Eastern Journal of Medicine 15 (2010) 93-96

Original Article

Cadmium induced renal toxicity in male rats, *Rattus rattus*

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Abstract. Cadmium (Cd) is reported to cause harmful effects on organs such as kidneys, lungs, bones, liver and testes. But, the kidneys are the major target organs of Cd action. At sub-chronic exposure of $CdCl_2$ dose (LD_{50} 88mg kg^{-1}), the metal accumulates in the renal cortex and results in the malfunctioning of the kidneys. We report here the effect of Cd intake in *Rattus rattus* of 0.6mg /kg b.wt/day of $CdCl_2$ on rat at subchronic level. Our findings demonstrate that a regular oral intake of $CdCl_2$ solution (in drinking water) for 30 days causes severe damage to rat kidneys. At this exposure of $CdCl_2$, cortex region is most affected whereas glomeruli as well as proximal tubules showed wall thickening. Cytosolic damaged bodies were also observed in the renal tubular epithelium. Since in Cd-treated rats proximal tubules in renal cortex were more heavily stained that suggesting increased protein contents in the cells. No such changes were observed in control group, which were fed with normal tap water. It is concluded that even at the high dose selected here, the extent of damage to kidneys of rat is limited.

Key words: Cytotoxic damage, *Rattus rattus*, cadmium toxicity, histopathology

1. Introduction

Literature is available on the action of heavy metals in industrial effluents. The heavy metals are non-biodegradable and accumulate in living system through active circulation by food chain (1,2). Cadmium (Cd) is a well-known heavy metal present in environment and causes damage to several human organs such as kidneys, lungs, bones (3,4), liver and testes (5). Soon after exposure, cadmium is known to induce biosynthesis of metallothionein (MT), a low molecular weight cysteine rich protein (6). The increase in MT also leads to disturbances in zinc and copper levels (5). The presence of Cd in diet diminishes iron absorption while absorption of zinc through gastrointestinal tract is enhanced (7). Active role of Cd in calcium-metabolism leading to osteomalacia has also been demonstrated (8).

Kidney is the major target organ of Cd action. During chronic and sub-chronic exposure the metal may interfere the metabolic process via renal cortex resulting in malfunctioning of kidneys (9).

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Extensive work has been carried out to test the effects of heavy metals, particularly Cd on different group of vertebrates (4,5,9-11). As far as we know, these studies have been limited to investigate the effect of Cd exposure for short time intervals and lower doses of $CdCl_2$ (4,10,11). The present work was undertaken to demonstrate the changes in cell types of rat kidneys which are presumed to play significant contribution in normal functioning and providing a proper electrolyte ambience after a prolonged sub-chronic exposure of cadmium dose of 0.6mg/kg b.wt/day of rat for 30 days.

2. Materials and medhods

2.1. Test animals

Total animals were divided into five groups and each group was comprised of four male healthy rats, *Rattus rattus* weighing 100±20g, which were selected and kept in well-aerated polycarbonate cages with stainless steel wire top under standard conditions (30±2°C; light: dark=1:1 cycle). They were acclimatized for a week and regularly fed with commercially available sterilized feed and water *ad libitum*. Out of five groups of rats three groups were selected for treatment with cadmium chloride solution while the other two groups served as control. In control groups, rats received an equivalent amount of 0.9% NaCl, whereas remaining were kept at normal tap water and diet.

The rats belonging to either of groups were sacrificed in compliance with the ethical regulations formulated by the Ethical Committee (Reg. No. 401/CPCSEA) of the University.

2.2. Chemicals

Cadmium chloride (CAS No. 10108-64-2; 98% purity) was purchased from Himedia Laboratories Chemicals Limited, India. Other chemicals used in the present study were of analytical grade.

2.3. Treatment

Oral LD_{50} of $CdCl_2$ is 88mg/kg b.wt of rat (12). Stock solution was prepared by dissolving 12mg of $CdCl_2$ in 2L of distilled water. Three groups were given treatment of $CdCl_2$ as solution in drinking water, orally. In the dose preparation of $CdCl_2$, 40 ml solution containing 2.4mg of $CdCl_2$ was given to rats in a treated group on daily basis up to 30 days for sub-chronic exposure. The kidneys of sacrificed rats were carefully removed for further processing.

2.4. Histopathology

Dissected kidneys were cut into small pieces to proceed for microscopic examination (13). Tissues were fixed in Bouin's solution for overnight, dehydrated through alcohol-graded series and xylene followed by embedding in paraffin wax. Sections of 5µ*m* each were cut and stained with Haematoxylin and Eosin (13). Clean slides were examined under light microscope at low (45×10x) as well as high (100×10x) magnifications. The best slides with complete details were photographed.

3. Results

Kidneys were treated for 30days with 0.9% NaCl solution and commercially available diet did not show any damage. Histopathological slides show the transverse section (T.S.) of control rats kidney at low or high magnifications (Fig.1 A and B).

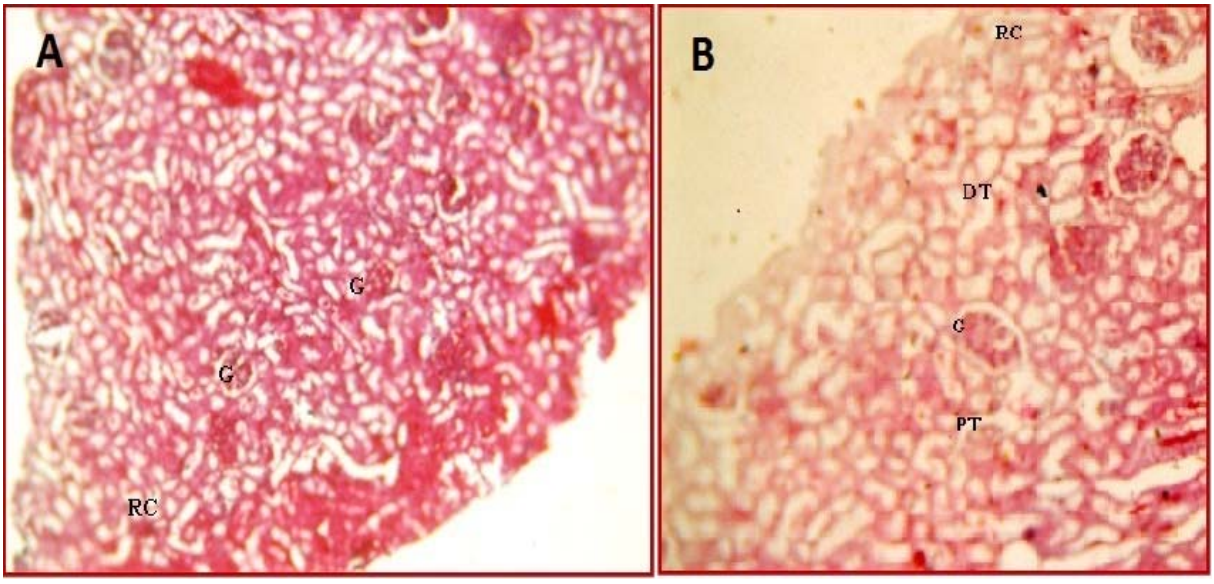

Fig. 1. Photomicrographs of Transverse Section (TS) of the normal kidney in untreated (control) rat,
(A): at day one (45x10X); (B): at day 30 (100x10X).
Symbols are: G, glomeruli; PT, proximal tubules; DT, distal tubules; RC, renal cortex.

On the other hand, $CdCl_2$ dose of 0.6mg/kg b.wt/day on rat caused the considerable damage to kidneys and in its cell types in 30 days of regular treatment (Fig. 2 A and B). $CdCl_2$ damaged the renal cortex, brush border membrane, cellular membrane, proximal tubules and distal tubules in kidneys of treated rats. Glomeruli were the least affected and showed wall thickenings only. Certain cytosolic bodies were also detected at high magnification, as part of the damage caused by oral intake (in drinking water) of $CdCl_2$ due to sub-chronic exposure (Fig. 2 B).

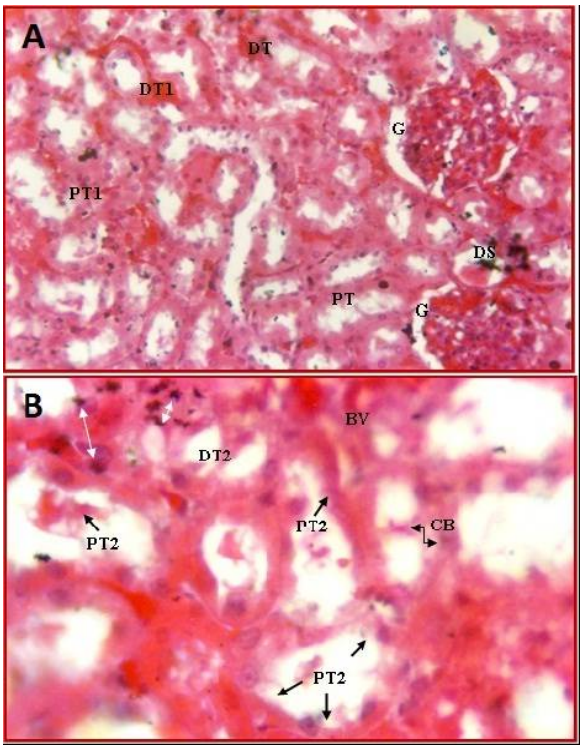

Fig. 2. Photomicrographs of kidney (T.S.) of rats treated with sub-chronic dose of $CdCl_2$ for 30 days; (A): at a magnification of 45x10X; and (B): at higher magnification of 100x10X. Symbols are: G, glomeruli; PT, proximal tubules; DT, distal tubules; RC, renal cortex; PT1, damaged PT; PT2, damaged PT membrane; DT1, damaged DT; DT2, damaged DT membrane; DS, dark stain due to increased protein content; CB, cytosolic bodies; BV, blood vessels and double headed arrows show the stained protein.

4. Discussion

Non-biodegradable cadmium (Cd) along with chloride enters in the living system and accumulates through their active circulation by food chain affecting the functioning of kidneys (1,2). Cadmium causes damage primarily to kidney, bone and lungs (3). Reports available on cadmium chloride ($CdCl_2$) toxicity further suggest that during the sub-chronic and chronic exposure the accumulated metal in the renal cortex also results in disturbance of normal functioning of kidneys (9).

The present study where the damage is shown in kidneys due to regular oral intake (in drinking water) of $CdCl_2$ differs in the dose selection (0.6mg/kg b.wt. of rat/day) as well as the duration for which the rats were fed upon. Previously damage due to $CdCl_2$ intake with drinking water for 24 months in the kidneys of rats (1.1mg/kg b.wt/day of rat) has also been shown (14). Other studies also support the kind of damage caused due to Cd intake (3,5,9,11). Our findings are in agreement with these studies taken though we have taken longer duration in the present as reported earlier. Cadmium causes severe damage to the kidneys and its cell types, particularly our findings are an indicative of the damage in renal cortex, proximal tubules membrane, distal tubules membrane, cell nuclei and blood vessels in kidneys of cadmium treated rats (Fig.2 A and B).

Existence of cytosolic bodies and swelling in glomeruli were also observed at relatively high magnification (details are provided in legend of Fig. 2). Although, the extent of damage shown here is slightly higher than reported previously (5,9,11), which may be due to either variation in the selection of dose or the time chosen to feed the rats with $CdCl_2$. Available literature also suggests that cadmium also induces increased secretion of both low and high molecular weight proteins due to defect in the re-absorption of protein through the proximal tubules (6,10,11). In our case also, the $CdCl_2$ treated rats showed heavy staining of proximal tubules in the cortex region of the kidneys that may suggest the dose and time selected in this case are sufficient to induce the secretion of proteins as well as to create the malfunctioning in re-absorption process of rats.

Though the selected dose of cadmium induced the renal toxicity in rats treated for 30 days, however it appears that insufficiency to induce the *in vivo* damage to kidneys at a relatively higher extent is still not achieved.

Therefore, it may be suggested that this is due to the unavailability of intermediate products entering the metabolic machinery at the peak response time of $CdCl_2$ in the *Rattus rattus* which might have been synthesized and spared at a lower Cd intake.

Our recent findings on the dose and time-dependent chromosomal breakage due to DNA damage in the bone marrow cells of *Rattus norvegicus* due to chloroacetic acid and chlorobenzene also supports the utility of intermediate metabolites at the time of action (peak response) of the above compounds (15). Hence, it is advised that further investigations shall be carried out to demonstrate the role of such intermediate products/metabolites entering the metabolic machinery of *R. rattus* and causing renal toxicity.

Acknowledgements

Author is grateful to the Chairman, Department of Zoology for providing necessary laboratory facilities. Thanks are also due to Mr. Ghulam Rasool for the assistance provided by him during the tenure of the author's M.Sc. dissertation work.

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