Evaluation of Renal Function: A Comparison Between Camera-Based Tc-99m MAG3 and 24-Hour Creatinine Clearances

Fabio P Esteves, MD: Department of Radiology, Division of Nuclear Medicine, Emory University Hospital, Atlanta, GA
Raghuveer K Halkar, MD: Department of Radiology, Division of Nuclear Medicine, Emory University School of Medicine and Veterans Affairs Medical Center, Atlanta, GA
Muta M. Issa, MD, MBA: Department of Urology, Emory University School of Medicine and Veterans Affairs Medical Center, Atlanta, GA
Sandra Grant, CNMT: Nuclear Medicine Service, Veterans Affairs Medical Center, Atlanta, GA
Andrew Taylor, MD: Department of Radiology, Division of Nuclear Medicine, Emory University School of Medicine and Veterans Affairs Medical Center, Atlanta, GA

Department of Radiology, Division of Nuclear Medicine, Emory University School of Medicine and Veterans Affairs Medical Center, Atlanta, GA

Emory University Hospital
Department of Radiology, Division of Nuclear Medicine
1364 Clifton Road N.E.
Atlanta, GA  30322

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Corresponding Author: Andrew Taylor, M.D.
Emory University Hospital
Department of Radiology, Division of Nuclear Medicine
1364 Clifton Road N.E.
Atlanta, GA  30322
Phone: 404-727-4852
Fax: 404-327-6685
E-mail: ataylor@emory.edu

Major Paper
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ABSTRACT

OBJECTIVE: The 24-hour creatinine clearance is the standard clinical technique to measure renal function; however, this measurement is cumbersome and inconvenient for patients. We hypothesized that a camera-based Tc-99m mercaptoacetyltriglycine (MAG3) clearance obtained simultaneously with a standard MAG3 scan would correlate well with the 24-hour creatinine clearance and could serve as a simple marker of renal function.

MATERIALS AND METHODS: Data were obtained from a retrospective analysis of 28 patients with varying degrees of renal dysfunction and 85 subjects evaluated for kidney donation. The MAG3 clearance was calculated using a camera-based technique without blood or urine sampling. The creatinine clearance was measured using the plasma creatinine and a 24-hour urine collection. The MAG3 and creatinine clearances were corrected for body surface area and values in normal subjects and patients were compared using paired T-test analysis. The linear association between the MAG3 and creatinine clearances was expressed by Pearson’s correlation coefficient.

RESULTS: The mean MAG3 clearance in the potential renal donors was 321 ± 95 ml/min (95% C.I. 171-546 ml/min), significantly higher than the mean creatinine clearance of 152 ± 51 ml/min (95% C.I. 79-278 ml/min, p<0.001). The mean MAG3 clearance in patients was 153 ± 70 ml/min (95% C.I. 32-316 ml/min) and was also significantly higher than the mean creatinine clearance of 74 ± 36 ml/min (95% C.I. 21-138 ml/min, p<0.001). The ratio of the mean creatinine clearance to the mean MAG3 clearance was essentially the same for volunteers and patients, 0.47 and 0.48,
respectively. The Pearson’s correlation between the MAG3 and creatinine clearances was 0.80 (95% C.I. 0.72-0.86).

CONCLUSION: The camera-based Tc-99m MAG3 clearance correlates well with the 24-hour creatinine clearance and can provide a simple and convenient index of renal function.

Key Words: renal scan, renal function, MAG3 clearance, creatinine clearance
INTRODUCTION

Measurement of renal function can provide crucial data to assist in scan interpretation and clinical management decisions. The serum creatinine is often used in clinical practice as an index of renal function but abnormal values may not be present until the glomerular filtration rate (GFR) has decreased by 50-80% [1]. Because of the limitations associated with the serum creatinine, the 24-hour creatinine clearance is still the standard clinical technique to measure GFR but even this measurement is far from ideal. A 24-hour urine collection is an inconvenient outpatient measurement that restricts mobility, mandates two trips to the hospital/clinic, and requires urine collection, storage and transport. Most important for both outpatients and inpatients, the creatinine clearance measurement will not be accurate if the urine collection is incomplete. Even if the urine collection is complete, the clearance measurement can be affected by muscle mass and diet. Creatine from ingested meat is converted to creatinine and can account for as much as 30% of total creatinine excretion [2]. Creatinine is not only excreted by glomerular filtration but it is also secreted by the renal tubule. The secretion of creatinine varies substantially both in the same individuals over time and between different individuals [3,4]. In addition, the proportion of total renal creatinine excretion due to tubular secretion increases with decreasing renal function [5]. This is particularly problematic in the follow-up of patients with a significant degree of renal dysfunction because the glomerular filtration rate can fall more rapidly than indicated by either serum creatinine or creatinine clearance.

Tc-99m mercaptoacetyltraglycine (MAG3) was introduced in 1986 as a replacement for iodine-131 hippuran (OIH) [6,7] and is currently used for 60-70% of the renal scans
performed annually in the United States [8]. The clearance of Tc-99m MAG3 is highly correlated with the clearance of OIH and is used as an index of effective renal plasma flow (ERPF) [9]. Plasma sample techniques for the measurement of the MAG3 clearance have been recently reviewed [10]; however, the need for a high degree of technical competence to perform plasma-based clearances has led to the development of camera-based techniques that do not require plasma or urine samples [11-14]. The camera-based MAG3 clearance can be generated at the time of a routine MAG3 renal scan on many commercial camera/computer systems. Although MAG3 is primarily eliminated by renal tubular secretion, we hypothesized that tubular secretion and GFR would provide comparable estimates of overall renal function and that there would be a good correlation between the Tc-99m MAG3 and 24-hour creatinine clearances.
MATERIALS AND METHODS

Subjects

Review of patient records was approved by the Institutional Review Board. The study population initially consisted of 89 subjects being evaluated for kidney donation at Emory University Hospital between August, 1998 and March, 2001. Preoperative evaluation included clinical laboratory studies of blood and urine samples, creatinine clearance, magnetic resonance renal arteriography, and MAG3 renal scan. These studies were performed within a week of each other. Twenty-four patients with varying degrees of renal dysfunction from the Veterans Affairs Medical Center in Atlanta studied between May, 1998 and February, 2000, had a creatinine clearance measured within 24 hours of the MAG3 renal scan and were included in the data base. Finally, a reviewer requested additional patients with impaired renal function. Consequently, a retrospective chart review was performed of all the MAG3 studies performed at Emory Hospital from July 2003 to January 2005. Five patients with an abnormal 24-hour creatinine clearance measured within one week of the MAG3 renal study were identified and included in the study.

Infiltration was calculated by drawing a region of interest (ROI) over the injection site at the conclusion of the study. Counts in the injection site ROI were corrected for decay and divided by dose injected to obtain a conservative estimate of the infiltrated dose. Five subjects were excluded because of dose infiltration exceeding 1%. The remaining 113 subjects comprised the study group (85 normal subjects and 28 patients). The range of
the creatinine clearance for the normal subjects and patients was 71-309 and 19-139 mL/min/1.73m², respectively. For the MAG3 clearance, the range for the normal subjects and patients was 155-635 and 29-334 mL/min/1.73m², respectively.

**Procedure**

Each study was performed with 1-11 mCi (37-407 MBq) of Tc-99m MAG3 (Mallinckrodt Medical, St. Louis, MO). The patients at Veterans Affairs Medical Center received 1-2 mCi, whereas the potential renal donors and patients at Emory University Hospital received 7-11 mCi of Tc-99m MAG3. Radiochemical purity was 95.0 ± 2.2 (Sep-Pak Cartridge - Millipore, Milford, MA). The data were processed and the camera based MAG3 clearance was calculated using the QuantEM™ software, which was developed specifically for Tc-99m MAG3 scans. The technique was similar to the camera based technique described to calculate GFR [15]. Briefly, the percent of the injected dose of MAG3 accumulated by the kidneys between 1-2.5 (VA subjects) or 2-3 minutes (Emory subjects) post-injection was converted to a MAG3 clearance by the use of a regression equation [11,12]. To determine the percent injected dose in the kidney at a specific time interval, the dose injected was counted on the camera. If 7-11 mCi were to be administered, a 1-2 mCi dose was counted on the camera to avoid deadtime losses and the 1-2 mCi dose and the dose to be injected were counted in a dose calibrator; the ratio of counts in the dose calibrator was used to convert the 1-2 mCi dose counted on the camera to the counts injected. A region of interest was placed over the whole kidney and time zero was defined as the time the bolus reached the kidney. Counts in the kidney were determined at 1-2.5 or 2-3 minute intervals and corrected for background and
attenuation using an attenuation coefficient of 0.123 [11,12]. The kidney counts were
divided by the counts injected to obtain a percent dose in the kidney at 1-2.5 or 2-3 min
post-injection. This percent dose in the kidney was then converted to a MAG3 clearance
using regression equations derived from a multicenter study that related the percent
injected dose in the kidney at 1-2.5 or 2-3 minutes to a multiple plasma sample MAG3
clearance[12].

The creatinine clearance was determined from a 24-hour urine creatinine with the serum
creatinine collected at the end of the 24-hour urine collection. Each clearance
measurement was corrected for body surface area (BSA) using the following equation:
\[ \text{BSA}(m^2) = (\text{weight in kg}^{0.425})(\text{height in cm}^{0.725})(71.84)/10,000 \] [16]. The clearances were
corrected for BSA because the magnitude of the GFR, ERPF and MAG3 clearances
correlates with BSA; larger individuals have higher clearances and smaller individuals
have lower clearances [17]. The BSA correction adjusts for the effect of size on the
absolute clearance measurement and reduces variability; BSA-corrected clearances
standardized to 1.73m² provide a better comparison to standard normal values.

For statistical analysis, Pearson’s correlation coefficient was used to express the
linear association between the BSA-corrected MAG3 and creatinine clearances. The
linear relationship between the MAG3 and creatinine clearances was determined by
regression analysis with the MAG3 clearance as the independent variable and the
creatnine clearance as the dependent variable. Student’s t-test was used to compare
clearance results between the MAG3 and creatinine clearances. A p value ≤ 0.05 was considered to be significant.
RESULTS

The 85 potential renal donors were 41% male, had a mean age of 41 ± 11 years, a mean BSA of 1.90 ± 0.24 m$^2$ and a mean creatinine clearance of 152 ± 51 ml/min/1.73m$^2$ (95% C.I. 79-278 ml/min), which was significantly less than the mean camera-based MAG3 clearance of 321 ± 95 ml/min/1.73m$^2$ (95% C.I. 171-546 ml/min, p<0.001). Twenty-seven out of 28 patients were men with a mean age of 66 ± 8.6 years, a mean BSA of 2.03 ± 0.25 m$^2$, and a mean creatinine clearance of 74 ± 36 ml/min/1.73m$^2$ (95% C.I. 21-138 ml/min), which was also significantly less than the mean MAG3 clearance of 153 ± 70 ml/min/1.73m$^2$ (95% C.I. 32-316 ml/min, p<0.001).

The MAG3 and creatinine clearances (Figure 1) were highly correlated (r=0.80, p<0.001). Linear regression was used to derive the following equation: Creatinine clearance (ml/min/1.73m$^2$) = 20 + .407 x (MAG3 clearance in ml/min/1.73m$^2$). The standard error of measurement for the intercept (20 ml/min/1.73m$^2$) was 8.75 ml/min/1.73m$^2$. The 95% confidence interval for the intercept ranged from 2.2 to 36.8 ml/min/1.73m$^2$ and the intercept was greater than zero (p=0.03).
DISCUSSION

Tc-99m MAG3 is a radiotracer with a rate of urinary excretion essentially equivalent to iodine-131 orthoiodohippurate (OIH) [6-9]. Compared to I-131 OIH, MAG3 has the advantages of lower radiation exposure to the patient and better imaging characteristics because of the 140 keV photon of Tc-99m. The renal clearance of MAG3 is substantially higher than the renal clearance of Tc-99m DTPA (diethyltriaminepentaacetic acid) and MAG3 has become the radiopharmaceutical of choice for renal scans in many clinical contexts, particularly in patients with suspected obstruction and patients with impaired renal function [8, 10, 18]. Measurement of the MAG3 clearance at the time of the scan adds important functional information to help direct patient management and detect an early loss in renal function when the images and the renogram curves may still appear normal [8]. A camera-based MAG3 clearance can be obtained at the time of the scan without blood or urine sampling and the camera based measurement correlates well with the more complex methods involving plasma sampling [11-14].

The line of regression (Fig. 1) comparing the camera-based MAG3 and creatinine clearances has an intercept of 20 ml/min/1.73m² with a 95% confidence interval of 2.2 – 36.8 ml/min/1.73m². If the MAG3 and creatinine clearances provided a perfectly equivalent measurement of renal function, then a MAG3 clearance of zero would correspond to a creatinine clearance of zero. In fact, the intercept (Fig 1) was slightly greater than zero, p = 0.03. There are several possible explanations for the observation that the intercept was slightly greater than zero: (1) The MAG3 and creatinine clearances may not be perfectly correlated. (2) The camera-based MAG3 clearance is not a perfect
measure of the MAG3 clearance; principal sources of error of the camera-based
technique include corrections for attenuation and background subtraction. (3) There were
not enough patients with very poor renal function. (4) Finally, and perhaps most
importantly, the creatinine clearance is not a perfect measure of GFR. Although GFR can
be estimated from the Cockcroft-Gault [18] and MDRD [19] formulas, these estimates
may deviate substantially from the true GFR in patients with fluid overload, hepatic
insufficiency, and azotemia. GFR can be measured using I-125 iothalamate but this is a
tedious and time consuming technique and is far too labor intensive to be used in a
general radiology practice [10]. At our institution, the standard to measure of GFR in
potential renal donors is the creatinine clearance. Using the creatinine clearance to
measure GFR is not as much of a problem in patients with normal renal function but the
creatinine clearance overestimates GFR in patients with poor function due to secretion of
creatinine by the tubules [3,4]; tubular secretion may explain the fact that the line of
identity did not run through zero. Conceivably, the MAG3 clearance may correlate
better with an inulin or I-125 iothalamate clearance than with a creatinine clearance.

Tc-99m MAG3 is excreted primarily via proximal tubular secretion; consequently, its
clearance is a measurement of tubular cell function and is not a measure of GFR [9]. For
this reason, the regression equation should not be used to calculate the creatinine
clearance from the MAG3 clearance; nevertheless, the regression equation does show
that, on average, the creatinine clearance is about 40% of the MAG3 clearance. If a loss
in renal function results in a proportional loss in GFR and tubular function, then either
measurement will serve as an acceptable index of renal function. Our study suggests that
despite being handled differently by the kidneys, the BSA-corrected MAG3 and creatinine clearances are highly correlated (Pearson’s correlation=0.80). Consequently, in normal patients and those with chronic renal impairment, either measurement can serve as an index of renal function. This argument is further supported by the fact that the standard deviation of the MAG3 and creatinine clearances (expressed as percent of the mean) in normal subjects was 30% for MAG3 and 34% for the creatinine clearance, suggesting that the two measurements are similar for defining normality. Finally, preliminary data suggest that the camera-based MAG3 clearance is more reproducible than creatinine clearance in patients with stable renal disease [21].

In summary, the camera-based MAG3 clearance avoids the cumbersome nature, inconvenience and incomplete urine collections associated with a 24-hour creatinine clearance and can easily be obtained at the time of a MAG3 renal scan. The camera-based MAG3 clearance is highly correlated with the creatinine clearance and provides a simple, safe and convenient test of renal function.
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REFERENCES


FIGURE LEGENDS

**Fig. 1.** Scatter plot showing the correlation between the camera-based MAG3 and creatinine clearances (mL/min/1.73m²). The Pearson’s correlation is 0.80.
Fig. 1