ORIGINAL ARTICLE

Nephrotoxicity of CDDP Assessed Estimating Glomerular Filtration Rate With ^{99m}Tc-DTPA Plasma Sample Method

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ABSTRACT

Objective: To assess early nephrotoxicity of CDDP (Cis-diamminedichloroplatinum) manifested by a decline in the glomerular filtration rate (GFR) estimated by plasma two sample clearance method (PSC 2) after ^{99m}Tc-DTPA injection.
Study Design: Descriptive study.
Place and Duration of Study: Department of Nuclear Medicine, Karachi Institute of Radiotherapy and Nuclear Medicine, Karachi, from September 2004 to January 2005.
Methodology: The renal function was assessed on 36 patients suffering from different types of cancer and receiving CDDP in doses of ≥ 50 mg/m^2 before and after in each of six CDDP cycles. The GFR was determined by PSC 2 method after ^{99m}Tc-DTPA injection). A paired sample t-test was used for comparision of the mean value with significance at $p < 0.01$.
Results: There were (28 males and 8 females; age range being16-68 years) The average decline in GFR baseline to the end of sixth cycles was 43.86 ml/min/1.73m^2 (p=0.000) as estimated by PSC 2 method. There was a significant fall of average 9.36 ml/min/1.73m^2 ($p < 0.01$) in GFR as observed in each cycle of CDDP estimated by the PSC 2 method. In the initial four cycles, CDDP produced a major nephrotoxic effect of average 10.27 ml/min/1.73m^2 ($p < 0.01$) fall in GFR. This then gradually declined to a plateau of an average decline in GFR of 7.76 and 7.31 ml/min/1.73m^2 (p=0.000) after the 5th and 6th cycle respectively.
Conclusion: CDDP produced an early nephrotoxicity which was manifested by a significant decline in GFR in each cycle. Tc-99m PSC 2 method for GFR estimation should be used periodically for the early detection of nephrotoxicity induced by CDDP.

Key words: *Nephrotoxicity. CDDP. Glomerular filtration rate. PSC 2. DTPA.*

INTRODUCTION

CDDP (Cis-diamminedichloroplatinum), a heavy metal complex, remains a major antineoplastic agent for the treatment of solid tumours.[1] The full therapeutic potential of CDDP is limited by long-lasting and potentially debilitating toxicity, the principal target organ being the kidney. This toxicity is manifested by reduced renal function and leads to serum-electrolyte changes and pathological changes in the urine analysis.[2,3] So the assessment of the function of the kidneys in patients treated with CDDP is necessary at an early stage to avoid permanent renal damage.[4]

The glomerular filtration rate (GFR) is considered to be a representative parameter for evaluating the functional state of the kidney.[5,6] Measurements of GFR are based on the renal clearance of a marker in plasma, expressed as the volume of plasma completely cleared of the marker per unit time.[5,7]

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Plasma sample method following a single-injection after ^{99m}Tc-DTPA injection has been proved effective as an alternative to the continuous infusion method with inulin for the determination of GFR in a clinical practice.[8,9]

The objective of the study was to detect changes in GFR from baseline as estimated by PSC 2 ^{99m}Tc-DTPA method after each cycle of CDDP therapy.

METHODOLOGY

This study was conducted after informed consent from patients and approval by the Hospital Ethics Committee at the Department of Nuclear Medicine, Karachi Institute of Radiotherapy and Nuclear Medicine, Karachi, from September 2004 to January 2005. Subjects were prospectively on referral for a GFR measurement by the Chemotherapy outdoor patient department of the Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN).

Sample selection of the study was non-probability purposive. Inclusion criteria was planned cases for CDDP therapy in doses ≥ 50 mg/m^2 for various solid tumours, non-hypertensive/non-diabetics, with adequate baseline renal status (GFR ≥ 70 ml/min/1.73m^2) patients. Those who were taking other nephrotoxic drugs or doses of CDDP < 50 mg/m^2, known cases of renal failure or GFR < 70 ml/min/1.73m^2, hypertensive, diabetics, or hemodynamically unstable patients were

excluded from study. The renal status of all patients were assessed by PSC 2 method of GFR estimation as a baseline (two days prior to start of CDDP) and after every successive cycle of CDDP therapy.

^{99m}Tc-DTPA was used to measure GFR which was prepared by Isotope Production Division, PINSTECH, Islamabad. The labeling and quality control tests were carried out according to the instructions of the manufacturer. The radiochemical purity was ensured to be more than 90% before injection.

The GFR of each patient was measured before and after each of the six CDDP cycles by Plasma Clearance by two sample 60-180 min, Russell method after ^{99m}Tc-DTPA injection by Biodex Medical System Atomlab 950 version 3.08.10

^{99m}Tc-DTPA was prepared by following the package insert directions and two or more 5-mCi aliquots were drawn aseptically using a 3-cc syringe with a 22-gauge needle. One of the 5-mCi aliquots was set aside as the standard and the remainder were used for patient doses. The standard and the doses was calibrated carefully so that the percent difference between standard and dose should not under any circumstances exceed 5%.

The standard was prepared in a 1:10000 dilution. Seventy-five ml of water was added into each of the two 100 ml beakers; the standard dose was added into one beaker labeled 'A' or 1:100 dilutions. The syringe was rinsed into the 1:100 flasks and filled up to the 100 ml mark with water. With a volumetric pipette, 1 ml of solution from 1:100 dilution flasks was pipetted into another 100 ml beaker labeled 'B' or 1:10000 dilutions, filled up to the mark with water and mixed well. One test tube was labeled for standard and 0.1 ml of the 1:10000 dilutions was pipetted into the tube. The 5 mCi of ^{99m}Tc-DTPA was injected intravenously to the patient and the time of injection was recorded. The empty syringe was also recorded in the same way as the full syringe, both with camera and well counter and must be less than 3% of the dose. In the two samples method, the samples were drawn first at 60 minutes and second at 180 minutes from the contralateral arm in a collection bottle containing EDTA (Ethylene Diamine Tri-acetic-Acid), mixed well and centrifuged for 10 minutes. The sample was removed as soon as the centrifuge stopped. Then 0.1 ml of filtrate was pipetted out into the labeled test tube by using a micropipette. By using the Atomlab system, the GFR was automatically calculated in ml/min and then corrected for body surface area in ml/min/1.73m^2.

Data was analyzed by using Microsoft Excel 2003 and, Statistical Programme for Social Sciences (SPSS) version 11.0 data base programme. In order to observe statistical significance, patient data including the mean change in GFR from baseline, in response to each CDDP cycle, was compared using paired sample t-test. A p-value of less than 0.001 was considered significant.

RESULTS

The demographic characteristics of the study population are summarized in Table I. From 36 (28 males and 8 females) patients, 2 patients expired (one during the first week of the first cycle and the second after the third cycle). One patient was lost to follow-up after the third cycle, while 3 patients developed severe renal dysfunction. In addition to CDDP, the patients received 5-Flourouarcil and Etoposide which were not nephrotoxic.

Table I: Demographic characteristics of study population.

Demographic features	Mean ± S.D
Age	45.3 years ± 14.13
Body surface area (m^2)	1.54 ± 0.15 m^2
Average dose of CDDP/cycle (mg/m^2)	114.027 ± 22.32

S.D= Standard Deviation.

All patients were subjected to measure GFR by PSC 2 method as a baseline, before and after each of the six CDDP cycles. There was a significant decline in the GFR of the patients treated with CDDP from baseline to the end of the sixth cycle. The average decline in GFR was 43.86 ml/min/1.73m^2. There was a significant decline of an average of 9.36 ml/min/1.73m^2 in GFR as observed in each cycle of CDDP estimated by the PSC 2 method. The GFR values estimated (as stated in Table II) after the first dose of CDDP within the first week of the cycle (95.364±24.19 ml/min/1.73m^2) were significantly different ($p < 0.001$) from those of the baseline GFR estimated two days prior to the CDDP cycle (106.735±19.98 ml/min/1.73m^2).

Figure 1 demonstrates that CDDP produced a significant decline in GFR in each cycle even after the first dose. In the initial four cycles, the CDDP produced a major nephrotoxic effect of an average 10.27 ml/min/1.73m2 ($p < 0.001$) decline in GFR but with good recovery in-between successive cycles which indicated its reversibility.

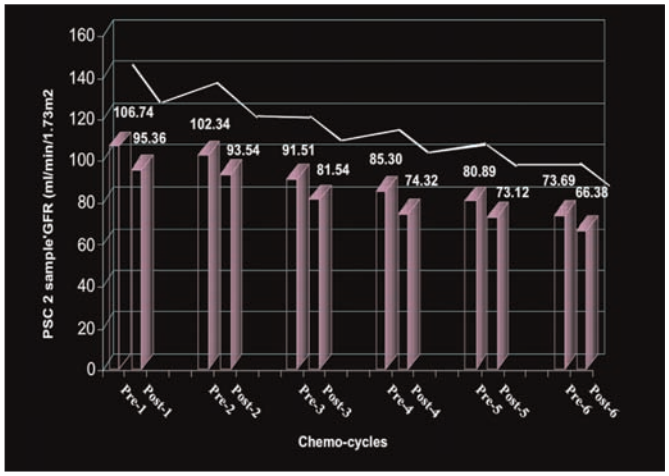

Figure 1: GFR values by PSC 2 methods in each pre and post-CDDP cycles.

Table II: Mean, SD and CID values of PSC 2 sample method in each CDDP cycles.

No. of patient	Chemo-cycles	PSC 2 sample's GFR (ml/min/1.73m^2)	Mean difference± SD b/w pre and post-chemo (ml/min/1.73m^2)	p-value	95% Confidence interval of difference	
					lower	upper
36	Pre1 vs post1	106.74	11.37± 10.48*	0..000	7.83	14.92
		95.36				
35	Pre2 vs post2	102.34	8.79 ± 14.13*	0.001	3.94	13.65
		93.54				
35	Pre3 vs post3	91.51	9.98 ± 5.89*	0.000	7.95	11.99
		81.54				
33	Pre4 vs post4	85.29	10.97 ± 5.44*	0.000	9.04	12.90
		74.32				
33	Pre5 vs post5	80.89	7.76 ± 4.23*	0.000	6.26	9.26
		73.12				
33	Pre6 vs post6	73.69	7.31 ± 4.38*	0.000	5.75	8.86
		66.38				

**Significantly higher (p-value<0.001); S.D= Standard Deviation; CID= Confidence interval of Difference.*

After the fourth cycle, the recovery gradually declined to a plateau. The least recovery was observed between the 5th and 6th cycles.

DISCUSSION

CDDP was the first heavy metal compound to be studied extensively and to achieve therapeutic usefulness as an antineoplastic agent. It binds directly to DNA, inhibiting its synthesis by altering the DNA template via the formation of intra-strand and inter-strand cross-links.[11,12] The cytotoxic effects of CDDP are not cell-cycle dependent. The dominant mode of action of CDDP appears to involve the formation of a bifunctional adduct resulting in DNA cross-links. CDDP is cleared rapidly from plasma during the first 2 hours after intravenous injection, but clearance proceeds much more slowly thereafter due to binding to plasma proteins and erythrocytes.[13,14] CDDP is excreted primarily in the urine, with 23 to 70% recovered in the urine within 24 hours and 90% recovered within 5 days. The nephrotoxicity of CDDP was originally felt to be dose-limiting.[15-17] The long-term follow-up of patients post-CDDP therapy has demonstrated upto 30% persistent decrease in GFR but little evidence of long-term renal tubular dysfunction.[18]

This study was designed to evaluate the nephrotoxic effect of CDDP by plasma two sample clearance method of GFR estimation. One patient expired during the first week of chemotherapy because of generalized metastasis secondary to small cell carcinoma of the lung and the second one expired after the third cycle due to cardio-pulmonary arrest secondary to lung carcinoma (extensive disease with chest tube in-situ). A total of 33 patients were studied for all 6 cycles of CDDP and out of those, only 3 patients (9% of total patients) went into severe renal dysfunction (GFR less than 50 ml/min by definition) at the end of the 6th cycle. According to Malcolm, the nephrotoxic effect was found to be a long-term (reported after one year) complication of CDDP.[18] It was observed that the fall in GFR during the CDDP therapy depicting its nephrotoxicity however, It was also found that kidneys tried to recover given due time as shown by the rise in GFR during the cycle.

In this study, there was a significant fall in GFR in each cycle estimated by PSC 2 method particularly in the first four cycles. There was also an overall fall in mean GFR between successive CDDP cycles. The GFR of each patient was estimated two days prior to the CDDP cycle as a baseline and within the first week of the same cycle by the PSC 2 method. It was demonstrated in the results very clearly that there was a significant fall (average 9.36 ml/min/1.73 m^2) in GFR in each cycle, even in the first cycle. On the basis of these results it can be suggested that CDDP produced the earliest change in GFR in the first week of cycle. The greatest change was observed in the first four cycles and the least but also significant change in GFR was observed in the fifth and sixth cycles. This means that CDDP produces its earlier change in GFR during first week. A major fall in GFR was observed from the first half of cycles but with a good recovery of average 3.8 ml/min/1.73 m^2 which indicates its reversibility. After fourth cycle, the recovery gradually declined to a plateau and the least recovery of an average 0.57 ml/min/1.73 m^2 was observed between the 5th and 6th cycles, causing severe nephrotoxicity. Each successive insult caused gradual renal damage which was remarkable following the last two cycles as observed by the failure to recover to the baseline level. Malcolm, *et al.* monitored the potential problems in a long-term follow up that may follow cancer therapy and observed about 30% persistent fall in GFR within the first year of CDDP therapy when followed every three months.[18] Typical clinic schedules might include visits every three months for the first year, every four months for the second and third year, every six months in the fourth year and annually thereafter. The important overall concept is that the renal function of patients on CDDP therapy, particularly those having low baseline GFR, should be monitored after each cycle in order to

minimize the potential risk for renal failure by appropriate hydration as well as dose modification of CDDP. Secondly, these patients should not be lost to follow-up once treatment is completed but monitored on a regular basis, especially during the period of highest risk for complication. The accuracy, accessibility, low cost, low radiation hazard, and short half-life of ^{99m}Tc-DTPA make it an excellent substance for measuring GFR. Regarding the availability, most oncology setups have their own nuclear medicine department providing the ease of performing this test frequently.

PSC 2 method measured an average GFR of 85.75 ml/min/1.73 m^2 (range=32.92-184.66 ml/min/1.73m^2). Multiple plasma sample technique using ^{99m}Tc labeled DTPA correlates well with inulin clearance and is considered reliable but is time consuming and not acceptable to patients.[19-21] Fleming, *et al.* suggested the ^{99m}Tc-DTPA as a suitable radiopharmaceutical alternative to ^{51}Cr-EDTA on the basis of sufficiently small systematic differences in the values of GFR obtained by both radiopharmaceuticals.[22] The reasons for using ^{99m}Tc-DTPA instead of 51Cr-EDTA in our study were its low cost, easy availability, low radiation hazard, and shorter half-life.

There were few limitations and possible source of bias in this study. Personal error could be introduced due to incorrect dose calculation and injection of DTPA. The bias could add to the results if the sample was not drawn at correct time and from the correct arm.

CONCLUSION

CDDP produces an early nephrotoxicity manifested by significant decline in GFR in each cycle. Tc-99m PSC 2 method for GFR estimation should be used periodically for the early detection of nephrotoxicity induced by CDDP, which is necessary for CDDP dose modification to prevent its permanent nephrotoxic effect.

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