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Research Article

Role of Vitamin D3 in Prevention of Paracetamol Induced Acute Hepatotoxicity in Male Rabbits

Alsaady Malath Azeez*

Pharmacology, College of Dentistry, University of Babylon –Iraq.

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ABSTRACT

Background: Liver is major organ of metabolism, which required to be protected from drugs and their metabolites harmful effect by using substances like vitamins and herbs. Objective: To evaluate vit. D3 protective effect in paracetamol induced hepatotoxicity of male rabbits. Material and method:18 male local rabbits divided to three groups. First group receive paracetamol in three spaced doses for 24 hours to induce acute hepatoxicity while the second group receive vit.D3 as single intramuscular injection 24 hours prior induction of acute hepatoxicity and third group was control without treatment. After 24 hours from paracetamol, induce acute hepatotoxicity blood samples collected to measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and albumin. Results: There were significant elevation ($p \leq 0.05$) in serum liver enzymes of treatment groups in relation to control and non-significant decrease in alanine aminotransferase (ALT), aspartate aminotransferase (AST) of vit.D3 treated group. Conclusion: As conclusion, a model of acute paracetamol induced hepatotoxicity successfully established with no mortality. Although, non-significant vit.D3 possess protective effect in relation to liver function test.

Keywords: Hepatotoxicity, paracetamol, vit.D3.

INTRODUCTION

Liver is major organ of metabolism exhibit various biochemical reactions aimed to detoxify and eliminate various dietary and drugs substances[1]. Preservation of normal liver function is of great interest, proper use of medication, protection from infections that deteriorate hepatocyte function play a role in maintenance of normal liver function however, certain factors like genetic variations and idiosyncratic reactions to drugs difficult to determine. Drug induced hepatotoxicity have great attention due to their ability to cause acute or chronic liver failure. Some drugs or their metabolites associated hepatotoxicity is the main reason for removing from the markets. More than 1000 of drugs known for their hepatotoxicity effect like paracetamol, antibiotics, antiepileptic's, immunosuppressant's, statins and others[2,3,4].

Depletion of reduced glutathione; covalently binding to proteins, lipids, or nucleic acids; or inducing lipid peroxidation in addition to immune reaction have direct or indirect effect on hepatocytes organelles leading to great stresses that impair normal functions causing hepatocyte injury and death[5,6]. Protection of hepatocytes form injury by drugs or other substances is important to decrease drug induced adverse reaction. Many substances implicated to achieve that goal including herbal or vitamins supplements[7]. Previous studies show the efficiency of vitamins like vitamin C. and E in amelioration of drugs induced hepatotoxicity[8,9]. Vitamin D is fat-soluble vitamin necessary for bone health and calcium metabolism also important in modulation of immune response and decrease insulin resistance in type2 diabetes mellitus[10]. Vitamin D is well tolerated with therapeutic dose while in high doses cause hypercalcemia without hepatotoxicity[11]. Many studies show the efficiency of vit.D in protection against oxidative stresses and decrease of lipid peroxidation through binding to its specific receptor in beta cells[12]. In addition to its immune modulating ability in viral hepatitis[13], which encourage further investigations to highlight vit.D protective, role. Now a days using of vit.D supplement in different forms as D3or D2 is important to preserve normal function and prevention[14]. This study was to evaluate the protective effect of vitamin D against paracetamol induced acute hepatotoxicity in male rabbits.

MATERIAL AND METHOD

18 Healthy male rabbits purchased from local market weighing 1000 to 1300 g. included in this study kept in standard rabbit's cages with free access to food and water in animal house of college of medicine, at a constant temperature of 20° ± 1℃ with a 6 am to 6 pm light cycle. The animals randomly divided in to 3 groups according to computer numbering randomization program. Institutional committee approved protocol of experimental design.

Drugs

Paracetamol (Apmol) 500mg/5ml, for I.M, I.V injection (Ajanta.pharma limited, India).

Cholecalciferol (vit.D3).300.000I.U./1ml for injection (Dibase, ABIOGEN PHARMA., Italy).

Study design

*Author for Correspondence: Malathazeez1122@gmail.com

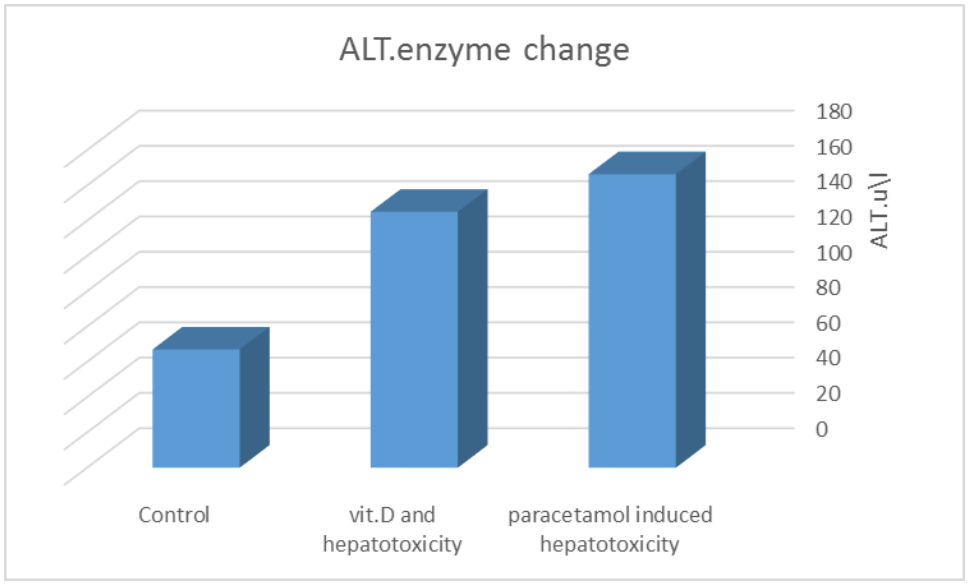

Figure 1: changes of ALT. enzyme by means among treatment groups.

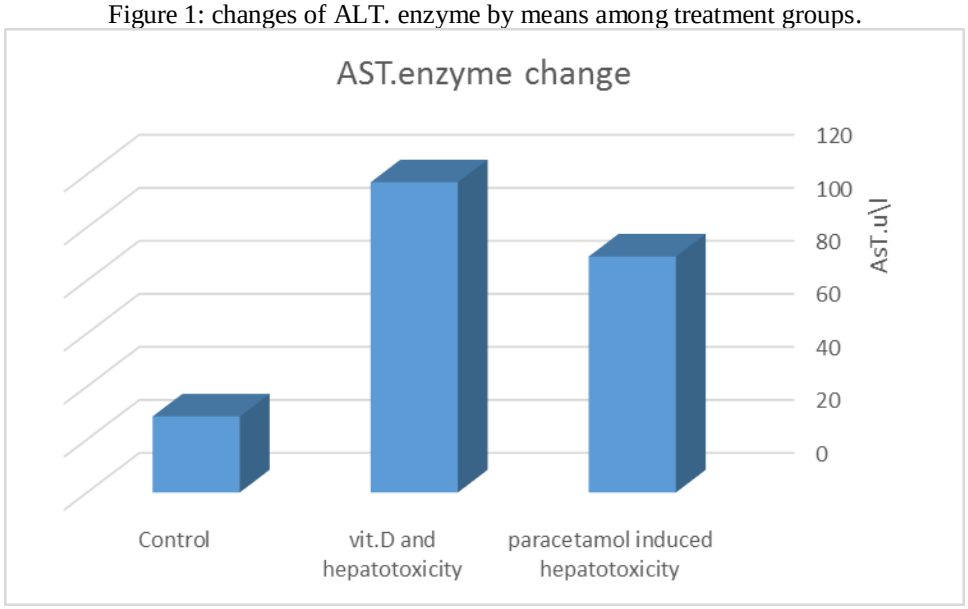

Figure 2: changes of AST. enzyme by means among treatment groups.

Animals randomly divided into three groups as:

Group 1: six rabbits with paracetamol induced hepatotoxicity.

Group 2: six rabbits receive single I.M. injection of vit.D3 about 100.000 I.U. /0.33 ml. 24 hr. before Paracetamol induced hepatotoxicity

Group 3: six rabbits control with no treatment.

Induction of hepatotoxicity

A model of paracetamol induced acute hepatotoxicity made according to (Francavilla et al, 1989)[15] with modification in dose strength; in which three spaced doses of paracetamol intramuscularly injected of 500 mg for each. First dose given at 9 a.m. morning, then after nine hours the second dose administered and 24 hours from the first dose the last paracetamol dose given.

24 hours later, a sample of blood was taken from marginal ear vein 3-5 ml of blood obtained, transferred into a non-heparinized tube, allowed for 30 minutes to clot. Serum separated by centrifugation at 3000 rpm for 20 minutes. 1 ml of fresh serum used for measurement of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), and albumin levels.

Statistical Analysis

Independent-samples Students t test was used to detect differences in liver function test and albumin using SPSS version 22 for analysis of data at level of significance of $p \leq 0.05$.

RESULTS

In this study the model of paracetamol, induced acute hepatotoxicity was successfully obtained with no mortality. There were significant elevation ($p \leq 0.05$) of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) between group 1 and 2 as compared with group 3 (control) table 1 .fig.1, 2.

No significant differences ($p \geq 0.05$) of means observed between group 1 and 2 in alanine aminotransferase (ALT)

Table 1: changes of liver function tests and albumin among study groups expressed by mean ± standard deviation (SD).

Liver enzymes	Group1 paracetamol induced hepatotoxicity	Group2 (vit.D and paracetamol induced hepatotoxicity	Group3 Control no treatment
ALT.u\l	161.333 ± 32.254*	145.0 ±6.082*	67.666 ± 22.722
AST. u\l	89.00 ± 19.052*	117.00 ±20.421*	28.666 ± 2.0816
ALP.u\l	28.333 ± 22.279	50.666 ±18.823	90.666 ± 43.661
Albumin g\l	2.933 ± .378	3.266 ±.153	3.333 ±.11547

*$p \leq 0.05$

and aspartate aminotransferase (AST) with lower levels observed in vit.D treated group as shown in table 1. Also, alkaline phosphatase (ALP), and albumin means show no significant differences
($p \geq 0.05$) between group 1 and 2 table 1.

DISCUSSION

The present study to evaluate vit.D protective effect in paracetamol induced acute hepatotoxicity by observing liver function test changes. We chose Paracetamol as it safe, cheap and widely used analgesic for various types of pain in addition to its ability to induce dose dependent hepatic failure either suicidal or Unintentional for pain or fever leads to daily doses exceeding the 4 g/day[16]. Liver enzymes is important indication of normal hepatocyte function especially ALT. and AST enzymes. The model of acute hepatotoxicity used in this study based on Francavilla and college 1989[15] with increase in paracetamol dose at the same dosing intervals show great success to establish simple model of acute hepatotoxicity in male rabbits with no mortality observed. Using that model is easier for researchers than other models that use paracetamol in large doses orally or intravenously, as these models associated with more animals' mortality due to other causes rather than hepatotoxicity [17]. The current study show significant elevation in ALT and AST enzymes in treated groups as compared to control group. This result prove the successes of our model of acute hepatotoxicity as paracetamol known for its effect on hepatocyte causes necrosis and apoptosis that leads to increase liver enzymes in serum[18]. Non significance differences in liver enzymes observed between vit.D treated group and paracetamol induced hepatotoxicity group although, levels of ALT. was lower in vit.D treated group but fail achieve statistical significance may be due to small sample size or lower amount of vit.D supplements . Vit.D recognized for its ability to ameliorate drug induced toxicity in pancreas and renal system in addition to decrease oxidative stresses and reduces hepatic steatosis[19]. No significance differences in ALP and albumin among study groups and that agree with Chun and college[20] that noticed less increase in ALP in paracetamol induced hepatotoxicity.

CONCLUSION

A model of paracetamol induced acute hepatotoxicity successfully established with no mortality. Although, non-significant vit.D3 possess protective effect in relation to liver function test which require further study to prove

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