

# Assessing Tubular Damage due to Cisplatin Nephrotoxicity, using Tc-99m MAG3

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## Abstract

Cisplatin causes direct injury to proximal convoluted tubules of the kidneys, toxicity similar to its tumour cytotoxicity. This study was performed to assess the utility of Tc-99m MAG3 to detect tubular damage. Ten patients, who were advised Cisplatin therapy as a part of chemotherapy plan for various types of cancer, were recruited to the study following ethical approval and informed consent. A baseline dynamic renal study was performed in all patients and was repeated approximately 5 weeks after the first dose of the Cisplatin. All patients had normal serum urea and creatinine levels at the time of both visits. T-max and T<sub>1/2</sub> were determined from renograms time activity curves. Total renal uptake (TRU) of Tc-99m MAG3 was calculated from the integrated area under the curve from 1-2 minutes of the renogram. Furthermore ERPF was also estimated by using the single plasma sample method for Tc-99m MAG3. Results showed no significant difference in mean pre-therapy and post-therapy values of T-max ( $p=0.407$ ) and T<sub>1/2</sub> ( $p=0.922$ ). TRU was reduced from  $27.8 \pm 8.2\%$  at baseline to  $24.5 \pm 8.7\%$  after Cisplatin therapy, a reduction of 11.9% from the base line value. However this difference was not statistically significant ( $p=0.121$ ). The reduction in ERPF was found to be 17.9% with mean  $\pm$  SD value of  $487.3 \pm 79.4$  ml/min/1.73m<sup>2</sup> in the pre-treatment study and  $400.0 \pm 38.8$  ml/min/1.73m<sup>2</sup> in the post-treatment study. This was found to be statistically significant ( $p=0.009$ ). It was concluded that ERPF determined from single sample formula using Tc-99m MAG3 may be used clinically to evaluate the tubular damage by cytotoxic drugs. The renogram parameters have less value in this regard.

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## Introduction

Nephrotoxicity is the major dose-limiting factor for Cisplatin (cis-diamminedichloroplatinum) therapy. The acute form of toxicity can be prevented to some extent by adequate patient hydration. However, the strong emetic effect of the drug can reduce hydration status (1). Hence the functional status of the kidneys during and after the treatment should be monitored. During subclinical renal damage proximal tubules are primarily affected (2). The routine renal functional assessments such as blood urea nitrogen, serum creatinine, creatinine clearance and protein analysis in urine are less reliable (3, 4). Effective renal plasma flow (ERPF) is an absolute parameter for the quantification of the functional capacity of proximal convoluted tubules. It has been employed to determine the nephrotoxic effects of Cisplatin (5, 6).

Tc-99m mercaptoacetyltriglycine (MAG3) is a renal tubular agent, which is accepted as the radiopharmaceutical of choice for dynamic renal scintigraphy (7-9) and is widely applied to measure ERPF (10). Ninety percent of Tc-99m MAG3 in plasma is bound to proteins (11) and only free 10% is subjected to glomerular filtration. If the normal value of filtration fraction is 20% then only 2% of Tc-99m MAG3 is filtered out, which is negligible. Bubeck et al. (12) have therefore described clearance of MAG3 as 'Tubular Extraction Rate' (TER). It is defined as 'virtual plasma volume per minute from which a substance is completely removed by tubular extraction'. Furthermore renal uptake of Tc-99m MAG3 has also been used effectively as functional parameter of renal tubules (13).

The present study was conducted to evaluate the utility of Tc-99m MAG3 by taking into consideration the changes in its parameters following Cisplatin administration. The study was initiated after approval from the local ethical committee.

S. No.	Age (yrs)	Sex	Body Surface Area (m <sup>2</sup> )	Cisplatin Dose (mg/m <sup>2</sup> )	Diagnosis
1	62	M	1.91	344	Bronchogenic Carcinoma
2	30	F	1.55	232	Nasopharyngeal Carcinoma
3	36	F	1.54	154	Squamous Cell Carcinoma
4	39	M	1.76	792	Squamous Cell Carcinoma
5	38	F	1.66	332	Transitional Cell Carcinoma
6	24	M	1.69	152	Seminoma Testis
7	48	M	1.65	330	Bronchogenic Carcinoma
8	26	F	1.40	196	Ovarian Carcinoma
9	57	M	1.63	163	Squamous Cell Carcinoma
10	54	M	1.54	185	Bronchogenic Carcinoma

**Table-1.** Demographic profile of the patients included in the study with respect dose of Cisplatin administered before the second visit

## Materials and Methods

### Patients

Ten patients, six males and four females, with a mean age of 41.4 years (SD= 13.3) were included in the study (Table-1). They were advised Cisplatin therapy for various solid tumours. Informed consents were taken from all the patients prior to the study. They had received an average of 288 mg/m<sup>2</sup> (range: 152 to 792 mg/m<sup>2</sup>) Cisplatin dose prior the second visit for renal scintigraphy. They were kept adequately hydrated during the therapy.

### Scintigraphic Study

Commercially available lyophilised MAG3 kit (Isotope Production Division of PINSTECH, Islamabad, Pakistan) was boiled for ten minutes with freshly eluted Tc-99m pertechnetate. The labelling efficiency was found to be >97%. The baseline scan was done before the start of chemotherapy with approximately 200 MBq of Tc-99m MAG3. It was repeated 4-5 weeks (35.8±7.2 days) after initialisation of first cycle of Cisplatin with almost similar dose of the radiopharmaceutical and under similar physiological conditions. All patients were asked to drink 200-300 ml of water for maintaining the hydration during the study. Full and empty syringe counts were acquired before and after acquisition respectively.

Dynamic images were acquired on Siemens Orbiter gamma camera. A total of 138 frames were acquired out of which the first 60 were at a rate of one second/frame starting immediately after injection of the bolus. Twenty-four frames at a rate of 5 seconds/frame and 54 at a rate of 30 seconds/frame immediately followed it. The whole acquisition was completed in 30 minutes.

### Biochemical Studies

Serum levels of electrolytes, urea and creatinine were assessed in all patients during both visits. Urine was also

examined routinely for proteins, glucose and pH, and microscopically for red blood cells and casts.

### Data Analysis

Activity-time curves (renograms) were generated using dedicated computer software and time to the maximum activity in the kidneys (T-max) and time to the half of its value (T1/2) were determined. Renal uptake of Tc-99m MAG3 during the second minute of the study was calculated by using following equation by Itoh et al. (13) based on Schlegel (14) and Gates (15) methods:

$$\% \text{RU} = (C/De^{-0.15d}) \times 100 \quad (\text{equation- 1})$$

Where: %RU is the percent renal uptake of one kidney, C is background corrected 1-2 minutes post-injection counts of that kidney and D is injected dose. Depth correction factor (d) for the right kidney is 13.631(W/H)<sup>0.6996</sup> and for left kidney is 14.0285(W/H)<sup>0.7557</sup>, calculated from body weight in kg (W) and height in cm (H). Total renal uptake (TRU) was calculated by adding the % uptake of radioactivity (RU) by the right and left kidneys.

ERPF was determined from the built-in software that uses Bubeck's single sample formula (16) and estimates ERPF from 'tubular extraction rate' (TER):

$$\text{TER (MAG3)} = ? \ln (ID/C_n) \text{ ml/min/1.73m}^2 \quad (\text{equation- 2})$$

Where:  $-517e^{(-0.011t)}$ ,  $295e^{(-0.016t)}$ , ID = injected activity in counts per second (cps), C<sub>n</sub> = plasma counts (cps/litre) at time "t" normalised to 1.73 m<sup>2</sup> body surface area. The blood sample was taken at about 40 minutes post-injection.

### Statistical Analysis

Mean ± SD of all the parameters was calculated. The student paired *t* test was used to determine the difference between various parameters in the baseline scan and post-therapy. Parameters having p-value less 0.05 was considered as significantly different.

## Results

The analysis of renogram parameters did not reveal any significant change in the T-max value from its mean pre-Cisplatin therapy value of 4.88 (SEM = 2.48) to the mean post Cisplatin therapy value of 5.52 (SEM = 2.81) with a *p* value of 0.407 (Table-2). There were also no significant difference in the mean  $T_{1/2}$  values before ( $12.49 \pm 4.46$  minutes) and after ( $11.53 \pm 5.48$  minutes) Cisplatin therapy, with a *p* value of 0.922 (Table-2)

The total renal uptake of Tc-99m MAG3 was reduced from  $27.8 \pm 8.2\%$  at the baseline to  $24.5 \pm 8.7\%$  during the post-therapy evaluation (Table-3). The mean fall in all the patients was 11.9%, which however was not found to be statistically significant (*p* = 0.121).

Table-3 also shows the comparison of ERPF values that were estimated from the tubular extraction rates (TER) of Tc-99m MAG3 of the patients in baseline and post-therapy scans. There were significant difference in the mean ERPF values before ( $487 \text{ ml/min}/1.73\text{m}^2$ ) (SD = 79) and after ( $400 \text{ ml/min}/1.73\text{m}^2$ ) (SD = 39) Cisplatin therapy with a *p* value of 0.009. The mean reduction in the ERPF was 17.9%.

No abnormal finding was seen in the biochemical and microscopic analysis of blood and urine in any patient before or after the therapy.

## Discussion

Cisplatin, chemically named as cis-diamminedichloroplatinum II (CDDP), is a cytotoxic agent commonly used for the treatment of solid tumours. It is an integral part of standard regimens for advanced ovarian and metastatic head and neck cancers. It can bring about complete cure in about 70-80% germ cell tumours and is also used effectively for bladder, lung cervical and endometrial cancers (17). Nephrotoxicity is one of the major concerns in the use of this drug for chemo therapy. It inflicts direct injury to the proximal convoluted tubules. Adjustment of the dose of a chemotherapeutic agent on the basis of renal function concomitantly is an essential component of oncologic practice (1). The decrease in effective renal plasma flow (ERPF) and tubular dysfunction has been used as measures of the damage. 2-microglobulin levels are sensitive parameters to detect the proximal tubular damage. However its abnormalities are detected primarily during the early tubular damage i.e. within 1 to 3 hours (18). Furthermore 2-microglobulin is unstable in acidic urine (19).

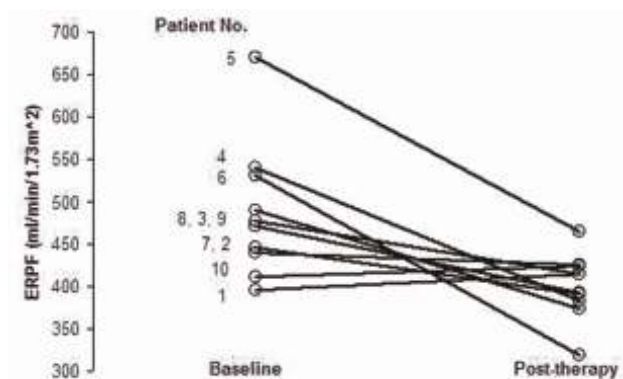
The ERPF has been used effectively to monitor the nephrotoxicity of Cisplatin. Meijer et al. (6) used I-131-orthoiodohipurate (OIH) to determine ERPF in patients treated with Cisplatin. He found reduction of ERPF from the median value of 705 ml/min to 514 ml/min with no

Parameter	Baseline	Post-therapy	<i>p</i> value
T-max	4.88±2.48	5.52±2.81	0.407
$T_{1/2}$	11.53±5.48	12.49±4.46	0.992

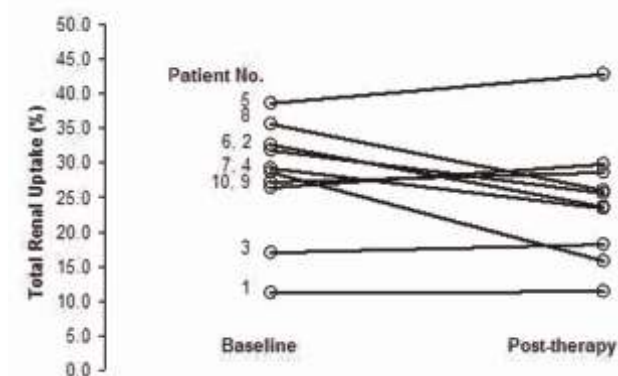
Table-2: Comparison of renogram parameters before and after Cisplatin therapy

S.No.	Total Renal Uptake (%)		ERPF (ml/min/1.73m <sup>2</sup> )	
	Baseline	Post-Therapy	Baseline	Post-Therapy
1	11.2	11.3	396	414
2	31.8	14.7	445	391
3	17.1	22.3	478	415
4	28.6	22.5	540	384
5	38.6	42.9	671	465
6	32.6	23.5	531	319
7	29.3	23.5	440	425
8	35.5	26.0	489	373
9	26.4	29.8	471	392
10	27.2	28.6	412	423
Mean±SD	27.8±8.2	24.5±8.7	487±79	400±39
	<i>p</i> = 0.121		<i>p</i> = 0.009	

Table-3. The values of TRU and ERPF before and after the Cisplatin therapy



**Figure 1.** Graphical representation of fall in post-therapy ERPF values following Cisplatin treatment



**Figure 2.** Graphical representation of fall in post-therapy renal uptake values

significant change in glomerular filtration rate, filtration fraction and serum creatinine. Tc-99m MAG3 is the most widely used dynamic tubular agent for the clinical evaluation renal functions. Its renal clearance is used for measurement of ERPF and has adequate reproducibility (10, 20). There is very limited published data available in literature describing its utility in the evaluation of renal toxicity. We calculated ERPF from Tc-99m MAG3 clearance using a single sample method and found the results similar to those described by Meijer et al. (6). There was a significant downward trend of the ERPF values after Cisplatin therapy ( $p = 0.009$ ). Figure 1 is the visual representation of the changes in the ERPF after Cisplatin therapy.

The uptake of Tc-99m dimercaptosuccinic acid (Tc-99m DMSA) has been found to be useful in detecting subclinical tubular injury caused by a nephrotoxic agents (20, 21). However its absolute uptake is not a true representative of absolute renal function (22). The uptake of Tc-99m MAG3 on the other hand is being used for estimation of its clearance (13, 14). In our study, there was 11.9% fall in the total renal uptake (TRU) of Tc-99m MAG3 after Cisplatin therapy, but it did not reach statistically significant level ( $p=0.121$ ). The comparison of TRU values before and after Cisplatin therapy shown in figure 2, exhibits an overview of the lack of any significant change.

The fall in TRU and ERPF values did not show conclusive correlation with the Cisplatin doses ( $r = 0.45$  and  $0.19$

respectively). For example, patient No. 6 received the lowest dose of Cisplatin, but the fall in TRU values was significant, i.e. 9.08% (which is 27.9% of the baseline value) and the reduction of ERPF value was the highest of all the patients ( $212.12 \text{ ml/min/1.73m}^2$ , which is 39.9% of the baseline value). On the other hand, patient No. 4, who received the highest dose of Cisplatin showed a comparatively smaller reduction of 6.1% (which was 21.3% of the base line value) in TRU. Concomitantly the reduction in the ERPF was also relatively low ( $156.71 \text{ ml/min/1.73m}^2$ , which was 29.00% of the baseline value).

The scintigraphic images obtained in our study did not show much difference between the baseline and post-therapy scans. One of the patients showed a photopaenic area in the bladder. It was found to be due to metastatic infiltration of the bladder wall by the primary ovarian adenocarcinoma. The semi-quantitative parameters i.e. T-max and T1/2 failed to demonstrate any deterioration in the renal functions. The previous study done with Tc-99m ethyl cysteinate dimer (Tc-99m EC) has also shown no scintigraphic change to revealing chemotherapy related nephrotoxicity (21).

## Conclusions

The single sample technique to measure ERPF from Tc-99m MAG3 clearance can be used routinely in clinical settings to monitor renal function in a patient receiving Cisplatin therapy. The biochemical analysis and the renogram parameters like T-max and T1/2 have no significant role in the detection of subclinical injury to proximal convoluted tubules.

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