^{99m}Tc-TETRACYCLINES: PREPARATION AND BIOLOGICAL EVALUATION

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The broad-spectrum antibiotic, tetracycline, and three of its analogs have been successfully labeled with ^{99m}Tc. Organ distribution studies indicated potential clinical utility for these compounds as kidney and gallbladder imaging agents. Of the four radiopharmaceuticals studied, ^{99m}Tc-tetracycline had superior pharmacodynamics and was selected for further study. Stability studies showed the complex to be rather labile but if kept at 4°C in the absence of light and oxygen, its stability was satisfactory for use in diagnostic nuclear medicine. Investigations carried out with double-labeled tetracycline (^{99m}Tc and ^{119m}Sn) and ^{119m}Sn-tetracycline shed light on the role of stannous ion and its effect upon biodistribution. Acute and sub-acute toxicity studies yielded no undesirable effects and a clinical evaluation in selected patients is currently in progress.

It has been known for some time that reduced ^{99m}Tc ion is capable of forming a large number of organo-metallic complexes (*1,2*). Recently, radiopharmaceutical research has led to the synthesis of stable chelates and complexes between reduced technetium ion and DTPA (*3,4*), penicillamine (*5,6*), gluconic acid (*7*), citrate (*8,9*), caseidin (*10*), and diatrizoate and other contrast materials (*11*).

Biologic clearance studies of organo-metallic complexes show that the majority of stable chelates are excreted primarily by the kidneys (*12,13*), implying a certain degree of clinical utility for such chelates as renal imaging agents. The antibiotic tetracycline and its pharmacologically active analogs are known chelating agents (*14–16*) and it was our premise that they would form strong chelates with reduced ^{99m}Tc.

In this paper we report on the successful labeling of tetracycline (*17*) and three of its analogs with reduced ^{99m}Tc and on their pharmacokinetics, with particular attention to the dynamics of the renal, blood, and hepatic concentrations.

MATERIALS AND METHODS

Preparation. Pure samples of the hydrochloride salts of tetracycline (T), oxytetracycline (OT), chlortetracycline (CT), and demethylchlortetracycline (DMCT) were obtained from commercial sources. The labeling of the tetracyclines was performed in the following manner.

1. In an amber-colored serum vial, 20 mg of the antibiotic are dissolved in 3 ml of nitrogen-purged distilled water.
2. Stannous chloride (1.0 mg of $SnCl_2 \cdot 2H_2O$) freshly dissolved in 0.75 *N* HCl (0.1 ml) is then added. The pH of the solution at this point is between 2.1 and 2.5.
3. Sodium pertechnetate (1–3 ml in saline containing the desired amount of activity) is added and mixed by gentle agitation for 2 min.
4. The solution is neutralized to pH 7.4 by using a bicarbonate buffer (pH 8.5) or a NaOH-$NaHCO_3$ buffer (pH 11.0).
5. The final product is filtered through a 0.22-micron Millipore filter and kept under refrigeration at 4°C until use.

The serum vials used are either evacuated or filled with nitrogen, all solutions are prepared from sterile, nonpyrogenic, nitrogen-purged water, and care is taken at each step to exclude air from the preparation.

Quality control. Ascending paper chromatography was performed on Whatman No. 1 and No. 3 strips

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as well as on Gellman ITLC strips using either 85% methanol or acetone as the solvent. The chromatograms were carried out in a nitrogen-filled chamber at 4°C in a refrigerator.

The stability of ^{99m}Tc-tetracycline after preparation was studied in vitro by sequential chromatographic analysis and in vivo by organ distribution in C3H brown mice (20–25 gm; Charles River strain) and Sprague-Dawley rats (150–250 gm). The radiopharmaceutical was administered intravenously in the tail vein of mice and the saphenous vein in rats (in the rat studies nembutal was given prior to making the incision and injection).

Biologiacl distribution. The tissue distribution of the four ^{99m}Tc tetracyclines as a function of time was investigated in mice and rats. The animals were sacrificed at predesignated times and the organs and biological fluids of interest removed. The samples were counted either in a gamma scintillation counter (NaI well crystal) or an ionization chamber depending upon the administered dose.

In addition to the ^{99m}Tc-labeled compounds, the distribution of double-labeled tetracycline chelates (^{99m}Tc and ^{119m}Sn) and tetracyclines labeled only with ^{119m}Sn were studied.

Since urine was of major interest, animals were usually placed in metabolic cages immediately after injection.

In an attempt to understand the protein binding characteristics of the four labeled compounds and the subsequent effect on blood clearance and overall tissue distribution, a dialysis model was used in which human serum albumin represented blood proteins. A 0.2 ml sample of ^{99m}Tc-tetracycline or one of the analogs was mixed with 3 ml of HSA and transferred to cellophane tubing (dry-width 0.39 in., Visking Corp.). A control was prepared in each experiment in which albumin was replaced by 3 ml of saline. The samples were dialyzed at 4°C for 24 hr in an Oxford multiple dialysis chamber.

Toxicologic evaluation. Acute toxicity studies were performed in mice and rats by a single intravenous injection of the ^{99m}Tc-labeled tetracycline. Doses of the order of 1,000 times the average human dose were given to mice and 250 times the average human dose given to rats. The animals were sacrificed 24 and 48 hr after injection; organs and tissues of interest were removed, fixed, and sent for histopathological examination.

Chronic toxicity experiments were carried out over a 15-day period in New Zealand rabbits. The rabbits were injected in the ear vein daily for 14 consecutive days. Each injection was 50 times the average human dose and 20 times the maximum human dose giving a cumulative dose of about 700 times the average human dose. Blood samples were taken on Days 0, 1, 7, and 15. The blood was sent to the hematology laboratory for a CBC and differential count and to the clinical chemistry lab for an SMA12. The rabbits were sacrificed on Day 15, organs of interest excised, fixed, and sent for histopathological examination. Additional tests were performed in exactly the same manner in four purebred beagle dogs.

RESULTS

Labeling efficiency. Results of chromatographic analysis performed as described earlier indicated that 2–5% of the technetium activity in the final product remained in the pertechnetate form. The ^{99m}Tc activity was considerably smeared from the point of application. The high adsorption of the ^{99m}Tc-tetracycline complex on ion-exchange resin and Sephadex columns precluded the use of these analytical techniques for the identification of different components.

Stability. The shelf-life of the ^{99m}Tc-labeled complexes was studied using both in vitro and in vivo assay systems. The complexes were found to be relatively unstable at room temperature; the stability curve presented in Fig. 1 shows the effect of refrigeration on the shelf-life of the agent. The time in hours on the abscissa indicates the time from preparation to intravenous injection; the rats were sacri-

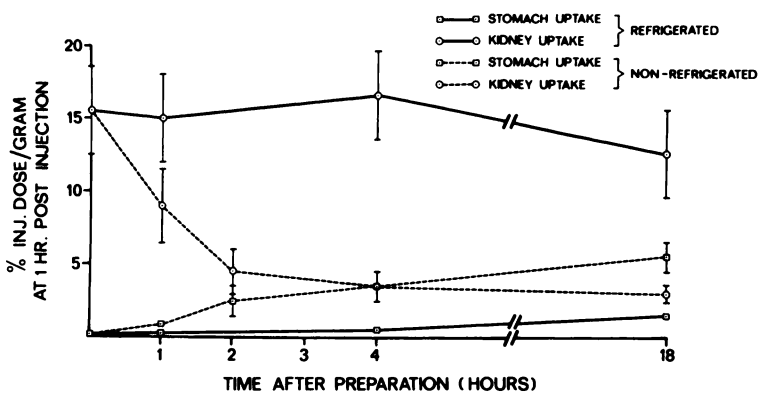

FIG. 1. Stability of ^{99m}Tc-tetracycline.

ficed 1 hr after administration of the complex. The fall in renal activity of the nonrefrigerated sample is accompanied by a corresponding rise in the stomach concentrations of $^{99m}TcO_4^-$ released from the breakdown of the ^{99m}Tc-tetracycline chelate. The chromatographic results of each sample bioassayed corroborate the in vivo results. Refrigeration increases the shelf-life of the labeled chelate to better than the desired value of 6–8 hr.

The in vivo stability of the administered chelate was determined using chromatographic analysis of body fluids withdrawn at various times after injection. Samples of whole blood, serum, bile, and urine were taken from mice, rabbits, and dogs over an 8 hr period. In all cases chromatography revealed that 80–90% of the ^{99m}Tc activity remains bound to tetracycline. In blood, 80–85% of the ^{99m}Tc-tetracycline activity is associated with the serum component.

Biological evaluation. The tissue distribution of the four labeled tetracyclines as a function of time was studied in mice, rats, rabbits, and dogs although the bulk of the studies were performed in mice and rats. Figures 2 and 3 show the distributions of labeled complexes 1 hr after injection in rats expressed as percentages of injected dose per organ and per gram of tissue, respectively. For tabulation of the activity distribution in the entire body of the rat, the assumption was made that 40% of the body weight represents muscle, 10% corresponds to bone, 6% to blood volume, and 1% to fat. In this manner we were able to account for essentially all of the administered activity. The number of rats sacrificed in each experiment was usually six and the results are expressed with error bars corresponding to ±1 s.d.

The general trends of organ distribution in rats, as shown in Tables 1 and 2, indicate that the renal uptake increases with time after injection and reaches a maximum value at 1–4 hr. For the sake of brevity, the 4 hr points have been omitted from Table 2; the kidney values for the oxy, chloro, and demethylchloro analogs are 22.9, 12.2, and 19.6, respectively.

The highest renal concentration is achieved with the tetracycline analog at 1 hr (30%) whereas the administered activity excreted in the urine at 1 hr is similar for all four complexes (40%). With the noted exception of the oxy derivative, the hepatic concentration of the other three analogs decreases with time. The blood level reflects a moderate clearance rate with very little residual activity at 24 hr. Muscle activity follows similarly, although on a regional gram basis abdominal muscle exhibits higher concentrations than thigh muscle. The low stomach activity indicates the absence of significant free TcO_4^- in the preparation. Activity in the small bowel reaches its highest level at about 2 hr. The subsequent high activity in the large bowel after 4 hr reflects the physiological transit of bowel content. After 24 hr 20–30% of the administered dose was found in the feces. The total activity excreted through

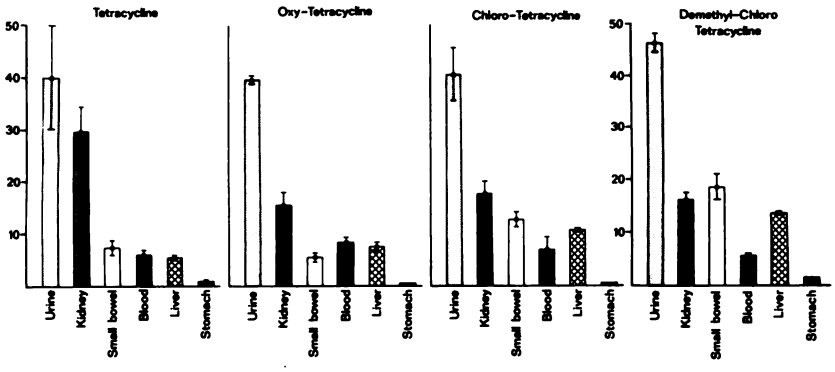

FIG. 2. Organ distribution of ^{99m}Tc-tetracyclines in rats 1 hr postinjection expressed as percent administered activity per organ.

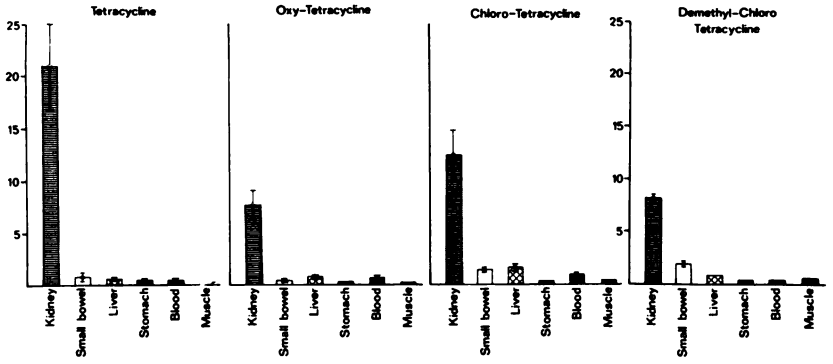

FIG. 3. Organ distribution of ^{99m}Tc-tetracyclines in rats 1 hr postinjection expressed as percent administered activity per gram.

TABLE 1. ORGAN DISTRIBUTION AND TIME ACTIVITY COURSE OF ^{99m}Tc-TETRACYCLINE IN RATS

Organ	Percent of injected dose per organ					
	15 min	30 min	1 hr	2 hr	4 hr	24 hr
Blood	9.7 ± 1.9	6.4 ± 1.3	6.0 ± 1.1	2.8 ± 1.2	3.0 ± 0.7	1.5 ± 0.3
Muscle	17.3 ± 1.6	15.9 ± 1.5	16.4 ± 1.5	7.6 ± 2.7	4.9 ± 1.3	2.8 ± 0.6
Kidney	17.0 ± 2.9	21.0 ± 3.6	29.4 ± 5.0	20.2 ± 2.1	22.8 ± 2.1	15.2 ± 1.1
Liver	7.0 ± 0.5	6.6 ± 0.5	5.8 ± 0.4	4.4 ± 0.3	4.9 ± 0.3	3.8 ± 0.7
Spleen	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Heart	0.3 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.0 ± 0.0
Lungs	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	0.3 ± 0.0	0.2 ± 0.1	0.2 ± 0.0
Stomach	0.6 ± 0.1	0.6 ± 0.2	0.9 ± 0.5	0.3 ± 0.1	0.2 ± 0.0	0.1 ± 0.0
Small bowel	7.4 ± 1.4	5.9 ± 1.1	7.5 ± 1.5	10.3 ± 1.9	5.0 ± 1.1	0.7 ± 0.2
Large bowel	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.0	5.5 ± 1.0	4.3 ± 0.8
Urine	8.2 ± 2.1	20.4 ± 5.1	37.7 ± 9.6	40.0 ± 9.9	48.0 ± 6.0	65.0 ± 8.4

TABLE 2. ORGAN DISTRIBUTIONS OF ^{99m}Tc-OXYTETRACYCLINE, ^{99m}Tc-CHLORTETRACYCLINE, AND ^{99m}Tc DMCT IN RATS AT 1 HR AND 24 HR AFTER INJECTION

Organ	Percent injected dose per organ					
	^{99m}Tc-oxytetracycline		^{99m}Tc-chlortetracycline		^{99m}Tc-DMCT	
	1 hr	24 hr	1 hr	24 hr	1 hr	24 hr
Blood	8.6 ± 1.1	0.5 ± 0.1	6.4 ± 2.7	1.3 ± 0.2	4.5 ± 0.3	0.4 ± 0.0
Muscle	12.6 ± 1.6	6.3 ± 0.8	8.6 ± 0.6	4.6 ± 0.3	4.7 ± 0.2	0.0 ± 0.0
Kidney	16.2 ± 2.4	5.3 ± 0.8	17.4 ± 2.0	6.4 ± 0.7	16.5 ± 1.1	7.7 ± 0.7
Liver	7.9 ± 1.0	12.1 ± 1.5	10.7 ± 0.1	4.0 ± 0.1	7.1 ± 0.7	1.7 ± 0.3
Spleen	0.1 ± 0.0	0.0 ± 0.0	0.2 ± 0.0	0.4 ± 0.1	0.0 ± 0.0	0.0
Heart	0.1 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.3 ± 0.0	0.0 ± 0.0	0.0
Lungs	0.5 ± 0.1	0.0 ± 0.0	0.3 ± 0.1	0.4 ± 0.1	0.2 ± 0.0	0.0
Stomach	0.3 ± 0.0	0.2 ± 0.0	0.4 ± 0.1	1.2 ± 0.3	0.4 ± 0.1	0.0
Small bowel	5.5 ± 0.8	1.4 ± 0.2	12.9 ± 1.4	2.6 ± 0.2	18.0 ± 3.2	0.0
Large bowel	0.3 ± 0.0	10.9 ± 1.2	0.4 ± 0.0	3.9 ± 0.9	—	0.9
Urine	39.5 ± 0.6	51.0 ± 5.6	40.4 ± 5.4	—	44.7 ± 6.1	—
Bone	—	—	4.4 ± 0.6	—	1.8 ± 0.2	0.0

urine and feces at 24 hr accounts for 75–80% of the administered dose.

The overall distribution patterns for the four analogs in mice (Table 3) appear to be significantly different from those obtained in rats. The renal uptake is similar for tetracycline and oxytetracycline but lower by a factor of three for the remaining two analogs. The hepatic uptake is higher by 2–3 times. The gallbladder concentration of 4.9% at 1 hr with ^{99m}Tc-tetracycline strongly suggests clinical utility for biliary diagnosis. The clearance pattern in mice is generally more rapid than in rats.

Renal distribution in dogs. In order to determine the activity distribution in the renal cortex and medulla of a dog with respect to that in the blood 24 hr after injection of ^{99m}Tc-tetracycline, the cortex was carefully dissected and removed from the medulla and the activity distribution for a cortex/medulla weight ratio of 13.6:1.0 was determined. The activity ratio was 164:1.0. On a gram basis, the values of medulla/blood = 1.25:1.0, cortex/blood = 13.4:1.0, and cortex/medulla = 10.8:1.0 were obtained. The autoradiographic pattern of ^{99m}Tc-penicillamine (*5*) in a dog shows a similar pattern of distribution.

Effect of stoichiometry on organ distribution. In a study of the effect of varying proportions of reactants on organ distribution in rats, ^{99m}Tc-tetracycline with 10, 15, 20 and 25 mg of tetracycline hydrochloride and 1.0 mg of $SnCl_2 \cdot 2H_2O$ was prepared and injected. Results indicated that with increasing amounts of tetracycline hepatic uptake decreases whereas renal uptake exhibits a concomitant increase. The optimum tetracycline hydrochloride/$SnCl_2 \cdot 2H_2O$ ratio for renal uptake was found to be 20:1. Additional experiments employing 5 and 20 mg of DMCT and 1.0 mg $SnCl_2 \cdot 2H_2O$ further confirmed a maximum kidney concentration for the 20:1 ratio.

When pertechnetate is reduced by stannous ion, residual colloid can occur in the preparation of certain radiopharmaceuticals even if terminal filtration

TABLE 3. ORGAN DISTRIBUTIONS OF ^{99m}Tc-TETRACYCLINE, ^{99m}Tc-OXYTETRACYCLINE, ^{99m}Tc-CHLORTETRACYCLINE, AND ^{99m}Tc-DMCT IN MICE, AT 1 HR AND 2 HR AFTER INJECTION

Organ	Percent injected dose per organ							
	^{99m}Tc-tetracycline		^{99m}Tc-oxytetracycline		^{99m}Tc-chlortetracycline		^{99m}Tc-DMCT	
	1 hr	2 hr	1 hr	2 hr	1 hr	2 hr	1 hr	2 hr
Blood	4.2 ± 0.5	3.5 ± 0.5	3.7 ± 0.9	5.8 ± 1.5	4.2 ± 0.6	3.7 ± 0.6	2.0 ± 0.3	1.2 ± 0.1
Muscle	—	—	3.2 ± 0.7	1.8 ± 0.2	7.8 ± 1.6	8.5 ± 1.0	—	—
Kidney	19.0 ± 2.1	29.8 ± 5.2	19.2 ± 2.5	7.1 ± 0.9	4.6 ± 0.8	4.6 ± 0.6	4.7 ± 0.6	4.7 ± 0.7
Liver	14.2 ± 1.8	6.9 ± 0.8	22.7 ± 2.4	14.8 ± 1.9	15.0 ± 2.2	9.3 ± 1.1	11.9 ± 1.5	9.7 ± 1.0
Gallbladder	4.9 ± 0.3	0.4 ± 0.2	3.4 ± 0.7	2.6 ± 0.7	0.3 ± 0.1	2.5 ± 0.3	1.7	—
Spleen	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.3 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Heart	0.3 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Lungs	0.4 ± 0.1	0.5 ± 0.1	0.3 ± 0.1	0.1 ± 0.0	0.4 ± 0.1	0.4 ± 0.0	0.3 ± 0.0	0.2 ± 0.0
Stomach	1.3 ± 0.1	0.6 ± 0.1	3.0 ± 0.6	2.6 ± 0.5	0.7 ± 0.1	2.3 ± 0.2	1.0 ± 0.1	0.5 ± 0.1
Small intestine	13.8 ± 1.7	14.7 ± 1.6	16.1 ± 2.1	11.4 ± 1.4	24.7 ± 2.8	11.6 ± 1.2	21.6 ± 2.8	14.1 ± 1.5
Large intestine	0.8 ± 0.1	4.4 ± 0.5	0.9 ± 0.1	13.4 ± 1.5	0.7 ± 0.1	15.4 ± 2.1	0.8 ± 0.1	18.5 ± 2.0
Bone	—	—	2.0 ± 0.6	1.9 ± 0.5	2.5 ± 0.3	3.5 ± 0.4	—	—
Urine and bladder	—	5.2 ± 1.2	(29.1 ± 3.6)	—	40.7 ± 8.5	1.6 ± 0.2	1.7 ± 0.9	1.7 ± 0.5

is performed with 0.22 or 0.025-micron Millipore filters. In an attempt to show that the hepatic uptake mentioned above was largely due to colloid formation resulting from an insufficient quantity of chelating agent, stannous hydroxide colloid (*18*) labeled with both ^{99m}Tc and ^{119m}Sn was prepared in the exact manner in which ^{99m}Tc-tetracycline is produced, but with and without addition of the tetracycline. In the absence of tetracycline, the pH 7.4 solution deposits the majority of its activity on a 0.025-micron Millipore filter. A greater proportion of the ^{119m}Sn remains on the filter than does the ^{99m}Tc presumably due to the presence of unbound pertechnetate. The filtrate, consisting of colloid significantly smaller than 0.025 microns and pertechnetate, was injected in rats and the biodistribution determined at several times after administration. Counting of excised organs was performed on both ^{99m}Tc and ^{119m}Sn channels and the distribution results reflect this fact. Technetium-99m activity at 30 min indicates 40–50% deposition in liver (colloid) with bone and bone marrow having 20–25% and lesser but significant amounts in blood (13%), kidney (5.3%), and intestine (6%) due to the presence of pertechnetate. In contrast, tin activity exhibited the same 40–50% in liver (double-labeled colloid) but 40% in bone and bone marrow and insignificant quantities in the other reference tissues.

On the other hand, when 20 mg of tetracycline hydrochloride was incorporated in the preparation, only 10–15% of the activity was retained on the 0.025 micron filter and biodistribution of the filtrate indicated only 5–6% of the activity was deposited in the liver.

Albumin binding. Differences in the retention of ^{99m}Tc within the dialysis tubing between sample and control were determined to be 32, 38, and 35% higher than the control for oxytetracycline, tetracycline, and chlorotetracycline, respectively. The control samples turn nearly colorless due to loss of tetracycline into the dialysate. These data indicate only very slight variation in the degree of albumin binding of the three ^{99m}Tc-tetracyclines and cannot be used to explain differences in the rate of blood clearance and tissue distribution of the ^{99m}Tc-labeled analogs.

An attempt was made to comprehend fully the uptake and clearance patterns of the three main components in the preparation: ^{99m}Tc-tetracycline (90–95% of activity), ^{99m}Tc-stannous hydroxide colloid (5–10% of activity), and Sn-tetracycline (the major chemical ingredient in the preparation with the exception of the antibiotic starting material).

To study the role of stannous ion in the labeling procedure and its pharmacological fate after administration, ^{119m}Sn (24 KeV x-ray, $T_{1/2}$ 245 days) was added to the carrier tin in HCl solution and the labeled tetracycline prepared in accordance with the standard procedure. The chromatographic data indicated that most of the stannous ion used was chelated by the tetracyclines (*17,19*). The bioassays of ^{99m}Tc-tetracycline and ^{119m}Sn-tetracycline in rats showed that the biodistribution and metabolic pathways of the ^{99m}Tc- and ^{119m}Sn-chelates are markedly different. The renal concentration of the ^{119m}Sn-chelate is only one-fourth (3–8%) that of the ^{99m}Tc agent 1 hr postinjection, whereas the bone uptake of the ^{119m}Sn-chelate is higher by a factor of four.

DISCUSSION

Although no attempt was made to understand or characterize the mechanism of binding of reduced

technetium ion to the various tetracyclines, stable ^{99m}Tc complexes are generally found when donor atoms (N,O,S) are present in functional groups of organic molecules (*20*). Examination of the tetracycline molecule suggests that reduced technetium ion, with a relatively high charge distribution over a small ionic radius (0.6 Å), could form a reasonably stable octahedral structure using a d^2sp^3 hybrid orbital configuration. It has been postulated that hexachlorotechnetate ions in hydrochloric acid solution form an octahedral structure (*21*).

Due to the possibilities of coordination at different sites on the tetracycline molecule, the formation of a mixture of stereoisomers is possible with a specific stereoisomer the predominant one under a particular set of experimental conditions. It is conceivable that different isomers could have different biological specificity and this would be reflected in variations in organ distribution for what was thought to be a single compound.

Tetracycline and its analogs were found to combine with divalent copper, nickel, and zinc ions, forming 2:1 complexes through coordination at the C-4 dimethylamino groups and either C-3 or C-12 hydroxyl groups (*16*). In the case of ^{99m}Tc-tetracycline where tetracycline molecules are always in excess with respect to reduced ^{99m}Tc, the formation of a 2:1 tetracycline technetium complex is quite likely. When tetracycline and its analogs (labeled with ^{99m}Tc or unlabeled) undergo thermal- and/or photodecomposition, the color of the solution changes from light yellow to deep orange (*22*). The release of unbound TcO_4^- which occurs under these circumstances may indicate that reduced ^{99m}Tc forms bonds to the sites which are split under these conditions. Preliminary results aimed at elucidating the stoichiometry, oxidation state, and coordination chemistry of this new radiopharmaceutical support our initial hypothesis and will be the subject of a separate report.

Terminal filtration of the preparation through 0.22 micron (or smaller) filters is essential, not only for ensuring sterility but for removal of residual colloidal or particulate material. The solubility of the tetracyclines in water passes through a minimum at pH 4; hence colloids may form during neutralization with bicarbonate buffer as the solution goes from pH 2 to pH 7.4. In some instances, unfiltered preparations gave hepatic deposition of 25–30% of the administered activity whereas this value fell to 5% or less after filtration.

A comparison of the biological handling of ^{14}C-labeled tetracyclines with that of ^{99m}Tc-tetracyclines reveals many similarities in the patterns of organ distribution, protein conjugation, biliary excretion, and renal clearance (*23–28*). The metabolic cycle suggested by Böttiger may be applicable to ^{99m}Tc-tetracyclines, and, in fact, the alternate pathway for excretion through the liver-gallbladder-intestine-feces has been confirmed in mice and dogs (*29*).

In summary, tetracycline and three of its analogs were labeled with ^{99m}Tc produced by reduction of pertechnetate ion with stannous chloride. Factors influencing labeling efficiency, biological distribution, and stability were elucidated. Among the agents studied, ^{99m}Tc-tetracycline exhibited the highest kidney uptake; 29% in rats 1 hr after injection and 29% in mice 2 hr after administration. Gallbladder concentration was significant for all four analogs between 1 and 2 hr after administration. Acute and chronic toxicity studies of ^{99m}Tc-tetracycline in mice, rabbits, and dogs revealed no untoward effects. This agent is currently in clinical evaluation as a renal and gallbladder imaging agent.

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TECHNOLOGIST SECTION
THE SOCIETY OF NUCLEAR MEDICINE
21st ANNUAL MEETING

June 11–14, 1974 **Town and Country Hotel** **San Diego, California**

SIXTH CALL FOR SCIENTIFIC EXHIBITS:
NUCLEAR MEDICINE TECHNOLOGISTS' PROGRAM

The Technologist Scientific Sessions Committee announces that abstracts of exhibits are now being reviewed for the 21st Annual Meeting. Abstracts of exhibits are welcomed from technical affiliates.

All exhibits will be illuminated by available room light. There will be no provisions for transillumination, e.g., view boxes. The exhibit should be mounted on poster board not exceeding 30 in. X 30 in. No more than two boards may be entered for a subject. Exhibits should be clearly titled.

Abstract format: Exhibitor's name; title of exhibit (10 words maximum); abstract (100 words); dimensions (A maximum of two boards not exceeding 30 in. X 30 in.).

Exhibit Awards: The section is pleased to announce the presentation of 1st, 2nd and 3rd place awards for the three most outstanding scientific exhibits. These are judged on the basis of scientific merit, originality, display format, and appearance.

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