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ORIGINAL ARTICLE

HISTOMORPHOLOGICAL EFFECTS OF CISPLATIN ON KIDNEY OF MALE WISTAR ALBINO RATS

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ABSTRACT: Cancer is the most dreaded disease and currently taking a heaviest toll of human lives. The number of cancer patients diagnosed is growing at an alarming proportion. So, its treatment forms an important part of modern health care. Cisplatin is one of the important anticancer drugs used to treat a number of cancers like that of head and neck, prostate, breast, cervix, uterus etc. Though comparatively a safe drug it has got many side effects amongst which nephrotoxicity is of common occurance. Hence, a study was conducted, in the Department of Anatomy Government Medical College Jammu, on 40 male albino Wistar rats, obtained from the Animal house of Department of Pharmacology Government Medical College Jammu, to determine the toxic effects of Cisplatin on kidney of rats. The rats were divided into 4 groups where 3 groups were given the test drug Cisplatin I. P. (Intraperitoneally) in doses of 0.2mg/kg body weight for 7 days, 1 mg/kg body weight for 7 days and 45 mg/kg body weight as a single dose respectively, whereas in the 4th group or control group normal saline of same volume was injected I. P. These rats were subsequently anaesthetised, dissected and their kidneys were taken out. The kidneys were then subjected to standard histological slide preparation by paraffin embedding method and longitudinal and transverse sections so prepared were stained by H &E stain and observed under a light microscope. In group I (Control group) no macroscopic as well as microscopic changes were seen in the kidneys. In group II, III, IV, well-marked microscopic changes were seen in the kidneys.
KEYWORDS: Cisplatin, Albino rats, Kidney.

INTRODUCTION: Nearly 2.5 million people suffer from cancer at any given time. Around 70,000 new cases are added every year. The age related mortality rate is 61 per 100,000 males and 58 per 100,000 females.(1) Discovery of anti-neoplastic drugs has considerably improved the prognosis of cancer. Cisplatin is currently used as one of the most effective anticancer drugs. It is used to treat a variety of cancers including that of head and neck, Prostate gland, breast, cervix and uterus as it prevents cancer cells from dividing further. However, severe side effects are observed with Cisplatin therapy. Earlier studies demonstrated mainly renal side effects with clinical evidence of uraemia and reduced creatinine clearance.(2) Recently there has been an increase in the number of diagnosed cancer patients, so their treatment has become an important component of healthcare. Although, Cisplatin administration has an acceptable outcome in chemotherapy of various cancers, it also exhibits moderate to severe toxicity and undesirable side effects. However there is little data available on the effects of this drug, on the general organ toxicity in our literature. So, in the present study, we will observe the histomorphological side effects of Cisplatin on the kidney of male Wistar albino rats and also elucidate that whether these renal side effects are dose related or not.

MATERIAL AND METHODS: The present study was conducted in the Department of Anatomy Government Medical College Jammu. The study was carried out on 40 male Wistar albino rats

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weighing between 150 to 200 grams. The rats were procured from the Central Animal house, Department of Pharmacology, Government Medical College Jammu and divided into 4 groups of ten animals each.

Group I = Normal Control.
Group II = Low Dose.
Group III = Therapeutic Dose.
Group IV = High Dose.

The animals were group housed in small iron cages in a room and were fed with standard pellet diet. Their body weight was recorded before the onset of the experiment.

The group I animals were given no Cisplatin but the vehicle in which drug has been dissolved (normal saline).

The group II were given single daily dose of 0.2 mg/ kg body weight for seven days.

Group III were given 1mg/kg body weight for seven days.

Group IV were given a single dose of 45 mg/kg body weight.

All injections were given by I/P (Intra-peritoneal) route.

The animals of group I, II, and III were sacrificed on the 8th day while animals of group IV were sacrificed after 16 hours.

The kidneys were removed after dissecting the abdomen of the rats and cut into small pieces of approximately 5mm. These tissues were fixed in 10% formalin solution for 24 hrs and then prepared for microtomy by paraffin wax embedding method. Tissue blocks were sectioned to generate 7 micrometer thick sections using Rotary microtome. The sections were mounted and stained with Haematoxylin and Eosin (H & E) and observed under microscope.

OBSERVATIONS: Changes observed on macroscopic and microscopic examination were classified as per the severity and were graded as;

- Mild (+)
- Moderate (+)
- Severe (+++)

GROUP I (Control group): No microscopic or macroscopic changes observed in the kidney (Fig. 1).

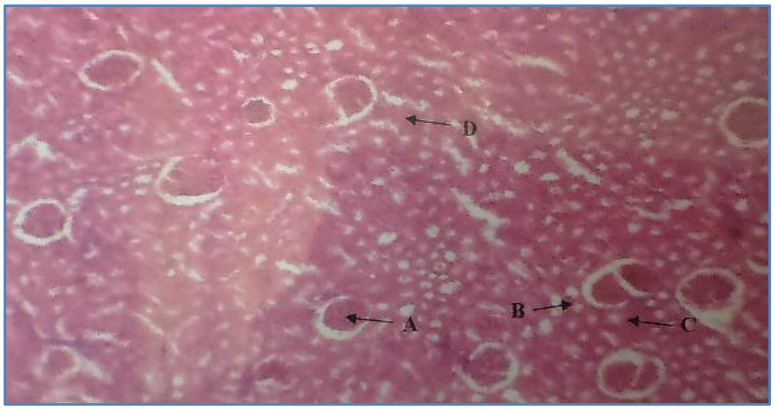

Fig. 1: T. S. Of kidney of group-I albino rat (control group) showing glomerulus (A), convoluted tubules (B & C) and interstitium (D) H & E stainx100

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GROUP II: No macroscopic changes seen in the kidneys.

Microscopic examination revealed congestion and haemorrhage (++) of glomeruli, focal atrophy (+++) of the tubules, RBC (+++) in the lumen of the tubules and foci of chronic inflammatory cells in the interstitum (++). (Fig. 2)

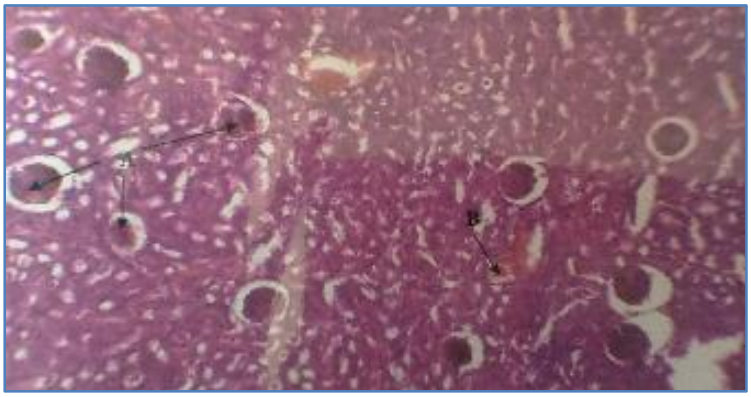

Fig. 2: T. S. of kidney of group-II albino rat showing congestion and haemorrhage in glomeruli (A) congestion of interstitium (B) H & E stainx100

GROUP III: No macroscopic changes seen in the kidneys.

Microscopic examination revealed congestion and haemorrhage (++) of glomeruli and presence of (++) RBC in the renal tubules. Vacuolar degeneration (+++) was also seen in the tubular epithelium. Also Haemorrhagic area (++) in the interstitial tissue was observed. (Fig. 3)

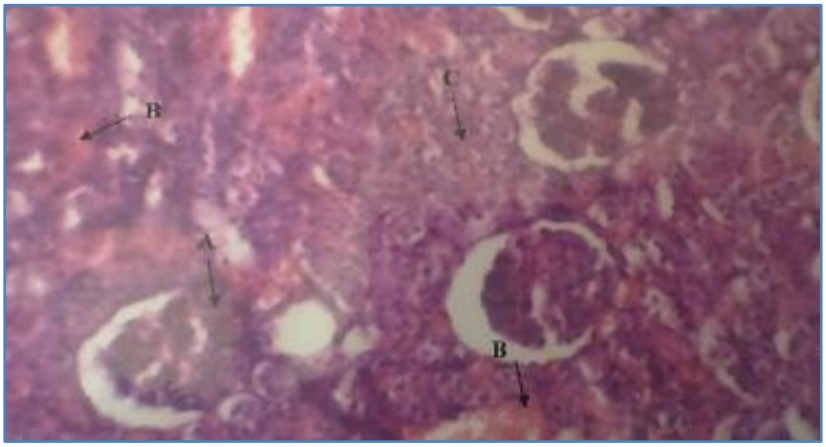

Fig. 3: T. S. of kidney of group-iii albino rat showing glomerular congestion (A) haemorrhages in interstitium (B) RBC inside renal tubules (C) H & E stain x100

GROUP IV: No macroscopic changes seen in the kidney.

Microscopic examination revealed congestion and haemorrhage (+++) of glomeurli and focal tubular atrophy in PCT (+++) and DCT (++). Many renal tubules show RBC casts within them. Interstitial tissues shows infiltration by chronic inflammatory cells (++) and congestion (++). No necrosis was seen. (Fig. 4)

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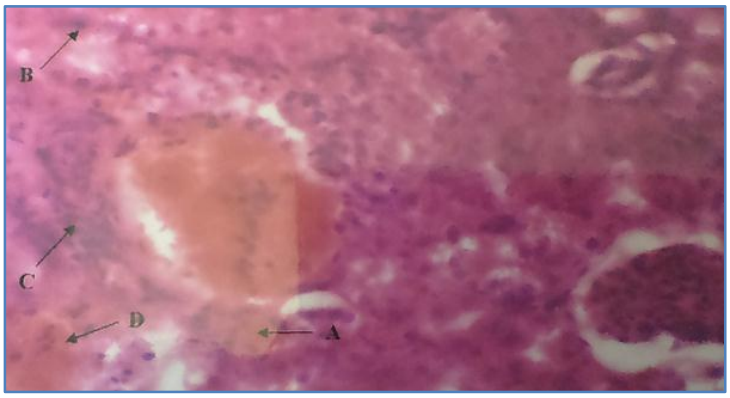

Fig. 4: T. S. of kidney of group-iv albino rat showing RBC within tubules (A), focal tubular atrophy (B), infiltration of interstitium by chronic inflammatory cells (C), congestion of interstitium (D) H&E stain x 400

DISCUSSION: Platinum heavy metals have been known for many years to be toxic to cells. CDDP (cis-dichlorodiamminoplatinum) is a potent broad spectrum anti tumour drug known as heavy metal alkylating agent. It kills the cancer cells and prevents their further growth, as it forms cross links with double stranded DNA. However its clinical utility has been restricted because of renal toxicity, with maximum toxicity in the PCT (Proximal convoluted tubule). In our study, the glomeruli were mostly affected with all doses of Cisplatin in group II, III, and IV. Renal tubular changes were observed in all the three groups which were given Cisplatin. All these groups revealed tubular focal atrophy of equal magnitude which is more marked in the PCT. This is in accordance to Arany & Safirstein[3] who reported that PCT cells take up the anti-tumour agent (Cisplatin) which leads to higher concentration of Cisplatin in PCT than that of plasma. This results in Cisplatin toxicity in PCT which is morphologically characterized by tubular necrosis.

The finding of present study are also similar to those reported by Chirino et al[4] who found tubular necrosis, vacuolization of cells in the PCT of kidney in male Wistar rats (Cisplatin given in the dose of 7.5mg/kg body wt intraperitoneally for three days).

Morigi et al[5] have also reported similar acute Cisplatin nephrotoxicity in the form of degenerated and highly congested glomeruli. Karimi et al [6] used single dose of cisplatin 3mg/kg body wt daily for 5 days and observed severe tubular necrosis.

Behling et al[7] also suggested finding similar to our observation that cisplatin mainly acts on PCT of kidney.

Our study corroborated with the work done by Abdelmeguid N.E et al[8] who observed acute tubular necrosis both in PCT and DCT and loss of basement memberane of PCT, swollen PCT cells with pyknotic nuclei, vacuolated cytoplasm (cells), infiltration with inflammatory cells but DCT (distal convoluted tubule) showed few tubular changes.

Our findings are also in accordance with Abdel-Gawad S K & Mohamed A K G [9] who observed that PCT was most severely affected followed by DCT in the form of vacuolated cytoplasm and necrotic changes in the form of nuclear pyknosis along with intratubular casts with desquamated renal tubular cells. In the present study chronic inflammatory foci with infiltration of cells were seen in all the three groups along with haemorrhages and congestion. Similar findings were seen by Abdel-Gawad et al.[9]

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The present study has clearly demonstrated that kidney is effected by Cisplatin and the principle site of damage is PCT as compared to DCT. The observed histomorphological changes in the kidney of male albino rats were of the same magnitude in all the three Cisplatin treated group.

SUMMARY: Renal changes were seen in all the three Cisplatin treated groups of male Wistar rats. The changes were congestion and haemorrhage of glomeruli, Tubular changes in PCT & DCT, were manifested as loss of microvilli with sloughing of epithelium, vacuolisation of cells leading to focal tubular atrophy and presence of RBC's in tubules. These changes were evidently more marked in PCT as compared to DCT.

It was also observed in our study that the histomorphological changes in the kidneys after Cisplatin administration was not dose related.

Site & Effects	Gp -I	Gp-II	Gp III	Gp-IV	Remarks
Glomerular- Congestion & haemorrhage	-	++	++	++	All cisplatin doses have same effects barring the control gp
Tubules- PCT DCT, LH	- -	+++ ++	+++ ++	+++ ++	PCT more affected. No change in control gp
Interstitium-ch. inflammatory foci & haemorrhage	-	++	++	++	Same changes except in control gp

Table 1: Comparison of nephrotoxic effects of different doses of cisplatin in albino rats

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