Effect of Selenium on Antioxidant Status, Lipid Peroxidation, Enzyme Activities and Biochemical Parameters in CCl4-Induced Experimental Liver Injury in Rats

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ABSTRACT: The objective of the present study was to investigate the role of selenium on carbon tetrachloride (CCl4)-induced toxicity in male Wistar rats. Significant ($P<0.05$) elevated mean levels of malondialdehyde (MDA) and lowered mean levels of total antioxidant capacity were observed in plasma of CCl_4-induced rats when compared to values in normal control. The activities of aspartate aminotransferase (AST), and alanine aminotransferase (ALT), alkaline phosphatase (ALP), acid phosphatase (ACP) and lactate dehydrogenase (LDH) were significantly ($P<0.05$) increased in plasma of CCl_4-induced rats. Also, significant ($P<0.05$) increase in the mean values of total cholesterol (TC), urea, creatinine and total bilirubin (Tb) were observed in plasma of CCl_4-induced rats compared to the values in normal control, whereas, significant ($P<0.05$) decrease in the mean values of total lipids (TL), total protein, and albumin were recorded in the plasma of CCl_4-injected rats. All enzyme activities and blood parameters as well as lipid peroxides (MDA) and total antioxidant capacity in CCl_4 group injected with selenium were arranged to comparable values to those of control group. In conclusion, it is suggested that selenium application is able to antagonize the oxidative damage caused by CCl_4 (at 0.15 ml/kg body weight) in liver and kidney of Wistar rats.

Keywords: Antioxidants, Malondialdehyde, Selenium, Liver function enzymes, Lipid peroxidation, CCl_4.

INTRODUCTION

Carbon tetrachloride (CCl_4) is a potent, lipid-soluble hepatotoxic agent that when bound to lipid and protein, produces peroxidative degeneration of many tissues (Cabre et al., 2000; Simibe et al., 2001). The fundamental structure of the liver of rats and humans is similar (Kogure et al., 1999), therefore the administration of CCl_4 to rats is an accepted experimental model to produce damage to hepatic and other tissues such as kidney, heart, lung, testis, brain and blood (Ohta et al., 1997; Ozturk et al., 2003). Several studies have demonstrated that CCl_4 modulates toxic effects operate through its haloalkane metabolites. These reactive metabolites are produced during biotransformation of CCl_4 and may cause the oxidative damage of lipids, lipoproteins, and other cellular components, such as enzymes, DNA and proteins (Biasi et al., 1991; Parola et al., 1992). The oxidative damage due to excessive production of haloalkane radicals can damage tissues and cells by alteration of lipid peroxidation, protein or nucleic acid structure and function. Thus, abnormal levels of the liver enzymes in plasma are usually indicative of the hepatic cellular injury in experimental animals (Miao et al., 1990; Parola et al., 1992; Knook et al., 1995).

Among antioxidant micronutrients, selenium (Se) is an essential element. It plays an antioxidant role, binding active site of glutathione peroxidase (GSH-Px) and thioredoxin reductase. The most important metabolic roles of Se in mammalian cell occur due to its function in the active site of selenoenzyme GSH-Px. GSH-Px not only protects cells against damages by free radicals, but also permits regeneration of a membrane lipid molecule through reacylation (McPherson, 1994). Se also facilitates the action of vitamin E in reducing peroxy radicals through permitting higher levels of vitamin E to be absorbed (Machlin, 1991). Antioxidants may prevent oxidative damage caused by free radicals in biological structures. Interaction relations between antioxidants and CCl_4 may change the toxicity of hepatotoxic agent (Sies and Stahl, 1992; McPherson, 1994; Ozardah et al., 2004).

The interrelationships between protective effects of antioxidants and toxic effects of CCl_4 have been investigated and it has been reported that administration of selenium (Casaril et al., 1989; Karakilcik et al., 2003) and β-carotene (Olmez and Karakilcik, 2003) protected the animals from some harmful effects of CCl_4. Therefore, the current study was conducted to determine the efficiency of Se in antagonizing the toxic effects of CCl_4 on lipid peroxidation, biochemical parameters and liver function enzyme activities in plasma of male rats induced with CCl_4.

MATERIALS AND METHODS

Animals and treatment:

This study was carried out on 60 Wistar albino male rats weighing 200–250 g body weight. Rats were kept in clean cages at 20-24℃ temperature, 12 hour light/12 hour dark cycle and 52% relative humidity in the animal house at King Saud University, Riyadh, Saudi Arabia. All rats were fed rodent pellets and drinking water *ad libitum*. The animals were randomly divided into three equal groups of 20 rats each.

The first group was used as control and only placebo (physiological saline - 0.9%) was injected intraperitoneally. The second group animals were intraperitoneally injected with CCl_4 (0.15 ml/kg body weight) dissolved in 0.6 ml olive oil. Animals of the third group were intraperitoneally injected with CCl_4 (0.15 ml/kg body weight) plus Se (Na_2SeO_4, 0.2 mg/kg body weight) was given using gastric catheter three times in a week. CCl_4 was diluted with olive oil (1/4 v/v) for experimental groups and these treatments were administrated three times in a week for 60 days.

Mortality rates ranged from 5 to 20%, which are similar to those reported by investigators using this model (Manna et al., 1996). CCl_4 was purchased from Merck AG (Darmstadt, Germany). Se and olive oil were obtained from Sigma Chemical Co. (St. Louis, MO, USA).

Blood samples and analytical methods:

The blood of all animals was taken by cardiac puncture 12 h after the last application of CCl_4 and Se. Whole blood samples were collected in the heparinized tubes

subsequently centrifuged at 2000 g for 15 min at 4°C and their plasma was removed into disposable pipettes. Plasma concentrations of total antioxidant capacity were determined using the total antioxidant status assay kits, according to the method of Miller et al. (1993). This assay relies on the ability of antioxidants in the sample to inhibit oxidation of 2, 2′-azino-di-[3-ethylbenzthiazoline sulphonate] (ABTS) to ABT^+ by metmyoglobin. The amount of $ABTS^+$ produced can be monitored by reading absorbance at 600 nm. Plasma concentrations of malondialdehyde (MDA) were determined by using the malondialdehyde assay kit according to the method of Ohkawa et al. (1979).

Plasma enzyme activities and biochemical parameters determinations were performed by standard procedures with the Vitros analyzer (Ortho-Clinical Diagnostic Systems, Johnson and Johnson company) as follows: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) according to the method of Bergmeyer et al. (1986), and alkaline phosphatase (ALP), acid phosphatase (ACP) and lactate dehydrogenase (LDH) were assayed according to the methods of Bretaudiere et al. (1977), Moss et al. (1994), and Greenberg and Byrne (1985) respectively. Total protein (TP), albumin, and total bilirubin (Tb) were performed according to the methods of Doumas et al. (1981), Doumas and Biggs (1972) and Doumas et al. (1973) respectively. Urea and creatinine were measured according to the methods of Sampson et al. (1980), and Doumas et al. (1989) respectively. Plasma concentrations of total cholesterol (TC) and total lipids were determined according to the methods of Allain et al. (1974) and Knight et al. (1972). Globulin concentrations were determined by difference in TC and albumin.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences software (SPSS, version 11.0). Descriptive statistics were adopted to display data in means ±SD. One way analysis of variance (ANOVA) was used to compare the mean values obtained among the different groups. Differences were considered significant whenever $P<0.05$.

RESULTS

Lipid peroxidation and total antioxidants

The results in Table 1 indicate that MDA concentration was significantly ($P<0.05$) increased while concentration of total antioxidant capacity was significantly ($P<0.05$) decreased in plasma of CCl_4-induced rats (Group II) compared to values in normal rats (Group I). Treatment with Se and CCl_4-treated rats (Se/CCl_4-induced rats) (Group III) caused significant ($P<0.05$) decrease in plasma MDA while total antioxidant capacity significantly ($P<0.05$) increased compared to values of CCl_4-induced rats (Group II). But, it was comparable to the values of control (Group I).

Table 1. Effect of selenium on plasma antioxidant capacity and malondialdehyde in experimental liver injury of rats*.

Parameter	Group I (control)	Group II (CCl_4)	Group III (CCl_4 + Selenium.)
Antioxidant capacity (mM)	1.23 ± 0.22^{a}	1.09 ± 0.15^{b}	1.26 ± 0.27^{a}
Malondialdehyde (nmol/ml)	1.46 ± 0.20^{b}	2.45 ± 0.27^{a}	1.49 ± 0.22^{b}

*Values are expressed as mean ± SD for twenty animals, ^{abc}Different letters in a given row denote significant difference, $P<0.05$

Liver Function enzyme activities –

The data in Table 2 show that treatment with CCl_4 (Group II) significantly ($P<0.05$) increased the activities of AST, ALT, ALP, ACP and LDH in plasma as compared to values in control (Group I). Treatment with Se and CCl_4 (Group III) significantly ($P<0.05$) decreased the activities of ALT, ALP, ACP and LDH except the activity of AST, which decreased but not significantly ($P<0.05$) as compared to CCl_4-induced rats (Group II). Also, most of studied enzymes in plasma of Se and CCl_4-induced rats (Group III) showed activity values comparable to that of control rats (Group I).

Table 2. Effect of selenium on plasma enzyme activities in experimental liver injury of rats*.

Parameter	Group I (control)	Group II (CCl_4)	Group III (CCl_4 + Selenium)
AST (U/L)	51.9 ± 1.74^{b}	65.4 ± 1.17^{a}	57.2 ± 1.39^{b}
ALT (U/L)	58.2 ± 0.79^{b}	73.7 ± 1.99^{a}	61.2 ± 1.19^{b}
ALP (U/L)	60.3 ± 0.99^{c}	80.3 ± 1.89^{a}	71.6 ± 1.89^{b}
ACP (U/L)	11.9 ± 1.23^{b}	15.1 ± 0.89^{a}	13.1 ± 0.72^{b}
LDH (U/L)	962 ± 48.2^{b}	1210 ± 45.8^{a}	1079 ± 35.7^{b}

Values are expressed as mean ± SD for twenty animals, ^{abc}Different letters in a given row denote significant difference, $P<0.05$

Biochemical Parameters

The data presented in Table 3 showed that treatment with CCl_4 to rats (Group II) caused significant ($P<0.05$) increase in the mean values of plasma TC, Tb, urea and creatinine, but significantly ($P<0.05$) decreased TL, TP, and albumin as compared to values in control (Group I). On the other hand, globulin did not change. Treatment with Se to CCl_4-induced rats (Group III) significantly ($P<0.05$) decreased plasma TC, Tb, urea and decreased creatinine, but not significantly ($P<0.05$) compared to values in CCl_4-induced rats (Group II). On the other hand, the mean levels of plasma TL, TP and albumin in Se/CCl_4-induced rats (Group III) were significantly ($P<0.05$) increased compared to value of CCl_4- induced rats (Group II). In the same respect, the biochemical values of Tb, TL, TP, albumin, urea, and globulin in plasma of Se and CCl_4-induced rats (Group III) were

obtained nearly to control values (Group I), while TC and creatinine values still significantly (P<0.05) higher than that of control (Group I).

Table 3. Effect of selenium on plasma biochemical parameters in experimental liver injury of rats *.

Parameter	Group I (control)	Group II (CCl_4)	Group III (CCl_4 + Selenium)
Total cholesterol (mg/dl)	151.2 ± 2.01^{c}	190.3 ± 2.24^{a}	166.2 ± 3.38^{b}
Total lipids (mg/dl)	506.3 ± 10.01^{a}	355.1 ± 12.20^{b}	436.2 ± 31.38^{a}
Total protein (mg/dl)	8.65 ± 0.09^{a}	7.21 ± 0.08^{b}	8.28 ± 0.13^{a}
Albumin (mg/dl)	5.52 ± 0.89^{a}	4.72 ± 0.29^{b}	5.07 ± 0.42^{a}
Globulin (mg/dl)	2.98 ± 0.23^{a}	2.77 ± 0.22^{a}	2.96 ± 0.17^{a}
Total bilirubin (mg/dl)	0.88 ± 0.02^{b}	1.10 ± 0.05^{a}	0.98 ± 0.04^{b}
Urea (mg/dl)	50.2 ± 1.03^{b}	60.4 ± 1.10^{a}	54.2 ± 1.13^{b}
Creatinine (mg/dl)	0.76 ± 0.02^{b}	0.96 ± 0.03^{a}	0.86 ± 0.02^{a}

Values are expressed as mean ± SD for twenty animals, ^{abc}Different letters in a given row denote significant difference, P<0.05

DISCUSSION

As indicated in many literatures, carbon tetrachloride caused histopathological alterations in hepatic and kidney tissues. Haloalkane free radicals produced during biotransformation of CCl_4 in liver and kidney were probably responsible for severe tissue damage, leading to necrosis of hepatocytes. CCl_4 is metabolized in mixed function oxidase system utilizing the nicotinamide adenine dinucleotide phosphate (NADPH) – cytochrone. P-450 electron transport chain at the level of the hepatic smooth endoplasmic reticulum and the hemolytic cleavage may occur during the formation of the haloalkane free radicals such as trichloromethyl (CCl_3) radical and trichloromethylperoxy (CCl_3OO) radical (Ozardali et al., 2004). These radicals cause the oxidative damage of lipids, lipoproteins, enzymes, nucleic acids and proteins.

Ozardali et al. (2004) mentioned that damage of these components may be an important factor in the pathogenesis of different liver diseases. In addition, haloalkane free radicals may bind to cellular macromolecules and can react with free amino groups on proteins and then the macromolecules may lose their physiological functions (Miao et al., 1990; Biasi et al., 1991). Therefore, enhanced lipid peroxidation associated with depletion of total antioxidant capacity in the plasma is a characteristic observation in CCl_4-intoxicated rats.

Lipid peroxidation and total antioxidant status

Malondialdehyde, a secondary product of lipid peroxidation, is used as an indicator of tissue damage (Ohkawa et al., 1979). Sipes et al. (1997) reported that the trichloromethyl radical could abstract hydrogen atom from a fatty acid to form a lipid

radical. The formed radicals may then react with oxygen to initiate lipid peroxidation. In the present study, such a disruption of fatty acids possibly accounted for the observed increase in MDA levels in the plasma of CCl_4-induced (Group II) rats when compared to normal rats (Group I). Elevated levels of MDA following CCl_4–administration have been well documented in various organs such as liver and kidney (Srinivasan et al., 2005; Tirkey et al., 2005) and liver, kidney and heart (Thieophile et al., 2006).

The total antioxidants are important reductants in the cell, where they protect against free radicals, peroxides and other toxic components. They maintains the normal structure and function of cells, also affecting detoxification of the reactive metabolites of cells (Halliwell, 1996). Thus, significant ($P<0.05$) reduction in the levels of total antioxidant capacity observed in plasma of CCl_4-induced rats (Group II) are consistent with the results of other workers. The lower levels of total antioxidant capacity in this group of rats might reflect the increased oxidative damage. These results are consistent with those observed by Srinivasan et al. (2005) and Rudnicki et al. (2007). They observed that administration of CCl_4 to rats, reduced the activity of antioxidant enzymes (catalase, superoxide dismutase [SOD] and glutathione peroxidase [GSH- Px]) as well as reduced glutathione. They attributed the reduced activities of these enzymes to feed-back inhibition or oxidative inactivation of protein caused by excess generation of reactive oxygen species (ROS). The significant ($P<0.05$) reduction in the MDA level and the increases in total antioxidant capacity in the plasma of rats treated with selenium and CCl_4 (Group III) suggests tissue protective potential of Se. The antioxidant Se may diminish the harmful effects of the reactive intermediary metabolites of CCl_4, through its function in the active site of selenoenzyme GSH- Px which catalyzes the destruction of hydrogen peroxide and lipid hydroperoxides via reduced glutathione. Se increases the total antioxidant capacity in plasma of rats by increasing the activities of antioxidant enzymes, such as SOD, GSH-Px, and catalase, as well as the increase in the mean of reduced glutathione. Similar elevation of these enzyme levels by supplementation of antioxidant sources has already been reported (Balu et al., 2005). These results suggest that the decreased total antioxidant capacity contributes to increase oxidative damage and lipid peroxidation in CCl_4-induced rats. Whereas, supplementation with Se to CCl_4 induced rats antagonize this effect by increasing total antioxidant capacity and decreasing oxidative damage and lipid peroxidation.

Liver function enzyme activities

Significant ($P<0.05$) increase in AST and ALT activities in CCl_4-induced rats (Group II, Table 2) is expected to occur in association with a pathology involving necrosis of the liver and kidney. Plasma AST increases in such cases and escapes to the plasma from the injured hepatic cells. In addition, plasma ALT level is also useful in indicating the existence of liver diseases, as this enzyme is present in large quantities in the liver. It increases in plasma when cellular degeneration or destruction occurs in this organ (Hassoun and Stohs, 1995).

In the same respect, the significant ($P<0.05$) increase in the activities of ALP, ACP and LDH in plasma of CCl_4-induced rats (Group II, Table 2) might be due to the increased

permeability of plasma membrane or cellular necrosis of liver and kidney. These results are in accordance with the findings of Sodhi et al. (2008) and Ozardli et al. (2004). Indeed, it has been reported that haloalkane free radicals were held responsible for CCl_4 hepatotoxicity and caused the oxidative injury of unsaturated lipids in some cellular components of hepatic tissues (Comporti, 1985; Miao et al., 1990). Yuan and Tang (1999) reported that Se is one of the necessary trace elements in the human body, which has the ability to counteract free radicals and protect the structure and function of protein, DNA and chromosomes against the injury of oxidation. The present results showed that treatment with Se and CCl_4 to rats (Group III, Table 2) caused a significant ($P<0.05$) decreases in the enzyme activities of AST, ALT, ALP, ACP and LDH in plasma.

The antioxidant Se may diminish the hepatotoxic effects of CCl_4 metabolites by means of their interactive relations with intermediary metabolites. The most important antioxidant aspect of Se is its function in the active site of selenoenzyme GSH. Px. GSH. Px containing Se catalyzes the destruction of hydrogen peroxide and lipid hydroperoxides via reduced glutathione (McPherson, 1994). Also, GSH. Px and other antioxidants such as SOD and catalase may protect cellular membranes against oxidative damage caused by toxic free radicals and so may partially diminish certain types of hepatic cellular degeneration. In addition, GSH. Px not only allows the removal of the toxic ROOH, but also permits the regeneration of lipid molecules through reacylation in the cellular membrane (Parola et al., 1992; McPherson, 1994). Ozardali et al. (2004) found that, the necrotic fibrotic and cirrhotic changes in the liver sections were reduced after being treated with Se and they suggest that Se can diminish liver injury fibrosis and cirrhosis induced by CCl_4.

Biochemical Parameters

The significant ($P<0.05$) increase in cholesterol and the significant decrease in total lipids (Group II, Table 3) in plasma of CCl_4-induced rats indicated a loss of membrane intergrity (Cabre et al., 2000; Simibe et al., 2001). This was further confirmed when CCl_4 treatment was found to have a significant ($P<0.05$) effect on the various membrane-bound enzymes (Group II, Table 2). These results suggest that CCl_4-induced hepatotoxicity lead to disturbances of lipid metabolism and an elevation of plasma cholesterol. The elevation in plasma urea and creatinine levels in CCl_4-treated rats is considered as a significant marker of renal dysfunction (Group II, Table 3) and this is supported by the finding of Szilagyi et al. (1994) who reported that alterations in serum urea may be related to metabolic disturbance (e.g. renal function, cation-anion balance). Ozturk et al. (2003) reported that CCl_4 has been implicated in the pathogenesis of several clinical disorders, including renal dysfunction. The increase in urea concentration in plasma of animals treated with CCl_4 may be due to its effect on liver function, as urea is the end-product of protein catabolism and/or referred to kidney dysfunction as proven by Ozturk et al. (2003). The increase in plasma total bilirubin (Group II, Table 3) may result from decreased liver uptake, conjugation and increased bilirubin production from hemolysis (Ohta et al., 1997). The decrease in the levels of protein in plasma of CCl_4-induced rats might be due to changes in protein synthesis and/or metabolism (Ohta et al., 1997).

A significant ($P<0.05$) increase in TL, TP and albumin, but, significant decreases in the levels of urea, creatinine, Tb and cholesterol in Se/CCl_4-induced rats (Group III) as compared with CCl_4-induced rats (group-II) were observed. All these values were comparable to the values of control (group I) except TC and creatinine which are still significantly higher than that in plasma of control (group I). Sahin et al. (2002) reported that higher dietary vitamin E results in a decrease in urea and cholesterol concentrations while protein and albumin concentrations increased. Hoffman and Heinz (1998) found that Se treatment caused an increase in total protein while urea decreased. Sodium selenite is able to maintain a functional renal state in the case of renal dysfunction (Rudenko et al., 1998).

In conclusion, CCl_4 caused injury in the liver and kidney of treated rats as indicated by significant increase of malondialdehyde, lowered level of total antioxidant activity, significant increase in liver and kidney enzyme activities and changes in some biochemical parameters such as plasma TL, Tb, urea and creatinine. Se proved to be beneficial in decreasing the levels of free radicals, lipid peroxides, liver function enzyme activities, urea, creatinine and total bilirubin, and increasing total protein, total lipids, albumin and total antioxidant capacity in plasma of CCl_4-treated rats. Thus, Se is able to antagonize the oxidative damage caused by CCl_4-induced hepatotoxicity in rats. Therefore, Se may also play an important role to prevent the induction of hepatic and kidney cellular injury. However, there is a need for more detailed studies in order to assess the possible relationships between antioxidants and CCl_4-induced hepatic and kidney damage.

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تأثير السيلينيوم على حالة مضادات الأكسدة، وأكسدة الليبيدات، ونشاط الإنزيمات وبعض القياسات الكيميائية الحيوية في الجرذان المعاملة بمركب رابع كلوريد الكربون لإحداث تلف بالكبد

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الملخص: كان الهدف من هذه الدراسة معرفة دور السيلينيوم على السمية الناتجة عن حقن مركب رابع كلوريد الكربون في ذكور الجرذان البيضاء، وأظهرت النتائج أن حقن الجرذان بمركب رابع كلوريد الكربون عند مستوى 0.15 مل/كجم من وزن الجسم أدى إلى حدوث زيادة معنوية في مستوى مركب المالونالدهيد مع انخفاض معنوي لمستويات السعة الكلية لمضادات الأكسدة في بلازما الجرذان مقارنة بقيمها في الجرذان غير المحقونة بمركب رابع كلوريد الكربون. لوحظ أيضا زيادة معنوية في نشاط إنزيمات الأسبارتات أمينوترانسفيريز والفوسفاتيز القلوي والحامضي وإنزيم اللاكتات ديهيدروجينز، وقيم الكولسترول الكلي واليوريا والكرياتينين، والبليروبن الكلي مع نقص معنوي في مستويات الليبيدات الكلية، البروتين الكلي والالبيومين في بلازما الجرذان المحقونة بمركب رابع كلوريد الكربون مقارنة بهذه القيم في الجرذان غير المحقونة (الكنترول). ولكن عند تغذية الجرذان المحقونة بمركب رابع كلوريد الكربون على علائق مدعمة بمركب السيلينيوم لفترة 45 يوماً حدث تعديل لنشاط الإنزيمات وجميع القياسات الكيميائية الحيوية المدروسة بالإضافة إلى مركب المالونالدهيد والسعة الكلية لمضادات الأكسدة لتقترب من قيمها في حيوانات المقارنة.

لذا فإن التدعيم بالسيلينوم في العليقة يمكن أن يوقف أو يقلل من التأثيرات المدمرة لرابع كلوريد الكربون في كبد وكلى الجرذان البيضاء.

كلمات مفتاحية: مضادات الأكسدة، الملونالدهيد، السيلينوم، إنزيمات وظائف الكبد، رابع كلوريد الكربون.