Technetium-99m-MAG3 Renal Studies: Normal Range and Reproducibility of Physiologic Parameters as a Function of Age and Sex

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The normal range and reproducibility of common physiologic parameters for ^{99m}Tc-MAG3 renal studies were quantitated in normal subjects. **Methods:** Six females and six males in each of three age groups, 21–40, 41–60 and 61–80 yr, were each studied twice. Renal clearance (camera based method), percent function in each kidney, time of peak renal parenchymal activity and half time of parenchymal activity following the peak were evaluated. The peak and half times were determined with regions of interest (ROIs) over the entire kidney and over the cortex only. **Results:** There were no significant differences between sexes for any parameter. The only significant difference among age groups was a decrease in renal clearance, normalized for body surface area, with increasing age ($p < 0.01$). The percent function in each kidney, time of peak parenchymal activity and half time following the peak were symmetrical and did not vary with age or sex. The peak times were always less with cortical ROIs ($p < 0.05$). In serial studies in the same subject the percent s.d. for clearance and percent function in each kidney was less than half of the percent s.d. in single studies, suggesting that at least one half of the error is due to intersubject variation ($p < 0.05$). **Conclusions:** We conclude that: (1) renal clearance decreases with age in normal subjects, (2) cortical ROIs are superior to renal ROIs in measuring peak parenchymal activity, and (3) variation in clearance and percent function per kidney in serial studies is approximately one half the variation in single studies.

Key Words: renal studies; technetium-99m-mercaptoacetyltriglycine (MAG3); normal volunteers; clearance measurements; reproducibility

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Since its introduction in 1986, Tc-99m-mercaptoacetyltriglycine (MAG3) has become the renal radiopharmaceutical of choice (*1,2*). This success reflects the fact that ^{99m}Tc-MAG3 combines the advantages of the favorable imaging characteristics of a ^{99m}Tc label with the favorable biological properties of a compound that is cleared by tubular secretion (*2*).

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In order to maximize the clinical usefulness of ^{99m}Tc-MAG3, we studied a relatively large number of normal subjects in order to determine the normal range in single studies and the reproducibility in serial studies of several commonly measured physiologic parameters. In addition, the parameters were evaluated in males and females in three different age groups to determine the effects of age and sex.

METHODS

Subjects

Informed consent was obtained from all subjects and the study protocol was approved by the institutional ethics committee. Each of 36 normal subjects was paid to undergo two ^{99m}Tc-MAG3 renal studies. Six males and six females were evaluated for each of three age groups: 21–40, 41–60 and 61–80 yr-of-age. Each subject was required to have no history of renal disease, a normal urinalysis and a normal serum creatinine. The two studies in each subject were performed at least two days apart.

Radiopharmaceutical and Imaging System

Each study was performed with approximately 5 mCi of ^{99m}Tc-MAG3 (Mallinckrodt Medical, St. Louis, MO). Radiochemical purity was determined each time the radiopharmaceutical was prepared using a Sep-Pak Cartridge (Millipore, Milford, MA) and averaged 98.72% ± 1.17% (mean ± s.d.) Images were acquired with a 15 inch field of view camera and a high-resolution collimator attached to a Picker 512 Plus computer. At the beginning of the study the linearity of the camera/computer system was determined demonstrating no drop off through 5 mCi.

Imaging Method

The subject was hydrated with at least 600 ml of water one hr prior to the study (*3*). Initially, a 1-min image of the syringe containing the dose was obtained with the syringe placed 30 cm in front of the center of the gamma camera (*4–6*). The subject was then positioned supine over the gamma camera with the kidneys and bladder within the field of view. The dose was injected intravenously using the tourniquet technique (*7*). Serial 3-sec digital images were obtained for the first min followed by serial one min digital images for the next 22 min; all images were acquired in a 128 × 128 matrix. The acquisition sequence and subsequent analysis were largely determined by the Picker 512 Plus computer used for renal studies.

At the end of the acquisition, three additional images were acquired for estimation of the percent of injected dose that was infiltrated. One min images were acquired of the injection site at

zero cm and of the postinjection syringe at zero and 30 cm. The ratio of the counts from the syringe at zero and 30 cm, usually 0.95, was used to normalize the counts from the injection site to the counts of the preinjection syringe. Studies with estimated percent extravasation above 3% were excluded.

Data Analysis

ROIs were drawn over the entire kidney, cortex and background on each side. The kidney ROIs were constrained to an ellipse, the cortical ROIs were drawn manually from the 1–2 min image in a crescent shape over the outer aspect of the kidney so as to exclude the collecting systems, and the background ROIs were drawn as square boxes six pixels on a side just below the kidneys and lateral to the ureters. Background corrected time-activity curves were constructed for each kidney using both the renal and cortical ROIs. The cortical ROIs were done retrospectively and only 23 of 36 subjects had data available for analysis.

The time-activity curves were quantitatively analyzed for clearance, percent of function in the left and right kidneys and parenchymal transit time. Clearance in terms of percent uptake was determined using a camera-based method without blood or urine sampling (*4–6*). The background corrected counts for each kidney in the 1–2 min image were corrected for attenuation, using Schlegel's method, to give the percent dose cleared by each kidney at 1–2 min following injection (*6,8*). The exact algorithm leading to determination of the percent dose in each kidney was contained in proprietary software of unknown content. The result is inherently normalized for total blood volume and therefore body surface area.

The percent of total renal function or clearance in each kidney was determined from the percent dose values. The parenchymal transit times were calculated from the times of peak activity in the renal and cortical time-activity curves. The washout or decrease in tracer following the peak was determined from the time of the peak to one half of the peak or half time. Because the renal program in our computer is limited to a temporal resolution of one min for the delayed images, a half min was added to the start time of each collection frame to minimize the effect of the relatively poor temporal resolution.

Statistical Analysis

The Student's t-test was used to compare results between groups and the linear correlation coefficient was used when data were analyzed across all subjects without regard to age group. The percent change in the various parameters between serial studies in the same subject was calculated in relative terms, not in absolute percentage units.

RESULTS

Subject Data

Seven subjects were excluded and replaced because of computer error during acquisition (*1*), extravasation of the dose (*1*), dehydration (*1*) or unexpected renal abnormalities (*4*). The mean, s.d. and range of ages for males and females for the three age groups, the serum creatinine levels, the time between paired studies and the percent dose infiltration in the first and second studies are given in Table 1.

Renal Clearance

There was no significant difference between the percent dose clearance of the left and right kidneys for any age group or for either sex (Table 2). However, there was a significant difference in clearance as a function of age (Fig. 1). There was a trend toward decreasing clearance with increasing age among the three age groups with a significant difference between the youngest and oldest groups ($p < 0.05$). In addition, there was a significant inverse correlation coefficient when all groups were tested together ($r = -0.88$, $p < 0.01$).

Other Parameters

For the other physiologic parameters, there was no significant difference between males and females among the three age groups, or between the two sides (Table 3). However, the results of peak times with cortical ROIs were significantly less than with renal ROIs for all age groups ($p < 0.05$). In addition, the results for half times were significantly less with cortical ROIs than with renal ROIs in the oldest age group, but there was no significant difference between the two ROIs in the other two age groups.

Reproducibility

The percent s.d. for differences between serial studies in the same subjects was approximately one half the percent s.d. between studies in different subjects for clearance and percent of function on a side ($p < 0.05$) (Table 4). Differences in the percent s.d. between intra- and intersubject studies was less uniform for peak and half times (Table 4). In addition, the correlation coefficient between total percent dose at 1–2 min in the first and second studies was 0.99

TABLE 1
Subject and Study Data

Parameter/Group	N	Mean	s.d.	Range
Females 21–40 yr	6	27.0	4.9	23–36
Males 21–40 yr	6	28.2	3.7	25–35
Females 41–60 yr	6	45.7	4.4	41–53
Males 41–60 yr	6	50.3	6.9	40–59
Females 61–80 yr	6	64.3	2.4	61–67
Males 61–80 yr	6	66.0	4.7	61–72
Serum creatinine (mg/dl)	36	1.0	0.2	0.6–1.4
Time between studies (dy)	36	5.3	3.6	2–20
Dose infiltration—first study (%)	36	0.9	0.5	0.0–2.7
Dose infiltration—second study (%)	36	0.9	0.5	0.5–2.5

TABLE 2
Renal Clearance (% Dose)*

Group	N	Left	Right	Total
Age 21–40 yr				
Females	6	11.3 ± 3.8	11.0 ± 3.9	22.3 ± 7.6
Males	6	10.4 ± 4.0	10.4 ± 1.4	20.7 ± 9.5
Females + Males	12	10.8 ± 2.9	10.7 ± 2.7	21.5 ± 5.6†
Age 41–60 yr				
Females	6	9.0 ± 1.4	8.4 ± 0.9	17.4 ± 1.4
Males	6	10.4 ± 3.4	11.1 ± 3.7	21.4 ± 6.8
Females + Males	12	9.7 ± 2.6	9.7 ± 2.9	19.4 ± 5.1
Age 61–80 yr				
Females	6	8.6 ± 2.6	8.8 ± 2.5	17.4 ± 4.9
Males	6	7.0 ± 1.3	8.3 ± 1.4	15.3 ± 2.4
Females + Males	12	7.8 ± 2.1	8.5 ± 1.9	16.3 ± 3.9†
All ages				
Females	18	9.6 ± 2.9	9.4 ± 2.8	19.0 ± 5.5
Males	18	9.2 ± 2.8	9.9 ± 2.6	19.1 ± 5.1
Females + Males	36	9.4 ± 2.8	9.6 ± 2.6	19.1 ± 5.3

*Data are presented as percent of injected dose in the kidney(s) at 1–2 min after injection (mean ± s.d.). All data are from the first study in each subject.
†Difference between these two results is statistically significant when $p < 0.05$.

($p < 0.001$); similar to that reported by others for camera-based clearance methods (*4*).

Normal Limits

Suggested key normal limits are presented in Table 5. The selected parameters are the ones that are felt to be most important in evaluating a renal study. Cortical ROIs were used rather than renal ROIs because they have a narrower normal range. The numbers are rounded in order to make them easier to use and remember. Usually, but not always, the numbers are rounded in a fashion to increase the normal range and, thus, to be more conservative.

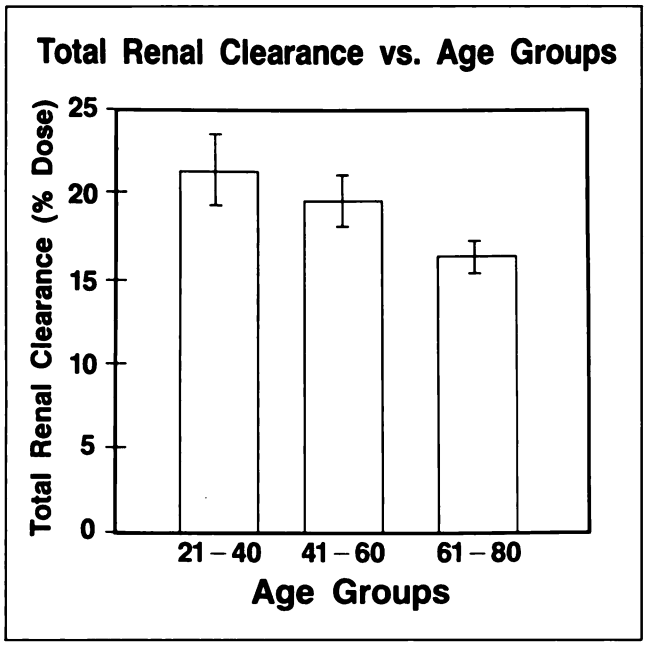

FIGURE 1. Total renal clearance as percent dose at 1–2 min after injection (mean ± S.E.M.) is shown for each of the three age groups. The average clearance for the two studies in each subject was used in calculating these results. There is a trend toward lower clearance values with increasing age. The difference between the youngest and oldest age groups and the correlation coefficient between clearance and age was statistically significant ($p < 0.05$).

DISCUSSION

This study delineates the normal range and reproducibility of several important physiologic parameters of renal function as measured in ^{99m}Tc-MAG3 studies without blood or urine sampling. Renal clearance was the only parameter that varied with age. Clearance normalized for body surface area showed a significant decrease with increasing age. This finding is consistent with previous studies although previous studies have focused more on renal perfusion and glomerular filtration rather than tubular se-

TABLE 3
Results for Parameters other than Clearance*

Group	N	Left	Right
Percent of total clearance	36	49.4 ± 3.9	50.6 ± 3.9
Peak time			
Renal ROI (min)†	36	3.3 ± 2.0	3.8 ± 2.3
Cortical ROI (min)†	23	2.5 ± 0.2	2.5 ± 0.4
Half-time			
Renal ROI (min)	36	5.5 ± 1.6	6.4 ± 3.5
Cortical ROI (min)	23	5.0 ± 1.5	5.5 ± 2.0

*All data are from the first study in each subject and are given as mean ± s.d.
†Difference between these two results is statistically significant when $p < 0.05$ level.

TABLE 4
Intersubject Versus Intrasubject Variability (%)*

Parameter	N	Left	Right	Total
Single studies				
Clearance†	36	20 ± 19	20 ± 18	21 ± 18
Percent of total clearance†	36	6 ± 5	6 ± 5	—
Peak time (renal ROI)	36	30 ± 52	37 ± 47	—
Half time (renal ROI)	36	23 ± 16	50 ± 19	—
Peak time (cortical ROI)	23	3 ± 8	8 ± 14	—
Half time (cortical ROI)	23	19 ± 22	23 ± 27	—
Serial studies				
Clearance†	36	10 ± 7	13 ± 9	11 ± 7
Percent of total clearance†	36	3 ± 4	3 ± 3	—
Peak time (renal ROI)	36	17 ± 26	20 ± 26	—
Half time (renal ROI)	36	29 ± 48	15 ± 16	—
Peak time (cortical ROI)	23	15 ± 24	18 ± 23	—
Half time (cortical ROI)	23	23 ± 16	49 ± 63	—

*The data indicate the percent change (mean ± s.d.) between individual first studies and the average of all first studies for intersubject variability, and from the first to the second study for intrasubject variability.
†Differences between intrasubject and intersubject variability for these results are statistically significant when $p < 0.05$.

cretion (*9*). There were no differences in any of the parameters between the sexes or between the left and right kidneys. The normal range for differences in clearance and percent of function in each kidney in serial studies was approximately one-half the normal range for single studies. This finding is important since a large percentage of ^{99m}Tc-MAG3 renal studies are serial studies in patients with chronic conditions. It also suggests that at least one-half the normal range for single studies is due to intersubject variability, and the remainder is secondary to the error of the method.

Quantification of renal clearance with radiopharmaceuticals has been performed in many different ways ranging from a totally visual method to methods requiring collection of one or more blood and/or urine samples (*10–12*). In the present study a camera-based method without blood or urine sampling was chosen because it does not require bench top chemistry skills and can be more easily instituted in most hospitals (*12*). However, some reduction in accuracy occurs as a result of the increased convenience (*11,13,14*).

We elected to express renal clearance in terms of the percent dose cleared by the kidneys at 1–2 min rather than the traditional effective renal plasma flow (ERPF) in order

TABLE 5
Suggested and (Actual) Key Normal Limits*

Parameter	Left	Right	Total
Single study			
Clearance: 21–40 yr (% dose)	—	—	10–33
	—	—	(10.3–32.7)
Clearance: 41–60 yr (% dose)	—	—	9–30
	—	—	(9.2–29.6)
Clearance: 61–80 yr (% dose)	—	—	8–25
	—	—	(8.5–24.1)
Percent clearance (%)	42–58	42–58	—
	(41.6–57.2)	(42.8–58.4)	—
Single or serial studies			
Cortical peak time (min)	≤4	≤4	—
	(2.1–2.9)	(1.7–3.3)	—
Cortical half time (min)	≤10	≤10	—
	(2.0–8.0)	(1.5–9.5)	—
Serial studies			
Clearance change (%)	—	—	≤25
	—	—	(0–25)
Percent clearance change (%)	≤10	≤10	—
	(0–11)	(0–9)	—

*The data represent the mean ± 2 s.d.s. The percent change for serial studies is in relative, not absolute, percentage terms.

to maximize simplicity and to minimize overall error. ERPF determinations that do not involve para-aminohippurate and blood or urine samples depend on a regression equation to convert the data to ERPF. However, the regression equation never fully accounts for all the factors that affect the percent uptake measurement. In addition, each time a new renal radiopharmaceutical is introduced, it is difficult to repeat the comparison between the percent uptake and a reference standard, such as para-aminohippurate, with blood sampling (*15,16*). It is simpler to determine a new normal range for percent of dose in the kidneys at 1–2 min in normal subjects for the new radiopharmaceutical. Also, conversion of percent uptake to ERPF assumes a constant extraction efficiency for the radiopharmaceutical in normals and in various disease conditions, an assumption that is probably not valid (*15,17*). Others have also elected to simplify the clearance measurement by using percent dose in the kidneys at 1–2 min (*18*).

The percent of total function in the left and right kidneys is particularly amenable to measurement by imaging techniques because many factors that are otherwise difficult to accurately account for, such as kidney depth, blood volume and infiltration of part of the injected dose, essentially cancel out. This favorable situation is reflected in the relatively low percent s.d. for single measurements of percent kidney function, 8% for either side.

The transit time through the renal parenchyma may be measured in several ways. The time of peak activity will correspond closely to the leading edge parenchymal transit time since the initial blood radioactivity level, and, therefore, initial radioactive filtrate will have the highest levels of radioactivity. When this initial filtrate leaves the parenchyma to enter the larger collecting system, parenchymal activity will peak and drop. The half time from the time of peak activity will be an estimate of washout of activity from the parenchyma or mean parenchymal time. Both of these transit times will be more accurately measured by ROIs that exclude the calyces and renal pelves since there is a relatively large amount of variation in collecting system size, both between subjects and between kidneys in the same individual. Our results support this contention and we suggest that the spatial resolution of gamma cameras has reached the point at which cortical ROIs should replace whole kidney ROIs.

Serial renal studies are performed in a relatively large number of patients including those with renal transplants and para- or quadraplegia. In this situation it is important to know the normal limits for change in serial measurements in the same patient rather than single measurements because the range is likely to be less, increasing the sensitivity of the test. Our results indicate that the percent standard deviation for serial studies of clearance and percent of function in each kidney were approximately one half of the percent s.d. for single studies. However, there was no consistent decrease in the percent s.d. for transit time measurements. This difference may reflect the fact that transit time measurements depend on relative change in counts over time rather than on absolute count measurements and are, therefore, relatively insensitive to variation in attenuation and background subtraction in single studies as well as serial studies.

There are several limitations to the present study. First, computer software algorithms for renal studies vary somewhat from one manufacturer and computer model to another. Consequently, the normal ranges presented here will not necessarily exactly apply to other institutions. However, large variations are probably unlikely. Although not practical, each institution would ideally determine its own normal ranges. Second, the serial studies were performed only a few days apart. There may be more intrasubject variation when studies are performed weeks, months or years apart as is often the case clinically. Third, our particular renal software placed some limitations on the temporal resolution of our studies. This may have had a small effect on the exact transit times, but not on the relative results. Fourth, an improved method for estimating kidney depth has recently been developed that was not used in our study (*19*). In addition, the commercial formulation of ^{99m}Tc-MAG3 sold in Europe differs somewhat from that sold in the United States, and, therefore, our results may not be directly applicable to the European formulation (*2*).

CONCLUSION

We conclude that renal clearance decreases significantly with increasing age and cortical ROIs are preferable to renal ROIs for transit time measurements. In the case of renal clearance and percent of function in each kidney, the normal range for serial measurements is approximately half that of single studies.

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