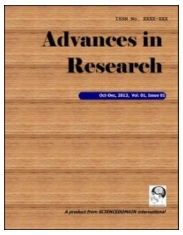

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Effects of Dose Level of Anti-thyroid Drug Carbimazole on Thermoregulation and Blood Constituents in Male Rabbits (*Oryctolagus cuniculus*)

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Authors' contributions

This study was performed in collaboration between all the authors. Author AMA designed the study protocol and participated in writing the manuscript. Author IHS carried out the laboratory analysis and wrote the initial version of manuscript. Author MEA participated in preparation of the manuscript and presentation of the results. All the authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Carbimazole (CBZ) is an anti-thyroid drug commonly used in the treatment of hyperthyroidism**.** The objective of this study was to evaluate the effects of dose level of CBZ on thermoregulation and blood constituents in mature male rabbits. Twenty animals were assigned to 4 groups (A, B, C, D) of 5 each. Group A served as control and treated animals in groups B,C,D, received daily orally CBZ doses of 10, 15 and 20 mg/animal for 3 weeks, respectively. The values of rectal temperature (Tr,), respiration rate (RR) and heart rate (HR) decreased in treated rabbits and the mean values of HR decreased with increase in the dose level of CBZ. The packed cell volume (PCV), Hb concentration and total leukocyte count (TLC) were lower in CBZ treated rabbits. Serum levels of total protein and globulins increased and serum albumin level decreased in treated groups of rabbits. Serum urea level was lower in CBZ treated groups and there was an increase in serum urea level with increase in CBZ dose level. Serum cholesterol level was higher in treated groups and there was an increase in serum cholesterol level with increase in CBZ dose level. Plasma glucose level decreased significantly in CBZ treated groups compared

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with the control and the mean values decreased with increase in the dose level of CBZ. The results indicate that the responses of basic physiological parameters were almost dose dependent in the range adopted in this study.

Keywords: Antithyroid drug; carbimazole; thermoregulation; blood constituents; rabbits.

1. INTRODUCTION

Several compounds have the ability to inhibit thyroid hormones synthesis with various mechanisms of action. The antithyroid drugs interfere directly with the synthesis of thyroid hormones [1,2], while inhibitors block the iodide transport mechanism [3,4,5] . Iodine in high concentration suppresses the thyroid [6] and radioactive iodine damages the gland with ionizing radiations [7].

The chemical compounds carbimazole (CBZ), propylthiouracil (PTU) and methimazole (MMI) are thioureylenes which belong to the family of thionamides [8]. The thionamides inhibit the synthesis of thyroid hormones by inhibiting the thyroid peroxidase catalyzed reactions to block iodine organification [9]. PTU also blocks extrathyroidal conversion of thyroxine to triiodothyronine [10,11]. Hypothyroidism induced by PTU in rabbits was associated with significant lowering in T3, T4, free triiodothyronine (FT3) and free thyroxine [12]. Mannisto et al. [13] reported that in rats receiving graded doses of the antithyroid drugs PTU and MMI, the concentrations of T3 and T4 decreased and serum TSH level increased.

Chronic administration of CBZ to hyperthyroid cats depressed the serum total thyroxine level and decreased the heart rate and respiratory rate. CBZ also induced hematological changes which included lymphocytosis and agranulocytosis [14,15,16] and anemia [17,18]. CBZ is used as antithyroid drug for the presurgical treatment and with radio-iodine for the control of hyperthyroidism in humans [19]. It proved to be a safe and effective drug in both the short and long term management of hyperthyroidism in humans [8] and the responses to CBZ may differ with dose level and thermal environment. The use of CBZ was reported to be accompanied by deleterious effects which include agranulocytosis, immunosuppression and hepatotoxicity associated with cholestatic jaundice [20,21]. Also liver abnormalities may occur in mammals treated with CBZ [21], indicating that secondary effects must be considered when interpreting responses to this drug. Therefore studies are needed to evaluate the efficacy and side effects of this drug.

The aim of this study was to evaluate the effects of dose level of CBZ on thermoregulation and blood constituents in male rabbits. As the optimal dose regimen for CBZ in the treatment of hyperthyroidism remains uncertain [22], it was intended to establish a suitable effective dose of CBZ to induce experimental hypothyroidism in rabbits.

2. MATERIALS AND METHODS

2.1 Experimental Animals and Management

Twenty local breed adult healthy male rabbits with an initial mean body weight of 1.20 kg and aged 8-10 months were used. The study was conducted at the animal house of the Department of Physiology during summer (mean ambient temperature (Ta): 28.98±1.81ºC, mean relative humidity (RH): 21.70±4.0%). Animals were subjected to thorough clinical

examination and were give anthelmintic injection (Ivomec: 0.02 ml/kg BW: Alpha Laboratories Ltd, India) and antibacterial injection (Oxytetracycline: 7.5 mg/kg BW: Alpha Laboratories Ltd, India). The animals were kept in an animal house provided with adequate ventilation under natural light-dark photoperiod. Animals were kept for a preliminary adaptation period of 2 weeks and then they were subjected to the experimental protocol for 3 weeks. During the adaptation and experimental periods, the animals were fed fresh lucerne (*Medicago sativa*) (CP: 161.5 g/kg; ME: 7.3 MJ/kg) and sorghum grains (CP: 130.2 g/kg; ME 13.6 MJ/kg) and were given free access to tap water.

2.2 Experimental Design

The animals were randomly assigned to 4 groups (A, B, C, D) of 5 animals each. Group A served as control and the treated groups B, C, D received daily oral doses of 10, 15 and 20 mg of CBZ/animal for 3 weeks, respectively. The drug CBZ (Neomercazole, Roche products Ltd., England) was ground thoroughly and dissolved in distilled water before administration. During the experimental period, the rectal temperature (T_r), respiration rate (RR) and heart rate (HR) were measured at appropriate selected time intervals at 8 a.m. Jugular blood samples were collected every 4 days and the body weights (BW) of the rabbits were obtained on day 0, 12 and 21.

2.3 Measurements of Rectal Temperature (Tr), Respiratory Rate (RR), Heart Rate (HR) and Body Weight (BW)

Tr was measured by a digital clinical thermometer (Hartman-United Kingdom). RR was measured by visually counting the flank movements for one minute. HR was obtained by monitoring heart sounds for one minute using a stethoscope. The BW of animals was measured using a standard balance (Every – United Kingdom).

2.4 Collection and Processing of Blood Samples

One blood sample (5 ml) was obtained by jugular vein-puncture of each rabbit using disposable syringe. 1mmediately after withdrawal, 1 ml of blood was transferred to a clean dry test tube containing K_2-EDTA as an anticoagulant and was used for the hematological analysis. Then 1 ml of blood was kept in a clean test tube containing sodium fluoride to inhibit enzymatic reaction. The blood sample was mixed with the anticoagulant gently to prevent clotting and was centrifuged at 3000 r.p.m. for 15 min to separate plasma, which was used for glucose determination. The rest of the blood sample was allowed to stay for 2 hrs at room temperature and then centrifuged (Gallenkamp junior) at 3000 r.p.m. for 15 min to separate serum. Hemolysis-free serum samples were pipetted into clean vials and immediately frozen at -20ºC for subsequent analysis.

2.5 Hematological Measurements

The hemogram parameters were determined according to the standard methods [23]. The PCV was measure in plain capillary tubes using a microhaematocrit centrifuge (Hawksley, London). The Hb concentration was determined by cyanmethaemoglobin technique using Drabkin's solution. Improved Neubauer hemocytometer was used to perform total leukocyte count (TLC) using Turk's solution as a dilution fluid.

2.6 Blood Metabolites

The Biuret reagent was used to determine serum total protein concentration [24]. The colorimetric method [25] was used to determine serum albumin concentration. Serum urea concentration was determined by the enzymatic-colorimetric test (Berthlot) kit (Spinreact, S.A., Spain). Serum cholesterol concentration was determined by enzymatic colorimetric method using a kit (Randox Laboratory Ltd., London). Plasma glucose level was determined by colorimetric method using a commercial kit (Spinreact S. A., Spain).

2.7 Statistical Analysis

The experimental data collected were subjected to standard methods of statistical analysis using statistical analysis system [26]. Analysis of variane (ANOVA) test as factorial completely randomized design was used to examine the effect of dose level of CBZ on the parameters measured. The data are expressed as mean values ± standard deviation (SD). The separation of means was done by Duncan Multiple Range Test.

3. RESULTS

3.1 Rectal Temperature (T_r)

Fig. 1 shows that the initial values of T_r were close to each other (≈ 39.4ºC). However, for all experimental groups, there were considerable fluctuations in T_r during the experimental period. The general pattern indicates that there was a decrease in T_r of treated groups compared with the control group. On day 3, the mean values of T_r with the high dose of CBZ (20 mg/animal/day) was significantly ($P< 0.05$) lower than the value obtained for the control group. The treated groups also maintained lower values of T_r compared to the respective control values on days 12 and 15. On day 18, the high dose group had significantly ($P< 0.05$) lower T_r compared to the value of the control. On day 21, the pattern indicates that there was graded decrease in T_r with increase in CBZ dose.

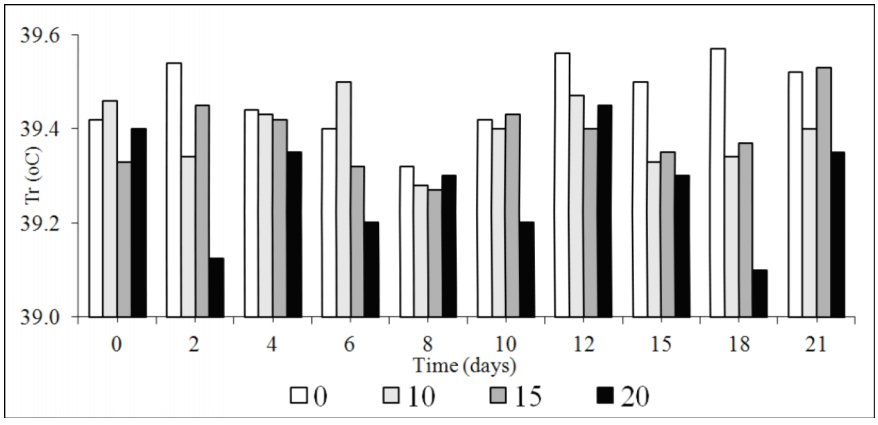

Fig. 1. Effect of dose level of CBZ (mg/animal/day) on rectal temperature (Tr) in male rabbits

3.2 Respiration Rate (RR)

Fig. 2 shows the effect of dose level of CBZ on RR. The initial values of RR were not similar and there were considerable fluctuations during the experimental period. On day 6, the group receiving the low dose (10 mg/animal/day) of CBZ had significantly ($P< 0.05$) lower RR compared to the value obtained for the group receiving the medium dose (15 mg/animal/day). On day 9, the treated groups had significantly ($P< 0.01$) lower RR values compared to the value of control group. The high dose group had significantly ($P< 0.01$) lower RR value compared to the value of the control on day 18. The results indicate that the treated groups had lower RR than control on day 21.

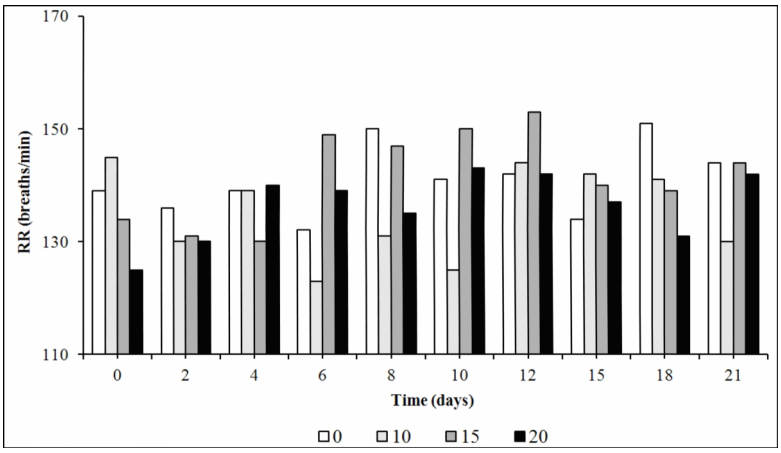

Fig. 2. Effect of dose level of CBZ (mg/animal/day) on respiratory rate (RR) in male rabbits

3.3 Heart Rate (HR)

Fig. 3 shows the results of the effects of dose level of CBZ on HR of rabbits. The general pattern indicates that all groups maintained high HR values until day 9. Thereafter, there was progressive decline in HR for all groups, with slight elevations after day 15. On day 6, the control group and the groups receiving low and high doses maintained significantly ($P< 0.05$) lower HR compared to the value of the group receiving the medium dose. The high dose group had significantly ($P< 0.01$) lower HR than other groups on day 9. The mean values of HR of treated groups were lower compared to the control on days 12, 15, 18 and 21. On day 18, the HR was significantly ($P< 0.01$) lower with the high dose compared to the control value. Fig. 3 shows that on day 21, the high dose group had significantly ($P< 0.05$) lower HR compared to values obtained for other groups.

3.4 Body Weight (BW)

Fig. 4 shows the effects of dose level of CBZ on the mean BW of rabbits. The initial values of BW ranged between 1.19 and 1.25 kg. There was an increase in the mean BW of all groups during the experimental period. The treated groups maintained higher values of BW compared to the respective control values. On days 12 and 21, the group receiving medium dose (15 mg/animal/day) had higher mean values of BW than other groups.

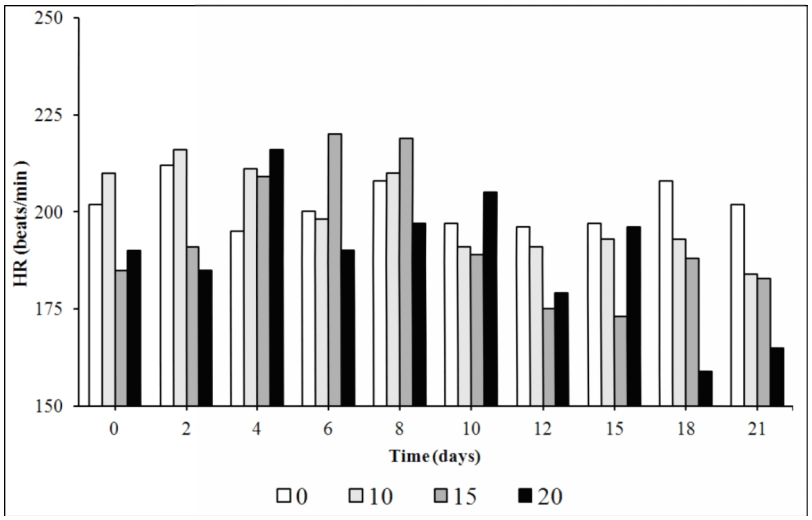

Fig. 3. Effect of dose level of CBZ (mg/animal/day) on heart rate (HR) in male rabbits

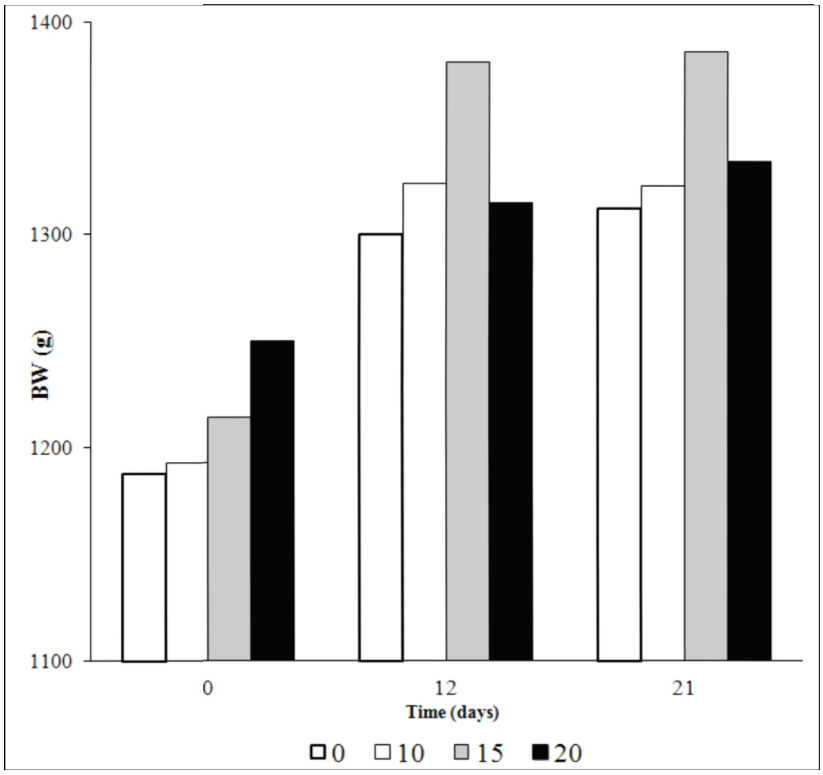

Fig. 4. Effect of dose level of CBZ (mg/animal/day) on body weight (BW) in male rabbits

3.5 Packed Cell Volume (PCV)

Fig. 5 shows the results of effect of dose level of CBZ on PCV level. The general pattern indicates that the PCV level for the control and low and medium dose groups showed a decrease on day 5, followed by progressive increase until day 13. Thereafter, there was progressive decrease until day 21. For the high dose group, however, the PCV decreased progressively until day 17; this lower value was maintained on day 21. The analysis indicates that on day 17, the group of rabbits receiving the high dose of CBZ had significantly ($P< 0.05$) lower PCV level compared to the value obtained for the medium dose group.

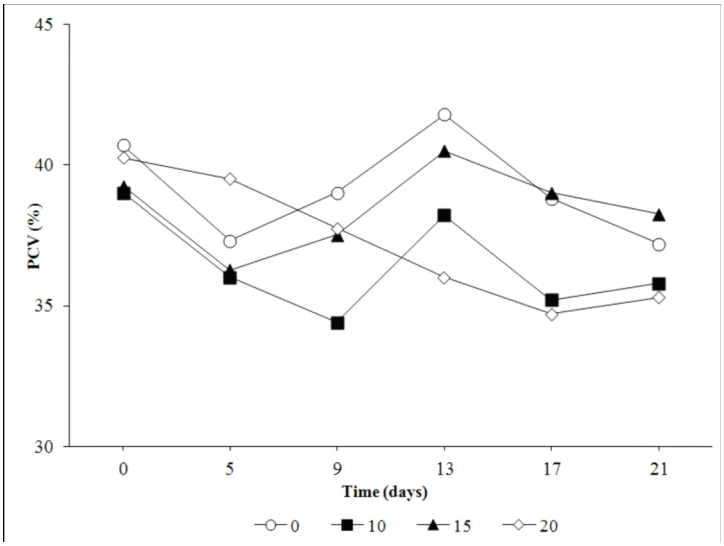

Fig. 5. Effect of dose level of CBZ (mg/animal/day) on packed cell volume (PCV) in male rabbits

3.6 Hemoglobin Concentration (Hb)

Fig. 6 shows that the treated groups of rabbits maintained lower mean values of Hb concentration compared with the values of control group on days 9 and 13. On day 13, the group receiving high dose of CBZ had significantly ($P< 0.05$) lower Hb concentration compared with the control. On day 17, the high dose group had significantly ($P< 0.05$) lower Hb concentration value compared to the group receiving medium dose of CBZ. Both groups receiving low and high dose of CBZ had lower mean values of Hb compared with control on days 17 and 21. For the high dose group, the mean values of Hb concentration decreased progressively during the experimental period.

3.7 Total Leukocyte Count (TLC)

Fig. 7 shows that the initial values of TLC were close to each other ranging between $5.25x10^3/\mu l$ and $5.47x10^3/\mu l$. The general pattern indicates that there was an initial increase in TLC on day 9, and then there was progressive decline in TLC values of all groups until day 17. The treated groups maintained lower mean values of TLC compared to the control on days 13, 17 and 21.

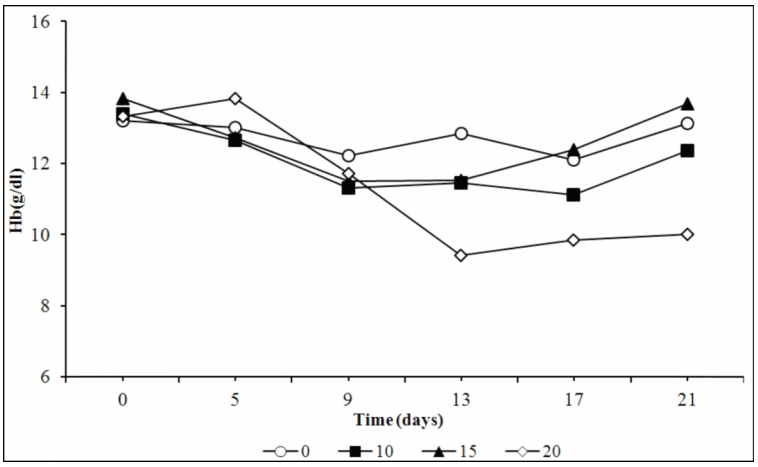

Fig. 6. Effect of dose level of CBZ (mg/animal/day) on hemoglobin concentration (Hb) in male rabbits

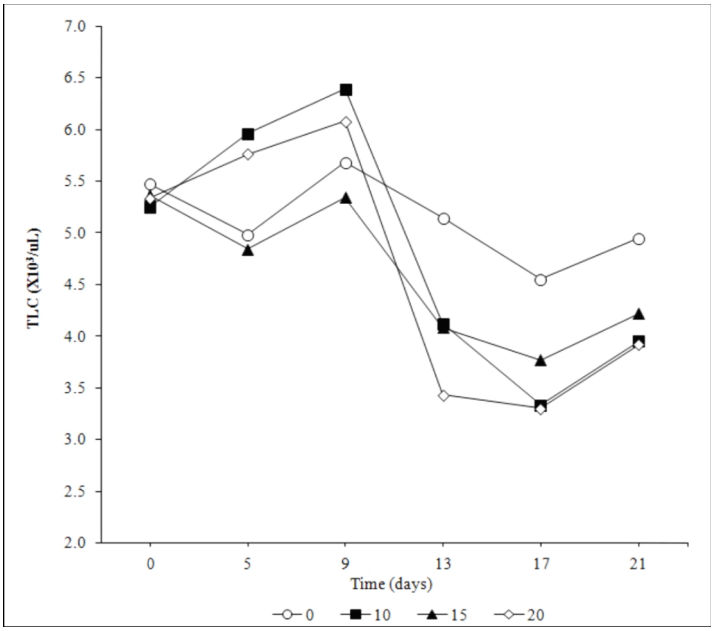

Fig. 7. Effect of dose level of CBZ (mg/animal/day) on total leukocyte count (TLC) in male rabbits

3.8 Serum Total Protein

Fig. 8 shows that the initial values of total protein ranged between 6.24 and 6.80 g/dl. However, there were considerable fluctuations during the experimental period. On day 5, the group receiving high dose (20 mg/animal/day) of CBZ had significantly ($P< 0.05$) higher total protein level compared to the control. On day 13, the treated groups maintained lower values

of total protein compared to the control. On days 17 and 21, the treated groups had higher mean values of total protein compared with respective values obtained for the control.

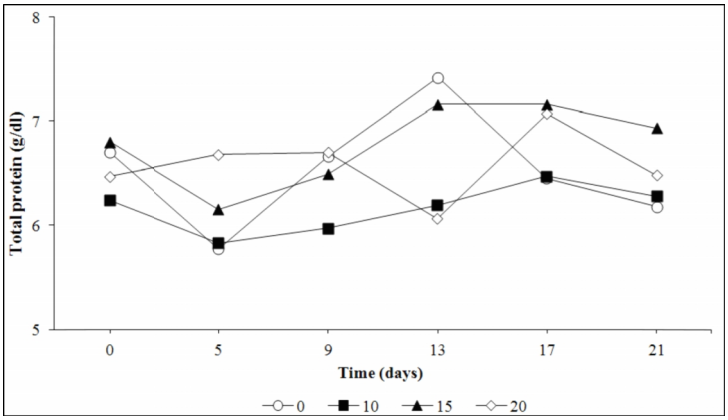

Fig. 8. Effect of dose level of CBZ (mg/animal/day) on serum total protein concentration in male rabbits

3.9 Serum Albumin

Fig. 9 shows that the initial values of albumin concentration ranged between 4.1 and 4.3 g/dl. The CBZ treated group's maintained lower values of albumin level compared with the control during the experimental period. On day 13, the group receiving the high dose of CBZ had significantly ($P< 0.05$) lower albumin level compared with the control. For both groups receiving medium and high CBZ dose, the albumin level declined sharply after day 13. On day 17, the mean values of albumin decreased as the dose was increased to medium and high level.

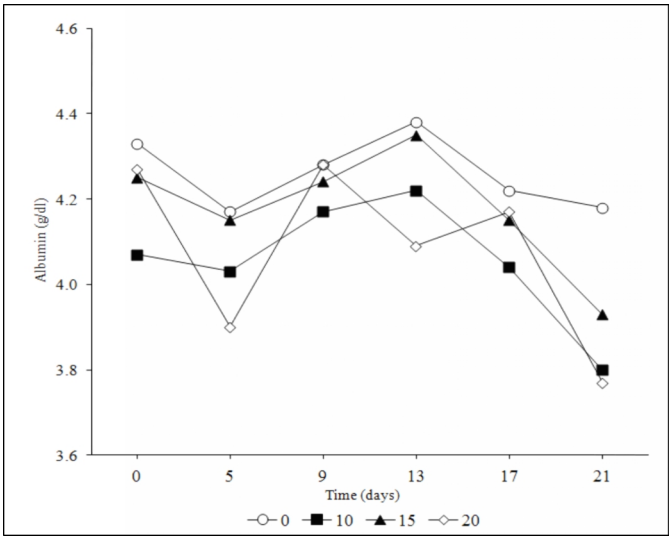

Fig. 9. Effect of dose level of CBZ (mg/animal/day) on serum albumin level in mail rabbits

3.10 Serum Urea

Fig. 10 shows that on day 13, both groups receiving low and high doses of CBZ maintained lower urea level compared to the control. On day 21, the treated groups maintained lower values of serum urea level compared to the control. There was a gradual increase in serum urea level with the increase in the dose level of CBZ.

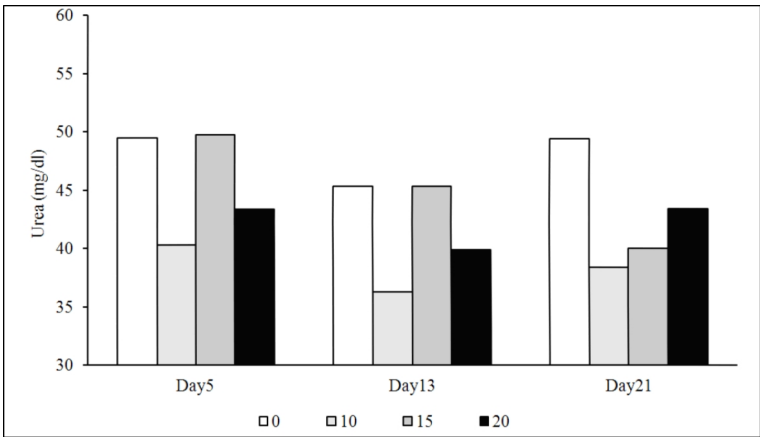

Fig. 10. Effect of dose level of CBZ (mg/animal/day) on serum urea level in male rabbits

3.11 Serum Cholesterol

Fig. 11 shows that the initial values of cholesterol ranged between 45.5 and 52.5 mg/dl. The general pattern indicates that the treated groups maintained higher serum cholesterol level compared with the control, particularly following day 9. The mean values of serum cholesterol were higher for the treated groups on days 13, 17 and 21.

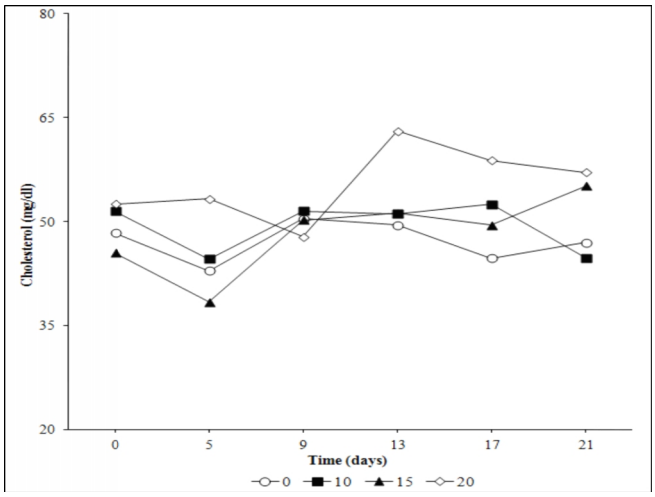

Fig. 11. Effect of dose level of CBZ (mg/animal/day) on the serum cholesterol level in male rabbits

3.12 Plasma Glucose

Fig. 12 indicates that although the plasma glucose level tended to decline during the experimental period for all groups, the treated groups maintained lower values compared to the control. There was gradual decline in glucose level with increase in the dose level of CBZ. The mean values of glucose with the high dose of CBZ was significantly ($P< 0.05$) lower compared to the respective values obtained for the control group on days 9, 13 and 17. There was progressive decline in plasma glucose level with increase in CBZ dose to the medium and high levels.

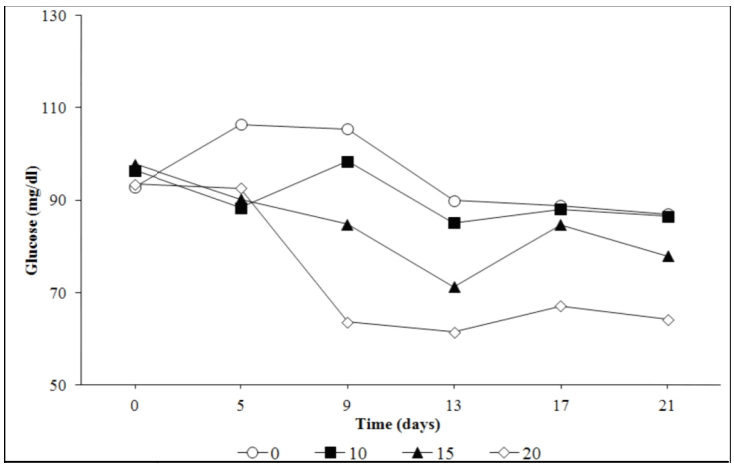

Fig. 12. Effect of dose level of CBZ Dose (mg/animal/day) on the plasma glucose level in male rabbits

4. DISCUSSION

This study investigated the effects of dose level of the antithyroid drug CBZ on thermoregulation and blood constituents in male rabbits. Generally, thioureylene antithyroid drugs are well absorbed from the gastrointestinal tract of monogastric animals [27]. CBZ inhibits thyroid hormone synthesis, but it does not affect deiodinase activity [28,29]. Since the synthesis rather than the release of hormones is affected, the onset of the effect of CBZ is slow [9]. Accordingly, the inconsistent pattern and marked fluctuation reported for most of the parameters investigated in the present study could be related to slow responses of rabbits to graded increase in CBZ dose.

The administration of CBZ decreased the rectal temperature (T_r) in rabbits as from day 12 but treated groups had variable responses to CBZ dose level. This is clearly related to decrease in the secretion of thyroid hormones which reduced the metabolic rate and heat production of rabbits. Mannisto et al. [13] reported that methimazole at 10 and 25 mg/litre in drinking water decreased T4 and increased TSH in rats. The findings in the present study are in agreement with previous studies which demonstrated that basal metabolic rate (BMR), O_2 consumption and energy expenditure decreased in thyroidectomized rabbits [30], rats [30,31] and dogs [32] and in hypothyroidism in humans [33] . Bianco and Silva [34] indicated that hypothyroid rats could not maintain their body core temperature when exposed to cold and the abnormality was rapidly corrected by administration of T4.

The respiratory rate (RR) was lower in rabbits receiving CBZ and the group receiving the high dose had significantly lower RR on day 18. This finding may be attributed to the fact that a decrease in thyroid hormones was associated with lower rates of utilization of O_2 and formation of CO_2. This leads to a decrease in pulmonary ventilation manifested mainly by a decrease in the frequency of respiration. The present findings are consistent with the observations [14] which indicated that in cats receiving 15 mg CBZ/day, hypothyroidism was associated with lower respiratory rate.

Administration of CBZ resulted in a significant decrease in heart rate (HR) and the decrease was proportionate to the dose level of CBZ. This response is related to decrease in the number and affinity of β-adrenergic receptors in the heart and consequently decrease of its sensitivity to the inotropic and chronotropic effects of catecholamines [35]. Seppet et al. [36] indicated that the depression in the contractile function in hypothyroid rat heart is paralleled by slower aerobic energy production and depressed activity of Ca^{2+} pump. Similarly the HR was decreased in thyroidectomized rabbits [37] and in cats treated with CBZ [14]. Granner [38] also found that hypothyroidism in humans was associated with lower HR. The decrease in HR with increase in the dose level of CBZ from 10 to 20 mg in the present study might be attributed to a gradual decrease of the level of thyroid hormones with the increase in dose level of CBZ. In rats, the increase in the dose level of MMI from 10 to 25 mg/litre in drinking water was associated with graded decrease in plasma T4 level [13].

The administration of CBZ resulted in a slight increase in the mean body weight (BW) of rabbits. This response is partially attributable to accumulation of fluid in the interstitial tissue. In hypothyroidism, complexes of protein combined with polysaccharides accumulate in the skin promoting water retention [35]. Also the gain in BW of treated groups might be related to a decrease in BMR. The slow onset of hypothyroidism lowers the BMR and causes reduction in the catabolism of proteins and use of energy for body functions and this causes transient weight gain. In thyroidectomized dogs, the gain in BW was associated with a decrease in BMR [32].

The results indicate that the PCV and Hb concentration were lower in treated groups. Administration of CBZ at 20 mg/animal /day induced progressive decline in both PCV and Hb concentration following day 5. This response is related to decrease in concentration of thyroid hormones which stimulate growth of erythroid colonies directly by stimulating bone marrow metabolic rate or indirectly through erythropoietin production [35]. The current result is consistent with reported decrease in PCV level in thyroidectomized rats [39].

The anaemia of hypothyroidism might be normochoromic or hypochromic and might be due to decrease in production rate of erythrocytes, decrease in iron absorption, decrease in folic acid absorption or to autoimmune pernicious anaemia [9]. Fein and Rivlin [40] indicated that in the absence of thyroid hormones, anemia frequently develops and might be hypochromic-microcytic in hypothyroid subjects. Also CBZ-dependent antibodies were detected in the sera of anemic patients treated with CBZ [18].

The results revealed a decrease in TLC in rabbits receiving CBZ following day 13. This might be related to myeloid hypocellularity in the bone marrow of hypothyroid rabbits. Andre's et al. [16] found that in humans treated with CBZ or MMI, the bone marrow showed myeloid hypocellularity with apparent cessation of myeloid precursor maturation. Research reports of neutropenia associated with antithyroid drugs suggested involvement of an immune-mediated mechanism [41,42]. The findings in the present study are in agreement with the observations [43] that the antithyroid compounds CBZ, MMI and PTU decreased leukocyte

count in humans. Mooney et al. [14] reported that CBZ treatment was associated with leukcopenia in cats.

In the present study, administration of CBZ resulted in an increase in serum levels of total protein and a decrease in albumin level. The increase in total protein and globulins levels may be related to increased rate of synthesis in liver. The decrease in serum albumin level obtained in the present study is attributable to an increase in its urinary excretion. In hypothyroid rats, the urine excretion was increased and the urinary concentrating ability was decreased [44]. The present results are in agreement with Nogues et al. [45] who reported that low T3 level was associated with hypoalbuminaemia in humans.

The lower serum urea concentration in CBZ treated rabbits is presumably related to the fact that a decrease in the level of thyroid hormones resulted in a decrease in tissue protein catabolism. Furthermore, hypothyroidism was reported to be associated with a reduction in renal blood flow and glomerular filtration rate (GFR) and hence, reduced clearance of urea and creatinine [46] while hyperthyroidism induced an increase in urea level [47].

The increase in serum cholesterol level in the groups of rabbits receiving CBZ is attributed to a decrease in the formation of low density lipoprotein (LDL) receptors in the liver resulting in a decrease in hepatic removal of cholesterol from the circulation. Previous studies demonstrated that hypothyroidism was associated with hypercholesterolaemia in rabbits [12] and in humans [48,49] . The increase in cholesterol level with increase in the dose level of CBZ in the present study confirms the findings [50] which reported a significant negative correlation between the plasma concentrations of cholesterol and T4 in pigs. Studies on humans also reported that CBZ treatment was associated with a decrease in T_4 level and increase in serum total cholesterol [51].

The decrease in plasma glucose level in rabbits receiving CBZ is probably related to decrease in intestinal absorption of glucose and lowering of insulin degradation in hypothyroid rabbits. Sawaya and Lunn [52] observed that plasma insulin concentration increased in rats treated with CBZ. In small animals, hypothyroidism was associated with hypoglycaemia [53]. The gradual decrease in glucose level with increase in the dose level of CBZ in the present study may be related to anticipated gradual decrease in the level of thyroid hormones in blood.

5. CONCLUSION

The study generally established the relationship of dose level of the antithyroid drug CBZ to thermoregulation and blood constituents in the rabbit model. The findings have clinical implications in the management of hyperthyroidism in humans.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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