International Journal of Academic Multidisciplinary Research (IJAMR)
ISSN: 2000-006X
Vol. 3 Issue 3, March – 2019, Pages: 21-24

Regulation of Trace Elements by Vitamin A in Paracetamol-induced Liver Toxicity in Rats

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Abstract: *This study was aiming to determine the effect of the Vitamin A on paracetamol-induced hepatotoxicity. Fifteen rats were randomly divided into five groups; (three rats each) control group, paracetamol (1000 mg/kg body weight) was used to induce hepatotoxicity in albino rats. Vitamin A (Retinyl palmtate) administered at the dose levels of 100, 500 and1000 IU/kg body weights orally for 7 days prior to paracetamol dose. Hepatic toxicity was observed in paracetamol group; aspartate aminotransaminase (AST) level was high as compared with control group (p = 0.003). The significant hepatoprotective effect of Vitamin A was observed at doses 500 and 1000 IU/kg body weight, as there was significant reduction of serum AST when compared to paracetamol group (p = 0.01 and 0.003 respectivly), where 100 IU/Kg vitamin A not significantly decrease AST. Liver trace element determined by X-ray fluorescence (XRF) (K, Ca, Fe, Cu, Zn and Rb) in paracetamol-treated group were found to be higher than that of the control group, although the only significant increase was observed with Cu. Br shows slight decrease compared to the control group. There were no significant differences between Vitamin A groups (100 mg/kg 500mg/kg and 1000mg/kg) and PCM-treated group in the liver tissue content of Ca, K, Zn, Cu, Rb and Br where Fe concentrations were significantly decrease at doses 500 and 1000IU/l (P value 0.05 and 0.045 respectively). Vitamin A shows protective effect by regulating liver tissue Fe. We recommend to perform further investigation on the mechanisms of Vitamin A hepatoprotective mechanisms of action.*

Keyword: Vitamin A, Paracetamol, Hepatoprotective, Trace element

1. INTRODUCTION:

Vitamin A and its metabolites (Retinoids) are potent natural regulators , it is one of the fat soluble vitamins, and plays an important role in vision, reproduction, immune function, cell proliferation, differentiation, apoptosis, as well as cell growth and communication (1). The concentrations of constituent elements in animal organs and tissues are sometimes good indicators of the physiological and pathological conditions of the animals(2). It is estimated that 98% of the body mass of man is made up of nine nonmetallic elements.(3).The four main electrolytes namely sodium, magnesium, potassium, and calcium constitute about 1.89%, while the rest 0.02% or 8.6 g of an average human adults is made up of 11 typical trace elements(4). Most of them mediate vital biochemical reactions by acting as a cofactor or catalyst for many enzymes. They also act as centers of building stabilizing structures such as enzymes and proteins. The accumulation of metals or deficiency of these elements may stimulate an alternate pathway which might produce diseases (5). In this study we investigate the hepatoprotective mechanisms of vitamin A.

2. MATERIALS AND METHODS:

Paracetamol (PCM) was obtained from local market, Khartoum, Sudan, Amipharma Laboratories Ltd. It was dissolved in distilled water and administered orally as a single dose of 1000 mg/kg body weight.
Vitamin "A": Was obtained from local market, Kahira Pharm & Chem.ind.co. It was dissolved in olive oil and given daily as an oral dose of 1000mg/kg.
Study Design: fifteen healthy, albino Wister male rats with an average weight of 100gm were selected for this study and randomly divided into five groups (3 rats in each). In the normal control group 1, the rats received no treatment during the experimental period. Group 2 received a single oral dose of 1000mg/kg PCM at day 7. Rats in group 3, 4 and 5 received single daily doses of 100, 500 and 1000 IU/kg body weight of Vitamin A, respectively, for one week and on day 7 they received a single oral dose of PCM of 1000mg/kg body weight, then all rats in all groups were sacrificed at day 8.

3. PREPARATION OF SAMPLES:

Blood Sample: blood samples collected from rats were centrifuged at 3000 rpm at room temperature for 15 minutes and the clear serum samples were

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aspirated and stored in a freezer set at 4°C for spectrophotometric measurement of serum AST, using assay kit from Biosystems, Spain.

Liver Specimen: A section of liver was dissected out of each animal and dried at -50°C for approximately 24 h in a freeze dryer and used for trace elements analysis by using X-ray fluorescence (XRF) technique.

Statistical Analysis: Statistical analysis was performed using Statistical Package for Social Science version 22, and Microsoft Excel Worksheet 2010. Results were expressed as mean ± SD or mean ± SE. Independent T-test was used to compare different studied parameters between groups. P-value of ≤ 0.05 considered significant.

4. RESULTS:

The mean enzymatic activity of serum AST in control group was significantly different when compared to that of the PCM group (P = 0.003). The mean activities of AST in groups 1(100IU/kg) was found to be decreased but not statistically significant when compared to the PCM group (p values = 0.15), where (500 and 1000 IUg/kg) were found to be significantly decreased when compared to the PCM group (p = 0.01 and 0.003 respectively) as shown below in figure (1).

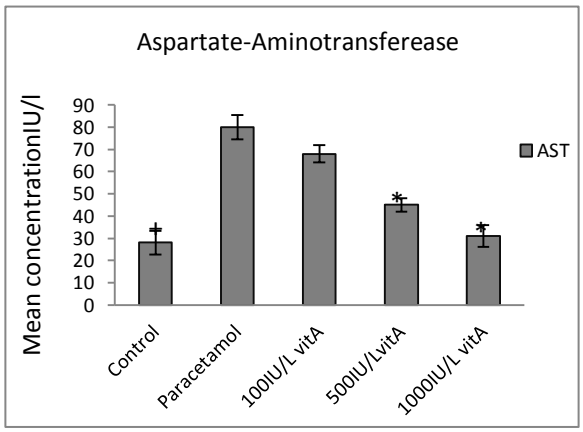

Figure 1: Effect of (different doses of Vitamin A + PCM) on serum AST levels compared to control group and PCM group. Results are expressed as mean ± SE. * indicate the significant difference between the PCM and Vitamin A-treated groups. + indicate the significant difference between the PCM and control groups.

The mean concentrations of K, Ca, Fe, Cu, Zn and Rb in paracetamol-treated group were found to be higher than that of the control group, although the only significant increase was observed with Cu. Br shows slight decrease compared to the control group as shown in table (1).

Table(1): Mean concentration of K, Ca, Fe, Cu, Zn, Br, Rb in control group and PCM group. Results are expressed as mean ± STD.

Element	Control group	PCM-treated group	P value
K	9923 ± 2846	10760 ± 2200	0.78
Ca	1373 ± 135	1537 ± 499	0.67
Fe	760 ± 302	814 ± 151	0.76
Cu	2.33 ± 0.84	3.14 ± 0.58	0.04
Zn	49.8 ± 19.6	82.30 ± 25. 0	0.09
Rb	54.1 ± 20.4	58.2 ± 14.97	0.69
Br	9.7 ± 1.4	7.57 ± 2.97	0.17

There were no significant differences in Vitamin A-treated groups (100 IU/kg 500IU/kg and 1000IU/kg) when compared to the PCM-treated group in the liver tissue content of Ca, K, Zn, Cu, Rb and Br as shown in Figures (2,3,4,5). Only significant dose dependent decrease was noticed with Fe mean concentration at dose 500 and 1000 IU/kg b.w (P value 0.05and 0.045) as shown in Figures (4).

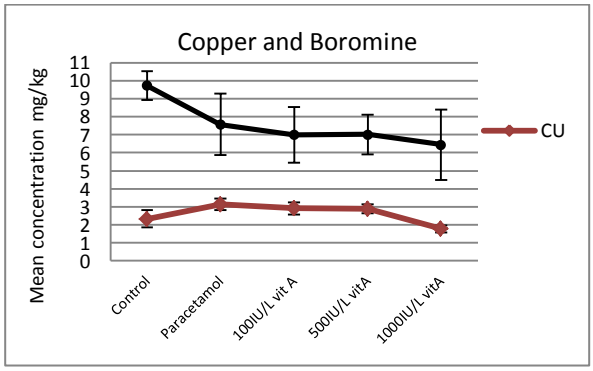

Figure 2: Effect of (different doses of Vitamin A + PCM) on liver Copper and Boromine levels compared to control group and PCM -treated group**.**

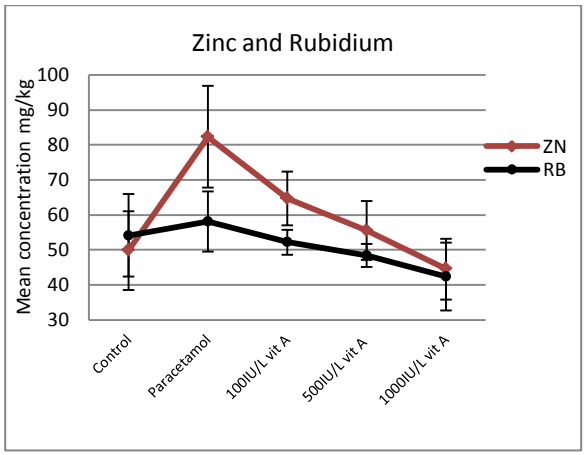

Figure 3: Effect of (different doses of Vitamin A + PCM) on liver Zinc and Rubidium levels compared to control group and PCM induced group.

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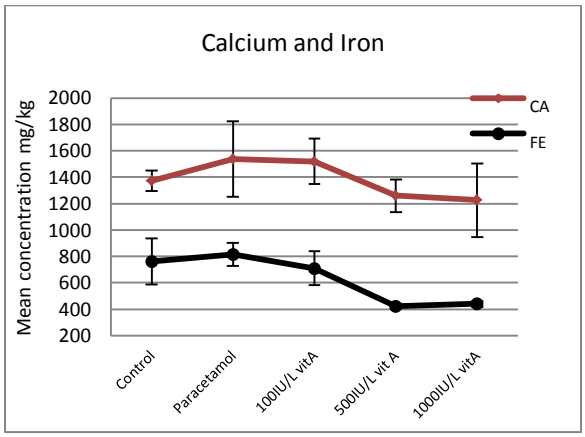

Figure 4: Effect of (different doses of Vitamin A + PCM) on liver Calcium and Iron levels compared to control group and PCM-treated group.

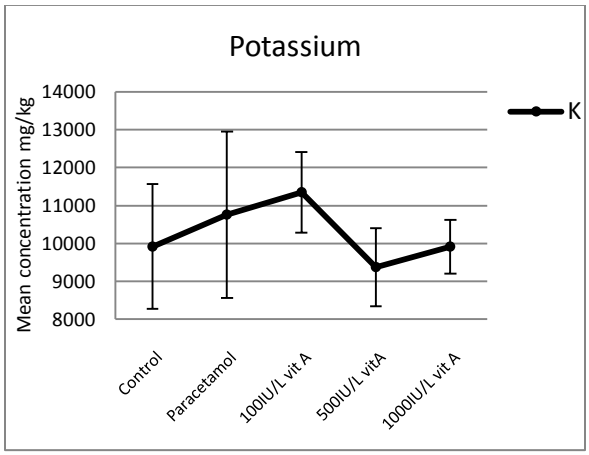

Figure 5: Effect of (different doses of Vitamin A + PCM) on liver potassium levels compared to control group and PCM-treated group.

5. Discussion:

Paracetamol as analgesic/antipyretic is extensively used worldwide. It is known to be toxic and associated with morbidity and mortality when used in overdose amount (6). In liver damage induced by paracetamol or any other causative agent, the determination of enzyme activities such as ALT and AST is largely used. The data obtained from the current study, revealed that the administration of Vitamin A in rats prior to treatment by paracetamol decreases the serum AST activity when compared with paracetamol-treated group (Figure1).Witch mean that vitamin A has hepatoprotective antioxidant activity. Paracetamol is well known of its ability to induce damage to the structural integrity of the liver and since AST is an intracellular enzyme, this damage leads to its leakage and release in the circulation. The reduction of AST activity by the Vitamin A indicates either a protective role on hepatocytes from being damaged by paracetamol.

6. Hepatic elements

In the present study the mean concentration of calcium, potassium, iron, copper, zinc and rubidium in pracetamol group is slightly higher than control, whereas the mean concentration of bromium in pracetamol group is slightly lower than control group, this may be due to the toxicity and negative impact of paractamol on the liver metabolism causing disturbances in liver contents of elements. In all Vitamin A treated groups the elements mean concentrations were not significantly changed except Fe means concentration were significant decreases following increased dose of vitamin A indicating that the mechanism of the effect of Vitamin A in liver regeneration is may be by consumption of stored Iron because iron is play central role in DNA and ATP synthesis as well as oxygen transport and different critical action in enzymatic and non-enzymatic processes (7) Cu was significantly increased in paracetamol group; this may be due the involvement of Cu in Cu/Zn superoxide dismutase enzyme as cofactor, which is an antioxidant enzyme act to regulate the oxidant molecules that generated in oxidative stress cases in liver by toxic agents.

7. Conclusion:

Paracetamol-induced liver toxicity increases Cu concentration in liver tissue. Vitamin A showed hepatoprotective effect on paracetamol induced liver damage (low AST) in rat by regulating liver tissue**.**

8. Recommendation:

We recommend to measure other nutrient element like Sodium, Phosphorus, Magnesium, Manganese, Selenium, Sulpher because of their important role in enzyme activation and some of them as cofactors.

9. Acknowledgement

The authors wish to acknowledge with deep appreciation the biochemistry lab member in Sudan Atomic Energy Commission for their technical support.

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