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ORIGINAL ARTICLE

Light Microscopic Study on Possible Protective Effect of Vitamin E on Imatinib Induced Hepatic Central Vein Dilatation in Albino Rats

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ABSTRACT

Aim: To observe the changes in the caliber of hepatic central vein of Albino rats exposed to the oral administration of toxic doses of Imatinib and to assess the protective effect of vitamin E**.**
Study design: Experimental study
Place and duration of study: Department of Pharmacy, Peshawar Medical College Peshawar from 1st October 2015 to 31st March 2016.
Methodology: Twenty four male Sprague-Dawley rats (150- 200g) were selected for this study and these rats were divided into three groups. Group 1 was control group, Group II received oral Imatinib solution (50 mg/kg/day) and Group III received Imatinib solution (50mg/kg/day) orally along with vitamin- E (500MG/kg/day) for 14 days. At the end of experiment central vein dilatation in liver tissue of rats were observed.
Results: The increase in mean central vein dilatation in liver of group II were statistically significant (p=0.001) in comparison with the control. The mean central vein caliber of liver was decreased significantly in group III.
Conclusion: The simultaneous use of vitamin E as an antioxidant with Imatinib can protect the toxic effects of the Imatinib on hepatic toxicity which includes central vein dilatation.
Keywords: Imatinib mesylate, Hepatic tissue, Central vein dilatation, Vitamin E

INTRODUCTION

Chemotherapeutic drugs contain chemical substances, which circulate thought the body to stop the growth and kill the cancer cells that have metastasized to the other body parts from the original tumor. However it does not differentiate between cancer cells and other active cells of the body, such as digestive tract, hair follicles and blood. Side effects occurred when chemotherapy damage the fast growing healthy cells[1].

In developing country like Pakistan humans are suffering from different type of cancers, and optimal treatment is not provided to majority of patients, due to poor socio economic status, illiteracy and limited health resources. In Pakistan (tyrosine kinase inhibitors) therapy is given to the chronic myeloid leukemia patient in the form of Imatinib and it is still being used as first line of treatment in 70% of patients[2].

Among the several types of the chemotherapeutic drugs, Imatinib mesylate (CID 6395-Methanesulfonic acid) is a drug that targets bcr-abl tyrosine kinase, an enzyme that is regarded as the cause of Philadelphia chromosome- positive chronic myeloid leukemia (CML). It is the only effective and approved systemic agent for the treatment of patients with chronic myeloid leukemia[1,2] and advanced gastrointestinal stromal tumor[3].

Imatinib is largely metabolized in the liver by cytochrom P4503A4 system and has an active metabolites half life of approximately 40 hours[4]

Diffuse parenchymal congestion, dilatation of central vein and portal tract infiltration ,hepatocytolysis in zone 3 was found in the patients treated with Imatinib[1,5-8]

Hepatic toxicities were seen in the dogs after a two week course of Imatinib, in which mild multifocal hepatocelluler necrosis, central vein dilatation, single cell bile duct necrosis and bile duct hyperplasia. Bile duct hyperplasia remains after the recovery duration of four weeks and that was related with peribiliary fibrosis[4]

Vitamin E is an important fat soluble natural nutrient. Vitamin E consists of eight forms in which alpha tochopherol is the most important natural nutrient in the human body. Vitamin E serves the body as an anti-oxidant and is also used in regulating the gene expression, cell signaling and immune function.[9]

Antioxidants individually protect normal cells against some of the toxicities produced by the chemotherapeutic agents.[10]

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In animal studies, various preparations like vitamin E, vitamin C, vitamin B_6 have been studied, which combat or reverse the oxidative damage. Now a day, a lot of attention is being paid on the use of natural antioxidants because of their fewer side effects, and easy and cheap availability[11].

MATERIALS AND METHODS

This study was carried out at animal house of Peshawar Medical College, for a period of 15 days. Twenty four male rats of Sprague-Dawley strain weighted between 150-200g were obtained from the Pharmacy department of Peshawar Medical College. They were kept in the house with standard environmental conditions like 1 8-2 6°C (68-75.2°F) temperature with relative humidity of 40-70% and maintained at a 12/12 hours light/dark cycle. Proper and uniform light was provided within the cages to avoid any type of disturbance such as fluctuating lightening, heat clusters and shimmers etc, and also provided with standard rat chow and water ad libitum. Prior to conduction, all experiments used in the study were approved by ethical committee of the Institutional Review Board of the Prime Foundation Pakistan. After providing acclimatization period of one week the animals were divided into three groups.

Group I (control): This group comprised of 8 rats (n=8) and treated with plain water and rat chow for 15 days.
Group II (Experimental): Comprised of 8 rats and treated with Imatinib solution (50 mg/kg/day) orally once daily for 15 days.
Group III (Experimental): Comprised of 8 rats treated with Imatinib solution (50 mg /kg /day) orally once daily for 15 days along with the vitamin E (500mg/kg/day).

Imatinib solution was given orally through a nasogastric tube(Levin, size 5fr) At the end of the experiment after 15 days, the animals of control and experimental groups were anaesthetized by an over dose of ether and then decapitated. After sacrifice laparotomy was done and liver removed carefully and immersing them in jars containing 10% neutral buffered formalin. The liver tissue were fixed and processed and embedded in paraffin wax.

By using American optical rotary microtom 5µm liver tissue sections were cut and stained with Harris Hematoxylin and eosin (H & E) for histological analysis. Evaluation of slides were carried out by quantitative methods. Among the other histological changes the Central vein dilatation were specifically noted. For the calculation of central vein dilatation, ocular micrometer was used, which was calibrated with stage micrometer.

A scoring system was applied to evaluate and standardize the degree of toxic effect of Imatinib on the hepatic tissue of experimental animal. Under this scoring system, the degree (no

change, mild to moderate change and marked change) of central vein dilatation was observed. The scores given were: No change (0), mild to moderate change (1) and marked change (2).[6,12] The diameter of central vein of all groups was measure and compared by giving the scores. Statistical analysis was performed using the SPSS-20. A p<0.05 was considered as statistically significant.

RESULTS

This study revealed that the light microscopic examination of the liver sections obtained from the group I (control) the central vein of 7 animals out of 8 did not reveal any change and the scoring for them was 0. The histological examination of the liver tissues of 6 animals out of 8 of the group II (receiving Imatinib) showed marked degree of central vein dilatation. Among the animals of group III (receiving Imatinib + Vit E) 6 animals out of 8 showed mild to moderate change in central vein dilatation. There was a significant difference in the diameter of central vein dilatation among the control group (I) and the group II and III with a p=0.000 (Table 1).

From the aforementioned results regarding central vein dilatation revealed that the increase number of the animals which was treated with Imatinib only showed mark changes as compared with group III which was received antioxidant in addition the animals of this group were least effected thus conforming the protective roles of Vitamin E (Figs. 1-3).

Table 1: Degree of central vein dilatation

Degree of central vein dilatation	Group I (Control)	Group II (Imatinib)	Group III (Imatinib +Vit E)	Total	P value
Normal	7 (87%)	-	1 (13%)	8 (33.33%)	0.000
Mild to moderate change	1 (13%)	2 (25%)	6 (75%)	9 (37.5%)	
Marked change	-	6 (75 %)	1 (13%)	7 (29.16%)	

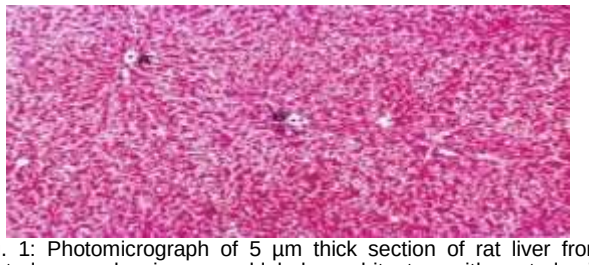

Fig. 1: Photomicrograph of 5 µm thick section of rat liver from control group showing normal lobular architecture with central vein (A) & (B). H&E stain

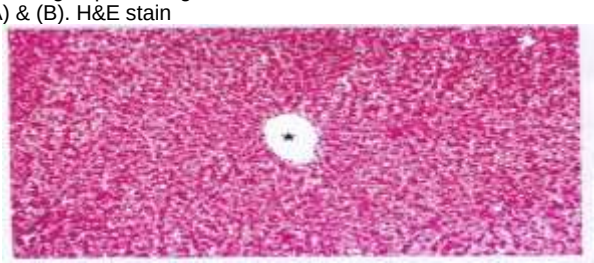

Fig.2: Photomicrograph of 5 µm thick section of rat liver from experimental group I showing central vein dilatation of marked degree (asterisk). H&E stain

Fig. 3: Photomicrograph of 5 µm thick section of rat liver from experimental group II showing central vein dilatation of mild to moderate degree (asterisk). H&E stain

DISCUSSION

The present study using male Albino rats yielding information on the toxic effect of Imatinib on the central vein of liver and the protective role of the vitamin E against Imatinib induced liver toxicity. In the current study, comparative analyses of central vein between the two experimental groups were also considered. In which (75%) animals of group I were found to have central vein dilatation of marked degree, in comparison the (group II)animals(75%) revealed mild to moderate degree of central vein dilatation. Our study to a greater extent is in conformity with the study conducted by S Kikuchi et al. in which they correlated the portal hypertension and central vein dilatation in patients on Imatinib treatment.[13]

With regards to central vein dilatation of hepatic tissue of experimental animals, we did find similarity to the findings of James et al[13] and statistically our study dose supports their findings.[14] The results of current studies are also in agreement with a study conducted by Guilhot[14] which revealed that Imatinib treatment is toxic in the patients of chronic myeloid leukemia and causes acute liver failure and histopathological findings demonstrating cytolytic hepatitis with necrosis, and portal and lobular inflammation.

At the same time our study is in agreement with the study done by Prasad et al.[15] They reported that if alpha tocopherol succinate is used as a supplement in cancer chemotherapy it can be useful by increasing tumour response and possibly subsiding the toxicities induced by cancer chemotherapy to normal cells.

Our study is also in agreement with the several clinical studies conducted by Sieja[16], Pace et al[17],

Bairati et al[18], Branda et al[19], Conklin[20] and Ferreira et al[21] who have reported that supplemental anti-oxidants with dietary nutrients were very useful in decreasing the side effects of chemotherapy in cancerous patient.

CONCLUSION

The simultaneous use of antioxidant vitamin E can prevent the hepatic toxicity which includes portal hypertension and central vein dilatation which can be caused by Imatinib.

RECOMMENDATION

In developed and developing world, measures have been taken to monitor and minimize the toxic effects of chemotherapy, improve the efficacy, and to decrease the side effects of these drugs. The combination trails of antioxidants should be considered for better results.

Conflict of interest: Nil

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