med* 101: 152–156, 1967

24. LOCKSLEY HB, SWEET WH, POWSNER HJ, et al: Suitability of tumor-bearing mice for predicting relative usefulness of isotopes in brain tumors. *Arch Neurol Psych* 71: 684–698, 1954

25. BECK RN: A theoretical evaluation of brain scanning systems. *J Nucl Med* 2: 314–324, 1961

26. DEWEY WC, SINCLAIR WK: Criteria for evaluating collimators used in the in-vivo distribution studies with radioisotopes. *Int J Appl Radiat Isot* 10: 1–16, 1961

27. MATTHEWS CME: Comparison of isotopes for scanning. *J Nucl Med* 6: 155–168, 1965

28. WAGNER HN, RHODES BA: The radiopharmaceutical. In *Principles of Nuclear Medicine*, Wagner HN, ed, Philadelphia, WB Saunders Co, 1968, pp 263–264

29. OLDENDORF WH, LISAKA Y: Interference of scalp and skull with external measurements of brain isotope content. Part I. Isotope content of scalp and skull. *J Nucl Med* 10: 177–183, 1969

30. MIRD Dose Estimate Report No 2. Summary of current radiation dose estimates to humans from ^{66}Ga-, ^{67}Ga-, and ^{72}Ga-citrate. *J Nucl Med* 14: 755–756, 1973