^{99m}Tc(CO)$_3$(NTA): A ^{99m}Tc Renal Tracer with Pharmacokinetic Properties Comparable to Those of ^{131}I-OIH in Healthy Volunteers

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Studies in rats showed that the pharmacokinetics of the tricarbonyl core radiopharmaceutical ^{99m}Tc(CO)$_3$-nitrilotriacetic acid, ^{99m}Tc(CO)$_3$(NTA), were essentially identical to those of ^{131}I *ortho*-iodohippuran (^{131}I-OIH), the clinical gold standard for the measurement of effective renal plasma flow. Our objective was to compare the pharmacokinetics of these 2 tracers in healthy volunteers. **Methods:** ^{99m}Tc(CO)$_3$(NTA) was prepared with commercially available NTA and a commercially available kit and isolated by reversed-phase high-performance liquid chromatography. Approximately 74 MBq (2 mCi) of ^{99m}Tc(CO)$_3$(NTA) were coinjected with 9.25 MBq (250 μCi) of ^{131}I-OIH in 9 volunteers, and simultaneous imaging of each tracer was performed for 24 min. Plasma clearances were determined from 8 blood samples obtained 3–90 min after injection using the single-injection, 2-compartment model. Plasma protein binding, red cell uptake, and percentage injected dose in the urine at 30 and 180 min were determined. **Results:** There was no difference in the plasma clearances of ^{99m}Tc(CO)$_3$(NTA) and ^{131}I-OIH, 475 ± 105 mL/min versus 472 ± 108 mL/min, respectively. The plasma protein binding and red cell uptake of ^{99m}Tc(CO)$_3$(NTA) were 43% ± 5% and 9% ± 6%, respectively; both values were significantly lower ($P < 0.001$) than the plasma protein binding (75% ± 3%) and red cell uptake (17% ± 5%) of ^{131}I-OIH. There was no significant difference in the percentage injected dose recovered in the urine at 30 min and at 3 h; for comparison, the percentage dose in the urine at 3 h was 91% ± 4% for ^{99m}Tc(CO)$_3$(NTA) and 91% ± 6% for ^{131}I-OIH ($P = 0.96$). Image quality with ^{99m}Tc(CO)$_3$(NTA) was excellent, and the renogram parameters were similar to those of ^{131}I-OIH. **Conclusion:** Preliminary results in healthy volunteers suggest that the pharmacokinetic behavior of ^{99m}Tc(CO)$_3$(NTA) is comparable to that of ^{131}I-OIH.

Key Words: ^{99m}Tc-tricarbonyl; renal radiopharmaceuticals; ^{99m}Tc(CO)$_3$(NTA); ^{131}I-*ortho*-iodohippuran (^{131}I-OIH); ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3)

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Although ^{131}I-*ortho*-iodohippuran (^{131}I-OIH) has excellent pharmacokinetic properties as a renal tracer, its use has been compromised because of the suboptimal imaging characteristics of the 364-keV photon of ^{131}I and the delivery of relatively high radiation doses to kidney and thyroid in patients with impaired renal function (*1*). The limitations of ^{131}I-OIH led to the introduction of ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) as a ^{99m}Tc replacement for ^{131}I-OIH in 1986 (*2,3*). The image quality of the ^{99m}Tc-MAG3 images was superior to that of ^{131}I-OIH (*4*); moreover, the 40%−60% extraction fraction of ^{99m}Tc-MAG3 is substantially higher than the 20% extraction fraction of ^{99m}Tc-diethyltriaminepentaacetic acid (*5,6*). The higher extraction of ^{99m}Tc-MAG3 led to its superior performance compared with ^{99m}Tc-diethyltriaminepentaacetic acid in adult and pediatric patients with suspected obstruction (*7,8*). Currently, an estimated 70% of all the renal scans in the United States are performed with ^{99m}Tc-MAG3, and ^{131}I-OIH has been withdrawn from the market even though it had a higher extraction fraction than ^{99m}Tc-MAG3 (*5,9*).

Nevertheless, despite improved image quality and diagnostic superiority over ^{99m}Tc-diethyltriaminepentaacetic acid, ^{99m}Tc-MAG3 still has limitations. A small percentage of ^{99m}Tc-MAG3 is eliminated via the hepatobiliary pathway, and this percentage increases in patients with reduced renal function; the resulting activity in the gallbladder has been mistaken for activity in the kidney (*10,11*). A larger issue is the fact that the clearance of ^{99m}Tc-MAG3 is only 50%−60% of the clearance of ^{131}I-OIH (*3,4,12*); the fact that ^{99m}Tc-MAG3 does not provide a direct measurement of effective renal plasma flow led Jafri et al. (*12*) to conclude that ^{99m}Tc-MAG3 is not suitable as a replacement for ^{131}I-OIH for the measurement of effective renal plasma flow. Another reported problem is the reproducibility of ^{99m}Tc-MAG3 clearance based on plasma sample measurements. Kotzerke et al. evaluated the reproducibility of the plasma sample ^{99m}Tc-MAG3 clearance and concluded that it was not precise enough to evaluate a change in kidney function (i.e., after surgery or chemotherapy) (*13*). Piepsz et al. also observed marked differences in repeated ^{99m}Tc-MAG3

plasma clearance measurements and warned that changes in the ^{99m}Tc-MAG3 plasma clearance should be interpreted with caution in general clinical practice (*14*).

These limitations stimulated continuing efforts to develop a ^{99m}Tc renal radiopharmaceutical with both reduced hepatobiliary excretion and superior pharmacokinetic properties that would allow a more accurate and precise measurement of effective renal plasma flow. For almost 20 years, these synthetic efforts exclusively used the $\{TcO\}^{3+}$ core with technetium in its +5 oxidation state (*2,15–19*); the most successful of these agents were the ^{99m}Tc-L,L- and ^{99m}Tc-D,D-ethylenedicysteine isomers. These agents have clearances comparable to that of ^{99m}Tc-MAG3 but less than that of ^{131}I-OIH (*18*). The limited success using the $\{TcO\}^{3+}$ core coupled with the numerous synthetic advantages of the ^{99m}Tc water-stable organometallic tricarbonyl precursor, $[^{99m}Tc(CO)_3(H_2O)_3]^+$, led us to shift our focus to ^{99m}Tc renal radiopharmaceuticals based on a *fac*-$\{^{99m}Tc(CO)_3\}^+$ core with ^{99m}Tc in its +1 oxidation state (*20–23*).

The first class of renal radiopharmaceuticals with a tricarbonyl core tested in humans was the $^{99m}Tc(CO)_3$-lanthionine complexes (*21*). Although their clearances and rates of renal excretion were still less than those of ^{131}I-OIH, they proved to be excellent renal imaging agents in healthy volunteers and demonstrated the potential of renal radiopharmaceutical development based on this core. We subsequently chose ^{99m}Tc-tricarbonyl-nitrilotriacetic acid, $^{99m}Tc(CO)_3$(NTA), for further investigation because it would be formed as a single species, would be dianionic at physiologic pH, and, similarly to ^{99m}Tc-MAG3, would have a dangling carboxylate group favoring tubular transport (*23*). Initial studies of $^{99m}Tc(CO)_3$(NTA) showed that it was a stable complex with pharmacokinetic properties in Sprague–Dawley rats equivalent or superior to those of ^{131}I-OIH (*23*). This report compares the pharmacokinetic properties of $^{99m}Tc(CO)_3$(NTA) and ^{131}I-OIH in healthy volunteers.

MATERIALS AND METHODS

General

NTA was purchased from Aldrich. ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$) was eluted from a ^{99}Mo/^{99m}Tc generator (Amersham Health) with 0.9% saline. IsoLink vials were obtained as a gift from Covidien. $[^{99m}Tc(CO)_3(H_2O)_3]^+$ was prepared according to the manufacturer's insert by adding $^{99m}TcO_4^-$ generator eluent (1 mL, 1.11–3.7 GBq [30–100 mCi]) to the IsoLink vial, heating for 40 min at 100°C, and adding 1N HCl (120 μL) to neutralize the solution. The radiolabeled compound was analyzed on a high-performance liquid chromatography (HPLC) instrument (System Gold Nouveau; Beckman Coulter) 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 × 250 mm; Beckman Coulter). The solvent system was 0.05 M triethylammonium phosphate buffer, pH 2.5 (solvent A), and ethanol (solvent B), and the flow rate was 1 mL/min. The gradient method was the same as reported previously (*22*). Urine, plasma, and red blood cell radioactivity was measured with a γ-counter (Packard Cobra II γ-Counter; Perkin Elmer) with correction for ^{131}I scatter into the ^{99m}Tc window.

Radiosynthesis of $^{99m}Tc(CO)_3$(NTA) and ^{131}I-OIH

The NTA ligand was labeled as previously described (*23,24*). Briefly, 0.5 mL of a freshly prepared solution of the $[^{99m}Tc(CO)_3(H_2O)_3]^+$ precursor (pH ~7–8) was added to a vial containing approximately 1.0 mg of the NTA ligand in 0.2 mL of water. The pH of the solution was adjusted to about 7 with 1 M NaOH, heated at 70°C for 15 min, and cooled to room temperature, yielding the dianion, *fac*-$[^{99m}Tc(CO)_3(NTA)]^{2-}$, which we describe as $^{99m}Tc(CO)_3$(NTA). $^{99m}Tc(CO)_3$(NTA) was separated from unlabeled ligand by HPLC; the radiochemical purity was more than 99%. Ethanol was partially removed by N_2 gas, and the collected solution of $^{99m}Tc(CO)_3$(NTA) was buffered in a physiologic phosphate buffer at pH 7.4. The HPLC-purified complex in physiologic phosphate buffer (pH 7.4) was passed through a Sep-Pak Plus C_{18} cartridge (Waters Co.) (primed with 4 mL of ethanol) and sterile Millex-GS 22-μm filter (Millipore Co.) (primed with 4 mL of saline) into a sterile, pyrogen-free empty vial. The final concentration was 37 MBq/mL (1 mCi/mL), and the final pH was 7.4. Test samples were sent for analysis and determined to be sterile and pyrogen-free.

^{131}I-OIH was prepared by the isotope exchange reaction between nonradioactive OIH and radioactive sodium iodide ($Na^{131}I$) according to the method reported by Anghileri (*25*) and modified as previously described (*23*). ^{131}I-OIH was obtained with a 98%−99% labeling yield.

Healthy Volunteer Studies

All studies were performed with the approval of the Radioactive Drug Research Committee and the Emory University Institutional Review Board; signed consent was obtained from each volunteer. Nine healthy volunteers (3 men and 6 women; mean age ± SD, 33.8 ± 12.4 y; range, 20–55 y) participated in this study. Inclusion criteria required the absence of any history of kidney or bladder diseases and normal findings on a review of systems. Pregnancy was excluded by means of a urine pregnancy test. Measurements of blood pressure, heart rate, and temperature were obtained before and after injection for each volunteer; in addition, a complete blood cell count, standard chemistry panel, and urinalysis were obtained before and 24 h after injection.

Approximately 74 MBq (2 mCi) of $^{99m}Tc(CO)_3$(NTA) were coinjected with 9.25 MBq (250 μCi) of ^{131}I-OIH, and imaging was performed for 24 min using an Infinia (GE Healthcare) camera with a 9.5-mm (3/8-in) crystal fitted with a high-energy collimator; a 20% window was centered over the 365-keV photopeak of ^{131}I, and a second 20% window was centered over the 140-keV photopeak of ^{99m}Tc. Data were acquired in a 128 × 128 matrix using a 3-phase dynamic acquisition and processed on a Xeleris computer (GE Healthcare) using an in-house upgrade of the QuantEM 2.0 renal software; QuantEM is licensed to GE Healthcare by Emory University and provides a validated camera-based ^{99m}Tc-MAG3 clearance based on the integral of the injected dose from 1.0 to 2.5 min after injection (*26*). Renogram curves were generated using cortical (parenchymal) and whole-kidney regions of interest, and the time to peak height of the renogram curve (TTP) and 20 min–to–maximum count ratios (20 min/max) were calculated for both sets of renogram curves. Blood samples were obtained at 3, 5, 10, 20, 30, 45, 60, and 90 min after injection,

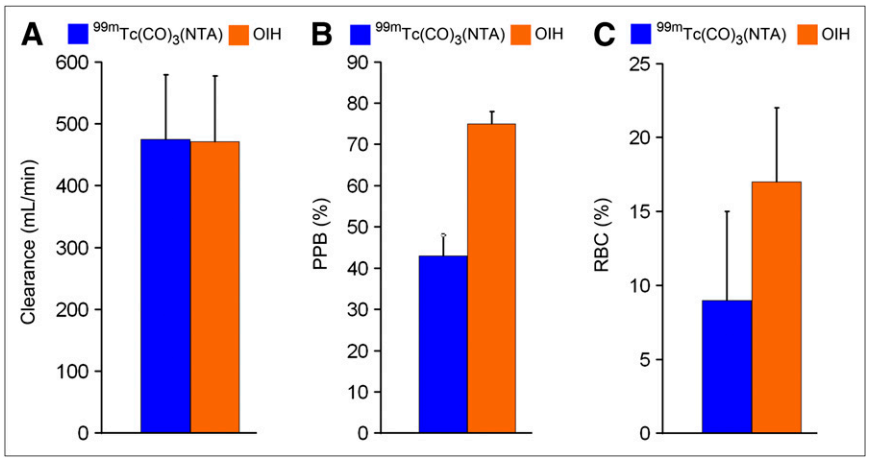

FIGURE 1. Bar graphs comparing clearance (A), plasma protein binding (PPB) (B), and red cell uptake (RBC) (C) of ^{99m}Tc(CO)$_3$(NTA) and ^{131}I-OIH in healthy volunteers.

and plasma clearances for ^{131}I-OIH and ^{99m}Tc(CO)$_3$(NTA) were determined using the single-injection, 2-compartment model of Sapirstein et al. (*27*). The volunteers voided at 30, 90, and 180 min after injection to determine the percentage dose in the urine. Plasma protein binding was determined by ultracentrifugation (Centrifree micropartition system; Amicon Inc.) of 1 mL of plasma: Plasma protein binding = (1.0 – [ultrafiltrate concentration/plasma concentration]) × 100. The percentage uptake in the erythrocytes was calculated from the whole blood (counts/g) and packed cells (counts/g). Percentage erythrocyte uptake = [(counts/g in erythrocytes × hematocrit)/counts/g in whole blood]. No correction was made for plasma trapped in the red blood cell sample. Plasma protein binding and erythrocyte uptake were calculated using duplicate samples, and the mean values were reported.

To determine whether the complex was metabolized or was excreted unchanged in the urine, a 1-mL urine sample from the 30-min urine collection from 1 volunteer was analyzed by reversed-phase HPLC and the tracing compared with reversed-phase HPLC analysis of the purified complex.

Statistical Analysis

All results are 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 to be statistically significant.

RESULTS

There was no evidence of any toxicity based on measurements of blood pressure, heart rate, temperature, complete blood cell count, standard chemistry panel, or urine analysis for any of the volunteers. The clearance of ^{99m}Tc(CO)$_3$(NTA) averaged 475 ± 105 (SD) mL/min, compared with 472 ± 108 mL/min for ^{131}I-OIH (Fig. 1). The plasma protein binding of ^{99m}Tc(CO)$_3$(NTA), 43% ± 5%, was significantly less than that of ^{131}I-OIH, 75% ± 3% ($P < 0.001$); similarly, red cell uptake for ^{99m}Tc(CO)$_3$(NTA), 9% ± 6%, was also significantly less than that of ^{131}I-OIH, 17% ± 5% ($P < 0.001$) (Fig. 1). Both tracers were rapidly excreted in the urine, with 69% ± 9% and 69% ± 11% in the urine at 30 min for ^{99m}Tc(CO)$_3$(NTA) and ^{131}I-OIH, respectively ($P = 0.95$), and 91% ± 4% and 91% ± 6% at 180 min ($P = 0.96$), respectively (Fig. 2). Reversed-phase HPLC analysis of an aliquot from the 30-min urine sample of one of the volunteers showed a single peak (Fig. 3A) with the same retention time as the purified complex (Fig. 3B), indicating that the tracer is excreted unchanged in the urine (Fig. 3).

^{99m}Tc(CO)$_3$(NTA) image quality was excellent, compared with that of ^{131}I-OIH, and the renogram curves were almost identical (Fig. 4). There was no significant difference in relative uptake (49.8% ± 3.4% for ^{99m}Tc(CO)$_3$(NTA) in the left kidney, compared with 49.0% ± 4.1% for ^{131}I-OIH ($P = 0.17$; Table 1). The TTP and 20 min/max of ^{99m}Tc(CO)$_3$(NTA) and ^{131}I-OIH for whole kidney and for cortical (parenchymal) regions of interest are shown in Table 1. For the cortical regions of interest, TTP for the left kidney was 2.52 ± 0.51 min for ^{99m}Tc(CO)$_3$(NTA), compared with 2.46 ± 0.73 for ^{131}I-OIH ($P = 0.71$, not statistically significant); for the right kidney, the cortical TTP was 2.60 ± 0.60 for ^{99m}Tc(CO)$_3$(NTA) and was greater than that of ^{131}I-OIH, 1.98 ± 0.60 ($P = 0.02$). The cortical 20 min/max was slightly greater for ^{99m}Tc(CO)$_3$(NTA) than for ^{131}I-OIH for both the left and the right kidneys (0.13 ± 03 vs. 0.10 ± 0.04 for the left kidney [$P = 0.03$] and 0.13 ± 0.02 vs. 0.10 ± 0.02 for the right kidney [$P = 0.046$]) (Table 1). The camera-based clearance of ^{99m}Tc(CO)$_3$(NTA) was 456 ± 130 mL/min/1.73 m^2 (Fig. 5).

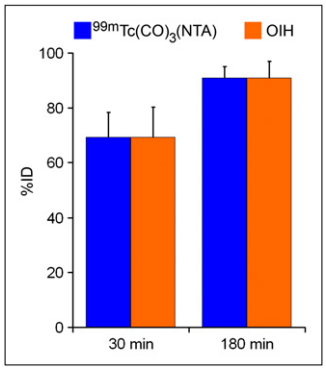

FIGURE 2. Bar graphs comparing urine excretion of ^{99m}Tc(CO)$_3$(NTA) and ^{131}I-OIH at 30 and 180 min in healthy volunteers.

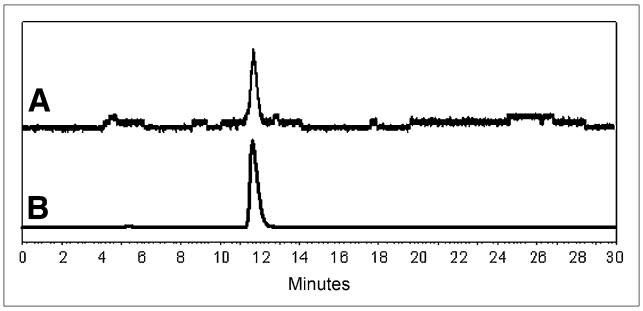

FIGURE 3. Urine sample from healthy volunteer injected with ^{99m}Tc(CO)$_3$(NTA) was subjected to reversed-phase HPLC analysis (A) and compared with reference HPLC ^{99m}Tc(CO)$_3$(NTA) tracing (B). Both tracings show single peak with same retention times indicating that ^{99m}Tc(CO)$_3$(NTA) is excreted unchanged in urine.

DISCUSSION

In our study, the ^{99m}Tc(CO)$_3$(NTA) plasma clearance was 100% of the ^{131}I-OIH clearance; in contrast, multiple studies have shown that the ^{99m}Tc-MAG3 plasma clearance is only about 50%−60% that of ^{131}I-OIH (*3,4,12,15*). Although our study did not directly compare ^{99m}Tc-MAG3 and ^{99m}Tc(CO)$_3$(NTA), the camera-based clearance measurement developed for ^{99m}Tc-MAG3 provides an indirect comparison (*26*); using this equation, the camera-based clearance of ^{99m}Tc(CO)$_3$(NTA) in our volunteers was 456 ± 130 mL/min/1.73 m^2, compared with a camera-based ^{99m}Tc-MAG3 clearance of 321 ± 69 mL/min/1.73 m^2 obtained in a prior study of 106 subjects referred for potential kidney donation (Fig. 5) (*28*). These results indicate that ^{99m}Tc(CO)$_3$(NTA) is accumulated more rapidly by the kidney than is ^{99m}Tc-MAG3, implying that ^{99m}Tc(CO)$_3$(NTA) has a higher clearance than ^{99m}Tc-MAG3.

The mean clearance of ^{131}I-OIH in our healthy volunteers (472 mL/min) was slightly lower than the mean ^{131}I-OIH clearance we obtained in an earlier study of healthy volunteers (530 mL/min) (*3*). The possibility of clearance variations points out the need for an internal standard such as ^{131}I-OIH in evaluations of the clearance of new ^{99m}Tc renal tracers. Overall, the differences between ^{131}I-OIH and

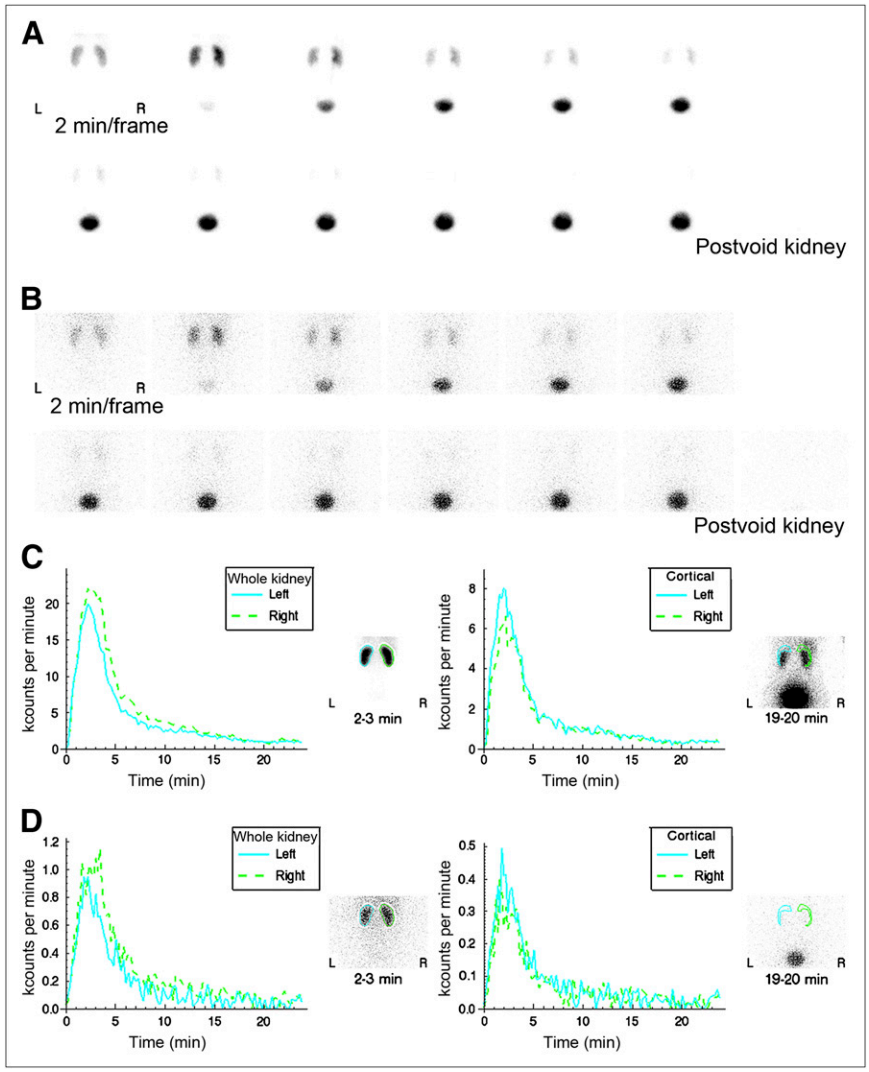

FIGURE 4. Two-minute kidney images after simultaneous injection of 79.2 MBq (2.14 mCi) of ^{99m}Tc(CO)$_3$(NTA) (A) and 8.9 MBq (240 μCi) of ^{131}I-OIH (B) in healthy 22-y-old female volunteer. Whole-kidney and cortical (parenchymal) renogram curves are displayed in C for ^{99m}Tc(CO)$_3$(NTA) and in D for ^{131}I-OIH. Renogram curves for ^{131}I-OIH are quite noisy because of relatively low counting rate resulting from lower administered dose and poor capture of 364-keV photon of ^{131}I by 9.5-mm (3/8-in) crystal.

TABLE 1. Renogram Parameters for Whole-Kidney and Cortical Regions of Interest of $^{99m}Tc(CO)_3(NTA)$ Compared with ^{131}I-OIH in Humans ($n = 9$)

	Left kidney			Right kidney			Left cortex			Right cortex		
Agent	Uptake (%)	TTP (min)	20 min/max	Uptake (%)	TTP (min)	20 min/max	TTP (min)	20 min/max		TTP (min)	20 min/max	
$^{99m}Tc(CO)_3(NTA)$	49.8 (3.4)	3.3 (1.6)	0.15 (0.04)	50.2 (3.4)	3.4 (1.9)	0.16 (0.04)	2.52 (0.51)	0.13 (0.03)		2.6 (0.6)	0.13 (0.02)	
^{131}I-OIH	49.0 (4.1)	2.6 (0.6)	0.11 (0.03)	51.0 (4.1)	2.8 (1.6)	0.11 (0.19)	2.46 (0.73)	0.1 (0.04)		1.98 (0.6)	0.10 (0.02)	
P	0.17	0.13	0.01	0.17	0.02	0.004	0.71	0.03		0.02	0.046	

Data are mean, with SD in parentheses.

$^{99m}Tc(CO)_3(NTA)$ were minimal. $^{99m}Tc(CO)_3(NTA)$ has the advantage of a slightly lower protein binding and red cell binding than does ^{131}I-OIH. A lower protein binding may increase the extraction fraction since unbound tracer can be filtered by the glomerulus as well as extracted by the tubules. The reduction in red cell binding is advantageous in obtaining an accurate measure of extraction fraction; the extraction fraction is based on the difference in the plasma concentration of the tracer in arterial and renal venous blood. The tracer bound to red cells is in equilibrium with the plasma; when a renal vein blood sample is obtained, tracer associated with the red cells reequilibrates with the plasma before the plasma can be separated from the red cells and results in an overestimation of the plasma tracer concentration.

^{131}I-OIH has slightly lower time to peak and 20 min/max than $^{99m}Tc(CO)_3(NTA)$; however, these differences are small (0.13 for $^{99m}Tc(CO)_3(NTA)$ vs. 0.10 for ^{131}I-OIH), and the accuracy of the 20 min/max for ^{131}I-OIH may have been reduced because of the low ^{131}I counting rate at 20 min. For comparison, the cortical 20 min/max for $^{99m}Tc(CO)_3(NTA)$ was 0.13 and that for ^{99m}Tc-MAG3 was 0.19 in an earlier study of 106 subjects referred for potential kidney donation (*28*).

In summary, $^{99m}Tc(CO)_3(NTA)$ is a promising renal tracer. It is a stable complex (*23*) with pharmacokinetic properties that are almost identical to those of ^{131}I-OIH in rats and healthy humans. The kinetics and metabolism of the NTA ligand itself have already been investigated in several species, including humans (*29–31*). The oral median lethal dose of $Na_3NTA{\cdot}H_2O$ in rodents is about 2,000 mg/kg of body weight (*32*). No adverse effects were noted after ingestion of a single dose of 10 mg of NTA by 8 human volunteers (*29*), and Health Canada has determined the acceptable daily intake of NTA in drinking water to be 10 μg/kg of body weight per day (*30*). In our studies, no free NTA ligand was injected because the ligand was separated from the complex by HPLC before injection, and the administered dose of the $^{99m}Tc(CO)_3(NTA)$ complex was extremely small (<0.2 μg/kg of body weight). In a typical kit formulation, free NTA ligand would undoubtedly be injected, but the

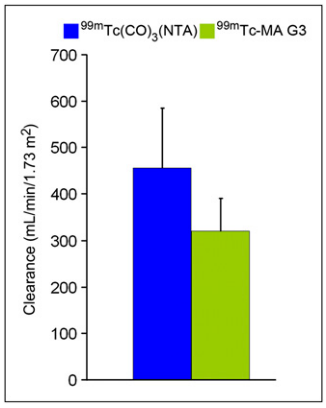

FIGURE 5. Camera-based clearance (mL/min/1.73 m^2) for $^{99m}Tc(CO)_3(NTA)$ and ^{99m}Tc-MAG3.

injected dose of NTA would likely still be below the daily acceptable limit established by Health Canada.

Our study did not evaluate hepatobiliary excretion. Hepatobiliary excretion tends to be more pronounced when renal function is compromised. One of the isomers of an early ^{99m}Tc renal tracer introduced by Fritzberg et al., ^{99m}Tc-N,N′-bis-(mercaptoacetyl)-2,3-diaminopropionate, performed well in rodents and healthy subjects but had a greater diminution in clearance relative to that of ^{131}I-OIH in patients with reduced renal function (*33*,*34*). Future studies will need to evaluate $^{99m}Tc(CO)_3$(NTA) in a patient population with impaired renal function.

CONCLUSION

Initial results in healthy volunteers showed that $^{99m}Tc(CO)_3$(NTA) is cleared from the blood and excreted in the urine as rapidly as ^{131}I-OIH. Previous studies have shown that $^{99m}Tc(CO)_3$(NTA) is stable, forms as a single species, and is amenable to kit formulation. Moreover, $^{99m}Tc(CO)_3$(NTA) has less protein binding and less activity associated with red cells than does ^{131}I-OIH. These results strongly suggest that $^{99m}Tc(CO)_3$(NTA) will prove to be a superior ^{99m}Tc renal tubular imaging agent and a superior ^{99m}Tc tracer for the measurement of effective renal plasma flow.

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