

# CHEMISTRY OF $^{99m}\text{Tc}$ TRACERS.

## II. IN VITRO CONVERSION OF TAGGED HEDP AND PYROPHOSPHATE (BONE-SEEKERS) INTO GLUCONATE (RENAL AGENT). EFFECTS OF Ca AND Fe(II) ON IN VIVO DISTRIBUTION

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***Sodium gluconate transforms the bone-seekers  $^{99m}\text{Tc}$ -HEDP and  $^{99m}\text{Tc}$ -pyrophosphate into the renal agent  $^{99m}\text{Tc}$ -gluconate. In these in vitro processes, pyrophosphate is displaced faster than HEDP, while the HEDP reaction is accelerated by calcium ions. The in vivo distributions of these bone and kidney agents are altered by the prior local injection of calcium or iron(II). These transformation and translocation phenomena are explained in terms of the mechanistic behavior of Tc(IV) complexes.***

A major thrust in the field of  $^{99m}\text{Tc}$ -labeled radio-pharmaceuticals has been the development of imaging agents for specific organs. The in vitro stability and in vivo distribution of these agents are influenced by a number of significant factors. We report the in vivo exchange of the bone agents  $^{99m}\text{Tc}$ -HEDP [(1-hydroxyethylidene)diphosphonate] (1) and  $^{99m}\text{Tc}$ -PP<sub>1</sub> (pyrophosphate) (2) into the renal agent  $^{99m}\text{Tc}$ -gluconate (3) in the presence of sodium gluconate.

### METHODS AND MATERIALS

The  $^{99m}\text{Tc}$ -HEDP (1) was prepared by mixing 1 ml of aqueous solution containing 0.5 mg of sodium (1-hydroxyethylidene)diphosphonate with 1 ml of tin solution (10 mg of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  in 100 ml of distilled water), and adding 2 ml of  $^{99m}\text{TcO}_4^-$  in physiologic saline. The  $^{99m}\text{Tc}$ -gluconate (4) was made by the substitution of 1 ml of 0.1 M sodium gluconate for the HEDP. To prepare the  $^{99m}\text{Tc}$ -PP<sub>1</sub>, 50 mg of  $\text{Na}_2\text{P}_2\text{O}_7 \cdot 10\text{H}_2\text{O}$  was dissolved in distilled water and the pH was brought to 6.8 with 0.13 ml of 0.1 M HCl. Next, 10 mg of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  was added, and a 1-ml aliquot was diluted to 10 ml with dis-

tilled water. One milliliter of this diluted solution was mixed with one milliliter of distilled water, and the addition of 2 ml of  $^{99m}\text{TcO}_4^-$  in physiologic saline produced the  $^{99m}\text{Tc}$ -PP<sub>1</sub> reagent. For in vitro experiments, the ligands and cations used were dissolved in distilled water and added to the preformed imaging agents to produce the desired molarities. After standing at room temperature for various times, 0.5 ml of the mixtures were injected into the tail veins of male Sprague-Dawley rats weighing ~ 200 gm. To explore the changes in tissue distribution produced by different agents, 0.5 ml of the test compound was injected into one hind foot pad of the rat and 0.5 ml of normal saline into the other. The imaging agent (0.5 ml) was then injected into the tail vein. At 1 hr after injection the rats were killed under ether anesthesia by exsanguination from the abdominal aorta.

### RESULTS

Table 1 shows the organ distributions of  $^{99m}\text{Tc}$ -gluconate (A),  $^{99m}\text{Tc}$ -HEDP (B), and  $^{99m}\text{Tc}$ -PP<sub>1</sub> (C). The results were the same whether the agents were injected immediately or after standing for 2 hr at room temperature. The kidney agent can be prepared from either sodium or calcium gluconate without changing the tissue distribution.

The in vitro addition of 0.5 mg of HEDP or sodium pyrophosphate to the  $^{99m}\text{Tc}$ -gluconate reagent had no effect on the distribution of the renal agent for periods of up to 2 hr. Table 1 shows the effects

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TABLE 1. DISTRIBUTION OF  $^{99m}\text{Tc}$  ACTIVITY IN RATS: IN VITRO TRANSFORMATIONS

Exp.	Reagent*	Time injected (hr after preparation)	Percent of injected dose (average of four rats)				
			Kidneys†	Liver†	Stomach†	Femur†	Carcass‡
A	Tc-G	2	20.0	0.7	0.05	0.1	7
B	Tc-HEDP	2	0.7	0.3	0.06	1.6	38
C	Tc-PP <sub>1</sub>	2	3.0	1.3	0.2	2.0	50
D	Tc-HEDP/NaG	2	4.0	0.3	0.04	1.6	31
E	Tc-HEDP/CaG	2	20.0	0.9	0.08	0.1	8
F	Tc-HEDP/CaCl <sub>2</sub>	2	0.7	17.0	0.09	1.0	41
G	Tc-PP <sub>1</sub> /NaG	0.09	11.0	0.6	0.1	0.7	22
H	Tc-PP <sub>1</sub> /NaG	1	18.0	0.8	0.09	0.08	10
I	Tc-PP <sub>1</sub> /CaG	1	22.0	0.7	0.05	0.09	6
J	Tc-PP <sub>1</sub> /CaCl <sub>2</sub>	1	14.0	23.0	0.2	0.06	6

\* Tc is  $^{99m}\text{Tc}$ , G is gluconate, HEDP is (1-hydroxyethylidene)diphosphonate, PP<sub>1</sub> is pyrophosphate. The amounts of added NaG, CaG, and CaCl<sub>2</sub> are stated in the text.

† Percent of injected dose per total organ. The average deviations were within  $\pm 20\%$  of the reported values.

‡ Carcass represents skin, muscle, and skeleton.

after 2 hr of making the  $^{99m}\text{Tc}$ -HEDP reagent 0.28 *M* in sodium gluconate (D), 0.14 *M* in calcium gluconate (E), or 0.14 *M* in calcium chloride (F). Also presented are the tissue distributions of  $^{99m}\text{Tc}$ -PP<sub>1</sub> after adding the same concentrations of sodium gluconate at 5 min (G) or at 1 hr (H), and of calcium gluconate (I) or calcium chloride (J) at 1 hr.

Calcium gluconate completely changes  $^{99m}\text{Tc}$ -HEDP into a kidney agent in 2 hr, while sodium gluconate produces only partial transformation in this time. Addition of calcium chloride results in a marked increase in liver activity. With  $^{99m}\text{Tc}$ -PP<sub>1</sub>, the addition of both calcium and sodium gluconate converts the bone agent into a kidney agent in 1 hr, with about 50% conversion occurring in 5 min with sodium gluconate. Adding CaCl<sub>2</sub> to  $^{99m}\text{Tc}$ -PP<sub>1</sub> produces substantial liver activity in 1 hr.

Due to the conveniently slower reaction rate of HEDP, further experiments were done with this agent. The  $^{99m}\text{Tc}$ -HEDP solutions were made 0.9–0.001 *M* in sodium gluconate. After 3 hr, the femur activities were within 10% of one another, indicating little dependence of the ligand exchange rate on substrate concentration. Experiments with 0.01 *M* ZnCl<sub>2</sub> and with Mg<sup>+2</sup>, Fe<sup>+3</sup>, or Fe<sup>+2</sup> sulphates indicated that Ca<sup>+2</sup> produced the greatest conversion of  $^{99m}\text{Tc}$ -HEDP into  $^{99m}\text{Tc}$ -gluconate.

Partially transformed  $^{99m}\text{Tc}$ -HEDP/gluconate mixtures were made 0.001 *M* in  $^{99}\text{TcO}_4^-$  to oxidize the Sn(II); they were then saturated with oxygen and injected after standing for 15 min. No oxidation (increase in stomach activity) was observed. Similar results were found with the individual agents (4). A  $^{99m}\text{Tc}$ (Sn) kidney agent prepared at pH 13 is readily oxidized under these conditions (5).

Table 2 presents the results of injecting various test preparations into the rat's foot pads, followed by tail vein injection of the bone and kidney agents. For the 0.14 *M* CaCl<sub>2</sub>/saline injections, there was a 50% relative increase in  $^{99m}\text{Tc}$  activity at the site of the calcium ion injection for both  $^{99m}\text{Tc}$ -HEDP and  $^{99m}\text{Tc}$ -PP<sub>1</sub> and a slight decrease in overall femur uptake. For 0.14 *M* Fe-gluconate/saline used with the bone agents, more than a twofold relative increase in activity is found for the iron-treated foot pad. The femur activity is substantially decreased and the  $^{99m}\text{Tc}$  activity in the kidneys increases from ~ 1% to over 10% of the injected activity. The liver activity increases in response to both Ca and Fe(II) with  $^{99m}\text{Tc}$ -PP<sub>1</sub> but not with  $^{99m}\text{Tc}$ -HEDP. The organ distributions of the renal agent  $^{99m}\text{Tc}$ -gluconate are unaffected by the Fe-gluconate/saline injection, except for a fourfold increase in  $^{99m}\text{Tc}$  activity at the Fe(II) injection site. This implies that the concentration of the bone agents in the kidneys in rats given Fe(II) is not primarily due to kidney damage by the ferrous ion.

#### DISCUSSION

We have previously shown (4) that the addition of carrier  $^{99}\text{Tc}$  does not alter the tissue distribution of  $^{99m}\text{Tc}$ -HEDP or  $^{99m}\text{Tc}$ -gluconate in rats. The oxidation state of  $^{99}\text{Tc}$  in these bone and renal agents was shown to be Tc(IV), having a 4d<sup>3</sup> electronic configuration. Many d<sup>3</sup> complexes are substitution-inert, i.e., the half-life for ligand substitution into the metal ion coordination shell is greater than 1 min for a 0.1 *M* concentration of entering ligand (6). This study confirms the predicted in vitro substitution-inertness of both  $^{99m}\text{Tc}$ -HEDP ( $t_{1/2} > 1$  hr)

TABLE 2. DISTRIBUTION OF  $^{99m}\text{Tc}$  ACTIVITY IN RATS: IN VIVO TRANSLOCATIONS

Exp.	Imaging agent*	Foot pad reagents* (Rt/Left)	Percent of injected dose (average of four rats)					Activity ratio (rt leg/left leg)
			Kidneys†	Liver†	Stomach†	Femur†	Carcass‡	
A	Tc-HEDP	CaCl <sub>2</sub> /saline	0.6	0.7	0.1	1.8	37	1.5
B	Tc-PP <sub>1</sub>	CaCl <sub>2</sub> /saline	1.4	5.6	0.2	1.7	39	1.5
C	Tc-PP <sub>1</sub>	NaG/saline	1.5	0.6	0.2	2.0	48	1.1
D	Tc-PP <sub>1</sub>	FeG/saline	16.0	8.0	0.4	0.6	33	4.0
E	Tc-HEDP	FeG/saline	11.0	1.0	0.2	1.0	35	2.4
F	Tc-G	FeG/saline	21.0	1.0	0.2	—	8	4.1

\* Tc is  $^{99m}\text{Tc}$ , HEDP is (1-hydroxyethylidene)diphosphonate, PP<sub>1</sub> is pyrophosphate, G is gluconate. Saline is normal saline; the concentrations of Fe, NaG, and CaCl<sub>2</sub> are listed in the text.

† Percent of injected dose per total organ. The average deviations are within  $\pm 20\%$  of the reported values.

‡ Carcass represents skin, muscle, and skeleton.

and  $^{99m}\text{Tc-PP}_1$  ( $t_{1/2} \sim 5$  min) using sodium gluconate, the latter reagent being the more labile. If the ligand exchange process were associative and bimolecular in character, the  $^{99m}\text{Tc-HEDP}$  reaction rate would be expected to increase with an increase in sodium gluconate concentration. The essential independence of the transformation rate on gluconate concentration indicates a dissociative mechanism, where the rate-determining factor is the slow dissociation of technetium from  $^{99m}\text{Tc-HEDP}$ . The liberated technetium rapidly combines with gluconate to produce the kidney agent  $^{99m}\text{Tc-gluconate}$ .

Calcium combines with pyrophosphate and forms large polynuclear species with HEDP (7). The increase in the reaction rate with gluconate/ $^{99m}\text{Tc-HEDP}$  in the presence of calcium could be due to the dissociation of the  $^{99m}\text{Tc}$  complex induced by the formation of polynuclear Ca-HEDP complexes and the subsequent scavenging of the liberated  $^{99m}\text{Tc}$  by gluconate. In the absence of scavenger gluconate ligands, the Ca/ $^{99m}\text{Tc-HEDP}$  reaction produces a significant amount of liver agent, which could be colloidal  $^{99m}\text{TcO}_2$ . The combination of Sn(II) with  $^{99m}\text{TcO}_4^-$  at neutral pH also forms a liver agent (4).

The altered distributions of the bone and kidney agents produced by high local concentrations of calcium or iron in vivo might be accounted for in a similar fashion. These metal ions could facilitate the dissociation of the  $^{99m}\text{Tc}$  from the carrier ligand, producing both  $^{99m}\text{Tc}$  deposition at the reaction site and translocation to other tissues, possibly with the migrant  $^{99m}\text{Tc}$  bound to another ligand (8). Such metal effects could provide a partial explanation of why  $^{99m}\text{Tc-PP}_1$  and HEDP are effective imaging agents for myocardial infarcts (9,10). It is proposed that metal ions produce changes in tissue distribution of the  $^{99m}\text{Tc}$  bone agents through the exchange of ligands at a given technetium oxidation level, whereas the altered  $^{99m}\text{TcO}_4^-$  distribution in rats given Sn(II)

is induced by a change in technetium oxidation state (11). Particularly noteworthy is the substantial kidney activity derived from the bone agents in vivo by FeSO<sub>4</sub> when no carrier kidney-agent ligand is present. Possibly, many  $^{99m}\text{Tc}$  kidney agents are transformed into a common in vivo  $^{99m}\text{Tc}$  form that carries the activity to the kidneys regardless of the nature of the in vitro ligand. This phenomenon may explain the present results with iron and also the fact that  $^{99m}\text{Tc(Sn)}$  at high pH and other appropriate dihydroxyglycols (gluconate, glucoheptonate, mannitol, ethylene glycol, and glycerol) all give essentially the same tissue distribution (5,12) as that noted in Table 1 for  $^{99m}\text{Tc-gluconate}$ .

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