A COMPARTIVE STUDY ON THE ADVERSE EFFECTS OF DEXAMETHASONE AND FLUNIXIN MEGLUMINE IN SHEEP

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ABSTRACT

The present study was conducted to compare the adverse effects of two anti-inflammatory drugs on haemogram, immunity as well as some biochemical parameters in sheep. Fifteen sheep aged 4 -10 months were used. They were divided into three equal groups each of 5. The first group was left without treatment and served as control. the second and third groups were injected intramuscularly with dexamethasone (0.20 mg/kg b. wt.) and flunixin meglumine (1.1 mg/kg b.wt.) respectively as therapeutic regimen for 5 successive days. Blood samples were collected at 5,10,15 and 20 days post last injection for studying the effect of the test drugs on haemogram, immunological and some biochemical changes.

Intramuscular injection of dexamethasone induced significant decrease in haemoglobin concentration, packed cell volume, erythrocytes, monocytes, eosinophilis, total proteins, gamma globulines, total globulines, T3, T4,I gG. IgM and soduim which remained low for two week post stopping of drug administration. On the other hand it induced an increase in total leucocytic count, neutrophiles, serum albumin AST, ALT, potassium, sodium and inorganic phosphorus for two weeks post drug injection.

Flunixin meglumine induced insignificant decrease in haemoglobin concentration, packed cell volume, erythrocyte basophil counts, albumin, alpha globulin and beta globuline. It also induced significant decrease in lymphocytes, monocytes, eosinophiles, total proteins, gamma globulin, total biltrubin, T3, T4, IgG, IgM and sodium but induced a siginficant increase in total leucocytic count, neutrophil count, serum ALT, potassium calcium and inorganic phosphorus.

It could be concluded that both dexamethasone and flunixin meglumine induced several hematological, immunological and biochemical changes in sheep but flunixin meglumine was more safer because it was less hazardous than dexamrthasone.

INTRODUCTION

Anti-inflammatory drugs have come to occupy a permanent place in modern clinical therapeutics. The most wiedly used Anti-inflammatory drugs are steroidal and non steroidal drugs **(Lee and katayama 1992)**. Anti-inflammatory drugs had also analgesic, antipyretic, antiprostaglandin effects.

Steroidal anti-inflammatory drugs are the most important and often life saving class of potent Anti-inflammatory agent used for the treatment of several pathological conditions **(Yeates and March 1980)**. Steroidal anti-inflammatory drugs are also used in the treatment of adrenal hormone deficiency **(Goodman and Gilman 1980)**, ketosis and shock **(Braun, 1989)**. Dexamethasone is one of the most important commonly used synthetic glucocorticoids in Egypt.

Non steroidal Anti-inflammatory drugs, may be classified chemically into two groups: the enolic acid group as phenylbutazone and carboxylic acid like flunixin (lees and Higgins 1985). They exert their effects through inhibition of prostaglandin biosynthesis by irreversible blocking of the enzyme Cyclooxygenase (prostaglandin synthetase) and thromboxane **(Taylor et. al. 1994)**. Flunixin is non a steroidal Anti-inflammatory agent used in horses for treatment of inflammatory diseases or colic **(Jaussand 1986)**. It is used as meglumine salt in Veterinary Medicine **(Reynolds 1989)**.

The present study was carried out to investigate the effect of parenteral administration of dexamethasone and flunixin meglumine on the haematological picture, serum biochemical parameters and immune response of the sheep.

MATERIALS AND METHODS

1- Drugs :

a- Dexamethasone: is one of synthetic glucocorticoid anti-inflammatory manufactured by Egyptian Co. for Chemical and pharm(Adwia) 10th of Ramadan City.

b- Flunixin meglumine (Finadyne)® it is one of non steroidal anti-inflammatory drugs manufactured by Schering- plough Company, USA.

2- Experimental animal :

A total of clinicaly healthy 15 sheep aged between 4-10 months old were used. They belonged to a farm at Sharkia Governorate and empolyed for this investigation the sheep were randomly divided into three equal group, 5 sheep in each. The first group was left without treatment and

served as control group. Second and third groups were injected intramuscularly with 0.20 mg dexamethasone /kg b. wt. and 1.1 mg flunixin meglumine /kg b. wt. respectively as therapeutic dose for five successive days.

3- Sampling :

Two blood samples were collected from each animal from jugular vein at 5, 10, 15 and 20 days post the last injection of both drugs. First sample was collected in heparinized tube for determination of haemoglobin percent (Hb%), erythrocytic count (R.B.Cs.), packed cell volume (P.C.V.%), total leucocytic count (T.L.C.) and differential leucocytic count were also estimated according to **(Coles 1986)**. The second sample was collected in centrifuge tube to obtain clear serum for determination of total protein according to **Doumas et. al. (1981)**, protein serum fractions were estimated after **(Kaneko 1989)**. Serum transaminases (AST . ALT) were determined colorimetrically according to Reitman and **Frankel (1957)**, serum total bilirubin **(Henry 1964)**, serum immunoglobulins (IgM- IgG) were estimated using SANDWICH Elisa method according to **Erhard et. al. (1992)**.

Tri-iodothyronin (T3), thyroxin (T4) were determined according to **Abraham (1981)** by RIA Kits. Triiodothyronin, thyroxin ratio were also estimated. Serum sodium (Na) and potassium (K) concentration were determined according to **Oser (1979)**, Calcium (Ca) **Glindler and King, (1972)**, inorganic phosphorus (P) **(Goldenberg 1966)**.

4- Statistical analysis :

The obtained data were tabulated and statistically analysed according to **Petrie and Watson (1999)**.

RESULTS

The effects of dexamethasone and flunixin meglumine on haematological picture are shown in Table (1) Therapeutic dose of dexamethasone induced significant decrease in erythrocytic count haemoglobin concentration, packed cell volume, lymphocytes, monocytes and eosinophil counts at 5,10 and 15 days post injection but induced significant increase in total leucocytic count and neutrophil at same peroid. Flunixin mglumine induced insignificant decrease in haemoglobin, packed cell volume and erythrocytic count all over the experimental period but induced significant increase in total leukocytic count, neutrophils count, and significant decrease in lymphocytic count at 5,10 days post injection.

Dexamethasone induced significant decrease in total proteins, gamma globulins, total globulins and significant increase in albumin at 5, 10, 15 days post injection meanwhile flunixin meg-

lumine induced significant decrease in total proteins. Dexamethasone induced decrease in total proteins, gamma globulins, total globulins and significant increase in albumin at 5,10,15 day post injection Meanwhile flunixin meglumine induced significant decrease in total proteins, gamma globulins, insignificant decrease in total globulins and insignificant increase in albumin at the same period (Table 2).

The results illustrated in table (3) and (4) revealed that dexamethasone injection increased serum transaminases (AST and ALT), potassium, calcium and phosphorus levels but induced reduction in T3, T4, IgG, IgM, and sodium. Flunixin meglumine induced significant increase in serum ALT and significant decrease in total bilirubin, T3, T4, IgG, IgM, sodium, potassium, calcium and phosphorus but there was insignificant increase in AST.

DISCUSSION

Anti-inflammatory drugs either steroidal or non steroidal are widely used in veterinary practice to provide symptomatic relief of acute and chronic inflammatory conditions.

Significant reduction of haemoglobin, packed cell volume and erythrocytic count were occurred after 5, 10, 15, days post I.M. injection of dexamethasone (0.20 mg /kg b.wt.) for 5 successive days. These results might be attributed to the deleterious effect of the drug on bone marrow resulting in bone marrow dysfunctions **(Yeates and March 1980)**. The effects on haemoglobin%, packed cell volume and erythrocytic count were supported by that previously recorded by **(Hass et. al. 1964, Nazifi et. al. 1998) (Fayed and Korshom 1998)** in horse and goats respectively. Also dexamethasone at the same dose induced a significant increase in total leucocytic count and neutrophils count, a significant decrease in lymphocytes, monocytes and esinophils counts. These together with results were parallel to those of **Zia-Ur-Rahman (1992)** he found that administration of dexamethasone to camels at dose (20 mg/kg b. wt.) I.M. or I.V. for 4 days induced an increase in total leucocytic count, neutrophil and decrease in lymphocytes counts. The results were reported by **(Habibadbadi et. al. 1997)** they reported that administration of isofluperdone acetate increased leucocytes, neutrophils and decreased in lymphocytes, monocytes and esinophils counts in sheep. The number of circulating esinophils resulted from endogenous or exogenous increase in adrenecorticotrophic hormone (A.C.T.H.) or adrenocortical steriod **(Raphal 1976)**.

In the present study flunixin meglumine (1.1 mg/kg b.wt.) caused non significant effect on haemoglobin %, packed cell volume % and erythrocytic count. Close similarity our results were nearly similar to that obtained by **(Carrick et. al. 1989) and (Taylor et. al. 1994)** They found that flunixin meglumine induces non significant change in haemogloben % packed cell volume %

and erythrocytic count. Our results showed a significant increase in total leucocytic count, neutrophils count and significant decrease in lymphocytes, monocytes counts. These results were in accordance with **Habibadbadi et. al. (1997)** who found that phenylbutazone induces significant increase in leucocytic count in sheep after 12 days post administration. In the same line, **Shalby (2000)** found that meloxicam (NSAIDs) induced a significant increase in total leucocytic count, neutrophil count and significant decrease in lymphocytes and monocytes counts in rabbit.

The intramuscular injection of dexamethasone (0.20 mg/ kg b.wt) induced a significant decrease in total proteins, gamma globulins, total globulins but albumin increased. These results agreed with those obtained by **Hefney (1996)** who reported that administratin of therapeutic dose of deponodrol and kenacort A to rabbits resulted in a significant decrease in serum total protein levels. **Abd El-Aliem (1999)** reported a significant decrease in serum total proteins and gamma globulin with therapeutic dose isofluperdone acetate in rabbits. These results could be attributed to the immunosuppressive effect of glucocorticoids **(Reynolds, 1989)**. Our reaults were conlermed by **Fayed and Korshom (1998)** They reported that dexamethasone induced significant decrease in total proteins, globulin and increased albumin. It is well known that glucocorticoids inhibit protein synthesis through decreased synthesis of messenger R.N.A. in fibroblast, DNA synthesis is impaired directly by corticosteroids **(Pratt and Aronow, 1966)**. Another explanation for the decrease in total proteins was confirmed by **Kayali, et. al. (1987)**. Glucocorticoids exert its catabolic effects on muscle protein haomeostasis and inhibit protein synthesis.

The present investigation revealed that flunixin meglumine at a dose of 1.1 mg /kg b. wt. induced significant decrease in total proteins and gamma globulins at 5,10 and 15 days post last injection and insignificant decrease in total globulins at same peroids. These results are in agreement with those of **Carrick, et. al. (1989)** who found a loss in total proteins by treatment of neonatal foals with different doses of flunixin meglumine for 5days. These results might be attributed to drug toxicity and immunosuppressive effect of flunixin meglumine as reported by **Cheng, et. al. (1998). Stegelmeir et. al. (1988)** stated that treatment of dog with flunixin meglumine induced hepatocellular damage and ledto a decrease in total proteins and serum globulin.

The significant increase in the liver enzymes of lambs treated with dexamethasone reflect the degree of tissue damage. These results are comparable with the finding of **Bush (1996)** who mentioned that hepatopathy was induced in dogs, cats or rabbits by single or multiple doses of glucocorticoids. Moreover, **El-Seidy et. al. (2002)** added that dexamethasone administration increased serum transaminases (AST and ALT) in rabbits.

Dexamethasone treatment induced insignificant increase in total bilirubin. These results are comparable with that obtained previously by **Badawi (1998).**

The present investigation revealed that flunixin meglumine induced significant increase in serum ALT and insignificant increase in serum AST but induced significant decrease in total bilirubin. These results are inagreement with that obtained by **Taylor et. al. (1994).** The authors reported that flunixin meglumine induced significant increase in serum ALT Vanhoose (1975) had noticed elevation in serum SGOT and SGPT in one treated horse from 7 to 21 days after treatment with flunixin meglumine. **Martin et. al. (1984)** found that phenylbutazone induced significant decrease in total bilirubin indicating a decrease in the breakdown of erythrocytes.

In the present study the, intramuscular injection of dexamethasone (0.20 mg/kg b. wt.) and flunixin meglumine (1.1 mg / kg b. wt.) caused significant decrease in T3 and T4 at 5.10 and 15 days post injection. Similar results were seen by **Madef et. al. (1997) and Fayed and Korshom (1998)** who found that dexamethasone induced significant decrease in T3 and T4 in pigs and rabbit respectively. Excess glucocorticoid may alter thyroid hormone metabolism by suppresing the hypothalamic - pituitary - adrenal axis and pertunbing peripheral hormone metabolism. These alterations were manifested by decreased total and free thyroxin and Triiodothyronin levels **Gamsted et. al. (1979). Ramirez et. al. (1997)** Also mentioned that phenylbutazone (4.4 mg /kg b. wt.) induced decrease in total and free thyroxin in horses.

The present investigation revealed that dexamethasone induced significant reduction of (IgG and IgM) but flunixin meglumine induced non significant reduction in serum IgG and IgM at 5,10 and 15 days post I.M injection.This observation was previously recorded by **Sangil, el. al. (1993) and Abd El-Aliem (1999).** These results might be possibly be attributed to the decrease in total proteins and globulin as suggested by **Coria and McClurkin (1978)** or might be attributed to lymphopenia as recorded in the present study. **Bate et. al., (1991)** found that isofluperedone acetate treated saw had a decreased concentration of I gG.

Effects of dexamethasone on serum minerals were pronounced and mainfested by reduction in serum sodium and elevation in potassium, calcium and inorganic phosphorus. Same results were reported by **El-Seidy et. al. (2002)** in rabbits. The increase in the serum calcium and inorganic phosphorus in lambs after treatment with dexamethasone were comparable with the results obtained before by **Habibadbadi, et. al. (1997) and (1998)** in sheep and horse respectively. Flunixin meglumine induced reduction in sodium, potassium, calcium and inorganic phosphorous after I. M. injection for 5 successive days. These changes coincided with the results of **Habibadbadi, et. al. (1997)** who reported that phenylbutazone (non steroidal antiinflammatory) induced decrease in sodium, potassium and inorganic phosphorous in sheep.

Table (1): Effects of Dexamethasone (0.20 mg / kg b. wt.) and flunxin meglumine (1.1 mg/kg b.wt.) on haemogram after intramuscular injection for 5 successive days in sheep (n=5)

Time of sampling and groups / Parameter	Control	5 Days		10 Days		15 Days		20 days	
	G1	G2	G3	G2	G3	G2	G3	G2	G3
Hb gm/dl	10.14±0.81	7.64±0.25*	9.80±1.93	6.88±0.18**	9.62±0.31	8.12±0.15*	9.58±0.58	9.8±0.33	10.02±0.48
P.V.C. %	35.33±1.21	30.16±0.93*	32.53±1.70	29.04±1.29**	32.85±1.18	30.8±1.01*	33.73±1.23	30.22±1.97	34.16±1.60
R.B.C.S.×10^6 mm3	9.16±1.01	6.76±0.17*	8.54±1.02	6.12±0.32*	8.46±0.97	6.76±0.25*	8.40±1.09	8.06±0.33	8.62±0.35
WB.CS. 10^3mm3	7.61±0.26	8.83±0.37*	8.50±0.19*	8.49±0.25*	8.30±0.11*	8.13±0.13	8.02±0.29	7.54±0.35	7.42±0.43
Lymphocyte 10^3mm3	3.92±0.15	3.12±0.22*	3.22±0.17*	2.93±0.35*	3.30±0.21*	3.16±0.23*	3.50±0.29	3.76±0.21	3.83±0.15
Neutrophil 10^3mm3	2.56±0.10	4.62±0.45**	4.10±0.50*	4.87±0.70**	3.95±0.61*	3.90±0.42*	3.33±0.57	2.82±0.31	2.40±0.35
Monocyte 10^3mm3	0.42±0.02	0.29±0.03**	0.31±0.04*	0.20±0.06**	0.29±0.04*	0.38±0.03	0.40±0.04	0.38±0.04	0.44±0.02
Eosinophil 10^3mm3	0.48±0.03	0.39±0.01*	0.45±0.04	0.31±0.07*	0.41±0.05	0.40±0.02*	0.51±0.01	0.53±0.08	0.45±0.02
Basophil 10^3mm3	0.24±0.05	0.35±0.02	0.36±0.01	0.23±0.04	0.29±0.03	0.20±0.05	0.23±0.01	0.19±0.07	0.26±0.02

* $P < 0.05$
** $P < 0.01$

Table (2): Effects of Dexamethasone (0.20mg / kg b. wt.) and flunixin meglumine (1.1 mg/kg b.wt) given by intramuscular injection for 5 successive days on total protein and protein fractions in sheep (n=5)

Time of sampling and groups / Parameter	Control	5 Days		10 Days		15 Days		20 Days	
	G1	G2	G3	G2	G3	G2	G3	G2	G3
T. protein gm/dl	6.96±0.69	5.04±0.30*	5.58±0.38*	4.76±0.18*	5.12±0.12*	5.12±0.10*	6.18±0.18	6.26±0.26	6.52±0.22
albumin %	42.44±0.99	42.78±1.35	41.62±1.04	46.8±0.87**	44.72±1.52	47.98±0.12**	43.56±0.33	42.04±1.23	41.34±1.14
α globulin %	13.2±0.63	11.50±0.49	11.52±0.43	11.26±0.68	11.98±0.34	12.16±0.61	12.44±0.29	13.22±0.51	12.7±0.24
β globulin %	19.59±1.61	23.90±2.08	22.84±1.63	23.34±1.18	22.76±1.75	23.64±1.14	23.69±0.97	22±0.56	21.16±0.65
δ globulin	24.77±0.57	21.17±0.49**	23.73±0.14	18.98±0.58***	20.79±0.46***	16.64±1.45**	20.16±0.82**	22.62±1.27	24.34±1.03
Γ. globulins %	57.56±0.44	56.57±1.94	57.99±1.22	53.58±1.58*	55.53±2.25	52.49±1.89*	56.29±0.78	57.74±1.12	58.2±1.39
A/G ratio	0.74±0.05	0.76±0.03	0.72±0.02	0.87±0.05	0.81±0.05	0.92±0.07	0.77±0.01	0.73±0.03	0.70±0.02

* P < 0.05
** P < 0.01
*** P < 0.001

Table (3): Effects of Dexamethasone (0.20 mg/ kg b. wt.) and flunixin meglumine (1.1 mg/kg b.wt) given by I.M. injection for 5 successive days on some serum biochemical parameters of sheep (n=5)

Time of sampling and groups	Control	5 Days		10 Days		15 Days		20 days	
Parameter	G1	G2	G3	G2	G3	G2	G3	G2	G3
AST (U/L)	43.72± 2.31	57.12±2.13**	49.20±3.15	61.33±2.81**	50.19±2.91	55.10±2.72	47.15±2.19	47.41±5.52	45.20±2.30
ALT (U/L)	20.31±1.23	25.17±1.40*	24.70±1.07*	28.10±2.83*	26.20±1.65*	24.35±2.20	23.11±1.93	21.73±1.78	21.93±1.75
Bilirubin (mg/dl)	0.31±0.03	0.35±0.01	0.23±0.01*	0.37±0.04	0.25±0.03	0.39±0.03	0.26±0.04	0.34±0.01	0.29±0.02
T3 (ng/dl)	130.2±3.35	111.40±4.41**	118.6±3.87*	119±2.45*	120±2.47*	126.2±3.18	124.8±2.42	131.6±3.43	127.41±2.30
T4 (ug dl)	3.73±0.1	2.72±0.24**	2.8±0.34*	2.68±0.28*	2.83±0.30*	2.96±0.26*	3.03±0.20*	3.14±0.27	3.34±0.19
T3 / T4	35.00±1.35	45.69±7.69	45.06±5.90	43.21±4.19	44.43±5.07	43.87±3.92	41.97±3.09	43.39±4.55	38.74±2.54
IgG (mg/ml)	18.68±1.03	14.05±0.99*	17.34±1.76	17.78±0.73*	15.48±1.56	16.04±0.47*	15.68±2.01	16.43±0.89	15.58±1.87
IgM (mg/ml)	2.76±0.13	1.91±0.11**	2.10±0.26	1.62±0.42*	1.90±0.43	1.86±0.33	1.95±0.36	2.30±0.32	2.10±0.36

* P < 0.05 ** P < 0.01

Table (4): Effects of Dexamethasone (0.20 mg/kg b. wt.) and flunixin meglumine (1.1 mg/kg b.wt) given by I.M. injection for 5 successive days on some serum major electrolytes of sheep (n=5)

Time of sampling and groups	Control	5 Days		10 Days		15 Days		20 days	
Parameter	G1	G2	G3	G2	G3	G2	G3	G2	G3
Na (m Eq/L)	145.60±3.22	107.66±4.95***	125.10±2.30***	100.06±2.989***	115±3.73***	124±6.60*	133.71±2.90*	132.4±5.07	140.10±2.30
K (m Eq/L)	4.93±0.39	7.83±0.50***	3.10±0.41*	7.08±0.56*	3.35±0.33*	6.46±0.47*	3.90±0.73	5.8±0.30	4.4±0.65
Ca (mg / L)	9.03±0.78	10.95±0.65*	8.40±0.51	9.84±0.69	8.10±0.65	9.46±1.22	8.70±0.55	9.09±1.07	9.20±0.83
ph (mg / L)	5.07±0.50	7.07±0.48*	4.20±0.40	6.83±0.37*	4.10±0.57	6.30±0.32	4.90±0.22	5.38±0.19	5.31±0.61

* P < 0.05 *** P < 0.001

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الملخص العربى

دراسة مقارنة على التأثيرات العكسية للديكساميثازون والفلونكسين مجلومين فى الأغنام

المشتركون فى البحث

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كان الغرض من هذا البحث مقارنة التأثيرات العكسية للديكساميثازون والفلونكسين مجلومين فى الأغنام. فى هذه الدراسة تم إستخدام ١٥ من الأغنام فى مزرعة خاصة بمحافظة الشرقية تتراوح أعمارها من ٤-١٠ شهور تم تقسيم هذه الأغنام إلى ثلاث مجموعات متساوية كلاً منها تضم ٥ أغنام الأولى ضابطة والثانية والثالثة حقنت بالجرعة العلاجية من عقارى الديكساميثازون والفلونكسين مجلومين لمدة خمس أيام متتالية فى العضل على التوالى بعد نهاية الحقن ب(٥، ١٠، ١٥، ٢٠ يوم تم أخذ عينتين دم من كل حيوان الأولى على هيبارين وذلك لدراسة تأثير العقارين على صورة الدم والأخرى لفصل المصل وذلك لقياس البروتين الكلى، الزلال، الجلوبيولين، هرمون الثيركسين، التراى ايودوثيرونين والنسبة بينهما IgG, IgM وبعض المؤشرات البيوكيميائية.

تشير النتائج أن الديكساميثارون بالجرعة العلاجية أدى إلى حدوث نقص معنوى فى تركيز الهيموجلوبين، حجم خلايا الدم المرصوصة، عدد كرات الدم الحمراء، الخلايا الليمفاوية، الملتهمة الكبيرة والحامضية، البروتين الكلى، الجاما جلوبيولين، الجلوبيولين الكلى، هرمون الثيروكسين والتراى ايودوثيرونين والنسبة بينهما IgG, IgM والصوديوم وهذا النقص إستمرلمدة إسبوعين بعد إيقاف الحقن كما حدثت زيادة معنوية فى العدد الكلى للكرات الدم البيضاء، الخلايا المتعادلة، الزلال، الترانس أمينيزسس (AST-ALT) البوتاسيوم، الكالسيوم والفسفور لمدة إسبوعين بعد إيقاف الحقن.

الفلونكسين مجلومين بالجرعة العلاجية أحدث نقصاً غير معنوياً فى تركيز الهيموجلوبين، حجم خلايا الدم المرصوصة، عدد كرات الدم الحمراء، الخلايا القاعدية، الزلال، جلوبيولينيات الألفا والبيتا كما أدى إلى نقص معنوى فى الخلايا الليمفاوية، الخلايا القاعدية، الزلال، جلوبيولينيات الألفا والبيتا كما أدى إلى نقص معنوى فى الخلايا الليمفاوية، الملتهمة الكبيرة والخلايا الحامضية البروتين الكلى، الجاما جلوبيولين، صبغة الصفراء، هرمون الثيروكسين والتراى أيودوثيرونين IgG, IgM والصوديوم بينما أحدث زيادة معنوية فى العدد الكلى لكرات الدم البيضاء، الخلايا المتعادلة ALT البوتاسيوم، الكالسيوم والفوسفور.

نستخلص من هذه الدراسة أن الديكساميثازون والفلونكسين مجلومين أحدثا تأثيرات عكسية على صورة الدم، المناعة، بعض القياسات البيوكيميائية وهرمون الغدة الدرقية فى الأغنام ولكن الفلونكسين مجلومين كان أقل فى إحداث التأثيرات العكسية.