

# EVALUATION OF $^{99m}\text{Tc}$ -DTPA FOR THE MEASUREMENT OF GLOMERULAR FILTRATION RATE

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Determination of glomerular filtration rate offers one of the best ways to evaluate renal function, especially the rate of progression of chronic renal disease (1). Although there is general agreement that inulin clearance is the best measure of glomerular filtration rate (GFR), its estimation by chemical methods is laborious. In the past few years, a number of agents labeled with radioactive tracers have been introduced for the measurement of GFR including several chelates such as  $^{51}\text{Cr}$ -EDTA (2),  $^{113m}\text{In}$ -DTPA (3),  $^{169}\text{Yb}$ -DTPA (4), and  $^{140}\text{La}$ -DTPA (5).

The recent development of a kit for the rapid and simple preparation of  $^{99m}\text{Tc}$ -DTPA (6) makes this chelate potentially the one most readily available for this type of clearance study. This study evaluates  $^{99m}\text{Tc}$ -DTPA as an agent for GFR measurements.

A substance used for the measurement of GFR must fulfill certain criteria. It must be

1. completely filterable at the glomerulus;
2. not bound to plasma proteins;
3. not synthesized or destroyed by the tubules;
4. not reabsorbed or excreted by the tubules; and
5. physiologically inert.

To obtain information about renal handling of  $^{99m}\text{Tc}$ -DTPA, a series of experiments was carried out in dogs using a constant infusion technique to compare the renal clearances of  $^{14}\text{C}$ -inulin,  $^{131}\text{I}$ -sodium iodohippurate, and  $^{99m}\text{Tc}$ -DTPA. A further comparison between  $^{99m}\text{Tc}$ -DTPA and  $^{125}\text{I}$ -sodium iothalamate was carried out in patients using a single-injection technique.

## MATERIALS AND METHODS

**Studies in dogs.** The experiments were performed under pentothal anesthesia in five adult female mongrel dogs weighing 17–26 kg each. The dogs were given 25-ml water/kg orally following overnight fasting and were further hydrated with Ringer's lactate solution intravenously.

Following a priming dose of 250-mg (442  $\mu\text{M}$ )  $\text{CaNa}_3$  DTPA and 500-mg (504  $\mu\text{M}$ ) inulin, a sustaining solution of 500-ml 0.9% NaCl containing 625-mg (1,150  $\mu\text{M}$ )  $\text{CaNa}_3$  DTPA, 1.0-gm (1,009  $\mu\text{M}$ ) inulin, 1.25-mg (5.5  $\mu\text{M}$ )  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ , 25  $\mu\text{Ci}$   $^{14}\text{C}$ -inulin, and 2.0 mCi  $^{99m}\text{Tc}$ -DTPA was started at a rate of approximately 2 ml/min. An equilibration period of 60 min was allowed before any urine or blood samples were collected. The level of radioactivity was continuously monitored with an external scintillation counter positioned over the heart region.

Three 20-min baseline clearance periods were obtained. At the end of each collection period the bladder was irrigated with 10-ml water and 10-ml air. Plasma samples were obtained 3 min before the midpoint of each collection period.

In dogs No. 1–3 the effect of urine flow on clearance rates was studied. At the end of the baseline clearance periods additional continuous infusion of 5% dextrose was administered and 50-ml 25% mannitol solution given i.v. as a single injection. When diuresis was reached, three more 20-min clearance periods were performed.

In dogs No. 4 and 5 tubular secretion was studied. In these animals 50- $\mu\text{Ci}$   $^{131}\text{I}$ -iodohippurate was added to the sustaining solution. At the end of the baseline clearance periods 20 ml of a 2% probenecid solution was administered intravenously to block tubular secretion (7). Three more 20-min clearance periods followed after this injection.

In addition to  $^{14}\text{C}$ -inulin,  $^{99m}\text{Tc}$ -DTPA, and  $^{131}\text{I}$ -iodohippurate clearance determinations, fractionation of urine and plasma samples as well as the infused product was performed to determine protein binding and/or breakdown of  $^{99m}\text{Tc}$ -DTPA. Analysis of the product was performed on a 35-cm gel chro-

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matographic column (Sephadex G25) eluted with nitrogen purged saline solution. With gel chromatography  $^{99m}\text{Tc}$  bound to protein is eluted at the void volume,  $^{99m}\text{Tc}$  chelates are eluted in 12–20 ml and pertechnetate is eluted in 38–46 ml. The  $^{99m}\text{Tc}$  adsorbed to the column represents the hydrolyzed fraction (8). The adsorbed  $^{99m}\text{Tc}$  was removed from the Sephadex as pertechnetate by eluting with 2 ml of a 0.1%  $\text{H}_2\text{O}_2$  solution followed by isotonic saline. A standard was also counted to assure balance of  $^{99m}\text{Tc}$  activity.

**Patient studies.** A comparison between  $^{99m}\text{Tc}$ -DTPA and  $^{125}\text{I}$ -sodium iothalamate plasma concentration and urinary excretion following a single-injection technique was carried out in 11 patients. The patients studied were under investigation for hypertension and had normal or mildly diminished renal function as evaluated by other renal-function studies.

Solutions of "instant"  $^{99m}\text{Tc}$ -DTPA were prepared by adding 3 ml of pertechnetate saline solution to 1 ml of stock DTPA solution as previously described (6). Following hydration with at least 1 liter of liquids  $\sim 3.0$  mCi  $^{99m}\text{Tc}$ -DTPA and 50  $\mu\text{Ci}$   $^{125}\text{I}$ -sodium iothalamate was administered intravenously. During the ensuing 24-hr period nine plasma samples were obtained at regular intervals and fractional urine collected. Data on plasma concentration and urinary excretion of the injected material were obtained by comparison to a known standard of the injected dose.

Clearance values for  $^{99m}\text{Tc}$ -DTPA and  $^{125}\text{I}$ -sodium iothalamate were calculated according to a two compartmental analysis according to principles previously described (9–12). Gel chromatography of the plasma samples was performed to determine protein binding of the radioactive label.

## RESULTS

**Studies in dogs.** The administration of mannitol followed by hydration (Table 1) resulted in a marked increase of urine flow with a mean increase from 0.8 to 3.7 ml/min. At the same time the mean clearances of  $^{99m}\text{Tc}$ -DTPA and  $^{14}\text{C}$ -inulin did not increase (mean values for  $^{99m}\text{Tc}$ -DTPA unchanged at 2.2,  $^{14}\text{C}$ -inulin changed from 2.9 to 2.8 ml/min/kg).

The administration of probenecid to produce tubular blockade (Table 2) resulted in a marked decrease of Hippuran clearance with a mean decrease from 6.8 to 3.3 ml/min/kg. At the same time the mean clearances of  $^{99m}\text{Tc}$ -DTPA and  $^{14}\text{C}$ -inulin was not significantly modified with a mean change for the  $^{99m}\text{Tc}$ -DTPA from 2.3 to 2.1, and for  $^{14}\text{C}$ -inulin

TABLE 1. EFFECT OF INCREASING URINE FLOW

Dog No.	Urine flow (ml/min)	$^{14}\text{C}$ -inulin clearance (ml/min/kg)	$^{99m}\text{Tc}$ -DTPA clearance (ml/min/kg)	$^{99m}\text{Tc}$ -DTPA clearance/ $^{14}\text{C}$ -inulin clearance
1	0.24	3.35	2.75	0.82
	1.30	2.96	2.57	0.87
2	0.75	2.47	1.96	0.79
	4.43	2.49	2.00	0.80
3	1.5	2.87	2.46	0.86
	5.3	2.84	2.61	0.92

For each dog the values reported in the upper line are the mean of three clearance periods measured at low urine flow; those in the lower line are the mean of three clearance periods measured at high urine flow.

TABLE 2. EFFECT OF TUBULAR BLOCKADE BY PROBENECID

Dog No.	Urine flow (ml/min)	$^{14}\text{C}$ -inulin clearance (ml/min/kg)	$^{99m}\text{Tc}$ -DTPA clearance (ml/min/kg)	$^{125}\text{I}$ -Hippuran clearance (ml/min/kg)	$^{99m}\text{Tc}$ -DTPA clearance/ $^{14}\text{C}$ -inulin clearance
4	5.52	2.88	2.41	6.92	0.84
	5.03	2.49	1.84	3.28	0.74
5	3.95	2.31	2.22	6.67	0.96
	3.89	3.38	2.42	3.41	0.72

For each dog the values reported in the upper line are the mean of three clearance periods measured before probenecid administration; those in the lower line are the mean of three clearance periods measured after probenecid administration.

from 2.6 to 2.9 ml/min/kg. The mean urine flow decreased only slightly from 4.7 to 4.5 ml/min during this experiment.

**Studies in human beings.** Total-body retention and plasma levels of  $^{99m}\text{Tc}$ -DTPA and  $^{125}\text{I}$ -iothalamate are compared in Figs. 1 and 2. Although the total-body retention and earlier plasma levels of the two compounds are very similar, the 24-hr plasma levels of  $^{99m}\text{Tc}$ -DTPA were slightly higher than that of  $^{125}\text{I}$ -iothalamate. Clearance rates calculated from plasma levels (Fig. 3) showed that  $^{99m}\text{Tc}$ -DTPA underestimated clearance by about 8% as compared with  $^{125}\text{I}$ -iothalamate.

The slopes and intercepts of the fast components of the two compounds are compared in Fig. 4.

**Protein binding and stability.** When a continuous infusion technique was employed in the dogs analysis of plasma samples obtained during the infusion period showed 6.6–15.3% (average 9.7%) of the radioactivity to be protein bound. Analysis of the product infused showed at least 95% of the  $^{99m}\text{Tc}$

present to be in the form of a chelate. No further breakdown of the chelate was detected at the end of the infusion period.

When a single-injection technique was used in five humans 1.8–5.9% (average 3.7%) of the <sup>99m</sup>Tc was found to be protein bound in plasma samples obtained 1 hr after administration.

DISCUSSION

Although accurate measurements of glomerular filtration rate have been simplified by radionuclide methods, measurements of GFR are subject to certain sources of error including protein and red cell binding and impurities and instability of the compound, as well as tubular handling of the substance. In dogs no change in <sup>99m</sup>Tc-DTPA clearance was noted with change in the rate of urine flow or following tubular blockade with probenecid. The values obtained for <sup>99m</sup>Tc-DTPA clearances in dogs were on an average 17% lower than those for <sup>14</sup>C-inulin. This difference is partly ascribed to protein binding of <sup>99m</sup>Tc-DTPA which amounted to about 10% of the <sup>99m</sup>Tc present in the plasma. The role of protein binding was less when a single-injection technique, instead of continuous infusion, was used and amounted to 3.7% in the samples collected 1 hr after administration.

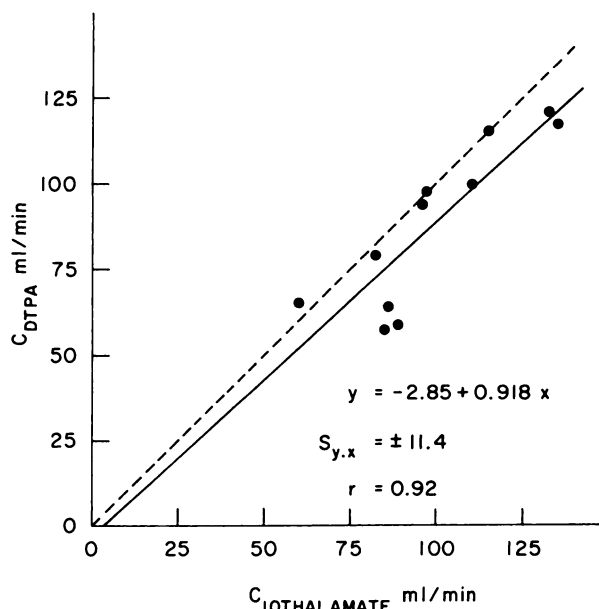


FIG. 3. Correlation of <sup>99m</sup>Tc-DTPA with <sup>125</sup>I-iothalamate clearance values obtained by single injection technique in 11 patients. Individual clearance values were obtained by computer. Broken lines indicate line of unity.

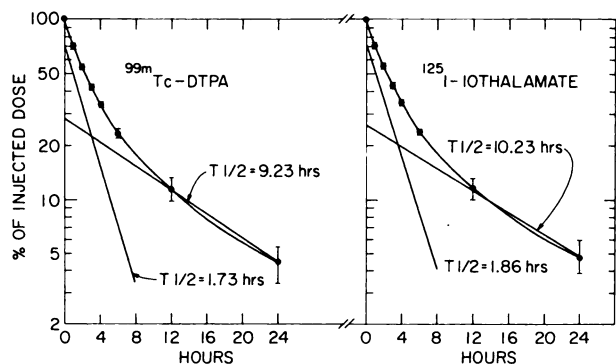


FIG. 1. Total-body retention (based on urinary excretion) of <sup>99m</sup>Tc-DTPA and <sup>125</sup>I-iothalamate expressed as percentage of injected dose in 11 patients.

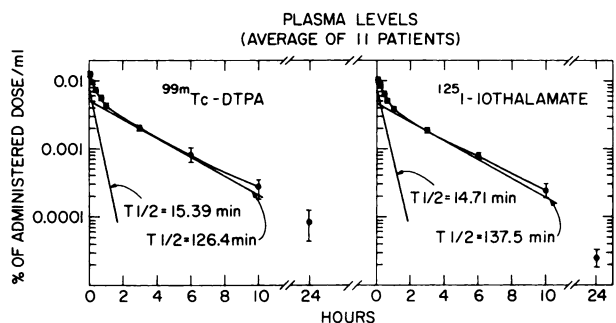


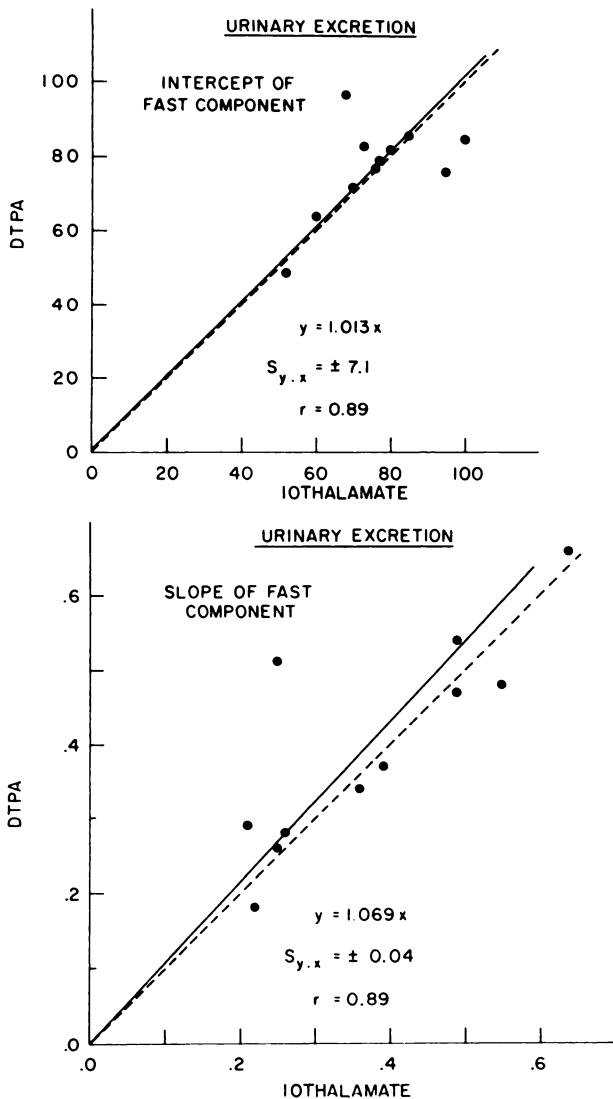
FIG. 2. Plasma levels of <sup>99m</sup>Tc-DTPA and <sup>125</sup>I-iothalamate in 11 patients. Results are expressed as percentage of injected dose.

It has previously been shown that <sup>125</sup>I-iothalamate sodium clearances give values close to unity when compared with inulin clearances done simultaneously (13,14). This relationship is probably due to a coincidence of a minor degree of protein binding and tubular secretion (15). The 24-hr urinary excretion of <sup>99m</sup>Tc-DTPA and <sup>125</sup>I-iothalamate was very similar, with average values of 95.6% and 95.3%, respectively. The lower clearances obtained in humans with <sup>99m</sup>Tc-DTPA as compared with <sup>125</sup>I-iothalamate sodium can partly be ascribed to protein binding of <sup>99m</sup>Tc-DTPA.

It should be pointed out that similar clearance values are not to be expected with a commercially available kit containing DTPA since this product does not behave like a true chelate due to its having a lower urinary excretion rate and higher kidney retention than the product evaluated in this study (16).

From this study it can be concluded that <sup>99m</sup>Tc-DTPA fulfills the criteria set for an agent used for the measurement of GFR except that it is partly protein bound. This amount, however, is small following a single injection but becomes larger if a continuous infusion is employed.

The advantages of using <sup>99m</sup>Tc-DTPA for GFR measurements are the rapid preparation of the chelate now possible and the excellent physical characteristics and ready availability of <sup>99m</sup>Tc. Radiation dosimetry has been previously calculated to be 0.016 and 0.555 rad/mCi to the whole body and bladder, respectively (17). Whole-body radiation has been



**FIG. 4.** Correlation of intercepts and slopes of fast components of urinary excretion of  $^{99m}\text{Tc}$ -DTPA with  $^{125}\text{I}$ -iothalamate in 11 patients. Broken lines indicate line of unity.

found to compare very favorably with other glomerular agents, both under conditions of normal and severely impaired renal function (4).

#### SUMMARY

The usefulness of  $^{99m}\text{Tc}$ -DTPA as an agent for measuring glomerular filtration rate was evaluated in five dogs and 11 human patients. In dogs, using a constant infusion technique, no change in  $^{99m}\text{Tc}$ -DTPA clearance was found at different urine flow rates or following tubular blockade with probenecid. In the patients clearance of  $^{99m}\text{Tc}$ -DTPA was 8% lower than that of  $^{125}\text{I}$ -iothalamate as determined by single-injection technique. The two compounds, however, had similar rates of plasma disappearance and urinary excretion. Thus  $^{99m}\text{Tc}$ -DTPA, rapidly

prepared by a kit method, is a useful addition to the list of radiopharmaceuticals that can be used for measurement of GFR.

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