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Original Article

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Morphological changes in liver of methimazole treated rats, a pilot study

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ABSTRACT

BACKGROUND & OBJECTIVE: Thyrotoxicosis is a disease in which thyroid hormones are raised, and we have seen multiple patients suffering from this ailment in Pakistan. Methimazole is an anti-thyroid drug for thyrotoxicosis. Hepatotoxicity and liver ailments were common with methimazole prescribed for hypothyroid patients. Hypothyroidism, a common side effect of this drug, has been seen in a majority of patients, but liver toxicity remained unaddressed. So, in this study, we have observed histological changes in the liver after methimazole administration.

METHODOLOGY: The pilot study was carried out in the University of Health Sciences (UHS), Lahore, and was ended in twenty-one days. We divided animals in 2 groups. Each group comprises 12 animals. Group-I was negative control, and water was given through the oral route for 21 days. Group-II was administered methimazole orally 60mg/kg/day for twenty-one days. At the end;S animals were dissected, and livers were removed for histological examination.

RESULTS: The histological picture of the liver showed 75% severe disruption in liver architecture, inflammation, and fatty change in group 2, indicating liver damage.

CONCLUSION: Methimazole, hepatotoxic with discernable damage to its architecture, epithelium, and inflammatory changes.

KEYWORDS: Methimazole, Thyroxine, and liver.

INTRODUCTION

Methimazole belongs to thioamide group that is given for hyperthyroid patients [1]. Methimazole blocks T3 and T4 synthesis by repressing thyroid peroxidase enzyme, which helps in the formation of thyroid hormones and in the conversion of T4 to T3[2,3]. Methimazole induced hypothyroidism also affects the liver that results in increased bilirubin levels and low antioxidants [4,5]. The reason could be reduced levels of catalase, glutathione-S-transferase, and glutathione [6,7]. Methimazole represses the enzyme thyroperoxidase, which is the main enzyme in thyroid hormone synthesis, helping iodine's addition to tyrosine residueson thyroglobulin. It suppresses sodium-dependent iodide transporter present on follicular cellsin basolateral membranes [8]. It is orally administered. Its bioavailability is 93%, and half-life is 5 to 6 hours. It is eliminated by the kidney [8]. Its major adverse effect is agranulocytosis. Other adverse effects are cellular damage, maculopapular rash, and gastrointestinal damage [9]. It may result in reduced thyroid levels due to its antithyroid activity when given in high dosage.

It results from suppression of thyroperoxidase enzyme and liver dysfunction. The adverse reactions of methimazole result in cholestatic jaundice. The most pronounced pathological findings are intrahepatic cholestasis, condensation of a nucleus, inflammation, and fatty infiltration [9,10]. Methimazole induced liver change can be a result of some hypersensitive reaction, increase in ROS, or disruption in bile from the liver to duodenum, which is prone to jaundice [11].

In our research, we administered methimazole to observe liver histology so that it can help Clinicians to reduce methimazole induced liver toxicity.

METHODOLOGY

Twelve albino rats, 6-8 weeks of age, were procured from the University of Health Sciences (UHS). They were housed in controlled room temperature (23±2°C). The animals were given a standardized rat diet and water and allowed to adapt for four days before the start of the experiment. The duration of the study was 21 days. Animals were segregated into two groups, each having 12 animals.

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Group-I taken as control, and 1ml DW was administered orally for 21 days. Methimazole was administered orally 60mg/kg/day for 21 days to group-II after experimental work; animals were anesthetized and the livers were removed for histological examination.

At the end of the experiment, rats were shifted to a plastic container with cotton wool soaked in chloroform; it was topped with a lid, and the animal stayed till it was numbed. Then it was placed in a supine position with its extremities fixed to dissecting board limbs. A vertical incision was made from the manubrium sterni to the symphysis pubis; sternum was divided from the center, the heart was exposed. The liver was taken out immediately and cleansed in saline, and preserved for the assessment of enzyme activities and histoarchitectural studies. Paraffin serial sections 6 micrometers thick were stained by hematoxylin and eosin stains.

Microscopic examination: The severity of the histopathological changes was assessed using following parameters like karyolysis, Disrupted epithelium, pyknosis, necrosis and fat cells. Grading of liver and specimens: These parameters were scored from at least 10 randomly selected non-overlapping fields per section. The results were graded as the percentage of the damage.

The sections were regarded as normal (-), mild (+), moderate (++), and severe (+++). Mild damage: The damage was considered as mild when the liver cells were sparsely damaged with single cell necrosis; or focal degenerative changes involving less than quarter of the total number of liver cells (<25%); Moderate damage: moderate damage (++), when few showing more than one cell involvement or involvement of less than half (26-50 %), Severe damage: severe damage (+++) when more than half of the liver cells showing necrosis (>50 %).

Data was analyzed using SPSS 21. Mean ± SD was given for quantitative data, and frequency and percentages were given for qualitative data. Fisher's Exact test was performed for qualitative data. p-value of ≤0.05 was considered statistically significant.

RESULTS

A 75% severe disruption in liver architecture was seen in group-II. Liver architecture remained normal in group 1. 83% fatty change was seen in group 2. On gross examination, the liver of both groups appeared reddish brown with a smooth surface. Mean weight of animals of group 1 at the start and end of experiment was 179.63 ± 61.6 gm and 203 ± 5.39 gm respectively and of group 2 was 184.13 ± 9.35 gm and 158.75 ± 4.20 gm respectively.

There was reduction in mean body weight ($p<0.001$) in group 2 as compared to group 1 at the end of the experiment. The liver in animals of group 1 showed normal epithelium(Figure-I). While liver cells in group 2 showed pyknotic and karyolitic nuclei and inflammation. (Figure-II) Fisher's exact test indicated a statistically significant association between groups regarding percentages of the above-mentioned histological parameters ($p<0.001$).

Table-I: Comparison of damage to liver architecture in different groups.

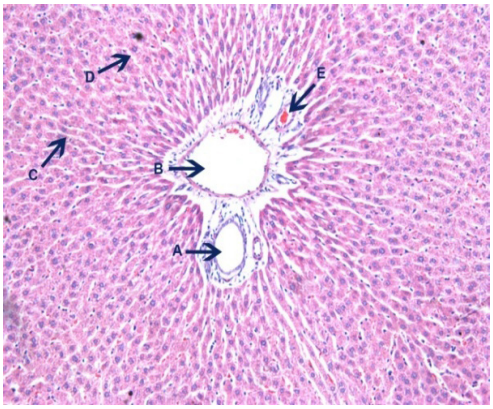
	Damage Severity	Group-I	Group-II	p-value
Liver architecture	Normal	12(100.0%)	0(0.0%)	< 0.001
	1-25%	0(0.0%)	0(0.0%)	
	26-50%	0(0.0%)	3(25.0%)	
	51-100%	0(0.0%)	9(75.0%)	
Total	12	12		

P< 0.05 is statistically significant.

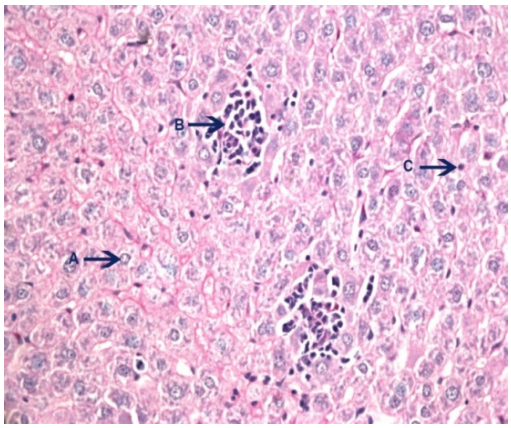
A significant association was observed in liver architecture among groups I, II.

Group-I: Showing normal liver architecture, HA-hepatic artery, CV-central vein, PV-Portal vein, HS-hepatic sinusoids, and SD-space of disse (40X).

A- Portal vein.
B- Central vein.
C- Hepatic sinusoid.
D- Space of disse.
E- Hepatic artery.



Group-I: Histology:H& E Stain:Liver.



Group-II: After administration of methimazole 60mg/kg/day for 21 days (40x).

A. Karyolysis
B. Inflammation
C. Pyknosis

Table–II: History about inflammation.

	Damage Severity	Group-I	Group-II	p-value
	Normal	12(100.0%)	0(0.0%)	
Inflammation	1-25%	0(0.0%)	0(0.0%)	
	26-50%	0(0.0%)	3(25.0%)	< 0.001
	51-100%	0(0.0%)	9(75.0%)	
Total	12(100.0%)	12(100.0%)		

p-value < 0.05 is statistically significant.

Significant association was observed in inflammatory changes among groups: I-II.

DISCUSSION

Thyroid hormones monitor the basal metabolic rate of liver cells; the liver then monitors the thyroid hormones and regulates their organ effects. T4 is transformed into T3 in the liver and other superficial tissues. Thus, there is an active link between the thyroid gland and liver [12,13].

Various drugs have the ability to affect organs such as the liver and thyroid, e.g., methimazole [14].

Cano-Europa E had investigated that Methimazole-induced hypothyroidism caused cellular damage in the spleen, heart, and liver. This drug has some side effects which can be seen clinically and experimentally in animal studies when used for short and long time [15,16].

The toxicity profile of methimazole has been seen in previous studies, but effects on the liver and its relevant treatment remain unaddressed [17]. Liu W, had seen the effect of methimazole-induced hypothyroidism on alveolar macrophages. This drug has the ability to affect multiple organs, specifically the liver and thyroid [16]. In large doses, it can result in hypothyroidism and liver disruption.

Thyroxine has been used till now for methimazole induced hypothyroidism, but liver dysfunction caused by methimazole remains unaddressed. So, there is a need to investigate new sources which may deal with all such side effects [16]. Our experimental study clearly indicated that methimazole at 60mg/kg dosage would cause hepatotoxicity at a histopathological level.

In our study, we had seen methimazole induced liver toxicity showing inflammatory change along with pyknosis

CONCLUSION

Methimazole (Anti-thyroid drug) at 60mg/kg body weight, when given orally for 21 days, resulted in pathological liver showing pyknosis, inflammation, and karyolysis. There is a need to investigate new sources which may manage all such adverse effects of such a common anti-thyroid drug.

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CONFLICT OF INTEREST: None.

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Author's Contribution:

Maira Bhatti: Designed this study and prepared this manuscript, and are responsible and accountable for the accuracy or integrity of the work.
Waqas Iqbal Butt: Discussion and histological study.
Shahnaz Fatima: Planned and carried out the experiments.
Fouzia Perveen: Compiled the results.
Sabeen Arjumand: Bibliography.
Amna Iqbal Butt: Sampling and data analysis.