RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Biological Distribution and Excretion of DTPA Labeled with Tc-99m and In-111

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Task Group—MIRD Committee

For the purpose of radiation dose estimates, organ assays and excretion measurements of the Tc-99m and In-111 complexes with DTPA were conducted in dogs at various time intervals up to 24 hr, and the results compared with available human data. The peak concentration of the Tc-99m complex, at 3 min after injection, was 5% of the administered dose for one kidney, 3.5% for the liver, and 3.5% for the small bowel. No organ system except the urinary tract reached a concentration higher than that in blood for several hours after the injection. The biliary excretion of these agents was extremely low, and their elimination in the feces was negligible. In man, it appears that the residual 4–5% of an administered dose not eliminated in the urine by 24 hr is widely distributed in various tissues. The distribution of the In-111 complex is similar but not identical to that of the Tc-99m complex.

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In considering a report on radiation dose estimates for the glomerular agent DTPA, tagged with Tc-99m and In-111, the MIRD Committee found insufficient information on the organ concentrations of these agents, particularly in nonrodent species. There were surprisingly few data, in contrast to relatively complete information on the newer renal agents such as the Tc-99m complexes of glucoheptonate or 2,3 dimercaptosuccinic acid (*1*). The plasma clearance and urinary excretion of the Tc-99m (Sn) complex of DTPA in man have been well described in previous reports (*2–5*). To provide more complete biological data for radiation dose calculations, organ assays were conducted in dogs, the renal uptake measured in humans, and the pertinent literature summarized.

MATERIALS AND METHODS

To quantitate the organ distributions of these two agents, standard radioassays were performed in 27 healthy mongrel dogs with a mean weight of 11.0 kg (range 7.8–14.8 kg). Following the simultaneous i.v. injection of Tc-99m DTPA* and In-111 DTPA*, the animals were killed after seven different time intervals up to 24 hr by the i.v. injection of saturated potassium chloride. For most of these time intervals, three animals were used. At 12 and 24 hr, however, the concentrations were so low that six animals were used to obtain more reliable data. The amounts of radioactivity administered had to be increased from 0.4 to 10 mCi for Tc-99m and from 120 to 300 μCi for In-111 at these longer time intervals to obtain statistically valid counts in the organ samples. The mean concentrations are listed in Table 1, and the changes in organ concentration with time are plotted in Fig. 1.

Hosain (*6*) showed previously that the biological behavior of Tc-99m DTPA closely resembled that of In-111 DTPA in dogs, provided that freshly prepared kits of the former were used. He demonstrated a deterioration of unrefrigerated nonlyophilized kits of DTPA after one week, this resulted in a slower plasma clearance and urinary excretion, not attributable to the presence of free

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TABLE 1A. DOG—% ADMINISTERED ACTIVITY IN WHOLE ORGANS (Tc-99m DTPA)*

	3 min	15 min	30 min	1 hr	3 hr	12 hr	24 hr
Blood	27.57	16.07	11.79	7.97	2.10	0.122	0.082
Plasma	—	—					
Kidney (single)	4.41	1.65	1.46	1.02	0.562	0.170	0.123
cortex	1.86	0.800	0.589	0.565	0.470	0.164	0.120
medulla	2.54	0.845	0.866	0.461	0.092	0.0060	0.0030
Liver	3.51	1.48	1.46	1.20	0.810	0.453	0.313
Spleen	0.261	0.292	0.103	0.130	0.0406	0.023	0.013
Stomach	0.859	1.12	0.872	0.550	0.201	0.021	0.041
Small bowel	3.61	1.95	1.68	1.46	0.473	0.070	0.058
Large bowel	—	—	—	—	—	0.0450	0.049
Muscle	22.15	13.88	12.88	9.08	1.89	0.126	0.106
Thyroid (X100)	0.434	1.37	0.402	0.657	1.10	0.121	0.0659
Urine	3.28	25.60	34.35	52.82	75.57	89.27	—
Large bowel contents	—	—	—	—	—	0.663	0.239

* Mean concentrations of Tc-99m and In-111 DTPA in canine organs and excreta. For renal and hepatic assays, whole organs were counted, as well as multiple tissue samples. Stomach and large and small bowel were counted as whole organs. Total blood volume was estimated as 8.5% of body weight, skeletal musculature as 43% of body weight, renal cortex as 74% of renal weight, and renal medulla as 13% of renal weight.

TABLE 1B. DOG—% ADMINISTERED ACTIVITY/1% BODY WEIGHT (Tc-99m DTPA)*

	3 min	15 min	30 min	1 hr	3 hr	12 hr	24 hr
Blood	3.24	1.89	1.39	0.938	0.247	0.0146	0.0094
Plasma	5.77	3.84	2.74	1.87	0.477	0.0137	0.0124
Kidney	17.0	8.79	8.62	4.67	1.47	0.487	0.429
cortex	9.88	5.60	3.92	3.07	2.31	0.675	0.558
medulla	76.4	33.7	32.7	13.9	2.40	0.105	0.0729
Liver	1.20	0.626	0.594	0.362	0.219	0.122	0.098
Spleen	0.900	0.535	0.474	0.216	0.151	0.060	0.035
Stomach	1.05	1.28	0.865	0.562	0.132	0.0161	0.0425
Small bowel	1.49	0.760	0.595	0.358	0.127	0.0872	0.0290
Large bowel						0.0711	0.0742
Muscle	0.515	0.323	0.300	0.214	0.044	0.00292	0.00246
Thyroid	0.657	1.23	0.418	0.575	0.287	0.123	0.0765
Bile	0.00553	0.0399	0.217	0.212	0.432	0.366	0.360
Large bowel contents						0.518	1.02

* See footnote to Table 1A.

pertechnetate. Accordingly, only freshly prepared Tc-99m complexes of DTPA were used in the present experiments. Three minutes after injection was selected as the first time interval after sacrifice, since previous in vivo studies in dogs using camera-computer techniques showed that the mean peak concentration of Tc-99m DTPA in the kidneys occurs at that time. The renal uptake of Tc-99m DTPA, corrected for radioactive decay and expressed as the percentage of administered activity in each kidney, was measured by Kirchner in three adult patients (two female, one male) by camera-computer technique and comparison with renal phantom. Values were obtained every 2 min for 20 min and at 2, 4, 8, and 24 hr after injection.

RESULTS AND DISCUSSION

Blood and plasma clearance. Kempi (*7*) and Atkins found no significant diffusion of these agents from plasma into the cellular blood fractions; hence the total blood content is virtually the same as the total plasma radioactivity. In the human studies conducted at the Brookhaven National Laboratories (*4,5*), using multiple plasma samples at intervals from 5 min to 24 hr, the

TABLE 1C. DOG—% ADMINISTERED ACTIVITY IN WHOLE ORGANS (In-111 DTPA)*

	3 min	15 min	30 min	1 hr	3 hr	12 hr	24 hr
Blood	26.50	14.58	10.43	6.40	2.45	0.033	0.013
Plasma							
Kidney (single)	4.57	1.57	1.44	0.870	0.396	0.159	0.132
cortex	1.81	0.707	0.528	0.431	0.306	0.154	0.130
medulla	2.77	0.864	0.916	0.439	0.0892	0.00492	0.0025
Liver	3.16	1.08	0.986	0.516	0.291	0.117	0.120
Spleen	0.231	0.228	0.0778	0.0737	0.012	0.0063	0.0069
Stomach	1.49	1.13	0.913	0.462	0.227	0.0089	0.0081
Small bowel	3.65	1.76	1.69	1.17	0.0606	0.039	0.033
Large bowel	—	—	—	—	—	0.0406	0.037
Muscle	21.77	12.32	12.84	7.50	1.50	0.178	0.068
Thyroid (×100)	0.483	1.29	0.408	0.405	0.0462	0.017	0.0055
Urine	2.72	28.56	38.80	59.17	84.07	92.7	—
Large bowel contents	—	—	—	—	—	0.718	0.174

* See footnote to Table 1A.

TABLE 1D. DOG—% ADMINISTERED ACTIVITY/1% BODY WEIGHT (In-111 DTPA)*

	3 min	15 min	30 min	1 hr	3 hr	12 hr	24 hr
Blood	3.12	1.72	1.23	0.753	0.288	0.00389	0.00126
Plasma	5.87	3.41	2.25	1.12	0.304	0.00639	0.00269
Kidney	18.8	9.47	8.57	4.43	2.26	0.604	0.540
cortex	9.59	4.95	3.51	2.35	1.40	0.718	0.614
medulla	83.01	34.45	34.73	13.25	2.36	0.109	0.053
Liver	1.14	0.456	0.401	0.159	—	0.035	0.042
Spleen	0.783	0.416	0.356	0.121	0.0639	0.022	0.024
Stomach	1.53	1.29	0.906	0.475	0.151	0.007	0.007
Small bowel	1.17	0.688	0.597	0.286	0.181	0.012	0.011
Large bowel	—	—	—	—	—	0.058	0.106
Muscle	0.506	0.287	0.299	0.173	0.0348	0.00415	0.00156
Thyroid	0.666	1.16	0.424	0.255	0.0604	0.026	0.00804
Bile	0.00496	0.00690	0.043	0.136	0.0916	0.048	0.032
Large bowel contents	—	—	—	—	—	0.499	1.029

* See footnote to Table 1A.

plasma disappearance was described by multiple exponential components: 24% with a biological half-time of 15.6 min, 16% with $t_{1/2}$ = 118 min, and a small third component of approximately 2% with a biological half-time of 13.6 hr. A slow component representing about 2% of the total plasma activity was described also by Kempi (*7*), attributable to limited binding to plasma proteins with a biological half-time of 17–25 hr. The foregoing three components account for less than half of the administered dose of radioactivity, even in 5-min samples. Hence it is assumed that there is a fast component representing 58% of the administered radioactivity, with a half-time of ~3.8 min, due to rapid diffusion through capillaries into extravascular extracellular fluid space. The plasma levels in eight normal individuals, with the Tc-99m complex of DTPA obtained commercially (unpublished data, M. A. McLeod, Royal Naval Hospital, Haslar Gosport Hants, U.K.), agreed closely with the values obtained with the material prepared at the Brookhaven National Laboratory (*4*). The 1-hr plasma levels of Tc-99m DTPA were also similar to those obtained with C-14 DTPA (*8*). The renal clearances in 11 patients—as measured by plasma disappearance following a single i.v. injection—averaged 8% lower than those obtained with I-125 iothalamate (*4*). The plasma-protein binding of Tc-99m DTPA at 1

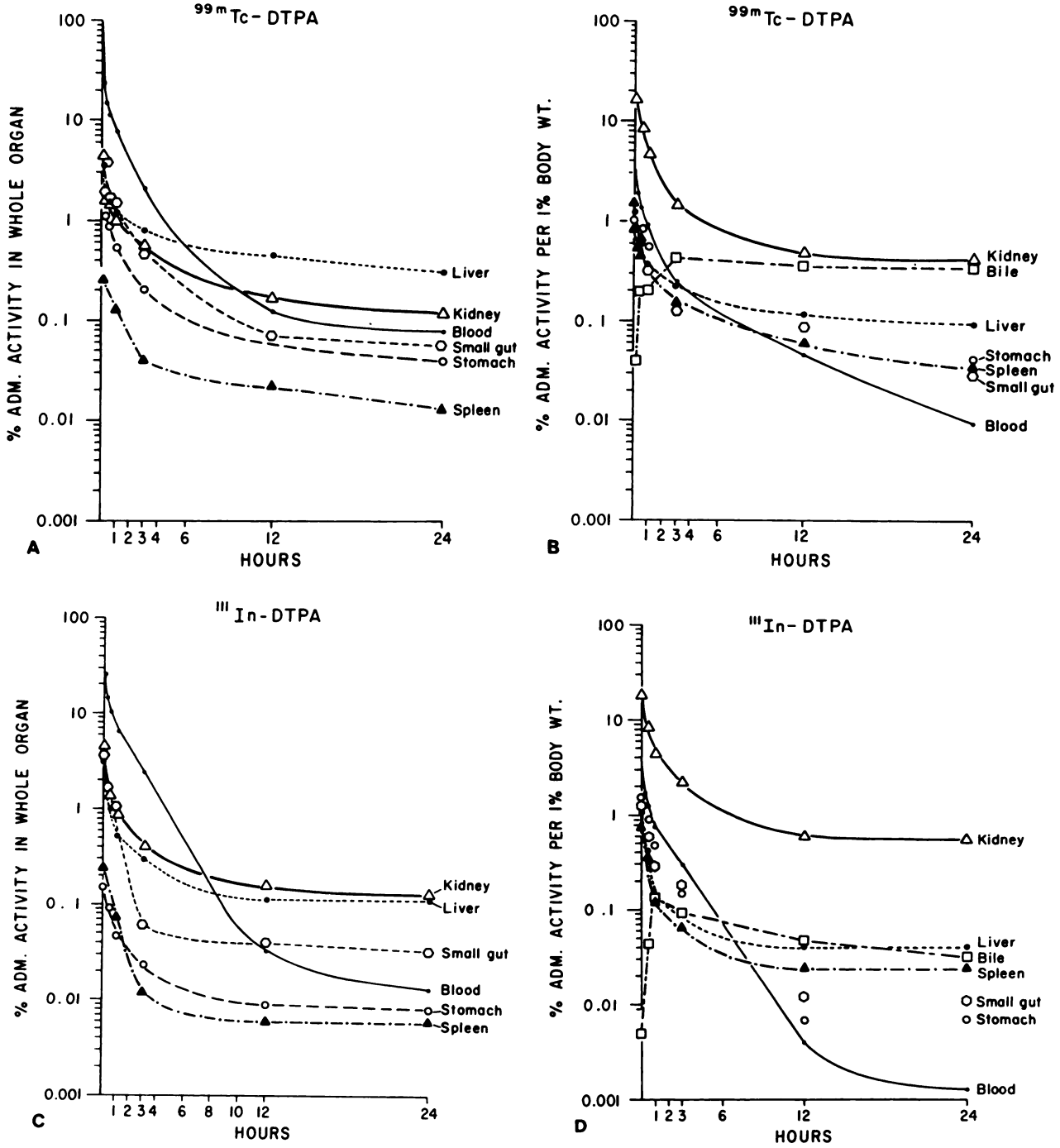

Fig. 1. Mean concentrations of DTPA complexes in selected canine organs and bile at various time intervals, corrected for radioactive decay. (A) Tc-99m DTPA and (C) In-111 DTPA. Concentrations expressed as % administered activity in whole organ. (B) Tc-99m DTPA and (D) In-111 DTPA. Concentrations expressed as % administered activity per 1% of body weight.

hr in five humans averaged 3.7 (range 1.8–5.9%) (*4*).

In the current study, the blood and plasma clearances in dogs were considerably more rapid than in man, particularly beyond 1 hr after injection. The plasma clearance in the rat (*9*) was even more rapid than in the dog.

Renal distribution. The peak renal concentration occurred early. From human in vivo measurements of Tc-99m DTPA performed by Atkins, the time intervals from i.v. injection to peak activity were 3.51 ± 1.39 for the right kidney and 3.83 ± 1.54 for the left kidney. In another study of 14 normal patients, the mean renal transit time, as computed by deconvolution analysis, was 3.0 ± 0.5 min compared with 2.23 ± 0.27 min for radioiodinated Hippuran (*10,11*). At later intervals, there was much less cortical retention of Tc-99m DTPA in

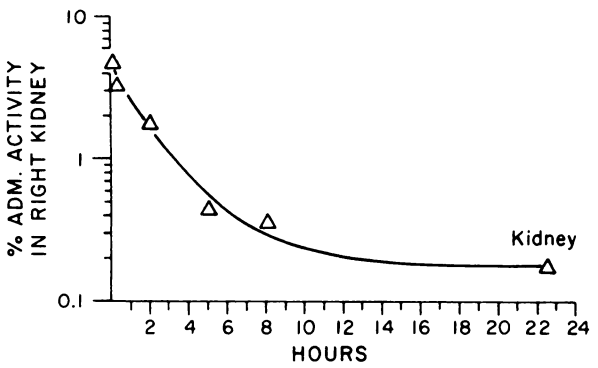

FIG. 2. Time-activity curve for Tc-99m DTPA in one normal subject, expressed as % administered activity in right kidney, by comparison with renal phantom, corrected for decay (from Kirchner, unpublished data).

gross autoradiographs in rabbits (*13*) than of other renal agents such as Tc-99m glucoheptonate or 2,3-dimercaptosuccinic acid.

In the current canine study, the peak concentration in one kidney averaged 4.4% of the administered radioactivity, rapidly declining thereafter. At the peak, the medullary concentration was about nine times that of the cortex. The medulla, however, cleared more rapidly than the cortex, so that after 1 hr the remaining cortical activity exceeded that of the medulla.

In three in vivo studies in humans by Kirchner, using camera-computer techniques, the count rates in the renal regions of interest, at various times up to 24 hr, showed an early peak concentration of 5% of the administered radioactivity in each kidney in comparison with those obtained from a renal phantom. The renal clearance curves (Fig. 2) approximated that measured in the canine studies by direct organ assay. In a previous study of Tc-99m glucoheptonate in humans, the peak concentration in one kidney was also 5%, but this level persisted between 1 and 6 hr following injection (*1*). Kempi (*7*) estimated that 5% of an administered dose of Tc-99m DTPA localized in one kidney and that the biological half-life was 2.3 hr.

Using the available information for radiation dose estimates, we may assume that 5% of an administered dose of Tc-99m(Sn)DTPA localizes in one kidney 3 min following i.v. injection. Using the current canine concentration data, 3% of the maximal renal concentration still remains in the kidney at 24 hr; 66% has a biological half-time of 8-12 min; 26%, 1.6 hours; and the remaining 5% has a biological half-time of 26 hr.

Distribution in other organs. The clearance of Tc-99m DTPA in nonrenal organs is considerably slower in the dog than in the rat (*9*). In both species, however, no organ system other than the urinary tract has a higher concentration than the blood within the first 2 hr. The highest concentration in the liver in the present canine study was 3.5% of the administered activity at 3 min. Of this total hepatic activity, 9% remained in the organ at 24 hr, 44% had a biological half-time of 12 min; 29%, 84 min; and 19%, 21 hr. Although the bile contained measurable amounts of Tc-99m DTPA, particularly at 3 hr, this represented less than 0.1% of the administered radioactivity in the total bile contents.

The entire small intestine contained approximately 3.5% of the administered radioactivity at 3 min, like the total hepatic content. Although the concentration in skeletal muscle was low, the total organ activity was similar to that of blood. The testicular concentration was not measured at all time intervals in the dog. However, the concentration, expressed as percentage administered radioactivity per unit weight, was approximately half that of the splenic concentration; hence, the intrinsic gonadal concentration of Tc-99m DTPA was extremely low.

From comparative studies of the distribution of I-131 serum albumin in dogs killed within 5-10 min after injection, it was calculated that 70-90% of the hepatic concentration of Tc-99m- or In-111 DTPA in the liver was due to its blood content. For other organs, including the kidneys, bowel, and muscle, the blood radioactivity did not contribute significantly to the total organ activity. It was assumed, therefore, that most of the radioactivity in these organs was contained in the extravascular extracellular tissue-fluid space.

Excretion and total body retention. The urinary excretion of Tc-99m DTPA is considerably faster in the dog than in man for several hours, but by 12 hr the cumulative excretion is similar (approximately 90%). On the basis of urinary excretion measurements in 11 patients, Klopper et al. (*4*) quantitated the total-body retention as having two components. However, 4-5% of the administered radioactivity could not be accounted for in the urine at 24 hr. It was previously suspected (*4*) that up to 5% of the administered radioactivity was excreted in the feces. In the present dog studies, however, the total activity in the 24-hr feces, combined with the activity within the intestinal contents, was 1% or less. Moreover, in a previous study of C-14 DTPA (*8*) administered intravenously in humans, no radioactivity was detected in the feces. The urinary excretion of the C-14-labeled material, however, was similar to that obtained with Tc-99m DTPA (*4*). With commercial Tc-99m DTPA* (unpublished data, MA McLeod) in eight normal adult individuals, the urinary clearance was somewhat faster than when measured with the material prepared at Brookhaven.

Using the foregoing information for radiation dose estimates, we may assume that the fecal excretion of Tc-99m DTPA is negligible, that 4% of the administered radioactivity is still retained in various body tissues at 24 hr, that 69% is eliminated by the kidneys with a biological half-time of 1.73 hr, and that the remaining 27% has a biological half-time of 9.23 hr.

CONCLUSIONS

From the current canine studies and the literature review, it is concluded that the biological distributions of the Tc-99m and In-111 complexes of DTPA are similar but not identical. In the dog studies, the blood clearances of the two agents are similar up to 6 hr, but thereafter the In-111 complex clears more rapidly. In normal humans up to 90 min, the plasma clearances of the two are virtually identical (unpublished data, MA McLeod). There is no significant difference in the organ distribution of these agents during the first hour, but the concentrations of In-111 DTPA become lower thereafter, especially at 24 hr. The liver concentration for In-111 DTPA is considerably lower than for the Tc-99m complex, at least in the dog. In normal human subjects, the urinary excretion of In-111 DTPA is somewhat faster than that of the Tc-99m complex. Approximately 50% of the administered radioactivity of the former is excreted within 1 hr, and of the latter within 90 min (unpublished data, MA McLeod). Likewise, in the dog the urinary excretion of the In-111 complex is faster than that of the Tc-99m complex, particularly within the first 3 hr. For both complexes the small fraction of the administered radioactivity that is still distributed within various tissues after 12 hr is excreted very slowly; in all likelihood, this minimal residue is no longer chelated to DTPA.

FOOTNOTE

*Diagnostic Isotopes, Inc., Bloomfield, NJ.

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