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Protective effect of zinc aspartate against acetaminophen induced hepato-renal toxicity in albino rats

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ABSTRACT

Zinc is an essential nutrient that is required in humans and animals for many physiological functions, including antioxidant functions. The evidence to date indicates that zinc is an important element that links antioxidant system and tissue damage. Acetaminophen (AP), a widely used analgesic and antipyretic, produces hepatocyte and renal tubular necrosis in human and animals following overdose. In human, AP is one of the most common causes of acute liver failure as a result of accidental or deliberate overdose. Moreover, the initial event in AP toxicity is a toxic metabolic injury with the release of free radicals and subsequent cellular death by necrosis and apoptosis. This study was designed to evaluate the potential protective role of zinc aspartate in case of acetaminophen induced hepato-renal toxicity in rats. A total number of 32 adult male albino rats were divided into 4 equal groups: group I (control group), group II (zinc aspartate treated group), group III (acetaminophen treated group; by a single oral dose of 750 mg/kg body weight) and group IV acetaminophen plus zinc treated group; (zinc aspartate was intraperitoneally given one hour after acetaminophen administration in a dose of 30 mg/kg body weight). Serum levels of: alanine aminotransferase, aspartate aminotransferase, direct bilirubin, blood urea nitrogen, creatinine, uric acid, xanthine oxidase (XO), glutathione (GSH), malonaldehyde (MDA) and nitric oxide (NO) were assessed in all groups. The results of this study showed that treatment with acetaminophen alone (group III)' produced a significant increase in serum levels of the liver enzymes and direct bilirubin. Moreover, in the same group there was a significant increase in the blood urea nitrogen and serum creatinine compared to the control group. In addition, there was a significant increase in XO and MDA and a significant decrease in GSH and NO level. Injection of rats with zinc aspartate after acetaminophen treatment could produce a significant protection against the toxic effect of acetaminophen, in comparison with that of acetaminophen treated group. In conclusion, biochemical evaluation revealed

that zinc aspartate has a partial protective effect against acetaminophen induced hepato-renal toxicity and oxidative stress. Accordingly, zinc may be an effective therapeutic agent in prevention and treatment of acetaminophen hepatotoxicity, nephrotoxicity and free radical production.

Keywords: zinc, acetaminophen, malonaldehyde, glutathione, xanthine oxidase, nitric oxide, hepatotoxicity, nephrotoxicity.

INTRODUCTION

Zinc is the second most abundant trace element in the body. It is particularly important in cellular function because it is an integral component of numerous proteins, including metalloenzymes, structure proteins and transcriptional factors [(1)].

Highly reactive molecules called free radicals can cause tissue damage by reacting with polyunsaturated fatty acids in cellular membranes, nucleotides in DNA, and critical sulfhydryl bonds in proteins. Free radicals can originate endogenously from normal metabolic reactions or exogenously as components of tobacco smoke and air pollutants and indirectly through the metabolism of certain solvents and drugs, as well as through exposure to radiation [(2)]. There is some evidence that free radical damage contributes to the etiology of many chronic health problems such as inflammatory diseases and cancer [(3)]. Defenses against free radical damage include superoxide dismutase (copper, zinc, and manganese), glutathione and several metalloenzymes including glutathione peroxidase (selenium) [(4)]. Moreover, the extent of tissue damage is the result of the balance between the free radicals generated and the antioxidant protective defense system [(5)]. The evidence to date indicates that zinc is an important element that links antioxidant system and tissue damage [(6)].

Floersheim *et al.* [(7)] found that organic zinc salts were superior to inorganic zinc salts and that zinc aspartate provided protection against the deleterious effect of free radicals formed as a result of radiation exposure. Moreover, the same authors indicated that zinc aspartate did not inhibit the radiotherapeutic effect of gamma rays on human tumors grown as xenografts in immunosuppressed mice. This differential protection of neoplastic and normal cells may be of considerable benefit in clinical cancer radiotherapy, provided that zinc aspartate is better tolerated and has a favorable therapeutic index in human [(8)].

Acetaminophen is one of the most popular analgesic and antipyretic drugs and its overdose, which can cause severe damage to liver and kidney, is one of the most common reasons of emergency admissions [9]. They also added that, the precise mechanism of hepatorenal injury caused by acetaminophen is unknown, but the oxidative damage is the most likely reason. Also, Imaeda *et al.* [10] reported that hepatotoxicity and nephrotoxicity are major complications of acetaminophen and the reactive oxygen metabolites or free radicals are important mediator for acetaminophen toxicity. However, there is no specific treatment for acetaminophen induced hepatic and renal damage.

Acetaminophen is metabolized into several chemical compounds; the most reactive intermediate is N-acetyl-p-benzoquinone imine (NAPQI) [11]. It is detoxified by glutathione through conjugation. Large doses of acetaminophen cause glutathione depletion; followed by an increase of NAPQI level, then cell death and apoptosis appear through oxidative damages [12-14].

Acute acetaminophen nephrotoxicity in rats was observed in a dose-dependent way and this might be due to renal hemodynamic changes in the form of impairment in glomerular filtration rate (GFR) and clearance of p-aminohippuric acid (CP AHA) which might induce an alteration in tubular function principally in distal structures of medullary tissue. These effects occurred coupled with hepatotoxicity proved by a diminution in hepatic glutathione (GSH) levels at every acetaminophen dose [15].

In view of the abovementioned information, this study was designed to investigate the potential protective role of zinc aspartate against acetaminophen induced hepato and nephrotoxicity in male albino rats.

MATERIAL AND METHODS

Animals

Adult male albino rats weighing from 120-140 g were used in this study. Animals were maintained under standard conditions of ventilation, temperature, humidity and adequate rodent diet.

Experimental Design

After 2 weeks of adaptation, the animals were divided into four equal groups (n=8):

Group I (control group): Rats of this group were received single oral dose of saline (vehicle).

Group II (zinc aspartate group): Rats of this group were intraperitoneally injected by a single dose of zinc aspartate (30 mg/Kg body weight). Zinc aspartate was prepared according to the method of Ivan *et al.* [16].

Group III (Acetaminophen treated group): Rats of this group were administered by a single oral dose of acetaminophen (Misr Co., Egypt) (750 mg/kg body weight) by mean of a stomach tube.

Group VI (Acetaminophen plus zinc aspartate treated group): Rats of this group were intraperitoneally injected by zinc aspartate (30 mg/Kg body weight) one hour after the oral dose of acetaminophen (750 mg/Kg body weight).

Blood sampling and biochemical assay

All the animal groups were sacrificed 24 hours post acetaminophen or zinc aspartate administration (Woo *et al.,* 1995). Blood samples were obtained after an overnight fasting from rats by decapitation; blood was collected in clean centrifuge tubes without anticoagulant. Serum was separated by centrifugation of blood at 3000 rpm for 15 minutes and stored frozen at -20^{o} until assayed.

Laboratory Investigations:

1. Serum AST and ALT activity was estimated according to the method of Rec [17].
2. Serum direct bilirubin was estimated according to Young *et al*. [18].
3. Estimation of blood urea nitrogen (BUN) and serum creatinine was carried out according to the method of Murray [19].
4. Estimation of serum uric acid was done according to the method of Schultz [20].
5. The activity of GSH was determined by a colorimetric method according to Beutler *et al*. [21].
6. The level of MDA was determined by a colorimetric method as stated by Buege and Aust [22].
7. The concentration of NO was determined by ELISA technique as described by Ignarro *et al.* [23].
8. The activity of XO was determined by the method of Kaminski and Jewezska [24].

Statistical analysis

The results were presented as mean value ± standard deviation. One way analysis of variance (ANOVA) were used for the statistical analysis of the present study according to Mclauchlan and Gowenlock [25].

RESULTS

As presented in Table 1 the concentrations of serum AST, ALT**,** bilirubin, BUN, and creatinine were significantly increased in acetaminophen group. The animal group injected with zinc aspartate after acetaminophen administration revealed a significant decrease in the concentration of serum AST, ALT**,** direct bilirubin, BUN and creatinine and no significant change in serum uric acid compared to the acetaminophen group. Animal group injected with zinc aspartate showed no significant changes in the concentration of serum AST, ALT**,** direct bilirubin, BUN, creatinine and uric acid compared to the control group.

Table (1): Effect of zinc aspartate and/or acetaminophen administration to rats on the level of serum ALT, AST, direct bilirubin, BUN, creatinine and uric acid.

	ALT (U/L)	AST (U/L)	bilirubin (µmol/L)	BUN (mg/dl)	creatinine (mg/dl)	Uric acid (mg/dl)
Control group	20.24±1.65	30.26±1.16	1.83±0.71	18.28±1.53	0.93±0.43	6.03±1.35
Zinc aspartate group	19.87±1.48	31.27±1.18	1.81±0.62	19.65±1.42	0.91±0.34	6.43±1.00
Acetaminophen group	129.12±12.46 [a]	148.88±9.57[a]	2.30±0.77[a]	43.08±5.65[a]	4.63±1.02 [a]	6.73±1.83
Acetaminophen plus Zinc aspartate group	44.25±6.81 [b]	46.48±5.19 [b]	2.04±0.64[b]	28.62±3.06[b]	2.21±0.72 [b]	6.50±1.55

(a) Significant different from control group.

(b) Significant different from acetaminophen group.

As shown in Table 2, GSH activity was significantly decreased in the acetaminophen treated group. Animal groups intraperitoneally injected by zinc aspartate (30 mg/Kg body weight) one hour after the oral dose of acetaminophen revealed a significant increase in the GSH activity compared to the acetaminophen group. In addition, XO activity was significantly increased in the acetaminophen treated group. Acetaminophen animal group intraperitoneally injected by zinc aspartate revealed a significant decrease in the XO activity compared to the acetaminophen group.

The results also showed that MDA concentration of acetaminophen treated group significantly increased in the serum, treatment with zinc aspartate one hour after the oral dose of acetaminophen led to a significant decrease in the MDA level compared to acetaminophen group. As regard to NO activity, significant decrement in its level was recorded in the acetaminophen treated group. Acetaminophen animal group intraperitoneally injected by zinc aspartate revealed a significant increase in the NO activity compared to the acetaminophen group. No significant alterations in serum GSH, XO, MDA and NO activity were noticed in animal group treated only with zinc aspartate compared to the control group.

Table (2): Effect of zinc aspartate and/or acetaminophen administration to rats on the level of serum GSH, XO, MDA and NO.

	GSH (mU/ml)	XO (mU/ml)	MDA (nmol/ml)	NO (nmol/ml)
Control group	18.40±0.95	1.46±0.08	75.50±1.19	22.50±1.14
Zinc aspartate group	17.72±0.92	1.35±0.06	75.23±1.20	23.33±1.19
Acetaminophen group	10.43±1.12 [a]	2.56±0.12 [a]	133.03±5.37 [a]	0.98±1.04 [a]
Acetaminophen plus Zinc aspartate group	15.97±1.14 [b]	1.70±0.09 [b]	83.18±3.65 [b]	16.96±0.98 [b]

(a) Significant different from control group.

(b) Significant different from acetaminophen group.

DISCUSSION

Zinc is a widely distributed element in the human body and is now identified as a part of about 120 enzymes, including many antioxidant enzymes. Zinc has been shown to be essential for the structure and function of a large number of macromolecules and is also essential for over 300 enzymatic reactions [(26)]. In addition, zinc showed significant benefits in many health

statuses such as prevention of atherosclerosis and diabetes in experimental animals [27] induction of cancer cell death [28]. This study makes an effort to elucidate the protective role of zinc in the prevention of oxidative stress caused by acetaminophen administration.

Acetaminophen toxicity is one of the most widespread drug induced side-effects worldwide and damages to the liver and kidneys. Acetaminophen metabolites produced in the liver and other organs are likely to be the main contributor into the mechanism of its toxicity [29]. These metabolites, mainly (NAPQI), interact with a range of cellular proteins via covalent binding, disrupting their function and causing apoptosis and necrosis and finally, organ failure occurs [30].

In the present study, a single oral toxic dose of acetaminophen was followed by six folds increase in serum ALT, five folds increase in serum AST and significant change in direct bilirubin, which was also shown by Kheradpezhouh *et al*. [9]. The increase in the serum activities of these enzymes was directly proportional to the degree of liver cellular damage [31]. On the other hand, zinc aspartate treatment markedly suppressed the elevated liver enzymes level which was accompanied by less damage in the hepatic tissue.

These findings are in line with those of Woo *et al.* [32] who reported that, in cases of acetaminophen induced hepatic toxicity, zinc sulphate showed protection by dose-dependently reducing alanine aminotransferase and malondialdehyde levels. They also concluded that, this action is likely to be mediated through replenishment of hepatic glutathione levels, and the use of zinc sulphate alone or in combination with N-acetylcysteine could be another alternative for the treatment of acetaminophen overdose in view of possible side effects produced by N-acetylcysteine. Moreover, previous reports have shown that zinc has hepato protective effect under a variety of toxic conditions [6]. The same effect of zinc was observed in alcohol induced hepatitis, as zinc can inhibit ethanol induced hepatocyte apoptosis by several independent mechanisms. As well, zinc supplementation prevented long term ethanol elevated serum and hepatic tumor necrosis factor levels [33].

Blood urea nitrogen and creatinine are two markers of renal function, which are used to diagnose acute and chronic renal diseases. In the present study, significant increase occurred in the concentration of serum BUN and creatinine, while no significant changes occur in uric acid level in acetaminophen group. Animal group treated with zinc aspartate after

acetaminophen administration showed a significant decrease in the level of serum BUN and creatinine compared to acetaminophen group, suggesting the protection capacity of zinc aspartate to preserve normal function of the kidney. In addition, acetaminophen induced nephrotoxicity was manifested by significantly high levels of BUN and serum creatinine was also shown by Kheradpezhouh *et al*. [9]. They also added that these biochemical changes were accompanied by acute tubular necrosis and infiltration by inflammatory cells in the histopathological study. Moreover, Parham *et al.* [34] showed that zinc supplementation decreases microalbuminuria in type 2 diabetic patients and these beneficial effects of zinc on microalbuminuria suggests that zinc has a renoprotective effect, putatively via its antioxidant property.

In the current study, a significant decrease in the activity of serum GSH and NO was observed in acetaminophen group. Also, a marked increase in the activity of XO and MDA level was observed in the serum of acetaminophen group. On the other hand, acetaminophen group treated with zinc aspartate 1 hour after acetaminophen administration showed a significant increase in the activity of GSH and NO while, significant decrease was observed in the activity of XO and MDA concentration compared to the acetaminophen group.

Glutathione provides a protective action against damage from reactive oxygen species and free radicals formed during drug metabolism [35]. Metabolites of acetaminophen are detoxified by conjugation with glutathione. When depletion of glutathione occurs due to its massive consumption, these metabolites remain unbound. As a result, lipid peroxidation is increased, cellular homeostasis is disrupted and cellular apoptosis and necrosis are induced [36]. Also, zinc may have a physiologic role as an antioxidant by protecting sulfhydryl groups against oxidation and by inhibiting the production of reactive oxygen by transition metals [37].

The initial event in acetaminophen induced toxicity is a toxic-metabolic injury leading to cellular death by necrosis and apoptosis. This results in secondary activation of the innate immune response involving up-regulation of inflammatory cytokines with activation of natural killer (NK) cells, NKT cells, and neutrophils [38]. Previous reports have shown that inhibition of oxidative stress is involved in zinc protective action" [39- 41]. Cellular zinc exits in only one redox state (II); thus, it cannot undergo redox reactions that are commonly responsible for the generation of reactive oxygen species, but zinc also has the ability to reduce OH- formation and preserve cellular thiol pools [42]. Reactive

oxygen species can directly affect the conformation and/or activities of all sulfhydryl-containing molecules, including transcription factors, by oxidation of their thiol moiety [43].

Thus, the antioxidant action of zinc could lead to protection against oxidative stress-induced alterations in transcription factors. Increasing evidences indicate that cellular zinc status is a critical regulator in gene expression and function of zinc finger transcription factors" such as peroxisome proliferator-activated receptor (PPAR), Erg-1, and P53 [44]. Zinc also has an important role in modulation of transcription factors that do not contain structural zinc, such as nuclear factor-kappaB (NF-κB) and activator protein (AP)-1 [45].

Zinc treatment has been shown to attenuate TNF–α induced interleukin 8 production by endothelial cells through inhibition of redox-sensitive transcription factors, NF-κB and AP-1 [46]. Zinc treatment also has been shown to suppress generation of reactive oxygen species and activation of NF-κB and AP-l in endothelial cells in response to linoleic acid or TNF-α treatment [45]. Other studies have demonstrated that zinc supplementation prevents spontaneous and experimentally induced diabetes through regulation of NF-κB and AP-l in the pancreas of mice [47, 48]. Therefore, regulation of transcription factors may be an important mechanism of Zinc protective action [1].

Zinc has been shown to protect animals from the subacute and subchronic toxicity of metals such as cadmium, mercury and chromium [49]. It is an integral part of many metalloenzymes, and is believed to stabilize membranes and protect cells against free radical injury and apoptosis and it is an essential oligo element for cell growth and cell survival [50]. It also controls the activity of zinc-metalloenzymes, which participate in cell metabolism, and plays an essential structural function in zinc requiring proteins that influence gene expression at different stages of cell proliferation and death [51]. On the other hand, it is reported that zinc supplementation prevented ethanol induced decreases in glutathione concentration in the liver [41]. Furthermore, zinc supplementation caused a decrease in lipid peroxidation (as a marker of Oxidative stress), together with an increase in metallothionein concentration in alcoholic rats [52]. Moreover, Zhou *et al.* [41] reported that, zinc sulfate supplementation has a protective effect against lipid peroxidation in the liver.

CONCLUSION

Biochemical evaluation revealed that zinc aspartate has a partial protective effect against acetaminophen induced hepato-renal toxicity and oxidative stress. Accordingly, zinc may be a therapeutic agent in prevention and treatment of acetaminophen hepatotoxicity, nephrotoxicity and free radical formation.

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مجلة البحوث الإشعاعية
والعلوم التطبيقية
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التأثير الواقى للزنك أسبرتيت فى حماية الكبد و الكلى من التأثير السام لعقار الاسيتامينوفين فى الجرذان

إيهاب توفيق محمد ، عمرو إبراهيم سعيد ، سامر عبد الفتاح السيد

قسم البحوث الصحية– المركز القومي لبحوث و تكنولوجيا الإشعاع – هيئة الطاقة الذرية.

يعد عنصر الزنك من العناصر الأساسية فى جسم الإنسان والزنك مكونا أساسيا فى ١٢٠ إنزيم داخل الجسم أهمهم الإنزيمات المضادة للأكسدة. وتتركز أهمية الزنك كمضاد للأكسدة حيث يعادل الشوارد الحرة التى قد تسبب تدميرا للخلايا. يستخدم عقار الاسيتامينوفين كمسكن للألم وكخافض للحرارة و لكن له أثار جانبية كثيرة على الكبد والكلى إذا أعطى كجرعات زائدة للإنسان أو الحيوان.

و لهذا صممت هذه الدراسة للوقوف على مدى تأثير الزنك اسبرتيت كعنصر حماية من التسمم بالجرعة الزائدة من عقار الاسيتامينوفين فيما يخص الكبد والكلى. وقد أجريت الدراسة على ٣٢ من ذكور الجرذان البيضاء وقسمت إلى أربع مجموعات كما يلى:- المجموعة الأولى وهى المجموعة الضابطة والمجموعة الثانية وهى مجموعة تم حقنها بالزنك اسبرتيت والمجموعة الثالثة وهى مجموعة تمت معالجتها بجرعة زائدة من عقار الاسيتامينوفين عن طريق الفم والمجموعة الرابعة تمت معالجتها بنفس العقار مع حقنها بالزنك فى التجويف البريتونى بعد ساعة.

وقد أجريت على كل المجموعات التحاليل الخاصة بدراسة مدى كفاءة وظائف الكبد وأهمها مستويات إنزيمات الكبد ومستويات الصفراء المباشرة فى مصل الدم وأيضا التحاليل الخاصة بدراسة مدى كفاءة وظائف الكلى مثل مستويات نيتروجين اليوريا والكرياتينين وحمض اليوريك فى مصل الدم وأيضا تم قياس نشاط إنزيم الزانثين اكسيديز ، والجلوتاثيون ، ومستوى أكسيد النيتروجين، والملونالدهيد.

وقد وجد أن مجموعة الجرذان التى تم حقنها بعقار الاسيتامينوفين بها زيادة معنوية في مستويات إنزيمات الكبد و فى نسبة الصفراء المباشرة فى مصل الدم كما وجد زيادة معنوية في مستويات كل من نيتروجين اليوريا والكرياتينين مع عدم حدوث تغير فى مستويات حمض اليوريك فى مصل الدم. وجد أيضا زيادة فى نشاط إنزيم الزانثين اكسيديز، و فى مستوى الملونالدهيد ومن جهة أخرى وجد نقص معنوى فى مستوى أكسيد النيتروجين ، وفى نشاط الجلوتاثيون فى مصل الدم. وقد تحسنت المجموعة التى تم حقنها بالزنك اسبرتيت بعد عقار الاسيتامينوفين تحسنا ملحوظا فى جميع القياسات التى تم إجرائها بالمقارنة بالمجموعة التى تمت معالجتها بجرعة زائدة من عقار الاسيتامينوفين.

بناءا على هذه النتائج نستنتج أن تناول الزنك يحمى الكبد والكلى من التأثير الضار للجرعات الزائدة أثناء العلاج بالعقاقير المسكنة و الخافضة للحرارة وبخاصة عقار الاسيتامينوفين.