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99mTc MAGS & 99mTc DTPA;
COMPARISON TO EVALUATE RENAL FUNCTIONS IN RENAL TRANSPLANT PATIENTS

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ABSTRACT

Background: Renal scintigraphy evaluates the renal function non-invasively. The present study was conducted to compare 99mTc MAG3 and 99mTc DTPA in renal transplant patients for the evaluation of renal functions. **Materials & Methods:** 99mTc MAG3 and 99mTo DTPA studies were performed on 33 renal transplant patients and 10 normal subjects, with 1 day interval in between the two studies. Renal transplant patients were categorized as normal, acute tubular necrosis, rejection, urine outflow obstruction and urinary tract infection groups on the basis of routine clinical investigations and preliminary results of scintigraphic studies. **Results:** Both radiopharmaceuticals, 99mTc MAG3 and 99mTc DTPA were having equal diagnostic efficacy, however image quality with 99mTc MAG3 was superior to that of 99mTc DTPA. Renograms clearly differentiated various renal groups. Correlation between glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) was good ($r=0.89$ at $P<0.00001$). In terms of perfusion index (PI) our results with both agents were similar ($r=0.96$ at $p<0.00001$), clearly differentiating all cases of rejection from acute tubular necrosis. PI was raised in rejection cases, while normal in all other groups. In cases of acute tubular necrosis and rejection, 99mTc MAG3 based parenchymal retention index (R-20/3) was markedly raised, compared to that of 99mTc DTPA ($p<0.00001$). **Conclusion:** 99mTc- MAG3 and 99mTc DTPA have equal diagnostic efficacy in renal transplant patients. However visual delineations of the kidneys is better with 99mTc MAG3, especially in cases with compromised renal functions.

KEYWORDS: Renal functions, renal transplant, DTPA, MAGS, Perfusion Index, Parenchymal retention Index.

INTRODUCTION

Renal scintigraphy is a non-invasive and reliable technique for diagnostic evaluation and follow-up of renal transplant patients[1-2]. 99mTc MAG3 and 99mTc DTPA are equally popular radiopharmaceuticals for the evaluation of renal function. 99mTc DTPA is a glomerular filtration agent and is being used since long time. 99mTc MAG3 is a relatively new agent and has been introduced as an alternative of ortho-iodo-hippurate[3,4,5]. It has biologic properties similar to those ot 1311OIH and can be labeled with 99mTc which has suitable energy and better dosimetry for imaging.

99mTc MAG3 and 99mTc DTPA measure two different parameters! especially during early phases of renal scintigraphy. With exception of a few clinical conditions,

both of them are equally useful for the assessment of renal function. Some researchers have claimed 99mTc MAG3 to be superior to 99mTc DTPA for renal scintigraphy[6-7]. After its availability in kit formulation, because of its high extraction fraction, some centers have switched over to 99mTc MAG3 for routine clinical studies. This study was aimed at the comparison of two radiopharmaceuticals for renal scintigraphy. We have done head to head comparison to evaluate renal functions in patients with renal transplantation.

MATERIAL & METHODS

Ethics committee of the institute approved study protocol. Informed written consent was obtained from all the participants. A total of 33 patients with renal transplants (19 M: 14 F, mean age 32 + 13.5 yrs, duration since renal transplant ranges from 2 days to 8 yrs) and 10 normal control subjects (7M: 3F, mean age 27+11.3 yrs) were enrolled.

All the normal subjects were screened for any disease particularly affecting the renal functions. Routine investigations (blood and urine complete examination, serum urea, serum creatinine, ultrasonography) and scintigraphy were performed for all the subjects. All the subjects (patients and controls) had gone through renal scintigraphy with both 99mTc MAG3 and 99mTc DTPA (random sequence) with 1 day interval in between. Ultrasound based renal depth was calculated in each subject and later used for calculation of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF).

On the basis of these investigations patients with renal transplants were categorized as normal (n = 10), having acute tubular necrosis (n= 9), acute rejection (n = 4), chronic rejection (n = 4), renal artery thrombosis (n = 2), urine outflow obstruction (n = 2) and urinary tract infection (n = 2).

Acquisition was done on Toshiba GCA-40A gamma camera fitted with low energy parallel hole collimator. All control and patients were positioned supine on the imaging table; posterior requisition was performed for control group and anterior acquisition for transplant patients after an intravenous injection of 57 mCi of radiopharmaceutical. Pre and post injection syringe counts were taken for 1 min. Data was acquired in frame mode on dedicated computer in 64 x 64 matrix as dynamic sequential study with initial frame rate of 1 frame per second for 30 seconds, followed by 9 frames of 10 second each.

Then acquisition was continued at the rate of 30 second per frame for 28 minutes. Analogue images were also acquired starting immediately after injection of the tracer. First image was taken for 30 second (starting when activity appeared in aorta). The second image was taken at 1 minute for 400 K counts and its time was noted. Subsequent images were acquired at the time 5,10,20 and 30 minutes after injection of tracer. In routine, 40 mg of frusemide was given intravenously to all patients at 15 minutes of study.

A composite image (60-120 seconds) of the study was used for drawing regions of interest around the kidneys and for background counts. Renal time activity curves were generated which were subsequently used for calculation of various parameters. GFR from 99mTc DTPA and ERPF from 99mTc MAG3 study were calculated using the Gate's[8] and Schlegel's formula[9] respectively.

One pixel thick region of interest was defined over iliac artery in transplant cases or over aorta in control subjects just distal to the origin of renal artery. Similar regions of interest were drawn over the renal cortex and background area inferolateral to respective kidney. Background corrected arterial and renal parenchymal time activity curves were displayed for first 30 frames to expand initial vascular phase. Area under arterial curve for interval between start and time to first peak (Aa), and area under renal parenchymal curve for same timing (Ak) were determined. Perfusion index (PI) was calculated by using Hilson's formula[10] as given in equation 1.

Perfusion index = (Aa/Ak)--------- Equation 1.

Background subtracted renal parenchymal curve was used to determine one minute integral counts between 2 to 3 min. (C1) and 19 to 20 min. (C2) which were used to calculate *Parenchymal retention index*" with the following formula:

R-20/3 = C2/C1

Mean, standard deviation (SD) and correlation coefficient

(r) were calculated for values of functional renal parameters from DTPA and MAG3.

RESULTS

Visual interpretation of analogue images showed mild enlargement of kidney in well functioning renal transplants and those with acute rejection. Shrunken size and irregular outline was observed in cases of chronic rejection. Perfusion images showed markedly reduced perfusion in cases of rejection which was normal in all other groups.

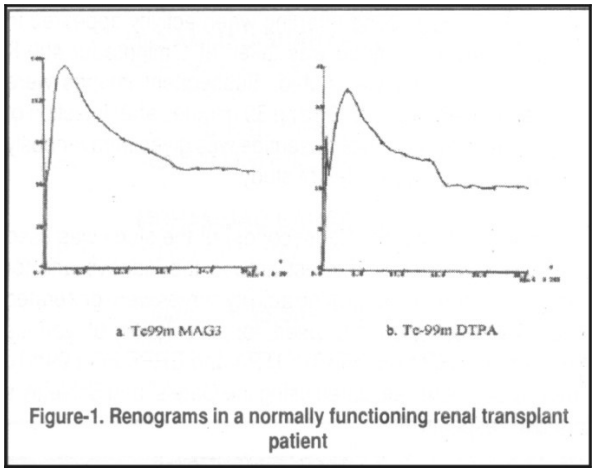

Figure-1. Renograms in a normally functioning renal transplant patient

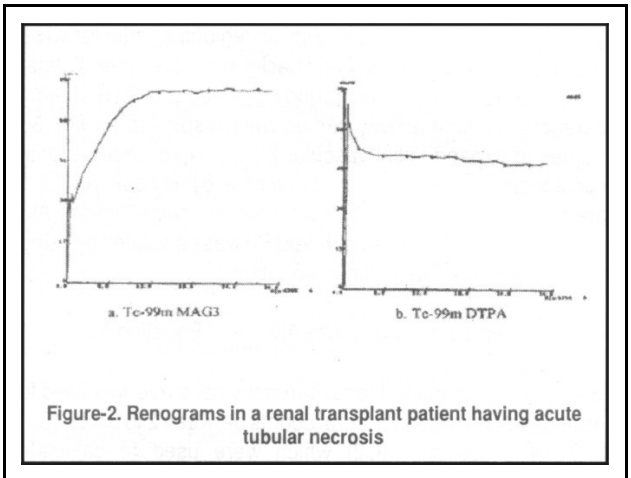

Figure-2. Renograms in a renal transplant patient having acute tubular necrosis

Radiotracer accumulation was more in well functioning renal transplants as compared to control group. In cases of acute tubular necrosis (ATN) and rejection, radiotracer accumulation was diminished and excretion was impaired. Background was high in cases of acute tubular necrosis and rejection, while low in all other groups.

In patients with partial urine outflow obstruction, marked hold up of tracer was noticed in pelvicalyceal system, which failed to clear after diuretic stress. 99mTc MAG3 image quality was superior to that of 99mTc DTPA in all groups due to higher tracer accumulation, rapid dynamics, prompt excretion and high target to background ratio. Delayed 99mTc MAGS images showed marked parenchymal retention of tracer in patients having ATN and rejection as compared to that of 99mTc DTPA.

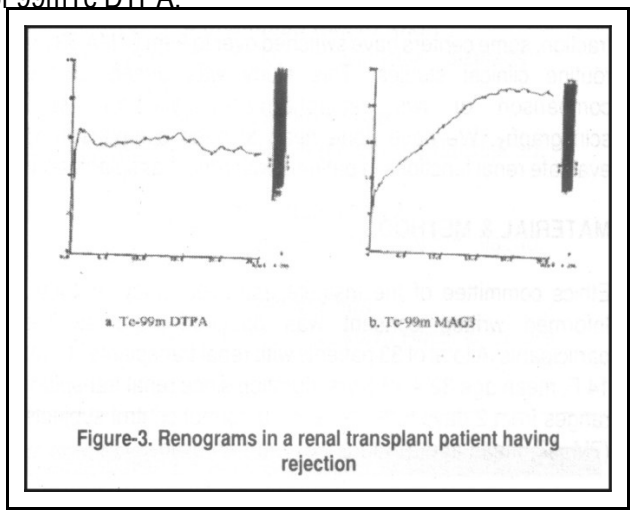

Figure-3. Renograms in a renal transplant patient having rejection

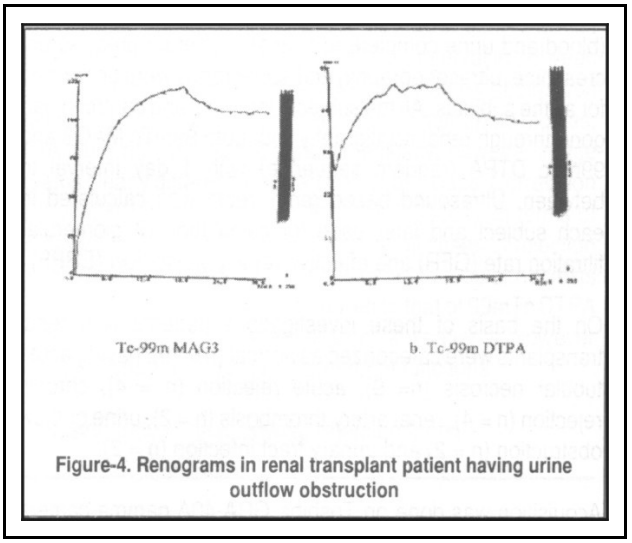

Figure-4. Renograms in renal transplant patient having urine outflow obstruction

Renograms generated in scintigraphy with 99mTc MAG3 and 99mTc DTPA in normal functioning renal transplant, acute tubular necrosis, rejection and urine outflow obstruction are shown in fig 1 -4 respectively.

Perfusion phase was markedly diminished in patients having rejection, while normal in all other groups. Parenchymal uptake and peak height were relatively high in persons having normal functioning renal transplants.

These parameters were markedly diminished in ATN and rejection due to compromised renal function. Excretory phase was also impaired in patients having acute tubular necrosis and rejection.

In patients having urine outflow obstruction, rising third phase was observed because of pelvicalyceal hold up with no response to diuretic stress. In all groups except for ATN and rejection categories, 99mTc MAG3 renograms were similar to those of 99mTc DTPA, but with higher peak height, shorter T-max, T2/3 and T1/2, with more steep up and down slopes.

In patients with ATN and rejection, renograms showed identical perfusion and uptake phase with both radiopharmaceuticals, however excretory phase was quite different.

In contrast to 99mTc DTPA renogram demonstrating almost flat curve, 99mTc MAG3 demonstrated rising third phase in the absence of pelvicalyceal hold up of tracer due to marked parenchymal retention of 99mTc MAGS in delayed images.

Table-I shows the value of GFR and ERPF in various renal groups. Normal functioning renal transplant group was having higher values of GFR and ERPF compared with those of control group.

In ATN and rejection, marked reduction in GFR and ERPF was noted. In renal transplant patients having urinary tract infection and outflow obstruction, GFR and ERPF flow were fairly maintained. Good linear correlation (r = 0.89) was observed between these two parameters.

Values of PI determined in control and renal transplant groups are shown in table-II. PI values were within normal range in controls and well functioning renal transplants. ATN group showed higher values but less than 1.5.

Patients with acute and chronic rejection showed a PI greater than 1.5. In urinary tract infection and outflow obstruction patients, PI was well maintained within normal limits. PI calculated with both agents was maintained within normal range in all groups except in cases of rejection.

No statistically significant difference was noted in PI calculated by 99mTc MAG3 and 99mTc DTPA first pass studies in different renal groups. An excellent linear correlation (r = 0.96) was observed between 99mTc DTPA and 99mTc MAG3 for PI. R-20/3 (parenchymal retention index) values for control and renal transplant patients are given in table 3.

Values obtained for normal functioning renal transplant group were relatively higher than those of controls. In patients having ATN and rejection, R-20/3 was markedly raised. There was a poor correlation (r=0.63) between 99mTc MAG3 and 99mTc DTPA for the calculations of parenchymal retention index.

DISCUSSION

In this study, we have compared 99mTc MAG3 and 99mTc DTPA to evaluate renal functions in patients with renal transplants. Our results demonstrated equal diagnostic efficacy of both agents. However superior image quality with 99mTc MAG3 was found in all the subjects, more marked when renal function were compromised.

Delayed 99mTc MAG3 images showed marked parenchymal retention of tracer in cases with ATN and rejection as compared to that of 99mTc DTPA. With respect to perfusion and parenchymal uptake phase 99mTc MAG3 and 99mTc DTPA renograms behaved similarly in all groups, however kinetics were more rapid with 99mTc MAG3.

In contrast to 99mTc DTPA flat renograms in ATN and rejection group of patients, 99mTc MAG3 demonstrated rising third phase in the absence of pelvicalyceal hold up.

Good linear correlation was observed between GFR and ERPF. No statistically significant difference was noted in PI calculated by 99mTc MAGS and 99mTc DTPA.

R-20/3 values with 99mTc MAG3 were significantly higher in acute tubular necrosis and rejection groups than those with 99mTc DTPA. Poor correlation was observed between two radiopharmaceuticals for this parenchymal retention index.

99mTc DTPA is a glomerular filtered radiopharmaceutical having 2 to 3 times lower first pass extraction fraction than that of 99mTc MAG3, which is a tubular secreted agent[12,13]. This difference in first pass extraction is responsible for rapid dynamics and better image quality observed with MAG3, as shown in our study[6].

Table -1. GFR(ml/min.) In and transplant patients

Kidney Group	GFR		ERPF		R	P
	MEAN	SD	MEAN	SD		
Normal control	57.8	7.46	245.96	64.77		<0.00001
Normal transplant	67.4	16.9	316.1	64.3		<0.00001
ATN transplant	26.5	6.2	168.8	34.9	0.89	<0.00001
Rejection transplant	18.2	9.19	139.45	19.25		<0.0004
UTI transplant	60.5	34	286.3	8.1		★
outflow obstruction	65.4	10.5	302	52.4		★

**= P values was not calculated because of only two patient in the category*

Table -11. Perfusion index of control and renal transplant groups

Kidney Group	Tc-99m MAG3		Tc-99m DTPA		R	P
	MEAN	SD	MEAN	SD		
Normal control	1.17	0.17	1.19	0.24		<0.00001
Normal transplant	1.11	0.24	1.13	0.22		<0.00001
ATN transplant	1.25	0.19	1.29	0.16	0.96	<0.00001
Rejection transplant	2.03	0.1	2.36	0.71		<0.00001
UTI transplant	1.04	0.14	1.23	0.1		★
outflow obstruction	1.18	0.15	1.16	0.11		★

**= P values was not calculated because of only two patient in the category*

Table -111. R-20/3 in control and renal transplant patients (Cortical Retention index)						
Kidney Group	Tc-99m MAG3		Tc-99m DTPA		R	P
	MEAN	SD	MEAN	SD		
Normal control	0.33	0.14	0.47	0.1		<0.00001
Normal transplant	0.52	0.18	0.65	0.21		<0.00001
ATN transplant	1.15	0.18	0.65	0.13	0.63	<0.00001
Rejection transplant	1.66	0.49	1.13	0.21		<0.00001
UTI transplant	0.6	0.11	0.64	0.1		★
outflow obstruction	0.61	0.09	0.68	0.12		★
*= P values was not calculated because of only two patient in the category						

In normal kidneys, 99mTc DTPA shows good selective accumulation at 2 minutes with transit into the collecting system by 5 min with good renal clearance [10]. 99mTc MAG3 shows 2-3 times higher tracer uptake, better quality image, low background and earlier appearance of radioactivity in urinary bladder[7]. With image quality as parameter, our results are similar to the findings of previous studies[7,16]. Britton et al.[12] used four folds greater administered activity of 99mTc DTPA than 99mTc MAG3 and found superior images obtained with 99mTc MAG3 especially in cases of deteriorating renal transplant. Marked parenchymal retention of 99mTc MAG3 observed in delayed images of ATM could be due to proximal tubular ceJi damage, basement membrane disruption and delayed transit time with increased absorption of solute[1]. In renal transplant patients having urine outflow obstruction, our results are similar to the previous studies[6, 14-17] demonstrating pelvicalyceal hold up and rising third phase of renogram, which failed to respond to diuretic stress.

Renograms are integral part of renal scintigraphy for evaluation of transplant kidney[1,6,18]. In normal subjects and patients having normal functioning renal transplant, renograms of both radiopharmaceuticals behave in a similar fashion. However in transplant subjects, peak height is higher and excretory phase is prolonged as compared to controls, most likely due to compensatory renal hypertrophy.

In cases of ATN, although renograms of two radiopharnaceuticals are similar with respect to perfusion and uptake phase, but excretory phase behavior is quite different. Instead of flat 99mTc DTPA curve, a slowly rising curve indicating marked parenchymal retention of 99mTc MAG3 is observed.

Patients with moderate to severe rejection showed similar perfusion and uptake phases of renograms, however excretory phase was different, that is, rising curve with 99mTc MAG3 compared to flat curve with 99mTc DTPA. This slow rising curve observed with 99mTc MAG3 in the absence of pelvicalyceal hold up of tracer is attributed to marked parenchymal retention in delayed images of ATN and rejection

PI is a reliable parameter to differentiate ATN from rejection especially in serial studies which is normal in ATN while raised in rejection?[9,22]. Padhy et. al. observed that Pi has a sensitivity of 100 % and specificity of 98 % in the diagnosis of acute rejection[21]. In our study there is a good correlation for PI between the two agents.

It has been reported that 99mTc MAG3 gives higher cortical PI compared with 99mTc DTPA[23]. PI is independent of radiotracer agent being injected and

mechanism of its renal uptake, however markedly affected by the quality of bolus. Variability of injection plays a major role in interfering with its reproducibility[24-25]. The difference of our results compared with previous studies may be due to use of different bolus technique employed.

In general R-20/3 is similar for both radiopharmaceuticals except in the cases of ATN and rejection. In these two subgroups of patient, although similar pattern is seen with both radiopharmaceuticals, however values differ which may be attributed to the flat or shallow 2nd phase of 99mTc DTPA and rising third phase of 99mTc MAGS renograms, and marked parenchymal retention of the later one in delayed images. In the absence of hold up tracer in pelvicalyceal system, significant rise in R-20/3 with 99mTc MAG3 is characteristic of acute tubular necrosis and rejection. Moreover, degree of rise in R-20/3 has been found to correlate strongly with the severity of acute tubular necrosis and rejection[11]. Poor correlation between the two radiopharmaceuticals in renal transplant patients observed in our study could be due to marked parenchymal retention of 99mTc MAG3 in cases of acute tubular necrosis and rejection as compared to 99mTc DTPA.

CONCLUSION

99mTc MAG3 and 99mTc DTPA have equal diagnostic efficacy in evaluation of renal transplant. However in the presence of compromised renal function visual delineations of the kidneys is better with 99mTc MAG3. Those who are used to 99mTc DTPA studies and have little exposure to 99mTc MAG3, should be cautious in interpreting 99mTc MAG3 renograms in renal transplant cases due to difference in 3rd phase of renogram in ATN and rejection.

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