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ORIGINAL RESEARCH

Vitamin U ameliorates glycoprotein components, enzyme and tissue factor activities of amiodarone toxicity in liver

Ismet Burcu TURKYILMAZ, Refiye YANARDAG

ABSTRACT

In this study, we aimed to investigate the protective effect of Vitamin U (Vit U) on amiodarone (AMD)-induced hepatotoxicity. Male Sprague-Dawley rats were randomly divided into four groups. Group I was control animals receiving corn oil for 7 days, Group II consisted of animals receiving Vit U (50 mg/kg) for 7 days, Group III consisted of animals receiving AMD (100 mg/kg) for 7 days and Group IV consisted of animals given AMD and Vit U (in same dose and time). AMD and Vit U were administered to rats by gavage. On the 8th day, all the animals fasted overnight were sacrificed. Blood and liver tissue samples were taken from animals. Serum total cholesterol levels and liver gamma glutamyl transferase (transpeptidase) adenosine deaminase and tissue factor activities, liver glycoprotein component level such as fucose, hexose and hexosamine were determined. All the parameters were found to be increased in AMD group as compared to control group. Administration of Vit U reversed these effects in AMD group. According to these results, we can conclude that Vit U can prevent AMD-induced liver injury.

Keywords: Amiodarone, Glycoprotein, Liver, Tissue factor, Vitamin U

Ismet Burcu TURKYILMAZ, Refiye YANARDAG
Istanbul University, Faculty of Engineering, Department of Chemistry, 34320-Avcilar, Istanbul, TURKEY

Corresponding author:
Ismet Burcu Turkyilmaz
Istanbul University, Faculty of Engineering, Department of Chemistry, 34320 Avcilar / Istanbul, TURKEY
Phone:+902124737070
Fax:+902124737180
E-mail: burcut@istanbul.edu.tr, burchemistry@gmail.com

Refiye YANARDAG
Istanbul University, Faculty of Engineering, Department of Chemistry, 34320 Avcilar / Istanbul, TURKEY
Phone:+902124737037
Fax:+902124737180
E-mail:refiyeyanardag@yahoo.com

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1. INTRODUCTION

Amiodarone (AMD) is a benzofuran derivative and shows class III antiarrhythmic drug profile. This drug has been widely used for treatment of ventricular and supraventricular tachyarrhythmias (1). AMD has a long half-life and a weak bioavailability (2) and tends to accumulate in many tissue and organs. Thus side effects and toxicities occur in parts of the body with this way. The most affected organs and tissues can be numbered as liver (3), lung (4), kidney (5), thyroid (6), brain (7) and ocular tissue (8). AMD is also reported as a hepatic mitochondrial toxicant that damages electron transport system by inhibiting complex I as well as β-oxidation of fatty acids. These pathways are carrying vital value for liver. Lewis *et al.* (9) and Simon *et al.* (10) reported AMD studies that have been carried out with human and they observed micro/macrovesicular steatosis in patients during experiments. In addition to that AMD has also a tendency to produce free radicals which can be associated with its toxicity (11,12).

Glycoproteins, which are primarily known as hexose, hexosamine, fucose are important components of cell

membranes. They are composed of proteins which have carbohydrate moiety and this moiety is covalently bounded to their peptide side. The glycoproteins have many functions like mediating cell surface function, cell-cell recognition, cellular adhesion. The importance and increased levels of glycoproteins in various diseases have been reported as many researchers (13-15). The liver is a responsible organ for producing large amounts of glycoproteins present in blood (14).

Vitamin U (Vit U) is a methionine derivative compound that is found in flowering plants (16) and in the species of Brassicaceae family (17). Although it has been called vitamin, it hasn't been accepted into vitamin classification. Besides, this compound has many useful features like hypolipidemic (18), hepatoprotective (19) and gastroprotective effects (20) and wound-healing properties (21).

In this study, we aimed to investigate protective effect of Vit U on glycoprotein content and enzyme activities on amiodarone induced liver injury.

2. MATERIAL AND METHODS

2.1. Material

The experimental procedures were approved by the local Animal Care and Use Committee of Istanbul University, with the certification on the Application for the Use of Animals dated September 27, 2012 (approval ID: 2012 / 127). In this study, 3.5-4 months aged male Sprague-Dawley rats (Istanbul University Experimental Medical Research and Application Institute, DETAE) were used. Their diet consisted of standard animal pellet food and tap water *ad libitum*. Application of AMD dose and time were determined as Reasor *et al.* (22). Vit U dose were administered according to Sokmen *et al.* (19). A total of twenty nine rats were divided into 4 groups as follows. The groups include: Group I, control animals receiving corn oil for 7 days (n=6); Group II, animals receiving Vit U (50 mg/kg) for 7 days (n=7); Group III; animals receiving AMD (100 mg/kg) for 7 days (n=8); and Group IV, animals receiving Vit U (50 mg/kg) for 7 days 1 h prior to the administration of AMD (100 mg/kg) (n=8). AMD and Vit U were administered to rats by gavage. On the 8th day, all the animals fasted overnight were sacrificed.

Biochemical investigations were made in serum samples and liver tissues of all groups. Serum total cholesterol levels were determined according to Zlatkis *et al.* (23). The liver tissues were taken from animals under anesthesia. Tissue samples were washed with physiological saline (0.9% NaCl) and kept frozen until the day of the experiments. On the day of the experiments, liver samples were homogenized in cold 0.9% NaCl with a glass homogenizer to make up to a 10% (w/v) homogenate. The homogenates were centrifuged and the clear supernatant fraction was removed for biochemical analysis. In liver homogenates, gamma glutamyl transferase (transpeptidase) activity (γ–GT) was measured by Szasz method (24), adenosine deaminase activity was determined according to Karker (25), tissue factor (TF) activity according to Quick's one-stage method using normal plasma (26). Fucose levels of liver tissues were evaluated according to the method of Dische and Shettles (27) and hexose-hexosamine contents were estimated by the method by Winzler (28). The protein measurements in liver homogenates were determined according to Lowry *et al.* (29).

2.2. Statistical Analysis

Biochemical analysis was performed by one-way ANOVA followed by Duncan's Newman-Keuls multiple comparison test. The values are expressed as the mean ± standart deviation (SD). P values less than 0.05 were considered to be significant.

3. RESULTS AND DISCUSSION

The serum total cholesterol levels and liver γ–GT, ADA and TF activities were shown in Table 1. According to these results, the serum total cholesterol, liver γ–GT, ADA and TF activities were found to be increased in AMD group as compared to control group in a significant manner ($P < 0.05$, $P < 0.0001$). Administration of Vit U reversed serum total cholesterol levels insignificantly while the reverse effect of vit U on γ–GT, ADA and TF activity was in a significant manner in AMD group ($P < 0.05$, $P < 0.0001$).

In Table 2, liver fucose, hexose and hexosamine levels were seen. All the glycoprotein levels were observed to be significantly increased in AMD group when compared to control group ($P < 0.05$). Vit U decreased all the component levels of liver in this table in a significant manner in AMD group ($P < 0.05$).

The liver is a vital organ where the basic metabolic pathways like carbohydrates, lipids and proteins as well as detoxification of xenobiotic substances occur. This situation brings it to be a target organ for toxicity. As being reported in literature by Seeff (30) and Jaeschke (31), drug induced liver injury becomes a big problem day by day. So finding new solutions to prevent drug induced liver injury become important.

The liver has an importance for cholesterol and lipid metabolism. AMD is a phospholipase inhibitor and causes lipid accumulation in the liver. The studies that support this

Table 1. The serum total cholesterol levels, and the liver gamma glutamyl transferase (γ–GT), adenosine deaminase (ADA) and tissue factor (TF) activities of control and experimental groups

Groups	Total Cholesterol (mg/dL)*	γ–GT (U/g protein)*	ADA (U/g protein)*	TF (second)*
Control	43.25 ± 8.68	19.97 ± 8.06	8.40 ± 1.29	207.60 ± 20.90
Control + Vit U	51.16 ± 8.24	23.52 ± 6.91	15.63 ± 6.08	181.30 ± 9.83[a]
Amiodarone	57.81 ± 9.36[a]	33.16 ± 4.77[a]	14.49 ± 1.64[c]	110.42 ± 10.56[c]
Amiodarone + Vit U	54.69 ± 4.32	24.59 ± 2.79[b]	9.57 ± 2.16[b]	210.81 ± 14.07[d]

*Mean ± SD

[a]P < 0.05 versus control group, [b]P < 0.05 versus amiodarone group, [c]P < 0.0001 versus control group, [d]P < 0.0001 versus amiodarone group.

Table 2. The liver fucose, hexose and hexosamine levels of control and experimental groups

Groups	Fucose (μg fucose/mg protein)*	Hexose (mg glucose/mg protein)*	Hexosamine (μg glucosamine/mg protein)*
Control	0.18 ± 0.05	0.26 ± 0.04	0.47 ± 0.15
Control + Vit U	0.22 ± 0.01	0.30 ± 0.01	0.26 ± 0.21
Amiodarone	0.50 ± 0.08[a]	0.41 ± 0.08[a]	1.14 ± 0.39[a]
Amiodarone + Vit U	0.24 ± 0.12[b]	0.25 ± 0.08[b]	0.19 ± 0.12[b]

*Mean ± SD

[a]P < 0.05 versus control group, [b]P < 0.05 versus amiodarone group

idea especially associated with AMD hepatotoxicity have been published by many reporters (32-34). In parallel to this approach, we got elevated serum total cholesterol levels in AMD group according to the control group. Administration of Vit U decreased this level in AMD group. Seri *et al.* reported hypolipidemic effect of Vit U via helping the acceleration of lipid molecule excretion (35). We may suggest that Vit U reduced serum cholesterol levels via this way.

γ–GT is an enzyme which catalyzes the breakdown of glutathione, using its gamma glutamyl part for transporting free amino acids across the membrane and into the cell (36). The importance of γ–GT is being a marker enzyme for hepatic injury which is induced by drugs and this enzyme carries weight with in clinical practice. Some reporters have reported elevated γ–GT activity levels in various either human hepatocyte culture studies induced by amiodarone or chemical-induced hepatotoxicity cases (37-39). Increased activity of this enzyme shows impairment for membrane integrity. In our study, as parallel to these reports, we found elevated activity of γ–GT in the AMD group as we compared to the control group. However, administration of Vit U reversed this activity in the AMD group. The decreased activities of this enzyme in this group may be due to membrane repair property of Vit U which was reported before by Racz *et al* (17).

ADA is an important aminohydrolase in the purine metabolism which catalyzes deamination of either adenosine or deoxyadenosine to inosine or deoxyinosine. This reaction is one of the rate limiting steps in adenosine degradation (40). Increased activity of this enzyme indicates liver failure (41). In the present study, we got elevated ADA activity in AMD groups compared to control group. Vit U decreased this activity in AMD group. Elevated ADA activity may be associated with increased free radical levels caused by amiodarone. So we may suggest that Vit U showed its antioxidant activity by decreasing this enzyme activity in AMD group.

TF (tissue factor) is the principal cellular initiator of normal blood. It is a low molecular weight glycoprotein and a component of cell membrane. An increase in the activity of TF correlates with an increase in blood coagulation levels and a decrease in coagulation time. This elevated activity is also associated with alterations which occur in cell membrane due to either membrane composition or increased lipid peroxidation levels (42, 43). Increased TF activity has been

reported in many diseases such as diabetes, hyperlipidemia, atherosclerosis and kidney diseases (44, 45). In our study, TF activity was significantly increased in the AMD group when compared to the control group. Vit U reversed this activity in AMD group. We may suggest this reducing effect can be associated with the protective effect of Vit U on membrane stability (17).

Glycoproteins are compounds that include carbohydrate moiety attached to peptide side of proteins. They are present in the extracellular matrix and believed to contribute to the structure of the matrix. They play an important role in tissue stabilization and are found as hormones, blood group substances (13, 46). Their levels are important for determining many diseases like tuberculosis (47), autoimmune thyroiditis (48), diabetes mellitus (49) and hepatotoxicity (50). In the present study, we determined the glycoproteins like fucose, hexose and hexosamine levels of liver tissue. Levels of all the glycoproteins were found to be increased in the AMD group when compared to the control group. The elevation we have observed in the glycoprotein components of the AMD group may be a sign of a pathological process which results in the deposition of macromolecular components. This situation can be explained as cationic amphiphilic property of AMD. The hydrophobic ring structure and the hydrophilic side chain with a charged cationic amine group describe the nature of AMD. In addition to these properties, the halogen part of AMD enhances lipophilic character and provides to interact with membrane structure. So the membrane penetrability is affected by AMD. In a similar manner, administration of Vit U decreased these effects in the AMD group. We may suggest that Vit U exerted a protective effect on glycoprotein structure of the liver tissue due to its hypolipidemic effect which decreases lipid peroxidation levels, affecting the membrane stabilization.

4. CONCLUSION

This study shows that AMD induced hepatotoxicity can be prevented by Vit U, a methionine derivative substance. This protective effect of Vit U may be due to its antioxidant effect and membrane stabilizing property. In conclusion, we can suggest Vit U may be used on preventing AMD-induced hepatotoxicity.

5. ACKNOWLEDGEMENTS

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6. CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

Vitamin U karaciğerde amiodaron toksisitesinin glikoprotein düzeyi, enzim ve doku faktör aktivitelerini iyileştirir

ÖZ

Bu çalışmada, amiodarone (AMD) ile oluşturulan hepatotoksisite üzerine U Vitamini (Vit U)'nin koruyucu etkisi araştırıldı. Erkek Sprague-Dawley sıçanlar rastgele dört gruba ayrıldı. Grup I; 7 gün boyunca mısır özü yağı verilen kontrol grubu, Grup 2; 7 gün boyunca Vit U (50 mg/kg) verilen hayvanlar, Grup III; 7 gün boyunca AMD (100 mg/kg) verilen hayvanlar ve Grup IV; aynı doz ve sürede AMD ve Vit U verilen hayvanlar. AMD ve Vit U sıçanlara gavaj yöntemiyle verildi. Sekizinci gün, bir gece aç bırakılan bütün hayvanlar sakrifiye edildi. Hayvanlardan kan ve karaciğer örnekleri alındı. Serum total kolesterol seviyeleri ile karaciğer gama glutamil transferaz, adenozin dezaminaz ve doku faktörü aktiviteleri, fukoz, heksoz ve heksozamin gibi karaciğer glikoprotein düzeyleri tayin edildi. Bu parametrelerin hepsi, kontrol grubu ile karşılaştırıldığında AMD grubunda artış olduğu görüldü. Vit U verilmesi, AMD grubunda bu değerleri tersine çevirdi. Bu sonuçlara göre, AMD ile oluşturulan karaciğer hasarını U vitamininin önlediği sonucuna varabiliriz.

Anahtar kelimeler: Amiodaron, Glikoprotein, Karaciğer, Doku Faktörü, Vitamin U

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