ORIGINAL ARTICLES

Reno - Protective Efficiency of Coenzyme Q10 on Adriamycin-Induced Nephrotoxicity in Rats

Nahla H. Aly

Biochemical & Nutrition Department, Women's Collage, Ain Shams University.

ABSTRACT

The nephroprotective effect of coenzyme Q10 (CoQ10) was investigated in rats with acute renal injury induced by the anthracycline antibiotic doxorubicin (Adriamycin). A total of sixty rats were allocated into four groups. Group I: the rats were given only saline throughout all thirty days experimental period (control group). Group II (CoQ10 group): the rats were daily injected intraperitoneally (i.p) with 50mg CoQ10/kg body weight all through the experimental period. Group III (Adriamycin “Acute renal failure” group): The rats were bi-daily injected (i.p) as a cumulative dose of adriamycin (10mg/Kg b.w.), which divided into 6 equal injections over a period of two weeks. Group IV (Therapeutic group): the rats were injected with adriamycin to induce acute renal failure and then treated intraperitoneally with 50mg of CoQ10/kg b.w. for 30 days. In regard to the induction of acute renal failure in rats by adriamycin administration, the obtained results showed a significant elevation in the serum levels of urea and creatinine with disturbance in the serum electrolytes (sodium, potassium, calcium and inorganic phosphorus) levels. Also, a significant increment in both parathyroid hormone (PTH) and β2-microglobulin (β2-MG) levels was recorded in adriamycin rats group. A considerable disturbance in the autoimmune system was pronounced in adriamycin rats group represented by depletion in the activities of superoxide dismutase (SOD) and catalase (CAT) and the level of glutathione (GSH) with elevation in the concentration of thiobarbituric acid reactive substances (TBARS) as lipid peroxidation in the kidney tissues. The results of the current study indicated that CoQ10 effectively protected the kidney tissue against adriamycin induced acute nephrotoxicity in rats. The antioxidant and anti-inflammatory activities can be considered the main factors responsible for the nephroprotective effect of CoQ10. Therefore, CoQ10 represents a potential candidate to prevent renal injury and dysfunction which is a major and dose-limiting problem during adriamycin therapy.

Key words: Acute renal failure – Adriamycin - Coenzyme-Q10 – Rats.

Introduction

Acute renal failure (ARF) is a complex syndrome involving several mechanisms including renal vasoconstriction, extensive tubular damage and glomerular injury (Weinberg, 1991). ARF is responsible for renal dysfunction in kidney transplantation and may occur following surgical revascularization of the renal artery, partial nephrectomy, treatment of suprarenal aortic aneurysms and after cardiac surgery (Myers et al., 2006). The mechanisms involved in ARF injury include anoxia, release of reactive oxygen species (ROS) such as superoxide radicals (O2·−), hydrogen peroxide (H2O2) and hydroxyl radicals (OH·) during reperfusion and neutrophil accumulation and subsequent release of additional ROS and lytic enzymes (Bonventre & Weinberg, 2003). ARF induces inflammatory disorders and activates the arachidonic acid metabolic pathway.

The anthracycline antibiotic doxorubicin (Adriamycin) is an antineoplastic agent with high antitumor efficacy in solid malignancies (Mihm et al., 2002). Moreover, adriamycin-induced kidney toxicity was observed in 2–20% of the patients receiving anthracyclines and was dose dependent (Minotti et al., 2004). The antitumor activity of adriamycin is likely to be distinct from the mechanism of its kidney toxicity. Adriamycin antitumor activity is thought to be due to DNA damage and inhibition of cell replication of highly proliferative tumors (Singal et al., 1987).

Pharmacokinetic studies have shown that the rapid tissue uptake of adriamycin within 5 min after administration was followed by a terminal half-life of 20–48 h (Davies & Doroshow, 1986). Adriamycin is metabolized in the liver where the quinone nucleus of doxorubicin undergoes redox cycling. The reduction of adriamycin to a semiquinone free radical is catalyzed by NADPH-dependent cytochrome P450 reductase and reconversion to the quinone is accompanied by reduction of molecular oxygen to superoxide anions (O2·−), forming peroxynitrite (ONOO−) in a reaction with nitric oxide. Both hydroxyl radicals and peroxynitrite can initiate protein oxidation and lipid peroxidation (Davies & Doroshow, 1986). Increased production of
superoxide, OH-, conjugated dienes, malonaldehyde and enzymatic activity changes of GSH peroxidase and catalase following anthracycline treatment has been observed in several biological systems (Mimnaugh et al., 1985).

Coenzyme Q10 (CoQ10) is an endogenous lipid-soluble benzo-quinone compound that functions as a diffusible electron carrier in the mitochondrial respiratory chain (Upaganlawar et al., 2006). CoQ10 also acts as a powerful antioxidant which scavenges free radicals, prevents the initiation and propagation of lipid peroxidation in cellular biomembranes, and helps regeneration of α-tocopherol (Bentinger et al., 2007).

In addition, CoQ10 has anti-inflammatory properties decreasing the production of proinflammatory cytokines as tumor necrosis factor-α (Schmelzer et al., 2007 & 2008). Previous studies demonstrated the protective effects of CoQ10 in various models of oxidative and inflammatory tissue damage (Upaganlawar et al., 2006; Sohet et al., 2009 and Spindler et al., 2009). Therefore, CoQ10 has the potential to protect against renal tissue injury and renal dysfunction induced by cisplatin. However, four week’s of supplementation with CoQ10 in patients after renal transplantation did not successfully reduce enhanced lipid peroxidation as demonstrated by the MDA+ 4-HNE level (Długosz et al., 2004).

This was encouraging to conduct the current study in order to evaluate the possible protective effect of CoQ10 in rats exposed to acute adriamycin nephrotoxicity. Also, the possible mechanisms underlying this effect were investigated and discussed according to available recent researches.

Material and Methods

Animals:

Sixty adult male albino rats weighing 150±10g were employed in this study. They were housed in a well ventilated in the Animal House. The animals were caged in wire bottom galvanized metal wall boxes under controlled environmental and nutritional conditions (25°C). The animals fed on a standard diet according to National Research Council (NRC, 1977) and fresh tap water was ad libitum.

Experimental Design:

The rats were classified into four groups (Fifteen animals each):

Group I (control group): The rats were given only saline all through the experimental period (30 days).

Group II (CoQ10 group): The rats were daily injected intraperitoneally (i.p) with 50mg CoQ10/kg b.w. according to Rauscher et al., (2001), all through the experimental period (30 days).

Group III (Adriamycin "induced acute renal failure" group): the rats were initially injected (i.p) by adriamycin (every two days) as a cumulative dose to induce acute renal failure, which was divided into 6 equal injections over a period of two weeks (10mg/Kg b.w.) according to the method of Podjarny et al. (1997). Then, the rats were fed with control diet for the rest of experimental period (30 days).

Group IV (Therapeutic group): the rats were injected with adriamycin as proceeded on the previous group (Group III) to the end of full induction of acute renal failure and then were intraperitoneally treated on daily basis with 50mg of CoQ10/kg b.w. for thirty days.

Blood Sampling And Tissue Preparation:

At the end of each experimental period (10, 20 and 30 days) and after overnight fasting, animals were scarified and the blood samples were collected from each rat on specified time interval. Blood samples were centrifuged for 10 minutes at 3000 rpm within an hour of the blood collection and the sera were obtained. Sera were separated and divided into considerable aliquots to avoid the effects of repeated thawing and freezing. All specimens of sera were stored at -20°C until use.

Determination Of Serum Urea And Creatinine:

The serum parameters were analyzed spectrophotometrically by using double beam UV-Visible spectrophotometer (UV-Visible spectrophotometer, VIS-JR, model 1601). Estimation of serum urea and creatinine were carried out using respective diagnostic kits purchased from Biodiagnostic Company (Cairo, Egypt) according to the methods of Fawcett & Scott (1960) and Seeling & Wust (1969) respectively.

Determination Of Serum Electrolytes:

Sodium (Na) and Potassium (K) analysis were accomplished by emission flame photometry after suitable dilution as described by Dean (1960). Serum calcium was determined colorimetrically using commercial kits.
(Human, Germany) according to the method of Barnett et al. (1973). Serum inorganic phosphorus was determined colorimetrically using kits supplied by Randox, Ltd., Co. (UK) and according to the method of Goldenberg & Fernands (1966).

**Estimation Of Serum Parathyroid Hormone (PTH):**

Parathyroid hormone (PTH) was assayed by radioimmunoassay (RIA) kit using solid phase component system (Phoenix Pharmaceuticals, Inc., USA) as described by Patrono & Peskar (1987).

**Estimation Of Serum Rat ß2-Microglobulin (ß2-MG):**

Serum rat ß2-microglobulin (ß2-MG) was assayed using commercial rat ß2-microglobulin ELISA kit. This kit was purchased from American Laboratory Products Company (ALPCO Diagnostics, USA) according to method of Cunningham et al. (1973).

**Determination Of Antioxidant Enzymes And Lipid Peroxidation:**

After animals sacrifice, the kidneys were quickly removed and washed in ice-cold saline. The kidney tissue was homogenized in ice-cold tri-hydrochloride buffer (pH 7.2). The homogenate was centrifuged and then the supernatant obtained was used for the estimation of reactive oxygen metabolites in terms of lipid peroxidation as thiobarbituric acid reactive substances (TBARS) according to Ohkawa et al. (1979), glutathione (GSH) according to Baker et al. (1990) superoxide dismutase (SOD) according to Oyanagui (1984), catalase (CAT) according to (Aebi, 1974), and total protein estimation (Lowry et al., 1951). The commercial ELISA kits of TBARS, SOD, CAT and GSH were purchased from Cayman Chem. Co., USA.

**Statistical Analysis:**

Data were presented as mean ± standard error (SE) and were statistically analyzed using analysis of variance (ANOVA) followed by Duncan’s multiple range test according to Duncan (1955) and Snedecor & Cochran (1982) by MSTAT-C program, Version 4, USA.

**Results:**

The data presented in Table (1), revealed no remarkable changes in both serum urea and creatinine levels in control rats during the study period (10, 20 & 30 days). In comparison with the normal control animals, a numerical change but not significant change was occurred in the both serum urea and creatinine levels as a result of CoQ10 supplementation.

On the other hand, for acute renal failure rats group (treated with adriamycin 10 mg/kg b.w.), a significant (P< 0.05) elevation was realized in both serum urea and creatinine levels as compared with those control one dependent on time (Table 1).

Furthermore, a marked decrease was occurred in both serum urea and creatinine levels after acute renal failure rats group was injected intraperitoneally with 50mg CoQ10/kg b.w. (Table 1). This amelioration in both serum urea and creatinine levels was dependent on the time of treatment and reached to the best one at 30 days (last interval).

Table (2) had demonstrated that the serum sodium, potassium, inorganic phosphorus and total calcium levels in normal rats group were more or less constant figures during the course of the study. Also, no significant change was occurred in the serum sodium, potassium, inorganic phosphorus and total calcium levels as a result of CoQ10 supplementation.

After the animals were treated with 10 mg/kg b.w. adriamycin for 6 equal injections over a period of two weeks to induce acute renal failure, a significant (P< 0.05) depletion in both the levels of serum sodium and calcium was occurred dependent on the time (Table 2). While, the administration of adriamycin led to a significant (P< 0.05) elevation in both the levels of serum potassium and inorganic phosphorus was observed dependent as compared with those control one and dependent on the time (Table 2).

A considerable improvement was observed in the serum sodium, potassium, inorganic phosphorus and total calcium levels of the nephrotoxic rats group after treatment of rats with antioxidant (50mg CoQ10/kg b.w.) This improvement was depending on time of treatment (Table 2).

Detecting the obtained data of the serum parathyroid hormone (PTH) and ß2-microglobulin (ß2-MG) levels were presented by table (3) and showed that the normal control rats designated similar levels during the study period (10, 20 & 30 days). In relation to the normal control animals, no considerable changes were occurred in
the both serum parathyroid hormone (PTH) and β₂-microglobulin (β₂-MG) levels as a result of CoQ₁₀ supplementation (Table 3).

On the other hand, in nephrotoxic rat group (animal treated with adriamycin 10 mg/kg b.w.), a significant (P< 0.05) elevation was shown in both serum PTH and β₂-MG levels as compared with the normal control rats group. These elevations in the levels of serum PTH and β₂-MG were increased gradually with time intervals (10, 20 & 30 days). These data were tabulated in table (3).

Table 1: Effect of coenzyme Q₁₀ administration into nephrotoxic rats on serum urea and creatinine at various intervals.

<table>
<thead>
<tr>
<th>parameters</th>
<th>days</th>
<th>Control group</th>
<th>CoQ₁₀ group</th>
<th>Nephrotoxic Adriamycin group</th>
<th>Nephrotoxic Treated with CoQ₁₀ group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dl)</td>
<td>10</td>
<td>14.91 ± 0.57</td>
<td>15.18 ± 0.59</td>
<td>56.53 ± 1.61</td>
<td>46.61 ± 1.56</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>15.03 ± 0.58</td>
<td>15.07 ± 0.64</td>
<td>68.11 ± 1.52</td>
<td>39.94 ± 1.42</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>15.12 ± 0.58</td>
<td>14.88 ± 0.51</td>
<td>77.67 ± 1.73</td>
<td>26.23 ± 1.54</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>10</td>
<td>0.57 ± 0.09</td>
<td>0.59 ± 0.08</td>
<td>1.58 ± 0.09</td>
<td>1.16 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>0.55 ± 0.08</td>
<td>0.57 ± 0.07</td>
<td>1.99 ± 0.11</td>
<td>0.99 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>0.58 ± 0.07</td>
<td>0.59 ± 0.07</td>
<td>2.44 ± 0.12</td>
<td>0.78 ± 0.05</td>
</tr>
</tbody>
</table>

- Values are expressed as means ± S.E.  - Number of rats in the group=15.
- Means bearing different superscripts (A,B,C) within the same row are differ significantly (P<0.05).
- Means bearing different subscripts (a,b,c) within the same column are differ significantly (P<0.05).

Table 2: Effect of coenzyme Q₁₀ administration into nephrotoxic rats on serum electrolytes at various intervals.

<table>
<thead>
<tr>
<th>parameters</th>
<th>days</th>
<th>Control group</th>
<th>CoQ₁₀ group</th>
<th>Nephrotoxic Adriamycin group</th>
<th>Nephrotoxic Treated with CoQ₁₀ group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (meq/L)</td>
<td>10</td>
<td>132.3 ± 1.97</td>
<td>133.4 ± 1.94</td>
<td>127.9 ± 1.86</td>
<td>126.7 ± 1.89</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>135.7 ± 1.88</td>
<td>136.1 ± 1.91</td>
<td>126.3 ± 1.89</td>
<td>129.8 ± 1.81</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>136.5 ± 1.92</td>
<td>137.1 ± 1.83</td>
<td>120.3 ± 1.77</td>
<td>133.7 ± 1.92</td>
</tr>
<tr>
<td>Potassium (meq/L)</td>
<td>10</td>
<td>4.41 ± 0.11</td>
<td>4.45 ± 0.12</td>
<td>4.81 ± 0.13</td>
<td>4.78 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>4.39 ± 0.10</td>
<td>4.41 ± 0.11</td>
<td>5.02 ± 0.12</td>
<td>4.43 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>4.44 ± 0.08</td>
<td>4.43 ± 0.11</td>
<td>5.59 ± 0.15</td>
<td>4.41 ± 0.08</td>
</tr>
<tr>
<td>Inorganic Phosphorus (mg/dl)</td>
<td>10</td>
<td>8.69 ± 0.19</td>
<td>8.68 ± 0.17</td>
<td>9.50 ± 0.16</td>
<td>9.03 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>8.66 ± 0.19</td>
<td>8.67 ± 0.16</td>
<td>9.89 ± 0.18</td>
<td>8.69 ± 0.19</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>8.67 ± 0.16</td>
<td>8.69 ± 0.14</td>
<td>10.31 ± 0.19</td>
<td>8.69 ± 0.18</td>
</tr>
<tr>
<td>Total Calcium (mg/dl)</td>
<td>10</td>
<td>9.28 ± 0.16</td>
<td>9.24 ± 0.18</td>
<td>8.63 ± 0.19</td>
<td>8.66 ± 1.19</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>9.24 ± 0.16</td>
<td>9.27 ± 0.17</td>
<td>8.31 ± 0.23</td>
<td>8.99 ± 1.20</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>9.29 ± 0.17</td>
<td>9.26 ± 0.18</td>
<td>7.94 ± 0.23</td>
<td>9.23 ± 1.18</td>
</tr>
</tbody>
</table>

- Values are expressed as means ± S.E.  - Number of rats in the group=15.
- Means bearing different superscripts (A,B,C) within the same row are differ significantly (P<0.05).
- Means bearing different subscripts (a,b,c) within the same column are differ significantly (P<0.05).

Table 3: Effect of coenzyme Q₁₀ administration into nephrotoxic rats on serum PTH and β₂-MG at various intervals.

<table>
<thead>
<tr>
<th>parameters</th>
<th>days</th>
<th>Control group</th>
<th>CoQ₁₀ group</th>
<th>Nephrotoxic Adriamycin group</th>
<th>Nephrotoxic Treated with CoQ₁₀ group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/ml)</td>
<td>10</td>
<td>14.89 ± 0.24</td>
<td>14.99 ± 0.22</td>
<td>21.34 ± 0.31</td>
<td>20.13 ± 0.29</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>15.12 ± 0.21</td>
<td>15.06 ± 0.20</td>
<td>25.27 ± 0.32</td>
<td>18.79 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>15.22 ± 0.24</td>
<td>14.94 ± 0.23</td>
<td>28.88 ± 0.29</td>
<td>15.28 ± 0.25</td>
</tr>
<tr>
<td>β₂-MG (ng/ml)</td>
<td>10</td>
<td>12.21 ± 0.19</td>
<td>12.17 ± 0.18</td>
<td>17.59 ± 0.22</td>
<td>16.36 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>12.33 ± 0.17</td>
<td>12.26 ± 0.19</td>
<td>20.72 ± 0.25</td>
<td>15.09 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>12.38 ± 0.19</td>
<td>12.29 ± 0.18</td>
<td>24.31 ± 0.29</td>
<td>13.74 ± 0.21</td>
</tr>
</tbody>
</table>

- Values are expressed as means ± S.E.  - Number of rats in the group=15.
- Means bearing different superscripts (A, B, C) within the same row are differ significantly (P<0.05).
- Means bearing different subscripts (a, b, c) within the same column are differ significantly (P<0.05).
Moreover, after the nephrotoxic rats were injected intraperitoneally with 50mg CoQ10/kg b.w., the data recorded a decrease in the levels of serum PTH and ß2-MG dependent on the time of treatment (Table 3).

Table (4) illustrated glutathione (GSH) content, superoxide dismutase (SOD) activity, catalase (CAT) activity and thiobarbituric acid reactive substances (TBARS) level in the kidney tissues in all studied animals groups. No remarkable changes were noted in GSH content, SOD activity, CAT activity and TBARS level in the kidney tissues in control rats during the study period (10, 20 & 30 days). In relation to the normal control animals, a numerical change but not significant change was occurred in all previous studied parameters as a result of CoQ10 supplementation.

While, in nephrotoxic rats group (treated with adriamycin 10 mg/kg b.w.), a significant (P<0.05) depression was observed in GSH content, SOD activity and CAT activity in the kidney tissues as compared with those control ones dependent on time (Table 4). Moreover, a significant (P<0.05) elevation was observed in lipid peroxidation represented as TBARS and reached to the maximum levels at the last interval (30 days).

<table>
<thead>
<tr>
<th>parameters</th>
<th>days</th>
<th>Control group</th>
<th>CoQ10 group</th>
<th>Nephrotoxic Adriamycin group</th>
<th>Nephrotoxic Treated with CoQ10 group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione (mg/g protein)</td>
<td>10</td>
<td>1.68 ± 0.09 A</td>
<td>1.68 ± 0.07 A</td>
<td>1.30 ± 0.06 B</td>
<td>1.29 ± 0.17 B</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1.66 ± 0.07 A</td>
<td>1.70 ± 0.06 A</td>
<td>1.09 ± 0.06 B</td>
<td>1.41 ± 0.19 C</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>1.65 ± 0.06 A</td>
<td>1.69 ± 0.07 A</td>
<td>0.78 ± 0.14 B</td>
<td>1.64 ± 0.15 C</td>
</tr>
<tr>
<td>Superoxide dismutase (N/60 min/mg protein)</td>
<td>10</td>
<td>5.03 ± 0.09 A</td>
<td>4.84 ± 0.08 A</td>
<td>3.03 ± 0.06 B</td>
<td>3.61 ± 0.05 C</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>4.94 ± 0.06 A</td>
<td>5.27 ± 0.09 A</td>
<td>2.91 ± 0.06 B</td>
<td>4.30 ± 0.07 C</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>5.11 ± 0.07 A</td>
<td>5.59 ± 0.08 A</td>
<td>2.53 ± 0.07 B</td>
<td>4.51 ± 0.06 C</td>
</tr>
<tr>
<td>Catalase (nmol/ 60min /mg protein)</td>
<td>10</td>
<td>41.90 ± 0.81 A</td>
<td>41.99 ± 0.82 A</td>
<td>29.75 ± 0.64 B</td>
<td>30.27 ± 0.61 B</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>41.63 ± 0.73 A</td>
<td>42.48 ± 0.90 A</td>
<td>22.06 ± 0.62 B</td>
<td>33.13 ± 0.72 C</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>40.83 ± 0.79 A</td>
<td>43.52 ± 0.88 A</td>
<td>18.13 ± 0.71 C</td>
<td>37.34 ± 0.78 D</td>
</tr>
<tr>
<td>TBARS (nmol/g tissue)</td>
<td>10</td>
<td>113.6 ± 1.29 A</td>
<td>112.4 ± 1.18 A</td>
<td>171.5 ± 1.78 B</td>
<td>167.4 ± 1.78 B</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>114.5 ± 1.31 A</td>
<td>106.7 ± 1.09 B</td>
<td>206.2 ± 1.98 C</td>
<td>151.9 ± 1.52 C</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>117.1 ± 1.39 A</td>
<td>104.8 ± 1.23 B</td>
<td>252.1 ± 2.34 C</td>
<td>129.3 ± 1.57 D</td>
</tr>
</tbody>
</table>

- Values are expressed as means ± S.E.
- Number of rats in the group=15.
- Means bearing different superscripts (A,B,C, D) within the same row are differ significantly (P<0.05).
- Means bearing different subscripts (a,b,c) within the same column are differ significantly (P<0.05).

Obviously, a significant (P< 0.05) correction was occurred in the GSH content, SOD activity, CAT activity and TBARS level after nephrotoxic rats group was injected intraperitoneally with 50mg CoQ10/kg b.w. (Table 1). These amelioration effects of CoQ10 treatment were occurred on all previous investigated parameters in the kidney tissues depending on the time of treatment and reached to the best ones at 30 days (Last interval). Yet, these ameliorative effects still were not comparable to their corresponding results in the normal control rats group (Table 4).

Discussion:

One of the most common manifestation of nephrotoxic damage is acute renal failure which characterized by decline in glomerular filtration rate with resulting azotaemia (Heibashy & Abdel Moniem, 1999 and Heibashy et al., 2009). Adriamycin, an anthracyclin antibiotic represents a class of anticancer agents. It shows broad spectrum anti-tumour activities in certain human cancers including breast cancer, small cell carcinoma of the lung and acute leukaemia (Chabner et al., 2001). The optimal use of doxorubicin is limited by a number of side-effects; the most important are cardiotoxicity, haematotoxicity and a dose-limiting nephrotoxicity. The exact mechanism of doxorubicin-induce nephrotoxicity is not yet known. However, it has been suggested by many investigators that cellular damage induced by doxorubicin is mediated by the formation of an iron-anthracyclin free radical which in turn causes severe damage to the plasma membrane (Sung et al., 2008).

Despite the wide use of adriamycin in the treatment of cancer patients, its mechanism of action is still not well known. However different mechanisms of free radical formation have been described. The first of it's implicates is formation of a adriamycin semi-quinone free radical by the action of NADPH dependant reductases. In the presence of oxygen, the semi-quinone form yields super oxide radicals (O2−). Free radicals can also be produced by a non-enzymatic mechanism that involves reactions of iron– adriamycin complex that can reduce oxygen to H2O2 and...
other ROS (Chabner et al., 2001 and Jung et al., 2009). The dose of adriamycin used in this study corresponds to the dose that currently being used in clinical practice (Podjarny et al., 1997). The last authors demonstrated that the acute cardio-renal failure in rat after 72 h of a single dose of adriamycin (10 mg/kg) administration. The results of the renal function test revealed that adriamycin administration produced intrinsic acute renal failure, which was evident from the elevated levels of serum urea and creatinine similar to those obtained in the current study.

Moreover, these data are in harmony with those obtained by Injac & Strukelj (2008) and Lahouel et al. (2010). The authors attributed these data to the affinity of adriamycin for pronouncing the severity of renal insufficiency which occurred in association with the sudden fall in glomerular filtration rate. Because of the majority of administrated adriamycin enters specifically the proximal tubular epithelial cells and binds to anionic phospholipids in the target cells inducing abnormalities in the function and metabolism of multiple intracellular membranes and organelles then developed injury in the proximal tubular epithelial cells of kidney that caused acute renal failure.

Serum electrolytes were disturbed significantly (p<0.05) in adriamycin treated rats as compared with control animals. Lower value of serum sodium indicates inability of kidney to conserve sodium and chloride. As well, haemodilution may be involved in the fall of sodium value via excess of water intake and/or increased production of endogenous water. In turn, the reversed increases of potassium appeared to be due to reduced excretion of K aggravated by leakage of intracellular potassium into blood stream as a result of adriamycin induced lesions in renal tubular epithelium. These results are in harmony with the data obtained by Herman et al. (2000); Javaid et al., (2001) and Jovanovic et al. (2002). Serum inorganic phosphorus, PTH and ß_{2}-MG were significantly (p<0.05) increased, conversely, serum total and ionized calcium were significantly (p<0.05) decreased in adriamycin injected rats (Table 2 &3). Similar results were obtained by Yoneko et al. (2007); Injac, & Strukelj (2008) and Lahouel et al. (2010). They attributed these disturbances to the elevated parathormone level which produced after adriamycin administration. Furthermore, increased glucocorticoids levels enhance deposition of calcium as calcium phosphate and carbonate in injured skeletal muscle (Lahouel et al., 2010). Also, the toxicity of adriamycin may cause an increase in the urinary excretion of calcium and inhibited calcium intake into mitochondria and stimulate ionized calcium from mitochondria (Ayla et al., 2011).

The traditional clinical parameter used to detect drug induced nephrotoxicity has been serum creatinine; however, various indicators have been examined to identify renal toxicity in its earliest stages (Mihm et al., 2002; Myers et al., 2006 and Heibashy et al., 2009). The plasma protein ß_{2}-microglobulin (ß_{2}MG) has been identified as a sensitive indicator of renal injury Yoneko et al. (2007) and Injac et al. (2008). While, the mechanism of anthracycin induced tubular toxicity has been described and shown to correlate with elevation in the serum level of ß_{2}-microglobulin. Similar results were obtained in the current investigation (Table 3).

The elevation in the serum level of ß_{2}-microglobulin as a result of nephrotoxicity induced by adriamycin administration may be due to the excessive in the gene expression of the proximal-tubule brush border enzyme alanine aminopeptidase (AAP).

Regarding the results of adriamycin administration to rats, the activities of renal superoxide dismutase (SOD) and catalase (CAT) and level of glutathione (GSH) were decreased (p< 0.05) significantly while, the level of lipid peroxidation as thiobarbituric acid reactive substances (TBARS) was increased (p< 0.05) significantly (Table 4). These results may be attributed to tissue damage and cell membrane destruction by free radicals resulted from adriamycin administration. As, Yoneko et al., (2007) reported that adriamycin is able to generate free radicals as hydrogen peroxide, hydroxyl radical and superoxide anions in rat renal mitochondria. These data are confirmed by Ayla et al. (2011).

Modern medicine seems to be based on an "attack strategy", a philosophy of treatment formed in response to the discovery of antibiotics. Like the vitamins discovered in the early part of this century, CoQ_{10} is an essential element of food that can now be used medicinally to support the sick host in conditions where nutritional depletion and cellular dysfunction occur (Judy et al., 1981).

Since, CoQ_{10} is essential to the optimal function of all cell types. It is not surprising to find a seemingly diverse number of disease states which respond favorably to CoQ_{10} supplementation. All metabolically active tissues are highly sensitive to a deficiency of CoQ_{10}. Also, CoQ_{10} function as a free radical scavenger which led to the protein manifestations of CoQ_{10} deficiency. Preliminary observations in a wide variety of disease states have already been published (Langsjoen et al., 1991 and Lockwood et al., 1994).

Several authors reported the nephrotoxicity of adriamycin and related drugs may well relate to free radical generation and this might explain the benefit of CoQ_{10} in its capacity as a free radical scavenger (Pavlovic et al., 2000; Upaganlawar et al., 2006 and Ishikawa & Homma, 2011).

The antioxidant or free radical quenching properties of CoQ_{10} serve to greatly reduce oxidative damage to tissues as well as significantly inhibit the oxidation of LDL cholesterol (Upaganlawar et al., 2006). The authors attributed these results to the ability of CoQ_{10} which improve the auto-immune system and increase the ß-oxidation of free fatty acids in the matrix of mitochondria due to its pharmacokinetics and pharmacodynamics.
So, the supplementation of CoQ_{10} to normal rats (non-treated with adriamycin) led to improve in all investigated parameters however, these improvements are numerically but not significantly. Obviously, the kidney function tests and the antioxidant status of kidney corrected after the nephrotoxic rats treated with CoQ_{10} dependent on the time of treatment. These results may be due to the enhancement in the thiol pool and xenobiotic metabolism in the cell (Lahouel et al., 2010). Also, the antioxidant powerful of CoQ_{10} led to decrease of uremic toxin protein such as PTH and β_{2}-microglobulin in blood circulation.

In conclusion, the overall results of this study have clearly shown that CoQ_{10} is a good candidate for offering protection against the deleterious renal side-effects of doxorubicin. In the near future, CoQ_{10} could constitute a lead to discovering a novel drug which will be useful in treatment of drug-induced nephrotoxicity.

References


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