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EXPERIMENTAL CARBIMAZOLE (NEOMERCAZOLE) TOXICOSIS IN NUBIAN GOATS

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ABSTRACT

Four out of seven 6-9-month-old Nubian goat kids were given carbimazole (neomercazole) at 6 mg/kg .W/day for 21 days by drench. One animal died on day 13 and survivors were killed on days 19 and 21. Loss in condition, gelatinization of renal pelvis, mesenteric and pelvic fat, alterations in the size and colloid content of the thyroid follicles, hepatic fatty change, decreases in iodine concentrations in the thyroid gland, liver and kidneys and increases in selenium levels in the semimembranosus muscle were the main features of carbimazole toxicosis in goat kids.

Changes in the activities of aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) and in the concentrations of total cholesterol, triglycerides and other constituents in the serum of carbimazole-dosed goat kids were also investigated.

INTRODUCTION:-

In human beings, a course of the antithyroid drug, carbimazole, lasting from 6 months to 18 months in different reported studies, is often the initial therapy of choice for Grave's disease (**Reglinski *et al*, 1992**). It has been suggested that carbimazole inhibits thyroid hormone production, but controversy still exists as to whether or not it acts directly on the immune system (**Wilson *et al*, 1988**). Intracellular glutathione, although found to be oxidized as a consequence of carbimazole therapy, probably does so via an interaction of hypoiodous acid with the cell membrane (**Arthur, 1991**).

Several side effects of anti-thyroid drug therapy including myalgia, arthralgia, arthritis, fever and rash have been referred to as the anti-thyroid arthritis syndrome (**Shabtai *et al*, 1984**). Muscle disorder, proximal myopathy in thyroid disease, was detected by electrography of patients with hyperthyroidism (**Ramsey, 1968**). This author has suggested that the development of muscle pains in patients after the start of carbimazole and the association of symptoms with carbimazole therapy and the rapid resolution on transfer to propylthiouracil in patients with hyperthyroidism strongly indicate a drug-related myositis.

The thyroid gland is known to regulate lipid metabolism. For example in human hyperthyroidism, decreased (**Sandhofer, *et al*, 1966**), normal (**Tulloch, *et al*, 1973**) and increased (**Nikkila and kekki, 1972**) plasma concentrations of triglycerides were reported. Although during human hyperthyroidism high plasma concentrations of triglycerides are usually detected (**Sandhofer, *et al*, 1966; Tulloch, *et al*, 1973**), normal values are also described (**kutty, *et al*, 1978**).

Hypocholestrolaemia and Hypercholestrolaemia associated with hypothyroidism and hyperthyroidism, respectively, are also known to occur (**Peters and Man, 1950; Walton *et al*, 1965**). The open literature does not contain investigations of carbimazole toxicity in young ruminants. Because the goat was found susceptible to altered thyroid and other vital organ function (**Abdel Gadir and Adam, 1999; 2000**), the present study was conducted to examine the effects on Nubian goat kids of orally administered carbimazole at the dose equivalent to that used in human beings.

MATERIALS AND METHODS:-

Animals and dosing:-

Seven 6-9 month-old Nubian goat kids of either sex, were used. The animals were clinically healthy, housed in pens within the premises of the Department of Veterinary Medicine, Pharmacology and Toxicology, University of Khartoum and allowed a 2 week-adaptation period during which time they were fed Lucerne and goat concentrate ration. The animals were injected with prophylactic doses of oxytetracycline (Agropharm Ltd, UK) and sulphadimidine (sulphamethazine, Havee Co., the Netherlands) against bacterial infections and coccidiosis, respectively. Water was provided *ad libitum*. At the end of the preliminary period the goat kids were allotted to two groups. Animal 44, 45 and 46 were the untreated controls (group 1). Carbimazole tablets (neomercazole, Nicholas Laboratories Ltd, UK) were powdered, dissolved in distilled water and given by

drench to animals 47, 48, 49, and 50 at 6mg/kg **B.W** /day for 21 days (group 2).

Parameters:-

Body weights were recorded before dosing started and at weekly intervals thereafter. Blood samples were collected by jugular vein puncture on several occasions before dosing began and at appropriate intervals afterwards for serum analysis and haematology.

Sera were analyzed for the concentrations of total protein, albumin, globulin, triglycerides, cholesterol, bilirubin, creatinine, calcium, magnesium, iodine and selenium and for the activities of alkaline phosphatase (ALP), aspartate transaminase (AST) and gamma glutamyl transferase (GGT) by commercial kits (Randox Laboratories Ltd, UK).

Haemoglobin (Hb) concentration, packed cell volume (PCV), red blood cell (RBC) and white blood cell (WBC) counts, mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC) were determined by standard methods (**Schalm, *et al*, 1975**).

Necropsies were performed on all goats and specimens of thyroid gland, kidneys, urinary bladder, heart, spleen, intestines, liver, gall bladder, genital organs, semi-membranosus muscle, brain and peripheral nerves were fixed in 10% neutral buffered formalin, embedded in paraffin wax, sectioned at 5μm and stained with haematoxylin and eosin (H&E).

Iodine and selenium concentrations in the thyroid gland, liver, kidneys, heart, spleen, and semimembranosus muscle were determined by inductively coupled plasma-mass spectrometry (ICP-MS) as described by **Beauchemin (1991).**

Statistical analysis:-

The significance of differences between means was compared at each time point using Duncan's multiple range test after ANOVA for one way classified data **(Snedecor and Cochran, 1989).**

RESULTS:-

The details of goat kids given daily oral doses carbimazole are given in **Table 1.**

Clinical signs:-

No clinical abnormalities were observed in any of the control goat kids 44, 45 and 46 (group 1). In goat kids 47 and 48 in group 2 receiving carbimazole at 6 mg/ kg day, the signs were first observed on day 7 and included inappetence, weakness of the limbs and recumbency. Goat kid 47 died on day 13 and goat kid 48 was slaughtered in extremis on day 19. The goat kids 49 and 50 in group 2 showed loss in condition and were slaughtered on day 21.

Post – mortem findings:-

In group 2, there was a distinct gelatinous material on the pelvic org-

ans and abdominal viscera which was particularly seen on the mesentery and haemorrhage on the urinary bladder and genital organs. The thyroid gland was pale in colour and soft in texture. The liver revealed fatty change and congestion, the renal pelvis contained gelatinous material, the corticomedullary junction appeared congested and the urinary bladder was distended with urine. The control goat kids in group 1 showed no lesions.

Histopathological findings:-

The thyroid gland follicles of carbimazole treated goat kids varied in size and colloid content; many of the follicles appeared smaller in size with densely stained colloid and others were dilated with varying amounts of colloid and aggregates of lymphocytes in the interstitium were detected. Infiltration of lymphocytes was also seen in the liver, renal cortex and between the cardiac muscle fibres. The liver revealed fatty cytoplasmic vacuolation of the centrilobular hepatocytes, the renal tubules appeared focally degenerated and the glomerular tufts became shrunken or infiltrated with lymphocytes. The control goats (group 1) showed no lesions.

Changes in serum constituents:-

Changes in the activities of AST, GGT and ALP and in the concentrations of total protein, albumin, globulin, creatinine, calcium, magnesium, selenium and iodine in the serum of carbimazole–dosed goat kids are given in **Table 2.** In group 2, the activity of serum AST was higher ($P<0.001$) and that of ALP and GGT were lower ($P<0.01$) than the controls (group 1). The concentrations of triglycerides and cholesterol were lower ($P<0.05$) in group 2 than in the controls (group 1).

Other parameters did not show significant differences between the test group and the control group.

Haematological changes:-

There were no significant differences in the values of Hb, RBC, MCHC and WBC between the test group and the controls. In carbimazole-dosed goat kids (group 2), PCV value tended to decrease and MCH value was lower ($P<0.05$) than the controls (group 1).

Changes in tissue iodine and selenium concentrations:-

The concentrations of iodine and selenium in the thyroid gland, liver, kidneys, heart, spleen and semimembranosus (SM) muscle of goat kids orally dosed with carbimazole (group 2) are presented in Table 3. The concentration of iodine was significantly lower ($P<0.05$) in the thyroid gland and higher ($P<0.05$–0.01) in the liver, spleen, kidneys and SM muscle of the carbimazole – dosed goat kids (group 2) when compared to the control goat kids (group 1).

In group 2, selenium concentration was higher (P<0.001) in the SM muscle than in the controls (group 1) but it did not change in the thyroid gland, kidneys, liver, heart and spleen of these animals.

Table 1. Details of goat kids given carbimazole for 21 days by drench.

Group No.	Goat No.	Age (month)	Sex	Dose of drug (mg/kg/day)	Total amount of drug given (g)	Survival times (days)	Fate of animals
1- (Controls)	44	8	Female	Nil	Nil	21	Slaughtered
	45	8	Male	Nil	Nil	21	Slaughtered
	46	7	Male	Nil	Nil	21	Slaughtered
2- (Carbimazole - treated animals)	47	8	Female	6	0.780	13	Died
	48	8	Female	6	1.140	19	Slaughtered in extremis
	49	6	Male	6	1.260	21	Slaughtered in extremis
	50	9	Male	6	1.260	21	Slaughtered in extremis

Table 2. Changes in serum constituents of goats given carbimazole for 21 days by drench

Group No.	ALP ± (IU)	GGT ± (IU)	AST ± (IU)	Total protein ± (g/dl)	Albumin ± (g/dl)	Globulin ± (g/dl)	Triglyceride (mg/dl)
1	118.55 ± 5.55	43.59 ± 3.4	34.14 ± 0.49	6.95 ± 0.25	2.50 ± 0.27	4.45 ± 0.49	83.5 ± 2.30
2	82.70 ± 14.8**	34.60 ± 1.7**	70.55 ± 1.56	6.40 ± 0.57^{NS}	2.47 ± 0.18^{NS}	3.93 ± 0.59^{NS}	85.20 ± 1.01*

...../contd.

Group No.	Cholesterol ± (mg/dl)	Creatinine ± (mg/dl)	Bilirubin ± (mg/dl)	Calcium ± (mg/dl)	Magnesium ± (mg/dl)	Selenium ± (mcg/ml) pg/ml	Iodine ± (ug/dl)
1	72.00 ± 3.60	1.17 ± 0.13	0.39 ± 0.2	6.40 ± 0.25	1.20 ± 0.30	0.39 ± 0.03	0.14 ± 0.03
2	59.10 ± 1.20*	1.14 ± 0.15^{NS}	0.33 ± 0.13^{NS}	5.90 ± 0.36^{NS}	1.07 ± 0.18^{NS}	0.38 ± 0.02^{NS}	0.08 ± 0.01^{NS}

Values are means ± SD; NS= Not Significant; * = P<0.05; **= P<0.01; ***= P<0.001

Groups: 1= Controls; 2= Carbimazole at 6 mg/kg/day

Table 3. Iodine and selenium concentrations in tissues of carbimazole-dosed goats

Tissue	Iodine (ug/g) Groups		Selenium (ug/g) Groups	
	1	2	1	2
Thyroid	316.6±13.6	199.10±20.6*	0.310±0.049	0.34±0.005^{NS}
Liver	0.066±0.003	0.230±0.015**	0.196±0.003	0.44±0.10^{NS}
Kidneys	0.058±0.005	3.000±0.54*	0.644±0.03	0.67±0.06^{NS}
Heart	0.102±0.001	0.067±0.012^{NS}	0.128±0.005	0.29±0.07^{NS}
Spleen	0.091±0.001	0.193±0.03*	0.201±0.001	0.40±0.052^{NS}
SM Muscle	0.150±0.03	0.310±0.10^{NS}	0.066±0.003	0.33±0.003***

Values are means ± SD; NS= Not Significant; * = P<0.05; **= P<0.01; ***= P<0.001
Groups: 1= Controls; 2= Carbimazole at 6 mg/kg/day

DISCUSSION:-

Carbimazole treatment in goat kids caused gelatinization of the mese-nteric, peri-renal and renal pelvis fat and decreases in thyroid iodine and serum triglyceride concentrations.

The hypoglyceridaemia might have resulted from decreased output of triglyceride by the liver as a consequence of fat atrophy in the depots. It is well known that when triglyceride is not secreted, for example, when blocked by various hepatotoxins or in several pathogenic states or when the maximum rate of triglyceride output has been exceeded because of a large available pool of fatty acids, triglycerides accumulate in the liver and produce hepatic steatosis (**Heimberg *et al*, 1978**). The presence of fatty cytoplasmic vacuolation of the hepatocytes of carbimazole – dosed goat kids is in accordance with the biochemical picture. **Abdel Gadir (1995)** found that the oral administration of carbimazole to goats at 6 mg/kg/day causes a marked decrease or even complete ioss of total body fat when body components were expressed as percentage of empty body weight. This confirms the fact that fat is the most variable and the first to be affected with any stress and/or reduction in the energy concentration (**Preston and Willis, 1970; Abdalla, 1993**).

Under our experimental conditions, carbimazole did not markedly affect the blood cellular elements, total protein, bilirubin, creatinine and other constituents concentrations in the serum of goat kids but treatment with carbimazole for longer period

may have effects on those parameters.

We conclude that the oral administration to Nubian goat kids of carbimazole at 6 mg/kg/day produces anti-thyroid activity associated with gelatinization of the mesenteric and renal pelvis fat as well as inappetence, weakness of the limbs and recumbency.

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REFERENCES

Abdalla, G. A. (1993). Studies on Pesticides. MVSc Thesis, University of Khartoum, Sudan.

Abdel Gadir, W. S. (1995). Role of Millet (*Pennisetum typhoides*) in the Genesis of Goitre and Interaction with Potassium Iodate in Nubian Goats. PhD Thesis, University of Khartoum, Sudan.

Abdel Gadir, W.S. and Adam, S.E.I. (1999). Development of goitre and entrohepatonephropathy in Nubian goats fed with Pearl millet (*Pennisetum typhoides*). Vet. Jour 57: 178-185.

Abdel Gadir, W.S. and Adam, S.E.I. (2000). Effects of Pearl millet (*Pennisetum typhoides*) and fermented and processed fermented millet on Nubian goats. Vet. Hum. Toxicol. 42: 133-136.

Arthur, J.R. (1991). The role of selenium in thyroid hormone metabolism. Can Jour Physiol. Pharmacol **69**: 648-651.

Beauchemin, D. (1991). Inductively coupled plasma mass spectrometry in hyphenation: A multi-elemental analysis technique with almost unlimited potential. Tr Analyt Chem **10**: 71-76.

Heimberg, M., Goh, E.H., and Klausner, H. A. (1978). Regulation of hepatic metabolism of free fatty acids. Interrelationships among secretion of very low density lipoproteins, ketogenesis and cholesterogenesis. Am physiol. Soc **15**: 251-267.

Kutty, K.M., Byrant, D.G. and Farid, N.R. (1978). Serum lipids in hypothyroidism a re-evaluation. Jour Clin Endocrinol Metab **46**: 55-60.

Nikkila, E.A. and Kekki, M. (1972). Plasma triglyceride metabolism in thyroid disease. Jour Clin Invest **51**: 2103-2114.

Peters, J.P. and Man, E.B. (1950). The significance of serum cholesterol in thyroid disease. Jour Clin Invest **29**: 1-11.

Preston, T. R. and Willis, M.B. (1970). Intensive Beef Production, Pergamon Press, Oxford.

Ramsey, I.D. (1968). Thyrotoxic muscle disease. Postgrad Med Jour **44**: 385-388.

Reglinski, J., Smith, W.E. and Wilson, R. (1992). Nuclear magnetic resonance studies in intact erythr-

ocytes: Changes in cellular metabolism as a consequence of carbimazole therapy. Clin Endocrinol 37: 319-322.

Sandhofer, F., Sailer, S., and Braunsteiner, H. (1966). Plasma lipide bei storungen der chilldurn senfunktion des menschen. Klin Wochenschr 44: 433-436.

Schalm, O.W., Jain, N.C. and Carroll, G.H. (1975). Veterinary Haematology, 3rd edn, Lea and Febiger, Philadelphia.

Shabtai, R., Shapiro, M.S. and Orenstein, D. (1984). The anti-thyroid arthritis syndrome reviewed. Arth-Rheum 27: 227-230.

Snedecor, G.W. and Cochran, W.G. (1989). Statistical Methods 8th edn, Iowa State University Press, Ames, Iowa.

Tulloch, B.R., Lewis, B. and Fraser, T.R. (1973). Triglyceride metabolism in thyroid disease. Lancet i: 391-392.

Walton, K.W., Scoot, P.J. and Dykes, P.W. (1965). The significance of alterations in serum lipids in the thyroid dysfunction. II. Alteration of the metabolism and turnover of 1131- low density lipoproteins in hypothyroidism and thyrotoxicosis. Clin Sci 29: 217-238.

Wilson, R., Mckillop, J.H. and Pearson,D.M.W (1988). Differential immunosuppressive action of carbimazole and propylthiouracil. Clin Exp Immunol. 37: 312-31.

الملخص العربى

التسمم التجريبى للكاربمازول (نيومركازول) فى الماعز النوبى

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تم تجريع قموى لأربعه من صغار الماعز النوبى فى عمر ٦ - ٩ أشهر بعقار الكاربمازول (نيومركازول) فى جرعه قدرها ٦ مج/ كجم يوميا لمدة ٢١ يوم بينما أستخدم ٣ من صغار الماعز النوبى كمجموعة ضابطة. نفق واحد من صغار الماعز الذى أعطيت عقار الكاربمازول فى اليوم الثالث عشر من التجريع و قتلت الحيوانات التى لم تمت بعد ١٩ و ٢١ يوم من بداية التجريع. كان أهم مظاهر التسمم بالكاربمازول فقدان الحاله الصحيه ، جيلاتينية دهن حوض الكليه و المساريقا و الحوض ، تغييرات فى حجم و محتوى إفراز تجويفات الغده الدرقيه ، تغير دهنى كبدى ، نقص فى تركيز اليود فى الغده الدرقيه و الكبد و الكليتين و زيادة فى تركيز السلنيوم فى العضله شبه الغشائيه. تم أيضا فحص التغيرات فى نشاط انزيمات سبارتيت ترانس أمنيز ، الكالين فوسفاتيز و جاما جلوتاميل ترانس فريز و فى تركيز الكلسترول الكلى و الجسريدات الثلاثيه و مكونات أخرى فى مصل الماعز النوبى الذى جرعت بالكاربمازول.