Effect of Paracetamol(acetaminophen) Toxicity on Some biochemical Parameters In Albino Rats

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Abstract

Background/aim: Acetaminophen (APAP) overdose results in severe liver damage that may develop into acute liver failure. The goal of this study was to investigate the effect of acetaminophen on liver function due to toxic doses of acetaminophen. Methods:A total of 30 growing rats were divided into two equal groups, 10 rabbits each. The first group control dministered with normal saline and the second group paracetamol -treated rats) for 30 days. Blood samples were withdrawn to measure serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), protein, and bilirubin activities were assayed.Results:In paracetamol -treated group, significant increases in aspartate aminotransferases,and alanin aminotransferases activities, and significant decreases in catalase bilirubin activities levels were determined compared to the control group.Conclusion: paracetamol administration produces noticeable biochemical changes in a dosedependent manner associated with increased liver enzyme.

Keywords: Antioxidant, protein, bilirubin, Paracetamol, ALP.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for various indications. They are generally considered as safe medication, but are also known to cause different adverse events, which potentially limit their use.Paracetamol (PRM); acetaminophen or N-acetyl-p-aminophenol (APAP); is a widely analgesic medication in many countries. An overdose of paracetamol is a frequent reason for liver and renal toxicity and possible death.The exact mechanism of such toxicity is not clear(1-4).Although *N*-acetylcysteine (NAC) is the current drug used to protect against liver injury induced by APAP, it is only effective when given an early period of APAP ingestion and associated with adverse effects such as nausea, vomiting, allergic reactions, and headaches.It is pivotal to find new therapeutic targets and effective agents(5-7).

It has an excellent safety profile when administered in proper therapeutic doses,after oral administration, about 63% of paracetamol is metabolized via glucuronidation and 34% via sulphation primarily in the liver. The water-soluble metabolites consisting of these metabolic pathways are excreted via the kidney. *N*-Acetyl-*p*-benzoquinone (NAPQI) is a reactive intermediate that occurs when oxidization of <5% percent of paracetamol takes place by the microsomal P-450 enzyme system[8-10].

At therapeutic doses of PCM, is metabolised by cytochrome P450 enzymes to form a minor but extremely reactive intermediate known as *N*-acetyl-*p*-benzoquinoneimine (NAPQI) that occurs when oxidization of <5% percent of paracetamol [11].Paracetamol is a widely used medication for fever and pain because of its low cost and effectiveness, but its overdose and long-term usage cause adverse effects that include liver damage. The main reason for development of such medical complication, when the toxic dose of paracetamol is ingested, excessive NAPQ1 is produced and consequently causes serious GSH reduction as well as overproduction of reactive metabolites leading to covalent attachment of sulfhydryl groups in cellular proteins. This produces disrupts homeostasis and starts apoptosis or programmed cell death, leading to tissue necrosis and eventually to organ dysfunction which leads to oxidative stress[12-14].

Its major functions include carbohydrate, protein, and fat metabolism, immunity, exogenous (drug) and endogenous (substance) detoxification, bile secretion, and vitamin storage.In hepatitis, liver tissue has a relatively high level of enzyme activity, with various enzymes altered. . the liver is responsible for the metabolism of paracetamol. Therefore, may cause hepatotoxicity during chronic administration [15,16].

The goal of this study was to investigate the effect of acetaminophen on liver function due to toxic doses of acetaminophen.

2. Materials and Methods

The experimental study was carried out on 30 rats (about 1.5-2.1 kg), during the period from January to June 2020,it has been achieved in the animal house of the college of veterinary medicine / Tikrit University. The animals were maintained under controlled environmental conditions. They were provided a free access to standard pellet diet and tap water.

The animals were divided into 3 groups each group consists of 10 animals:

Control group 1 (G1): It included 10 adult rats, the animals of this group received 1 ml normal saline 0.9% for 4 weeks.

Treated group 2 (G2): It included 10 rats, each animal received 50mg/kg/day of paracetamol daily for continuous 30 days.

group 3 (G3): It included 10 rats, each animal received 100mg/kg/day of paracetamol daily for continuous 30 days.

Blood samples were collected through the jugular vein with the aid of a syringe. Samples were dispensed into plain tubes and allowed to clot.

The serum was collected after centrifugation within 30 minutes of specimen collection and stored at −40°C for hormone and biochemical measurements.

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Biochemical analysis of AST, ALT, and ALP were measured, and their levels were assayed using RANSEL kit (RANDOX laboratories).

Statistical analyses were performed using SPSS 11.5 (SPSS Inc., Chicago, IL). Data are presented as mean SD, with $P < 0.05$ being considered statistically significant.

3. Results

This study recealed that the levels of GOT, GPT, and ALP levels significantly increase in the paracetamol treated groups when compared to the control group, Wheares bilirubin levels significantly decrease in the paracetamol treated groups when compared to the control group

Table 1. Effect of paracetamol administration on biochemical parameters of rats

Parameters Groups	GOT	GPT	ALP	LDH	T. Protein	Billirobin
A	144.20±24.8 b	56.20±7.46 a	405.0±27.5 a	2101±72.7 a	6.6±0.271 A	0.56±0.152a
B	160.00±15.3 a	47.40±4.34 b	379.2±20.2 a	1696±69.7 a	6.76±0.321 A	0.52±0.192
C	123.33±12.42 c	42.67±8.33 c	357.67±13.58 a	1764±67.6 a	6.57±0.513 A	0.47±0.152 a
P – Value	0.0480 *	0.042 *	0.622 ns	0.800 ns	0.713 ns	0.757 ns

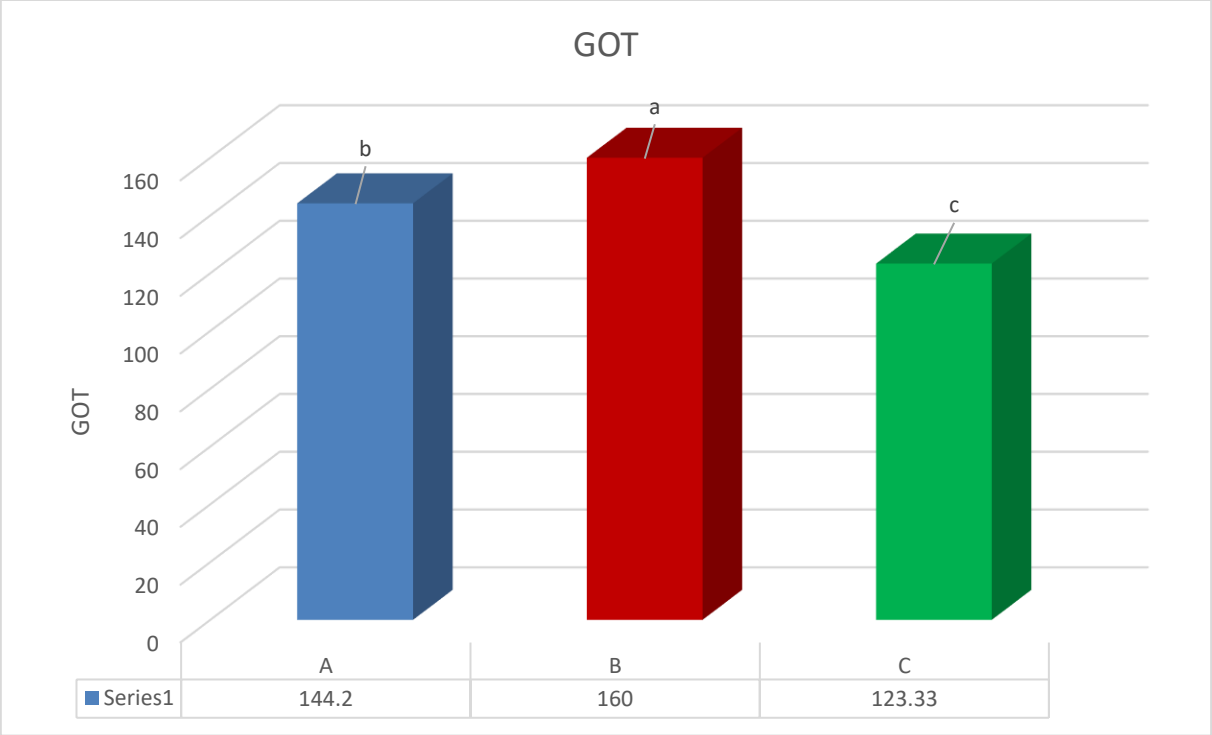

Figure 2: Effects of paracetamol on the serum GOT in adult rats.

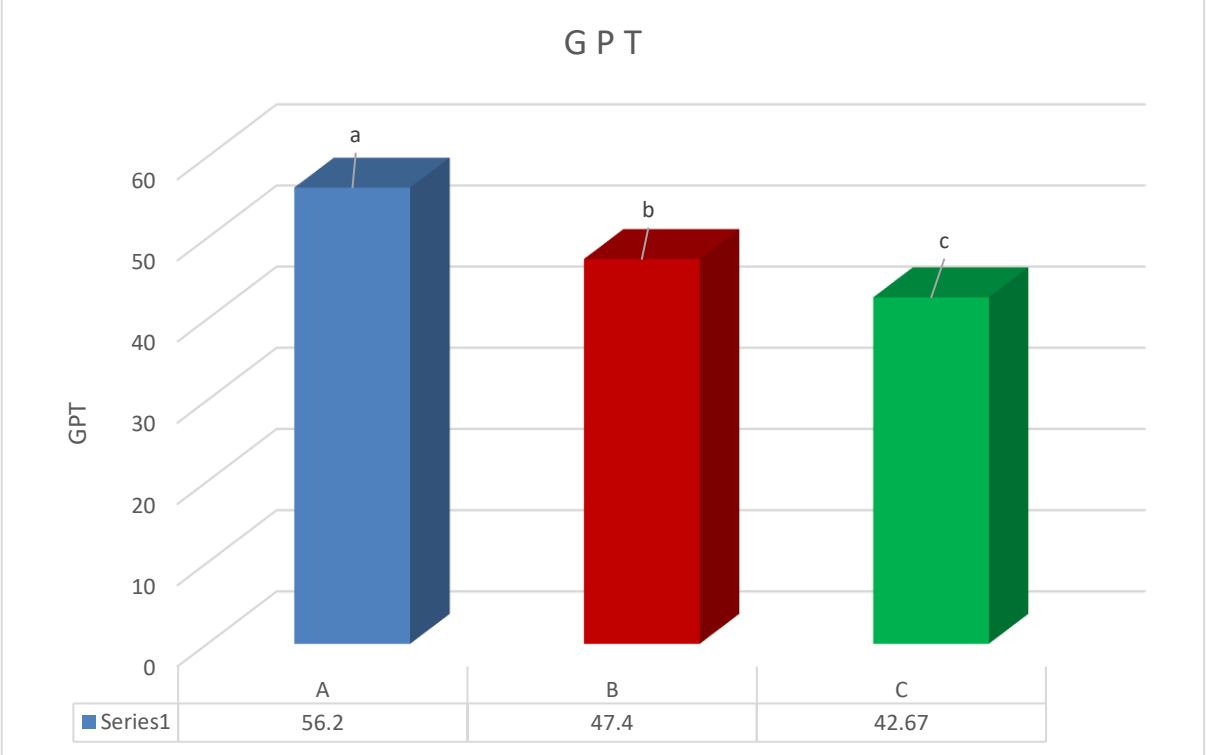

Figure 3: Effects of paracetamol on the serum GPT in adult rats.

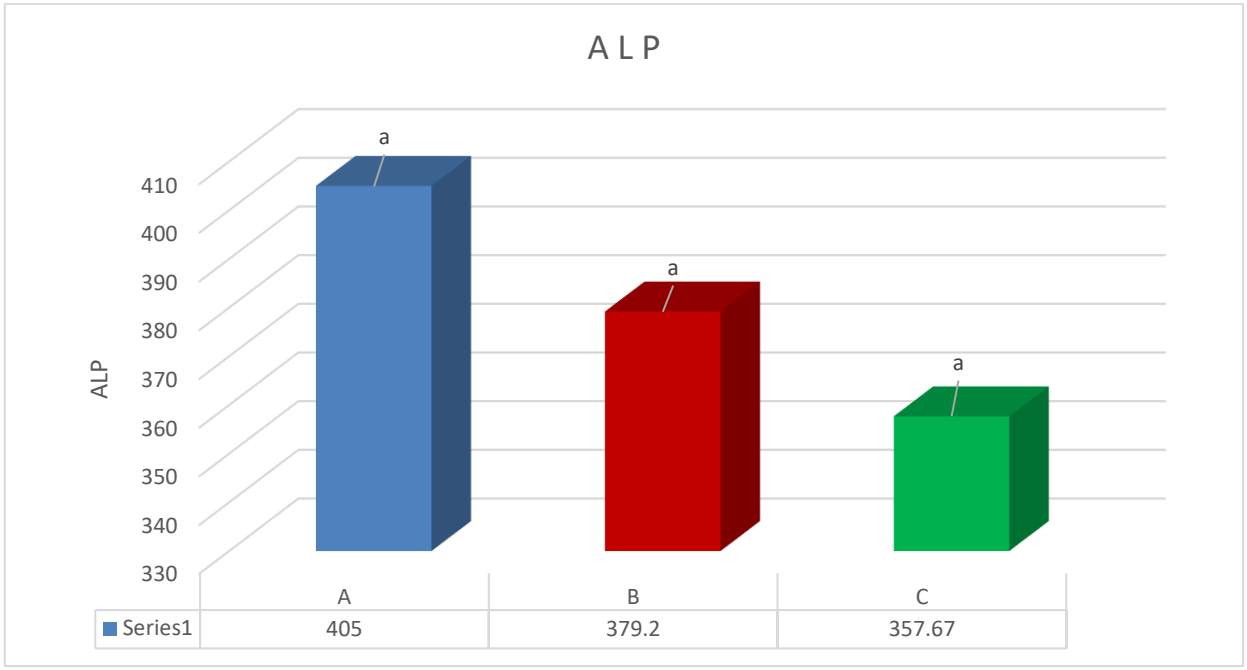

Figure 4:Effects of paracetamol on the serum ALP in adult rats.

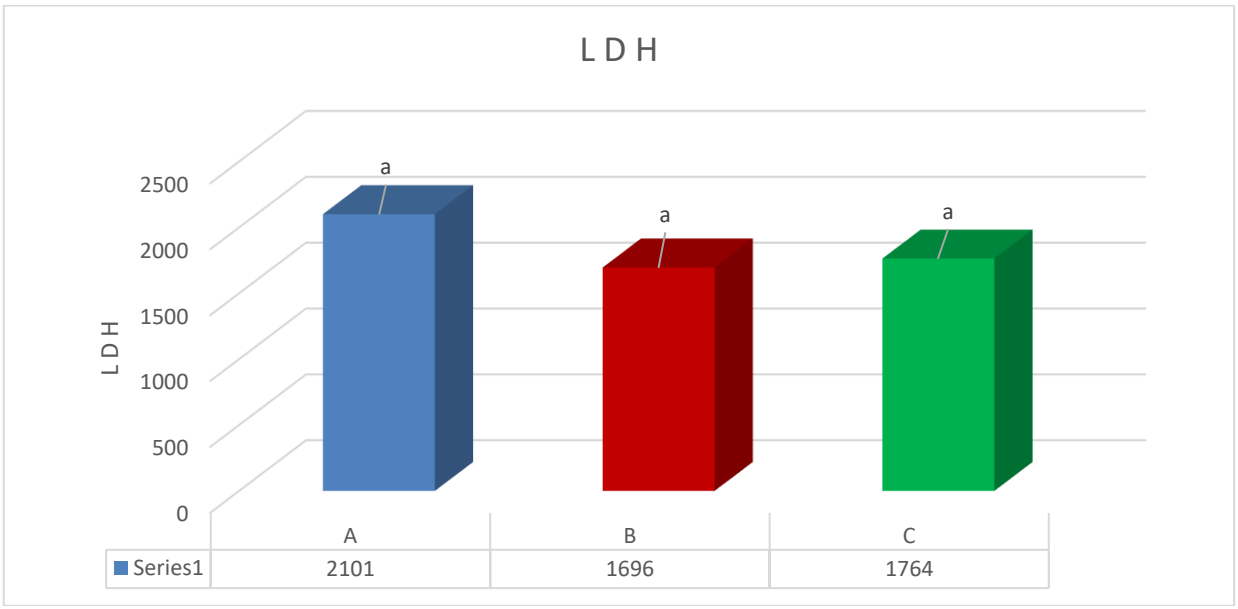

Figure 5: Effects of paracetamol on the serum LDH in adult rats.

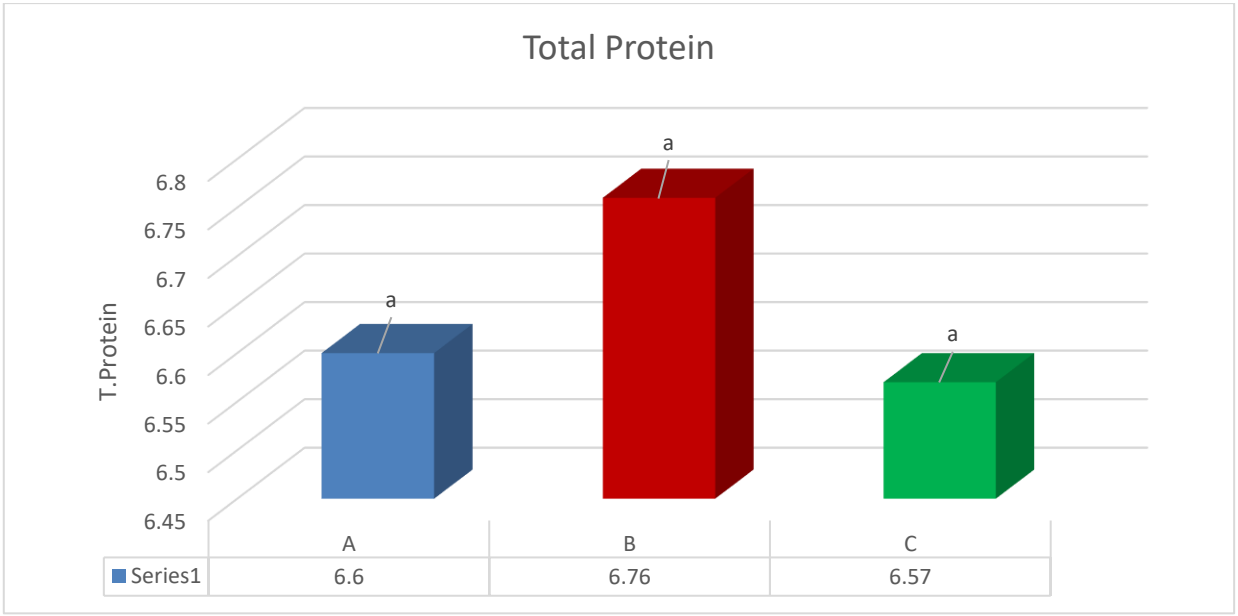

Figure 5.Effects of paracetamol on the serum TP in adult rats.

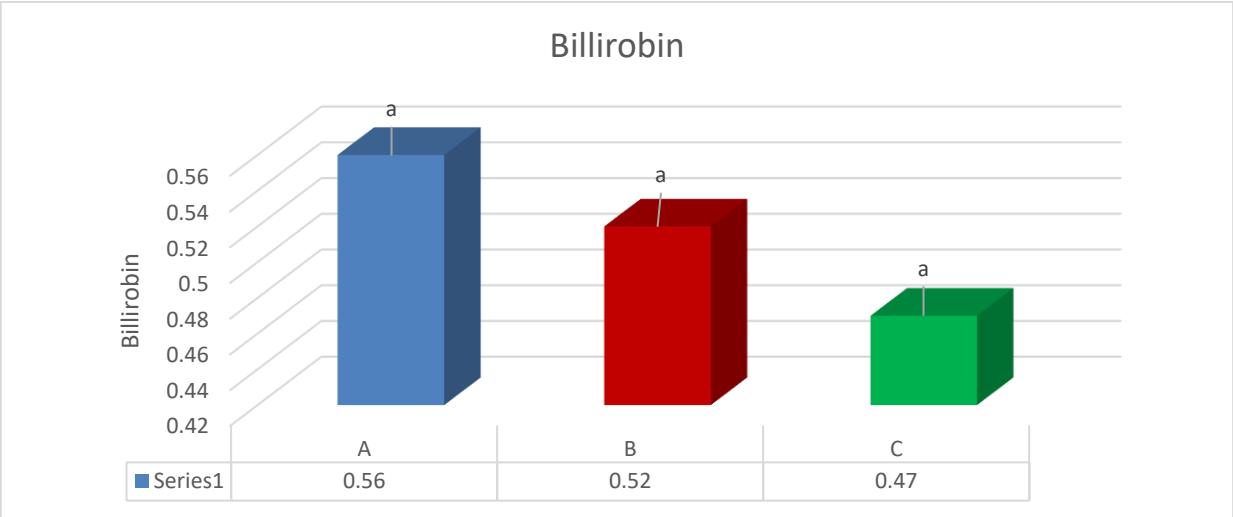

Figure 6: Effects of paracetamol on the serum bilirubin in adult rats.

4. Discussion

Acetaminophen (APAP) was selected to induce the liver injury to assess hepatoprotective effect in this study for two reasons. First, the model has its own prescreening lethality test, which serves as a prestudy test. Second, APAP induces hepatotoxicity, which resembles the liver injury in humans[17].

Though liver plays an important role in protein synthesis, changes in protein concentration is likely to occur in an acute liver disorder.Reduction of protein concentration in paracetamol overdose may be due to the formation of protein adducts. Primary cellular targets have been postulated to be mitochondrial proteins, with resulting loss of energy production, as well as proteins involved in cellular ion control.). Formation of reactive NAPQI metabolite results in covalent modification of cellular target proteins, cell death and organ damage.Covalent binding of NAPQI to proteins may induce denaturation of protein as well as changes in protein structures.Thus it can be concluded that reduction in protein concentration in animals treated with PCM may be due to disruption in protein structures and formation of protein adducts with the reactive metabolite (NAPQI) and also the possible involvement of nephrotoxicity that caused loss of protein through the renal route[9,10].

Aspartate aminotransferases are predominantly mitochondrial enzymes. Although an elevated level of AST in the serum is not specific for a hepatic disorder, it is used primarily to diagnose and confirm persistent cellular injury in conjunction with other enzymes such as ALT.In present study an increase in aminotransferase levels in serum might be mainly due to the leakage of these enzymes from the liver cytosol into the blood stream [31].Injury to the hepatocytes alters their transport function and membrane permeability, leading to leakage of enzymes from the cells. For it, the marked release of AST and ALT from liver cytosol into circulation refers to the extensive damage of hepatic tissue membranes[6,18-20]. A possible explanation by which serum ALP level was elevated may be related to the increase in its synthesis by cells lining bile canaliculi in response to cholestasis and increased biliary pressure.

Moreover, the elevated serum ALP level observed, in this study, could be attributable to defective hepatic excretion or increased ALP synthesis in its synthesis by cells lining bile canaliculi in response to cholestasis and increased biliary pressure, or , by hepatic parenchymal or duct cells in the presence of increasing biliary pressure as reported by Iyanda and Adeniyi[21,22]., an effective control of ALP activity is necessary and this points toward an early improvement in the secretory mechanism of the hepatic cell.

5. Conclusion

High dose of paracetamol in male rats leads to systemic toxicity which represents toxic effect on the structure and function of hepatic tissue,disturbance of liver function tests

6. References

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