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Effect Of Propylthiouracil On Fetal Mice Liver

Anatomy

KEYWORDS: Antithyroid drug, organogenesis, hepatotoxic.

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ABSTRACT

Background: Propylthiouracil, an antithyroid drug used to treat hyperthyroidism in pregnancy. Optimal treatment of hyperthyroidism during pregnancy is essential for favourable pregnancy outcome. Aim: The aim of this study is to observe the teratogenicity of Propylthiouracil given during organogenesis period of gestation on fetal liver. Methods: Pregnant Swiss albino mice were given Propylthiouracil in the dose of 100 mg/kg body weight/day orally on 6, 7 & 8th days of gestation, while control mice were given same volume of distilled water orally for same duration. The pregnant mice were sacrificed on 18th day of gestation and foetuses were collected. The fetal liver were dissected out, formalin fixed and processed for histological study with H&E staining. Result: The treated liver, on gross examination shows reduction in size and weight. While histological examination shows dilatation of central vein and sinusoids with breakage of their lining endothelium and clumping of pyknotic hepatoblasts around central vein along with destruction of liver parenchyma. Conclusion: Propylthiouracil should be used cautiously in pregnancy to avoid risk of congenital malformations due to its hepatotoxic effect.

Introduction-

Teratology is the study of abnormal prenatal development and congenital malformations induced by exogenous chemical or physical agents, which continues to be growing area of medical research in the quest for the eradication of preventable birth defects[1].

In pregnancy, the hyperthyroidism is treated with Propylthiouracil and Methimazole/Carbimazole (antithyroid drugs). Propylthiouracil, currently is recommended as the drug of choice during early pregnancy in hyperthyroid patients[2].

Propylthiouracil has been preferred over Methimazole because transplacental passage was thought to be lower; however, both Propylthiouracil and Methimazole cross the placenta equally[3]. Because of the few number of reports of foetal anomalies associated with maternal use of Propylthiouracil during pregnancy as compared to Methimazole, it has been assumed to have a more favourable teratogenic profile and is therefore recommended for use in pregnancy[4,5]. There have, however, been a small number of birth defects reported in association with prenatal Propylthiouracil use since its introduction in 1947[6,7,8]. Recently, a hepatotoxicity risk of Propylthiouracil has been uncovered, especially in children and pregnant women[9]. Thus, to minimize risks to the mother and foetus, it has been suggested that Propylthiouracil use be restricted to the first trimester of pregnancy and changed to Methimazole thereafter[10,11]. But recent studies show the teratogenic potential of Propylthiouracil even when given during first trimester of pregnancy or period of organogenesis. Propylthiouracil should not be used in children except in the case of Methimazole allergy[9,12].

Despite widespread antithyroid drugs usage in pregnancy, formal studies of teratogenicity have yet to be performed [13]. The aim of this study is to observe the teratogenic potential of Propylthiouracil during organogenesis period of gestation in pregnant mice, on fetal liver.

Methods

The present teratological study was conducted in the Teratology laboratory of the Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University, Varanasi, U.P., India after taking approval from Institutional Ethical Committee.

Twenty one female Swiss albino mice of an average body weight of 20-25 gm and about six weeks of age were used in this study. Animals were housed individually in plastic cages in departmental animal house on a light: dark cycle of 12:12 hours. The temperature was maintained at 20-25 0C with 65% relative humidity. Throughout the study animals were fed on pelleted diet and tap water provided ad libitum.

Female mice were shifted in the evening to the cages containing male mice of same stock in the ratio of 2:1. The presence of vaginal plug on the following morning indicates pregnancy and was considered as day 0 of gestation (GD 0). The pregnant mice were divided into two groups i.e. control and treated. Treated group received 2mg of the drug (100 mg/kg body weight/day) by oral gavages on 6, 7 & 8th days of gestation, while control mice were given same volume of distilled water orally for same duration.

The pregnant mice were sacrificed by cervical dislocation on 18th day of gestation. The foetuses were collected after performing laprotomy and fixed in 10% formalin solution. After 48-72 hours, liver were dissected out from the foetuses, weighed, observed for gross features and then processed for H&E staining. The microscopic findings of treated group were compared with the corresponding control.

Results

On gross examination, treated fetal liver shows reduction in size (Fig.2). There is also statistically significant decrease in fetal liver weight of treated mice as compared to the control weight (Table1,Fig.1). On microscopic examination, control liver shows well developed parenchyma with developing central veins and sinusoids (Fig. 3A,4A,5A). While, treated liver shows degenerated parenchyma, dilated central vein and sinusoids under low magnification (Fig.3B). On higher magnification, it shows dilated central vein with breakage of its lining endothelium (Fig.4B,5B) and clumping of pyknotic hepatoblast cells in peri-central vein area (Fig 6B).

Discussion

Propylthiouracil has been used in the treatment of hyperthyroidism, mainly in first trimester of pregnancy. Propylthiouracil easily crosses the placenta, therefore maternal treatment during pregnancy leads to considerable foetal exposure to the drug[3].

In the present study, liver showed reduction in size as well as weight. In a previous human study, it has been observed that Propylthiouracil causes hepatocellular type of liver injury in most cases evident by parenchymal necrosis, collapse of lobular architecture and pre-portal mixed inflammatory infiltrate [14,15]. The microscopic feature of

treated liver in present study showed destruction and degeneration of liver parenchyma and dilatation of central vein and sinusoids with destruction of its lining endothelium along with clumping of pyknotic hepatoblasts cells around central veins.

In vitro studies, has shown that Propylthiouracil can be metabolised into different intermediate metabolites namely propyluracil-2-sulfonate by both thyroperoxidase and myeloperoxidase system of phagocytic cells. It is a highly reactive compound that covalently binds to sulfhydryl groups of proteins to form sulphide adducts which may be responsible for the adverse immunological side effects of Propylthiouracil [16]. These reactive metabolites may probably explain the degenerative changes of liver found in present study.

Propylthiouracil causes altered differential gene expression that involves cytoskeletal remodelling, which in turn define cell cytostructure and cytodynamics by altered signalling pathways. These pathway components play a role in cytoskeletal organisation, epithelium morphogenesis and neuronal survival [2]. Ruoxing Yu et al. (2015)[17] classified Cat. D drugs into IV classes based on their differing effects on primitive streak formation, Propylthiouracil belongs to Class II according to this classification. Defective primitive streak formation leads to defective formation of all the three germ layers and structures derived from them. These theories reveal the basis for the destructive microscopic changes observed in liver in the present study.

Based on these data, it is logical to conclude that Propylthiouracil should be considered as teratogenic drug, especially during period of organogenesis. As hyperthyroidism is a common endocrinal disorder during pregnancy, antithyroid drug usage is mandatory to achieve better pregnancy outcome. So, Propylthiouracil should be used cautiously in women of reproductive age suffering from hyperthyroidism to avoid risk of congenital malformations.

Tables & Figures

S.No.	Parameter	Group	N	Mean	S.D.	S.E.	p-value
1.	Fetal Liver Weight(g)	Control	25	0.11676	0.006884	0.001377	p< 0.001
		Treated	35	0.10513	0.015178	0.002565	

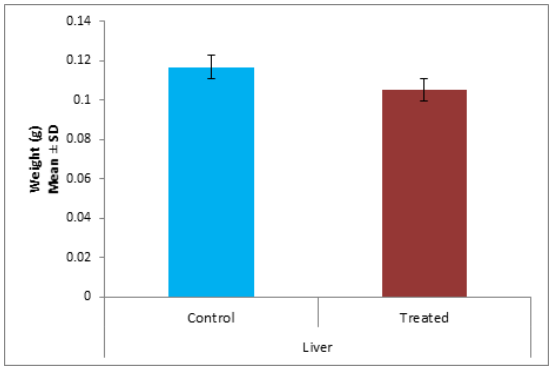

Fig 1: Bar diagram showing significant reduction in weight of treated liver.

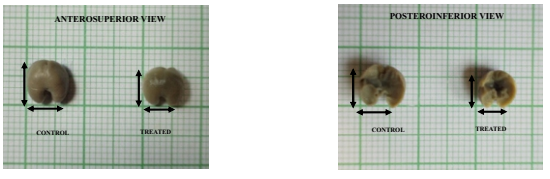

Fig 2 : Gross photograph of treated liver showing reduction in size as compared to control

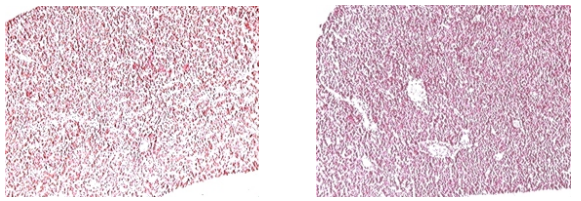

Fig 3,A: Photomicrograph of control liver showing normal architecture of the developing parenchyma;100X.

Fig 3,B: Photomicrograph of treated liver showing dilated central vein () and destruction of developing parenchyma; 100 X.

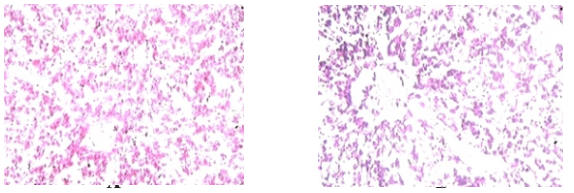

Fig 4,A: Photomicrograph of control liver showing normal appearance of the parenchyma, central vein and sinusoids with their endothelial lining; 400 X.

Fig 4,B: Photomicrograph of treated liver showing degenerated parenchyma, dilated central vein ()and sinusoids with destruction of their endothelial lining (); 400 X.

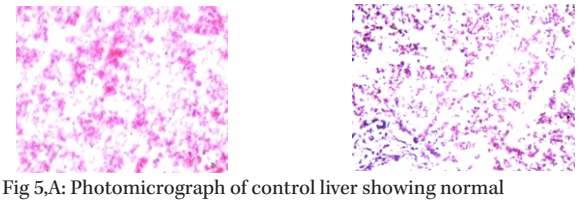

Fig 5,A: Photomicrograph of control liver showing normal appearance of sinusoids; 400 X.

Fig 5,B: Photomicrograph of treated liver showing degeneration of hepatoblast cells and dilatation of sinusoids (); 400 X.

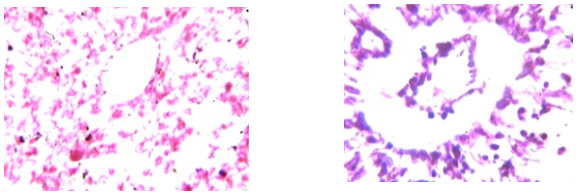

Fig 6,A: Photomicrograph of control liver showing normal appearance of the hepatoblast cells and central vein with its lining endothelium; 1000 X.

Fig 6,B: Photomicrograph of treated liver showing dilated central vein with breakage of its lining endothelial layer () and clumping of pyknotic hepatoblast cells in peri-central vein area (); 1000 X.

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