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PROTECTIVE ACTION OF ZINC AND SELENIUM AGAINST OXIDATION STRESS DUE TO BENZENE TOXICITY IN RATS

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ABSTRACT: ***The present study investigated the protective role of zinc plus selenium (Se) in attenuating the toxicity induced by benzene in rats injected with benzene (0.5 ml/kg body weight ip) and received diet supplemented with zinc plus Se. The dietary consumption and growth rate were measured. Several biochemical parameters representing antioxidant status were followed. The results showed that food intake and body weight gain of rats injected with benzene were significantly lower than that of control rats. Diet supplemented with zinc plus Se corrected these drop. Lower values of hemoglobin, hematocrit, iron, and ferritin were observed in rats injected with benzene. However, diet supplemented with Zinc plus Se corrected these parameters. Plasma malondialdehyde (MDA) was increased in rats injected with benzene, while the activities of the enzymes glutathione peroxidase, catalase and superoxide dismutase (SOD) as well as glutathione concentration were decreased. Supplemented diet resulted in a significant decrease in the levels of MDA and elevation in the levels of GSH, GSHPx, catalase and SOD and. Benzene injection enhances histopathological changes in the liver of rats. This study indicates that zinc plus Se supplementation can improve the antioxidant enzymes and the histological alterations during benzene toxicity.***

Key words: benzene, zinc, selenium, antioxidant enzymes, vitamins.

INTRODUCTION

Benzene is a pollutant compound, present in both occupational and general environment. It is used as a constituent in motor fuels; as a solvent for fats, waxes, resins, oils, inks, paints, plastics, and rubber; in the extraction of oils from seeds and nuts; and in photogravure printing. Individuals employed in industries that manufacture or use benzene may be exposed to the highest levels of benzene (ATSDR, 1997).

The known toxicity of benzene suggested that it caused the production of oxygen radicals or reactive oxygen species (ROS) (Parke, 1996). Reactive oxygen species play an important role in the etiology of many diseases and ageing that is associated with a high risk of micronutrient deficiency, it may increase the need for specific nutrients and/or interfere with their absorption, storage and utilization. (Machlin and Bendich, 1987; Nuckels, 1990).

As a response to the production of ROS the human body may develop antioxidant mechanisms; which include enzymes that have antioxidant activity. The main enzymes that provide cellular protection against damage due to ROS in human cells are superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) (Valko *et al.*, 2006). Animal studies have shown that antioxidant enzyme levels depends in part on the availability of some antioxidant nutrients in food. (Draper and Beeger, 1994). To achieve proper function of these enzymes, adequacy of some micronutrients such as, Zn, Cu or Se is essential.

The aim of the present study was to examine the effect of diet supplemented with some trace elements such as zinc and selenium on the antioxidant enzymes. Lipid peroxide levels and histopathological changes in rats due to benzene toxicity, were also investigated.

MATERIALS AND METHODS

Animals:

Thirty male Sprague Dawley rats (average weight 194 g), bred at the Central Animal House of the National Research Center, Dokki, Giza, Egypt were. After an initial 24 h acclimatization period, all rats were given a standard diet for one week. The animals were kept through the experimental period (9 weeks) under good ventilation and hygienic conditions, experimental diets and water were fed *ad-libitum*. Body weights were measured weekly, food intake was measured twice weekly and examined each day for general condition.

Diets :

The experimental diets were formulated to contain 10% fat and 14% protein (Table 1). The diet contains adequate vitamins and minerals according to the American Institute of Nutrition (Reeves *et al.*, 1993).

The experimental diet contained (g/100g): skimmed milk 35 (to provide 12 % protein), sucrose 10, sunflower oil 10, salt mixture 3.5, vitamin B mixture 1,

fiber 4, Choline bitartrate 0.25, L-Cystine 0.18 and starch 36.07. Diet supplemented with Zinc as zinc carbonate (16.5 g/kg salt mix.) and selenium as sodium selenate (0.1025 g/kg salt mix.) which provide 10 times the requirement. This supplemented diet was given to rats three days before benzene injection.

Experimental design:

The animals were randomly divided into three groups of 10 rats each, having more or less similar body weight within 194 ± 15gm. Animals were housed individually in stainless steel cages and benzene was injected three times a week (0.5 ml per kg body weight in corn oil 200 µL/ animal according to Ahmad *et al.*, 1994).

***Group 1*: Control rats were fed on the basal diet.**

***Group 2*: Rats were treated with benzene and fed on the basal diet.**

***Group 3*: Rats were treated with benzene and fed on diet supplemented with zinc and selenium.**

The experimental period lasted for 9 weeks during which rats were weighed weekly. At the end of the experimental period, animals were fasted over night and blood samples were collected in heparinized tubes under slight diethyl ether anesthesia by open heart puncture. The collected blood was divided into 2 parts:

The first one was used for the estimation of Hemoglobin concentration (Hb) by the cyanmethemoglobin method according to the Eagle Hemoglobin procedure (Van Kampen and Zijlstra, 1961). Hematocrit percent (Hct %) was measured using capillary tubes, reduced glutathione (GSH) concentration was determined by the method of Beutler *et al.*, (1963) and glutathione peroxidase (GSHPx) was determined using Kit provided by WAK-CHEMIE Medical GMBH, Germany, according to Ammerman *et al.* (1980).

The second part was centrifuged at (1500 xg) for 15 min to obtain blood plasma. The plasma was then aliquoted and stored at $^{-}$20 ^{o}C until used for the analysis. The extent of lipid peroxidation was quantitatively determined by measuring the concentration of thiobarbituric acid-reactive product as malondialdehyde (MDA) by the method of Satoh (1978). Iron & total iron binding capacity (TIBC) and ferritin were determined using the commercial kit provided by Biodiagnostic, Cairo, Egypt. The erythrocytes were washed three times in cold normal saline (0.9% Na Cl), then diluted with cold distilled water and vortex. The erythrocytes haemolysate was used for the assay of catalase (CAT) according to Beers and Sizer, (1952) and superoxide dismutase (SOD)

using kit provided by WAK-CHEMIE Medical GMBH, Germany (Arthur and Boyne, 1985).

Histopathological examination of the liver tissues:

Liver specimens were removed and rapidly washed in saline solution to remove the blood. The specimens were rapidly fixed in 10% neutral buffered formalin for 24 hr., then processed up to paraffin blocks and sections 6um thick were prepared and stained with hematoxylin and eosin, (Drury and wallington, 1980) for histopathological examination.

Statistical Analysis:

Results are expressed as means ± standard errors (SEM). Comparison between the means was accomplished using a one-way ANOVA, followed by Duncan Multiple Range Tests for all variables (Duncan 1955). Differences between groups were considered significant at $p< 0.05$.

RESULTS AND DISCUSSION

Effect of zinc plus selenium supplementationon food intake and body weight gain:

In the present study the variations in the food intake, body weights and food efficiency ratio of the animals subjected to different treatments are shown in Table 1. The results indicate that, there was significant decrease in the food intake of the animals injected with benzene compared to the control group. The net body weight gain and food efficiency ratio of the animals intoxicated with benzene was markedly less than the controls. These results are in agreement with that reported by Dempster *et al.* (1984) and Saillenfait *et al.* (2006). Zinc plus selenium supplementation improved the food consumption in rats injected with benzene, but that improvement was not significant compared to the benzene group. The body weight gain and food efficiency ratio of the intoxicated animals that were fed on the zinc plus selenium supplemented diet, were significantly increased relative to that of the benzene group (Table 1). This indicates that supplementation with zinc and selenium may be help to restore the growth retardation caused by benzene administration.

Table 1: Food intake (g), body weight gain (g), and feed efficiency ratio (FER) of control rats, those injected with benzene and the zinc plus selenium supplemented group.

Parameters	Control	Benzene group	Benzene + (Zn & Se)
Food intake (g)	1285±14.28 [b]	1146±14.15 [a]	1169±15.08 [a]
body weight gain (g)	114.7±3.77 [c]	68.0±3.89 [a]	80.2±3.84 [b]
FER	0.089±0.003 [b]	0.060±0.004 [a]	0.069±0.003 [a]

Values within a row with different superscripts are significantly different (P<0:05).

Effect of zinc plus selenium supplementation on the organs weights:

A significant increase in the liver weights was observed in benzene group (Table 2). It has been shown that exposure to benzene caused an increase in relative liver weight (Bar, 1999). The increased expression of drug metabolizing enzymes in the liver might be the most important reason for the relative increase of the liver weight (Heijne *et al.*, 2005). Rats exposed to benzene, showed a decrease of kidney and spleen weights. These findings are in line with previous work of Yamamura *et al.* (1999). Diet supplemented with zinc plus Se caused a significant decrease in the liver weight and increase in the weight of kidney and spleen.

Table 2: Liver weight (g), spleen weight (g) and kidneys weight (g) of control rats, those injected with benzene and supplemented group.

Parameters	Control	Benzene group	Benzene + (Zn & Se)
liver (g)	7.883±0.263 [a]	8.760±0.264 [b]	7.776±0.326 [a]
spleen (g)	1.188±0.048 [c]	0.843±0.015 [a]	0.941±0.038 [a b]
Kidney (g)	0.900±0.033 [a]	0.810±0.025 [b]	0.894±0.033 [b]

Values within a row with different superscripts are significantly different (P<0:05).

Effect of zinc plus selenium supplementation on hematological parameters:

Benzene is known to have toxic effects on the blood and bone marrow (Ross, 1996; d'Azevedo, *et al.*, 1996). Our results showed that hemoglobin, hematocrit, iron, and ferritin were significantly decreased, while TIBC significantly increased in rats exposed to benzene compared to the control group. These results agree with d'Azevedo, *et al.* (1996), who observed reduced erythrocyte counts, hematocrit and hemoglobin in rats from xylene and benzene exposure. The same finding was reported by Shimo *et al.* (1994) in rats exposed to nitrobenzene. Also Escorcia *et al.* (1997) found a reduction in the concentration of haemoglobin in rats treated with benzene. Rouach, *et al.* (1997) demonstrated that the nonheme iron level was significantly decreased in ethanol-fed rats. This decrease may be linked to the mobilization of iron from storage proteins by intracellular reductants (Shaw *et al.*, 1988 and Minotti, 1992). Such released iron might serve for the synthesis of hemeproteins such as CYP P450 (Minotti, 1992). Diet supplementated with Zn plus Se corrected the drop in the above mentioned parameters occurring due to benzene toxicity (Table 3). These results show that this supplemented diet is able to suppress the free radical formation.

Table 3: Hemoglobin (Hb) (g/dl), haematocrite (Hct %), iron (µg/dl), total iron binding capacity (TIBC) (µg/dl) and ferritin (µg/l) of control rats, those treated with benzene and supplemented group.

Parameters	Control	Benzene group	Benzene + (Zn & Se)
Hemoglobin (g/dl)	14.02±0.242 [b]	12.85±0.297 [a]	13.68±0.203 [b]
Hematocrit (Hct %)	44.0±1.116 [b]	39.6±1.455 [a]	42.7±1.012 [b]
IRON (µg/dL)	108.9±2.61 [b]	92.7±3.53 [a]	102.4±2.11 [b]
FERRITIN (µg/L)	85.8±6.54 [c]	52.2±4.60 [a]	58.3±5.07 [a, b]
(TIBC) (µg/dL)	258±2.83 [a]	347±3.90 [a]	288±8.27 [a,b]

Values within a row with different superscripts are significantly different (P<0:05).

Effect of zinc plus selenium on MDA and scavenging enzymes:

The plasma MDA level is one of lipid peroxidation indicators. The results show that MDA level was higher in benzene group (p<0.01) compared to

control group (Fig. 1). This result agree with the finding of Pandya *et al.* (1990) & Ahmad *et al.* (1994) who reported that benzene administration increased the level of MDA in albino rats. Rats fed on the supplemented diet showed a significant decrease in this parameter compared with benzene group ($p<0.01$). Plasma GSH concentration was lower in benzene group than control group (Fig. 2). Previous study indicated that GSH depletion is one of the important consequences of toxic injury and established the critical role of GSH in protecting tissues from toxic effects of accumulating reactive intermediates (Eckert, 1988).

The activity of scavenging enzymes SOD, catalase and glutathione peroxidase (GPx) decreased in benzene group compared to control group (Table 5). However the values reported in the supplemented group showed a significant increase compared to benzene group. A number of studies have suggested that zinc has a beneficial role during peroxidative damage (Chvapil *et al.*, 1972; Cabre *et al.*, 1999). It is essential for the function of several enzymes including Cu, Zn-SOD (Sandstead, 1994). Zinc is involved in stabilizing membrane structures and in protection at the cellular level by preventing lipid peroxidation and reducing free radical formation. Sidhu *et al.* (2004) reported that zinc is important in cell division, growth and reproduction and the removal of toxic metals. The hepatoprotective role of zinc in rat liver was investigated by Goel *et al.* (2005), they reported that zinc treatment resulted in an elevation in the levels of GSH, CAT and GST. Bolkent *et al.* (2006) suggested that zinc sulfate supplementation has a protective effect against lipid peroxidation in liver.

Some results claim that selenium supplementation at the dose of 5.0 microgram/kg cause a protective effect on lymphocytic system, before benzene's toxic effects (Aleksandrowicz *et al.*, 1977). The most important antioxidant aspect of Se is its function in the active site of selenoenzyme glutathione peroxidase. GSH-Px containing Se catalyzes the destruction of hydrogen peroxide and lipid hydroperoxides via reduced glutathione (Combs and Combs, 1984; McPherson, 1994). Also, GSH-Px and the other antioxidants such as superoxide dismutase and catalase may protect cellular membranes against oxidative damage caused by toxic free radicals and so may partially diminish certain types of the hepatic cellular degeneration. In addition, GSHPx not only allows the removal of the toxic ROOH but also permits the regeneration of lipid molecules through reacylation in the cellular membrane (Combs and Combs, 1984; McPherson, 1994). Thus Se may also diminish the harmful effects and the formation of the reactive intermediary metabolites of benzene.

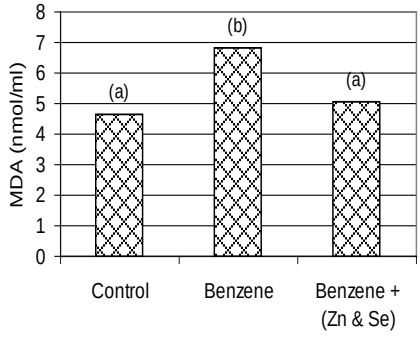

Fig.1.Malondialdehyde (MDA) (nmol/ml) of control rats, those treated with benzene and supplemented group.

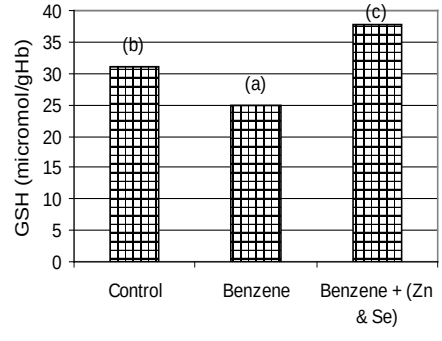

Fig. 2.Reduced glutathione(GSH) (µmol/gHb) of control rats, those treated with benzene and supplemented group.

Values with different superscripts are significantly different (*P*<0.05).

Table 5: Glutathione peroxidase (GPx) (U/L Hb), catalase (ku/g Hb), and superoxid dismutase (SOD) (U/g Hb) of control rats and those treated with benzene and supplemented group.

Parameters	Control	Benzene group	Benzene + (Zn & Se)
GSH-Px (U/L Hb)	4198±148 [a]	3762±169.5 [a]	4508±161.8 [b]
Catalase (ku/g Hb)	58.04±1.15 [b]	50.38±1.81 [a]	64.81±2.15 [c]
SOD (U/g Hb)	735.6±30.09 [b]	629.6±27.77 [a]	739.2±33.94 [b]

Values within a row with different superscripts are significantly different (P<0:05).

Effect of zinc plus selenium on Liver histopathology:

The microscopic examination of liver of control rats showed normal characteristics (Fig.3).

Examination of liver sections of rats received benzene showed periportal necrosis of the hepatocytes near the portal areas. The specimens also, showed dilated and congested portal vessels as well as mild areas of inflammatory cell infiltration especially in the vicinity of the portal veins and near the bile ductules. Some cells exhibited necrosis together with pyknosis of some nuclei. Slight hemorrhage was also noticed. Besides, dilated

sinusoids and the interlobular connective tissue showed marked thickening (Fig. 4). These results are in agreement with similar reports dealing with changes due to exposure to benzene or its derivatives in mice (Szymanska, 1998), in rats (Madej *et al.*, 1987) and in workers exposed to benzene (Cotrim *et al.*, 2004).

Administration of zinc and selenium along with benzene showed that liver appears more or less like normal except for some single cell necrosis (Fig. 5).

The present study suggests that feeding diet supplemented with zinc plus selenium minimized the hazards due to benzene toxicity, this was reported before by Bolkent *et al.* (2006) who suggested that zinc salts reduce tissue injury caused by a free radical-mediated mechanism. Also Ozardali *et al.* (2004) reported that selenium may play an important role to prevent the induction of hepatic cellular injury induced by carbon tetrachloride.

In conclusion, our results showed that benzene caused an increase the level of lipid peroxidation products (MDA), decreased the activity of antioxidant enzymes in blood and induced hepatic injury. Zinc plus Se supplementation provides protection against benzene-induced oxidative stress as evidenced from decreased the levels of MDA. Therefore, It is recommended to provide extra Zn and Se to exposed persons to diminish the growth of the necrosis, fibrosis and cirrhosis induced by benzene and protected against benzene toxicity.

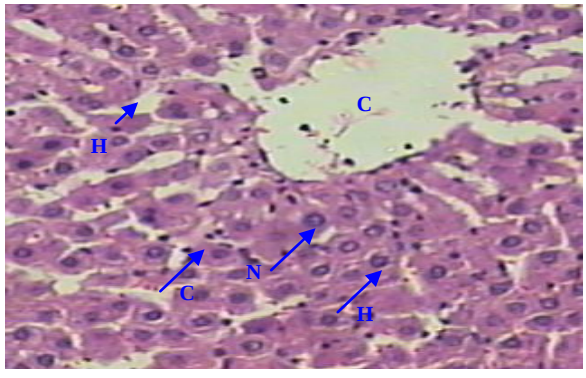

Fig. 3. A photomicrograph of section of control liver showing the architecture of a hepatic lobule. The central vein (CV) surrounded by the hepatocytes (HC) with strongly eosinophilic granulated cytoplasm (CY) and distinct nuclei (N). Between the strands of hepatocytes the hepatic sinusoids (HS) are shown. (H & E stain-X 300).

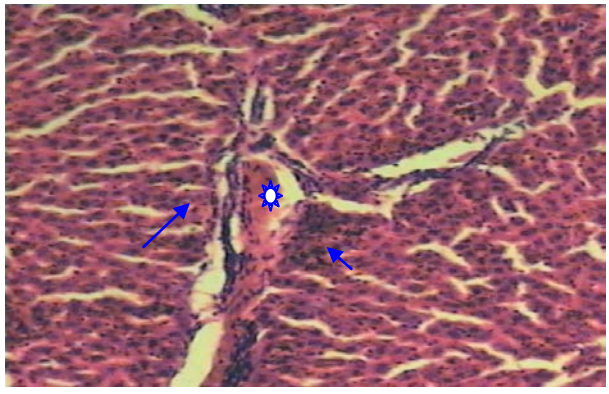

Fig. 4. A photomicrograph of section of liver of rat injected with benzene showing periportal necrosis of the hepatocytes near the portal areas (arrow). The specimens also, showed dilated and congested portal vessels (star) as well as mild areas of inflammatory cell infiltration (arrowheads) especially in the vicinity of the portal veins and near the bile ductules. Some cells exhibited necrosis together with pyknosis of some nuclei. Slight haemorrhage is also seen. (H & E stain-X 300).

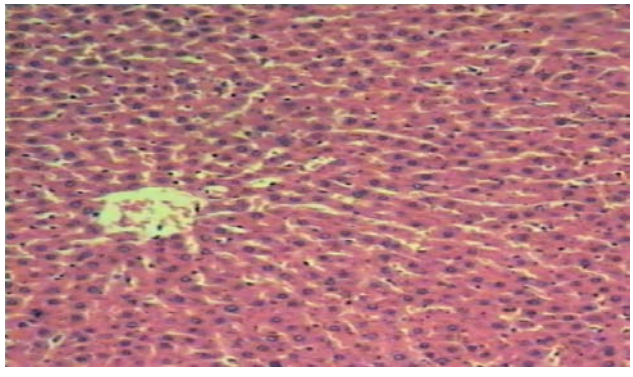

Fig. 5. A photomicrograph of section of liver of rat injected with benzene and supplemented with zinc plus selenium shows that the structure appears more or less like normal. (H & E stain-X 150).

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التأثيرالوقائى للزنك والسيلنيوم من الحمل الأكسيدى الناتج عن سمية البنزين فى الفئران

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المركز القومى للبحوث – مصر

الملخص العربى

اهتمت هذه الدراسة بمعرفة دور عنصر الزنك مع السلينيوم لزيادة كفاءة مضادات الأكسدة والتقليل من سمية البنزين على فئران التجارب.

إشمتلت هذه الدراسة علي ثلاثة مجاميع من الفئران كل منها تحتوي علي عشرة فئران و تم حقنها بالبنزين ثلاثة أيام في الأسبوع لمدة ٩ اسابيع (٠.٥ ملي /كجم من وزن الجسم داخل الغشاء البروتوني).

تم تغذية المجموعة الأولي علي الوجبة الضابطة و المجموعة الثانية حقنت بالبنزين و تغذت علي الوجبة الضابطة و المجموعة الثالثة حقنت بالبنزين و تغذت على الوجبة الضابطة المعززة بالزنك والسلينيوم . خلال فترة التجربة تم تقدير الوجبات المستهلكة يومياً ومعدل نمو الفئران. في نهاية التجربة تم أخذ عينات الدم وتم تقدير المدلولات البيوكيميائية التى تعكس حالة مضادات الأكسدة وكذلك التغيرات الهستوباثولوجية.

أظهرت النتائج أن معدل استهلاك الوجبات وكذلك معدل نمو الفئران التى حقنت بالبنزين أقل من المجموعة الضابطة. كذلك لوحظ إنخفاض فى مستوى الهيموجلوبين، الهيماتوكريت، الحديد والفرتين.

وكان مستوى مالون دي ألديهايد (MDA) في البلازما أعلى بينما كان نشاط أنزيم الجلوتاثيون بيراكسيديز والكاتاليز والسوبرأكسد ديسميوتيز أقل في الفئران التى حقنت بالبنزين من

المجموعة الضابطة , كما أظهرت وجود تغييرات للخلايا الدالة علي الإلتهابات في مقاطع من كبد الفئران المعاملة بالبنزين.

أدى تعزيزالوجبة بعنصرى الزنك مع السلينيوم إلى تحسن معدل نمو الفئران وكذلك تحسن فى مستوى الهيموجلوبين، الهيماتوكريت، الحديد والفرتين وزيادة نشاط الإنزيمات المضادة للأكسدة وكذلك إنخفاض مستوى مالون داي ألديهايد.

و تشير هذه الدراسة إلى أن تعزيزالوجبة بالزنك و السلينيوم يساعد فى زيادة كفاءة مضادات الأكسدة و تقليل التفاعلات الناجمة عن زيادة الشقوق الحرة بالجسم نتيجة التعرض للبنزين.