Evaluation in Dogs and Humans of Three Potential Technetium-99m Myocardial Perfusion Agents

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The biodistribution of the three cationic ^{99m}Tc complexes $[^{99m}Tc(TMP)_6]^+$, $[^{99m}Tc(POM\text{-}POM)_3]^+$, and $[^{99m}Tc(TBIN)_6]^+$—where TMP represents trimethylphosphite, POM-POM represents 1,2-bis(dimethyoxyphosphino)ethane, and TBIN represents *t*-butylisonitrile—have been evaluated in humans and dogs. Each agent was studied in three normal volunteers at rest, while $[^{99m}Tc(POM\text{-}POM)_3]^+$ and $[^{99m}Tc(TBIN)_6]^+$ were each studied in one normal volunteer at exercise. Even though all three agents yield good myocardial images in dogs, none appear suitable for clinical use as myocardial perfusion imaging radiopharmaceuticals. In humans, $[^{99m}Tc(TMP)_6]^+$ and $[^{99m}Tc(POM\text{-}POM)_3]^+$ clear very slowly from the blood and provide myocardial images only several hours after injection. $[^{99m}Tc(TBIN)_6]^+$ clears rapidly from the blood, but accumulation in the lung obscures the myocardial image for the first hour after injection; at later times, activity in the liver and spleen masks the apical wall. These results correlate with the blood-binding properties of the three complexes. $[^{99m}Tc(TMP)_6]^+$ and $[^{99m}Tc(POM\text{-}POM)_3]^+$ bind tightly to the plasma of human blood, but not to the plasma of dog blood; $[^{99m}Tc(TBIN)_6]^+$ does not bind tightly to the plasma of either dog or human blood. Among the Tc(I) complexes studied to date in humans, $[^{99m}Tc(TBIN)_6]^+$ appears to be unique in biodistribution pattern, blood-binding properties, and the fact that exercise improves the ultimate myocardial image. All the Tc(I) complexes appear to undergo myocardial accumulation by a mechanism different from that utilized by Tc(III) complexes. Animal studies alone are not adequate to evaluate the potential utility of ^{99m}Tc cationic complexes for myocardial perfusion studies.

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In 1981, it was shown that cationic complexes of technetium-99m (^{99m}Tc) accumulate in the normal myocardial tissue of test animals (*1*). Since then, great effort has been expended towards developing a cationic ^{99m}Tc radiopharmaceutical that would be clinically useful. Gerson and co-workers (*2,3*) have evaluated *tr*-$[^{99m}Tc(DMPE)_2Cl_2]^+$ and $[^{99m}Tc(DMPE)_3]^+$ in human volunteers and patients, while recently Thakur and co-workers (*4*) have similarly evaluated *tr*-$[^{99m}Tc(DEPE)_2Cl_2]^+$ (DMPE = 1,2-bis(dimethylphosphino)ethane; DEPE = 1,2-bis(diethylphosphino)ethane). None of these complexes are clinically useful despite the fact that they all provide acceptable myocardial images in test animals. Therefore it appears that, as a class, cationic ^{99m}Tc complexes undergo markedly species dependent biodistributions and it is difficult to predict the clinical utility of a particular complex from results obtained in animals (*5*). The primary aim of this study is to evaluate the biodistributions in man of three cationic ^{99m}Tc complexes that have recently been suggested as potential myocardial perfusion agents on the basis of animal studies: $[^{99m}Tc(TBIN)_6]^+$ (*6*), $[^{99m}Tc(TMP)_6]^+$ (*7,8*), and $[^{99m}Tc(POM\text{-}POM)_3]^+$ where TBIN represents *t*-butylisonitrile, TMP represents trimethylphosphite, and POM-POM represents 1,2-bis(dimethoxyphosphino)ethane (*9*). Because all three of these agents are complexes of technetium(I), as is $[^{99m}Tc(DMPE)_3]^+$ (*3*), whereas *tr*-$[^{99m}Tc(DMPE)_2Cl_2]^+$ (*2*), and *tr*-$[^{99m}Tc(DEPE)_2Cl_2]^+$ (*4*) are complexes of technetium(III), this study was also designed to provide some insight into the mechanisms of action of technetium(I) cations, and possibly into the comparative mechanisms of action of cationic Tc(I) and Tc(III) radiopharmaceuticals.

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After this comparative study of three ^{99m}Tc agents was completed, there appeared in the literature (*10*) a brief report on the biodistribution in humans of one of them, $[^{99m}Tc(TBIN)_6]^+$.

MATERIALS AND METHODS

General

Unless otherwise specified, all materials were of reagent grade. Solvents used in high performance liquid chromatography (HPLC) were specified as being of HPLC purity. Trimethylphosphite (TMP) was obtained commercially* and distilled before use; 1,2-bis(dimethoxyphosphino)ethane (POM-POM) was prepared according to King (*9*); *t*-butylisonitrile (TBIN) was obtained commercially* and used without further purification. All three reagents were stored and used in an inert atmosphere. Tetrabutylammonium borohydride was obtained commercially†.

High performance liquid chromatographic analyses were performed using an apparatus equipped with (a) a guard column containing LiChrosorb C18, (b) a 25 cm × 4.2 mm, 10-μ particle size, C-8 reversed phase column‡, and (c) a radiometric detection system centered at the 140 keV emission of ^{99m}Tc.

Radiopharmaceutical Preparations

Labeling was conducted in an inert atmosphere using "no-carrier-added" $^{99m}TcO_4^-$ obtained by eluting a $^{99}Mo/^{99m}Tc$ generator§. Hexakis(*t*-butylisonitrile)technetium(I) ($[^{99m}Tc(TBIN)_6]^+$) was prepared using a method analogous to that reported for the synthesis of the ^{99}Tc analog $[^{99}Tc(TBIN)_6]^+$ (*11*). An efficient synthesis of $[^{99m}Tc(TBIN)_6]^+$ has recently been reported in detail (*10*). Hexakis(trimethylphosphite)technetium(I) ($[^{99m}Tc(TMP)_6]^+$) was prepared in anhydrous methanol using a method analogous to that reported for the synthesis of the ^{99}Tc analog $[^{99}Tc(TMP)_6]^+$ (*8*). Tris(1,2-bis(dimethoxyphosphino)ethane)technetium(I) ($[^{99m}Tc(POM\text{-}POM)^3]^+$) was analogously prepared in anhydrous methanol using tetrabutylammonium borohydride as a reducing agent.

Methanolic solutions of $^{99m}TcO_4^-$ were prepared as follows. Tetrabutylammonium bromide was added to an aqueous solution of $^{99m}TcO_4^-$ and the resulting tetrabutylammonium pertechnetate salt was extracted onto a C18 column. The column was eluted with dichloromethane, and the resulting solution was dried over $MgSO_4$ before being evaporated to dryness. Addition of anhydrous methanol to the residue led to a solution which could be used for the preparation of both the TMP and the POM-POM complexes. In a typical preparation of $[^{99m}Tc(TMP)_6]^+$, 0.75 ml of methanolic $^{99m}TcO_4^-$ solution were degassed in a 5-ml borosilicate reaction vial and 0.75 ml of a 10% solution of TMP in methanol were added. The resulting solution was sealed in the reaction vial by use of a Teflon-lined cap and then heated at 100°C for 30 min. Preparations of $[^{99m}Tc(POM\text{-}POM)_3]^+$ were conducted similarly except that 40 mg of tetrabutylammonium borohydride were added to the preparation, and the reaction solution was heated at 140°C for 2 hr.

All radiopharmaceutical preparations were purified by selective elution from a reversed-phase SEP-PAK** cartridge, and then were passed through a 0.22-μ filter. The TMP and POM-POM radiopharmaceuticals were injected in a 40/60 ethanol/saline matrix, while the more lipophilic TBIN radiopharmaceutical was injected in a 70/30 ethanol/saline matrix.

Radiopharmaceutical Quality Control

The purity of the radiopharmaceuticals used in this study was assured by a combination of chemical and biologic quality controls. Chemical quality control was effected by HPLC on a C-8 reversed-phase column (*12*). For $[^{99m}Tc(TMP)_6]^+$ and $[^{99m}Tc(POM\text{-}POM)_3]^+$ the mobile phase was 85/15 methanol/water containing 0.01*M* sodium heptanesulfonate; for the more lipophilic $[^{99m}Tc(TBIN)_6]^+$ the mobile phase was 55/35/10 methanol/THF/water containing 0.01*M* sodium heptanesulfonate. At a flow rate of 1.5 ml/min, typical retention times for $[^{99m}Tc(TMP)_6]^+$, $[^{99m}Tc(POM\text{-}POM)_3]^+$, and $[^{99m}Tc(TBIN)_6]^+$ under these conditions are 6, 8, and 5 min. HPLC analyses showed that all radiopharmaceutical preparations used in this study were >93% pure, and the vast majority were >97% pure. Biologic quality control was effected by first monitoring the biodistribution of each of the three agents in at least six mongrel dogs and showing that for each agent this biodistribution is reproducible. Since each agent was also >95% pure by HPLC analysis, this preliminary work demonstrated that HPLC quality control is sufficient to ensure a reproducible biodistribution in dogs (*5,13*).

Dog Studies

An anesthetized (4–15 mg/kg Pentothal) mongrel dog was placed in the supine position with its chest centered under a large field gamma camera†† equipped with a low-energy, high resolution collimator, and centered on the 140 keV emission of ^{99m}Tc(20% energy window). Different dogs were injected in the calf vein with 4–7 mCi of $[^{99m}Tc(TMP)_6]^+$, $[^{99m}Tc(POM\text{-}POM)_3]$,$^+$ or $[^{99m}Tc(TBIN)_6]^+$, contained in 0.5 ml (Table 1). For the first hour after injection data were recorded continuously in a 64 × 64 matrix using a dedicated computer‡‡ in the frame mode (10 sec/frame). During the next hour, 1-min frames were acquired at 20-min intervals. An indwelling catheter, placed in the calf vein of the leg not used for injection, was used to collect 3-ml blood samples at 2, 4, 8, 10, 15, 30, 60, and 90 min after injection. Each blood sample was transferred to a heparinized tube immediately after collection.

Human Studies

Each agent was studied in three asymptomatic male volunteers at rest. With the subject supine, and the gamma camera centered over the thorax in the anterior projection, 7–13 mCi in 0.5 ml (Table 1) of the agent were injected into an antecubital vein. Using the same experimental setup as described above, data were continuously acquired in the frame mode (10 sec/frame, 64 × 64 matrix) for the first hour after injection. Thereafter, 1-min frames were acquired at 30-min intervals for the duration of the study (6 hr for $[^{99m}Tc(TMP)_6]^+$ and $[^{99m}Tc(POM\text{-}POM)_3]^+$, 4 hr for

TABLE 1

	Agent	Experimental day	Injection dose (mCi)	Blood clearance ($T_{1/2}$ min)	Myocardial / Blood pool 10 min	Myocardial / Blood pool 60 min	Myocardial / Blood pool 5 or 3 hr*	Myocardial / Lung 10 min	Myocardial / Lung 60 min	Myocardial / Lung 5 or 3 hr*	Myocardial / Liver 10 min	Myocardial / Liver 60 min	Myocardial / Liver 5 or 3 hr*
Dog 1	TMP	1	6.0	1.5	1.1	1.1		2.0	2.5		0.4	0.6	
Dog 2	POM-POM	2	4.8	1.5	1.2	1.2		3.5	3.5		0.4	0.6	
Dog 3	TBIN	3	6.6	1.0	1.5	1.5		1.1	2.5		1.5	0.7	
	Normal volunteer												
	POM-POM	2	9.1	42.0	0.5	0.5	1.1	1.3	1.6	2.2	1.0	0.6	0.6
	TBIN	3	8.0	1.5	1.3	1.2	1.2*	0.8	1.6	2.2*	0.4	0.2	0.2*
	TMP	4	9.4	57.0	0.6	0.8	1.1	1.3	1.4	2.0	0.7	0.4	0.4
	POM-POM	5	12.6	23.0	0.5	0.6	1.4	1.0	1.3	2.0	0.6	0.4	0.6
	TBIN	7	9.3	1.5	1.5	1.4	1.3*	0.9	1.7	2.4*	0.4	0.2	0.3*
	TBIN	7	9.6	1.5	1.6	1.3	1.2*	0.8	1.5	2.3*	0.3	0.2	0.2*
	POM-POM	8	11.1	51.0	0.7	0.8	1.1	1.8	1.7	1.9	1.0	0.7	0.7
	TMP	9	10.8	26.0	0.6	0.7	1.1	1.2	1.3	2.2	0.6	0.5	1.2
	TMP	9	10.1	36.0	0.6	0.7	1.0	1.0	1.1	1.3	0.6	0.6	1.1
	TBIN(STRESS)	6	7.3	3.0	1.6	1.7	1.8*	0.9	1.5	2.9*	1.2	1.0	0.8*
	POM-POM(STRESS)	8	10.3	49.0	0.7	0.8	1.1	1.6	1.8	2.7	0.9	0.7	0.8

$[^{99m}Tc(TBIN)_6]^+$). Magnified images (zoom = 2; 500,000 counts) were obtained in the anterior (ANT) and 40° left anterior oblique (40 LAO) projections at the end of the experiment. An indwelling catheter, placed in a vein of the arm not used for injection, was used to collect blood samples at 1, 2, 4, 6, 10, 15, 30, and 60 min after injection for $[^{99m}(TBIN)_6]^+$; samples for the other two tracers were collected at these times plus at 120 min.

$^{99m}Tc(POM\text{-}POM)_3]^+$ and $[^{99m}Tc(TBIN)_6]^+$ were each studied in a normal male volunteer during graded exercise using bicycle ergometry. At peak exercise, ~10 mCi of the agent were injected intravenously and exercise was continued for 1-min. Imaging and blood collection were performed as described above for the resting studies.

Data Analyses

Blood samples were weighed and then counted in a well counter[§§]. The plasma fraction was separated by centrifugation at 1,500 *g* for 10 min, and then it was also weighted and counted. Aliquots of the original radiopharmaceutical were also counted as internal standards. The activity in the blood (and in the plasma) was then corrected for decay and expressed as a percentage of the injected dose per mg of blood (or plasma). These data were then used to construct time-activity curves which were distinctly biphasic in all three dog studies and in the $[^{99m}(TBIN)_6]^+$ human study. Values for the half-lives ($T_{1/2}$) governing the first portion of the blood clearance were obtained from time-activity curves plotted on a semilog scale. The ratios of activity per mg of plasma to activity per mg of red blood cells (RBC) were also plotted as a function of time.

Regions of interest (ROI) were defined over the left anterolateral heart wall, cardiac blood pool, lung, and liver. The resulting counts, corrected for pre-injection patient background, were normalized to the area of the ROI. The ratios of counts in the left ventricle to counts in the cardiac blood pool, lung, and liver were calculated at each imaging time.

RESULTS

Blood clearance curves, for both dogs and humans, are given in Fig. 1. In dogs, blood clearance is fast for all three agents ($T_{1/2}$ values of 1.5, 1.5, and 1.0 min for $[^{99m}Tc(TMP)_6]^+$, $[^{99m}Tc(POM\text{-}POM)_3]^+$, and $[^{99m}Tc(TBIN)_6]^+$, respectively). However, in man the blood clearance of $[^{99m}Tc(TMP)_6]^+$ and $[^{99m}Tc(POM\text{-}POM)_3]^+$ is slow ($T_{1/2}$ values in the range 20–60 min), while the clearance of $[^{99m}Tc(TBIN)_6]^+$ is almost as fast as observed in dogs ($T_{1/2}$ of 1.5 min). The value of the plasma/RBC ratio remains constant in both dogs and man after ~30 min postinjection (Fig. 2). In dogs, the ratio is 0.8 for all three agents. In man, the ratio is a factor of ten larger for $[^{99m}Tc(TMP)_6]^+$ and $[^{99m}Tc(POM\text{-}POM)_3]^+$, but for $[^{99m}Tc(TBIN)_6]^+$ it is about the same (1.0) as that observed in dogs.

Table 1 summarizes the ratios of counts in the myocardial wall (a) to counts in the blood pool, (b) to counts in the lung, and (c) to counts in the liver, for both dog and man, at 10 min, 60 min, and 3–5 hr after injection.

In dogs, uptake of all three agents in the myocardial wall is evident at 1 hr after injection. For $[^{99m}Tc(TMP)_6]^+$ and $[^{99m}Tc(POM\text{-}POM)_6]^+$, there is extensive uptake in the biliary system, while for $[^{99m}Tc(TBIN)_6]^+$ there is a relatively high lung background.

Figure 3 shows selected scintiphotographs obtained in humans at various times after injection. For both $[^{99m}Tc(TMP)_6]^+$ and $[^{99m}Tc(POM\text{-}POM)_3]^+$ the heart wall is not visualized during the first hour after injection, but is evident in pictures obtained ~5 hr after injection. For both of these agents visualization of the myocardial wall is hindered by (a) high blood-pool activity which is present even after 5 hr, (b) lung activity which only slowly clears during the study, and (c) liver activity which is initially very high and then slowly clears through the biliary system. The behavior of $[^{99m}Tc(TBIN)_6]^+$ is quite different. This agent rapidly clears from the blood pool, allowing detection of the heart wall even a few minutes after injection. However, during this early

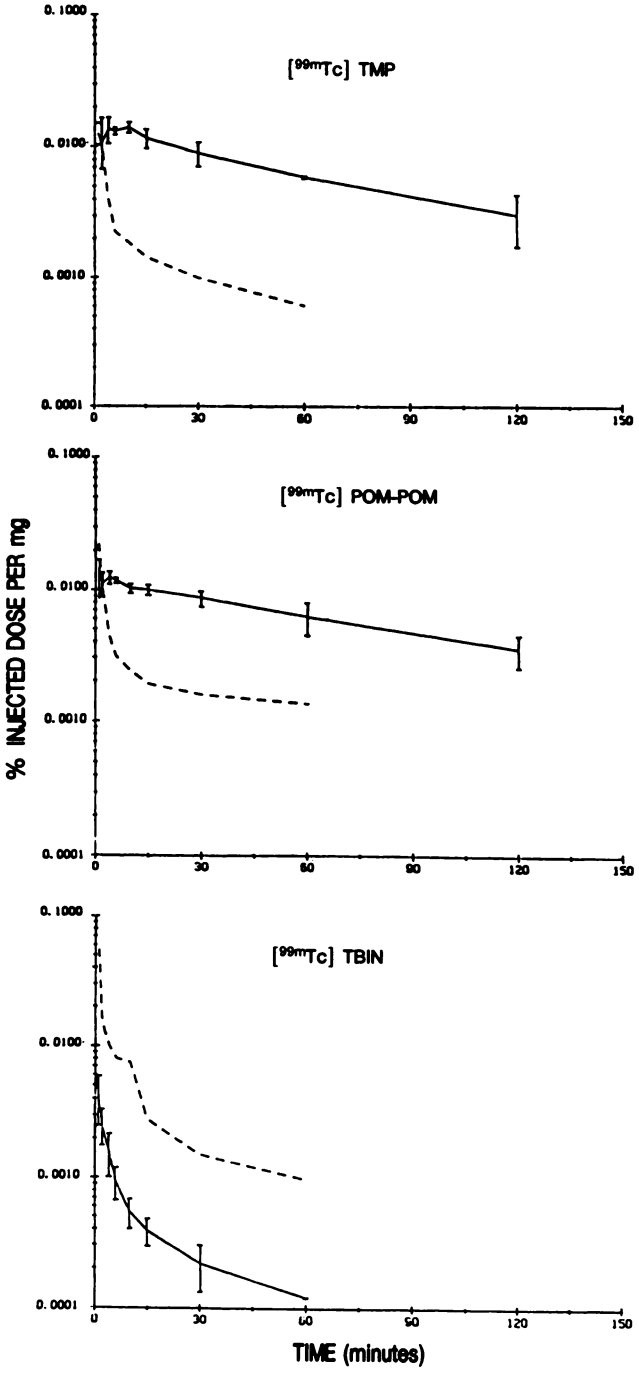

FIGURE 1
Whole-blood time-activity curves (semilog) for $[^{99m}Tc(TMP)_6]^+$, $[^{99m}Tc(POM\text{-}POM)_3]^+$ and $[^{99m}Tc(TBIN)_6]^+$ in dog (———) and in humans (mean ± s.d., I———I), normalized to injected dose and sample weight, and corrected for physical decay of isotope

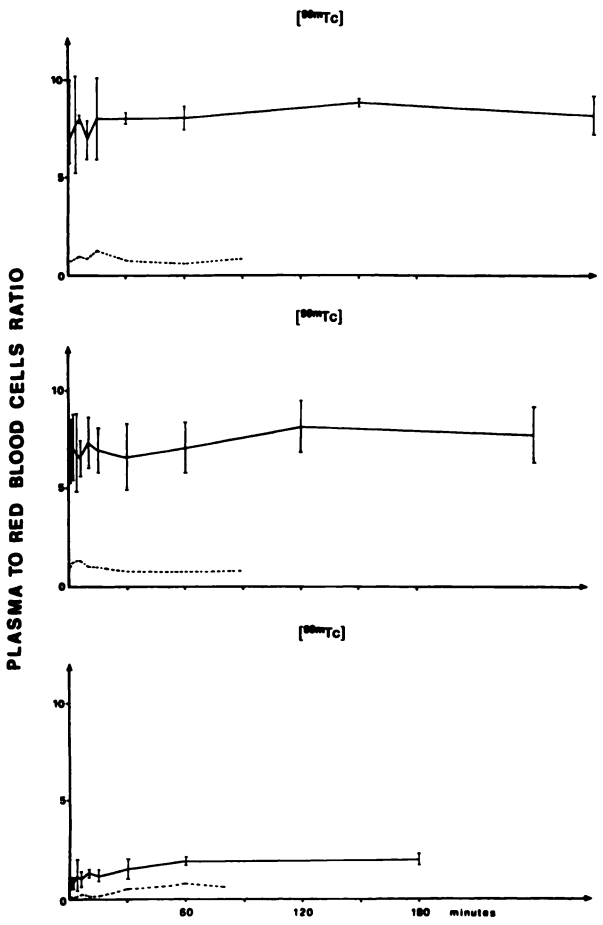

FIGURE 2
Plasma to red blood cell ratio vs. time for three cationic ^{99m}Tc complexes in dog (. . .) and in normal volunteers (mean ± s.d., I———I) at rest

phase the lung activity is particularly high (heart/lung = 0.85 ± 0.05 at 10 min postinjection) and details of the myocardial structure cannot be discerned. At 1 hr after injection the lung background is decreased to the point that the myocardium is readily visualized (heart/lung = 1.58 ± 0.10), although interference from the liver and spleen still obscures the apical wall.

The best myocardial images were obtained at the end of the study, about 3 hr after injection, even though the apex is still partially obscured by the high activity present in the liver and spleen.

Figure 4 shows scintiphotographs obtained using $[^{99m}Tc(POM\text{-}POM)_3]^+$ and $[^{99m}Tc(TBIN)_6]^+$ in an exercise study. Exercise clearly improves the $[^{99m}Tc(TBIN)_6]^+$ image in that the myocardial wall is much better defined, but exercise does not appear to significantly affect the $[^{99m}Tc(POM\text{-}POM)_3]^+$ image.

DISCUSSION

The ideal radiotracer for myocardial perfusion imaging should have a rapid blood clearance, a prompt and high uptake in the heart wall, and a favorable target to nontarget (lung, liver and spleen) uptake ratio. The search for a ^{99m}Tc agent that might exhibit these properties has focused on cationic complexes of Tc(III) and Tc(I). Before this study, three cationic ^{99m}Tc complexes had been evaluated as myocardial perfusion imaging agents in humans: *tr*-$[^{99m}Tc(DMPE)_2Cl_2]^+$ exhibits

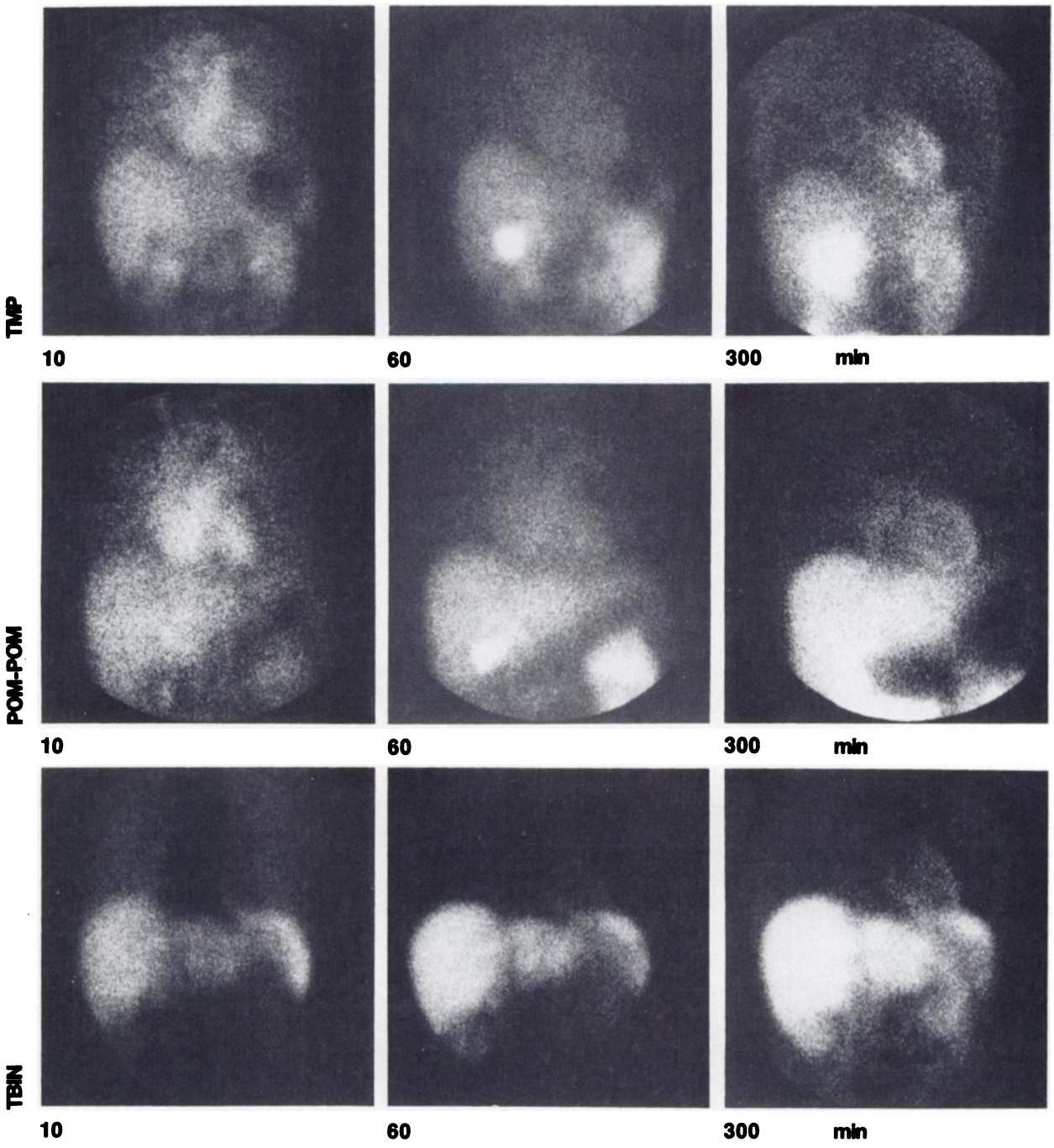

FIGURE 3
Scintiphotographs (anterior view) of humans (resting studies) obtained at various times during dynamic data collection

myocardial uptake, but high accumulation in the liver obscures the myocardial apex and prevents acquisition of clinically useful images (*2*); *tr*-$[^{99m}Tc(DEPE)_2Cl_2]^+$ does not detectably accumulate in the heart (*4*); $[^{99m}Tc(DMPE)_3]^+$ clears so slowly from the blood that myocardial images can be obtained only 6–10 hr after injection (*3*). After this study was completed, a brief report appeared (*10*) indicating that $[^{99m}Tc(TBIN)_6]^+$ can provide clinically useful myocardial images.

The results of this study show that in humans, $[^{99m}Tc(TMP)_6]^+$ and $[^{99m}Tc(POM\text{-}POM)_3]^+$ behave similarly to each other and similarly to $[^{99m}Tc(DMPE)_3]^+$. For all three complexes myocardial uptake is obscured for several hours by high blood background, slow lung clearance, and high liver uptake with subsequent release of activity to the biliary system. Thus, for all three agents, acceptable definition of the heart wall occurs only several hours after injection. The

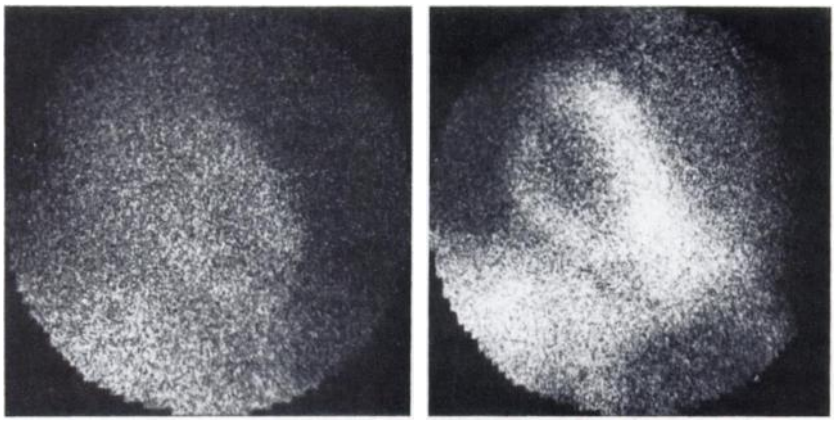

FIGURE 4
Anterior myocardial images acquired during exercise studies. Image using $[^{99m}Tc(POM\text{-}POM)_3]^+$ was acquired 360 min after injection, while image using $[^{99m}Tc(TBIN)_6]^+$ was acquired 70 min after injection

behavior of $[^{99m}Tc(TBIN)_6]^+$ in humans is considerably different. This agent rapidly clears from the blood, allowing identification of the heart wall within a few minutes after injection. Unfortunately, delineation of the myocardial wall is obscured by high and persistent lung uptake which results in an unsatisfactory heart/lung ratio for several hours after injection. In addition, as activity clears from the lung it also accumulates in the liver and masks the apical wall. These observations on the behavior of $[^{99m}Tc(TBIN)_6]^+$ in humans are in general agreement with those previously reported (*10*).

The currently available data allow the six cationic ^{99m}Tc complexes that have been evaluated in humans to be classified into three groups.

1. The Tc(III) complexes *tr*-$[^{99m}Tc(DMPE)_2Cl_2]^+$ and *tr*-$[^{99m}Tc(DEPE)_2Cl_2]^+$ exhibit very unfavorable heart/liver ratios, with the latter complex showing no detectable myocardial uptake (*2,4*). The *tr*-$[^{99m}Tc(DMPE)_2Cl_2]^+$ complex gradually washes out of the heart and accumulates in the liver; exercise hastens this process and thus detracts from the resulting myocardial image.

2. The three Tc(I) complexes $[^{99m}Tc(DMPE)_3]^+$, $[^{99m}Tc(POM\text{-}POM)_3]^+$ and $[^{99m}Tc(TMP)_6]^+$ all behave similarly. They clear from the blood very slowly, but they do not wash out of the heart. Exercise does not improve the images obtained with $[^{99m}Tc(DMPE)_3]^+$ or $[^{99m}Tc(POM\text{-}POM)_3]^+$.

3. The $[^{99m}Tc(TBIN)_6]^+$ agent is unique among the Tc(I) complexes in that it rapidly clears from the blood into the lung. Slow clearance from the lung into the liver yields clear myocardial images after about 1 hr. Again, this Tc(I) complex does not wash out of the heart. Exercise enhances myocardial uptake and improves the ultimate myocardial perfusion image.

Further evidence for placing $[^{99m}Tc(TBIN)_6]^+$ into a unique category comes from the study of the four Tc(I) agents in dogs. A persistent hindrance to the development of ^{99m}Tc myocardial perfusion imaging agents has been the fact that animal models are generally not predictive, of human biodistribution (*5*). In this study, $[^{99m}Tc(TMP)_6]^+$ and $[^{99m}Tc(POM\text{-}POM)_3]^+$ behave differently in dogs than in humans; in dogs, blood clearance is rapid and good myocardial images can be obtained 1 hr after injection, whereas in humans the blood clearance is very slow. The same is true for $[^{99m}Tc(DMPE)_3]^+$ (*3,5*). However, the blood clearance and biodistribution of $[^{99m}Tc(TBIN)_6]^+$ in dogs is very similar to that observed in man. The different blood clearance rates observed for the Tc(I) complexes in dogs and humans can be correlated with the blood binding properties of these agents. Figure 2 shows that the plasma/RBC ratios observed for $[^{99m}Tc(POM\text{-}POM)_3]^+$ and $[^{99m}Tc(TMP)_6]^+$ are significantly higher for humans than for dogs, whereas for $[^{99m}Tc(TBIN)_6]^+$ the ratios for humans are about as low as they are for dogs. Thus, the two agents that clear slowly from the blood of humans also preferentially bind to the plasma of human blood; these two agents clear rapidly from the blood of dogs, and also do not bind tightly to the plasma of dog blood. The $[^{99m}Tc(TBIN)_6]^+$ agent clears rapidly from both dog and human blood, and also shows no preferential binding for the plasma of either of these species. These observations strongly suggest that it is the differential binding of the Tc(I) complexes to plasma components that is the underlying cause for the species dependent biodistributions of these agents.

This result is not surprising since it has been shown several times over that the degree of plasma binding of both cationic and anionic pharmaceuticals is species dependent. Selected examples include salicylic acid

(*14,15*), penicillins (*16*), sulfonamides (*17,18*), amphetamines (*19*), propranolol (*20*), groups of acidic drugs (*21*), radioopaque agents (*22*) and chlorpromazine (*23*). Differences in protein binding among species can be considerable. In the case of salicyclic acid, 50–90% is bound in man, monkey, guinea pig and rabbit, whereas <20% is bound in a number of other species such as baboon, rat and dog. These differences arise because the nature and concentration of binding proteins differ among species (*24*). The net effect of these differences is to make it very difficult to extrapolate pharmacological data from animals to man.

In conclusion, none of the three Tc(I) agents evaluated in this study are suitable for routine clinical use as myocardial perfusion imaging radiopharmaceuticals. $[^{99m}Tc(TBIN)_6]^+$ provides the best myocardial images observed in humans to date. $[^{99m}(TBIN)_6]^+$ appears to be unique among the Tc(I) complexes in that it enjoys much lower plasma blood binding in humans. Myocardial accumulation of the Tc(III) agents appears to involve a mechanism different from that utilized by the Tc(I) complexes. Animal studies alone are not adequate to evaluate the potential utility of ^{99m}Tc cationic complexes for myocardial perfusion studies.

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FOOTNOTES

* Aldrich Chemical Company, Milwaukee, WI.

† Chemalog Inc., South Plainfield, NJ.

‡ Jones Chromatography Inc., Columbus, OH.

§ Sorin Biomedica, Italy.

** Waters Chromatography Dir., Millipor, Milford, MA.

†† General Electric Medical Systems, Milwaukee, WI. (Maxi Camera 400AC).

‡‡ General Electric Medical Systems, Milwaukee, WI. (Star Data General).

§§ Packard Instrument Co., Downers Grove, IL. (Model 500 C).

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