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Evaluation of a Simplified Measurement for Low Glomerular Filtration Rates With Indium-111 DTPA

L. E. Preuss, MS,* R. S. Michaels, MD, F. P. Bolin, MS,* N. W. Levin, MD,* and C. Artman, BS***

A rapid new method for measuring glomerular filtration rates using ^{111}In diethylenetriamine pentaacetic acid (^{111}In-DTPA) was evaluated with 39 patients who showed marked impairment of renal function (creatinine clearance less than 20 ml/min). A simple, single compartment system was assumed. For comparison, parallel inulin and creatinine clearances were performed. High linear correlations (r = 0.96 - 0.97) were demonstrated when ^{111}In-DTPA clearances were compared with the standard non-isotopic tests. Initial data indicate that reliable isotopic clearance values could be obtained for low clearances by withdrawing only two blood samples for assay at 6 and 48 hours after isotope injection (without urine assay).

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* Radiation Physics Research Laboratory, Henry Ford Hospital

** Department of Internal Medicine, Division of Nephrology, Henry Ford Hospital

Address reprint requests to Mr. Preuss, Radiation Physics Laboratory, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202

Due to difficulties with accepted techniques for measuring the glomerular filtration rate (GFR), efforts have concentrated on finding a simple yet accurate method for measuring this renal function.[1,2] The accepted standard is the inulin test, but assays are time consuming and the test is not routinely used in clinical practice. Clearance of endogenous creatinine is more widely used clinically, but it is not entirely satisfactory as a measure of very low glomerular filtration rates (GFR less than 20 ml/min). Existing methods for measuring filtration rates are liable to error in those cases which are associated with low urinary output, because of the difficulty of collecting accurate, complete urine specimens. Hence, a glomerular filtration measurement method independent of urine specimens could be most useful. In addition to providing information needed for dialysis schedules, an easily performed measurement that did not require urine collection would benefit transplant patients or those with urinary fistulae.

Ideally, such a low GFR measurement should: 1) require only a few samples; 2) avoid urine collection; 3) be administered in a simple, single test.

Numerous attempts have been made to develop a radioactive test for measuring GFR. The substances studied have included ^{51}Cr-EDTA, ^{169}Yb-DTPA, and ^{125}I-iothalmate.[2-5] Using a continuous infusion method, Garnett, et al[2] reported excellent correlation between ^{51}Cr-EDTA and inulin, while Milutinovic[4] achieved good results with ^{125}I-iothalmate as compared to inulin in hemodialysis patients with low GFR. Thus far, however, none of the isotopic tagged material studied has been entirely accurate nor capable of establishing a completely linear relationship with inulin over the entire GFR range. Also, most of the existing studies have not concentrated on the very low GRF region.

Formulating a test to measure GFR entails a comparison of clearance curves to determine optimum sampling intervals, so that little or no information is lost when the number of assays is reduced.

With these considerations in mind, a limited study was designed to collect data for comparing ^{111}In-DTPA clearances with standard inulin and creatinine clearances. At the same time, the isotope technique was to be evaluated to determine the minimum number of collection points needed to obtain an accurate slope for the disappearance curve.

This initial study used ^{111}In-DTPA to measure GFR. Diethylenetriamine-pentaacetic acid (DTPA) is accepted as a suitable substance for measuring filtration rates.[3,6,7] Its *in vivo* stability, which is lacking in such compounds as Fe-DTPA and Tc Fe-ascorbate, is not significantly decreased by the ^{111}In tag.[7] Also, the ^{11}In tag has gamma emissions of 173 keV and 247 keV suitable for studies of this type. The whole-body dose to the patient, primarily from the gamma emissions, is 48 mRad per 100 μCi injection. For the patient with low GFR, the benefits outweigh the risks from the radiation dosage, providing useful clinical information in exchange for a modest diagnostic radiation exposure.

Methods

For all 39 patients in the study a catheter was inserted into the antecubital vein and a sample of urine was withdrawn for background counting. Two background blood samples were also withdrawn (6-8 cc each). Solutions containing 150-200 μCi of ^{111}In-DTPA (a commercial sterile preparation of 500 μC/ml activity*) and 50 mg/kg of inulin were then injected intravenously and the time recorded. After injection, the venous catheter was attached either to a heparin lock or to a 5-10 cc syringe of heparin from which minute amounts were injected to maintain patency for subsequent blood withdrawals.

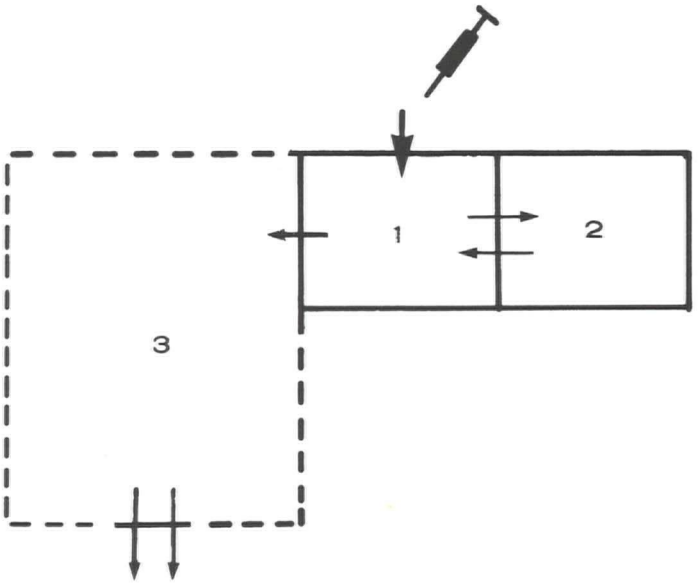
After a 45-minute interval to allow for equilibration of the inulin and the tagged DTPA, blood and urine samples were collected for inulin, isotope clearance and endogenous creatinine measurements. Following equilibration, 30-minute urine collections were made, from which 6 cc to 8 cc were obtained for the inulin analysis. For the isotope measurement, eight additional blood samples of 6 cc were withdrawn beginning one hour postinjection and continuing at 2, 4, 8, 12, 24 and 48 hours thereafter. The exact time of collection was noted for all samples, which were immediately refrigerated and cold-centrifuged for 15 minutes at 2000 rpm (r=23 cm). Plasma and urine samples were frozen for later standard analysis when radioactivity had reached negligible levels by decay.

When all eight blood samples for radioassay had been collected over a two-day period, they were cold-centrifuged for 15 minutes at 2000 rpm and plasma withdrawn in 0.5 cc volumes. These samples and a standard volume were then radioassayed on a Searle multisample gamma counter with analyzer windows set to count both the 173 keV and 247 keV emissions of ^{111}In.

Standard procedures for measuring inulin and creatinine were used, and isotopic, creatinine, and inulin clearance values were obtained.[8,9]

In the usual two-compartment or mamillary[10] model for renal clearance (Figure 1), the injected material disperses into the primary volume, the blood pool (compartment 1), which is exchanging with a closed volume (compartment 2) at the same time as it is being lost from compartment 1 into 3, from which no exchange back to 1 is permitted.[11]

Our ^{111}In-DTPA study used a single injection technique and a simplified mathematical description of the disappearance process.[12,13] Data collected by radioactive assay are converted to net counts/ml and treated graphically to determine ^{111}In clearance from compartment 1. Net counts/ml are plotted versus actual withdrawal times postinjection (Figure 2). The real disappearance curve is complex,[11] as it is the sum of more than one equilibrium and exchange process. The last portion of the plot, after about 60 to 120 minutes, is linear on a semi-log plot; it represents the result of isotope disappearance from the blood pool after equilibrium has been established in the reservoirs. This linear portion may be extended back to



MAMILLARY TYPE
OPEN 2-COMPARTMENT MODEL

Fig. 1

* Diagnostic Isotopes, Inc

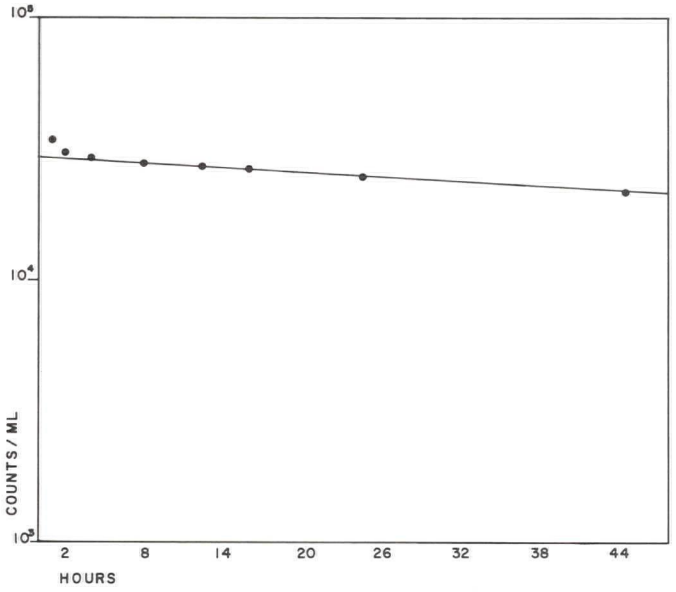


Fig. 2

A plot of ^{111}In-DTPA levels in the blood m (rate of change of concentration per unit time) is obtained from the slope established in the 4-48 hour period. Displacement of the two plots at 60 and 120 minutes represents the last phase of the early steep/slope section of the total disappearance curve.

the y-axis (by linear regression analysis) to find concentration A_o. This concentration is accepted as the blood activity per milliliter that would have existed at time zero, if dispersal had occurred instantly and been limited exclusively to the vascular system. Use of this zero time value also assumes that other reservoirs (exchange with the blood pool) are negligible in size or do not carry out rapid interchange with the blood pool.

With this much simplified mathematical approach,[13] the clearance was calculated as follows:

$$\text{Clearance (ml/min)} = \frac{-m\, I_o}{A_o}$$

Where m = slope of linear regression line (rate of change of ^{111}In plasma concentration)

I_o = total injected activity

A_o = activity/ml at time zero (y-intercept value)

These assumptions allow the test to be limited to a simple, single DTPA administration and a minimum of two plasma samples, as will be shown. However, as long as compartment 2 and free interchange exist, these assumptions will result in a plotted disappearance slope that is too shallow and a plasma volume $\frac{(I_o)}{(A_o)}$, derived from it that is on the high side. This pilot study was designed to ascertain the degree to which these two error factors would compensate for each other, particularly in low GFR subjects. Should they largely cancel out, then a simple, acceptable GFR test could result.

Results and Discussion

Thirty-nine patients with varied renal function were injected with ^{111}In-DTPA, which was used to measure glomerular filtration rates by measuring the changing isotopic ^{111}In blood levels. A few subjects with GFR greater than 20 ml/min were included for comparison. These higher clearances were done with ^{111}In and compared with simultaneous creatinine values. Simultaneous clearances of either inulin or creatinine were determined, with 29 comparisons made to creatinine and 10 to inulin.

The first 29 sets of data were plotted as ^{111}In-DTPA versus creatinine (Figure 3) and the second set of 10 data points was plotted as ^{111}In-DTPA versus inulin (Figure 4). The correlation coefficients for both (0.96 and 0.97, respectively) are sufficiently high to infer a satisfactory linear relationship between the isotopic and the two nonisotopic standard methods. In this study, the slope of 1.24 in Figure 3 indicates that ^{111}In-DTPA clearances, using the above assumptions, are lower than creatinine GFR values, while

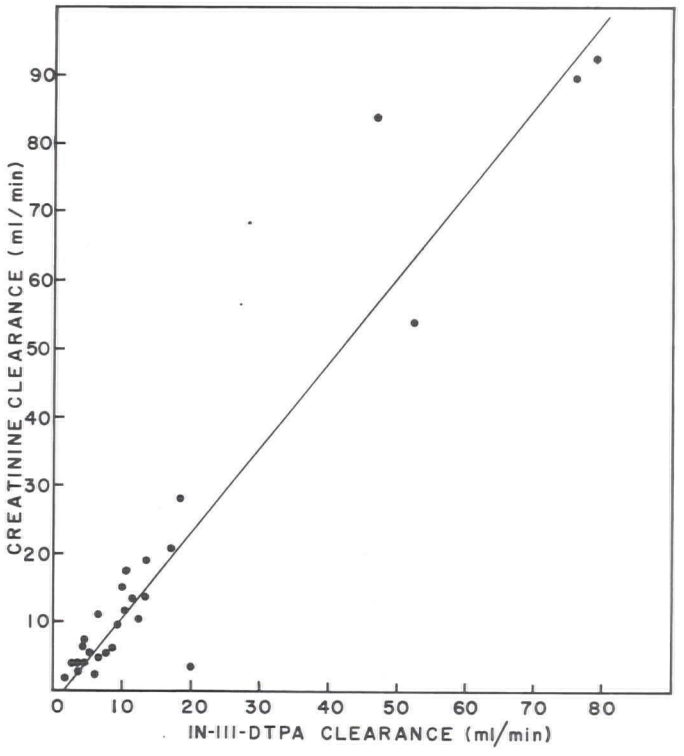


Fig. 3

^{111}In-DTPA clearances compared to the creatinine values for 7 subjects.

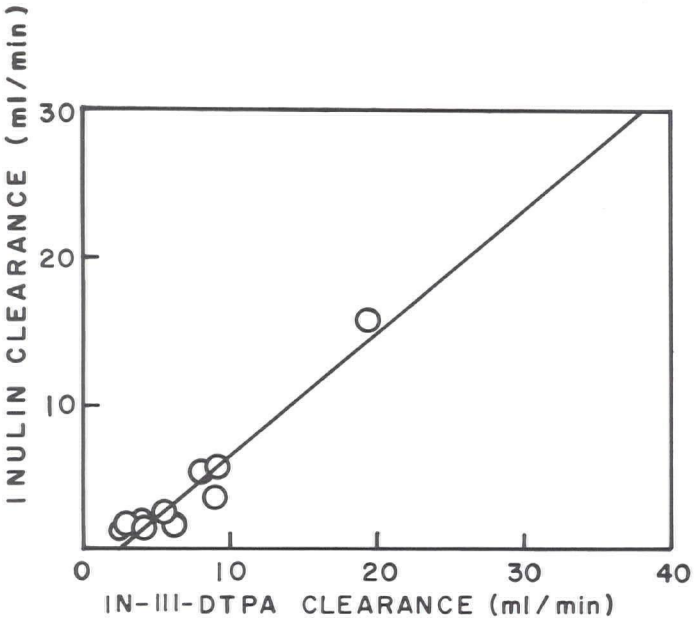


Fig. 4
Comparison of ^{111}In-DTPA and inulin clearances. Correlation coefficient is 0.97. DTPA values on average are greater than those for inulin.

TABLE I
Comparison of GFR Values

Patient	All Point Plot Clearance	2 Point Plot Clearance	Difference
1	6.1	6.2	0.2
2	4.3	3.5	0.8
3	8.2	8.6	0.4
4	2.9	2.8	0.1
5	3.0	2.8	0.2
6	6.3	6.4	0.1
7	5.8	6.0	0.2
8	22.5	22.5	—
9	4.1	4.5	0.4
10	19.5	19.5	—
11	17.4	17.4	—
12	9.3	9.8	0.5
13	9.4	11.0	1.6
14	4.1	3.9	0.2
15	8.0	7.9	0.1
16	10.6	10.4	0.2
17	16.9	17.3	0.4
18	12.6	12.2	0.4
19	2.2	1.8	0.4
20	4.3	4.3	—
21	2.7	3.0	0.3
22	4.1	4.6	0.5
23	9.4	10.1	0.7
24	8.9	8.9	0.1
25	11.4	11.1	0.3
26	18.5	18.7	0.2
27	6.6	6.8	0.2
28	5.6	5.3	0.3
29	12.7	13.1	0.4
30	3.9	3.6	0.3
31	3.7	3.7	—

the slope of 0.84 in Figure 4 shows that ^{111}In-DTPA values are greater than inulin clearances

Table I lists ^{111}In-DTPA clearances for 31 subjects calculated in two different ways. Column 2 contains clearance values obtained using all data points on the 4 to 48 hour linear portion of the clearance curve, whereas column 3 indicates results using only two of the data points, at plasma collection times of 4 and about 48 hours. Column 4, which lists the differences in clearance between the 6 and 2 point data, indicates that the absolute differences are small and consistent for all subjects tested. Moreover, the coefficient of correlation between the data of column 2 and column 3 is 0.997. The least squares line of the all-point data plotted against the two-point plasma sampling has a slope of 1.01 and and intercept of -0.01. This provides strong evidence that the two-specimen method can accurately determine the slope m (GFR) of the disappearance curve so that additional blood withdrawal is unnecessary.

The tabular and graphic results indicate that GFR determined with ^{111}In-DTPA linearly follows both inulin and creatinine and has good correlation in the range of GFR less than 20 ml/min. In fact, ^{111}In-DTPA clearance values are lower than creatinine but higher than inulin. In the case of low GFR, ^{111}In-DTPA clearance is more accurate than creatinine and less accurate (on the high side) than inulin, when measured against inulin as the standard. It is not surprising that inulin GFRs are not duplicated precisely, since with the simplified theory the equation is an approximation, lacking a term in the denominator.[11] The true picture is that of a two-pool mamillary system. With the second term in the denominator, it is likely that calculated clearances will be higher than true inulin clearances. Thus, we may conclude that the ^{111}In-DTPA monitors clearance as consistently as creatinine does but gives a closer approximation to inulin values, inulin being the accepted standard of measurement. The two-plasma sample measurement with ^{111}In is certainly less liable to the serious systematic errors inevitably associated with urine collections and particularly from subjects with very low filtration rates.

An interesting aspect of the ^{111}In-DTPA study has been the consistent production of the straight line disappearance plot for the 4-48 hour plasma collection. The slope is precisely and regularly delineated with an excellent r and may be accurately derived from only two plasma samples. Thus, this rate of change of blood ^{111}In-DTPA concentration (slope) may be the key to an acceptable, simplified clearance method for low GFR. This study also drew

blood samples to provide data that would determine the linear portion of the disappearance curve accurately (see Figure 1). While six data points were used to determine patient curves, we found that two data points could be used without any significant loss of accuracy (Table I).

Conclusion

Our study demonstrated the ^{111}In-DTPA may be used for an approximate determination of low GFR clearance, using a single-injection technique, withdrawal and counting of only two blood samples, as well as a simplified expression for disappearance. This test could be substituted for routine creatinine clearances in low GFR patients in order to save time and reduce the discomfort of the patient.

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