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 homogenesty 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 secrete 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-inhibiting hormone immunoglobulins are decreased after2,4and6 weeks of carbimazole treatment[7]. Frenais etal.[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 (Zingiber officinal) is an example of botanicals which play an important role in pharmacology and treatment of various diseases.(21) demonstrated that treating animals with dexamethasone and ginger revealed an improvement in the histological changes observed in animals treated with dexamethasone. 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 Taxol 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 breeded 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 throughout 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 hyperatrophy 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 homogenisty of colloid or absence of colloid in some follicles figure (6).
secretion of TSH which cause hyperatrophy of follicular epithelium [30,31,32]. Induce hypothyroidism in male rats stimulate CBZ which is anti thyroid drug inhabit the formation of 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 vascularity 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].

**REFERENCES**


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