Simultaneous Measurements of Glomerular Filtration Rate by Two Radioisotopic Methods in Patients Without Renal Impairment

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ABSTRACT
Isotopic clearance techniques have been widely used to measure GFR but may give variable results depending on the level of renal function and the technique used. GFR, measured by the technique of plasma disappearance of 99mTc-labeled diethylenetriaminopentacetic acid (99mTc-DTPA) was compared with simultaneously obtained urinary clearance of 99mTc-DTPA. GFR was also measured by concurrent 24-h clearance of creatinine. Forty-six measurements of GFR were obtained in 12 patients who had no evidence of renal disease. Plasma disappearance was measured from three timed plasma samples collected 60 to 180 min after the bolus injection of 200 μCi of 99mTc-DTPA and was calculated as the product of the volume of distribution (milliliters) at time zero and the clearance rate (per minute) as determined by the regression of the monoexponential plot. Urinary clearance was measured as the average of 3 1-h urinary clearances collected after a water diuresis was established. GFR measured by plasma disappearance was significantly greater (P < 0.001) than GFR measured simultaneously by urinary clearance. There was a linear correlation between GFR measured by urinary clearance and that measured by plasma clearance (r = 0.994). Plasma clearance exceeded urinary clearance by a constant factor of 1.3 over the range studied (urinary clearance range, 49 to 94 ml/min/1.73 m²). It was concluded that at relatively a normal

GFR, the plasma clearance of 99mTc-DTPA consistently overestimates the urinary clearance of 99mTc DTPA.

Key Words: Diethylenetriaminopentacetic acid, isotopic clearance, plasma disappearance, urinary clearance, GFR

There is now widespread interest in attempting to modify the progression of chronic renal disease by dietary modification or drug therapy. This results from the present perception that common pathophysiologic mechanisms may underlie the progressive loss of renal function seen in diverse renal diseases. A reliable, safe, and reproducible measure of renal function is required to assess the progression of renal disease over long periods of time (1).

The standard measure of GFR is the renal clearance of inulin (2,3). The technique of inulin clearance, however, is cumbersome and not suitable for extended outpatient studies, and the chemical analysis of inulin is time consuming (4). Endogenous creatinine clearance has long been used as a convenient measure of GFR. In this setting, serial creatinine clearance measurements frequently yield false estimations of renal function, especially at low levels of renal function (5-9). It has been advocated that isotopic measures of GFR be used to serially evaluate renal function in chronic renal failure (10).

A variety of techniques for measuring GFR on the basis of plasma disappearance or the urinary accumulation of isotopic markers have been developed (11,12). The most frequently used isotopic markers are [125I]iothalamate, [51Cr]EDTA, and [99mTc]DTPA. Interest in the use of these techniques is increasing, and they are being applied to the long-term study of the progression of renal disease.

The measurement of GFR by the determination of the plasma clearance of an isotopic marker after a single bolus is an attractive technique because it obviates the need for urine collection. The validity of this technique assumes that the volume of distribution of the isotopic marker is constant, that mixing in this volume is rapid so that concentration is uniform, and that the rate of clearance is constant over the interval being studied (3). Despite these theoretical constraints, GFR measured by the plasma clearance of [99mTc]DTPA has been reported to correlate closely with inulin clearance (13,14). The fractional
clearance of $[^{99m}Tc]DTPA$ has been reported to be identical to that of inulin over a wide range of renal function (6). Other investigators have found that at low levels of renal function, the plasma disappearance of $[^{99m}Tc]DTPA$ overestimates GFR compared with calculations using urinary accumulation (15). How these techniques compare among themselves and whether they vary at different levels of renal function remain controversial.

The evaluation of renal function early in the course of renal disease, before significant functional impairment has occurred, may be important. How isotopic measures of GFR compare at or near normal levels of renal function is unclear. In this study, we have compared simultaneous urinary clearances and plasma clearances of $[^{99m}Tc]DTPA$ in a group of patients without evidence of renal disease.

MATERIALS AND METHODS

Patients

Subjects for the study were 12 female patients with a mean age of 60.5 ± 1.6 yr. Six patients were hypertensive and had blood pressure controlled with 50 mg of hydrochlorothiazide daily. Six patients were normotensive. Serum creatinine values ranged from 0.7 to 1.4 mg/dL. Each patient had four evaluations of renal function over a period of 18 days. All studies were begun at 10:00 a.m. after an overnight fast. Studies were separated by 7 days.

GFR Measurements

One hour before the study, the patients consumed an oral water load of 10 to 15 mL/kg to establish a brisk urine flow. An i.v. bolus injection of 200 µCi of $[^{99m}Tc]DTPA$ was given. After 60 min, the patients voided, a blood sample was drawn, and three times sequential 1-h urine collections were obtained. Additional blood samples were drawn after each voiding. $[^{99m}Tc]DTPA$ activity in the samples was determined by being counted in a crystal scintillation counter. Urinary clearances of $[^{99m}Tc]DTPA$ were calculated for each 1-h collection period as urine activity times urine flow rate divided by average plasma activity. Average plasma activity was calculated as the mean of the plasma values over the interval from the beginning to the end of each urinary collection. The GFR was expressed as the average of the three 1-h collection values.

Plasma clearance of $[^{99m}Tc]DTPA$ was measured from three timed blood samples between 60 and 180 min after a bolus injection of the $[^{99m}Tc]DTPA$. GFR was calculated as the product of the volume of distribution (milliliters) at time zero and the clearance rate (per minute) deduced from the best-fitting regression line of the monoexponential plot (11,13,15–17).

Data Analysis

Data were analyzed by linear regression and t test for paired data. Results are expressed as the mean plus or minus the standard error. Statistical significance was defined as $P < 0.05$. The concomitant administration of medications, which may affect renal function, precluded the assessment of within-patient variability.

RESULTS

Twelve patients had measurements of GFR by simultaneous urinary $[^{99m}Tc]DTPA$ clearance, plasma $[^{99m}Tc]DTPA$ clearance, and 24-h urinary creatinine clearances on each of four different occasions. Two clearances were excluded because of technical difficulties, leaving a total of 46 paired GFR determinations for comparison. GFR measured by $[^{99m}Tc]DTPA$ plasma clearance ranged from 53 to 124 mL/min/1.73 m². GFR measured by the urinary clearance of $[^{99m}Tc]DTPA$ ranged from 49 to 94 mL/min/1.73 m². GFR measured by plasma disappearance was significantly greater ($P < 0.001$) than GFR measured simultaneously by urinary clearance. There was a linear correlation between GFR measured by urinary clearance and that measured by plasma clearance ($r = 0.990; P < 0.001$) (Figure 1). Plasma clearance of $[^{99m}Tc]DTPA$ exceeded urinary clearance by a factor of 1.30 ± 0.09 (slope of the regression line, 1.30; intercept, 0.4) over the range of GFR studied.

DISCUSSION

There is presently an intense interest among clinical investigators in factors that may modify the progression of chronic renal disease. Clinical studies of this kind require a safe, convenient, accurate, and reproducible measure of renal function. Twenty-four-hour urinary creatinine clearance, a frequently used measure of GFR, is known to have significant error, with the tubular secretion of creatinine becoming an increasing factor at low GFR (5,6,9). Outpatient collection of 24-h urine collections is also subject to error (8).

Inulin clearance has been regarded as the most accurate measure of GFR (2,3). Inulin clearance is, however, more cumbersome for outpatient measurements because of the requirement of a constant infusion of inulin. In addition, the chemical assay for inulin is involved and subject to error (4). Because of these issues, alternative isotopic clearance techniques with markers such as $[^{99m}Tc]DTPA$ or $[^{125I}]$iothalamate have been developed. These techniques, especially those based on the plasma clearance of isotopic markers, are attractive because of convenience and the ease of measurement associated with a radiolabeled marker (18). Plasma clearance techniques avoid the necessity for timed urine collections.
and the possibility of complications associated with water loading in patients with advanced renal disease or congestive heart failure. The measurement of GFR by the plasma clearance of $^{99mTc}$DTPA may be subject to the potential error introduced by extrarenal clearance. LaFrance et al. (15) measured plasma and urinary clearances of $^{99mTc}$DTPA and creatinine clearance in patients with GFR ranging from 5 to 35 mL/min. Over this range, they found that both the plasma clearance of $^{99mTc}$DTPA and the creatinine clearance overestimated by a large and variable amount the GFR measured by the urinary clearance of $^{99mTc}$DTPA. Walser (1) has noted that as GFR falls to very low levels (<10 mL/min), the proportion of extrarenal to true renal clearance of all isotopic markers increases.

Clearance values of $^{125}$Iothalamate based on urinary accumulation after i.v. or s.c. administration have in most studies correlated closely with insulin clearance (11,14,19,20), although variable degrees of tubular secretion have been reported to induce error in clearance measurements (21). Similar results have been reported with $^{51}$CrETDA (22–25), although this agent is not available for use in the United States. Shemesh et al. (6) noted that the urinary clearances of $^{99mTc}$DTPA and insulin were identical when measured in the setting of a continuous infusion of both markers in patients with GFR ranging from 10 to 140 mL/min. Similarly, Rehling et al. (13) found that uninephrectomized patients with a mean insulin clearance of 43.6 mL/min had a plasma clearance of $^{99mTc}$DTPA, which correlated closely with insulin clearance. Perrone et al. (14) have found that $^{99mTc}$DTPA urinary clearance correlated well with simultaneously obtained insulin clearances in patients ($N = 13$) with significant renal diseases (GFR less than 50 mL/min/1.73 m²) and that the variance of measurements made on sequential days with $^{99mTc}$DTPA was the same as measurements made with insulin. They noted that in four patients with no evidence of renal disease (mean GFR, 102 mL/min/1.73 m²), the urinary clearance of $^{99mTc}$DTPA was higher than that calculated using insulin clearance. The accuracy of these techniques at different levels of renal function and their relationship to each other remain uncertain.
Regression analysis of our data demonstrates that for the range of GFR values estimated from the urinary clearance of [99mTc]DTPA (49 to 94 mL/min/1.73 m²), corresponding values based on plasma clearance of the same agent were strongly correlated \( r = 0.9903 \) but consistently higher by a factor of 1.3. There are a number of possible explanations for the systematic difference such as leakage of tracer into the extravascular space. Homer Smith pointed out in 1951 that GFR calculated from plasma clearance after a single bolus injection requires that the volume of distribution be constant, that the mixing of the agent be instantaneous and complete, and that the clearance be constant over the interval being measured (3). Systematic deviation from these theoretical constraints may be a factor in our observed differences. A possible contributing factor is that the plasma tracer concentration in the denominator of the expression for urinary clearance is the simple arithmetic mean, which slightly overestimates (<4% in the worst case) the average plasma activity, which could be better approximated by the mean concentration based on exponential decay. This leads to a corresponding underestimation of GFR by urinary accumulation. A small systematic error is also introduced by the delay in transit time from the renal pelvis to the bladder. These disparities, however, are sufficient to account for only a small fraction of the observed difference between the two methods. Goates et al. [26] have pointed out that there is some degree of protein binding of [99mTc]DTPA. This is variable, and its contribution to the differences we observe is unknown. Whatever the cause or causes of the systematic difference, it appears to be consistent over the range of GFR values encompassed within this study.

The constancy of the observed difference between simultaneously measured clearances of [99mTc]DTPA from plasma and urine is such as to suggest that GFR values derived from plasma disappearance could be adjusted to agree with the more conservative GFR estimates provided by the urine collection technique. For the best-fitting regression line shown in Figure 1, the predicted value for urinary GFR \( \text{GFR}_u \), given a GFR value derived from plasma disappearance \( \text{GFR}_p \), would be:

\[
\text{GFR}_u = \frac{\text{GFR}_p - a}{b}
\]

where \( a \) is the zero intercept of the regression line (0.42 mL/min) and \( b \) is the slope of the line (dimensionless, 1.30 ± 0.09).

The standard error of a value for \( \text{GFR}_u \) so calculated is estimated to ±7.5 mL/min/1.73 m². The demonstrated validity of this approach, however, is necessarily limited to patients exhibiting GFR values falling within the range encountered in this study. Extrapolations beyond the range actually studied are to be made, if at all, with caution.

We concluded that within the tested range of GFR levels, those based upon the plasma clearance of [99mTc]DTPA yield significantly higher values than parallel estimates derived from the urinary clearance of the same tracer. Correction for the difference, which appears to be consistent, may allow an assessment of GFR by plasma disappearance that more closely agrees with results based on urinary accumulation. This could circumvent the need for more difficult urine collection techniques and the concomitant water loading associated with them. As a practical matter, urine collection is always cumbersome and is sometimes impossible. It is also frequently inexact in that one can seldom be assured that collection is at once precisely timed and its volume fully calculated. In contrast to those technical difficulties, plasma sampling is generally easier to accomplish, is more precise with respect to both time and volume, and remains possible even in oliguric patients. On the other hand, it must be acknowledged that urine collection methods are singularly free of the assumptions inherent in compartmental models used to derive GFR from plasma disappearance, so that the urine clearance technique may be preferable in logic, if not in its execution. We suggest that this study, by defining more precisely the systematic difference between these two isotopic techniques, may prove useful to the clinician facing the difficult choice between an acceptable method virtually certain to succeed and a putatively superior but more cumbersome one that may be subject to occasional failure.

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