



Carbimazole and its effects on thyroid gland of female rabbits

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Abstract

The present study aimed to investigate the histological ,histochemical changes of thyroid gland in case of induced hypothyroidism by carbimazole in domestic female rabbits .

Histological results revealed many histopathological changes compared with the control group there are hyperatrophy of follicular epithelium , hemorrhage ,edema and damage in the epithelium lining of the follicles.

Histochemical examination of thyroid gland of control rabbits show the intensity and homogenous staining of colloid figure while the thyroid gland of female rabbits treated with CBZ for 30 days show decreased of normal distribution of glycoprotein inside follicles ,the non-homogenous cord like materials and less intensity of colloid figure , also the thyroid gland of rabbits treated with CBZ for 60 days show less homogenisty of colloid or absence of colloid in some follicles .

Key Word: Carbimazol,thyroid gland,rabbit

INTRODUCTION

Formation of Thyroid gland

The thyroid gland is a butterfly- shaped endocrine gland lying in the neck in front of the upper part of the trachea [1] The thyroid gland consist of two lobes connected by a narrow band of thyroid tissue called the isthmus , it is surrounded by a double connective tissue capsule , two pairs of parathyroid glands are located on the posterior surface of thyroid gland [2]

The thyroid follicle or acinus ,which is the structural and functional unit of the gland , it is consist of a single layer of cuboidal epithelial cells , the follicular epithelium enclosing a central lumen containing a colloid substance rich in thyroglobulin an iodinated glycoprotein[3] The follicular epithelium contain scattered Para follicular cells also called C cells contain small cytoplasmic granules representing the stored hormone calcitonin which regulate calcium concentration in blood [4]

Thyroid gland secret three important hormones triiodothyronine T₃ ,thyroxin T₄ ,and calcitonin [5] The extracellular storage of thyroglobuline in the follicular lumen is essential for maintaining constant blood levels of thyroid hormones T₃ and T₄ .

Thyroid function is to synthesize the hormones T₃ ,T₄ which are important for growth ,for cell differentiation and for the control of oxygen consumption and basal metabolic rate of cells in the body .

Hypothyroidism is a deficiency of thyroid activity , it is results from reduced secretion of both T₃ and T₄[6] So ,this study was carried out in order to demonstrate the histological and histochemical effects of thyroid gland in case of induced hypothyroidism in domestic female rabbits

Carbimazole

Carbimazole is an antithyroid drug widely prescribed for treatment of hyperthyroidism. It is a 3-carbethoxy methimazole derivative, metabolized to methimazole in the liver.

Serum thyroxine,thyroid-stimulating hormone and thyrotropin-binding inhibitory immunoglobulins are decreased after 2,4and 6 weeks of carbimazole treatment[7]. Frenais et al.[8] reported that carbimazole is common oral treatment for hyperthyroidism in cats.On the other hand,

the use of carbimazole was associated with various adverse effects.

Ali et al.[9] showed that carbimazole produced mild necrosis of renal tubules in rats. Mar Azuela et al.[10] mentioned that carbimazole was capable of inducing acute pancreatitis and cholestasis hepatitis in 33-year old female. Zaidi et al.[11] reported that carbimazole administration even in therapeutic dose during pregnancy and lactation resulted into alteration of the thyroid microstructure of the newborn. Pulmonary hemorrhage and necrotizing glomerulonephritis were associated with carbimazole therapy[12]. Vilchez et al.[13] reported that carbimazole therapy caused both minor (e.g.pruritus,rash,urticaria, fever and arthralgias) and potentially life-threatening (e.g.agranulocytosis,hepatotoxicity with severe cholestasis jaundice) effects.

Carbimazole is an antithyroid medication which is generally used to treat hyperthyroidism [14] . Carbimazole is a prodrug of the active structure methimazole which keeps the thyroid peroxidase enzyme from coupling and iodinating the tyrosine deposits on thyroglobulin, consequently decreasing the generation of T₃ and T₄ Treatment with carbimazole typically proceeded for 12 to year and a half took after by a trial withdrawal . Also treatment with carbimazole was joined by numerous symptoms.

[15] observed that carbimazole treatment brought on some symptoms (e.g. pruritus, rash,urticaria, fever, arthralgias, agranulocytosis,hepatotoxicity with extreme cholestasis jaundice).

Following treatment of patients with propylthiouracil and methimazole, proliferative cell nuclear antigen (PCNA)expression is markedly reduced, proposing that carbimazole have an antiproliferative effect. The proposed mechanism of methimazole activity is intracellular: it brings down the level of proliferating cell nuclear antigen (PCNA). PCNA advances specific apoptosis in some T lymphocyte clones [16].[17] recorded that carbimazole has cytogenetic effect and increase the frequency chromosomal abnormalities in peripheral blood lymphocytes of ewe and ram sheep..[18] showed that treatment with carbimazole caused suppression of neurogenesis and enhancement of DNA fragmentation in the hippocampus rat pups.[19] reported that administration of methimazole was associated

with agranulocytosis and hepatotoxicity, which are the two most significant adverse effects. [20] concluded that carbimazole increased lipid peroxides from both thyroid gland and serum.

Large number of plants and their extracts are now used in medicine and treatment of various diseases. Due to the biological effects of these substances which have antioxidant properties, they are important in medicine.

The roots of ginger (*Zingier officinal*) is an example of botanicals which play an important role in pharmacology and treatment of various diseases. (21) showed that *Zingier officinal* improved the results in animals injected intraperitoneally by 5mg/kg busulfan solution. [22] demonstrated that treating animals with deltamethrin and ginger revealed an improvement in the histological changes observed in animals treated with deltamethrin. Examination of liver sections of ginger and metalaxyl treated animals revealed reduction of box and preservation of nearly normal histological structure with slight congested blood vessels and few cellular infiltration [23]. revealed that ginger extract has protective effect against cyclophosphamide which cause induction of chromosomal abnormalities in somatic cells of mice. [24] showed that ginger has anti-mutagenic action against the anti-cancer drug Taxon genotoxicity. Ginger exhibit antioxidant properties formalin by the increase of SOD and CAT activities [25&26].

MATERIALS AND METHODS

The studied animals included 32 female mature rabbits were divided into four groups: two control groups for 30 and 60 days ,two hypothyroidic groups for 30 and 60 days of treatment which were bred in the same Environmental condition. Hypothyroidism was induced by using carbimazole (5 mg /kg bw) dissolved in water and given orally by stomach tube daily through out the experiment while the control groups received normal saline .

Histological study :

Tissue samples were taken of thyroid gland ,these specimens were placed in fixative 10% buffered formalin immediately upon removal from the body, after tissue processing and embedding in paraffin section were cut at 6 microns thickness then the slides were stained with hematoxylin and eosin stain .

Histochemical study :

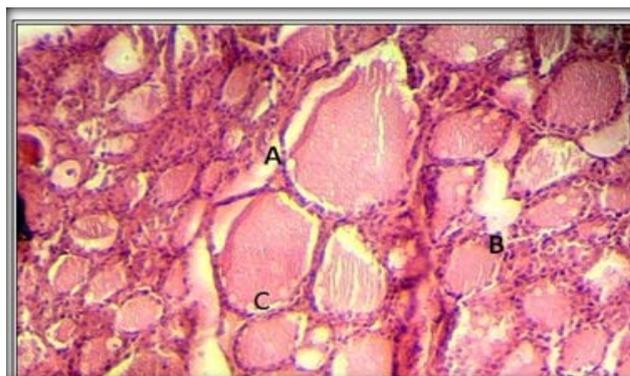
Paraffin section 6 microns thickness stained with periodic acid-shiffs reagent to demonstrate glycoprotein of thyroid follicles .

RESULTS

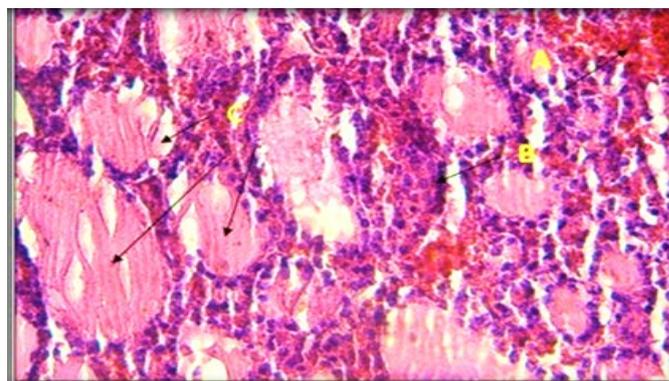
The results of histological study revealed histopathological alterations in thyroid gland in comparison with the control group figure (1) in case of hypothyroidism for 30 days of treatment with carbimazole figure (2) there is hyperatropy of follicular epithelium and non homogenous colloid or cord like materials inside follicles ,congested blood vessels and hemorrhage ,however in case of hypothyroidism for 60 days of treatment with carbimazole figure (3) there is hyper

atrophy of cell lining epithelium or follicular epithelium and infiltration of inflammatory cells with edema between connective tissue septa of thyroid gland and damage in the epithelial lining follicles, some follicles enlarged.

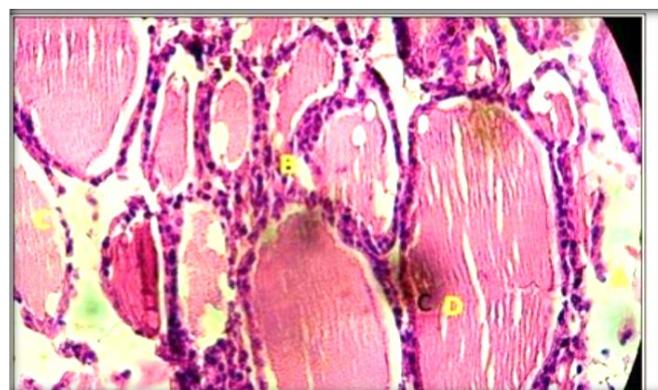
Histochemical examination of thyroid gland of control rabbits show the intensity and homogenous staining of colloid figure (4) while the thyroid gland of female rabbits treated with CBZ for 30 days show decreased of normal distribution of glycoprotein inside follicles ,the non homogenous cord like materials and less intensity of colloid figure (5) also the thyroid gland of rabbits treated with CBZ for 60 days show less homogeneity of colloid or absence of colloid in some follicles figure (6)



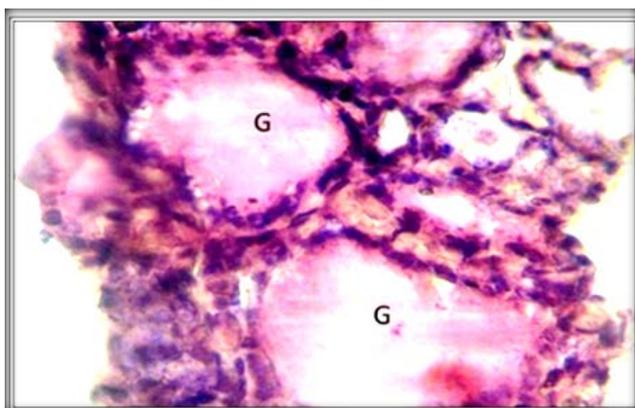
Fig(1) section of thyroid gland control female rabbit showing A=follicles B=parafollicular cells, C=colloid (H&E stain, 400x)



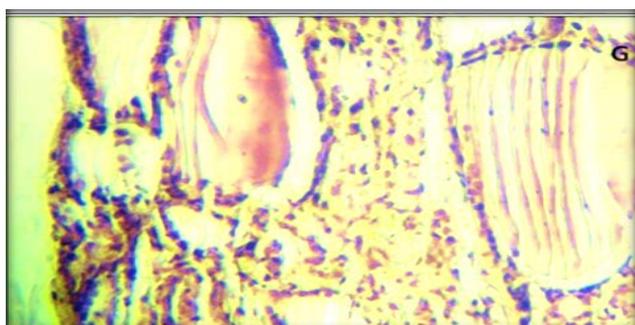
Fig(2) section of thyroid gland treated of female rabbit for 30 days showing A-hemorrhage B-hyperatropy of follicular epithelium C-cord like colloid .(H&E, 400X)



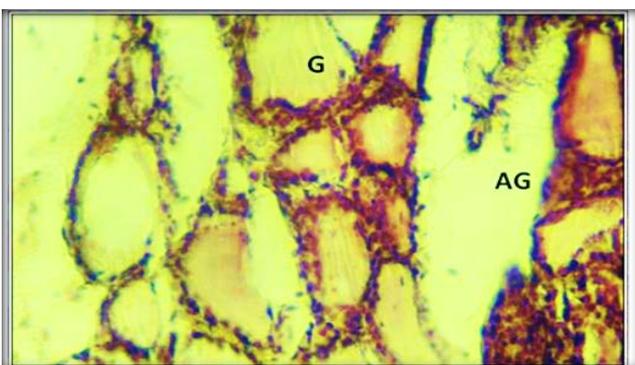
Fig(3) Section of thyroid gland of female rabbit treated for 60 days showing A-edema B-hyperatropy of follicular cell ,C-damage of follicular epithelium ,D-cord like colloid (H&E stain 400X)



Fig(4) Section of thyroid gland in control showing G-homogenous distribution glycogen in thyroid follicles (PAS stain 400X)



Fig(5) Section of thyroid gland of treated female rabbit for 30 days showing G-cord like colloid (PAS stain 400X)



Fig(6) section of thyroid gland treated female rabbit for 60 days showing G-colloid less homogeneity AG-absent of colloid in some follicles (PAS stain ,400X)

DISCUSSION

The histological results of thyroid gland after induction of hypothyroidism for 30 and 60 days by CBZ reveal hyperatrophy of follicular epithelium [27] mention that CBZ which is anti thyroid drug inhibit the formation of T3 and T4 , which stimulate the anterior pituitary gland to secrete more TSH and this hormone stimulate the growth of thyroid gland ,results hyper atrophy of follicular epithelium ,these results are in agreement with [28] found that induce hypothyroidism in mice by sodium fluoride characterized by follicular cells hyperplasia and hyperatrophy and increase in vascularity also the results are in agreement with [29] induce hypothyroidism in virgin and lactating rabbits by CBZ, and agreement with [30,31,32] induce hypothyroidism in male rats stimulate secretion of TSH which cause hyperatrophy of follicular

cells , also agreement with [33]CBZ in human cause hyperatrophy of follicular cells . On the other hand the results reveal congested blood vessels in 30 days of treatment and hemorrhage in 60 days of treatment in thyroid tissue [34] mention that because inhibit T3, T4 secretion from thyroid gland in case of hypothyroidism is made to exert a negative feedback of TSH synthesis and increase secretion , this hormone stimulate the vascularization of thyroid gland and consequently the gland enlarged , TSH increase blood flow to thyroid gland and other organs and tissues [35] so this may cause destruction to the blood vessels results hemorrhage in thyroid tissue. Low level of T3 T4 lead to hypoxia that result bloody congestion hepatic dysfunction lead to blood congestion due to hypoxia [36] . The results show edema in thyroid gland in female rabbits treated with CBZ for 60 days ,because of the destruction of large follicles of thyroid gland due to induction of hypothyroidism for long period ,some follicles appear empty with out colloid which may accumulated in thyroid tissue ,in which there is increase the filtration of fluid out of the capillaries and edema due to accumulation of osmotically active mucopolysaccharides in the interstitial fluid [37]or due to change in the permeability of congested blood vessels resulting edema .low level of T3 T4 cause hepatocytes damaged lead to adema appearance [38].

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