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Renal Uptakes of ^{99m}Tc-MAG$_3$, ^{99m}Tc-DTPA, and ^{99m}Tc-DMSA in Rabbits with Unilateral Ureteral Obstruction

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Abstract. *Renal function measurements using ^{99m}Tc-DTPA and ^{99m}Tc-MAG$_3$ dynamic scintigraphs were compared to those obtained using ^{99m}Tc-DMSA static scintigraphy. Eighteen experimental rabbits were randomly divided into ^{99m}Tc-DTPA–, ^{99m}Tc-MAG$_3$–, and ^{99m}Tc- DMSA–injected groups. Experimental unilateral renal damage was induced by ligating a unilateral right ureter in 18 rabbits. Scintigraphic images were obtained at 2 and 5 h after intravenous injection of ^{99m}Tc-DMSA, or immediately after administration of ^{99m}Tc-DTPA or ^{99m}Tc-MAG$_3$. For the dynamic images using ^{99m}Tc-DTPA and ^{99m}Tc-MAG$_3$, rapid sequential images were obtained every 2 s for 30 images up to 1 min. The three groups presented different relative renal functions between the left normal and the right abnormal kidneys at 1, 2, 3, and 4 weeks post-ligation ($p<0.05$). However, the between-group comparisons showed no significant differences at any time. These results suggest that dynamic images of ^{99m}Tc-DTPA and ^{99m}Tc-MAG$_3$ can be used to measure the relative renal function in place of the static image of ^{99m}Tc- DMSA.*

In evaluating renal disease, it is important to consider the functional parameter that is reflected by the administered radiopharmaceutical, as well as the underlying disease state. Kidney scans, or renograms, are often performed to determine differential renal function for patients who are undergoing or being evaluated for urologic surgery (1). Use of ^{99m}Tc-labeled compounds, such as mercaptoacetyltriglycine (MAG_3), diethylenetriamine pentaacetic acid (DTPA), and dimercaptosuccinic acid (DMSA), has made kidney scintigraphy one of the most useful nuclear medicine tools (2, 3).

^{99m}Tc-MAG$_3$ is a tubular excreted radiopharmaceutical used for renal function and imaging, while ^{99m}Tc-DTPA is excreted by glomerular filtration. However, the exact mechanisms that underlie differences between the 2 tracers are not well understood (4). ^{99m}Tc-DTPA is almost completely excreted by glomerular filtration without tubular reabsorption. Thus, the small amounts of protein-bound ^{99m}Tc-DTPA can be used to obtain accurate glomerular filtration rate (GFR) measurements (1). Gates (5) found that the fractional renal uptake of intravenously (IV) administered ^{99m}Tc-DTPA, within 2 to 3 min of radiotracer arrival in the kidney, is proportional to the GFR. ^{99m}Tc-DMSA, ^{99m}Tc-DTPA and ^{99m}Tc-MAG$_3$ have different renal uptake mechanisms, depending on the radiopharmaceutical administered. Therefore, these three agents can be used to compare the relative kidney uptake ratios at different periods of time: the relative renal functional characteristics reflected by ^{99m}Tc-DMSA, ^{99m}Tc-DTPA, and ^{99m}Tc-MAG$_3$ can be used for comparative measurements. ^{99m}Tc-DMSA, as a static renal radiopharmaceutical, is considered to be the most dependable method to measure relative renal function (6, 7). But ^{99m}Tc-DMSA has some disadvantages, such as its relatively high radiation dose and time consumption compared to ^{99m}Tc-DTPA or ^{99m}Tc-MAG$_3$. The aim of the present study was to measure by ^{99m}Tc-DTPA, ^{99m}Tc-MAG$_3$, or ^{99m}Tc-DMSA in experimental rabbits with right ureteral obstruction.

Materials and Methods

Animals. Eighteen healthy male New Zealand white rabbits (age: 12 weeks, mass: 2.7-3.2 kg) were randomly divided into 3 groups of 6 animals each: ^{99m}Tc-DMSA–treated, ^{99m}Tc-DTPA– treated, and ^{99m}Tc-MAG$_3$–treated groups. After general anesthesia, the proximal

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Table I. *Radiopharmaceutical uptakes of ^{99m}Tc-mercaptoacetyltriglycine (MAG_3), ^{99m}Tcdiethylenetriamine pentaacetic acid (DTPA), and ^{99m}Tc-mercaptoacetyltriglycine (DMSA) in the left normal and the right abnormal kidneys (unit: %).*

Agents	Kidney	Time (week) after surgical intervention				
		0	1	2	3	4
MAG3	Normal	49.93±0.66	65.18±10.89	89.22±6.54	86.49±5.66	90.26±6.45
	Abnormal	50.06±0.74	34.81±11.44*	10.78±7.87*	13.50±7.99*	9.73±5.02*
DTPA	Normal	50.31±0.54	72.56±15.89	78.90±9.30	81.17±10.55	88.54±6.84
	Abnormal	49.67±0.77	27.43±13.03*	21.09±8.20*	18.82±11.77*	11.45±4.32*
DMSA-2	Normal	50.38±0.56	81.03±9.14	88.39±3.15	89.58±5.67	89.06±5.37
	Abnormal	49.61±0.36	18.97±10.81*	11.60±2.99*	10.41±4.04*	10.95±6.49*
DMSA-5	Normal	50.00±0.47	81.50±13.68	87.97±2.78	89.90±5.90	88.95±7.45
	Abnormal	49.99±0.60	18.49±10.89*	12.03±2.57*	10.09±4.33*	11.04±6.55*

DMSA-2 and DMSA-5 indicate 2 and 5 h after DMSA injection, respectively. Values are expressed as the mean±S.D. (n=6). Significant differences as compared with normal kidney: *$p<0.05$.

part of the right ureter in rabbits was ligated with 2-0 silk at 2 places adjacent to the renal pelvis. All protocols employed in this study were approved by the Animal Care Committee of Chungbuk National University, Republic of Korea.

Scintigraphic evaluation. Scintigraphy was performed before surgical intervention, and at 1, 2, 3, and 4 weeks post–ureteral ligation. After rabbits were administrated subcutaneous atropine (0.05 mg/kg), anesthesia was induced with IV xylazine (1.1 mg/kg) and maintained with IV ketamine (11 mg/kg). Data were obtained using a dual-head gamma camera (Infinia Hawkeye, GE Co., USA) equipped with computed tomography. Scintigraphy was performed at 2 and 5 h after ear vein IV injection of 3 mCi ^{99m}Tc-DMSA. The rabbit was positioned on the detectors, a bolus injection of 3 mCi ^{99m}Tc-DTPA or ^{99m}Tc-MAG_3 was administrated into an ear vein, and the imaging was started immediately. Images were taken every 2 s for 1 min, and thereafter every 1 min for 25 min.

Measurement of regional radiopharmaceutical uptakes. To calculate the percentage of relative renal function, regions of interest (ROIs) were drawn around each kidney on both the anterior and posterior images of a ^{99m}Tc-DMSA static scan. ^{99m}Tc-DTPA or ^{99m}Tc-MAG_3 dynamic scintigraphy images were summed for 2 to 3 min after starting the scan. ROIs were drawn around both kidneys and the backgrounds around the kidneys (Figure 1).

Statistical analysis. We compared the scintigraphic data for the three agents. Differences between the measured values at different times were evaluated using the Kruskal-Wallis test. Results are given as the mean±S.D. Significance was defined at the $p<0.05$ level. Differences between the left normal and the right abnormal kidneys were compared using the Wilcoxon signed rank test.

Results

All ROIs used were pea-shaped, and quantitative analyses included calculations for both the kidney and background. The left kidneys appeared to be normally sized in the scintigraphic images during the experimental periods, but the ligated right kidneys slowly became larger with time. Therefore, the left kidney ROIs were all drawn at the same size, but new right kidney ROIs were drawn each week.

Statistical analyses of the uptake ratios for ^{99m}Tc-DMSA, ^{99m}Tc-DTPA, and ^{99m}Tc-MAG_3 are shown in Table I. ^{99m}Tc-DMSA, ^{99m}Tc-DTPA, and ^{99m}Tc-MAG_3 uptakes in the right kidney were lower than those in the left kidney after surgical intervention. However, no significant difference was observed in the between-group comparison of ^{99m}Tc-DMSA, ^{99m}Tc-DTPA, and ^{99m}Tc-MAG_3.

Discussion

A non-invasive means for determining individual renal function would be advantageous for surgical intervention or for the medical management of renal disease. These methods can be performed with different radiopharmaceuticals, such as ^{99m}Tc-DMSA, ^{99m}Tc-DTPA, or ^{99m}Tc-MAG_3. ^{99m}Tc-DMSA enters the proximal tubular cell either by glomerular filtration and subsequent reabsorption or by direct uptake from the peri-tubular capillaries. ^{99m}Tc-DMSA is largely bound to serum proteins (8). Following IV administration, ^{99m}Tc-DTPA is rapidly distributed throughout the extracellular fluid space, where it is promptly cleared from the body by glomerular filtration (9). Excretion of ^{99m}Tc-MAG_3 by the kidney is greater than that of ^{99m}Tc-DTPA (4).

The imaging provided by each agent reflects different renal functional parameters (10, 11). Although all of these methods accurately measure renal functional parameters, the agents do present some differences due to their distinct biological properties (1, 12), such as their renal excretion mechanisms, renal cell retention of radioactive material, and bound plasma-protein and plasma clearance levels (8, 13). As a static renal agent, ^{99m}Tc-DMSA is considered the most reliable method to measure relative renal function (14) and the most appropriate tracer for renal cortical imaging (15). Previous studies have revealed the effect of various

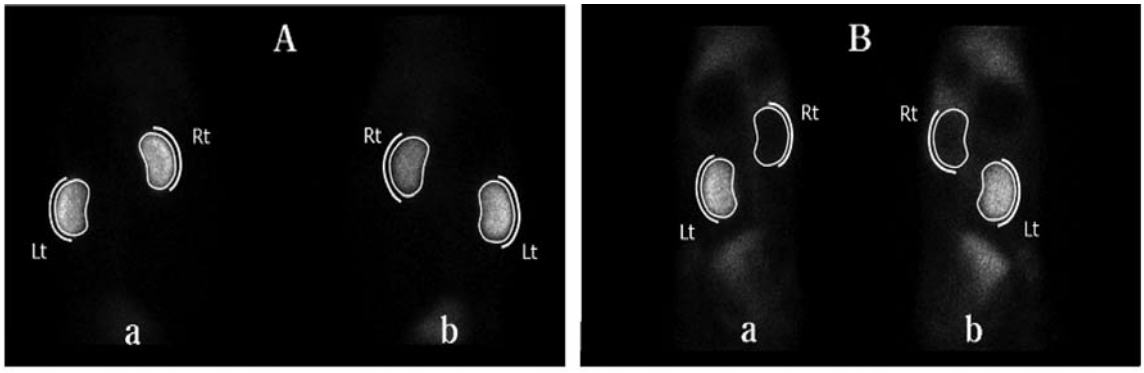

Figure 1. *Anterior (a) and posterior (b) views of ^{99m}Tc-DMSA–treated animals at 0 (A) and 4 weeks (B) after surgical intervention of the right ureter. Regions of interest are drawn around the right (Rt) and left (Lt) kidneys.*

parameters on renal disease, including age, duration between diagnosis and bacterial therapy initiation, and the presence of urinary anomalies, recurrent infections, or bladder dysfunctions (16).

We compared the renal uptakes measured using the above radiopharmaceuticals in experimentally unilateral ureteral-ligated rabbits. We observed no marked differences between the ^{99m}Tc-DMSA, ^{99m}Tc-DTPA, or ^{99m}Tc-MAG$_3$ agents in terms of visualization of the pathological focus or image quality. The relative renal function for each of the three agents was similar in rabbits with unilateral ureteral obstruction. We conclude that renal function measurements using ^{99m}Tc-DTPA and ^{99m}Tc-MAG$_3$ dynamic scintigraphs can be used to simultaneously measure the GFR. Acknowledgement This work was supported by a research grant of the Chungbuk National University, Republic of Korea, in 2009.

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