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The Ability of Vitamin A, Alone or in Combination with Vitamins C and E, in Ameliorating the Side Effects of Penicillin and Streptomycin on Hepatic Damage in Guinea Pigs

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Abstract

The administration of vitamin A (10000 IU/kg b.w), vitamin A, C and E (10000 IU/kg, 100 mg/kg 100 mg/kg b.w), penicillin (50000 IU/kg b.w), penicillin + vitamin A, penicillin + vitamin A, C and E, streptomycin (50 mg/kg b.w), streptomycin + vitamin A, streptomycin + vitamins A, C and E for 30 days caused a significant increase in the levels of AST, ALT and ALP, and also caused a significant decrease in the levels of total protein and albumin in penicillin and streptomycin treated groups. However, co-administration of penicillin and streptomycin with vitamin A alone or in combination with vitamins C and E ameliorated the harmful effects of penicillin and streptomycin in most of the tested parameters. Vitamin A, either alone or in combination with vitamin C and E, has a protective effect on the histological changes of liver tissues induced either by penicillin or streptomycin administration. The result of the present work reveals for the first time that vitamin A alone or in combination with vitamin C and E plays an important role as cytoprotective compounds on hepatic damage in guinea pigs. Hence, further studies on the possible uses of vitamins as protective compounds during treatment with antibiotics are needed.

Keywords: Vitamin A Alone, Vitamins A, C And E, Penicillin, Streptomycin, Histological And Biochemical Study.

1. Introduction

Antibiotics constitute a family of drug, which taken as a group, represents one of the most frequently prescribed around the world. Thus, not surprisingly antibiotic list on the top of causes of drug induced many side effects (Maliha *et al.*, 2009). The effects of penicillin and streptomycin on histological structure and function of liver are well studied (Al-Awar *et al*., 2013 and Akande *et al*., 2012). It has been reported that effects of aminoglycoside and β-Lactams are mainly due to the generation of an excessive amount of reactive oxygen species (ROS), resulting in the detrimental effects of the cellular antioxidant defense system as well as the enhancement of the lipid peroxidation (LPO) process (Westphal *et al*., 1994; Sha and Schacht 1999; and Goldstein and Ishak 1999).

Antioxidants protect key cell components from damage by neutralizing the free radicals (Dekkers *et al*., 1996). Antioxidants that occur naturally in the body or that are consumed through the diet may block damage to cells (Cherubini *et al.*, 2005). Therefore, supplementation of antioxidants can be considered as the alternative method for chelation therapy. In fact, several studies demonstrated that the cellular antioxidant activity is reinforced by the presence of dietary antioxidants (Prior and Cao, 2000). Accordingly, interest has recently grown in the role of natural antioxidants used as a strategy to prevent oxidative damage as a factor in the pathophysiology of various health disorders (Shireen *et al.*, 2008). Among antioxidants, vitamins A, C and E have the ability to counteract free radicals and protect the structure and function of proteins, DNA and chromosomes against oxidation injury, and they are the most powerful in reducing storage and toxicity of reactive oxygen species (Seham and Awatef, 2008). In this regard, studies on vitamins A, C and E added to diet are promising, mainly due to their antiradical activity, indicating that they could provide an important dietary source of antioxidants. Many studies indicate to protective effects of vitamins A, C and E against many alteration caused by organophosphate insecticides and some medicines that induced hepatotoxicity (Velanganni and Balasundaram, 2003; and Ukpanukpong *et al*., 2013). No data were available in the literature related to the

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protective effect of vitamin A alone or in combination against the side effect of antibiotics (penicillin and streptomycin) on hepatotoxicity. The present study is the first study undertaken to investigate the ability of vitamin A alone or in combination with vitamins C and E to ameliorate the side effect of antibiotics (penicillin and streptomycin) on hepatic damage in guinea pigs.

2. Materials and Methods

2.1. Animals

For this experiment, eighty male guinea pigs (5-6 months old) weighing between 800 - 900 g were obtained from the Zoo, Sana'a, Yemen. The animals were housed in plastic cages in the animal house of the Department of Biology- Faculty of Science- Sana'a University, under standard conditions in room temperature, fed a standard laboratory diet and water *ad libitum*. The animals were allowed to acclimatize to the laboratory environment for 30 days. All animal experiments were carried out in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institute of Health (NIH, 1978), and were approved by the Animal Experiments Local Ethics Committee at the Zoo, Sana'a, Yemen.

2.2. Drugs and Chemicals

Penicillin (Procaine G penicillin) and streptomycin were obtained from Ave Group-USA-Colombia-Mexico. Vitamin A (Retinol Assay:99 Appearance: Slightly yellow solid Formula: C20H30O Molecular Weight: 286.50) was supplied by Look for chemical (Hangzhou, China). Vitamin C ((L-) ascorbic acid Assay: 99%-100% Appearance: White crystalline powder Formula: C6H8O6 Molecular Weight: 176.14) was supplied by Carlo Erbo (Milano, Italy). Vitamin E (DL-alpha- tocopherol acetate Assay: 96% Appearance: low yellow powder Formula:C29H50O2 Molecular Weight: 430.71) was supplied by Merck (Germany).

2.3. Experimental Animals

Eighty adult male guinea pigs were divided randomly into 9 groups. Animals that received vitamins were administrated orally, whereas those that received antibiotics were administered intraperitoneally (i.p). Penicillin, streptomycin and vitamin C were dissolved in distilled water, while vitamin A and vitamin E were dissolved in corn oil. Treatments were carried out over a period of 30 days. Treatment groups were as follows:

Group 1: 10 animals received 0.5 ml/kg b.w corn oil orally and served as control.
Group 2: 5 animals treated with vitamin A (10000 IU/kg b.w).
Group 3: 5 animals treated with vitamins A, C and E (10000 UI/kg ,100 mg/kg & 100 mg/kg b.w), respectively.
Group 4: 10 animals treated with penicillin (50000 IU/kg b.w).
Group 5: 10 animals treated with penicillin (50000 IU/kg b.w) + vitamin A (10000 UI/kg b.w).
Group 6: 10 animals treated with penicillin (50000 IU/kg b.w) + vitamins A, C and E (10000 UI/kg ,100 mg/kg & 100 mg/kg b.w), respectively.
Group 7: 10 animals treated with streptomycin (50 mg/kg b.w).
Group 8: animals treated with streptomycin (50 mg/kg b.w) + vitamin A (10000 UI/kg b.w).
Group 9: 10 animals treated with streptomycin (50 mg/kg b.w) + vitamins A, C and E (10000 UI/kg ,100 mg/kg & 100 mg/kg b.w), respectively.

2.4. Collection the Blood and Tissue

24 h after last administration, animals of each group were autopsied; blood samples were taken from the heart and collected into sterile tubes centrifuged at rpm for 20 min, and serum was separated for biochemical tests. The liver of each guinea pig removed, small pieces of liver were taken, then fixed in 10% neutral formalin for 24 hours and were kept in alcohol for the tissue preparation.

2.5. Estimation of Liver Function

Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), Alkaline Phosphatase (ALP), Total protein and albumin were measured by spectrophotometry in serum using Spinreact commercial kits.

2.6. Histological Studies Liver

The liver specimens of each guinea pig were dehydrated in series of alcohol concentrations 80%, 90% and 100%, then cleared in xylene, embedded in paraffin wax at 58 °C. Blocks were cut at 4-5 µm thickness by using rotary microtome (Leica, Germany) and stained with hematoxylin and eosin (Humason 1979) for histopathological examination under light microscope.

2.7. Statistical Analysis

The data were analyzed using SPSS 16.0 for windows. A statistical analysis was performed using one-way Analysis of Variance (ANOVA), followed by Fisher's Protected Least Significant Difference (PLSD) test as a post hoc test for the comparison between the groups. All values were expressed as means ± SD. Differences were considered significant if $p< 0.05$.

3. Results

3.1. Biochemical results

Data in tables 1 and 2 shows that the treatment of penicillin and streptomycin resulted in a statistically high significant increase in the levels of ALT, AST and ALP in the serum of both treated groups, as compared to the control; this increase was higher in the streptomycin treated guinea pigs.

As shown in tables 1 and 2, the level of the total protein and albumin in the serum of guinea pigs, treated with penicillin and streptomycin, statistically shows a highly significant decrease compared to the control.

Data in tables 1 and 2 also shows that the treatment with vitamin A alone for 30 days in group 2 showed comparable results to the control regarding the levels of AST, ALT, ALP, albumin and total protein. The co-administration of vitamin A with penicillin in group 5 or

with streptomycin in group 8 caused a low significant increase in the level of AST, ALT and ALP, as compared to that of the control group. Meanwhile, results showed a low significant decrease in the level of the total protein and albumin as noticed in the serum of the treated guinea pigs in comparison to that of the control group.

Results in table 2 revealed that the treatment with Vitamins A, C and E in combination (group 3) gave comparable results to those of the control regarding the levels of AST, ALT, ALP, albumin and total protein.

The improvement in the tested biochemical parameters insured that vitamins A, C and E in combination have a protective role against the side effects of penicillin and streptomycin on liver. The co-administration of vitamins A, C and E in combination beside penicillin in group 6 or streptomycin in group 9 resulted in a non-significant increase in the level of AST, ALT and ALP as compared to that of the control group. Meanwhile, a non-significant decrease occurred in that total protein and albumin, as compared to that of the control group, as shown in table 2.

Table 1. The protective effect of vitamin A alone to reduce the adverse effects induced by penicillin and streptomycin on liver function tests of guinea pigs.

Treatment / **Parameter**	**Control C.Oil for 30days**	**Vit A for 30 days**	**Penicillin for 30days**	**Vit A & P for 30 days**	**Streptomycin for 30days**	**Vit A & S for 30days**
AST	22.86±2.49	21.90±0.9	46.88±4.9†††	29.14±2.2$^{\#\#\#\dagger}$	60.35±6.8†††	33.18±3.9***†
IU/L	……..	0.2%	113.6%	32.8%	174.9%	51.2%
ALT	27.82±1.21	29.07±1.8	63.06±5.6†††	34.41±3.5$^{\#\#\#\dagger}$	79.36±3.5†††	38.41±3.4***†
IU/L	……..	6.1%	130.1%	25.5%	189.5%	40.1%
ALP	53.03±2.28	53.69±1.6	78.06±4.3†††	58.44±3.5$^{\#\#\#\dagger}$	88.46±3.4†††	60.11±3.7***†
IU/L	……..	1.4%	47.5%	10.5%	67.2%	13.6%
Total protein	7.64±0.20	7.57±0.13	6.03±0.45†††	7.03±0.36$^{\#\#\#\dagger}$	5.44±0.35†††	7.01±0.26***
g/dl	……..	0.7%	19.8%	6.5%	27.27%	6.8%
Albumin	3.83±0.16	3.60±0.34	29.6±0.18†††	3.42±0.24$^{\#\#\#\dagger}$	2.29±0.12†††	3.08±0.15***
g/dl	……..	4.7%	21.7%	9.5%	39.4%	18.5%

Values are expressed as means ± SD; percentage of difference with control group. Comparisons are made between each group and (†): control group; (#): only penicillin treated group; (*): only streptomycin treated group**.**

Table 2. The protective effect of vitamin A,C and E in combination to reduce the side effects induced by penicillin and streptomycin on liver function tests of guinea pigs.

Treatment / **Parameter**	**Control. C.Oil for 30days**	**Vit A,C, E for 30days**	**Penicillin for 30days**	**Vit A,C, E & P for 30days**	**Streptomycin for 30days**	**Vit A,C, E & S for 30days**
AST	22.86±2.49	20.35±1.2	46.88±4.9†††	22.29±2.7$^{\#\#\#}$	60.35±6.8†††	23.13±2.1***
IU/L	……..	7.3%	113.6%	1.5%	174.9%	5.3%
ALT	27.82±1.21	26.75±1.7	63.06±5.6†††	30.23±2.2$^{\#\#\#\dagger}$	79.36±3.5†††	32.57±3.4***†
IU/L	……..	2.4%	130.1%	10.3%	189.5%	18.8%
ALP	53.03±2.28	53.78±2.0	78.06±4.3†††	52.63±3.0$^{\#\#\#}$	88.46±3.4†††	53.80±3.0***
IU/L	……..	1.6%	47.5%	0.5%	67.2%	1.7%
Total protein	7.64±0.20	7.70±0.20	6.03±0.45†††	7.50±0.14$^{\#\#\#}$	5.44±0.35†††	7.48±0.32***
g/dl	……..	2.4%	19.8%	0.3%	27.27%	0.5%
Albumin	3.83±0.16	3.93±0.41	29.6±0.18†††	3.71±0.20$^{\#\#\#}$	2.29±0.12†††	3.28±0.11***
g/dl	……..	4%	21.7%	1.9%	39.4%	13.2%

Values are expressed as means ± SD; percentage of difference with control group. Comparisons are made between each group and (†): control group; (#): only penicillin treated group; (*): only streptomycin treated group**.**

3.2. Histological Results

Examination of the section in the liver of control guinea pigs (Figure 1a), showed that the hepatic exhibits a normal architecture of the hepatocytes presenting a homogenous cytoplasm and a large spherical nucleus containing one or more nucleolus and a variable amount of dispersed and peripheral heterochromatin. Hepatocytes were arranged in trabecules running radiantly from the central vein and were separated by sinusoid containing kupffer cells. The lumen of sinusoid contained mainly erythrocytes and white blood cells.

Light microscopic examination of the liver after administration of vitamin A alone (Figure 1b) and vitamins A,C and E in combination for 30 days (Figure 2c) revealed a normal picture as in control group.

Histological examination of the liver after administration of penicillin and streptomycin for 30 days showed obvious histological changes in the form of distortion in the hepatic organization, dilatation and congestion of the blood sinusoids and central vein, neutrophils infiltration, hemorrhage, congestion and hyperplasia of the bile duct wall, as well as necrosis, vasodilatation and thickening in the central vein (Figures 2 a, b, c, d and f).

The administration of vitamin A or vitamins A, C and E in combination plus penicillin for 30 days (Figures 3a and 4a), respectively, and the administration of vitamin A or vitamins A, C and E in combination besides streptomycin (Figures 3b and 4b), respectively, revealed a normal structure as in control group.

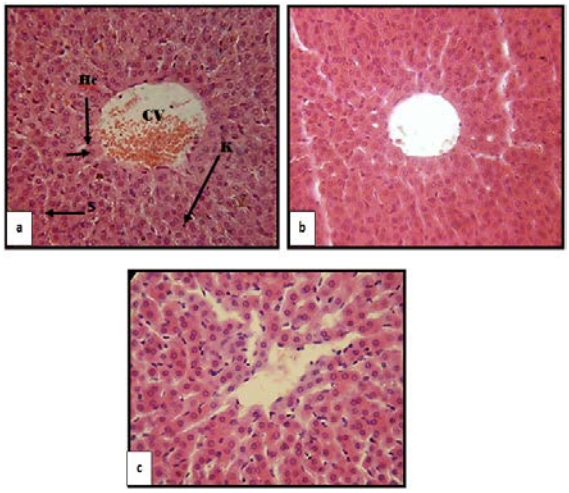

Figure 1. Light micrograph of section in the liver of guinea pigs. **(a):** control group showing a normal architecture without pathological alterations. Hepatocyte (Hc), Spherical nucleus (arrow), Sinusoids (S), Blood vessel (BV), and Kupffer cells (K). **(b):** Vitamin A; **(c):** vitamin A, C and E in combination, showed normal liver structure as in control group. (HE) stain (X400).

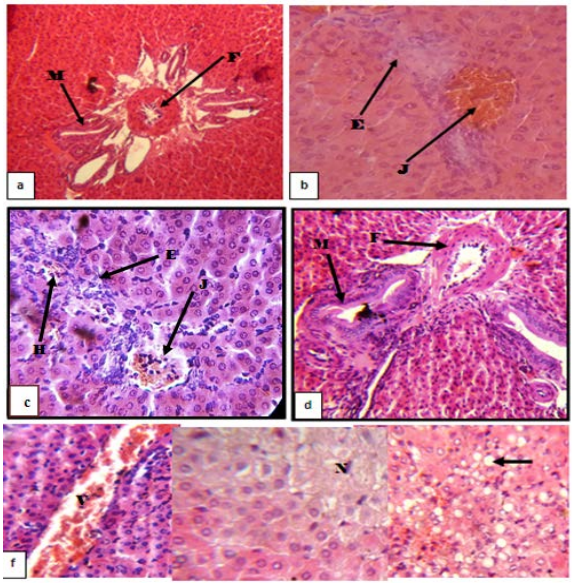

Figure 2. Light micrograph of section in the liver of guinea pigs. **(a,b,f):** Penicillin; **(c,d,f):** Streptomycin; showing obvious histopathological changes. Hemorrhage (H), Congestion (J), Inflammatory cells infiltration (E), Thickening in the central vein (F), Hyperplasia (M), Fatty changes (arrow), Necrosis (N), Vasodilatation (V). (HE) stain (X400).

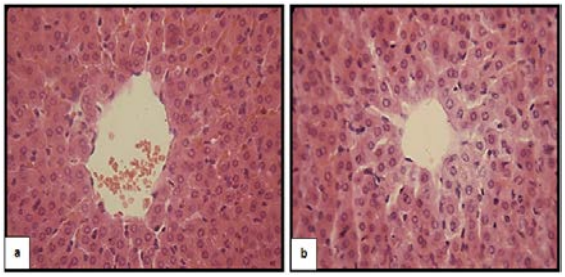

Figure 3. Light micrograph of section in the liver of guinea pigs. **(a):** Penicillin+ vitamin A; **(b)** Streptomycin +vitamin A; showing a normal liver structure as in control group. (HE) stain (X400).

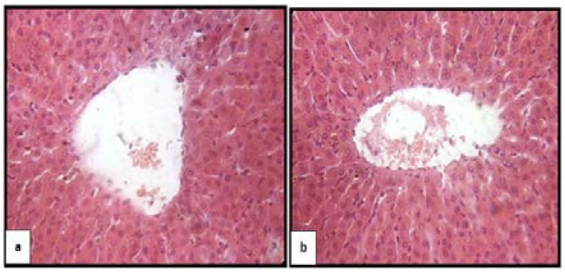

Figure 4. Light micrograph of section in the liver of guinea pigs. **(a):** Penicillin+ vitamins A,C,E in combination; **(b)** Streptomycin + vitamins A,C,E in combination; showing a normal liver structure as in control group. (HE) stain (X400).

4. Discussion

Our results clearly show the hepatotoxic effects of penicillin and streptomycin. The administration of penicillin and streptomycin caused marked increases in the enzymes AST, ALT and ALP as compared to those of the control. These results may indicate degenerative changes and hypo-function of liver (Adebajo *et al.*, 2009) as well as hepatic cell necrosis (Singh *et al.*, 2005), which increases the releasing of these enzymes in the blood stream (Jaramillo-Jurez *et al.*, 2008). Elevated levels of these enzymes in the serum are presumptive markers of drug-induced necrotic lesions in the hepatocytes (Singh *et al.*, 2005). The enhanced susceptibility of hepatocyte cell membrane to drug-induced peroxidative damage might have resulted in an increase releasing of these diagnostic marker enzymes into the systemic circulation. Our observations are highly supported by other studies suggesting the effect of penicillin and streptomycin on liver function tests (Alqadhi 2010; Akande *et al.*, 2012; Al-Awar *et al.*, 2013 and Al-Shaibani *et al.*, 2013).

Our present study also shows that administering penicillin or streptomycin to guinea pigs results in a significant decrease in the level of total protein and albumin compared with the control group. The decrease in the total protein and albumin recorded in the present study is supported by the results reported by Austin *et al.* (1993), Akande *et al.* (2012), Al-Awar *et al.* (2013), and Al-Shaibani *et al.* (2013). The reduction of the total protein and albumin levels indicates that the administration of drugs has caused an impairment of liver function, e.g. its capacity to synthesize albumin from the hepatic parenchyma. Khan *et al.* (2002) reported that there was a differential binding of penicillin and streptomycin with serum albumin, while Salih *et al.* (2008) observed that albumin secretion of gel entrapped hepatocytes was reduced by penicillin and streptomycin.

The mechanism of penicillins and aminoglycosides induced hepatotoxicity is found to be mediated through oxidative stress by free radical that cause damage to hepatocytes (Goldstein and Ishak (1974) and Sherlock and Dooley (2002)). AST, ALT and ALP increase in hepatic damage due to leakage of enzymes from the damaged hepatocytes into vascular compartment. Liver damage leads to a decrease in synthetic capability, leading to a fall in serum total protein and albumin levels (Sherlock and Dooley, 2002).

The present investigation clearly demonstrated that the injection of penicillin and streptomycin to guinea pigs had induced conspicuous alteration in the histological structure on the liver tissue in the treated guinea pigs. Our results are in agreement with those of Austin *et al.*, (1993), Al-Awar *et al.* (2013) and Al-Shaibani *et al.* (2013).

Histopathological changes in liver cells following injection of penicillin were the marked changes occurring in the liver in this study. This feature could be explained according to the suggestions of both Tayala *et al.* (2007) and Al-Awar *et al.* (2013). Al-Saibani *et al.* (2013) reported that histopathological changes in liver cells due to free radical generating and free radical scavenging enzymes may be disturbed and leading to disrupt signal transduction pathway and increase the cellular permeability by acting on the membrane phospholipids, resulting into a significant hepatic tissue injury.

The antioxidant activities are related to a number of different mechanisms, such as free radical-scavenging, hydrogen- donation, singlet oxygen quenching, metal ion chelation, and acting as a substrate for radicals such as superoxide and hydroxyle (Robards *et al.*, 1999). In the present investigation it was observed that the activities of these enzymes were reduced after the treatment by vitamin A alone or vitamin A in combination with vitamins C and E, when compared to penicillin and streptomycin treated guinea pigs alone. The penicillin and streptomycin induced oxidative stress has lowered, on hypothesis to explain the beneficial effects of vitamins A, C and E in ameliorating biochemical parameters and histological changes is that vitamins A, C and E considered antioxidant, scavenging and eliminating free radicals (Awodele *et al.*, 2010; Al-Awthan *et al.*, 2012). Recently, it has been found that vitamins A, C and E lead to increasing the levels of total protein and albumin in biological fluids and to reduce liver enzymes, such as AST, ALT and ALP in serum (Al-Awthan *et al.*, 2012; Ganesh *et al.*, 2012). vitamins A, C and E showed a significant improvement in liver tissues. Our results showed that vitamin A alone or in Combination with vitamins C and E administration decreased these histopathological changes. The structure of liver and hepatocytes appearance were more or less similar to control group as well its function. Vitamin A, in Combination with vitamins C and E, was more effective than vitamin A alone, which is consistent with Tarladacalisir *et al.* (2005), Seham and Awatef (2008), Awodele *et al.* (2010) and Ukpanukpong *et al.* (2013) . In conclusion, we suggest that a combination of vitamin A with vitamins C and E is more effective than vitamin A alone for ameliorating the side effects of antibiotics (penicillin and streptomycin) on hepatic damage. Also, the present study concludes that the pathological changes in biochemical parameters as well as liver tissue structure are higher in the streptomycin treated guinea pigs than in the penicillin treated groups.

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