ISSN 2310-4090

International Journal of Scientific Footprints

Open Access

Detection of Teratogenic Effect of Furdan on Pregnant Goats

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Keywords:
Furdan; Nubian Goat; Toxicity.

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Funding Information:
No funding information provided.

Manuscript History:
Received: September 2016
Accepted: November 2016

International Journal of Scientific Footprints 2016; 4(2): 97 - 108

Abstract

This study aimed to detect the teratogenic effect of the insecticide (Furdan) on pregnant Nubian goats. The study revealed that there was no teratogenic effect on pregnant goats. Furdan caused early abortion and death when it was given in two different doses to pregnant Nubian goats. The hematological investigation showed that there was a significance decrease in the Hb concentration, values of the PCV and RBCs count. There were no significance changes in the values of WBC count, MCH, MCV, and MCHC. Results were compared with control group. In the serobio-chemical investigation there were no significant changes in the concentration of serum sodium, potassium, calcium, phosphorus, magnesium, cupper, total bilurubin and the activities of ALT and ALP in any goat of the treated groups. Significant increase was observed in the serum concentration of glucose, total proteins albumin and globulins in groups A and B. But AST activity and urea concentrations were increased significantly in both treated groups. In the serum hormonal assay there was a decrease in the serum concentration of progesterone and Tri-iodthyronine (T3) and in the activities of serum acetycholinesterase. While there is an increase in the serum concentration of estradiol 17 β and 13, 14 dihydro keto prostaglangine F2α in both groups treated with furdan.

Introduction

The female goat is normally a very fertile animal [1]. However, goats have a high incidence of abortion when compared with other farm animals. Infectious cause of abortion plays an important role and could be a major source of economic loss in a goat herd. The most common infectious agents which cause abortion in goats are *Chlamydia psittaci*, *Toxoplasma gondii*, *Campylobacter spp.*, *Mycoplasma spp.*, *Coxiella burnetii* and *Brucella melitensis.* The common lesions in all cases of abortion are placentitis. Because of placentits, the fetus either dies due to inability to exchange nutrients through the placenta or became infected and died [2]. Many noninfectious agents have been named by producers as responsible for pregnancy loss in the goat, such as genetic factors, nutritional factors, toxic plant and pharmaceuticals .Teratogenic changes or abortion have been associated with several plant species , including *Gutierrezia* , *Lupinus formosus*,*Conium macculatum* ,*Nicotiana tabacum* and *Veratum californicum* [3] Nitrate poisoning may cause plant induced abortion in pregnant animals. Consumption of stressed nitrate accumulators such as oat or wheat hay, sorghum, Sudan, rape and others will change hemoglobin into met hemoglobin causing tissue

anoxia that is probable cause of abortion [4]. Various pharmaceuticals have proven to be abortifacients,or at least their use has been reported to be followed by abortion .phenothiazine given in last month of gestation may cause abortion, as might the use of levamisole. The use of xylazine or high dose of acetypromazine in first half of pregnancy may cause abortion because of their adverse effect on placental perfusion [5]. The indiscriminate application of hormones in pregnant goats will induce abortion. The goat is totally dependent on progesterone production by the corpus luteum throughout pregnancy. Little or no progesterone is produce by the carpine placenta.

Corticosteroids, estrogen and prostaglandins given to pregnant goats will induce abortion .Corticosteroids function by increasing esterogen production by the placenta. Whether from placenta production or exogenous administration, estrogen stimulates prostaglandine synthesis and sensitizes the myometrium to the effect of oxytocin [6]. The test of teratogenic effect of furdan or carbofuran was done by daily administeration of the insecicide (by gavage) to groups of pregnant female rats at dosages of 0.25, 0.50 and 1.20 mg/kg/day on gestation days 6 through 15.Caesarean sections were performed on all females on day 20 of presumed gestation. Fetuses were examined for soft tissue and skeletal abnormalities. Survival was 100% in all groups. All maternal and foetal parameters were comparable among the groups. Carbofuran was not teratogenic when administered by gavage at a dosage of 1.20 mg/kg/day. carbofuran was given to groups of pregnant female rabbits at dosage levels of 0, 0.12, 0.50 and 2.0 mg/kg/day by gavage during gestation days 6 through 18. On gestation day 29, all surviving dams were subjected to a Caesarean section and the foetuses were examined for skeletal and soft tissue abnormalities. At the 2.0 mg/kg/day dosage group, one dam died on gestation day 11. Decreased mean maternal body weight gains were also reported for the 2.0 mg/kg/day dosage group. All other maternal and foetal parameters were comparable among the groups. There was no evidence of teratogenicity in this study at a dosage of 2.0 mg/kg/day. A teratology and postnatal dietary study was conducted with carbofuran in the rat. Carbofuran was incorporated into the diet at concentrations of 0, 20, 60 and 160 ppm and administered to pregnant female rats only during gestation days 6 through 19. On gestation day 20, approximately half of the dams from each dosage group were submitted to Caesarean section and the foetuses were examined for skeletal and visceral abnormalities. The remaining dams were allowed to deliver and care for the pups for 21 post-partum days. At the end of the lactation period (post-partum day 21), the dams and pups were submitted to necropsy. Mean food consumption was slightly reduced in the 160 ppm group during the treatment period. Apparent dose-related mean maternal body weight losses occurred in the 60 and 160 ppm groups during the first two days of treatment (gestation days 6 and 7) and during the first 7 days of lactation. A statistically significant ($P < 0.05$) reduction in mean pup body weight for the 160-ppm group animals was reported on lactation days 0, 4, 7, 14 and 21. Examination of the foetuses and pups did not reveal any teratogenic response in this study at a dietary concentration of 160 ppm [7].

Materials and Methods

Insecticide used: Furdan (Carbofuran)

A carbamate systemic insecticide produced by (FMC) (Agriculture Chemical Group 1735 Market Street Philadelphia, PA19103 USA) with chemical name [2.3-dihydro-2, 2 dimethyl-7-benzofuranyl – methylcarbamate] and molecular formula ($C_{12}H_{15}NO_3$).

There are two forms of carbofuran: granular and flowable (liquid) . In this study granular formulate 10% was used .Furdan was obtained from North, Khartoum State Pesticide Market.

Animals

Twelve clinically healthy lactating female Nubian goats, of 2-3 years old, and 20-25 kg body weight were used in this study. They were purchased from Hilat Kuku Goat Market, Khartoum North. They were kept in standard pens at the College of Veterinary Medicine and Animal Production, Sudan University of Science and Technology. The animals were kept 16 days for adaptation and acclimatization, where each animal received antibiotic (Embacycline, oxytetracycline 5%, Coophavet, France) at rate of 1 ml/day/5 kg for 5 days intramuscularly, anthelmentic (Albendazole 25%, AVICO, Jordan) at rate of 1 ml/ 5 kg for one day then repeated after 14 days, by drench and anticoccidia (Amprocidia, Amprolium 60%, ACPVD, Jordan) at rate of 0.2 gm/day/ kg for 6 consequitivet days by drench for the control of bacterial diseases, worms and coccidiosis respectively. Goats were fed on forage sorghum (Abu- 70 *Sorghum vulgarae)* and provided water *ad libitum*.

After the end of the adaptation period, the experimental animals were randomly divided into two groups, A and B each group consist of 6 goats. Samples of milk were collected weekly for one month to determine the level of progesterone for the detection of pregnancy. After excluding pregnancy, each experimental goat was synchronized by using one intravaginal Chronolone-gest sponge containing 45 mg of Cronolone [Flugestone acetate Intervet International B.V.Boxmeer, Holland.]. For 12 days (Progestational phase). At the day of sponge- removal, a dose of 700 I.U., of Folligon was injected intramascularly (Follicular phase) [serum gonadotrophin (Chrono-Gest /PMSG) Intervet International B.V. Boxmeer, Holland]. Then the animals were let for natural mating. After 5 weeks the animals subjected to pregnancy diagnosis by usingan ultrasound technique (Red time Scanner, Proxima-Germany).

Dosing

After pregnancy was confirmed for the 12 animals, dosing was commenced as follows: Four out of the six goats in group (A) were given 5 mg/kg of furdan daily and the remained two goats were used as undosed control. Four goats in group (B) were dosed with 2.5mg/kg/day the remained two goats were undosed control. Daily dosing continued until animals were aborted, died or sacrificed.

Blood Sampling

Each experimental animal was subjected to blood samplings every week since the pregnancy was confirmed and then post-dosing until the animals were aborted, died or sacrificed. Additional samples were taken from animals in moribund condition. A volume of 10ml blood was collected from the jugular vein puncture using a disposable 10ml syringe with 18.5 gauge needle. Immediately, one ml of the collected blood sample was poured into a small clean 5ml vacutainer containing anticoagulant EDTA (ethylene diamintetracetic acid)for haematological investigations, and another one ml of the collected blood sample was poured into a small clean 5ml vacutainer containing fluoride oxalate as an anticoagulant and used immediately for glucose measurement. The remaining blood was kept to clot overnight, centrifuged at 3000 r.p.m. for 5 minutes and sera were collected and kept in a deep freezer at -20 °c for serobiochemical analysis.

Parameters Examined

Clinical Signs

Experimental animals were closely observed for toxic clinical signs, abortion, parturition and death or any behavioral changes.

Postmortem Findings

Aborted, dead or sacrificed animals were undergone postmortem examinations and lesions were recorded. Samples from the brain, spinal cord, heart, lungs, liver, spleen, kidneys, abomasums, omasum, small intestine and uterus were collected and fixed in 10 % neutral buffered formaline, embedded in paraffin wax, sectioned at 5µm and stained with haematoxyline and eosin (H&E) for histopathological investigation.

Hematological Investigation

EDTA anticoagulated blood were investigated for hemoglobin concentration (Hb), packed cell volume (PCV), red blood cells (RBC) count, white blood cells (WBC) count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC).

Serobiochemical Analysis

Collected sera were analyzed for the activities of aspartate amino–transferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and cholinesterase enzyme and concentrations of glucose, total bilirubin, total proteins, albumin, globulins,urea, calcium, inorganic phosphates magnesium, iron ,copper, potassium, andsodium. Also radioimmunoassay of hormones serum were analyzed for the concentration of hormones Progesterone,estradiol-17B,prostaglandine13,14,dihydroprostaglandin F2α and tri-iodothyronine.Ultrasound Scanning was performed to detect the state of pregnancy using Red-Time Scanning (Proxime–Germany) equipped with 3.5 MHZ curvilinear probe.

Statistical Analysis

The data were analyzed using Students t- test (Mendenhall, 1971).

Results and Discussion

Clinical Signs

In group (A), goats number 1, 2,3 and 4 showed in a few minutes, post-dosing signs of uneasiness, restlessness, excessive salivation, lacrimation, nasal discharges, constriction of the pupil, dyspnoea , grinding of the teeth, abdominal pain ,frequent urination, bloat, soft faeces , inappetence, abduction of the forelimbs, convulsions , tremors, stretching of the neck forward, and paresis of the hind limbs. Four hours later these signs were gradually disappeared and the animals retained normality. Goat number 4 aborted on day 30 post-dosing, after showing colic indicated by backward stretching of the hind limbs and forward stretching of forelimbs, curved the back downward , grinding of the teeth and mucus mixed with bloody vaginal discharge 2-3day prior to the abortion, and sacrificed on day 30. Goats number 1, 2 and 3 died on day19, 14 and 18 post-dosing, respectively. Goats number 5 and 6 which were control, delivered normal kids and sacrificed on day 150. In group (B), goats number 7, 8, 9, and 10, showed mild clinical sings, same as in group (A). Goat number 9 died on day 143. But goats number 7, 8 and 10 were sacrificed on day 150, after had been weak and exhausted. Goats number 11 and 12 which were control, delivered normal kids and sacrificed on day 150.

Postmortem Findings

Summary of postmortem findings of pregnant goats dosed with 5 and 2.5 mg/kg /day of Furdan was presented in Table (1). In group (A) Congestion of visceral organs was a common feature. In all animals, there was a gelatinous subcutaneous edema and the heart was flabby with hydropericardium. Kidneys showed thinning of the cortex, it was congested especially at cortico-medullary junction, and the capsule was thickened and easily removed. The uterus was edematous and contained fetuses of 50, 45 , 51 and 60 days of age in goats number 1, 2, 3and 4 respectively. No lesions were observed in control group. In group (B) goat's number 7, 8, 9 and 10 visceral organs appeared normal .The thyroid gland was enlarged, Necrotic foci were seen in the myocardium and the heart was flabby. The liver showed thickening of the dorsal lobe and rounded borders. The bile was diluted and light green in color. Uteri are of normal size and look normal and contained dead small foeti of 45-60 day of age and with normal foetal fluid and membranes. No lesions were observed in control goats.

Histopathological Findings

In group (A) the congestion was observed in all organs, widening of perivascular spaces with satolitosis was seen in the cerebrum of the brain tissue of all treated goats. The myocardial fibers appeared thin and separated, some of them stained more deeply eosinophilic than others (Hyaline degenaration), and mononuclear cell infiltration was observed in the interstitial tissue. In the kidneys, glomerular tufts appeared lobulated with widened Bowman´s space. The liver was congested and hepatocytic cytoplasm appeared granular. The spleen showed lymphoid hyperplasia in white pulp with prominent germinal centers. The intestines had blunt villi, elongated crypts and mucosal lymphoid nodules. The uterus showed uterine cells hyperplasia. In group (B) the treated goats showed the same histological changes as in group A, but were mild. No lesions were observed in control goats.

Hematological Findings

Summary of hematology of pregnant goats dosed with 5 and 2.5 mg/kg /day of Furdan was presented in Table (2).

Significance ($P<0.05$) decrease in the Hb concentration was observed in groups A and B. Also significance ($P<0.01$) decreases in the values of the PCV and RBC count in groups A and B. There were no significance changes in the values of WBC count, MCH, MCV, and MCHC. Results were compared with control subgroup.

Serobiochemical Findings

Summary of serum constituents of pregnant goats dosed with 5 and 2.5mg/kg/day of Furdan was presented in Table (3).

There were no significant changes in the concentration of serum sodium potassium, calcium, phosphorus, magnesium, cupper, and total bilurubin and in the activity of ALT and ALP in any goat of the treated groups. Significant ($P<0.05$) increases were observed in the serum concentration of glucose, total proteins albumin and globulins in groups A and B. But AST activity and urea concentration were increased significantly at ($P<0.01$) in both treated groups.

Hormonal Assay

Summary of serum hormonal assay of pregnant goats dosed with 5 and 2.5 mg/kg/day of Furdan, was presented in Table (4). There were decreases in the serum concentration of progesterone and Tri-

iodthyronine T_3 and in the activities of serum acetycholinesterase while an increases in the serum concentration of estradiol 17 β and 13, 14 dihydro keto prostaglangine $F_2\alpha$ in both groups treated with furdan.

Table 1 Postmortem Findings of Uteri Of Pregnant Nubian Goats Dosed with 5 And 2.5 Mg/Kg/Day Of Furdan

site	lesions	Subgroups		
		Group(A) 5mg/kg	Group(B) 2.5mg/kg	Group(C) untreated
Foetus	Size	Small.	Small	—
	Shape	—	—	—
	Age	45-60 days	45-60 days	150 days
	Dead or alive	dead	dead	live
	Deformities	—	—	—
Foetal fluid	Colour	Transperant	Transperant	—
	Volume	285 ml	Less than1203 ml	`1203 ml
Placenta	Cotyledons	—	—	—
	Intercodyledon junction	—	—	—

(—) = No changes and looks normal as the control group

Table 2 The Effect of 5 and 2.5 mg/kg /day of Furdan on the Hematology of Pregnant Nubian Goats

Parameters / subgroup	Hb (g/dL)	PCV (%)	RBC ($\times 10^6$/µL)	MCV (fl)	MCH (Pg)	MCHC (g/dL)	WBC (per/µL)
Subgroup(A)	15.3 ± 4.7 *	23 ± 3.3 **	10.90± 0.5 **	21.1± 3.1 NS	14.0 ± 3.0 NS	6.7± 3.1 NS	12800± 4.9 NS
Subgroup(B)	12.9± 2.2 *	18.5 ± 3.5 **	9.10± 0.7 **	20.3± 4.6 NS	14.2± 2.1 NS	7.0± 3.1 NS	12900± 5.1 NS
Subgroup(C)	17.3± 2.2	31.0± 3.7	13.80± 0.5	22.5± 3.0	12.5± 2.2	5.6.± 2.6	15300± 6.0
Control							

NS =not significant, * = Significant at (P< 0.05) **=Significant at (P<0.01).

Table 3 The Effect of 5 and 2.5 mg/kg/day/ of Furdan on the Serobiochemical Constituents for Pregnant Nubian Goats

Parameters / subgroups	Na (mEq/L)	K (mEq/L)	Ca (mg/dL)	P (mg/dL)	Mg (mg/dL)	Fe (µg /dL)	Cu (µg /dL)
Subgroup(A)	128.0±	4.30±	7.5±	4.40±	1.30±	101.3±	68.0±
	0.6	0.12	0.25	0.02	0.02	2.8	0.19
	NS	NS	NS	NS	NS	*	NS
Subgroup(B)	130.5±	4.30±	7.5±	4.30±	1.30±	93.7±	69.0±
	2.7	0.11	0.19	0.22	0.14	6.3	0.23
	NS	NS	NS	NS	NS	**	NS
Subgroup(C)	132.0±	4.20±	7.5±	4.35±	1.38±	147.0±	68.5±
	3.2	0.15	1.6	0.02	0.02	0.3	0.01

NS =not significant,* = Significant at (P< 0.05) **=Significant at (P<0.01)

Table 4 Hormonal Assay of pregnant Nubian Goats Dosed with 5and 2.5 mg/kg /day of Furdan

		5mg/kg furdan Group (A)		2. 5mg/kg furdan Group (B)			control group (C)	
Hormones	Goat No.	predosing	Postdosin •	Goat No.	predosing	Postdosing •	goat .No	untreated
Progesterone (ng/ml)	1 2 3 4	4.3 4.6 4.1 4.4	0.31 0.45 0.21 0.33	7 8 9 10	4.6 4.5 4.3 4.4	2.1 2.6 2.9 2.6	5 6 11 12	4.9 4.2 4.6 4.8
Estradiol 17B (Pg/ml)	1 2 3 4	49 51 52 50	75 80 76 70	7 8 9 10	49 48 51 50	72 76 81 77	5 6 11 12	51 46 53 54
13,14dihydro-15 keto prostglandine F2α PGFM (pg/ml)	1 2 3 4	95 90 95 85	950 1055 1100 1200	7 8 9 10	90 85 100 105	510 450 520 600	5 6 11 12	90 85 80 95
Tri-iodthyronene T_3 (nmoL/L)	1 2 3 4	1.5 1.7 1.6 1.7	0.3 0.4 0.2 0.5	7 8 9 10	1.8 1.5 1.6 1.7	0.8 0.9 0.9 1.2	5 6 11 12	1.7 1.6 1.6 1.5
Cholinestrase (%of pretreatment	1 2 3 4	100 100 100 100	70 65 60 75	7 8 9 10	100 100 100 100	82.1 80.6 76.9 79.5	5 6 11 12	100 100 100 100

• = % of pretreated

The objective of the present study is to investigate the toxic effects of furdan on pregnant Nubian goats. The lethal dose fifty LD_{50}which mentioned by the manufacturer's leaflet is 10 mg/kg. In the present study 5 and 2.5mg/kg/day were found toxic and fatal within 14-30 and150 days respectively. It is clear that old animals can tolerate toxic dosages than younger ones. This might be attributed to that; the capacity to detoxicate and eliminate furdan is not fully developed

in younger animals, but very old animals may be weak and debilitated and hence have a lowered general resistance [8]. In the present study it has been shown that the sex, also influence the susceptibility of Nubian goats. [9].found that young Brahaman heifers are more susceptible to Famfur toxicity than bulls. The clinical signs onset and severity, postmortem lesions and histologic changes are not far away from that described by [10] when studied the toxic effect of temik in Nubian goats. The present study indicates that furdan decreases serum acetyl cholinesrerase activity and it is well known that the clinical signs are the consequences of this effect. The clinical signs were that of muscarinic, nicotinic and central in nature. These may include hypersalivation, lacrimation ,defecation, diarrheoa, increased respiratory sounds (muscarinic), muscle stiffness,tremors, weakness and paralysis ,recumbency (nicotinic), restlessness and depression (central), and death is commonly attributed to respiratory failure ,resulting most often from inhibition of central (medullary) respiratory drive , as well as from excessive bronchial secretions and bronchospasm, and impairment of diaphragm and intercostal muscle contraction [11]. The pathological lesions observed in furdan toxicity are more or less similar to that described by [12] when studied experimental poisoning of propoxur in Nubian goats. The lesions consisted of varying degrees of congestion and hemorrhages in the different organs,pulmonary cyanosis and oedema , the trachea contained mucoid secretion somtimes tinged with blood ,the heart is flabby and hydropericardium might be noticed.The liver and kidneys shows fatty change and /or necrosis , while gastritis and entiritis were also seen. It is noticed that the amount of cholinesterase enzyme inhibited by furdan in pregnant goats is not high and this is might be attributed to the fact that the liver is stimulated to increase its synthesis of cholinesterase in response to the lowered serum levels or it might be due to the earlier faster recovery of some of the inhibited cholinesterase by spontenous hydrolysis of inhibited enzyme before the stable drug – enzyme complex is formed [13]. In the present study, there were decreases in Hb concentration, RBCs count, PCV and serum iron concentration, i.e iron deficiency indicating anaemia. The slight decrease in MCV indicats microcytic anaemia although there were no decreases in the MCH and MCHC. [14] mentioned that iron deficiency occurred because of chronic blood loss or inadequate dietary iron intake and the anaemia is classically microcytic hypochromic but may be normochromic.The type of anaemia can be classified as non-regenerative anaemia due to ineffective erythropoiesis without generalized bone marrow hypoplasia. In the present study non-cholinergic effects such as increases in the activity of AST and urea concentrations as well as degeneration and/or necrosis of hepatocytes and renal epithelial cells, are indicative of Furdan hepatorenal toxicosis. Hyperglycemia was evident in pregnant goats following exposure to furdan. This result is in line with that described by [15] who studied the hormonal consequences of organ phosphorus poisoning and attributed the hyperglycemia to catecholamine's released from the adrenal medulla following sympathetic stimulation and an increase in circulatory glucocorticoids which decrease peripheral glucose utilization consequently.

Increases in glucocorticoid are known to lower T_4 in cases of hypothyroxaemia [14]. The increases in the concentrations of estradiol and prostaglandins and the decreases in the progesterone reflect the wide opportunely to expel out foetus inducing abortion [16].

Conclusion

This study clearly revealed that Furdan is toxic to pregnant Nubian goats and causes abortion and embryo toxicity but it doesn't cause teratogenicity. Further studies are needed to elucidate the mechanism of embryo toxicity and teratogenicity.

Acknowledgement

Authors are thankful to the University authorities for providing necessary facilities to carry out this research work.

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