

Distribution of ^{99m}Tc and Tumour/Brain Concentrations in Rats

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Technetium-99m as pertechnetate, has been introduced by Harper, Beck, Charleston and Lathrop (1) as a new isotope for brain tumour localisation. It has the advantage of a very low dose in rads per mc injected owing to the short half life and low energy of the radiation emitted, the β dose being entirely due to conversion electrons, Auger electrons and fluorescent photons. Doses in rads to various organs have been given by Smith (2). The low energy γ ray emitted (140 kev) is easily collimated, and since the isotope can be obtained from a ^{99}Mo column, it is convenient to use. Thus, physically, it has considerable advantages compared with other isotopes.

However, the biological properties of ^{99m}Tc have not been investigated in such detail. It behaves in general rather like iodide in the body (1), and concentrates in the thyroid gland and in the stomach. Tumour/brain concentration ratios of between 2 to 3 and 22 have been found (3,4), and this range of values makes a considerable difference to the evaluation of this isotope for brain scanning (5). It seems important, therefore, to obtain some more information on the uptake of this substance in tumours and brain.

Although it is clearly preferable to obtain this information from patients, it takes a long time to accumulate enough data by this method, and since different tumours probably vary considerably in their uptake, results must be obtained from large numbers of patients to smooth out these variations. It is useful, therefore, to have a standard system in which to test different isotopes, and a transplanted subcutaneous fibrosarcoma in rats has been used for this purpose by Matthews and Molinaro (6). Rats were injected with 17 different radioactive substances and killed at different times after injection. The blood was also labeled with another isotope, ^{132}I labeled protein or ^{51}Cr red cells, so that extravascular radioactivity in each organ could be obtained. Extracellular spaces in the organs of control rats were measured using ^{82}Br . By comparison of the distribution of radioactivity of each isotope with that of ^{82}Br , it was found that many radioactive substances appear to equilibrate rapidly with the extracellular spaces of tumour and brain and other organs. These therefore all give about the same tumour/brain concentration ratio in any one tumour. The difference

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between tumour and brain uptake was found to be due to a lower brain concentration, rather than a higher tumour concentration, the tumour concentration per gm being similar to that in other organs. For most substances the radioactivity in the brain was only due to the blood in the brain; ^{82}Br gives a larger "space" in this organ probably because it penetrates into brain cells to some extent. Values of tumour/brain concentration ratios agreed with those found in patients for the few isotopes where such measurements had been made.

Technetium-99m uptakes have now been measured in the same rat tumour and in brain and other organs, and the results are given in this paper.

METHODS

The experimental procedure, measurement of radioactivity, animals used, dissection, etc., were all the same as described by Matthews and Molinaro (6), except that ^{132}I and ^{51}Cr were not used to label the blood. The radioactivity in each organ therefore includes blood in the organ. Tumours were again implanted subcutaneously by the method of Thomlinson (7). Two types of tumour were used, one the fibrosarcoma RIB5 which was used by Matthews and Molinaro, and the other another sarcoma, SBS1, also obtained from Dr. R. H. Thomlinson. The thyroid was not blocked.

^{99m}Tc

The ^{99m}Tc (half-life 6 hours) is obtained from a column of fine grade alumina onto which is absorbed the mother isotope, Molybdenum-99 (half-life 66 hours) in the form of ammonium molybdate.¹ The column is made of perspex, $\frac{5}{8}$ inches outside diameter and $1\frac{1}{32}$ inches inside diameter, overall length $4\frac{1}{2}$ inches. The alumina bed is held in position with a terylene cloth at the bottom and a porous polythene pad at the top; the length of alumina is 60 mm.

The ^{99m}Tc is milked from the column as follows: 5 ml of isotonic saline is passed through first, which contains less than $\frac{1}{10}$ th of the available activity; on passing a second 5 ml of saline, the remainder of the activity is obtained. Isotonic saline is used in preference to dilute hydrochloric acid, since it gives a better yield, and acid would require the pH to be adjusted prior to intravenous injection (8).

Because only 88 per cent of the ^{99}Mo nuclei disintegrate to give ^{99m}Tc , the technetium activity obtainable from a column in equilibrium cannot exceed this fraction of the ^{99}Mo present. Columns containing approximately 15 mC ^{99}Mo have been supplied and it has been found to be very simple to obtain quantities of ^{99m}Tc in excess of 10 mC from a recently delivered column. The ^{99m}Tc so obtained is in the form of the anionic pertechnetate (8).

No appreciable contaminants have been measured from columns used here in agreement with other workers (9).

RESULTS

The results are shown in Tables I, II and III. Table I shows the percent dose in the organs containing the largest amounts of radioactivity. The results in

¹Columns supplied by the Radiochemical Centre, Amersham.

this table are very similar to those for ^{131}I as iodide (6), except that for $^{99\text{m}}\text{Tc}$ the liver contains about three times as much radioactivity. As with ^{131}I , $^{99\text{m}}\text{Tc}$ equilibrated rapidly with the extracellular space in many organs, but in others the concentration rose in relation to the plasma radioactivity per ml and reached a higher value than in the plasma at the same time. These organs were intestine, skin, and kidneys, and their concentrations of radioactivity are shown in Table II together with whole blood and plasma concentrations, all normalised to 100 gm body weight. These results are also similar to those obtained with ^{131}I iodide except that kidneys contain 2–5 times more radioactivity for $^{99\text{m}}\text{Tc}$, and skin and intestines also have a rather higher concentration, with intestine rising instead of falling as for ^{131}I .

The other organs, including tumour and brain, appear to equilibrate quite rapidly with the extracellular space, and their concentrations are proportional to plasma concentrations. Ratios of these organ concentrations to plasma concentrations did not vary with time and were the same in the two tumours. Mean values are given in Table III and compared with values for ^{131}I and also for ^{82}Br , the latter giving a measure of the extracellular space (6). This space for $^{99\text{m}}\text{Tc}$ is considerably larger in liver and smaller in testes, lymph nodes and spleen than with ^{131}I or ^{82}Br .

Mean tumour/brain concentration ratios are also given in Table III; the value for $^{99\text{m}}\text{Tc}$ is very similar to that for ^{131}I . Tumour and brain concentrations of $^{99\text{m}}\text{Tc}$ and tumour weights are also shown in Table II.

DISCUSSION

The distribution of $^{99\text{m}}\text{Tc}$ in rats appears to be very similar to that of ^{131}I , at

TABLE I
 $^{99\text{m}}\text{Tc}$ PERCENT DOSE

Tumour: Hrs. after injection:	<i>RIB5</i>				<i>SBS1</i>	
	<i>0.57</i>	<i>1.24</i> (mean of two rats)	<i>3.00</i>	<i>4.25</i>	<i>0.83</i>	<i>4.37</i>
<i>Organ</i>						
G.I. tract	25	41	30	44	35	60
Skin	33	29	39	28	32	25
Liver	8.7	6.1	6.1	4.2	7.5	3.6
Carcass*	33	20	21	13	29	11
Whole body	101	99	97	89	101	99
Blood‡	21	12	14	6.9	17	7.0

*Muscle, bone and some blood.

‡Taking blood volume as 7% body weight.

TABLE II
^{99m}Tc PERCENT DOSE PER GM × BODY WEIGHT/100

Tumour: Hrs after injection:	RIB5				SBS1	
	0.57	1.24 (mean of two rats)	3.00	4.25	0.83	4.37
<i>Organ</i>						
G.I. tract	3.6	5.7	6.2	6.3	5.2	7.9
Skin	2.1	1.8	2.9	1.7	2.0	1.5
Kidneys	1.7	1.6	3.8	2.5	1.7	2.6
Blood	3.0	1.7	2.0	0.99	2.4	1.0
Plasma	3.7	2.3	2.7	1.4	3.2	1.3
Tumour	1.1	0.80	1.1	0.78	1.3	0.49
Brain	0.12	0.079	0.093	0.047	0.085	0.083
Tumour wt (gm)	0.90	1.9	0.75	0.87	0.64	0.78
Rat weight (gm)	245	265	263	285	230	255

TABLE III
 $100 \times \% \text{ DOSE/GM IN ORGAN} \div \% \text{ DOSE/GM IN PLASMA}$

	^{99m} Tc ¹	¹³¹ I ²	⁸² Br ²
Liver	76 ³	38	37
Lungs	50 ³	64	60
Tumour	45 ³	47	48
Lymph nodes	25	50	44
Spleen	26	43	39
Bone	30	38	27
Testes	18	33	48
Muscle	11	17	14
Brain	3.7	5.0	18 ⁴
Tumour/brain con- centration ratio:	12	11	

Footnotes

¹Mean of 5 rats with RIB5 tumours and 2 rats with SBS1 tumours.

²Reference (5).

³Excluding rats killed at 0.57 and 1.17 hrs for RIB5, where equilibrium with extracellular space had not yet been reached.

⁴Probably partly intracellular.

least for short times after injection, as reported by Harper *et al* (1). Tumor/brain concentration ratios also appear to be similar, since apparently both isotopes rapidly enter the extracellular spaces in tumour and brain. However, liver and kidney concentrations are definitely higher with pertechnetate than with iodide, and concentration in the gastrointestinal tract appears to increase with time for pertechnetate instead of decreasing as for iodide.

Only a few rats have been used, but it is felt that the results are sufficient, when taken together with those for ^{131}I and ^{82}Br , to indicate the extracellular distribution of $^{99\text{m}}\text{Tc}$. If this assumption is made, and the measured tumour/brain ratio is used, it is then possible to compare $^{99\text{m}}\text{Tc}$ quantitatively with other isotopes used for brain scanning and to calculate the minimum tumour size detectable (5). This calculation will not depend on the exact concentration found in these rat tumours, but only on the assumption of equilibration with the extracellular space. The tumor/brain concentration ratio for $^{99\text{m}}\text{Tc}$ is similar to values found with other extracellular substances and is lower than the value of 87 for ^{206}Bi citrate, approximately 15 for ^{74}As , and 15 for ^{131}I albumin, but similar to the value of 11 for ^{203}Hg neohydrin (1,10).

SUMMARY

The distribution of $^{99\text{m}}\text{Tc}$ as pertechnetate in rats has been measured and found to be similar to that of ^{131}I as iodide, but with higher concentrations of $^{99\text{m}}\text{Tc}$ in liver, kidney and gastrointestinal tract. Mean tumour/brain concentration ratio for two different transplanted rat sarcomata was 12 for $^{99\text{m}}\text{Tc}$ compared with 11 for ^{131}I .

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REFERENCES

1. HARPER, P. V., BECK, R., CHARLESTON, D. AND LATHROP, K. A.: Optimisation of a scanning method using $^{99\text{m}}\text{Tc}$. *Nucleonics* 22:50, 1964.
2. SMITH, E. M.: Radiochemical purity, internal dosimetry and calibration of $^{99\text{m}}\text{Tc}$. *J. Nucl. Med.* 5:383, 1964.
3. HARPER, P. V.: Medical Radioisotope Scanning, I.A.E.A., Vienna 1964, p. 45, Vol. II.
4. MCAFEE, J.: Personal communication, 1964.
5. MATTHEWS, C. M. E.: Comparison of isotopes for brain scanning. *J. Nucl. Med.* 1965. In press.
6. MATTHEWS, C. M. E. AND MOLINARO, G.: A study of the relative value of radioactive substances used for brain tumour localisation and of the mechanism of tumour:brain concentration. Uptake in transplantable fibrosarcoma, brain and other organs in the rat. *Brit. J. Exp. Pathol.* 44:260, 1963.
7. THOMLINSON, R. H.: An experimental method for comparing treatment of intact malignant tumours in animals and its application to the use of oxygen in radiotherapy. *Brit. J. Cancer* 14:555, 1960.
8. MAYNARD, J. C.: Personal communication, 1964.
9. HERBERT, R.: Personal communication, 1964.
10. MATTHEWS, C. M. E.: Unpublished results, 1963.