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Effects of cadmium chloride on reproductive parameters, nephrotoxicity, hepatotoxicity and oxidative stress markers in male guinea pig (*Cavia porcellus*)

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Abstract
Background: *This study aimed to evaluate the effects of cadmium on reproductive parameters and oxidative stress in male guinea pig (Cavia porcellus).*
Materials and methods: *Thirty two (32) male guinea pigs were randomly assigned to four groups of eight each. Group 1 received distilled water orally; groups 2, 3 and 4 were treated with cadmium chloride at doses 8.75, 13.13 and 26.25 mg/kg.b.w. respectively. After 90 days of treatment, all animals were sacrificed and data collected.*
Result: *Results revealed a significant ($p < 0.05$) increase of kidney and liver weights in cadmium chloride-treated animals compared to the control groups. Serum level of creatinine, urea, ALAT, ASAT significantly ($P < 0.05$) increased and serum total proteins and total cholesterol significantly ($P < 0.05$) decreased in all cadmium chloride-treated animals compared to the control. The weights of testes and epididymis and the volume of testes were significantly ($p < 0.05$) lower in treated guinea pigs compared to controls. Seminal vesicle and bulbo urethral gland weights significantly ($P < 0.05$) increased in group gavaged with the highest dose of cadmium chloride (26.25 mg/kg) compared to controls. Sperm mobility and count, the percentage of sperm with intact plasma membrane were significantly elevated in animals exposed to the highest dose of cadmium chloride (26.25 mg/kg) compared to controls. The percentages of micro -, macrocephalic and coiled-tailed spermatozoa were significantly increased in animals given the two largest doses (13.13 and 26.25 mg/kg) compared to controls. Serum testosterone concentration was significantly ($p < 0.05$) lower in animals gavaged with cadmium chloride compared to control. The testicular activity of SOD, catalase, total peroxidase, malondialdehyde increased in cadmium chloride treated animals compared to control.*
Conclusion: *In conclusion, exposure to cadmium chloride induced oxidative stress, renal, hepatic and reproductive toxicity in male guinea pig.*
Key words: *cadmium chloride, heavy metals, male guinea pigs, oxidative stress, reproduction.*

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I. Introduction

Cadmium is a key environmental toxicant and is spread in the environment in the form of cadmium oxide (CdO), cadmium chloride ($CdCl_2$) or cadmium sulfide (CdS), through agricultural fertilizers, industrial activities, such as the manufacturing of batteries, pigments, metal smelting, refining, and municipal waste incineration [19, 13], Which are responsible for soil contamination and also contaminates pasture [20, 29]. Because some plants can accumulate this toxcic metal, it can be ingested by animals grazing these plants or seeds [33, 30, 32, 11]. The major route of Cd exposure is the inhalation of fumes and dust containing Cd or incidental ingestion through contaminated hands, water and food [9].

Cadmium (Cd) is a non-essential heavy metal, toxic at low concentration. It has no known beneficial role in the organism [3, 9]. The exposure to Cd induces various health impairments, including hostile healthless development of testes or testicular degeneration and testicular necrosis [24]. Exposure to Cd affects male reproductive system while deteriorating spermatogenesis, semen quality especially sperm mobility and hormonal synthesis/release [24]. The toxic effects of Cd are mainly indirect. It is able to induce the

overproduction of reactive oxygen species (ROS) by inhibiting action of superoxide dismutase, catalase and glutathione peroxidase enzymes by indirect mechanisms [10, 9]. The disturbances caused by Cd lead to several harmful consequences for the cell [24]. The work of [5] showed that exposure of rats by gavage to cadmium chloride (1 mg/kg/day) for 17 days resulted in a significant decrease in testicular mass. Fischer 344 rats exposed to 1,060 µg of Cd/m^3 6 h/day, 5 days/week, for 62 days experienced increased relative testes weight, but without loss in reproductive success [17]. In a study to evaluate the mechanisms of cadmium-induced reproductive toxicity in a male mouse model, results demonstrated that the severity of testes injury increased with cadmium concentrations [1]. [7] report in their work that some sperm are more vulnerable to attack from pollutants such as cadmium. These are zebrafish sperm, which does not contain methalothionein that has been identified in other fishes sperm and which reduces the toxicity of cadmium.

Regarding the above results, which differ from one animal species to another, or from one author to another, what could be the effects of cadmium on reproduction in male guinea pig? The present study therefore aims to investigate the eff ects of cadmium chloride on male guinea pig reproductive parameters.

II. Materials And Methods

Animal material and lodging

Thirty two (32) adult male guinea pigs aged 3-4 months, with a mean body weight of 400±39.15 g were produced at the Teaching and Research Farm (TRF) of the University of Dschang. The animals were housed at room temperature and 12 hours light/dark cycle. Experimental protocols used in this study were approved by the Ethical Committee of the Department of Animal Science of the University of Dschang and was in conformity with the internationally accepted standard ethical guidelines for laboratory animal use and care as described in the European Community guidelines; EEC Directive 86/609/EEC, of the 24th November 1986.

Feeding and Heavy metal

Animals were fed a basal ration of elephant grass (*Peninisetum purpureum*) and a supplement of provender.
Cadmium chloride was obtained from GEOCHIM SARL. Commercial sources (Tianjin Fuchen Chemical Reagents Factory Trust ISO9000/0532-83889090).

Experimental Design

Animals were set into 4 groups of 8 animals each, comparable in terms of body weight. Each group was orally given one of the four doses of Cadmium Chloride (0, 8.75, 13.13 and 26.25 mg/kg bw). Group 1 being the control group, received distilled water (1 ml/kg bw). All the animals were treated for 90 days. Their body weight was recorded weekly and the doses of heavy metal adjusted accordingly. At the end of the trial, animals were sacrificed under ether vapor anesthesia.

Data collection and studied parameters

Serum testosterone concentration and biochemical parameters

The blood was collected by cardiac puncture and stored at room temperature. Serum was collected 12 hours later for the estimation of testosterone concentration, ALAT, ASAT, total cholesterol, total protein, albumin, creatinin and urea levels.

Sexual organs weight and sperm characteristics

Testes, epididymides, vas deferens, sexual accessory glands, liver and kidneys were excised out and weighed.
The cauda epididymides were weighed and minced in 10 ml of 0.9% NaCl solution (37 ◦C) for sperm characteristics evaluation as follows: 20 µl of the latter solution was placed on a slide and observed at 400 magnification under a light microscope, and sperm mobility score was attributed according to the method described by [4]. The sperm count was determined using a haemocytometer, sperm morphological abnormalities (small and big heads, tails winding) using an eosin-nigrosin solution and the integrity of the plasma membrane were evaluated using the hypo-osmotic test.

Kidneys and liver weights

Kidneys and liver were excised out and weighed.

Testicular concentration of SOD, POD, CAT and MDA

One of the testes was ground in a 0.9% NaCl solution to obtain 15% homogenates. This latter was centrifuged at 3000 rpm for 30 minutes, and the supernatant removed and stored at -20° C, and later Superoxide dismutase (SOD), total peroxidase, Catalase (CAT) activity and Malondialdehyde (MDA) were measured using the spectrophotometer (GENESYS 20.0) and according to the methods described respectively by [21] [12] [28] [25]**.**

Statistical Analysis

Data were analyzed using SPSS IBM statistics software 20.0. Diff erences among groups were assessed using one-way analysis of variance (ANOVA), followed by Duncan's test at 5% significance. Results were expressed as mean ± standard deviation.

III. Results

Biochemical parameters of kidneys and liver

Serum levels of ALAT, ASAT were significantly ($p<0.05$) higher in guinea pigs treated with cadmium chloride with reference to control. Serum total protein and total cholesterol levels decreased significantly ($p<0.05$) in heavy metal-treated groups compared to control. However, the serum albumin and globulins contents showed no significant difference ($p>0.05$) among treatments. The serum creatinine level increased significantly ($p<0.05$) in cadmium chloride-treated animals referring to the control. In contrast, the serum urea content was higher in guinea pigs treated with cadmium chloride compared to control. However, the difference was significant ($p<0.05$) only in animals treated with 13.13 mg / kg bw of cadmium chloride (Table 1).

Sexual organs, kidneys and liver weights

The weights of kidneys and liver increased significantly ($p<0.05$) in guinea pig orally receiving cadmium chloride compared to control (Table 1). The weights of testes and epididymis decreased ($p<0.05$) in heavy metal-treated guinea pigs compared to control. Seminal vesicle and bulb urethral gland weights increased in animals exposed to cadmium chloride compared to control. However, the difference was significant ($p<0.05$) only in animals receiving the highest dose (26.25 mg/kg bw). The weights of prostate and vas deferens were comparable ($p>0.05$) to those of the control groups. Sperm mobility and count generally dropped in guinea pigs exposed to cadmium chloride compared to control. However, the significant ($p<0.05$) difference was noted only with animals receiving the highest dose (26.25 mg/kg bw) of cadmium chloride (Table 2).

Sperm characteristics

The percentage of sperm with intact plasma membrane declined significantly ($p<0.05$) in cadmium-treated guinea pigs referring to the control. The percentages of micro -, macrocephalic, and coiled tailed spermatozoa increase in guinea pig gavaged with cadmium chloride. However, the difference was significant ($p <0.05$) only in animals orally receiving 13.13 and 26.25 mg/kg bw of cadmium chloride (Table 2).

Serum testosterone concentration

The serum testosterone concentration decrease significantly ($p<0.05$) in heavy metal-treated animals compared to the control group (Figure 1).

Testicular concentration of SOD, POD, CAT and MDA in male Guinea Pig

The activities of testicular superoxide dismutase and total peroxidases increased significantly ($p<0.05$) in animals given 8.75 and 26.25 mg/kg bw of cadmium chloride compared to control animals. Catalase activity was elevated in animals exposed to cadmium chloride with respect to the control group. However, the difference was significant ($p <0.05$) only in animals which receiving the highest dose (26.25 mg/kg bw) of cadmium chloride (Figure 3). The level of malondialdehyde increased in guinea pigs exposed to cadmium chloride as compared to the control group. However, the difference was significant ($p<0.05$) in animals exposed to the highest doses (13.13 or 26.25 mg/kg bw) of cadmium chloride. Treatments were all comparable ($p> 0.05$) for the testicular total proteins concentration (Table 3).

Table 1: Effects of cadmium chloride on weight and biochemical parameters of kidneys and liver function in male guinea pig

kidneys and liver parameters	Dose of cadmium chloride (mg/kg bw)				p
	0 (n = 8)	8.75 (n = 8)	13.13 (n = 8)	26.25 (n = 8)	
Weights of liver(g/100 g pc)	2.65±0.08^{c}	2.78±0.20^{bc}	2.85±0.17^{b}	3.03±0.14^{a}	0.001
Weights of kidneys (g/100 g pc)	0.71±0.06^{b}	0.77±0.06^{a}	0.77±0.04^{a}	0.79±0.03^{a}	0.038
ALAT (UI)	65.28±10.21^{c}	92.98±18.51^{b}	90.85±14.52^{b}	124.91±19.70^{a}	0.000
ASAT (UI)	47.78±13.62^{b}	69.83±11.95^{a}	66.25±10.10^{a}	77.88±16.47^{a}	0.001
Serum total protein (g/dl)	5.73±0.49^{a}	4.91±0.54^{b}	4.76±0.82^{b}	5.06±0.53^{b}	0.018
Albumin (g/dl)	3.70±0.42	3.34±0.36	3.28±0.63	3.36±0.44	0.305
Globulin (g/dl)	1.84±0.28	1.93±0.40	1.91±0.18	2.07±0.20	0.469
Serum total cholesterol (mg/dl) (mg/dl)	42.63±5.52^{a}	33.40±4.67^{b}	28.93±3.38^{c}	29.73±2.81^{bc}	0.000
Serum Creatinine (mg/dl)	0.59±0.07^{b}	0.78±0.17^{a}	0.85±0.17^{a}	0.83±0.10^{a}	0.003
Serum Urea (mg/dl)	45.78±3.51^{b}	49.10±3.15^{ab}	52.68±6.86^{a}	49.99±8.99^{ab}	0.049

a, b, c: within the same line, values with the same letters are not significantly ($p>0.05$) different. n: number of observations. bw: body weight. ASAT: aspartate aminotransferase ALAT: alanine aminotransferase; p=probability value

Table 2: Effects of cadmium chloride on reproductive parameters in male guinea pigs

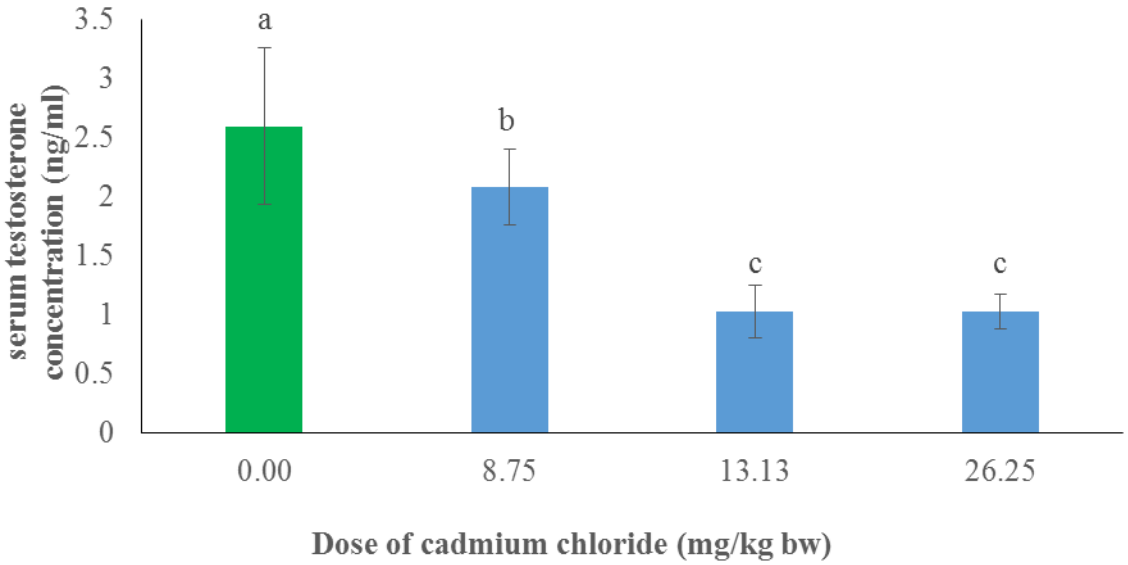
Reproductive parameters	Dose of cadmium chloride (mg/kg bw)				p
	0 (n = 8)	8.75 (n = 8)	13.13 (n = 8)	26.25 (n = 8)	
Organ weights (g per 100 g of body weight)					
Testes	0.53±0.05^{a}	0.46±0.03^{b}	0.48±0.05^{b}	0.47±0.03^{b}	0.013
Epididymides	0.094±0.015^{a}	0.080±0.009^{b}	0.080±0.011^{b}	0.074±0.013^{b}	0.017
Seminal vesicle	0.30±0.06^{b}	0.32±0.05^{b}	0.32±0.04^{b}	0.37±0.02^{a}	0.045
Prostate	0.13±0.01	0.11±0.02	0.11±0.02	0.11±0.01	0.124
Bulbo-uretral Gland	0.027±0.004^{b}	0.026±0.005^{b}	0.034±0.006^{a}	0.032±0.002^{a}	0.002
Vas deferens	0.042±0.008	0.045±0.008	0.043±0.007	0.046±0.006	0.711
Epididymal spermatozoa characteristics					
Mobility (%)	84.29±5.35^{a}	77.78±10.93^{a}	72.22±12.02^{ab}	62.86±18.90^{b}	0.023
Count per tail (×10^{7})	4.89±1.06^{a}	3.69±1.15^{b}	4.31±1.12^{ab}	3.21±0.71^{b}	0.027
Count per g of tail (×10^{7})	22.42±5.40^{a}	17.98±3.81^{ab}	19.90±2.32^{ab}	15.29±5.75^{b}	0.031
Spermatozoa with Integral Micro and macro cephalies (%)	71.82±2.83^{a} 0.27±0.18^{b}	60.85±4.44^{b} 0.15±0.23^{b}	55.63±5.83^{c} 0.89±0.20^{a}	55.91±1.93^{c} 1.05±0.19^{a}	0.000 0.000
Coiled tails (%)	0.45±0.12^{b}	0.89±0.20^{a}	0.97±0.26^{a}	1.10±0.23^{a}	0.000

a, b, c: within the same line, values with the same letters are not significantly (P>0.05) different. n: number of observations. bw: body weight. P=probability value

Table 3. Effect of cadmium chloride on oxidative Stress biomarkers in male guinea pig

Parameters	Dose of cadmium chloride (mg/kg bw)				p
	0 (n = 8)	8.75 (n = 8)	13.13 (n = 8)	26.25 (n = 8)	
SOD (µM/min/g)	0.47±0.09^{c}	0.59±0.08^{b}	0.49±0.07^{c}	0.68±0.09^{a}	0.000
Catalase (µM/min/g)	0.81±0.03^{b}	0.85±0.06^{b}	0.82±0.03^{b}	0.95±0.08^{a}	0.000
Peroxydase (µM/min/g)	9.02±0.86^{b}	10.37±1.05^{a}	9.86±1.07^{ab}	10.59±1.55^{a}	0.051
Malondialdéhyde (µM)	0.49±0.02^{b}	0.50±0.03^{b}	0.56±0.06^{a}	0.60±0.04^{a}	0.000
Protéine totale (g/dl)	1.96±0.05	1.91±0.07	1.92±0.07	1.90±0.06	0.178

a, b, c: within the same line, values with the same letters are not significantly (P>0.05) different. n: number of observations. bw: body weight. P=probability value. SOD : superoxide dismutase



a, b, c, : histograms values with the same letters are not significantly (P>0.05) different.

Figure 1: Effects of cadmium chloride on serum testosterone concentration in male guinea pigs

IV. Discussion

In this study, the impact of cadmium chloride on detoxifying organs in guinea pigs were assessed. The liver and kidneys are associated to the metabolism and excretion of toxic substances. Then, the evaluation of these detoxifying organs weight is of a great importance for the appreciation of the toxic potential of a substance [26, 22]. The significant increase in the weights of kidneys and liver in this study is similar to that reported by [6] in rat treated by potassium dichromate at a dose of 1 mg/kg for 90 days. This increase in kidneys and liver weights could be due to an enhancement of the permeability relative to the damage following oxidative stress caused by cadmium chloride [23].

Exposure of guinea pigs to cadmium chloride resulted in a significant increase in serum creatinine, urea, ALAT, ASAT and a significant decrease in serum total cholesterol. These results are similar to those of [8] in guinea pigs subjected to lead acetate. The increase in these characteristics is evidence of kidney and liver damage [27]. The levels of transaminases (ASAT or ALAT) in plasma reflects the functioning of the liver and are therefore used for the assessment of liver damage and dysfunction. The increased activities of these enzymes in the blood may be due to the rupture of the cytoplasmic membrane of hepatocytes by free radicals, induced by cadmium chloride [31]. Urea and creatinine are used to assess kidney function, because they are reliable markers of kidney function. Their increase or decrease reflects renal dysfunction [22]. The decrease in total protein levels recorded following exposure to cadmium chloride in this work could be due to reduced protein synthesis and increased protein catabolism, accelerated by reactive oxygen species. Indeed, the latter fragment proteins, making them susceptible to proteolysis [16]. The decrease in cholesterol levels observed in guinea pigs exposed to cadmium chloride is thought to be explained by the inhibition of cholesterol biosynthesis. Free radicals have been shown to accelerate lipid peroxidation and the degradation of polyunsaturated lipids as well as cell membrane lipoproteins.

The weight of testes, epididymis, seminal vesicle and bulbo- urethral gland were weaked in animals exposed to cadmium chloride. [5] also reported decreased reproductive organ weight in rate exposed to cadmium chloride (1 mg/kg) in rats for 17 days. This could be due to the attacks of free radicals induced by these factors on the reproductive cells causing their death.

Semen and sperm characteristics such as number, mobility and morphology are key clues for the assessment of male fertility [15]. Results obtained from this work show a decrease in sperm count and mobility and loss of sperm membrane integrity in guinea pig exposed to cadmium chloride. These findings are similar to those reported by [34] and [18] in rat expose to chrome and cadmium chloride respectively. The decrease in sperm quality could be a result of the plasma membrane disintegration following the overproduction of reactive oxygen species induced by cadmium chloride. In fact, spermatozoa are vulnerable to reactive oxygen species because their plasma membrane contains large amounts of polyunsaturated fatty acids [14, 2]. Thus, excessive generation of reactive oxygen species in semen by abnormal spermatozoa could be a cause of the low sperm quality [2].

Serum testosterone concentration decreased in guinea pigs treated with cadmium chloride This result is similar to that of [5] who reported that exposure of male rats to cadmium (1 mg/kg/day) for 17 days resulted in a decrease in serum testosterone levels. This could be justified by the decrease in testicular weight and volume observed in treated guinea pigs since there is a positive correlation between testicular development and testosterone production. The testes produce spermatozoa and the development of the testes being dependent on testosterone means that a low production of testosterone can lead to a decrease in the development of this organ and consequently negatively influence the characteristics of the spermatozoa.

This study revealed that the testicular activities of SOD, catalase, total peroxidases and malondialdehyde level were increased in the cadmium chloride treated batches. These results are similar to those of [5] in rats exposed to cadmium chloride (1 mg/kg) 17 days. Cadmium chloride would have induced an overproduction of free radicals, at the origin of lipid peroxidation and consequently a deterioration of biological membranes [15].

V. Conclusion

The results of this study revealed that cadmium chloride caused impairment of the reproductive function in male guinea pig. It induced nephrotoxicity, hepatotoxicity and oxidative stress.

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