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ORIGINAL ARTICLE

Chloroquine Induced Hepatotoxicity in Male Albino Mice: RCT

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ABSTRACT

Many drugs have been found to induce hepatotoxicity and acute liver failure. Chloroquine is one of those drugs, which can induce hepatotoxicity when it is given at higher dose

Purpose: To find the effect of chloroquine on liver function tests (LFTs)

Study Design: Randomized clinical trial

Methodology: Sixty male albino mice were taken into this randomized controlled study. Those were divided into two groups of 30 each. Group A was the control group while group B mice were given single oral dose of 970 mg/kg of body weight of chloroquine on 9th day of experiment. Terminal intracardiac blood sample was obtained on 17th day of experiment

Statistical analysis: SPSS version 23 was used for data analysis

Results: When results of group B were compared with those of group A, they depicted highly significant (p=0.000) rise in serum ALP. Serum albumin decreased significantly (p= 0.007). Serum AST increased significantly (p=0.005). Serum ALT, however, did not rise significantly (p=0.285) in group B. Similarly, serum total proteins did not decrease significantly (p=0.530) in group B

Conclusion: It was concluded that chloroquine induced mild hepatotoxicity in male albino mice when a single oral dose of 970 mg/kg of body weight of it is given

Key Words: Chloroquine, Hepatotoxicity and Alkaline Phosphatase.

INTRODUCTION

Liver plays vital role in the body. One of it's important functions is detoxification of xenobiotics. During detoxification process, several reactive oxygen species are generated. These attack the hepatocytes and destroy the structure of the hepatocytes and in turn compromise the function of the liver.[1] About 50 % of acute liver failure cases have been reported due to drug reactions.[2] More than 1000 drugs have been found to be responsible for drug induced hepatotoxicity.[3] Many drugs have been withdrawn from the market due to their potential to induce hepatotoxicity.

Chloroquine is a widely used drug in the developing countries for the treatment of malaria because it is cost effective and easily available.[4] Besides malaria, chloroquine and it's derivatives have been used for the treatment of rheumatoid arthritis and systemic lupus erythematosis [5] due to it's anti-inflammatory effects.

But chloroquine exhibits certain toxic effects when given for longer duration or at higher doses. Commonly noticed side effects include cardiotoxicity, retinopathy[6] and hepatotoxicity. The safe therapeutic dose in humans have been advised to be less than 6 gm/ kg of body weight per day.

Chloroquine has the potential to generate reactive oxygen species when given at higher dose.[4] These reactive oxygen species attack the lipids of membranes. Hence, these destroy the cell membrane. As a result of which, intracellular enzymes such as alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase are released into the blood.[7] Due to destruction of hepatocytes, liver is not able to make proteins also, because most of the plasma proteins are formed in the liver. Albumin makes 60 % of the total plasma proteins.

OBJECTIVES

To find the effect of chloroquine on liver function tests (LFTs).

METHODOLOGY

The study was conducted from March 2017 to December 2018 at Akhtar Saeed Medical and Dental College, Lahore. In this randomized controlled trial study, sixty male albino mice were taken from University of Veterinary Sciences, Lahore. The average weight of mice was 28 gm and age was 8-10 weeks. They were divided by lottery method into two separate groups i.e group A and group B. Each group contained 30 mice. Mice of each group were kept in seperate cages. They were acclimatized for about 1 week before the start of the experiment. They were kept at 26 + 2 ^{0}C with 12 hour light dark cycle.[8] The humidity was maintained at 55 %. Mice had free access to food and water.

Group A: (Control, n=30): was not administered chloroquine.

Group B: (Chloroquine, n=30): was administered a single oral dose of chloroquine (970 mg/kg of body weight) at 9th day of experiment.

Statistical Analysis: SPSS version 23 was used for data analysis. Liver enzymes with albumin were presented as mean ± SD. Student t-test was applied with p-value≤ 0.05 taken as significant.

RESULTS

Mean values of serum alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, albumin and total proteins were compared between groups A and B by using student's t test. Group B, in which chloroquine was given, depicted highly significant (p= 0.000) rise in serum ALP and significant (p=0.007) decrease in serum albumin. Serum AST raised significantly (p= 0.005). Serum ALT, however, did not rise significantly (p= 0.285) in group B. Similarly, serum total proteins did not decline significantly(p= 0.530) in group B as shown in table-1.

Table-1: Comparison of serum ALT, AST, ALP, albumin and total proteins between groups

Parameters	Group A (n=30)	Group B (n= 30)	p- value
ALT (U/L)	9.73 ± 4.35	11.47 ± 5.96	0.285
AST (U/L)	57.20 ± 22.50	61.13 ± 14.10	0.005**
ALP (U/L)	106.47 ± 10.87	234.77±100.14	0.000*
Total proteins (g/dl)	6.21 ± 1.79	6.10 ± 0.51	0.530
Albumin (g/dl)	2.70 ± 0.75	2.30 ± 0.28	0.007**

*p< 0.001 highly significant,**p< 0.05 significant

DISCUSSION

In the current study, chloroquine caused highly significant increase in serum ALP and significant decrease in serum albumin. It caused significant increase in serum AST. But it caused insignificant rise in serum ALT. Similarly, it caused insignificant decrease in serum total proteins. According to a study conducted by Giannini et al, (2005), hepatotoxicity is labelled as mild, moderate and severe.[10] Mild hepatotoxicity is labelled when alteration in values of serum AST and ALT are less than five times the upper limit of normal. Moderate hepatotoxicity is considered when alterations in values of serum AST and ALT are five to ten times the upper limit of normal. Marked hepatotoxicity is labelled when alterations in the values of serum AST and ALT are more than ten times the upper limit of normal.

By comparing the results of the current study with the study conducted by Giannini et al, (2005), it has been found that serum ALT and AST alterations are less than the five times the upper limit of normal in the present study. Hence, mild hepatotoxicity has occurred in the current study. The magnitude of elevation of ALT and AST is directly proportional to the number of hepatocytes that are damaged.[11]

Reactive oxygen species, generated by chloroquine, cause lipid peroxidation. Due to lipid peroxidation, cell membrane loses integrity.[12] AST, ALT and ALP are intracellular enzymes. ALP is present inside the cells which line bile canaliculi. As a result of loss of membranes, ALT and AST are released into the circulation. These results are different from those obtained by Pari et al, (2005), who gave chloroquine as a single oral dose of 970 mg/kg of body weight in female wister rats.[13] Significant elevation of ALT, AST and ALP was noticed in their study. The difference in results between the two studies was probably due to the difference in gender [14] and species.

Liver is the synthetic house of most of the plasma proteins except gamma globulins, which are formed by plasma cells. Albumin makes 60 %, of the total plasmal proteins.[15] In the current study, chloroquine administration caused significant reduction in the serum levels of albumins. But serum total proteins did not decrease significantly probably because gamma globulins are formed by plasma cells. That is why, total proteins declined insignificanly

Limitations: Limitations included limited time frame, resources and financial constrains.

CONCLUSION

It was concluded that chloroquine induced mild hepatotoxicity at the single oral dose of 970 mg/kg of body weight in male albino mice.

Author's Contribution: SK: Conceptualized the study, analyzed the data, and formulated the initial draft.

HJQ: Contributed to the histomorphological evaluation.

TL: Contributed to the proofreading the manuscript for intellectual content.

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