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BIOCHEMICAL AND PATHOLOGICAL EFFECTS OF CLOSANTEL AND LEVAMISOL IN FEMALE RABBITS

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A B S T R A C T

The effect of the anthelmintic drugs (closantel and levamisole) on biochemical, teratological and pathological changes was studied in female rabbits by using 15 pregnant female rabbits 8 months old and 15 male rabbit, 10 months old used for mating. Rabbit were divided into three equal groups (5 females and 5 males in each). 1st group left without treatment (control group), 2nd and 3rd groups were S/C injected with therapeutic dose of closantel and levamisole, respectevely as one dose at zero day of pregnancy. Pregnant rabbits were kept under daily observation until the 28th day of pregnancy, afterwards, caesarian sections were performed to determine the effects of the tested drugs on foetal numbers, weight and length. Two blood samples were collected at 15th and 28th day of pregnancy for haematological and biochemical evaluation. Samples from liver and kidney were taken for histopathological study. Subcutaneous injection of closantel and levamisole at zero day of pregnancy induces insignificacant decrease in number, weight and length of feti. The hematological study revealed that closantel and levamisole induced insignificant decrease in erythrocyte count, haemoglobin and packed cell volume 15th and 28thdays post injection. Closantel induced significant increase in leukocytes, eosinophils, monocytes. Levamisole induced significant elevation in count of leukocytes, neutrophils, lymphocytes. In the current work, closantel induce significant decrease in total protein and albumin. Pregnant rabbit treated with levamisole showed a significant increase in total proteins, albumin and globulin. Closantel induced histopathological changes mainfested by severe hydropic degeneration in hepatic cells. Renal tubules showed necrotic epithelial, hyperplasia of the glomerular tuft and hyaline casts were seen in the lumen of renal tubules in some cases specially at 15 days post-injection. Closentil induce severe destruction in the renal epithelia but levamisole induce hyperplasia of bile duct at 15 day post-treatment. Portal area infiltrated with eosinophils, round cells infiltration were seen between the renal tubules. It could be concluded closantel and levamisole have no effects on developing foeti, but still produce adverse effects on haemato-chemical picture.

KEY WORDS: Biochemical, Levamisole, Pathological, Rabbit

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1.INTRODUCTION

Many drugs are capable of crossing the blood placental barrier, which has important toxicologic implications for the foetus. Only a few drugs have been shown to be completely nontoxic when given to pregnant dam. Unfortunately, teratogenic potential of the majority of many drugs is unknown and, consequently, they are avoided during pregnancy [1]. Closantel is long acting broad spectrum antiparasitic salicylanilide derivatives [28]. It has a persistent anthelmintic activity against nematodes, cestodes and liver flukes for several weeks [12, 23] for its strong binding to plasma protein and prolonged plasma half-life [27]. Closantel have long terminal half-lifes (16.6 days)

[30]. Levamisole is widely used for control of gastrointestinal parasites in many animal species due to its broad spectrum action [8]. It is anthelmintic agent acting as a full agonist of the nicotinic receptor of nematode muscle [9]. Levamisole act as an immunostimulant agent [25]. Its immunostimulant effect may be related to T-cell activation and proliferation, augmentation of monocyte and macrophage activity and an increase in neutrophil mobility, adherence, and chemotaxis [34]. Levamisole has no cytotoxic effects [36].

The objective of present study was to evaluate the effect of closantel and levamisole on the pregnant female rabbits and their developing foeti as well as histopathological study.

2. MATERIALS AND METHODS

2.1. *Drug*

2.1.1. *Closantel* (Flukiver®) is developed by Janseen (UVEDCo) Uinited Veterinary Drug Industrial Company Limited. It is obtained in liquid form in 5% of 100 ml solution.

2.1.2. *Levamisole HCL* (Levamisole)^{R} injectable solution 7.5% obtained from CID Co., Egypt.

2.2. *Animals*:

The present study was carried out on 15 female rabbits, 8 months old, weighing 2.5-3kg and 15 male rabbits, 10 months old, weighing 3.25-3.5kg used for mating were obtained from a private rabbits farm in Sharkia Province. Rabbits were housed under hygienic conditions,

2.3. *Experimental design*:

Female rabbits were paired with males in a separate cage, mating was observed and considered as zero day of pregnancy, pregnancy confirmed by the presence of sperms in vaginal smears. Pregnant rabbits were divided into 3 equal groups.1stgroup was non treated (control group). 2nd and 3rd groups were injected S/C once at zero day of gestation with therapeutic dose (10 mg/kg b.wt. and 2.5mg/kg.b.wt.) closantel and levamisole HCL respectively (according to pamphlet of the manufacturing company).Pregnant rabbits were kept under daily observation until the 28th day of pregnancy, afterwards, caesarian sections were performed to determine the effects of tested drugs on foetal weight, length and number.

2.4. *Blood sample*

At 15th and 28thdays post injection 2 blood samples were collected from each animal, 1st sample was collected in a tube contain EDTA for estimation of erythrogram and leukogram [19], 2nd sample was collected for obtaining clear serum for estimation of aminotransferases (AST-ALT) enzymes [33] alkaline phosphatase [21], total protein [10], albumin (11) globulin by subtraction of albumin from total protein, urea [6], creatinine [17] and total bilirubin [20].

2.5. *Histopathological studies*

Specimen from liver and kidney were fixed in 10% formalin buffer and embedded in paraffin. Sections of 5 microns thickness were prepared, stained by haematoxylin and eosin stain and used for histopathological examination [3].

2.6. *Statistical analysis*:

The obtained data were statistically analyzed according to Petrie and Watson [32].

3. RESULTS

Closantel and levamisole given at zero day of pregnancy induced insignificant decrease in numbers, weight and length

of feti (Table, 1). Closantel and levamisole induced insignificant decrease in erythrocytic count, hemoglobin content and packed cell volume. Closantel induced leukocytosis, eosinophilia, monocytosis and insignificant decrease in of neutrophils, lymphocytes and basophils count at 15th and 28th days post injection but levamisole induced leukocytosis, neutrophilia, lymphocytosis and insignificant decrease in esinophils, basophils and monocytes (Tables 2& 3).

Our result showed that, closantel induced significant elevation in AST, AT, alkaline phosphates, urea, creatinine, total bilirubin and a significant decrease in total protein and albumin but globulin was insignificantly decreased at 15th and 28th days post injection. Pregnant rabbit injected with levamisole showed significant increase in AST, ALT, alkaline phosphatase, urea, total proteins, albumin, globulin and insignificant increase in creatinine but total bilirubin was insignificantly decreased at 15th and 28th days post injection (Tables 4& 5). The hepatic cells showed hydropic degeneration and fatty change at 15th days post closantel injection (Fig. 1). Renal tubules showed necrotic epithelia, hyperplasia of the glomerular tuft with epithelial and hyaline casts were seen in the lumen of renal tubules (Fig, 2).

The hepatic tissue showed hyperplasia of the bile duct at 15th day post levamisole injection (Fig. 3). The portal area was infiltrated with eosinophils, round cells were seen between the renal tubules and around the blood vessels at 15th day post treatment (Fig. 4).

The liver appears nearly normal at 28th day post treatment. In some cases closentel induce severe hydropic degeneration in hepatic cells (Figs. 5 & 6) and thickening in hepatic capsule (Fig. 7).

Table 1 Morphological changes in foeti obtained from dam rabbits treated with closantel or levamisole as one shot at zero days of gestation (n=5)

Group	No of feti	Fetal body weight (gm)	Fetal Length (cm)
Control	9.03±0.97	32.12±0.22	12.23±.63
closantel	8.32±1.56	30.08±0.32	10.12±0.54
Levamisole	8.74±0.89	31.14±0.48	11.08±0.60

Table 2 Erythrogram rabbits treated with closantel or levamisole (n=5)

Group		RBC (10^6/ mm^3)	Hb (Gm %)	PCV (%)
Control		5.63 ± 0.84	11.03± 0.73	31.94± 1.61
G2	15day	5.21± 0.64	10.63± 0.52	30.05± 1.58
	28day	5.53 ± 0.85	10.81± 0.73	30.22± 1.86
G3	15day	5.47± 0.52	10.91± 0.97	31.07± 1.83
	28 day	5.51± 0.89	11.21± 0.84	31.86± 1.93

Table 3 Leukogram rabbits treated with closantel or levamisole.(n=5)

Group			Absolute differential count(10^3/cmm)				
		TLC (10^3/mm^3)	N	L	E	B	M
G1		10.82±0.62	4.09±0.35	5.48±0.72	0.36±0.08	0.22±0.05	0.57±0.14
G2	15 day	13.00±0.30**	3.99±0.4	5.42±0.39	1.05±0.15**	0.18±0.04	1.26±0.25**
	28 day	13.06±0.61*	3.94±0.67	5.54±0.26	1.52±0.26**	0.19±0.03	1.87±0.32**
G3	15 day	12.78±0.59*	4.92±0.13*	7.14±0.15*	0.19±0.04	0.18±0.04	0.35±0.08
	28 day	11.34±0.74	4.52±0.92	5.96±0.38	0.21±0.05	0.15±0.03	0.45±0.10

*$p < 0.05$ and** $p < 0.01$

Table 4 Liver and kidney function of rabbits treated with closantel or levamisole (n=5)

Group		Liver function			Kidney function		T.bilirubin(mg/dl)
		AST(U/L)	ALT (U/L)	Al.ph.(U/L)	Urea (mg/dl)	Creatinine(mg/dl)	
G1		35.3±1.13	53.36±2.06	22.34±1.2	6.02±0.39	2.05±0.42	0.67±0.11
G2	15day	43.2±1.62**	61.24±1.86**	29.89±1.04**	8.07±0.33**	4.70±0.93*	1.23±0.21*
	28day	40.1±1.15*	57.51±1.10*	26.92±1.12*	7.64±0.42*	3.82±0.71*	0.99±0.10*
G3	15day	41.3±1.82**	60.17±1.52**	26.61±1.13*	6.36±0.21*	3.53±0.59	0.56±0.13
	28day	38.9±1.07*	58.75±1.17*	24.17±1.42	6.08±0.85	2.12±0.29	0.73±0.16

*p < 0.05 and** p< 0.01

Table 5 Protein profile of rabbits treated with closantel or levamisole (n=5)

Group		T.P. (gm/dl)	Albumin (gm/dl)	Globulin (gm/dl)	A/G ratio
G1		6.02±0.33	3.38±0.16	2.64 ±0.18	1.28±0.30
G2	15 day	4.77±0.34*	2.22±0.44*	2.55±0.31	0.87±0.17
	28 day	5.19±0.19*	2.75±0.15*	2.44±0.27	1.16±0.15
G3	15 day	7.36±0.42*	2.73±0.19*	4.64 ±0.51**	0.59±0.14
	28 day	6.98±0.15*	3.09±0.26	3.89 ±0.60	0.79±0.19

4. DISCUSSION

The present study illustrated that female rabbits injected with therapeutic dose of closantel and levamisole at zero day of pregnancy revealed insignificant decrease in number, weight and length of feti when compared with control group.

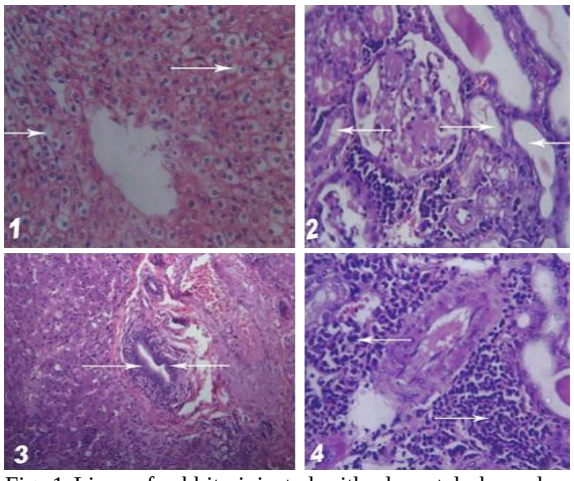

Fig. 1 Liver of rabbits injected with closantel showed hydropic degeneration and fatty changes (arrows) at 15th day post treatment. H&E., X 130. Fig. 2 Kidney of rabbits injected with closantel showed necrosis in the epithelial lining of the renal tubules and hyaline casts in the lumen (arrows) at 15th day post treatment. H&E., X 130. Fig. 3 Liver of rabbits injected with levamisole show hyperplasia of the bile duct (arrows) at 15th days post treatment H&E.X130. Fig. 4 Kidney of rabbits injected with levamisole showed round cells infiltration between the renal tubule (arrows) at 15th day post treatment. H&E., X 130.

The previous results are in accordance with the finding of [39] who found that closantel induced insignificant effects in embryo of rabbits. Our data clearly fit with those obtained previously by [24] stated that closantel had no teratogenic action in pregnant rats.

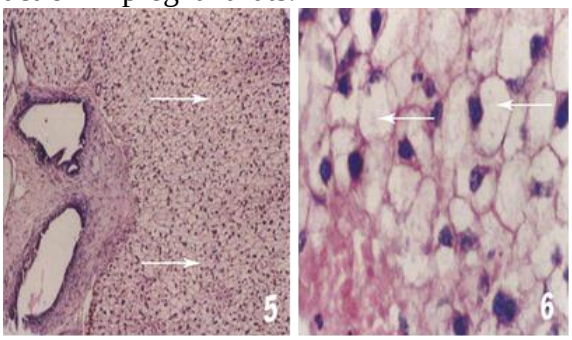

Fig. 5 Liver of rabbits injected with closantel showed severe hydropic degeneration in hepatic cells (arrows) at 15th days post treatment. H & E., X 130. Fig. 6 Liver of rabbits injected with closantel showed sever hydropic degeneration in hepatic cells (arrows) at 15th day post treatment (by high power) H & E., X 520

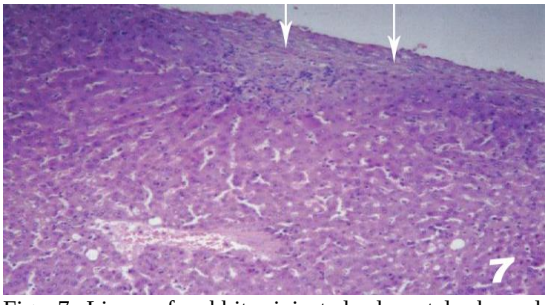

Fig. 7 Liver of rabbits injected closantel showed thickening of hepatic capsule (arrows) at 15th day post treatment. H & E.,X 130

Keeping with this line previously it was stated that closantel induced non teratogenic effects in pregnant ewes [5]. Teratogenic effects of a given drug could be predicted if the drug can successfully cross the blood placental barrier [29] and/or inhibit protein synthesis [38]. In support of the previous assumption, is the fact that closantel or its related metabolite not cross the blood placental barrier as its molecular weight is 662.82 [2]. Also, it has been stated that drugs with molecular weight of less than 600 do readily cross the placenta [15]. S/C injection of levamisole to ewes during pregnancy was found to have no significant effect in fetal weight [4]. These results were supported by [35] they stated that levamisole induce insignificant effect in average fetal size in rats. Levamisole do not have any teratogenic effects [22].

The present work revealed that, healthy rabbit injected with closantel and levamisole showed insignificant decrease in erythrocytic count, hemoglobin and packed cell volume. The previous results are in accordance [37] they found that closantel induced insignificant decrease in erythrocytic count, haemoglobin and packed cell volume in rabbit. Our results were in agreement with result recorded [31] who stated that other salicylanilide derivertive (rafoxanide) induce insignific-ant decrease in erythrocytic count haemoglobin content and packed cell volume Same results was recorded [18] stated that levamisole induced insignificant decrease in erythrogram in sheep.

The obtained results revealed leukocytosis, eosinophilia, monocytosis coupled with insignificant decrease in neutrophils, lymphocytes and basophils counts at $15^{th}$and 28^{th}day post closantel injection in rabbits. Levamisole induced leukocytosis, neutrophilia, lymphocytosis and insignificant decrease in esinophils, basophils and monocytes in the same period. Close similarity was seen between this finding and those obtained by [2] who reported that closantel induced significant increase in count of total leukocytes, eosinophils and monocytes with insignificant decrease in lymphocytes. The change in blood picture might be due to the high concentration of closantel residues in body for 42 days [16]. Our results were also similar to that reported by [31] who mentioned that other salicylanilid derivative (rafoxanide) induce significant increase in leukocytic count. Levamisole induced insignificant increase in count of leukocytes, neutrophils, lymphocytes in rabbits [26]. Elevation in leukocyte post treatment with levamisole was supported by [40] mentioned that levamisole induced leukocytosis in dairy cows and this elevation may be due to increase in lymphocytes and monocytes.

In the present experiment, a significant decrease in serum total protein, albumin and insignificant decrease in globulin in rabbit at15^{th}&28^{th}days post closantel injection was recorded. Meanwhile, levamisole induce significant elevation in serum total protein, albumin and globulin in rabbits. Same effect was obtained by [2], they stated that closantel induce a decline in total protein and albumin. These obtained results nearly agree with those observed by [34] who found an increase in total protein following levamisole treatment. Also, [18] found that levamisole caused an increase in immunoglobulin and immunity of the animals due to increase in globulin. The detected hypoprotinemia in the rabbit treated with closantel are supported by [41] said that closantel induce significant decrease in total protein, albumin and insignificant decrease in globulin in rabbits. Decreased protein and albumin may be parallel to the result recorded by [7]. They attributed hypoalbuminemia to the decrease in albumin synthesis due to

damage of liver parenchyma as a result to toxic effect of the drug. The effects of levamisol in protein profile are ascribed to its immunostimulant effect. These results are clearly reinforced by those obtained by [18] who found that levamisole induce significant increase in total protein and globulin in sheep. Our results were reinforced also by [26] they found that serum total protein and globulin significantly increased in rabbits treated with levamisol. The above mentioned results were also supported by the previous studies [14] mentioned that rats treated with levamisole show significant increase in total protein and globulin and such findings may be due to the ability the levamisole to enhance both cellular and humeral immune responses.

The results of our work, showed significant increase in serum AST, ALT, alkaline phosphatase, urea, creatinine and total bilirubin levels in healthy rabbit injected with closantel. On the other hand, levamisole induced significant increase in serum AST, ALT, alkaline phosphatase, urea and insignificant decrease in creatinine but total bilirubin was insignificantly decreased in pregnant rabbits. These results were supported by [31] he stated that other salicylanilide derivative (rafoxanide) induce significant elevation in AST, ALT and alkaline phosphatase. The elevation in liver enzymes in our study might be due to hepatotoxic effect of closantel in rabbits [41]. In keeping with these lines, [2] found that closantel induced significant elevation in AST, ALT, alkaline phosphatase and bilirubin in rabbits. Our findings agreed with those recorded by [12] they found that closantel intoxication in dogs caused an elevation of hepatic enzymes together with increase of bilirubin in blood and urine. Increase in AST, ALT, alkaline phosphatase, urea and insignificant decrease in creatinine and total bilirubin post levamisol treatment are in accordance with the finding of [13] they stated that levamisole induced a significant increase in the activities of AST, ALT, alkaline phosphatase and urea while creatinine insignificant changes.

In our study, closantel induced hydropic degeneration and fatty changes in liver at 15^{th} days post closantel injection. Renal tubules showed necrotic epithelia, hyperplasia of the glomerular tuft with epithelial and hyaline casts in the lumen of renal tubules. The hepatic tissue showed hyperplasia of the bile duct at 15^{th} day post levamisole injection. The portal area was infiltrated with eosinophils, round cells infiltration were seen between the renal tubules and around the blood vessels at 15^{th} day post treatment. The liver appears nearly normal at 28^{th} day post treatment. In some cases closantil induced severe hydropic degeneration in hepatic cells fig. (5 and 6) and thickening of hepatic capsule. Changes in both liver and kidney in the rabbits treated with closantel in this study may be attributed to a direct cytotoxic effect of closantel or its metabolites during its execration through the kidney and detoxicafication in the liver, [2]. Levamisol induce hyperplasia of the bile duct, portal area infiltrated with eosinophils, round cells infiltration between the renal tubules at 15 day post treatment. These results were in agreement with [13]. They stated that levamisole induce small focal necrotic areas in the liver beside necrosis and degenerative changes in epithelial lining of the renal tubules.

The observed results allowed the conclusion that, closantel and levamisole produced adverse effect on haematological liver and kidney function but not elicited any effects on feti.

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التأثيرات البيوكيميائية والباثولوجية للكلوزنتيل واليفاميزول في اناث الأرانب

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أقسام والكيمياء الباثولوجيا[1] والباثولوجيا الاكلينيكيه[2] – معهد بحوث صحة الحيوان (فرع الزقازيق)

الملخص العربى

كان الغرض من هذا البحث هو دراسة تأثير الكلوزنتيل والليفاميزول على التطور الجنينى و كذلك تأثيراتهم على صورة الدم, بعض الوظائف البيوكيميائية والباثولوجية في اناث الأرانب أثناء الحمل فى هذه الدراسة تم استخدام 15 أنثى و15 ذكور. الارانب سليمة ظاهريا واكلينكيا في مزرعة خاصة بمحافظة الشرقية. تم تقسيم الارانب إلى ثلاث مجموعات متساوية كلاً منها تضم 5 اناث و5 ذكور الأولى مجموعه ضابطة .اما المجموعه الثانية و الثالثة تم حقن الاناث تحت الجلد بالجرعة العلاجية من الكلوزنتيل واليفاميزول(فى اليوم الأول للحمل).فى اليوم15, 28 من الحمل تم أخذ عينتين دم من كل ارنب من الوريد الموجود فى الإذن العينه الأولى على EDTA وذلك لدراسة التأثير على صورة الدم والأخرى لفصل المصل وذلك لدراسة التأثير على بعض الوظائف البيوكيميائية. وفى اليوم الثامن والعشرين من الحمل تم أجراء العملية القيصرية لكل ارانب المجموعات السابقة واستخرجت الأجنة وتم عد ووزن الأجنة وقياس طولها وتم اخذ عينات من الكبد والكلى فى الفورما لين (وذلك لدراسة التأثير الهستوباثولوجى لتلك الادوية). وتشير النتائج ان اجنه الارانب المحقونة بالكلوزنتيل والليفاميزول وجود بها نقص غير معنوى فى طول وعدد ووزن الأجنة كما تشير النتائج أن عقارى الكلوزنتيل والليفاميزول أديا إلى حدوث نقص غير معنوي في عدد كرات الدم الحمراء, تركيز الهيموجلوبين ، حجم خلايا الدم المرصوصة بعد 15 و28 يوم من حقن العقارين . بينما احدث الكلوزنتيل زياده معنويه فى عدد كرات الدم البيضاء,الخلايا الحامضية والخلايا الملتهمة الكبيرة مع وجود نقص غير معنوى فى الخلايا المتعادله والخلايا الليمفاويه ولكن اليفاميزول بالجرعة العلاجية أحدث زيادة معنوية في عدد كرات الدم البيضاء, الخلايا المتعادلة,الخلايا الليمفاويه مع وجود نقص غير معنوى فى,الخلايا الحامضيه,الخلايا القاعديه و الملتهمة الكبيرة عند نفس المدد السابقه. وبدراسة التغيرات البيوكيميائية التي حدثت نتيجة استخدم الجرعة العلاجية من الكلوزنتيل فى الأرانب الحوامل وجدت زياده معنويه فى انزيمى الترانس امينز (AST-ALT) الفوسفاتيز القاعدى,الصفراء,اليوريا ,الكرياتين ونقص معنوى فى البروتين الكلى والزلال ونقص غير معنوي فى الجلوبيلوين بعد 15 و28 يوم من الحقن . اليفاميزول بالجرعة العلاجية أحدث زيادة معنوية فى زياده معنويه فى انزيمى الترانس امينز (AST-ALT) الفوسفاتيز القاعدى,اليوريا, البروتين الكلى, الزلال والجلوبيلوين مصحوبا بنقص غير معنوى فى الصفراء وزياده غير معنويه فى الكرياتينين بعد 15 و28 من الحقن.وبدراسة التغيرات الباثولوجية وجد أن هناك تاثير لعقار الكلوزنتيل على الكبد والكليتين وكانت التغيرات في الكبد عبارة عن استحالات وارتشاحات للخلايا الحمضية مع تتكرز واستحالات بخلايا الكليتين بعد 15 من الحقن. مما سبق فاننا توصى باستخدام الكلوزنتيل,اليفاميزول بالجرعات العلاجية للقضاء على الديدان الداخلية فى الحيوانات الحوامل لأنة امن على الأجنة ولا يسبب اى تشوهات فى الأجنة

(مجلة بنها للعلوم الطبية البيطرية. عدد 22 (2)، ديسمبر 2011: 136-144)