Head to Head Comparison of 99mTc(CO)3(NTA) and 99mTc-MAG3 in Patients with Suspected Obstruction

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Abstract

Purpose $^{99mTc}$-tricarbonyl-nitrilotriacetic acid, $^{99mTc}$(CO)$_3$(NTA), is a new $^{99mTc}$-renal radiopharmaceutical with a clearance equal to that of $^{131I}$-ortho-iodohippuran. Our purpose was to compare the performance of $^{99mTc}$(CO)$_3$(NTA) and $^{99mTc}$-MAG3 in patients with suspected obstruction.

Methods $^{99mTc}$(CO)$_3$(NTA) was prepared with commercially available NTA and CRS Isolink kit, and isolated by HPLC. Eighteen adult patients referred for diuretic renography received an intravenous injection of approximately 40 mg of furosemide 15 min prior to either $^{99mTc}$(CO)$_3$(NTA) or $^{99mTc}$-MAG3 (mean activity of 47 ± 4.4 MBq). Data were acquired for 24 minutes followed by an anterior image of the liver and gall bladder and a measure of voided volume. Patients received a second furosemide injection equal to one third of the original dose followed fifteen minutes later by administration of the alternate tracer, mean activity of 320 ± 34 MBq. Clearances were measured using a camera-based technique.

Results The clearance of $^{99mTc}$(CO)$_3$(NTA) was greater than that of $^{99mTc}$-MAG3, 331 ± 146 vs 271 ± 105 mL/min/1.73 m$^2$, respectively, $p < 0.0001$. The kidney to background ratio for $^{99mTc}$(CO)$_3$(NTA) was greater than that of $^{99mTc}$-MAG3 for both left and right kidneys, $p < 0.001$; the 20 min/maximum count ratio was significantly less, $p < 0.0001$. There was no significant difference in the voiding volumes following $^{99mTc}$(CO)$_3$(NTA) and $^{99mTc}$-MAG3 administration, 598 ± 237 mL vs 498 ± 170 mL, respectively, $p = 0.07$. Gall bladder activity was not observed with $^{99mTc}$(CO)$_3$(NTA) but was present in 6/17 $^{99mTc}$-MAG3 studies. Images and renogram curves were comparable except for two patients where the $^{99mTc}$(CO)$_3$(NTA) study excluded obstruction but the $^{99mTc}$-MAG3 study suggested an indeterminate or obstructed kidney.

Conclusions Unlike $^{99mTc}$-MAG3, $^{99mTc}$(CO)$_3$(NTA) is not eliminated via the hepatobiliary track. Moreover, $^{99mTc}$(CO)$_3$(NTA) has a higher kidney to background ratio and more rapid clearance than $^{99mTc}$-MAG3. These advantages should allow more robust camera-based clearance measurements and may lead to better discrimination between obstructed and non-obstructed kidneys.

Introduction

Adult and pediatric consensus groups consider $^{99mTc}$-mercaptoacetyltriglycine ($^{99mTc}$-MAG3) to be superior to $^{99mTc}$-diethylenetriaminepentaacetic acid ($^{99mTc}$-DTPA) for diuresis renography [1–5]. $^{99mTc}$-MAG3 has a much higher extraction efficiency than $^{99mTc}$-DTPA; consequently, less $^{99mTc}$-MAG3 remains in circulation during the washout period and less is entering the kidney at the time washout is evaluated [6, 7].

$^{99mTc}$-tricarbonyl-nitrilotriacetic acid, $^{99mTc}$(CO)$_3$(NTA), is a new tubular tracer with a clearance equal to that of $^{131I}$-orthoiodohippuran ($^{131I}$-OIH); in contrast, the clearance of $^{99mTc}$-MAG3 is only 50–60% that of
Moreover, a small percentage of the injected dose of $^{99m}$Tc-MAG3 is eliminated via the hepatobiliary pathway and that percentage increases as renal function deteriorates [6–11]. Activity in the gall bladder has been mistaken for renal activity and gut activity arriving via the hepatobiliary pathway may be interpreted as a urine leak [12–13]. $^{99m}$Tc(CO)$_3$(NTA), in contrast, has shown no hepatobiliary elimination [8, 9].

Because $^{99m}$Tc(CO)$_3$(NTA) is cleared more rapidly than $^{99m}$Tc-MAG3 and lacks hepatobiliary elimination, we hypothesized that $^{99m}$Tc(CO)$_3$(NTA) might be superior to $^{99m}$Tc-MAG3 in patients with suspected obstruction for the same reasons that $^{99m}$Tc-MAG3 is superior to $^{99m}$Tc-DTPA. The objective of this investigation was a direct comparison of $^{99m}$Tc(CO)$_3$(NTA) and $^{99m}$Tc-MAG3 in this clinically relevant patient population.

**Materials And Methods**

**Radiosynthesis of $^{99m}$Tc(CO)$_3$(NTA)**

Nitrilotriacetic acid (NTA) was purchased from Aldrich and labeled as previously described [14]. $^{99m}$Tc-pertechnetate ($^{99m}$TcO$_4^-$) in 0.9% saline was received from Triad Isotopes (Norcross, GA, USA). The “CRS Isolink kit” (Center for Radiopharmaceutical Science, Paul Scherrer Institute, Villigen, Switzerland) was used to prepare the $[^{99m}$Tc(CO)$_3$(H$_2$O)$_3$]$^+$ precursor according to the manufacturer’s insert. $^{99m}$Tc(CO)$_3$(NTA) was separated from unlabeled ligand by high-performance liquid chromatography (HPLC) instrument (System Gold Nouveau, Beckman Coulter, Brea, CA) equipped with a model 170 radiometric detector and a model 166 ultraviolet light-visible light detector, 32 Karat chromatography software (Beckman Coulter), and an octyldecyl silane column (C18 RP Ultrasphere; 5-µm, 4.6 x 250 mm; Beckman Coulter). The solvent system was 0.05 M TEAP buffer pH 2.5 (solvent A) and ethanol (solvent B) and the flow rate was 1 mL/min; the radiochemical purity was > 99%. The gradient method was the same as reported previously [15].

Ethanol was partially removed by N$_2$ gas, and the collected solution of $^{99m}$Tc(CO)$_3$(NTA) was buffered in a physiological phosphate buffer (PBS) at pH 7.4. The HPLC-purified complex in PBS (pH 7.4) was passed through a sterile Millex-GS 22 µm filter (Millipore Co., St Louis, MO) (primed with 4 mL of saline) into a sterile, pyrogen-free empty vial. The final concentration was 74–148 MBq/mL (2–4 mCi/mL) and the final pH was 7.4. Test samples were sent for analysis and determined to be sterile and pyrogen free.

**Patient Studies**

An eIND was obtained from the FDA and all studies were performed with the approval of the Radiation Safety Committee for Human Use of Radiation (RSC1) and the Institutional Review Board. Signed consent was obtained from each participant. Adult patients referred by urologists for diuretic renography were asked to participate. Nineteen subjects entered the protocol but one withdrew after signing the
consent due to lack of adequate venous access. Each of the remaining 18 subjects (mean age 51.3 ± 16.8 years, 11 females, 7 males) was monitored with measurements of blood pressure, heart rate, and temperature obtained before and after the study; they were under constant observation during the study and were further monitored via a follow-up phone call 24 hours later. Each patient drank 200 mL of water on arrival; an intravenous line was connected to a one-liter bag of normal saline for fluid replacement during the diuretic portion of the study.

Both studies were performed on the same day using a protocol similar to that of a two-stage ACE inhibition study [16]; a low activity acquisition was followed by a high activity acquisition to minimize the effect of residual activity on calculations derived from the second acquisition. Our intention was to alternate the order of $^{99m}\text{Tc}(	ext{CO})_3(\text{NTA})$ and $^{99m}\text{Tc-MAG3}$ administration but the HPLC preparation of $^{99m}\text{Tc}(	ext{CO})_3(\text{NTA})$ rarely yielded enough activity to allow $^{99m}\text{Tc}(	ext{CO})_3(\text{NTA})$ to be administered as the second administration; consequently, $^{99m}\text{Tc}(	ext{CO})_3(\text{NTA})$ was the first tracer administered in 16/18 subjects. The mean activity of the initial tracer was 47 ± 4.4 MBq. The majority of patients received an intravenous injection of 40 mg of furosemide 15 min prior to the administration of first tracer and 14 mg of furosemide prior to administration of the second tracer to maintain a comparable serum concentration of the diuretic [17]. Exceptions were patients 10 (60mg and 30 mg), patient 16 (30 mg and 10 mg) and patient 17 (80 mg and 27 mg).

Imaging was performed for 24 minutes following tracer injection using a General Electric Infinia camera (Milwaukee, WI) with a 20% window centered over the 140 keV photopeak of $^{99m}\text{Tc}$. Data were acquired in a 128 x 128 matrix by using a three-phase dynamic acquisition and processed on a General Electric Xeleris computer using non-commercial, in house update of the QuantEM™ renal software. Kidney regions of interest were automatically assigned and could be modified by the operator; background was automatically assigned as a peri-renal region of interest 2 pixels wide and one pixel outside of the renal ROI [18].

The acquisition was followed by an anterior image of the liver and gall bladder, and a measurement of voided volume. Patients drank an additional 200 mL of water before receiving the second injection of furosemide. Fifteen minutes following furosemide, the alternate tracer was administered, mean activity of 320 ± 34 MBq, and the same acquisition protocol was utilized. Intravenous hydration was continued throughout both acquisitions. Renogram curves were generated using whole kidney regions of interest (ROIs). Clearances were measured using a camera-based technique and the kidney to background ratios were calculated from the same summed frames (1-2.5 minutes after injection) used to calculate relative uptake and the camera-based clearance [19].

Two subjects had only one kidney. Six of 18 subjects had to void prior to completing the first 24 minute acquisition; all of these patients received $^{99m}\text{Tc}(	ext{CO})_3(\text{NTA})$. Two patients had to void prior to completing the second acquisition, one following $^{99m}\text{Tc-MAG3}$ and one following $^{99m}\text{Tc}(	ext{CO})_3(\text{NTA})$, and two studies
demonstrated marked $^{99m}$Tc(CO)$_3$(NTA) tracer infiltration at the injection site. Comparisons impacted by dose infiltration or incomplete 24 minute acquisitions were not included in the data analysis.

The camera-based clearance method in this study utilized a regression equation developed for $^{99m}$Tc-MAG3 that converts the percent injected dose in the kidney at 1-2.5 minutes post injection to a clearance expressed in mL/min/1.73m$^2$ [19]. To test the applicability of this regression equation for $^{99m}$Tc(CO)$_3$(NTA), we used the $^{99m}$Tc-MAG3 regression equation to calculate the camera-based clearance of $^{99m}$Tc(CO)$_3$(NTA) from two previous studies in which the $^{99m}$Tc(CO)$_3$(NTA) clearance was calculated determined using the single-injection, 2-compartment model of Sapirstein et al. [8, 9, 20]. These two studies contained 17 subjects, 9 volunteers with normal renal function and 8 with a diagnosis of chronic kidney disease [8, 9].

**STATISTICAL ANALYSIS**

All results were expressed as the mean ± SD. To determine the statistical significance of differences between the 2 groups, comparisons were made with the 2-tailed Student $t$ test for paired data; $P < 0.05$ was considered statistically significant. The concordance correlation coefficient was used to compare the camera-based and plasma based $^{99m}$Tc(CO)$_3$(NTA) clearances [21].

**Results**

The serum creatinine was not available for two patients; the mean serum creatinine for the remaining 16 subjects was 1.17 ± 0.59 mg/dL with 4 subjects having reduced renal function (serum creatinine > 1.3 mg/dL) (Table 1). The clearance of $^{99m}$Tc(CO)$_3$(NTA) was significantly greater than the clearance of $^{99m}$Tc-MAG3, 331 ± 146 vs 271 ± 105 mL/min/1.73 m$^2$, respectively, $p < 0.0001$ (Table 1). In every kidney but one, the kidney to background ratio was greater for $^{99m}$Tc(CO)$_3$(NTA) than $^{99m}$Tc-MAG3, mean of 6.2 vs 5.2 for the left kidney and 5.1 vs 4.0 for the right kidney, respectively, $p < 0.001$ (Table 2). Relative uptake was equivalent for the two tracers; the mean percent uptake (± SD) of $^{99m}$Tc(CO)$_3$(NTA) in the left kidney was 56.6 ± 17.6% compared to 56.4 ± 17.9% for $^{99m}$Tc-MAG3, $p = 0.75$ (Table 1). Hydration was also comparable; there was no significant difference in the voiding volumes following the $^{99m}$Tc(CO)$_3$(NTA) and $^{99m}$Tc-MAG3 acquisitions, 598 ± 237 mL vs 498 ± 170 mL, respectively, $p = 0.07$ (Table 1). In 2/18 patients, anterior images of the gall bladder 30 minutes after tracer injection failed to be obtained. In the remaining 16 patients, gallbladder activity was present in 6/16 $^{99m}$Tc-MAG3 studies; no gallbladder activity was observed following $^{99m}$Tc(CO)$_3$(NTA) administration (Fig. 1).
TABLE 1: Dose injected (MBq) of $^{99m}$Tc-(CO)3(NTA) and $^{99m}$Tc-MAG3, serum creatinine, voided volume, percent uptake and the camera based clearance.

| Subject | Dose Injected (MBq) | Creatinine (mg/dL) | Voided volume (mL) | Left Kidney (%) | Right Kidney (%) | Clearance (mL/min/1.73m²) |
|---------|---------------------|--------------------|-------------------|-----------------|-----------------|---------------------|
|         | NTA | MAG3 | NTA | MAG3 | NTA | MAG3 | NTA | MAG3 | NTA | MAG3 | NTA | MAG3 |
| 1       | 44.8 | 345.2 | 0.49 | *   | 52  | 53  | 48  | 47  | 526 | 368 |
| 2       | 312.3 | 44.4 | 0.98 | 360 | 350 | 80  | 82  | 20  | 18  | 123 | 72  |
| 3       | 46.2 | 337.8 | 0.5  | 1000 | 600 | 48  | 47  | 52  | 53  | 468 | 323 |
| 4       | 46.2 | 320.1 | NA  | 800 | 850 | NA  | NA  | 100 | 100 | 380 | 276 |
| 5       | 234.2 | 46.2 | 1.08 | 600 | 600 | 25  | 26  | 75  | 74  | 252 | 252 |
| 6       | 39.6 | 321.9 | 0.74 | 850 | 700 | 79  | 75  | 21  | 25  | 438 | 378 |
| 7       | 48.1 | 345.2 | 0.9  | *   | *   | 52  | 49  | 48  | 51  | 396 | 306 |
| 8       | 51.1 | 312.3 | 1.93 | 320 | 400 | NA  | NA  | 100 | 100 | 85  | 85  |
| 9       | 54.4 | 315.2 | 0.7  | *   | *   | 49  | 47  | 51  | 53  | 341 | 295 |
| 10      | 52.2 | 358.9 | 1.9  | *   | *   | 88  | 90  | 12  | 10  | 226 | 191 |
| 11      | 47.7 | 321.5 | 1.27 | *   | *   | 77  | 79  | 23  | 21  | 340 | 313 |
| 12      | 54.4 | 319.7 | 0.79 | 800 | 380 | 50  | 50  | 50  | 50  | 513 | 389 |
| 13      | 55.2 | 302.3 | NA  | *   | *   | 58  | 50  | 42  | 50  | 259 | 238 |
| 14      | 53.6 | 388.7 | 1.24 | 500 | 550 | 28  | 29  | 72  | 71  | 150 | 149 |
| 15      | 57.0 | 346.3 | 0.78 | 450 | 350 | 48  | 48  | 52  | 54  | 456 | 378 |
| 16      | 58.1 | 388.5 | 2.44 | 360 | 350 | 51  | 55  | 49  | 44  | 226 | 233 |
| 17      | 58.8 | 357.1 | 2.61 | 360 | 300 | 64  | 63  | 56  | 57  | 218 | 188 |
| 18      | 53.3 | 359.3 | 1.01 | 780 | 550 | 57  | 60  | 43  | 40  | 566 | 441 |

Mean: NC NC 1.17 588 498 56.6 56.4 48.7 48.9 331 271
SD: 0.59 0.59 0.75 0.75 0.75 0.0002

* Voiding volumes are not comparable since the patient voided prior to the completion of an acquisition
NA: Not available
NC: Not calculated since two NTA and two MAG3 patients received high and low amounts of tracer activity, respectively.
Patient 12 withdrew from the study prior to tracer injection.
TABLE 2: Kidney to background ratios of \(^{99m}\text{Tc(CO)\textsc{3}}\text{(NTA)}\) and \(^{99m}\text{Tc-MAG3}\)

| Subject | Left Kidney MAG3 | Left Kidney NTA | Right Kidney MAG3 | Right Kidney NTA |
|---------|------------------|-----------------|-------------------|-----------------|
| 1       | 7.7              | 9.5             | 5.6               | 7.6             |
| 2       | 2.0              | 3.1             | 0.4               | 0.8             |
| 3       | 7.0              | 9.2             | 6.2               | 7.6             |
| 4       | AK               | AK              | 10.1              | 14.3            |
| 5       | 3.0              | 3.7             | 4.0               | 5.0             |
| 6       | 4.1              | 6.6             | 1.8               | 2.4             |
| 7       | 7.2              | 8.2             | 6.7               | 7.2             |
| 8       | AK               | AK              | 2.6               | 3.3             |
| 9       | 5.2              | 5.9             | 4.7               | 5.3             |
| 10      | 5.0              | 5.3             | 0.9               | 1.4             |
| 11      | 6.2              | 6.2             | 1.7               | 2.2             |
| 13      | 7.9              | 10.3            | 6.0               | 8.1             |
| 14      | 2.5              | 2.9             | 2.2               | 2.3             |
| 15      | 1.7              | 2.1             | 3.1               | 3.9             |
| 16      | 7.7              | 8.8             | 6.0               | 7.3             |
| 17      | 2.8              | 3.0             | 2.1               | 2.6             |
| 18      | 5.1              | 6.0             | 2.8               | 3.0             |
| 19      | 8.2              | 8.5             | 5.4               | 7.3             |

Mean 5.2 5.2 4.0 5.1
SD 2.3 2.7 2.5 3.4
P= 0.0002 0.0003

AK: Absent kidney
Patient 12 withdrew from the study prior to tracer injection

For the left kidney, the mean time to peak activity was less for \(^{99m}\text{Tc(CO)\textsc{3}}\text{(NTA)}\) than \(^{99m}\text{Tc-MAG3}\), 2.6 ± 0.5 minutes vs 3.5 ± 1.4 minutes, respectively (P = 0.02). The mean time to peak activity did not attain significance for the right kidney, 4.0 ± 5.2 min vs 5.8 ± 5.6 min, respectively P = 0.07 (Table 3), but when the one kidney with time to peak activity greater than 20 minutes for both tracers was omitted, the mean time to peak for \(^{99m}\text{Tc(CO)\textsc{3}}\text{(NTA)}\) was less than that of \(^{99m}\text{Tc-MAG3}\), 2.7 ± 0.5 min vs 4.8 ± 3.7 min, respectively, P = 0.045.

The mean 20 minute to maximum count ratios for \(^{99m}\text{Tc(CO)\textsc{3}}\text{(NTA)}\) were lower than those of \(^{99m}\text{Tc-MAG3}\) for both the left and right kidneys, P = 0.02 and P = 0.003, respectively (Table 3). The mean postvoid/maximum count ratio, an important parameter for evaluating suspected obstruction, was significantly lower in the right kidney for \(^{99m}\text{Tc(CO)\textsc{3}}\text{(NTA)}\) than \(^{99m}\text{Tc-MAG3}\), P = 0.005, although no difference was noted in the left kidney, P = 0.20 [22] (Table 3). Images and curve parameters for the two tracers were comparable for the majority of studies; an example is illustrated in Fig. 2. In two patients, \(^{99m}\text{Tc-MAG3}\) studies may have been interpreted as indeterminate or representing renal obstruction whereas the \(^{99m}\text{Tc(CO)\textsc{3}}\text{(NTA)}\) studies excluded obstruction (Figs. 3 and 4) [4, 22]. One-year follow up of these two patients confirmed the absence of obstruction; no procedure was performed and a repeat
A 99mTc-MAG3 study at one year showed no change in renal function. Finally, there was very good agreement between the camera-based and plasma sample 99mTc(CO)3(NTA) clearances, \( r = 0.837 \), with a 95% confidence interval 0.608–0.937; the intercept (Table 4, Fig. 5).

### TABLE 3: Time to peak (min), 20 minute/maximum and postvoid/maximum count ratios for the right and left kidneys following administration of 99mTc(CO)3(NTA) and 99mTc-MAG3.

| Subject | Left Kidney TTP (min) | Right Kidney TTP (min) | Left Kidney 20min/max | Right Kidney 20min/max | Left Kidney PV/max | Right Kidney PV/max |
|---------|-----------------------|------------------------|------------------------|------------------------|-------------------|-------------------|
|         | NTA                  | MAG3                  | NTA                  | MAG3                  | NTA               | MAG3               |
| 1       | 2.6                  | 2.8                   | 2.8                  | 3.9                   | 0.12              | 0.17              |
| 2       | ID                   | ID                    | ID                   | ID                    | ID                | ID                |
| 3       | 2.5                  | 2.8                   | 2.5                  | 2.5                   | 0.14              | 0.21              |
| 4       | AK                   | AK                    | AK                   | AK                    | ID                | ID                |
| 5       | 3.7                  | 3.7                   | 3.2                  | 2.5                   | 0.51              | 0.52              |
| 6       | 3.2                  | 3.4                   | 2.1                  | 2.7                   | 0.18              | 0.23              |
| 7       | 2                    | 2.5                   | 2.6                  | 16                    | 0.08              | 0.17              |
| 8       | AK                   | AK                    | AK                   | AK                    | 0.58              | 0.88              |
| 9       | 2.4                  | 2.8                   | 2.3                  | 4.8                   | OT                | OT                |
| 10      | 2.1                  | 2.3                   | 3.2                  | 2.1                   | OT                | OT                |
| 11      | 2.2                  | 3.1                   | 2.6                  | 3                    | OT                | OT                |
| 12      | 2.2                  | 7.8                   | 2.4                  | 2.6                   | 0.54              | 0.79              |
| 13      | 3.2                  | 3.5                   | 2.5                  | 2.6                   | 0.59              | 0.64              |
| 14      | 3.2                  | 3.8                   | 3.5                  | 6.8                   | 0.6               | 0.67              |
| 15      | 3.2                  | 4.8                   | 2.5                  | 3.8                   | 0.2               | 0.15              |
| 16      | 2.5                  | 3.8                   | 3.5                  | 6.8                   | 0.6               | 0.67              |
| 17      | 2.7                  | 3.3                   | 2.1                  | 5.3                   | 0.29              | 0.46              |
| 18      | 1.9                  | 2.5                   | 2.6                  | 2.7                   | 0.2               | 0.15              |
| Mean    | 2.63                 | 3.53                  | 3.99                 | 5.84                  | 0.28              | 0.41              |
| SD      | 0.53                 | 1.35                  | 5.23                 | 5.55                  | 0.17              | 0.28              |
| P       | 0.0224               | 0.0677                | 0.020                | 0.003                 | 0.253            | 0.0048            |

AK: Absent kidney  
ID: Infiltrated dose  
NA: The postvoid image was not acquired and the ratio could not be calculated  
OT: Patient had to void before the study was completed  
Patient 12 withdrew from the study prior to tracer injection.
Rapid drainage of tracer from the kidney before or after a diuresis stimulated by furosemide administration excludes obstruction but evaluation of drainage can become challenging when there is substantial uptake of circulating tracer during the washout period. Tracers with a high extraction efficiency and rapid clearance allow a more straightforward evaluation of drainage; they minimize the amount of circulating tracer entering the kidney during the washout phase of the renogram. It is particularly important to minimize contamination of the washout curve in patients with underlying kidney disease since these patients typically have a slower than normal transit of the tracer through the kidney. We chose to study patients with suspected renal obstruction because that group provides a clinically relevant population to for the comparison of $^{99m}\text{Tc(CO)}_3$(NTA) and $^{99m}\text{Tc-MAG3}$.

Clearances were measured using a camera-based technique based on the cumulated renal activity 1–2.5 minutes after injection [18]. A higher clearance for $^{99m}\text{Tc(CO)}_3$(NTA) implies that the kidney has accumulated a higher percentage of the injected dose in the 1-2.5 minute interval than the injected dose of $^{99m}\text{Tc-MAG3}$. Optimally, a camera-based clearance regression equation for $^{99m}\text{Tc(CO)}_3$(NTA) would be

| Subject | Camera-based Clearance | Plasma Sample Clearance |
|---------|------------------------|-------------------------|
| 1       | 140                    | 185                     |
| 2       | 232                    | 215                     |
| 3       | 403                    | 295                     |
| 4       | 208                    | 159                     |
| 5       | 217                    | 200                     |
| 6       | 57                     | 84                      |
| 7       | 132                    | 144                     |
| 8       | 134                    | 134                     |
| 9       | 440                    | 363                     |
| 10      | 309                    | 300                     |
| 11      | 694                    | 473                     |
| 12      | 493                    | 466                     |
| 13      | 340                    | 433                     |
| 14      | 396                    | 562                     |
| 15      | 483                    | 651                     |
| 16      | 362                    | 371                     |
| 17      | 409                    | 492                     |

*Data are derived from subjects in references 8 and 9.

Discussion

Rapid drainage of tracer from the kidney before or after a diuresis stimulated by furosemide administration excludes obstruction but evaluation of drainage can become challenging when there is substantial uptake of circulating tracer during the washout period. Tracers with a high extraction efficiency and rapid clearance allow a more straightforward evaluation of drainage; they minimize the amount of circulating tracer entering the kidney during the washout phase of the renogram. It is particularly important to minimize contamination of the washout curve in patients with underlying kidney disease since these patients typically have a slower than normal transit of the tracer through the kidney. We chose to study patients with suspected renal obstruction because that group provides a clinically relevant population to for the comparison of $^{99m}\text{Tc(CO)}_3$(NTA) and $^{99m}\text{Tc-MAG3}$.
based on a large population comparing percent dose in the kidney at 1-2.5 minutes post injection with a multisample plasma clearance as was done for $^{99m}$Tc-MAG3; however, initial data from two earlier studies show that the regression equation developed for $^{99m}$Tc-MAG3 does provide a good measurement of the $^{99m}$Tc(CO)$_3$(NTA) clearance.

$^{99m}$Tc(CO)$_3$(NTA) was given first in 16/18 studies; consequently, any $^{99m}$Tc(CO)$_3$(NTA) activity remaining in the kidney when $^{99m}$Tc-MAG3 was administered would add to the renal activity measured at 1-2.5 minutes post injection and result in an overestimation of the $^{99m}$Tc-MAG3 clearance. This error was probably small since $^{99m}$Tc(CO)$_3$(NTA) is rapidly eliminated and a much more activity was administered for the $^{99m}$Tc-MAG3 injection but it may have biased our results toward an overestimation of the $^{99m}$Tc-MAG3 clearance. Despite this possibility, the $^{99m}$Tc(CO)$_3$(NTA) clearance was still significantly greater than that of $^{99m}$Tc-MAG3. In fact, the clearance of $^{99m}$Tc(CO)$_3$(NTA) is equal to that of $^{131}$I-OIH and will provide an equivalent measure of effective renal plasma flow [8, 9].

Background correction is of crucial importance for camera-based clearance methods since background counts may be relatively high during the first minutes of the study when camera-based clearances are calculated. For example, background counts during the 2nd to 3rd minutes following $^{99m}$Tc-DTPA administration are reported to reach 50–80% of the total non-corrected renal activity [23]. High background counts increase the difficulty of an accurate background correction and may compromise the accuracy of a camera-based clearance. $^{99m}$Tc(CO)$_3$(NTA) has a higher extraction efficiency than either $^{99m}$Tc-DTPA or $^{99m}$Tc-MAG3 and a higher kidney to background ratio; consequently, use of $^{99m}$Tc(CO)$_3$(NTA) will minimize the error associated with background correction, allow a more accurate assessment of renal activity and will likely result in more robust camera-based clearance measurements with better reproducibility. The lack of hepatobiliary elimination of $^{99m}$Tc(CO)$_3$(NTA) should also contribute to the accuracy and reproducibility of camera-based clearance methods.

The majority of patients received 40 mg of furosemide 15 minutes prior to the initial tracer injection. Six of 18 patients (33%) had to void prior to completion of the 24-minute acquisition. These results are similar to those reported by Liu et al where 30% of patients also failed to complete a 30-minute acquisition following an F-15 protocol [24]. In normal subjects, 40 mg of furosemide produces a maximal diuresis; the onset of diuresis begins almost immediately and reaches 80% of the maximum within 3–6 minutes of injection [17, 25]. Use of the F-15 minute protocol with the standard doses of furosemide increases the likelihood that bladder capacity will be overloaded and the patient will have to void before completing the acquisition.

The images and renogram curves were comparable for the majority of the studies. Depending on the criteria used, the $^{99m}$Tc-MAG3 study may have been interpreted in two patients as showing one kidney to be indeterminate for obstruction or possibly obstructed. In contrast, the $^{99m}$Tc(CO)$_3$(NTA) acquisition in these patients clearly excluded obstruction. The absence of obstruction was confirmed on follow up.
Neither patient had an intervention and repeat diuretic renography studies one year later showed stable renal function.

There are several limitations. Our intention was to alternate the order of $^{99m}$Tc(CO)$_3$(NTA) and $^{99m}$Tc-MAG3 administration but lack of sufficient activity in the $^{99m}$Tc(CO)$_3$(NTA) preparation required $^{99m}$Tc(CO)$_3$(NTA) to be administered first in 16/18 studies. This may have led to an overestimation of the $^{99m}$Tc-MAG3 clearance. Our protocol was designed to equalize the plasma concentrations of furosemide prior to each tracer administration in an attempt to equalize the diuretic responses; however, 33% of patients had to void prior to completion of the first acquisition whereas only 11% failed to complete the second acquisition. These results suggest that the diuretic response may have been greater following the $^{99m}$Tc(CO)$_3$(NTA) administration although there was an excellent diuretic response following each tracer and there was no significant difference in the voided volumes of patients who completed both acquisitions.

**Conclusion**

$^{99m}$Tc(CO)$_3$(NTA) has a more rapid clearance than $^{99m}$Tc-MAG3 and results in higher kidney to background ratios. The higher kidney to background ratios of $^{99m}$Tc(CO)$_3$(NTA) will minimize error associated with background subtraction and should result in more robust and reproducible camera-based clearance measurements. Unlike $^{99m}$Tc-MAG3, there was no elimination via the hepatobiliary tract. Moreover, $^{99m}$Tc(CO)$_3$(NTA) may be able to exclude obstruction in selected patients when $^{99m}$Tc-MAG3 studies are indeterminate or may even suggest an obstructed kidney. Finally, use of the F-15 minute protocol with the standard 40 mg doses of furosemide increases the likelihood that the patient will need to void prior to completing the acquisition.

**Declarations**

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**Conflicts of Interests/Competing Interests**: Andrew T. Taylor and Raghuveer Halkar are entitled to a share of the royalties for the use of QuantEM$^\text{TM}$ software for processing $^{99m}$Tc-MAG3 renal scans that was licensed by Emory University to GE Healthcare in 1993. They and their co-workers have subsequently developed a non-commercial, in house upgrade to the QuantEM$^\text{TM}$ software that was used in this study. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

**Ethics Approval**: An eIND was obtained from the FDA and all studies were performed with the approval of the Radiation Safety Committee for Human Use of Radiation (RSC1) and the Institutional Review Board. This statement is also included in the Patient Studies heading under Materials and Methods.
Consent to Participate: Signed consent was obtained from each participant. This statement is also included in the Patient Studies heading under Materials and Methods.

Availability of Data: Relevant data can be provided pending a justified request.

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