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Research Article

**ROLE OF ZINC SULPHATE IN PARACETAMOL TOXICITY**<sup>1</sup>Hafiz Ahmad Jalal, <sup>2</sup> Hafiz Ahmad Bilal, <sup>3</sup> Hafiz Ahmad Kamal, <sup>4</sup> Ayesha Khalid<sup>1</sup>Avicenna medical college Lahore, Pakistan<sup>2</sup>Mohiuddin Islamic medical college Mirpur khas, Azad Kashmir<sup>3</sup>Avicenna medical college Lahore, Pakistan<sup>4</sup>Frontier medical college Abbottabad, Pakistan**Abstract:**

**OBJECTIVE:** Research objective was the determination of the Zinc Sulphate role as an agent of hepatoprotective in the acetaminophen-induced changes of histopathological nature in the model of animals.

**DESIGN:** Research was Observational Experimental in nature.

**SETTING:** Research was carried out in the Pathology and Pharmacology Department Mayo Hospital Lahore from Dec, 2016 to Mar, 2017.

**METHODOLOGY:** Our research sample was 90 albino rats with the range of weight from 18 – 32 grams and we made three groups each group consisting of thirty albino rats. Control group was A group and normal saline level was maintained in this group as 0.9%; acetaminophen was given (250 mg / kg) in B group through a single dose; Zinc Sulphate (1 – 5 mg / kg) was given to C group for a duration of 1 – 7 days before the acetaminophen (250 mg / kg) single dose. After the six hours' duration was conducted biochemical studies after giving acetaminophen to albino rats. At last step of the treatment weight of all animals was checked at than sacrificed. Histopathological and gross examination was carried out for liver and statistical evaluation of the data was carried out through Chi-Square test.

**RESULTS:** Demonstration of the zinc's protective effect was made through serum concentration reduction level of the enzymes of liver such as aspartate aminotransferase, lactate dehydrogenase, alanine aminotransferase and serum sorbitol dehydrogenase, including the histopathological centrilobular congestion changes, necrosis and hepatocellular degeneration. We observed through the histopathological evaluation that typical changes in pathological environment of centri-zonal necrosis, leukocyte infiltration, steatosis, edema in animals and portal tiraditos those were treated only with acetaminophen. Animal pretreatment through zinc sulphate lead the whole procedure to dependent on the dose for the avoidance of various changes.

**CONCLUSION:** It is concluded that Zinc is responsible for the production of hepato-protective effect with the prevention of ultrastructural hepatic tissue injuries and also causes free amino acid metabolism disturbance which is a result of the acetaminophen toxic dose.

**Keywords:** Acetaminophen, zinc, liver toxicity and hepato-protective effect.

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**INTRODUCTION:**

There are potential complications related to the injuries induced through drugs almost from every medical prescription as the liver is at the center of the metabolic disposition and all the drugs almost virtually relate to the liver including all outer substances. There is a practice that drugs are metabolized in such a way that do not harm or pose any liver injury but at the same time numerous non-fatal and fatal reactions are associated to the occurrences every year. Metabolites are produced through few of the compounds causing injury of the liver in a uniform way depending on the quantity and time of the dose [1].

Acetaminophen (hydroxy-acetanilide, *N*-acetyl-*p*-aminophenol and paracetamol) is among the commonly used analgesics, which becomes toxic if a high dose is administered to certain illnesses. It is also among the safe for the therapeutic doses, if the condition of overdose happens, or in the condition of associated liver disease, there is a display of the acetaminophen toxicity which causes mortality and morbidity. Investigations are highly emphasized toxic mechanisms of acetaminophen and mammalian systems and detoxification. A major pathway of the acetaminophen removal seems through sulphate and glucuronidation, that is responsible to make it dissolvable in the water and also allows the removal from blood and liver with the help of urine [2]. There is documented evidence available for the Zinc sulphate offering protection about the dependency on the dose which decreases the levels of malondialdehyde and alanine amino transferase. Depletion can also be avoided through hepatic glutathione depletion. The results were not satisfying as of the *N*-acetyl cysteine. However, zinc sulphate combined with *N*-acetyl cysteine produces even enhanced effects of the protection. Furthermore, treatment of the drug does not produce any change in the serum levels of the acetaminophen. Our research concludes that both the drugs weaken acetaminophen-induced hepatic toxicity and it also mediates the levels of the hepatic glutathione replenishment. Zinc sulphate use alone or joined with *N*-acetyl cysteine can possibly pose another treatment alternative in the overdose of acetaminophen considering the possible side effects which are caused by the *N*-acetylcysteine [3]. Research objective was the determination of the Zinc Sulphate role as an agent of hepatoprotective in the acetaminophen-induced changes of histopathological nature in the model of animals.

**METHODS:**

Research was Observational Experimental in nature. Research was carried out in the Pathology and Pharmacology Department of Mayo Hospital Lahore from Dec, 2016 to Mar, 2017. Our research sample was 90 albino rats with the range of weight from 18 – 32 grams and we made three groups each group consisting of thirty albino rats. Group A, B and C were treated with acetaminophen, acetaminophen and zinc sulphate respectively and A group was also treated as controls.

**EXPERIMENTAL DETAILS:**

Control group was A group and normal saline level was maintained in this group as 0.9%; acetaminophen was given (250 mg / kg) in B group through a single dose; Zinc Sulphate (1 – 5 mg / kg) was given to C group for a duration of 1 – 7 days before the acetaminophen (250 mg / kg) single dose. After the six hours' duration was conducted biochemical studies after giving acetaminophen to albino rats. At last step of the treatment weight of all animals was checked at than sacrificed for onward Histopathological and gross examination.

**SAMPLE COLLECTION**

Blood and tissue samples were collected out of the animals. Cardiac puncture technique was used for the collection of blood samples after six hours of administering acetaminophen, further biochemical studies were carried out. Serum aspartate transaminase (AST) Biochemical assays were carried out and Randox kits were used for the alanine transaminase (ALT) on the basis of the Frankel and Reitman method. Determination of alkaline phosphatase serum was made through King and Armstrong method. Determination of albumin serum was made through BCG reaction with the help of Randox kits. Clotting of blood samples was carried out on the room temperature and separation and storing of the sera was made as per requirement on – 20°C.

Animals were sacrificed for the collection of tissue samples after confirmation of their weight by giving anesthesia. Amid line incision was carried out in the trunk middle part and identification and removal of liver was carried out. We observed the liver generally and noticed any change in the color, shape, consistency, contour and size through magnifying glass. After washing and weighing through normal saline, we fixed the liver for twenty-four hours in Bouin's fluid. Longitudinal division of the liver was

made and two equal parts were obtained to observe the inner side of the liver through dissecting microscope, and we again fixed the liver for twenty-four hours in fresh Bouin's fluid. Alcohol processing was carried out from 70%, 80%, and dehydration, tissue clearance was made in xylene and embedded and infiltrated in paraffin; (3 – 5) micron thickness sections were obtained and they were placed in a bathing tub at 40°C – 42°C. Glass slides were used to mount the tissues and their staining was carried out through (Periodic Acid Schiff) iron hematoxylin. Liver detailed morphometric observation were carried out through ocular reticule and ocular micrometer scale under a light microscope. Histopathological change was observed through one-step trachoma under the resolution of 40 – X; Hepatic lobule changes were scored through zones. Hepatocytes contents were stained through Oil Red-O. Liver cells fat contents were carried out through ocular counting reticule in the 40 – X objective through random selection of the hepatic lobule areas.

#### STATISTICAL ANALYSIS

SPSS – 16 was used for statistical analysis of the data and for the calculation of the mean and SD. Mann-Whitney U test and Student's t- test were also used for the analysis of the mean and SD in consideration with the p-value of (< 0.05).

#### RESULTS:

Outcomes reflected that acetaminophen administration to B – Group animals responded in the shape of a visible decrease in the serum alkaline phosphatase and transaminases concentration and a caused a decrease in the levels of serum albumin. However, pre-treated animals with zinc-sulphate for seven days produced noteworthy dependency on the for the avoidance of these biochemical changes. We also observed a significant improvement in the C – group biochemical parameters while treating them with zinc-sulphate (p-value as < 0.05 to < 0.001). Furthermore, a higher dose related significant (p-value as < 0.05 to < 0.001) response was seen in the increased zinc-sulphate dose. It was also observed through histological evaluation that a typical pathological B-group changes were observed in acetaminophen (250 mg / kg) group. An important change was observed in the central necrosis, leukocytes infiltration, steatosis, edema and portal tiraditos. In the pre-treatment of the groups “C – 1, C – 2 & C – 3” also reflected that histopathological changes were dependent on the dose in order to prevent these changes. Mild tiraditos was seen in C – 2 group and also a minimal venous congestion. Group C – 3 was observed with no histopathological changes.

#### DISCUSSION:

Hepatotoxicity is considered as an important issue as it is caused because of acetaminophen overdose (paracetamol). In the all hospital admission cases liver injury because of drug is observed as five percent and in the incidence of acute failure of liver it is 50% [4]. Commonly used analgesic is acetaminophen and also an antipyretic agent, causing poisoning issues all over the world. United States poison centers state that they made above 70,000 healthcare visits and observed about three hundred cases of death (2005) [5]. Acetaminophen poisoning can possibly because of the single overdose digestion or excessive repeated ingestion of doses or frequent intake of the doses for the therapeutic intention [6]. There is an increased recognition about the repeated serotherapeutic ingestion for clinical issues and associated problem. Acetaminophen is tolerated in the prescription and an overdose causes acute failures of liver over the world, reported as most painful incidence by the patients [7]. Acute hepatotoxicity death reports are low as in the twenty-four-hour duration with 2.5 grams. Liver damage is not because of the drug toxic metabolite (NABQI or A/-acetyl-p-benzoquinone imine NAPQI) produced by cytochrome (P450) liver enzymes [8]. Liver involvement in drug-induced toxicity is dependent on the anatomical location as primary entry part of the drug ingestion is liver and its biochemical and physiological functions due to the metabolizing enzymes abundance [9]. The human zinc essentiality was 1<sup>st</sup> noticed back in 1960. In the last three decades' deficiency of zinc is because of nutritional factors and also because of the states of several diseases which are recognized [10]. Zinc protective effect also shows reduced increase in the serum glutamic pyruvic transaminase (SGOT) and serum glutamic oxaloacetic transaminase (SGPT) activity which was apparent after the acetaminophen administration [11]. We also observed that albino rat's pretreatment with zinc sulphate prevents the serum liver enzymes escalation such as AST, alkaline phosphatase, ALT and serum albumin decrease associated to a certain acetaminophen hepatotoxicity [12]. In the same way, histological characteristic changes are associated with the acetaminophen toxicity including centri-zonal necrosis, sinusoidal enlargement and steatosis that can be prevented through zinc sulphate dependent on the dose [13]. International observations about the zinc sulphate are same as ours as zinc acts as a protection against acetaminophen-induced hepatotoxicity due to the induced changes of biochemical nature, which is not a result of mechanisms that are invoked [14]. Few of the authors have also used it as an acetaminophen overdose antidote examined on the mice. The

induction of hepatotoxicity was made through acetaminophen single dose (750 mg / kg) [15]. Numerous treatments such as normal saline, zinc sulphate 15 or 30 mg/kg, 150 mg/kg / V-acetyl cysteine, zinc sulphate, 15 mg / kg zinc sulphate + 150 mg / kg A/-acetyl cysteine) were also administered at the interval of one hour after the administration of overdose of acetaminophen [16]. However, zinc sulphate combined with *N*-acetyl cysteine which produced effective and better protections. Furthermore, treatment of the drug did not affect level of serum acetaminophen. We conclude that the action mediates with the replenishment of levels of hepatic glutathione and drugs weaken the acetaminophen-induced hepatic toxicity [17]. Zinc sulphate use unaccompanied or accompanied with A-acetyl cysteine can act as another treatment alternative for overdose of acetaminophen in the availability of the possible side effects that can be the result of *N*-acetyl cysteine.

### CONCLUSION:

It is concluded that Zinc is responsible for the production of hepato-protective effect with the prevention of ultrastructural hepatic tissue injuries and also causes free amino acid metabolism disturbance which is a result of the acetaminophen toxic dose. Zinc sulphate exerts a protection of the dose to liver in response to the acetaminophen toxicity. Hepato-protective zinc effect was reflected through low levels of SGPT, SGOT, serum albumin and serum alkaline phosphatase. Furthermore, histological changes which are induced through overdose of acetaminophen can be avoided through a zinc sulphate pre-administration.

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