^{99m}Tc-PERTECHNETATE TRANSPORT IN MAN: ABSORPTION AFTER SUBCUTANEOUS AND ORAL ADMINISTRATION; SECRETION INTO SALIVA AND GASTRIC JUICE

Marguerite T. Hays

Veterans Administration Hospital, Buffalo, New York and State University of New York at Buffalo, Buffalo, New York

Fifteen normal subjects were studied in multiple sessions after administration of $^{99m}TcO_4^-$ by the oral, subcutaneous, and intravenous routes. Using plasma radioactivity after intravenous administration as the norm for 100% absorption, subcutaneous $^{99m}TcO_4^-$ was absorbed promptly with 95% or more absorption occurring 45.8 ± 22.7 (s.d.) min after injection. Orally administered $^{99m}TcO_4^-$ was erratically absorbed with marked variability in the timing and extent of absorption. This variability occurred between subjects and between sessions in a single subject. The addition of human serum albumin to bind the oral $^{99m}TcO_4^-$ did not significantly affect absorption.

Six patients with gastrointestinal disease were studied for absorption of oral $^{99m}TcO_4^-$ and for quantification of $^{99m}TcO_4^-$ and ^{131}I transfer into the saliva and gastric juice after intravenous administration. Gastric juice pH did not affect absorption of oral $^{99m}TcO_4^-$. Gastric juice/plasma (G/P) and saliva/plasma (S/P) ratios were greater for ^{131}I than for $^{99m}TcO_4^-$ in all instances when measured simultaneously.

Technetium-99m-pertechnetate ($^{99m}TcO_4^-$) is generally administered intravenously. However, in some centers, it is given orally because of inappropriateness of the available radiopharmaceutical for parenteral use or for reasons of convenience. When intravenous injection is impractical, the subcutaneous route is said by some observers to be associated with a fairly smooth blood level of ^{99m}Tc, often even more suitable for brain scanning than after intravenous administration. In centers where large numbers of patients are studied after oral administration of $^{99m}TcO_4^-$, most studies are found to be satisfactory. However, an occasional patient inexplicably fails to take up the radionuclide. These observations stimulated interest in quantifying uptake into the circulating blood after administration of $^{99m}TcO_4^-$ by these alternate routes.

In addition to this practical problem, quantification of the extent and speed of transfer of $^{99m}TcO_4^-$ from one physiologic compartment to another is fundamental to development of an overall physiologic model to predict and explain its distribution. Such a model, to be described fully elsewhere, is currently under development. The present study examines the unidirectional transfer from the interstitial compartment into the plasma, transfer from the gut into the plasma, and aspects of transfer from the plasma into the gut.

MATERIALS AND METHODS

Absorption of $^{99m}TcO_4^-$ into plasma after subcutaneous or oral administration. Fifteen normal subjects, aged 21–35 years (paid volunteers), were studied after $^{99m}TcO_4^-$ administration in multiple sessions. Studies were performed in the morning after omission of breakfast. Five subjects (Group 1) were also studied by scanning techniques for concentration of the radionuclide in the thyroid and received 1 mCi of $^{99m}TcO_4^-$ each session. Before the administration of $^{99m}TcO_4^-$, an indwelling needle for repeated blood sampling was placed in an antecubital vein. Each subject was given the $^{99m}TcO_4^-$ intravenously (into the opposite arm) on one of his sessions. In the other sessions, he received $^{99m}TcO_4^-$ subcutaneously or orally. The subcutaneous dose was contained in 0.5 ml normal saline. The oral dose was diluted to 10 ml with normal saline. The medicine cup was then washed three times with 30 ml normal saline each and the washings were swallowed

Received Oct. 17, 1972; revision accepted Dec. 29, 1972.

For reprints contact: M. T. Hays, Nuclear Medicine Service, VA Hospital, 3495 Bailey Ave., Buffalo, N.Y. 14215.

by the subject. Six of the subjects in Group 2 (two of them in two sessions) also were studied after oral administration of $^{99m}TcO_4^-$ accompanied by 0.9 gm of human serum albumin (1% HSA added to the 90 ml normal saline wash of the medicine cup) (*1*). Albumin is known to bind pertechnetate (*1*) and this amount given orally causes a dramatic reduction in thyroxine absorption (*2*). Duplicate studies of subcutaneous pertechnetate were also performed in two subjects and triplicate studies of oral pertechnetate without added albumin were performed in two subjects.

After the administration of $^{99m}TcO_4^-$, blood samples were obtained at 2, 5, 10, 20, 30, 45, and 60 min in all subjects. In Group 2, the studies were extended for a second hour, with blood samples at 75, 90, 105, and 120 min.

Blood samples were placed in heparinized tubes, the plasma separated, and 1-ml aliquots pipetted for counting. Standards were made of appropriate dilutions of the administered dose. All counting was performed in a well-type scintillation counter, each count being related to a standard counted no more than ½ hr before or after.

The order of sessions for both Group 1 and Group 2 were counterbalanced by using a Latin square technique.

Results were expressed as the percentage of the administered dose per liter of plasma. Estimation of uptake into the serum pool was approximated by the ratio of plasma radioactivity after oral or subcutaneous administration to plasma activity at the same experimental time after intravenous administration. (This technique causes overestimate of absorption percentage because of the rapid early disposal of a portion of the intravenous dose. The ratio technique was adopted here because of its simplicity. It was felt that the systematic error introduced by this approach is small and should not affect comparative studies.)

Comparison of absorption ratio of oral $^{99m}TcO_4^-$, gastric pH, and trapping by the salivary glands and salivary mucosa. A series of six male patients, hospitalized for gastrointestinal disease (Group 3), were studied by a technique similar to that described above but, in addition, had repeated sampling of saliva and gastric juice. In these subjects an intravenous dose of 20 μCi $^{99m}TcO_4^-$ and 20 μCi ^{131}I were given at the beginning of the experiment. At 2 hr, 500 μCi of $^{99m}TcO_4^-$ was given orally. In the subsequent sampling, $^{99m}TcO_4^-$ plasma values were corrected for residue from the earlier dose, projected to the time of sampling.

The patients were asked to expectorate all of their saliva but no stimulation was used. Two of the six patients were unable or unwilling to produce saliva samples. In those patients who cooperated, saliva samples were obtained in 15-min aliquots. If saliva volume was inadequate for sampling after 15 min, the time period was extended to 30 min. Gastric juice was sampled through a nasogastric tube at 2, 5, 10, 15, 30 min, and every 15 min thereafter. In these subjects, blood samples were obtained on this schedule also. The gastric juice was sampled (duplicate

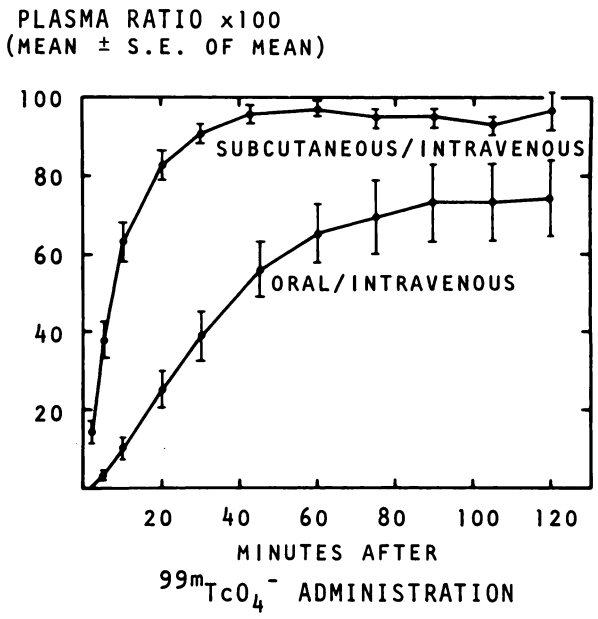

FIG. 1. Ratio of plasma radioactivity after oral or subcutaneous administration of $^{99m}TcO_4^-$ to that after intravenous administration as function of time. Pooled data from Groups 1 and 2 (0–60 min). Group 1 only (60–120 min).

TABLE 1. FOUR SUBJECTS WITH TRIPLICATE ORAL ADMINISTRATION SESSIONS: SERUM RATIOS (ORAL/INTRAVENOUS × 100)

Subject	Time after $^{99m}TcO_4^-$ administration	Session 1	Session 2	Session 3
CO	10 min	—0.2	11.0	2.9
	30 min	—0.2	28.2	3.2
	60 min	1.4	88.6	3.4
	120 min	0.4	149.3	4.5
QU	10 min	1.0	15.2	6.1
	30 min	71.2	64.1	63.2
	60 min	98.4	92.8	85.2
	120 min	92.7	100.7	79.7
BA	10 min	20.4	0.2	10.0
	30 min	75.8	4.3	76.3
	60 min	107.0	112.6	119.3
	120 min	109.8	135.4	131.9
PL	10 min	2.3	0.6	9.1
	30 min	19.4	8.4	85.4
	60 min	62.4	30.2	104.6
	120 min	67.2	66.9	92.8

1-ml pipetted specimens) and pH was measured. Any gastric juice beyond the 2 ml needed for counting was reinjected through the indwelling gastric tube. Hence, although a record of salivary flow was kept in patients producing saliva, no attempt was made to evaluate volume of gastric juice.

The saliva and gastric juice samples were counted following the same system described above for plasma samples. Results were expressed as percent of the dose per liter of plasma or gastric juice and also as the concentration ratio-to-plasma radioactivity.

RESULTS

Figure 1 shows for Groups 1 and 2 the means and standard errors of the individual ratios of serum radioactivity after subcutaneous or oral administration as related to intravenous administration. The subcutaneous/intravenous ratio reached unity fairly promptly. The time required for the leveling of this curve (95% of maximum or more) varied from 20 to 90 min with a mean of 45.8 ± 22.7 (s.d.) min.

Marked variability was observed in the absorption of an oral dose of $^{99m}TcO_4^-$ (note the large s.d. in Fig. 1). Even when a single subject was studied on three repeated occasions (Table 1), oral $^{99m}TcO_4^-$ absorption sometimes varied markedly. Figure 2 shows eight individual studies representative of the oral/intravenous ratio selected (from 27 such studies) to show the variability in extent and timing of absorption of oral $^{99m}TcO_4^-$. We were unable to explain this variability either between subjects or within one subject's repeated studies.

Because $^{99m}TcO_4^-$ is known to be bound to serum proteins, and in particular to albumin in man (*1*), it was thought that the addition of human serum albumin with $^{99m}TcO_4^-$ might retard absorption of the oral dose as occurs with oral radiothyroxine (*2*). However, Table 2 shows that no such retardation occurs.

Table 3 presents data about the six patients constituting Group 3. Three of these patients had high gastric pH and three had low. The time course of gastric pH during the experiment is detailed for the six subjects in Fig. 3. Table 3 shows that there is no correlation between pH and absorption of $^{99m}TcO_4^-$ (presented here as the mean of the absorption ratios for the second hour).

The other columns of Table 3 show that there is no consistent relationship between gastric juice pH and the effectiveness of trapping by the gastric mucosa. The patient with unusually high gastric trapping had a low pH and the patient with unusually low trapping had a high pH but, statistically, the G/P (the gastric juice/plasma ratio) was not significantly different in the two groups. These data show that both the gastric mucosa and the salivary glands concentrate ^{131}I with a higher concentration ratio than they concentrate $^{99m}TcO_4^-$. The degree to which ^{131}I concentration exceeds that of $^{99m}TcO_4^-$ appears to fluctuate among studies but is in the range observed by Harden and Alexander (*3*).

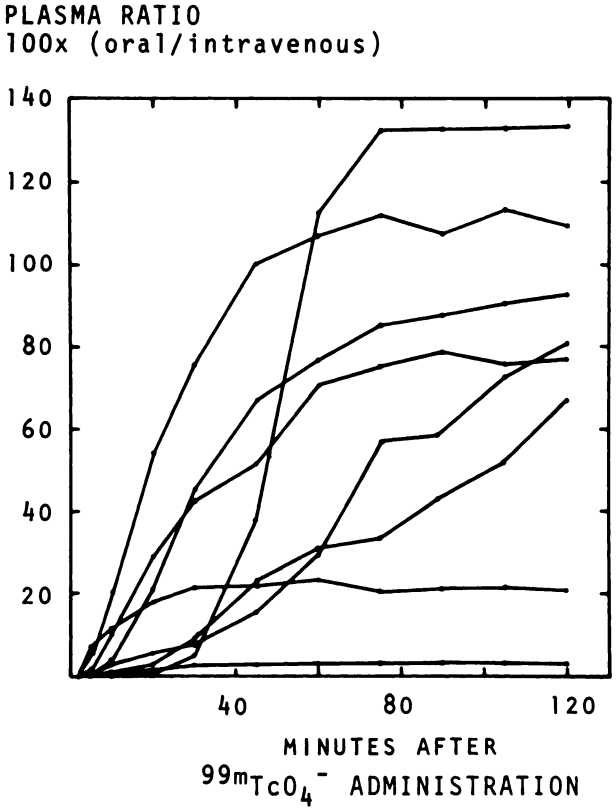

FIG. 2. Selected individual studies of ratio of plasma radioactivity after oral administration of $^{99m}TcO_4^-$ to that after intravenous administration as function of time. Curves were selected (8 of total of 27 studies) to illustrate diversity of timing and amount of absorption.

TABLE 2. INFLUENCE OF ADDED HUMAN SERUM ALBUMIN (0.9 GM) ON ABSORPTION OF ORAL $^{99m}TcO_4^-$

Subject	60–120 min mean of serum ratios: $\frac{\text{oral session}}{\text{intravenous session}} \times 100$	
	No albumin added	0.9 gm HSA added
KI	86.55	91.83
BA	110.07	127.17 (mean of 2 obs.)
WI	3.05	25.42
FR	59.66	95.99
PL	66.67	77.28 (mean of 2 obs.)
RW	87.25	1.93
Mean	68.88	69.77

TABLE 3. COMPARISON OF GASTRIC JUICE pH, ABSORPTION OF ORAL $^{99m}TcO_4^-$ AND GASTRIC JUICE/PLASMA (G/P) AND SALIVA/PLASMA (S/P) RATIOS OF ^{131}I AND ^{99m}Tc

Patient	Mean pH of gastric juice, 90–180 min	% $^{99m}TcO_4^-$ absorbed mean of 60–120 min ratio: oral/i.v. × 100	Mean of ratios, G/P		60–120 min, S/P		Total saliva ml, 60–120 min
			^{131}I	^{99m}Tc	^{131}I	^{99m}Tc	
FO	1.42	20.4	20.90	11.80	24.14	13.64	67.5
VS	1.75	86.1	73.67	37.00	—	—	0
MS	1.58	15.1	21.20	9.68	19.95	9.52	62
RO	6.81	23.6	6.71	3.54	13.42	5.54	49
BA	7.18	101.2	25.92	10.50	—	—	0
ME	7.58	70.2	25.16	16.71	23.80	16.55	29
Mean		52.8	28.93	14.87	20.33	11.31	

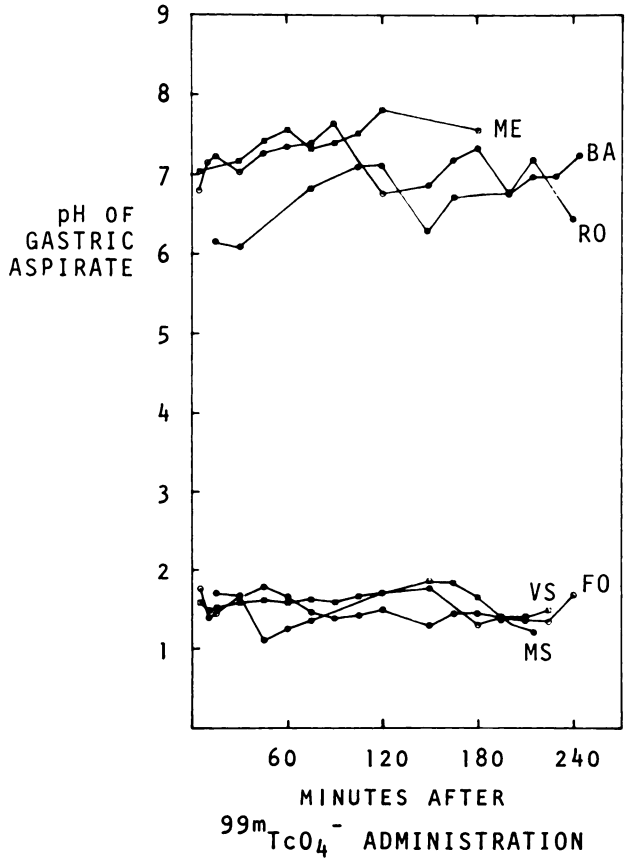

FIG. 3. Gastric juice pH as function of time during four experimental hr in six patients of Group 3.

DISCUSSION

Despite the widespread use of oral and subcutaneous $^{99m}TcO_4^-$, no quantitative studies involving significant numbers of observations have come to our attention. Andros, et al (*4*) observed in their initial studies significant and markedly varying percentages of the dose in the feces. From 0 to 36% of the dose was recovered in the feces after intravenous administration and up to 58% after oral administration. They observed that blood radioactivity levels in a single subject were lower after oral than after intravenous administration. Beasley, et al (*5*), using a technique which did not permit use of a subject as his own control, felt that oral absorption was essentially 100% over a 4-day period.

It has long been known that iodide is concentrated by the salivary glands and gastric mucosa and a similar concentration mechanism for $^{99m}TcO_4^-$ was observed in the earliest studies. Harden and Alexander (*3*) have shown that salivary clearance of pertechnetate in a series of 26 subjects was approximately one-half that of iodide, regardless of factors altering the iodide salivary clearance. This difference in clearance is probably due to serum binding of the $^{99m}TcO_4^-$ (*1*), but it has been suggested also that it is due to a different concentration site both for the salivary glands (*6*) and the stomach (*7*). Although concentration of $^{99m}TcO_4^-$ by the stomach has been observed repeatedly in the nuclear medicine clinic, this concentration appears not to have been previously quantified in man.

These studies clearly show that absorption of oral $^{99m}TcO_4^-$ is so variable during the first 2 hr after administration as to render the oral route virtually useless when early quantitative uptake is needed. However, subcutaneously administered $^{99m}TcO_4^-$ is absorbed essentially quantitatively, usually within the first hour, and it would appear to be very useful for scanning studies performed after the first hour. In our experience the subcutaneous radiopharmaceutical was well tolerated with no complications of any type.

Technetium-99m-pertechnetate is known to have a larger volume of distribution than ^{131}I. Both ions might be expected to distribute rapidly into the interstitial space and its greater volume of distribution has lead to the speculation that $^{99m}TcO_4^-$ also has significant intracellular distribution. However, the studies of Andros, et al (*4*) and Beasley, et al (*5*), combined with the observations presented here, indicate a significant amount of pooling of $^{99m}TcO_4^-$

in the gut, followed by a significant degree of fecal excretion. This is in contrast to radioiodide, which, while pooled in the stomach after secretion by the salivary glands and gastric mucosa, is rapidly reabsorbed once it passes into the small intestine. Gastrointestinal pooling could well explain the relatively great volume of distribution of $^{99m}TcO_4^-$.

Technetium-99m-pertechnetate is known to be bound to serum proteins (Ref. *1* and others). This binding presumably accounts for the fact that serum $^{99m}TcO_4^-$ levels are higher than concurrent ^{131}I after simultaneous administration. This binding should also be adequate to explain the relatively decreased concentration ratios in the salivary glands and gastric mucosa. Additional studies following various types of physiologic maneuvers to alter the trapping of these tissues, and also histologic studies in man, will be necessary before discounting in the human the possible presence of anatomic differences such as have been shown in the mouse salivary gland by Stephen, et al (*6*) and in the cat gastric mucosa by Meier-Ruge and Fridrich (*7*). Marsden, et al (*8*) reported in abstract form that in dogs the gastric antral mucosa concentrates ^{131}I and $^{99m}TcO_4^-$ selectively more than does the corpus in animals who respond to histamine stimulation.

This preliminary study might lead one to predict that achlorhydric patients would have smaller concentration ratios of both ^{131}I and $^{99m}TcO_4^-$ in their gastric juices than do patients with normal or excessive acid. Our data, while somewhat suggestive, in no way prove this hypothesis.

The binding of $^{99m}TcO_4^-$ to proteins, in contrast to the free state of the iodide ion, can explain the somewhat slower removal into the serum after subcutaneous injection. The transfer data presented in Fig. 1 conform very closely to the prediction of Welch, Adatepe, and Potchen (*9*), based on a simple compartmental analysis of blood $^{99m}TcO_4^-$ radioactivity. These data also fit well the rate constant for transfer from the subcutaneous pool into the intravascular pool predicted by a multicompartmental model for pertechnetate distribution under study in this laboratory.

ACKNOWLEDGMENTS

The author wishes to thank Mrs. Barbara Stelmach for expert technical assistance. This work was supported by VA Designated Research Funds RCS 15-4 and by Grant USPHS AM 13397 from National Institutes of Health.

REFERENCES

1. HAYS MT, GREEN FA: In vitro studies of Pertechnetate-99m binding by human serum and tissues. *J Nucl Med* 14: 149–158, 1973

2. HAYS MT: Absorption of oral thyroxine in man. *J Clin Endocr* 28: 749–756, 1968

3. HARDEN RMcG, ALEXANDER WD: The relation between the clearance of iodide and pertechnetate in human parotid saliva and salivary flow rate. *Clin Sci* 33: 425–431, 1967

4. ANDROS G, HARPER PV, LATHROP KA, et al: Pertechnetate-99m localization in man with applications to thyroid scanning and the study of thyroid physiology. *J Clin Endocr* 25: 1067–1076, 1965

5. BEASLEY TM, PALMER HE, NELP WB: Distribution and excretion of technetium in humans. *Health Physics* 12: 1425–1435, 1966

6. STEPHEN KW, HARDEN RMcG, ROBERTSON JWK: Sex differences in the iodide and pertechnetate concentration of the submandibular salivary gland of the mouse. *Arch Oral Biol* 16: 1251–1253, 1971

7. MEIER-RUGE W, FRIDRICH R: Die Verteilung von Technetium-99m and Jod-131 in der Magenschleimhaut. *Histochemie* 19: 147–154, 1969

8. MARSDEN DS, ALEXANDER C, FRIEDMAN MHF, et al: The secretion of iodide and technetium pertechnetate by various regions of the dog's stomach and clinical implications. *J Nucl Med* 11: 635–636, 1970

9. WELCH MJ, ADATEPE M, POTCHEN EJ: An analysis of technetium ($^{99m}TcO_4^-$) kinetics: The effect of perchlorate and iodide pretreatment. *Int J Appl Radiat* 20: 437–445, 1969