COMPARISON OF INULIN, IOTHALAMATE, AND ^{99m}Tc-DTPA FOR MEASUREMENT OF GLOMERULAR FILTRATION RATE

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Clearances of inulin, ^{125}I-iothalamate, and ^{99m}Tc-Sn-DTPA were measured simultaneously in five mongrel dogs exhibiting a wide range of glomerular filtration rates (GFR). Standard constant-infusion inulin clearance was compared to radionuclide clearances after subcutaneous injection of the emitters mixed with aqueous epinephrine. All three substances were found to have virtually identical clearances. The accuracy, accessibility, low cost, low radiation hazard, and short half-life of ^{99m}Tc-Sn-DTPA make it an excellent substance for measuring GFR. The subcutaneous technique offers an accuracy comparable to the more difficult constant-infusion method.

Determination of glomerular filtration rate (GFR) requires the utilization of a substance that is freely filtered by the glomerulus and is neither secreted nor reabsorbed by the renal tubule. Inulin, a fructose polysaccharide that exhibits these characteristics, was proposed by Richards (*1*) and Shannon (*2*) as a marker for GFR. Inulin must be administered intravenously since it is hydrolyzed to fructose in the gastrointestinal tract and is erratically and poorly absorbed from subcutaneous or intramuscular sites (*3*). Other inherent difficulties in the use of inulin clearance as a measure of GFR include the necessity for a constant-infusion apparatus and awkward chemical analyses of blood and urine samples. To further compound the problems in clinical practice, shortages of sterile inulin suitable for patient use have recently developed. Because of these factors, other substances have been evaluated as substitutes for inulin.

Radioactive iothalamate (Glofil^{125}I, Abbott Laboratories, North Chicago, Ill.) has been shown to be a suitable replacement for inulin (*4*), but it also requires an appropriate loading dose and a constant-infusion apparatus. Recently a subcutaneous injection method, utilizing ^{125}I-iothalamate mixed with epinephrine solution, has yielded close correlations in man with the standard simultaneously determined inulin clearance (*5*). Chelating compounds such as DTPA (diethylenetriaminepentaacetic acid) have been studied and show close correlation with the clearance and volume distribution of inulin (*6*). Radioactively labeled DTPA and inulin (^{113m}In and ^{14}C, respectively) have clearance ratios of 0.99 over wide ranges of GFR, confirming similar renal handling (*7*). Similar correlations have been found using DTPA labeled with yttrium-90, lanthanum-140, and ytterbium-169 (*8*). This paper describes the comparison of simultaneously determined clearances of inulin (C_{In}), ^{125}I-iothalamate (C_{ioth}), and ^{99m}Tc-Sn-DTPA* (C_{Tc}) in dogs over a wide range of renal function.

METHODS AND MATERIALS

Studies were performed on five mongrel dogs of either sex, weighing 30–36 kg. Anesthesia was induced with intravenous injection of 32 mg/kg body weight of sodium phenobarbital, with supplements as needed. All animals were intubated, and respiration was supported by a Harvard large-animal respirator. An intravenous catheter was placed in a foreleg vein for infusion of inulin, and a second catheter was placed in the contralateral jugular vein for venous blood sampling. Both ureters were cannulated through a small lower midline incision. A

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* Here ^{99m}Tc-Sn-DTPA is technetium-99m chelated with DTPA in the presence of tin.

TABLE. 1. COMPARISON OF CLEARANCES OF INULIN, ^{99m}Tc-DTPA, AND IOTHALAMATE IN DOGS

Study	Kidney	Number of samples	C_{In}*	C_{Tc}*	C_{Ioth}*
1	R‡	3	28.76 (2.19)†	28.63 (1.75)	26.10 (1.73)
1	L	3	52.89 (1.81)	53.67 (5.25)	52.20 (2.51)
2	R	3	70.30 (2.74)	72.17 (2.56)	68.23 (3.95)
2	L‡	3	24.87 (1.35)	27.07 (0.92)	24.97 (1.31)
3	R	11	40.05 (0.99)	——	41.75 (1.79)
3	L	11	40.93 (0.90)	——	40.15 (1.51)
4	R	10	39.19 (0.37)	33.40 (1.56)	33.65 (0.97)
4	L	10	38.62 (0.54)	34.86 (1.76)	34.88 (1.34)
5	R	5	30.20 (1.75)	31.16 (0.99)	28.73 (0.84)
5	L	5	30.20 (2.61)	30.98 (1.24)	28.71 (1.15)

* C_{In} = inulin clearance; C_{Tc} = ^{99m}Tc-Sn-DTPA clearance; C_{Ioth} = ^{125}I-iothalamate clearance. All clearances expressed in ml/min.

† Figures in parentheses represent standard error of the mean.

‡ Induced unilateral renal disease.

water load of 15 ml/kg of 5% dextrose solution was given intravenously to achieve a water diuresis. Throughout the study urine output was replaced with equal amounts of the 5% dextrose solution. In two dogs unilateral renal disease was induced 1 week prior to study by the injection of a 1-ml suspension of 45-μm-diam polyethylene microspheres into one renal artery.

In all experiments the loading dose of inulin (50 mg/kg) was followed by a continuous infusion of inulin at 50 mg/kg-hr for the duration of the experiment. Radioactively labeled materials were administered subcutaneously at separate sites in the anterior chest wall: 20 μCi of ^{125}I-iothalamate and 1 mCi of ^{99m}Tc-Sn-DTPA, each mixed with 0.1 ml of 1:1,000 aqueous epinephrine solution. The radioagents were administered at the same time as the inulin loading dose.

After 90–150 min for equilibration the studies were begun. Timed urine samples (15–20 min each) and matched-midpoint blood samples were collected. Urine flows averaged 1–2 ml/min and did not fluctuate significantly during the study period. Inulin concentration in blood specimens and aliquots of output urine was determined by acid hydrolysis to fructose; assays were carried out in an Auto Analyzer (Technicon Instruments, Tarrytown, N.Y.). One-milliliter aliquots of urine and serum were placed in plastic counting tubes and measured in a well scintillation counter with an automatic sample changer (Packard), using the appropriate spectrometer settings for each radionuclide. Counts for ^{99m}Tc-Sn-DTPA were performed within 18 hr of sampling, but counts for ^{125}I-iothalamate were performed after 5 days to allow for decay of the ^{99m}Tc-Sn-DTPA activity. Sufficient counts were obtained to ensure less than 1% counting error.

Clearance rates of the various substances were calculated from the formula $C = U \cdot V/P$, where U is the urine concentration of inulin (counts/min from the individual emitter per milliliter of urine), V is the urine output (ml/min), and P is the plasma concentration of inulin (counts/min from the individual emitter per milliliter). Statistical analysis was performed using least-squares regression and calculations of the correlation coefficient.

RESULTS

In the ten separate kidneys studied, GFR, as measured by C_{In}, ranged over 24.87–70.30 ml/min. During one experiment malfunction of the scintillation counter prevented the calculation of C_{Tc}. Extremely close correlation existed between all three methods for measuring GFR. The reproducibility of clearance measurements was approximately the same for all three methods. The standard error of the mean in individual experiments ranged over 0.37–2.74 for C_{In}, 0.925–5.25 for C_{Tc}, and 0.84–3.95 for C_{Ioth}. The results of all determinations from individual kidneys in each experiment are shown in Table 1.

Plasma levels of inulin and the radiotracers remained relatively constant throughout the procedure (Fig. 1). Stability of the plasma tracer level reflects equilibration between absorption and excretion and documents the validity of matched-midpoint blood samples for clearance determinations.

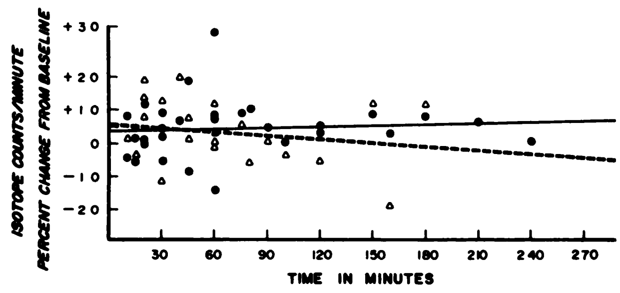

FIG. 1. Plasma levels of ^{99m}Tc-Sn-DTPA (●) and ^{125}I-iothalamate (△) plotted as a function of time. Individual points are expressed as percent change from stable baseline values obtained 90–150 min after subcutaneous radiopharmaceutical injection. Continuous line denotes linear regression for ^{125}I-iothalamate; broken line denotes linear regression for ^{99m}Tc-Sn-DTPA.

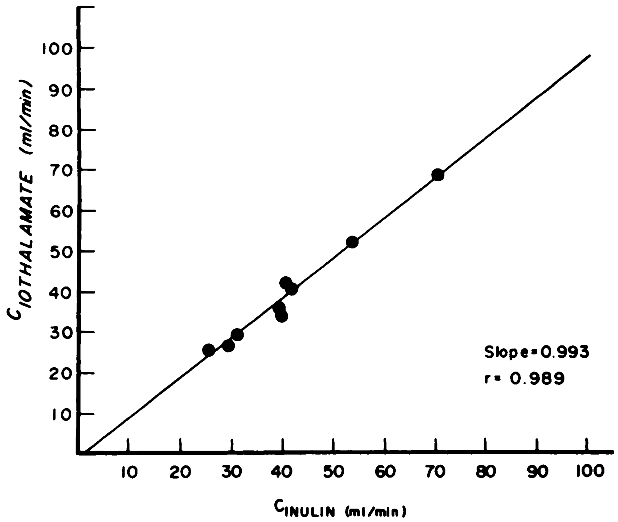

FIG. 2. Comparison of [125]I-iothalamate clearance with standard inulin clearance.

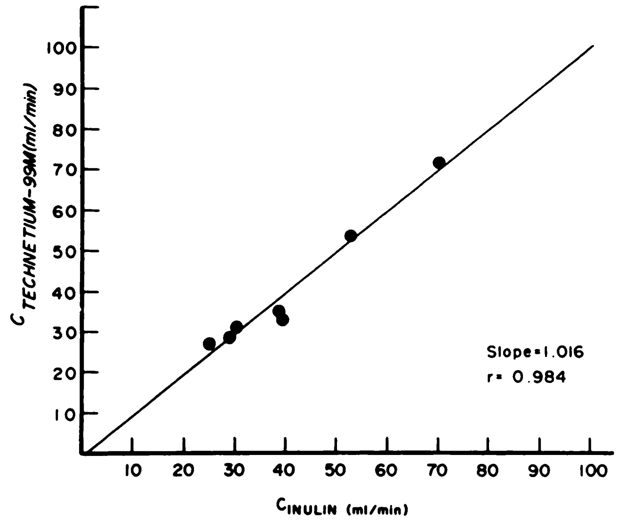

FIG. 3. Comparison of ^{99m}Tc-Sn-DTPA clearance with standard inulin clearance.

The individual correlations of the radionuclide and inulin clearances are shown in Figs. 2 and 3. Figure 2 depicts the close correlation of C_{Ioth} and C_{In}. The slope of the regression line is 0.993 with a highly significant correlation coefficient ($r = 0.989$). Figure 3 shows C_{Tc} to be almost identical with C_{In} (the slope is 1.016 and $r = 0.984$). The slope of each of these curves is not statistically different from 1.0 ($p < 0.05$).

DISCUSSION

Reliable GFR measurement is often needed for the clinical evaluation and followup of patients with renal disease and particularly renal-transplant recipients. Animal experiments involving studies of various tubular functions of the whole kidney also require precise measurement of GFR. The difficulties encountered in the measurement of inulin clearance have been somewhat alleviated by the introduction of radioactively labeled iothalamate. Initial studies with radioactive iothalamate required utilizing the continuous-infusion technique, however, and were still cumbersome.

Recently several reports have utilized the single intravenous injection of ^{125}I-iothalamate, and clearance calculations were derived by total-body monitoring or plasma decay curves (*9,10*). These techniques assume that plasma clearance results solely from renal excretion, which is not always a valid assumption (*11*). The subcutaneous injection technique, combining ^{125}I-iothalamate and aqueous epinephrine solution, has shown stable blood levels of the tracer after equilibration and virtual identity of the simultaneous inulin and iothalamate clearances (*5*). In the present study the subcutaneous injection was used for both ^{125}I-iothalamate and ^{99m}Tc-Sn-DTPA. Simultaneously measured clearances of inulin and the two tracers were identical and showed a high degree of reproducibility over a wide range of renal function.

Although ^{125}I-iothalamate is commercially available and has been documented as a suitable tool for measuring GFR, it has some drawbacks. The cost is not prohibitive ($130 for 1-mCi vial, or approximately $3 per dose), but unless this compound is used frequently each determination will be expensive. In contrast, the use of ^{99m}Tc-Sn-DTPA for GFR measurement is simple and cheaper ($3 for a 3–5-dose vial, or approximately $1 per dose) and affords a much smaller radiation risk to the patient. The radiation dose to the kidney of ^{99m}Tc-Sn-DTPA in man has been calculated to be 40 mrads/mCi (*12*), as opposed to 110 mrads/mCi from ^{125}I-iothalamate (*13*). The common use of ^{99m}Tc-Sn-DTPA for scanning procedures could make it readily accessible.

We conclude that the subcutaneous injection technique of administering ^{99m}Tc-Sn-DTPA mixed with aqueous epinephrine is an easy, inexpensive, and nonhazardous method of accurately measuring GFR.

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