CADMIUM CHLORIDE TOXICITY AND THE POSSIBLE ROLE OF VITAMIN A

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ABSTRACT
This study was carried out on thirty adult male albino rats. The rats were divided into three equal groups the 1st group fed ordinary rat diet was used as control, the second group was administered cadmium chloride (Cdcl$_2$) at a dose of 8 mg/kg b.wt., orally daily for 8 weeks, the 3rd group were given vitamin A 250 IU/kg b.w., daily orally for 7 days prior to cadmium and for another 8 weeks during cadmium chloride (Cdcl$_2$) administration. The following biochemical parameters were done; renal profile (serum creatinine, blood urea), hepatic profile (SGOT, SGPT, ALP and TSB), serum sodium, potassium , calcium, testosterone, serum and tissue cadmium level. The biochemical results showed highly significant increase in serum renal, hepatic profiles, sodium, calcium and significant decrease in serum potassium and serum testosterone after Cdcl$_2$ ingestion. Regarding serum and tissue Cdcl$_2$ level, there is a significant increase of both levels in kidney and liver in contrast there was no alteration in testicular cadmium. The prior and co-administration of vitamin A before cadmium administration succeeded to restore liver, kidney functions and serum testosterone to their normal level.

INTRODUCTION
Among the various toxic elements, cadmium which is certainly prevalent in nature due to high industrial use and the hazard from cadmium exposure may extend to the general population especially in food and inhaled tobacco smoke (Stoeppler, 2004 and Nogawa et al., 2004). The major toxicological effects of cadmium are targeted toward the pulmonary system during chronic exposure (Seidal, et al., 2002 and Goering, and Waalkes, 1994). Gastrointestinal absorption, is lesser than respiratory absorption, which is enhanced by dietary deficiencies of calcium, iron and low protein feed (Kazantzis, 2004). The low dietary calcium stimulate the synthesis of calcium binding protein
which in turn enhances cadmium absorption. Although, only 5% of the ingested cadmium is absorbed, the biological half life of cadmium in tissues is extremely long and persistent along 10-25 year (Atesdr, 1989). Cadmium is transported in blood bound to red blood cells, albumin and a fraction of blood cadmium may be transported by metallothionein (Sauer et al., 1997). Inhalation exposure to cadmium may be associated with an increased incidence of respiratory tract cancer (Barbee and Prince, 1999). Recently, it has been shown that vitamin A can alter the toxicity of cadmium in the rat (John, et al., 1997). Therefore, the objective of this study was to determine how retinol pretreatment might affect the acute toxicity of cadmium chloride (Cdcl2) and elucidate the possible mechanisms in counteracting the deleterious effects of Cdcl2 on liver, kidney and testes of albino rats.

MATERIALS & METHODS

Animals:

Thirty adult male albino rats (200-250 g) were used for this study, classified into 3 equal groups each of it is ten. The 1st group were used as control group, the second group was administered cadmium chloride (Cdcl2) at a dose of 8 mg/kg b.wt., orally daily for 8 weeks, cadmium was obtained in the form of cadmium chloride powder (Al Gomhoria Pharmaceutical Co., ARE) “Cdcl2”.

the 3rd group was given vitamin A 250 IU/kg bw daily orally for 7 days prior to cadmium and for another 8 weeks during cadmium chloride (Cdcl2) exposure vitamin A was obtained in the form of capsules (Kahira Pharmaceutical Co., ARE) 5000 IU / capsule.

Blood samples were obtained by scarifying the rats 24 hrs after the last administration into clean dry tubes and left to clot and centrifuged to obtain serum the following parameters were measured blood urea nitrogen according to method described by (Fawcett and Scott, 1960), serum creatinine by standard colorimetric procedure (Owen, et al., 1954), serum sodium and potassium by flam photometry according to (Simon and Proda, 1970), serum testosterone according the method of (Callo, 1939), calcium according to (Trudeau and Freier, 1967), serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) according the method of (Reitman and Frankel, 1957), alkaline phosphatase (ALP) as method described by (Besseget et al., 1946), total serum bilirubin (TSB) according to (Malloy and Evelyn, 1938). Cadmium serum level was measured by atomic absorption spectrophotometry according to (Onosaka, et al., 1978) and Cadmium tissue level it was also measured by atomic absorption spe-
ctrophotometery in liver, kidney and in the testis. About 100 mg of tissue was digested over night in nitric acid. The solutions were filtered with a 0.45 Mm Millex-HV syringe-tip filter and brought to a final volume of 5 ml using ultra pure H₂O. Samples were on an atomic absorption spectrophotometer at 228. 8 mm using a cadmium lamp and cadmium concentrations were calculated using a standard curve according to (Nakamura, et al., 1991). The obtained data were statistically analyzed using (ANOVA) test followed by Duncan test according to (Snedecor and Cochran, 1982).

RESULTS
As shown in Table (I) there were a significant increase in the mean values of hepatic profile (SGOT, SGPT, ALP and total bilirubin) and kidney profile (urea and creatinine), whereas serum testosterone significantly decrease in rats administered cadmium. The prior and co-administration of vitamin A succeeded to restore the studied biochemical parameters to their normal values as compared to control group.

Table (II) demonstrated that a significant increase in serum sodium, calcium and significant decrease in serum potassium, vitamin A supplementation prior to cadmium exposure produced prophylactic action evidenced by restoring the studied biochemical parameters to their normal values.

Table (III) showed a significant increase in serum cadmium, regarding tissue cadmium level there was a significant increase in hepatic and renal cadmium level, in contrast there was no alteration in testicular cadmium. The supplementation with vitamin A one week prior to cadmium administration succeeded to normalize the studied biochemical parameters as compared to control group.

Table (I): Biochemical Parameters including SGOT, SGPT, ALP, total TSB, BUN, S-creatinine and testosterone (Testes.); in groups of control, cadmium chloride administered and vitamin A with cadmium chloride (Mean ± S.E) n = 10 rats.

<table>
<thead>
<tr>
<th>parameter Group</th>
<th>SGOT (U/L)</th>
<th>SGPT (U/L)</th>
<th>ALP Kau/dl</th>
<th>TSB (mg/dl)</th>
<th>BUN (mg/dl)</th>
<th>Screat (mg/dl)</th>
<th>Testes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group(1) (control)</td>
<td>7.11±c</td>
<td>9.23±c</td>
<td>54.0±c</td>
<td>0.24±ab</td>
<td>30.9±c</td>
<td>0.29±c</td>
<td>1.72±b</td>
</tr>
<tr>
<td></td>
<td>1.42</td>
<td>152</td>
<td>±11.3</td>
<td>0.06</td>
<td>3.12</td>
<td>0.07</td>
<td>0.6</td>
</tr>
<tr>
<td>Group(11)</td>
<td>14.00±b</td>
<td>16.00±b</td>
<td>114±b</td>
<td>0.31±b</td>
<td>52.0±b</td>
<td>0.63±b</td>
<td>0.22±a</td>
</tr>
<tr>
<td></td>
<td>4.24</td>
<td>7.24</td>
<td>20.3</td>
<td>0.09</td>
<td>7.60</td>
<td>0.06</td>
<td>0.13</td>
</tr>
<tr>
<td>Group(111)</td>
<td>7.31±a</td>
<td>9.64±a</td>
<td>58.0±a</td>
<td>0.22±b</td>
<td>31.5±a</td>
<td>0.30±a</td>
<td>1.90±b</td>
</tr>
<tr>
<td></td>
<td>1.53</td>
<td>1.60</td>
<td>12.4</td>
<td>0.02</td>
<td>4.0</td>
<td>0.16</td>
<td>0.51</td>
</tr>
<tr>
<td>F-test</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>LSD</td>
<td>6.519</td>
<td>6.112</td>
<td>4.917</td>
<td>0.816</td>
<td>4.862</td>
<td>0.08</td>
<td>0.411</td>
</tr>
</tbody>
</table>

* Significant at (P<0.05) ** Highly Significant (P<0.01)
Different letter in the same column indicates sign. Differences.

**Table (2): Na\(^+\), K\(^+\) and Ca\(^{2+}\) level in groups of control, cadmium chloride administered and vitamin A with cadmium chloride (Mean ± S.E) n=10 rats.**

<table>
<thead>
<tr>
<th>Parameter Group</th>
<th>Na(^+) (mmol/L)</th>
<th>K(^+) (mmol/L)</th>
<th>Ca(^{2+}) mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group1 (control)</td>
<td>139±8.12(^{ab})</td>
<td>3.9±0.07</td>
<td>8.8±0.17</td>
</tr>
<tr>
<td>Group11</td>
<td>162±9.22(^a)</td>
<td>3.1±0.03(^*)</td>
<td>10.3±0.22(^*)</td>
</tr>
<tr>
<td>Group111</td>
<td>141±8.17(^b)</td>
<td>3.8±0.06</td>
<td>9.0±0.19</td>
</tr>
<tr>
<td>F-test</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>LSD</td>
<td>102.33</td>
<td>4.11</td>
<td>7.917</td>
</tr>
</tbody>
</table>

* Significant at (P<0.05) ** Highly Significant (P<0.01)

Different letter in the same column indicates sign. Differences.

**Table (3): Serum, hepatic, renal and testicular cadmium, in groups of control, cadmium chloride and vitamin A with cadmium chloride (Mean ± S.E) n=10 rats.**

<table>
<thead>
<tr>
<th>Parameter Group</th>
<th>Serum cad. (µg/L)</th>
<th>Hepatic cad. (ug/100gm tissue)</th>
<th>Renal cad. (ug/100gm tissue)</th>
<th>Testes cad. (ug/100gm tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group1 (control)</td>
<td>1.40±0.02(^{ab})</td>
<td>1.30±0.02(^a)</td>
<td>1.17±0.08(^a)</td>
<td>0.021±0.00(^b)</td>
</tr>
<tr>
<td>Group11</td>
<td>2.10±0.44(^b)</td>
<td>18.0±6.04(^b)</td>
<td>9.9±0.15(^b)</td>
<td>0.023±0.00(^b)</td>
</tr>
<tr>
<td>Group111</td>
<td>1.29±0.48(^a)</td>
<td>22.10±3.90(^c)</td>
<td>1.23±0.09(^c)</td>
<td>0.022±0.00(^b)</td>
</tr>
<tr>
<td>F-test</td>
<td>*</td>
<td>**</td>
<td>**</td>
<td>*</td>
</tr>
<tr>
<td>LSD</td>
<td>0.03</td>
<td>2.81</td>
<td>0.87</td>
<td>0.41</td>
</tr>
</tbody>
</table>

* Significant at (P<0.05) ** Highly Significant (P<0.01)

Different letter in the same column indicates sign. Differences.
DISCUSSION

In the present study, clear evidence of testicular and hepatorenal toxicity was observed following cadmium chloride (Cdcl\(_2\)) administration, while pretreatment with vitamin A significantly ameliorated these toxicities. Cadmium is unique metal because of its toxicity in low dosage, long biological half life (30 hours in humans), its low rate of excretion from the body, and it is stored mainly in the liver, kidney and testis (Barbier et al., 2005). Metabolic transformations of cadmium are limited to its binding to protein and nonprotein sulphydryl groups, and various macromolecules, such as metallothionein which is especially important in the kidneys and liver (Klaassen, 1998). Cadmium is excreted primarily in the urine.

In this study the significant increase in the mean values of hepatic profile (SGOT, SGPT, ALP and total bilirubin), kidney profile (urea and creatinine) whereas serum testosterone significantly decrease in rats administered cadmium, these finding agree with the work of (Brzó; ska et al., 2002) who found that a wide range increase serum levels of GOT, GPT, ALP, bilirubin, urea, creatinine, decreased urinary urea, creatinine clearance and serum testosterone decrease in rats. Cadmium is highly hepatotoxic even in a very small dose with a significant increase in AST, ALT, bilirubin and a significant decrease in total protein and albumin (Rana and Rastogi, 1998). Regarding the extra-hepatic toxicity of cadmium, first nephrotoxicity of cadmium (Bernard, 2004). Cadmium exposure to rats led to acute onset nephrotoxicity (Hotz et al., 1999).

The significant decrease in serum testosterone was in agreement with the work of (Goyer, 2004) who showed sever testicular toxicity and damage with a significantly decrease in serum testosterone after cadmium administration both in mice and rats. At least 48 hours must pass for cadmium’s toxicity to be evident in the soft tissues namely liver, kidney and testicles (Starey, 1995).

The results should a significant increase in serum calcium in rats exposed to cadmium and the co-administration of vitamin A succeeded to normalize calcium level. The increased in calcium level results from the marked decrease in calcium efflux across the erythrocytic membrane (Kazantzis, 2004 and Kazantzis, 1999). Cadmium affects a number of calcium associated processes as it inhibits Ca-ATPase (Failla et al., 1997) and inhibits calcium influx into hepatocytes possibly through its interaction with membrane SH groups and induces its toxicity (Verbest et al., 1997).
However the recorded significant increase serum Na\(^+\) and A significant decrease in serum K\(^+\) in cadmium exposed rats. In this respect (Rajanna et al., 2004) reported that cadmium interferes with Na\(^+\) and K\(^+\) influx and inhibits Na\(^+\)/K\(^+\)-ATPase. and the decrease in Na\(^+\)/K\(^+\)-ATPase activity in cadmium exposed rats could be attributed to the erythrocyte membrane damage, ultra structure changes and defect in phosphorylation of the membrane polypeptides, such membrane damage may be due to the disruption of the antioxidant enzyme system. Cadmium exerts its toxic effects by inhibiting glutathione peroxidase and catalase activities and affects the oxidative phosphorylation. The co-administration of vitamin A diminishes the toxic effect of cadmium by restoring the activity of the antioxidant enzyme to normal levels (Nehru and Bansal, 2003 and Tietz, 1999).

The noticed significant increase serum, hepatic, renal and testicular cadmium were came in accordance with the finding of (Svarten and Lind, 1999) who postulated that cadmium level were increased in serum and hepatic, renal and testicular tissue in rats treated with cadmium. This result agree with (Cherian, 1994) who find that cadmium exposure to rats led to increase in hepatic and renal tissue cadmium with acute onset nephro and hepatotoxicity. Cadmium toxicity to be evident in the soft tissues namely liver, kidney and testicles (Zalups, 2003). The significant increase finding regarding Cadmium also like other metals is detoxified from the body through metallothionine MT (Klaassen, 1998).

MT is a cysteine rich low molecular weight metal binding protein which binds cadmium with high affinity and thus reduces its access to molecular targets in the cell (Webb, 1995).

The co-administration of vitamin A diminishes the toxic effect of cadmium by increasing hepatic metallothionine levels by seven folds (Nogawa, 2004). Elevation in the quantity of MT have been directly related to reduced cadmium toxicity (Hideaki, et al., 1997). Vitamin A mediate such effect through nuclear biding receptors which interact with DNA via retinoic acid regulatory element to alter MT gene expression, which lead to increase hepatic MT synthesis (Underwood, 1997).

Vitamin A (Retinol) pretreatment lead to significant mitigation of cadmium induced hepatic and extrahepatic toxicities. The mechanism of retinol induced-tolerance to cadmium toxicity appears to be mediated by the induction of hepatic metallothionine synthesis (Enarest and Sipes, 1993).

It was concluded that retinol exhibited a protective effect against cadmium induced toxicity. It may be used as an alternative antidote in cadmium intoxications.

Recommendations is also done to give workers who are at high risk of cadmium exposure vitamin A to
prevent the accident or occupational hazards of cadmium.

REFERENCE


التأثير السمي للكادميوم والدور المحتمل لفيتامين (أ)

حسين رشاد محمد – *صلاح إبراهيم سليم - مجدى فكرى أبو الفتوح

لدراسة التأثير السمي للكادميوم ودور فيتامين (أ) المحتمل للوقاية أجريت الدراسة على ثلاثين فأرا قسمت إلى ثلاثة مجموعات متساوية كلها من فئران. الأولى استخدمت كمجموعة ضابطة والثانية جرعت كlorid الكادميوم لمدة ثمانية أسابيع عن طريق الفم بجرعة 0.8 مجم/كم والمجموعة الثالثة جرعت فيتامين (أ) بجرعة 250 وحدة دولية/كم أسبوع قبل تجريعها الكادميوم واستمر التجريع لمدة ثمانية أسابيع أخرى أثناء تجريعها بالكادميوم. وأسفرت النتائج بعد تحليلها إحصائيا على ما يلي:

حدث زيادة معنوية في إنزيمات الكبد والبليروبين والفوسيفس القلوى ووظائف الكلي البولينا والكرياتينين وفی تركز الصوديوم والكالسيوم بينما حدث انخفاض معنوي في كل من البوتاسيوم والتيستستيرون وكذلك حدث زيادة معنوية عالية في تركز الكادميوم في سيرم الدم والأنسجة.

عند تجريع الفئران بفيتامين (أ) قبل واثناء تجريعها بالكادميوم أوضحت الدراسة الدور الحيوي المهم والوقائي لفيتامين (أ) ومساهمتها في إعادة وظائف الكبد والكلي والصوديوم والكالسيوم والبيوتامين والتيستستيرون إلى مستوياتها الطبيعية.