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Original Article

The Role of Technitium^{99m} – Mercapto – Acetyltriglycin "MAG_3" in Pediatric Renal Diseases

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Abstract

Objectives: This work was conducted to evaluate the role of the relatively newly developed radiopharmaceutical ^{99m}Tc MAG_3 in pediatric renal diseases.

Methods: Fifty children with different renal diseases with age ranging from one month up to 13 yrs were subjected to clinical, lab. assessment [blood urea nitrogen, s. creatinine, urine analysis]; radiological assessment including plain X ray [all cases] intravenous urography (33 patients) and conventional cystourethrography (for 7 patients with vesico-ureteric reflux); ultrasonography [all cases]; and radio-nucleotide assessment including ^{99m}Tc MAG_3 examination [all cases] to visualize renal perfusion and generate renogram curves to obtain separate renal function of each kidney; static ^{99m} Tc DMSA [25 cases]; and finally indirect radionucleotide cystography for cases of vesico-ureteric reflux (VUR).

Results: When we compared the results we considered each kidney and its ureter separately as a renal unit. 17 renal units showed pelvi-ureteric junction obstruction. False positive obstruction was present in 2 renal units, while there were no cases of false negative obstruction. From the 12 renal units of VUR (shown by micturating cystourethrogram), indirect radio-nucleotide cystography detected 9 units (75%) while the other 3 units (25%) were not discovered. In the renal failure group (10 units) renogram curves showed a plateau pattern (4 units) and a downward sloping pattern (6 units). Four renal units (stone group) showed relative function ranging from 5.5-31.1%. Four renal units with Wilm's tumor showed the lesion as a photopenic area with reduced relative function. Multicystic renal disease group (4 units) showed no accumulation of radiotracer. Regarding renal agenesis; ectopic kidney (3 units); and horseshoe kidney (2 cases) ^{99m}Tc MAG_3 visualized all cases successfully. When comparing ^{99m}Tc MAG_3 with ^{99m}Tc DMSA in detection of scarring, it failed to discover scarring in 3 units visualized by DMSA while MAG_3 visualized 7 units of renal scarring not detected by intravenous urography (IVU).

Conclusion:

1. ^{99m}Tc MAG_3 is an ideal radiopharmaceutical for the investigation and follow-up of obstructive lesions; also for estimation and follow-up of differential and total renal function but is less effective in the detection of focal cortical scarring than ^{99m}Tc DMSA
2. ^{99m}Tc MAG_3 can visualize some renal anomalies (ectopic kidney and renal agensis).
3. Finally usage of ^{99m}Tc MAG_3 in pediatric field has no allergic reaction and physiological changes.

INTRODUCTION

The use of nuclear medicine procedures in the evaluation and management of pediatric diseases has dramatically increased over the past 15 years[1]. The radionucleotides, which are most commonly used in renal studies include orthoiodohippurate (OIH) labelled with ^{131} I or ^{123} I, dimercapto-succinic acid (DMSA), diethylene triaminepentaacetic acid (DTPA). Mercapto-acetyl triglycine, (MAG_3), labelled with ^{99}Tc, introduced recently, has gradually replaced OIH

and DTPA in clinical practice[2]. ^{99m}Tc MAG_3 is considered a good substitute for ^{131}I-OIH in quantitative renal function protocols and in generation of renogram curves that are used routinely in practice[3]. ^{99m}Tc MAG_3 is an excellent renal radiopharmaceutical in routine use. It has many advantages over ^{99m}Tc DTPA with comparable relative function and transit time studies and it is particularly suitable for the evaluation of renal transplants[4]. Therefore we conducted this study to evaluate the role of the relatively newly developed radiopharmaceutical ^{99m}Tc MAG_3 in different renal diseases in pediatrics.

PATIENTS AND METHODS

This study was carried out on 50 children with age ranging from one month up to 13 yrs with mean age 7.02 yrs ± 3.43 S.D of both sexes [M:F 2:1]. They were selected from patients of Zagazig University Hospitals [pediatrics, urology and nephrology departments] and the out-patient clinic of the National Research Centre. The patients were classified according to their diagnosis into different groups including pelvi-ureteric junction (PUJ) obstruction (11 cases), renal failure (5 cases), urinary tract calculi (4 cases), vesico-ureteric reflux (VUR) (7 cases), Wilm's tumor (4 cases), multicystic renal disease (4 cases), agenesis of one kidney (4 cases), renal ectopia (3 cases), duplex kidney (4 cases), nephrotic syndrome (4 cases), horseshoe kidney (2 cases), operated ectopia vesica (1 case) and posterior urethral valve (1 case). These patients were referred to the nuclear medicine unit, radiology department, Zagazig University. The children were subjected to clinical and labaratory assessment. Radiological investigation included plain X ray of urinary tract (all cases), IVU (38 cases) and conventional cystography for 7 patients with VUR 2 weeks before scintigraphy, ultrasonography for all cases. Radionucleotide assessment included ^{99m}Tc MAG_3 and ^{99m}Tc DMSA using Toshiba digital gamma camera model GCA-901 A/HG with 107 photomultiplier tubes and low energy parallel hole high resolution collimator linked to Toshiba computer system (GM 5500A).

Method of ^{99m}Tc MAG_3 Examination:

After preparation of the child with good hydration and sedation with chloral hydrate in a dose of 50 mg/kg B.W., he was scanned in the supine postion and injected with ^{99m}Tc MAG_3 I.V rapidly according to B.W as 4MBQ ^{99m}Tc MAG_3/kg B.W., followed by saline flush. computer acquisition was started immediately with injection in a series of 1-second frames for 60 seconds [angiographic phase]; then 5 second frames for 4 minutes, to assess renal function, then sequential images were taken as 25 second frames for 25 min. (60 frames). From the collected data between 1-5 min. after injection we calculated the relative or differential function of each kidney and built a renogram curve for each kidney. The renogram analysis data included T max (time to reach maximum activity), C max (maximum count) and $T^{1/2}$ (time needed to reach half activity) for each kidney. Static ^{99m}Tc DMSA was performed within 1-2 weeks after MAG_3 examination to 25 cases with urinary tract infection (UTI) associated

with other renal diseases and some renal anomalies to compare the results obtained from MAG_3 study as regards cortical scarring. Finally, the VUR group was subjected to indirect radionucleotide cystography (IRC) at the end of ^{99m}Tc MAG_3 study. Data were statistically analysed using software computer package supplied with EpiInfo package for medical statistics[5]. p-value less than 0.05 was considered statistically significant.

RESULTS

When comparing the results we considered each kidney and its ureter separately as a renal unit. The results are summarized in Tables (1 – 14).

Table (1) demonstrates renal parenchymal thickness on US study. It was observed that the left is more thick than the right kidney and this slight difference was not significant statistically. On the other hand, Table (2) illustrates renal depth (in cm) on ^{99m}Tc MAG_3 study. It was observed that the right (RT) kidney has more depth than the left (LT). However, this slight difference was not significant statistically.

Table (3) shows maximum count [in kc/min] at both kidneys. It was observed that maximum count over LT kidney was more than that over RT kidney. Table (4) illustrates time to peak (T max) in min. at both kidneys. It was observed that T max at LT kidney was more than that of RT kidney but with no statistically significant difference. Table (5) describes time to reach one half activity ($T^{1/2}$) in min at both kidneys. It was observed that there was no difference between both kidneys.

Table (6) illustrates the size of PUJ obstruction units with US. It was observed that there were 17 obstructed renal units. Ten units were enlarged in size (59%), 5 units had normal size (29%) and 2 were small in size (12%). Table (7) demonstrates a comparison between IVU and MAG_3 results regarding functioning units of the PUJ group. It was found that IVU study showed 7 functioning units while ^{99m}Tc MAG_3 examination showed only 4 non-functioning of these 7 while the other 3 units exerted tracer acumulating activity with relative function ranging from 20.9%-26.1%.

Table (8) describes parenchymal thickness and back-pressure changes at the 4 non functioning units in Table (7). We found that thickness by US was less than 4 mm. Two units showed marked back-pressure changes, while another 2 units showed slight back-pressure denoting post-obstructive atrophy of these units. Table (9) illustrates excretion rate of PUJ obstruction group. $T^{1/2}$ was taken as an indication of excretory function of the kidney. $T^{1/2}$ less than 10 minutes was considered normal[6]. From this table we noticed that 5 units had delayed excretion [$T^{1/2}$ more than 10 min and less than 30 min] with $T^{1/2}$ ranging from 20.8-29.3 min. Another 8 renal units showed markedly delayed excretion. ^{99m}Tc MAG_3 study showed obstructed renogram pattern of 17 units which was defined as steadily rising renogram curve with failure to drain promptly at 10 min. Two false + ve obstructed units were seen in our study. Table (10) demonstrates a comparison between micturating cysto-urethrogram

Table (1): Renal parenchymal thickness on ultrasound examination

	Range	Mean	S.D.
Right kidney	2-15 mm	9.92	± 6.52
Left kidney	3-15 mm	10.59	± 5.67

Table (2): Renal depth (in cms) on both sides

	Range	Mean	S.D.
Right kidney	2.15-5.87 cms	4.03	± 1.47
Left kidney	2.17-5.62	3.9	± 1.47

Table (3): Maximun count (in kc/min) at both kidneys

	Range	Mean	S.D.
Rt kid	1.46-57.58	20.26	± 18.20
Lt kid	2.67-123.59	25.9	± 30.95

Table (4): Time to peak (Tmax) in min at both kidneys

	Range	Mean	S.D.
Rt kid	0.67-29.17	5.92	± 6.89
Lt kid	0.38-28.75	7.72	± 7.84

Table (5): Time to reach half activity ($T^{1/2}$) in min at both kidneys (∞ means that time could not be reached till end of examination)

	Range	Mean	S.D.
Rt kid	3.83-∞	13.62	± 12.73
Lt kid	3.5-∞	13.60	± 12.95

Table (6): Size of PUJ obstruction units

Size	Number of units	%
Normal	5	29 %
Enlarged	10	59 %
Small	2	12 %

Table (7): Delayed and non-functioning units in IVU and MAG_3 examination

	IVU	MAG_3
Delayed function	In 3 Units	.....
No function	In 7 Units	4 Units

Table (8): Parenchymal thickness and back pressure changes at the 4 non-functioning units in ^{99m}Tc MAG$_3$ examination

	Parenchymal thickness	Back pressure
Unit 1	3 mm	Marked
Unit 11	2 mm	Marked
Unit 111	2 mm	Slight residual
Unit IV	3 mm	Slight residual

Table (9): Excretion rate of PUJ obstruction group

Excretion rate	Number of renal units	%
Delayed	5	25%
Markedly delayed	8	47%

Table (10): Comparing MCUG and IRC in detection of VUR

	MCUG						IRC					
	Rt		Lt		Total		Rt		Lt		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Reflux	7	58	5	42	12	100	6	50	3	25	9	75
No reflux	--	--	--	--	--	--	1	8	2	17	3	25

Table (11): Plain film, IVU, US and ^{99m}Tc MAG$_3$ data of the 4 renal units with stones

	Plain IVU data			US data			^{99m}Tc MAG$_3$ data	
	Stones	Hydronephrosis	Contrast excretion	Size	Back-pressure	Parench. thickness	Excretion rate	Relative function
First unit	2 stones at lower ureter and lower calyx	Mild Hydrorephnosis	Good	Normal	Mild	Normal	Delayed	24.3%
Second Unit	Small stone at renal pelvis	Mild Hydronephrosis	Good	Normal	Mild	Normal	Delayed	31.6%
Third Unit	Stone upper pole & stone midpart ureter	Moderate Hydronephrosis	Good	Normal	Moderate	Reduced (8 mm)	Markedly Delayed	13.1%
Fourth Unit	Big stone pelvi-ureteric region	No function	Non-Functioning	Normal	Marked	Minimal (4 mm)	Markedly Delayed	17.4%

Table (12): Data concerned with the multicystic kidney group

Case	Age	Presentation	IVU	US	MAG_3
				Appearance	Examined
1st case	1 mon	Accidental discovery during prenatal US examination	Not done because of young age	- Enlarged - Irregular outlines - Multiple cysts - No parenchy	No definite radiotracer accumulating function
2nd case	3 mon	Accidental discover during prenatal US examination	Not done	- Enlarged - Lobulated - Multiple cysts - No parenchy	No accumulating Function
3rd case	4 yrs	Abdominal swelling	Unilateral non-functioning kidney with normal other kidney	As above	No accumulating Function
4th case	4.6 yrs	Abdominal swelling	Unilateral non-functioning kidney with normal other kidney	As above	No accumulating Function

Table (13): Comparison between ^{99m}Tc MAG_3 and ^{99m}Tc DMSA in detection of renal scarring (40 kidneys in 20 pts)

A:

	^{99m}Tc MAG_3						^{99m}Tc DMSA					
	Rt		Lt		Total		Rt		Lt		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Scar	14	70	14	70	28	70	15	75	16	80	31	78
No scar	6	30	6	30	12	30	5	25	4	20	9	22

$X^2 = 9.87$ $p < 0.05$

B:

^{99m}Tc DMSA	^{99m}Tc MAG_3	
	Scar	No scar
Scar	28	3
No scar	--	9

Table (14): Comparison between ^{99m}Tc MAG_3 and IVU in detection of renal scarring (40 kidneys in 20 pts)

A:

	^{99m}Tc MAG_3						^{99m}Tc DMSA					
	Rt		Lt		Total		Rt		Lt		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Scar	14	70	14	70	28	70	10	50	11	55	21	53
No scar	6	30	6	30	12	30	10	50	9	45	19	47

$X^2 = 8.751$ $p < 0.05$

B:

IVU	^{99m}Tc MAG_3	
	Scar	No scar
Scar	21	0
No scar	7	12

(MCUG) and IRC results in detection of VUR. From the table we observe that IRC succeeded in detection of VUR in 9 units of 12 [75%] and failed to detect it in 3 units [25%]. The comparison was stastistically significant (p value < 0.05). As regarding the renal failure group (5 cases, 10 renal units); ^{99m}Tc MAG_3 study showed markedly decreased radiotracer accumulating function of all renal units [C max (1.46-4.94 kc/min), T max (0.38-1.28 min) less than normal which is (2.5–5min)]. Renogram curves showed a plateau pattern (4 units) and downward sloping pattern (6 units). Table (11) illustrates a comparison between results of plain film, IVU, US and ^{99m}Tc MAG_3 of 4 renal units with stones. In the renal tumor group [4 renal units with Wilm's tumor]; MAG_3 showed the lesion as photopenic areas with reduced relative function of all units ranging from 24.7%-33.3%.

Thus the role of ^{99m}Tc MAG_3 study in these cases is to assess perfusion of the tumor and function of the contralateral kidney pre-operatively. Table (12) shows data concerned with the multicystic kidney group (4 units). It was observed that kidneys in 4 units were non-functioning and kidneys on the other side were normal by MAG_3 study. Table (13) demonstrates a comparison between ^{99m}Tc MAG_3 and ^{99m}Tc DMSA in detection of renal scarring (40 kidneys in 20 patients). It was observed that 28 renal units showed in both investigations while 9 units showed no scar in both investigations, 3 units showed + ve scarring in DMSA examination and – ve scarring with MAG_3. A significant comparison was present between the two investigations. With ^{99m}Tc MAG_3 sensitivity was 90% in detecting scarring. Table (14) illustrates a comparison between ^{99m}Tc MAG_3 and IVU in detection of renal scarring (40 kidneys in 20 patients). From this table we noticed the presence of scarring in renal units at both investigations. No scar was detected in 7 units at IVU

examination, but it was detected by ^{99m}Tc MAG_3 examination. However, the two investigations showed no scar in 12 renal units.

DISCUSSION

Renal scans in children allow quantitative measurment of total and individual renal function. It allows adequate visualization of the kidney in neonates and older children with poor renal function[7]. ^{99m}Tc MAG_3 which is a relatively new developed radiopharmaceutical is increasingly being used to evaluate adult and pediatric renal tract disease[8]. As regards PUJ obstruction group all 17 renal units were diagnosed with MAG_3 renal scan, and also by US and IVU and follow-up at operation. False + ve obstruction was present in 2 renal units while no cases of false – ve obstruction were found. Wong et al.[9] in their study of 27 obstructive cases found 18 renal units with PUJ and these were all proved by US and operative procedure. They also found false + ve obstruction in one unit. They attributed this false obstruction to the effect of gravity as they noticed that there was good clearance with gravity-assisted drainage, but we suggest that this is due to improper hydration of a child young of age (one unit) and noncoopreation (another unit). Also Rossleigh et al.[10] found 3 false - ve units in their 50 children studied. They attributed this to what is called the phenomenon of transitional hydronephrosis, in which progressive renal maturation may result in either progression or resolution of obstruction. As a whole, our results showed that MAG_3 renal scan in PUJ obstruction is reliable in the diagnosis and assessment of the extent of disease and this was the same in the work of Wong et al.[9]. When we shift to cases of VUR, our study revealed that the youngest child who had successful IRC was 4 yrs old. Pickworth[11] showed that the youngest child with successful IRC was 2 years and 4 months old. From our study; in 12 renal units of VUR (shown by MCUG), the IRC detected 9 units (75%) while the other 3 units 25% were not discovered which were of early grade reflux. Our data was in agreement with Sadeleer et al.[12]. On the other hand, the Pickworth group[11] showed that ^{99m}Tc MAG_3 IRC discovered reflux in 4 renal units which were not discovered by MCUG and failed to detect reflux in 8 renal units already diagnosed by MCUG. Thus IRC has an important role in diagnosis of VUR and follow-up of cases of proved reflux, as it has several advantages over MCUG especially in the pediatrics field. Its main disadvantages include less accuracy in early grade refluxes, and lack of anatomical information. Regarding renal scarring in this study, our results showed scarring in 70% of renal units studied for UTI while DMSA discovered renal scarring in 78%, and MAG_3 failed to detect 3 units shown scarring with DMSA examination, but no renal units were shown to be scarred with MAG_3 and by DMSA. Tc MAG_3 has 90% sensitivity in comparison. Our results coincide with the results of Pickworth[11] and Piepsz et al.[13] and Al-Kaylani[14].

From these comparisons we notice that ^{99m}Tc MAG_3 was less effective for detection of focal cortical scarring than ^{99m}Tc DMSA because of higher information density and

multiple projections routinely imaged in DMSA study but MAG_3 scan has the benefit of lower radiation dose to children at this sensitive age. In addition, ^{99m}Tc DMSA may underestimate the degree of cortical scarring especially in instances where there is bilateral global cortical scarring[15]. Also our results showed that MAG_3 was superior to IVU in detection of renal scarring with significant correlation between the two investigations. MAG_3 detected 7 renal units with scarring which were not detected by IVU. Our results were in agreement with Pickworth and his colleagues[11] Concerning multicystic renal disease (MCD) all the 4 units in our study showed no accumulating function with no anomalies at the other side by MAG_3 scan. The same results were seen with Tyrrell et al.[8] who studied 10 children with MCD and found that in all units renal function was absent, but they stated that abnormalities of the contralateral kidney may be present in up to $\frac{1}{3}$ of cases including VUR, PUJ obstruction, renal hypoplasia or malrotation.

From these results we can propose that ^{99m}Tc MAG_3 can replace Tc DMSA in MCD of the kidney as it allows better assessment of the contralateral kidney and permits full differentiation between MCD of the kidney and congenital hydronephrosis. Regarding other congenital anomalies in our study such as renal agenesis, ectopic kidney, renal duplication and horseshoe kidney, we discovered these cases successfully with MAG_3 and also we can assess the relative renal function. Regarding renal failure cases, stone formation, posterior urethal valve and nephrotic syndrome cases in our study, MAG_3 examination added important information about relative renal function and presence of associated infection and scarring in these cases. In Wilm's tumor MAG_3 can visualize it as a space occupying lesion in the kidney with assessment of accumulating function of the contralateral kidney. Finally MAG_3 injection showed no allergic reactions and physiologic changes. This is in agreement with Torizuka et al.[16] who studied the safety and efficacy of ^{99m}Tc MAG_3 on 110 children and adults and documented that neither adverse reactions nor abnormal laboratory finding were observed due to IV injection of ^{99m}Tc MAG_3.

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