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Full Length Research Paper

The effect of CoQ_{10} and vitamin E on serum total sialic acid, lipid-bound sialic acid, some trace elements and minerals in rats induced with doxorubicin

Gökhan Oto[1]*, Suat Ekin[2], Semih Yaşar[3], Hülya Özdemir[1] and Fatmagül Yur[4]

[1]Department of Pharmacology, Medical Faculty, Yuzuncu Yil University, Van, Turkey.
[2]Department of Biochemistry, Faculty of Arts and Sciences, Yuzuncu Yil University, Van, Turkey.
[3]Department of Biochemistry, Faculty of Arts and Sciences, Bingöl University, Bingöl, Turkey.
[4]Department of Biochemistry, Faculty of Veterinary, Yuzuncu Yil University, Van, Turkey.

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This study was designed to evaluate the effect of CoQ_{10} and vitamin E on serum total sialic acid (TSA), lipid bound sialic acid (LSA) and some elements in rat administered doxorubicin (DXR). Cu levels were increased in the group treated with DXR + vitamin E in comparison with DXR ($p<0.05$) and CoQ_{10} groups ($p = 0.001$). Furthermore, copper levels were increased in the group treated with DXR + CoQ_{10} in comparison with CoQ_{10} group ($p < 0.05$). Zn levels were decreased in the group treated with DXR + vitamin E in comparison with CoQ_{10} group ($p < 0.05$). Mg levels were decreased in subjects treated with DXR + vitamin E in comparison with the control group values ($p < 0.05$). Particularly, the observed increase in Cu levels in rats from DXR + vitamin E group might be due to the decrease of vitamin E. However, the oxidative damage could be as a result of DXR occurence and may be helpful to clinicians in chemotherapy using anthracycline.

Key words: Doxorubicin, total sialic acid (TSA), lipid bound sialic acid (LSA), trace elements, minerals.

INTRODUCTION

Doxorubicin (DXR) (also known as adriamycin or 14-hydroxydaunorubicin) is an anthracycline-type antitumor (antineoplastic or cytostatic) drug that is used in chemotherapy for treatment of various cancers (Arcamone et al., 1969). DXR is an effective anti-neoplastic agent, application of which has been limited due to its cardiotoxic side effects (Balaei et al., 2010; Wold et al., 2005). The mechanism of DXR-induced cardiomyopathy remains unclear, but most of the evidence indicates that free radicals accompanied by a decrease of endogenous antioxidants and the subsequent increase in oxidants results in enhanced oxidative stress leading to a slow loss of myofibrils and vacuolization of myocardial cells which are the typical changes in the DXR-induced heart failure (Singal and Iliskovic, 1998). Furthermore, myocardial damage may be caused by an increase in tissue calcium, the inhibition of nucleic acid protein synthesis, lipid peroxidation, the release of vasoactive amines, TNF-*a* and interleukin-2, liberation of cytokine from the tumor, changes in adrenergic function, lysosomal alterations and the inhibition of the CoQ_{10} and the sodium-potassium-activated ATPase (Simpson et al., 2004; Iarussi et al., 2001).

CoQ_{10} (ubiquinone) is a mitochondrial coenzyme which is essential for the production of ATP (Littarru, 1994; Kumar et al., 2009). Being at the core of cellular energy processes, it assumes importance in cells with high energy requirements like the cardiac cells which are extremely sensitive to CoQ_{10} deficiency produced by cardiac diseases. CoQ_{10} has thus, a potential role in the prevention and treatment of heart ailments by improving cellular bioenergetics (Kumar et al., 2009). Furthermore, CoQ acts as a potent antioxidant in the inner mitochondrial membrane. It inhibits lipid peroxidation by either scavenging free radicals directly or reducing α-tocopheroxyl radical to α-tocopherol (Ernster and Dallner, 1995; Lass and Sohal, 1998).

α-Tocopherol is known to function *in vivo* as antioxidant

*Corresponding author. E-mail: gokhanoto@hotmail.com.

and to provide cell membranes with protection against peroxidative and hydroxyl radical damage (Halliwell, 1996). $CoQ_{10}H_2$ acts as a chain-breaking radical scavenger (Kagan et al., 1990), synergizes with α-tocopherol via reduction of the α-tocopherol-derived phenoxyl radical (Kagan et al., 1990[2]) and thus, inhibit tocopherol-mediated peroxidation (Bowry and Stocker, 1993).

Serum sialic acid levels have been used as laboratory markers in a variety of pathological conditions (Kario and Matsuo, 1993; Hakamory, 1984). Sialic acid (SA), an important component of glycoproteins and glycolipids, is found in negatively charged surface polyanions on various cell membranes and plays an important role in the antigenic characterization of cells (Lehninger et al., 1993). Total sialic acid (TSA) levels are elevated in many circumstances, such as myocardial infarction (Güngör et al., 2004; Succari et al., 1982), cancer (Seyrek et al., 2005), some auto-immune disorders (Maneva et al., 1995), diabetes mellitus (Crook et al., 1993), infections and chronic glomerulonephritis (Işler et al., 1993).

Minerals and trace elements play a dual role in the biological system through their interaction with biomolecules (Strong and Garruto, 1994). In biological and medical research, the determination of the concentration of trace elements and minerals as well as their distribution pattern is extremely important since it could provide unique information about various physiological and patho-physiological processes in the investigated tissues (Seeley et al., 1996). Some trace elements, particularly copper and zinc are in fact implied in both humoral and cellular immunity (Berger et al., 1998). These essential micronutrients can interfere directly with the propagation stage of free radical generation and scavenge free radicals (Kulikowska and Moniuszko, 2004).

So far, in literatures, there is no report related to the effect of CoQ_{10} and vitamin E on trace elements, sialic acid and lipid-bound sialic acid, despite the fact that several studies that are related to the effect of the other parameters on doxorubicin are available. The aim this study was to evaluate the effects of vitamin E and CoQ_{10} treatment on serum total sialic acid, lipid-bound sialic acid, some trace element and mineral levels on DXR-induced cardiotoxicity in rat model.

MATERIALS AND METHODS

Animals and drug administration protocols

All procedures described were studied and approved by the Local Institutional Committee for the Ethical Use of Animals. Wistar albino rats (180 to 200 g) were used in these experiments. The rats were obtained from the Department of Virology, Firat University, Veterinary Research Institute. All animals were housed in standard cages at room temperature (22 ± 2°C), with artificial light from 7.00 am to 7.00 pm, and provided with standard pelleted food and water *ad libitum*.

Rats were divided into four groups (n = 6/group). In the first group, DXR with 2.5 mg/kg normal saline were applied intraperitoneally once a week for 6 weeks period. In the second group rats in addition to DXR, CoQ_{10} was applied intraperitoneally with the ratio of 4 mg/kg/live weight on daily bases. In the third group rats, only CoQ_{10} was applied with the ratio of 4 mg/kg/live weight on daily bases. In the fourth group rats, in addition to DXR, vitamin E was applied with the ratio of 10 mg/kg/subcutaneous two times a week for 6 weeks. The study period were planned as 6 weeks.

Serum samples preparation

Blood samples were collected at the beginning of application (0th) and at the 60th day of the application period by the intra cardiac method and centrifuged in 500 *g*-force (rpm) for 15 min to obtain sera which was later stored at -70°C until all experimental procedures were carried out.

Serum analysis

Serum TSA and serum lipid bound sialic acid (LSA) levels were measured by colorimetric method using ATI UNİCAM UV/V spectrometer (Katopodis et al., 1982; Sydow, 1985). Serum trace element (Zn, Cu and Fe) and mineral (Ca, Mg and Na) concentrations were measured using a solar atomic absorption (Thermo Electron Corporation, Solar House, Cambridge England) spectrophotometer.

Statistical analysis

Data are presented as $\overline{X}$ ± SEM (standard error of mean). Differences in biochemical parameters were statistically evaluated using one-way analysis of variance (Anova) followed by Tukey multiple comparison test.

RESULTS

No death was observed in any of the experimental groups. Average serum TSA, LSA, trace element (Fe, Cu and Zn) and mineral (Ca, Mg and Na) levels between groups are shown in Table 1 ($\overline{X}$ ± SEM) and Figures 1 to 3.

Serum levels of TSA and LSA

Data on the serum levels of TSA and LSA of the animals in the control, DXR, CoQ_{10}, DXR + CoQ_{10} and DXR + vitamin E groups are summarized in Table 1 and Figure 1. The levels of TSA and LSA among the different treatment groups showed no difference as compared to the control group ($p > 0.05$).

Serum levels of trace elements

Data on the serum levels of trace elements (Fe, Cu and Zn) of the animals in the control, DXR, CoQ_{10}, DXR + CoQ_{10} and DXR + vitamin E groups are summarized in Table 1 and Figure 2. The serum levels of Fe among the different treatment groups showed no difference when compared to the control group ($P > 0.05$). The serum levels of Cu was increased in the DXR + vitamin E treated group

Table 1. Average concentrations of TSA, LSA, trace element (Fe, Cu and Zn) and mineral (Ca, Mg and Na) levels in serum samples of the control, DXR, CoQ_{10}, DXR + CoQ_{10} and DXR + vitamin E groups.

Group	Control ($\bar{X}$ ± SEM)	DXR ($\bar{X}$ ± SEM)	CoQ_{10} ($\bar{X}$ ± SEM)	DXR + CoQ_{10} ($\bar{X}$ ± SEM)	DXR + Vit E ($\bar{X}$ ± SEM)
TSA (mg/dl)	80.48 ± 5.29	94.43 ± 7.21	79.32 ± 10.33	93.74 ± 6.19	86.02 ± 2.39
LSA (mg/dl)	21.65 ± 0.29	23.59 ± 0.40	20.83 ± 0.83	22.39 ± 0.85	21.83 ± 0.47
Fe (mg/L)	2.80 ± 0.34	2.61 ± 0.38	2.50 ± 0.17	1.71 ± 0.26	1.66 ± 0.43
Cu (mg/L)	1.19 ± 0.06	0.97 ± 0.10^{b}	0.75 ± 0.05$^{a.b1}$	1.21 ± 0.12^{b1}	1.44 ± 0.12$^{a.b}$
Zn (mg/L)	1.03 ± 0.07	0.93 ± 0.05	1.15 ± 0.03^{b}	0.84 ± 0.09	0.78 ± 0.23^{b}
Ca (mg/dl)	11.25 ± 0.83	9.17 ± 0.60	9.96 ± 0.67	9.19 ± 1.04	11.39 ± 0.57
Mg (mg/dl)	2.68 ± 0.14^{b}	2.44 ± 0.20	2.47 ± 0.03	2.64 ± 0.32	1.88 ± 0.09^{b}
Na (mg/ml)	2.88 ± 0.03	2.77 ± 0.02	2.86 ± 0.02	2.79 ± 0.03	2.86 ± 0.05

a, $p = 0.001$; b, $p < 0.01$; b_1, $p < 0.05$.

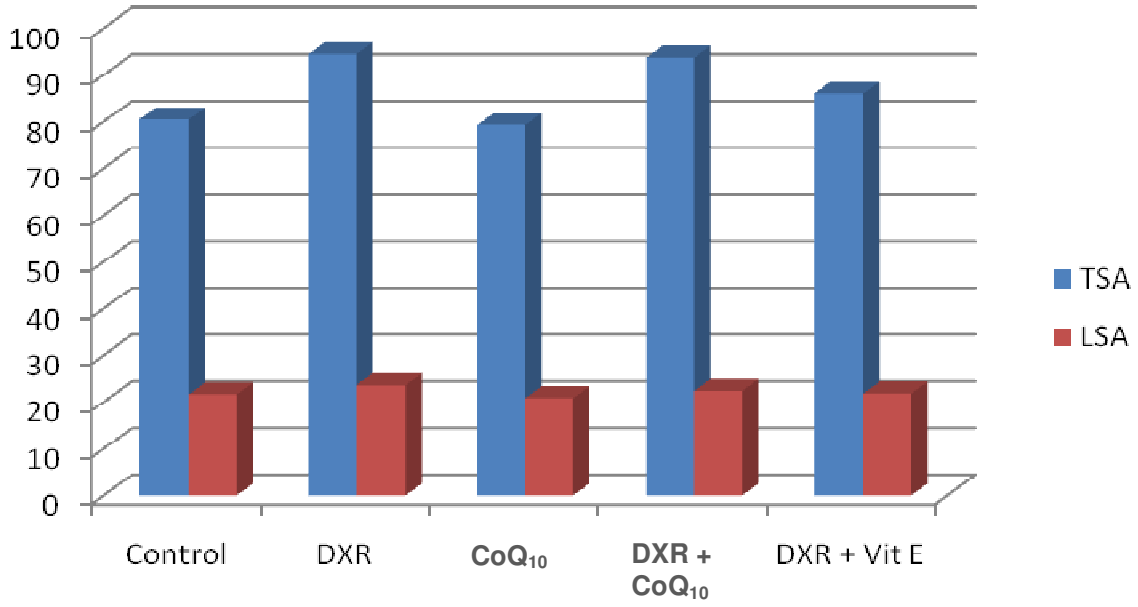

Figure 1. Comparison of TSA and LSA levels in serum samples of the control, DXR, CoQ_{10}, DXR + CoQ_{10} and DXR + vitamin E groups.

when compared to DXR group ($P < 0.01$). Furthermore, it was increased in the DXR + vitamin E and DXR + CoQ_{10} treated groups when compared to the CoQ_{10} group ($P = 0.001$ and $p < 0.05$, respectively). The serum levels of Zn was decreased in the DXR + vitamin E treated group as compared to the CoQ_{10} group ($P < 0.01$).

Serum levels of minerals

Data on the serum levels of minerals (Ca, Mg and Na) of the animals in the control, DXR, CoQ_{10}, DXR + CoQ_{10} and DXR + vitamin E groups are summarized in Table 1 and Figure 3. The serum levels of Ca and Na among the different treatment groups showed no difference as compared to the control group ($p > 0.05$). The serum levels of Mg was decreased in the DXR + vitamin E treated group as compared to the control group ($p < 0.01$).

DISCUSSION

Cytostatic agents are known to exert their antitumour action by interacting with specific cell structures or metabolic pathways of cancer cells (Sangeetha et al., 1990). Several studies have demonstrated the protective properties of various antioxidants against the harmful action of cytostatic drugs such as doxorubicin, and cisplatin *in vitro* (Miura et al., 1994). Experimental animal studies have shown that the co-administration of free radical

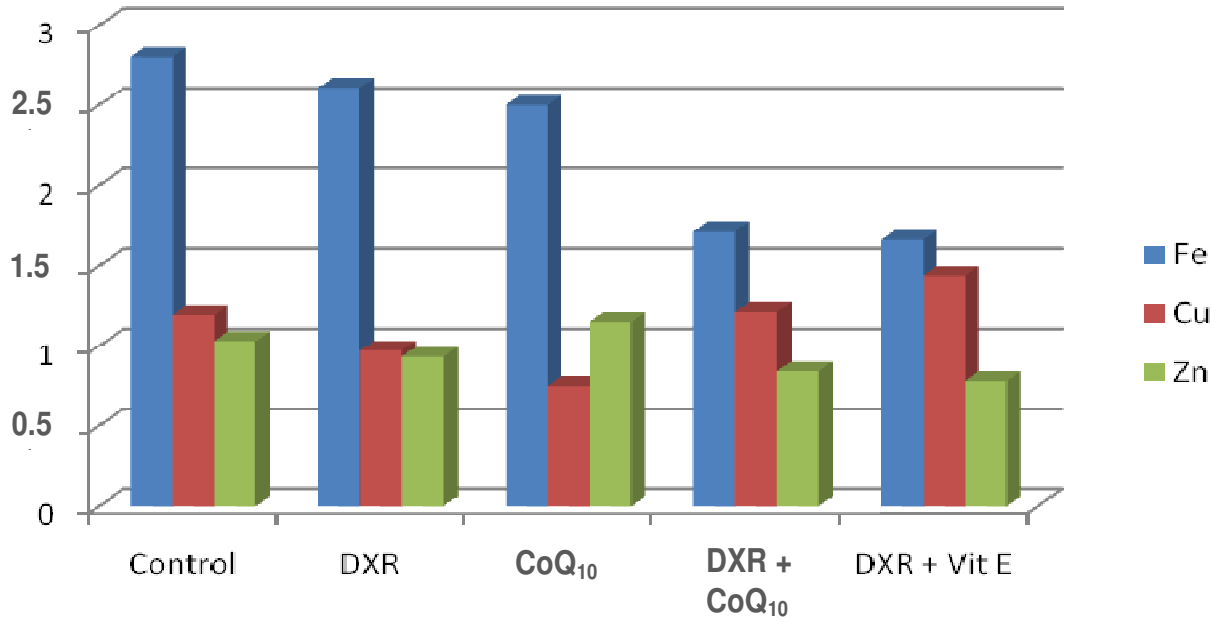

Figure 2. Comparison of trace element (Fe, Cu and Zn) levels in serum samples of the control, DXR, CoQ_{10}, DXR + CoQ_{10} and DXR + vitamin E groups.

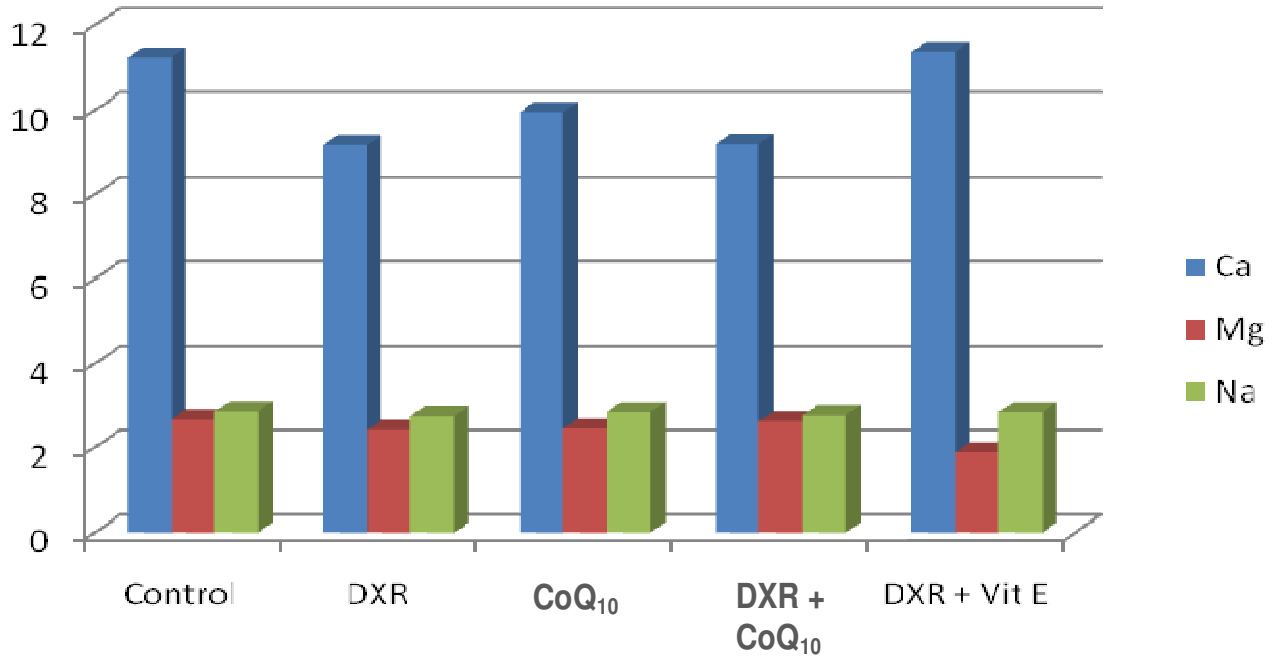

Figure 3. Comparison of mineral (Ca, Mg and Na) levels in serum samples of the control, DXR, CoQ_{10}, DXR + CoQ_{10} and DXR + vitamin E groups.

scavengers did not reduce the antitumour effect of agents such as doxorubicin (Keizer et al., 1990; Siveski-Iliskovic et al., 1995).

Cardiomyopathy and heart failure have been observed in DXR-treated cancer patients (Singal and Iliskovic, 1998) The cardiotoxic effect of DXR are mediated via different mechanisms (Wang et al., 2004). Doxorubicin induced heart failure is associated with an increase in oxidative stress (Lou et al., 2006). Assaying sialic acid may be of value for diagnostic purposes since sialic acid

content has been reported to be altered in cardiovascular disease (Lindberg et al., 1991). It has been reported that plasma sialic acid concentrations are elevated in coronary heart disease and myocardial infarction (Allain et al., 1996; Crook et al., 1994). Deepa and Varalakshmi (2005) showed that the mean plasma sialic acid concentration in DXR- treated rats was significantly higher than those of the other treatment groups. In this study, serum TSA and LSA levels in the DXR group were increased in comparison with the control group.

The human body possesses several molecules that protect healthy tissues from the damaging action of free radicals (Halliwell and Gutteridge, 1993). Some trace elements have an important role in free radical protection. The trace elements are incorporated in the structures of the proteins, enzymes and complex carbohydrates to participate in biochemical reaction. Trace elements with enzymes, for example, are necessary for the functioning and maintenance of the immune system (Bang et al., 2002). Most enzymes contain trace elements, such as selenium in glutathione peroxidase and zinc and manganese and copper in superoxide dismutase (Weijl et al., 1997; Coudray et al., 1992). Overexpression of cardiac-specific catalase prevents injury to the heart following oxidative insults such as exposure to the anticancer agent, doxorubicin (Kang et al., 1996). Cu deficiency can lead to reduction in catalase activity in tissues such as heart and liver (Strain, 1994). Chemical studies have shown that doxorubicin is a powerful iron chelator and the resultant iron-drug complex is an efficient catalyst of the conversion of hydrogen peroxide to the highly reactive hydroxyl radical (Ortega et al., 2001).

The levels of Zn is associated with levels of Cu and Fe due to the antagonistic relationships between these metals (Disilvestro and Blostein-Fujii, 1997). It has been suggested that an imbalance between Cu and Zn may be a factor in the aetiology of cardiovascular diseases (Tiber et al., 1986). Costa and Nepomuceno (2006) reported that minerals such as Cu and Zn protects the organism against the genotoxic effects of chemotherapeutics such as DXR. Morishima et al. (1999) reported that DXR decreased plasma zinc levels in rat. We observed a significant increase in the levels of Cu following DXR + vitamin E treatment group as compared to DXR group. Furthermore, the serum levels of Zn was decreased in the DXR + vitamin E treated group as compared to CoQ_{10} group.

Eckenhoff and Somlyo (1998) reported that the levels of mitochondrial Ca and Mg did not change in the DXR-injected animals, even in severely symptomatic rats 5 days after DXR administration. In this study, the serum levels of Mg decreased in the DXR + vitamin E treated group as compared to the control group.

The results of this study indicated that serum TSA and LSA levels in the DXR group were increased in comparison with the control group. The levels of TSA and LSA were lower in the CoQ_{10} and vitamin E groups when compared with the DXR group. Particularly, the observed increase in the Cu levels in rats from DXR + vitamin E group might be due to the decrease of vitamin E. However, the oxidative damage could be as a result of DXR occurence and may be helpful to clinicians in chemotherapy using anthracycline.

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