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Comparative study between steroidal and non- steroidal compound in rats.

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Abstract

Comparative effects of non steroidal (Ibuprofen) and steroidal (dexamethazon) compound in rats were studied. A total of 60 male albino rats, about 130_150 grams were used and classified into 3 groups. The 1st.group injected distilled water intramuscularly and left as a control. The 2nd and 3rdgroup were injected Ibuprofen and dexamethazon at a dose of 0.9 mg and 0.8 mg/100gm b. wt. intramuscularly respectively for **5** consecutive days. The samples were taken after 1,7,15 and 45 days after stopping injection.

The results revealed that, ibuprofen and dexamethasone induced significant decrease in haemoglobin, red blood cells, total leucocytic count and lymphocytes beside total protein, albumin and globulin. On the other hand, significant increase neutrophil, ALT, AST,ALP, urea , creatinine, total lipid, cholesterol ,triglyceride A/G ratio, glucose and liver glycogen in tissue.

Our results indicated that Ibuprofen and dexamethazon caused dysfunction in blood picture, liver and kidney functions in rats. The study was showing the pathogenesis of Ibuprofen or dexamethazon which could be poisonous in therapeutic doses in rodents.

Key word: Blood picture, lipid profile, biochemical parameters, steroidal drug, non steroidal drug, rats.

Introduction

Non steroidal anti-inflammatory drugs (NSAIDs) are most prescribed drugs in human and veterinary medicine that provide anti-inflammatory, antipyretic, analgesic, antispasmodic, and anticoagulant effects **(Vane and Bottling, 2003)**. NSAIDs are effective in controlling the joint pain and swelling in rheumatoid arthritis and have also shown in recent times to prevent the formation of cancer in different tissues **(Sengupta et al., 2003)**. However, NSAIDs reduce inflammation and relieve fever and pain by blocking enzymes and proteins made by the body. The anti-

inflammatory action of NSAIDs can be explained by their capability to inhibit the synthesis of prostaglandins, particularly to inhibit the cyclo-oxygenase (COX) enzymes. COX is demonstrated to be existing as three distinct isoforms, in human kidney and brain, while its expression is being induced in many tissues during inflammation, normal wound healing and neoplasia **(Bombardier et al., 2000).**

Therefore, it was proposed that the selective COX-2 inhibitors may become more effective and safe chemo preventive agents than classical NSAIDs which preferentially inhibit COX-1. Also, the selective COX-2 inhibitors are effective and well tolerated in treatments for rheumatoid arthritis and other inflammatory disorders (**Matsumoto et al., 2002).** Non steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen and indomethacin are extensively used as analgesics and anti-inflammatory agents and produce their therapeutic effects through the inhibition of prostaglandin synthesis **(Klaassen, 2001).**

Each of anti-inflammatory drugs non steroidal or steroidal and antimicrobial agents had its specific adverse effect on blood, biological and chemical parameters **(Abatan, et al., 2006). (Ritter et al., 1999)** stated that cortisol enhances hyperglycemia hypercholesterolemia, and decrease protein synthesis and increase red blood cells.

It has being a local practice to use the NSAIDs most especially indomethacin as a rodenticide which from personal observation is effective.

The study was therefore carried out to verify the pathogenesis of NSAIDs which could be poisonous in therapeutic doses in rodents.

Material and Methods

Animals:-

A total of 60 male albino rats (130 -150 gm.), were used in this study. They were obtained from the laboratory animal house of Ophthalmic Research Institute Giza. They acclimated to laboratory condition before used. Animals were fed on balanced ration and water ad labium.

Experimental Design:

This was planned to study the effect of Ibuprofen and dexamethazon on blood picture, biochemical parameters and liver glycogen in rats. For this purposes 60 mature rats were divided into 3 groups 20 rats each. The groups were divided as follow:

The 1st group rats were injected 0.3ml distilled water intramuscularly for 5 consecutive days and left as control.

The 2nd group rats were injected intramuscularly with Ibuprofen for 5 consecutive days at a dose 0.9mg /100 gm body weight.

The3rd group rats were injected intramuscularly with dexamethazon for 5 conseccutive days at a dose 0.8mg /100 gm body weight.

Blood and plasma samples:

Five blood samples were collected from rats for each group at 1st day, 7 days' 15 days, and 45 days in two clean, dry and sterile tubes. The first tube contained anticoagulant was used for determination blood picture. The second tube centrifuged for 10 minutes, and then plasma was removed and stored in sterile tube until used.

Liver tissue sample:

Specimens of fresh liver weighing one gram were collected from sacrificed rats at 1st day, 7 days' 15 days, and 45 days post injected the drugs. The samples were used for liver glycogen determination.

Methods:

Blood picture:

Blood hemoglobin values were estimated as described by **Oser (1979)**. Red and white blood cells according to the method described by **Schalm et al (1975).**

Biochemical parameters:

Plasma samples were used for determination of total lipids (**Knight et al .,1972)** cholesterol (**Fasce 1982),** triglyceride (**fossati and princip 1982)**, total protein (**Sonnen Wirth and Jaret 1980)** , albumin (**Drupt 1974).**Alanine amino transeferase (ALT) and aspartate amino transeferase (AST) activities (**Retman and Frankel 19557),** plasma alkaline phosphatase (ALP) **Belfield and Goldberg (1971).**Urea and Creatinine (**Wypenga et al., 1971and Bartels 1971**respectively) , uric acid(**Oser 1979).** Glucose **Trinder (1969).**

Glycogen was determined in liver tissue (**Van Handel 1965).**

Statistical Analysis:

The obtained data were statically analyzed using student's t-test according to **Petrie and Watson (1999).**

Results and Discussion

Intramuscularly injection of Ibuprofen and dexamethazone at dose of 0.9mg and 0.8mg /100 gm body weight respectively for 5 successive days caused significant decrease in hemoglobin concentration at 1^{st}, 7^{th} and15^{th} days post dosing and RBC_S counts on the 7^{th} days. These results are similar to those reported by **Yokoyama, et .al, (2013) and Aprioku et al., (2014)** in case of Ibuprofen. While dexamethazone showed significant decrease on hemoglobin concentration and RBC_S counts on the 7^{th} day (table 1), our results agree with **(Abd Elazem and Seham. 2015) and (Safarmashaei and Hasanpour ,2011).** They reported that dexamethazone cause anemia and changes in hemogram in post administration, which may be due to deleterious effect of the drug on bone marrow.

Ibuprofen and dexamethazone significantly increase neutrophiles and significant decreased in lymphocytes table(2).These results were confirmed with those obtained by **(Er et al., 2013 and Saravanan et al., 2012)** attributed neutrophilia with coexistent lymphopenia to severe condition and reflect stress. **(Flaherty et al., 1993)** who found that corticosteroids decrease the total leucocytic counts and lymphocytes with an increase in segmented neutrophils. These results could be attributed to the atrophy of lymphatic organs or may be due to the direct action of corticosteroids on neutrophils (**Hassan,1998).**

Table (3) showed insignificant increase of plasma total lipid ,cholesterol and triglyceride ,while tested drugs insignificantly increase of cholesterol at 7^{th} days. **(Aprioku et. al., 2014, Lucena et al., 1999** and **Nagashima et al., 1992)** concluded that corticosteroid administration showed a tendency toward an increase in triglyceride and cholesterol. They attributed these results to vacculation of hepatocytes in the middle zone of the liver examination or due to obstructive changes caused secondary to increased viscosity of pancreatic secreation induced by dexamethazone.

Table 4 detected that Ibuprofen and dexamethazone caused decrease in total protein, albumin and globulin, while A/G ratio significantly increased. Our results were supported by **(Abd Elazem and Seham ,2015)** in goat and **(Goodrich et al., 1998).** .The lowered values in these parameters could be attributed to their loss into

the gastrointestinal tract, into the urine or decreased protein synthesis. (**Hefney, 1996)** who reported that the decrease in protein in goats injected with dexamethasone may be due to inhibition in protein synthesis through decrease synthesis of messenger R.N.A. in fibroblast, DNA synthesis is impaired directly by corticosteroids.

The obtained results revealed that the effect of the used drugs evoked significant increase in the liver enzyme activities (AST, ALT and ALP) at 7th and15th day post dosing table 5 Our results agreement with **(Singh et.al. 2011**, **Aprioku et al., 2014** and **Abd Elazem. and Seham. 2015).**They recorded that elevation in serum levels of alanine transaminase (ALT), alkaline phosphatase (ALP) and aspartate aminotransferase (AST) by ibuprofen is indicative of cellular injury to the liver and dose, time dependently.

Ibuprofen and dexamethazone insignificant increase in urea and creatinine levels when compared with control group table 5.Our results in agreement with **(Aprioku, and Uche,2013, Knights et al., 2009 and Traynor, et.al, 2006).** Who observed that the renal effect of tested drugs correlates with its dose and duration of exposure, which is consistent with previous reports on NSAIDs In addition, the results also show that prolong use of standard dose levels of Ibuprofen and dexamethazone may alter renal function **.**Also ,they recorded that urea is incompletely reabsorbed at the kidney tubules and the rate of reabsorption is inversely proportional to urine flow rate, more urea was lost through the nephron as urine excretion increased.

In regard to the effect of Ibuprofen and dexamethazone on plasma glucose level and liver glycogen concentrations, the present data showed significant increases on 1st, 7th and 15th days' post injection .Similar finding were recorded by **(Knights et al 2009 and Thauany et al., 2013).**All previous researchers found that, the mean glucose values increased sharply after initial low dose of dexamethazone. They attributed the hyperglycemic effect and glucose intolerance seen with glucocorticoids to hepatic and peripheral insulin resistance. **(Zheng et al., 2009)**also illustrated that insulin usually acts to suppress enzymes involved in hepatic gluconeogenesis, as well as to facilitate glucose utilization in peripheral. Several possibilities might explain the response: a slow conversion of protein to glucose, less protein being converted to glucose and released than previously thought, glucose from protein being incorporated into hepatic glycogen stores but not increasing the rate of hepatic glucose release, or because the process of gluconeogenesis from protein occurs over a

period of hours and glucose can be disposed of if presented for utilization slowly and evenly over a long time period.

We can conclude that both ibuprofen and dexamethasone induced several hematobiochemical changes in the rats. Side effects of ibuprofen and dexamethasone were disappeared after 45 days after stopping injection. Also, ibuprofen is safer because it is fewer hazards than dexamethasone.

Table (1): Effect of Ibuprofen and Dexamethazone on blood profile in rats after stopping injection.

groups / parameters	1day			7days			15days			45days		
	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3
Hemoglobin g/100ml	12.45 ±0.44	11.08 ±0.12*	11.67 ±0.48	12.83 ±0.61	9.98 ±**0.52****	10.93 ±0.21*	12.00 ±0.23	11.01 ±0.25*	11.72 ±0.51	13.47 ±0.55	12.68 ±0.36	13.13 ±0.84
Red blood cellsX$10^6$$mm^3$	6.86 ±0.36	6.18 ±0.35	6.21 ±0.51	7.04 ±0.51	5.42 ±0.32*	6..36 ±0.30	6.60 ±0.21	6.14 ±0.36	6.18 ±0.45	7.26 ±0.45	7.33 ±0.43	7.38 ±0.62
White blood cellsX$10^6$$mm^3$	7.30 ±0.70	6.17 ±0.65	6.11 ±0.40	7.70 ±0.23	5.30 ±0.62	5.30 ±0.55	7.73 ±0.4	6.47 ±0.41	5.50 ±0.59	8.13 ±0.36	7.43 ±0.76	7.40 ±0.41

G1=control G2=Ibuprofen G3=Dexamethazone

Data are presented as mean ± S.E Significant at * (p≤ 0.05) **(p≤ 0.01) and *(p≤ 0.01).**

Table (2): Effect of Ibuprofen and Dexamethazone on white blood cells differntioal in rats after stopping injection.

groups / parameters	1day			**7days**			**15days**			**45adys**		
	G1	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**
Neutrophiles%	**26.00** ±0.79	**31.25** ±1.42*	**35.66** ±1.15***	**27.11** ±1.83	**34.86** ±1.17***	**33.01** ±1.26*	**27.04** ±1.77	**32.66** ±1.06*	**31.833** ±2.07	**26.67** ±1.55	**29.91** ±1.60	**29.33** ±1.78
Lymphocytes%	71.50 ±0.50	67.12 ±1.17**	61.90 ±1.52***	70.05 ±2.02	62.31 ±1.51***	64.15 ±1.53**	**69.59** ±1.72	**64.56** ±1.80	**65.49** ±1.61	**70.04** ±0.99	**67.10** ±1.50	**67.15** ±3.00
Monocytes %	**1.83** ±0.12	**2.15** ±0.33	**1.67** ±0.50	**1.92** ±0.34	**2.09** ±0.50	**2.00** ±0.37	**2.40** ±0.50	**2.10** ±0.29	**2.00** ±0.26	**2.33** ±0.88	**2.11** ±0.52	**2.66** **0.54**
Esinophiles%	**0.67** ±0.33	**0.42** ±0.25	**0.83** ±0.43	**0.93** ±0.33	**0.74** ±0.21	**0.83** ±0.41	**0.95** ±0.28	**0.67** ±0.20	**0.70** ±0.21	**1.00** ±0.33	**0.87** ±0.22	**0.86** ±0.32

G1=control G2=Ibuprofen G3=Dexamethazone

Data are presented as mean ± S.E Significant at * (p≤ 0.05) ** (p≤ 0.01) and * (p≤ 0.001)**

Table (3): Effect of Ibuprofen and Dexamethazone on lipid profile in rats after stopping injection.

groups / parameters	1 day			7 days			15 days			45 days		
	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3
Total lipid mg/dl	565.00 ±15.10	575.12 ±37.85	572.48 ±13.55	570.33 ±23.44	633.66 ±20.44	628.33 ±15.96	585.67 ±17.90	626.67 ±19.87	616.00 ±14.54	585.00 ±29.32	695.67 ±17.93	606.90 ±13.99
Cholesterol mg/dl	110.00 ±9.25	120.79 ±10.72	126.85 ±12.16	101.50 ±8.15	130.25 ±9.19*	137.15 ±5.02***	110.96 ±9.36	144.98 ±11.17*	127.52 ±9.98	114.88 ±10.91	116.90 ±9.11	117.85 ±6.14
Triglyceride mg/dl	90.21 ±6.46	98.11 ±8.73	93.22 ±3.25	90.00 ±7.17	102.30 ±7.51	124.66 ±12.92*	102.16 ±8.18	113.69 ±6.4	128.91 ±8..22*	92.23 ±5.55	96.13 ±5.17	105.46 ±7.22

G1=control G2=Ibuprofen G3=Dexamethazone

Data are presented as mean ± S.E Significant at * ($p \leq 0.05$) ** ($p \leq 0.01$) and * ($p \leq 0.001$)**

Table (4): Effect of Ibuprofen and Dexamethazone on protins profile in rats after stopping injection.

Groups / parameters	1day			7days			15days			45days		
	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3
T.protein	6.82 ±0.48	5.65 ±0.45	5.86 ±0.07	6.71 ±0.65	5.82 ±0.04	5.71 ±0.82	6.59 ±0.36	7.11 ±0.25	6.52 ±0.53	6.54 ±0.67	7.02 ±0.60	6.12 ±0.35
Albumin	1.80 ±0.18	1.78 ±0.16	1.77 ±0.17	1.97 ±0.17	1.24 ±0.16**	1.26 ±0.10***	1.83 ±0.13	1.59 ±0.13	1.53 ±0.07	1.91 ±0.21	1.85 ±0.13	1.53 ±0.11
Fibrinogen	0.48 ±0.03	0.3 ±0.02***	0.50 ±0.03	0.47 ±0.04	0.46 ±0.02	0.42 ±0.06	0.68 ±0.05	0.67 ±0.07	0.66 ±0.08	0.48 ±0.07	0.61 ±0.04	0.54 ±0.04
T.globulin	4.53 ±0.29	3.57 ±0.38	3.59 ±0.26	4.41 ±0.19	4.11 ±0.1	4.03 ±0.55	4.41 ±0.23	4.75 ±0.25	4.33 ±0.44**	4.26 ±0.19	4.56 ±0.52	4.06 ±0.23
A/G ratio	0.04 ±0.02	0.49 ±0.02**	0.49 ±0.03*	0.45 ±0.03	0.30 ±0.03***	0.31 ±0.04**	0.44 ±0.02	0.33 ±0.04**	0.35 ±0.01**	0.45 ±0.02	0.41 ±0.03	0.37 ±0.02

G1=control G2=Ibuprofen G3=Dexamethazone

Data are presented as mean ± S.E Significant at * (p≤ 0.05) ** (p≤ 0.01) and * (p≤ 0.001)**

Table (5): Effect of Ibuprofen and Dexamethasone on liver (µ\L) and kidney (mg\dL) function in rats after stopping injection.

Group / Parameters		1day			7 days			15 days			45 days		
		G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3
Liver Function (µ\L)	**AST**	28.00 ±1.77	31.30 ±3.30	32.32 ±3.45	28.30 ±1.16	41.18*** ±1.96	39.73*** ±2.6	27.64 ±1.40	40.30** ±3.80	44.67*** ±2.8	31.64 ±2.27	33.15 ±2.93	35.53 ±2.64
	ALT	17.33 ±1.66	20.00 ±3.01	22.64 ±1.84	19.33 ±2.70	28.33** ±1.31	28.00** ±2.00	17.00 ±2.1	25.00* ±1.88	27.01** ±2.21	18.5 ±2.58	22.31 ±2.06	24.42 ±1.90
	ALP	164.19 ±5.15	172.20 ±4.34	176.96 ±2.67	167.93 ±4.07	185.51** ±4.27	188.76* ±5.11	162.88 ±4.90	179.46* ±3.46	175.88** ±3.48	166.94 ±5.48	172.55 ±5.01	170.12 ±3.36
Kidney Function (mg\dL)	**Urea**	37.00 ±2.27	51.90 ±7.31	39.60 ±7.69	35.80 ±5.64	54.85* ±3.28	31.22 ±5.27	39.50 ±3.1	53.86* ±4.04	32.00 ±4.85	38.11 ±3.51	34.14 ±2.69	34.66 ±5.40
	Creatinine	0.83 ±0.05	0.92 ±0.04	0.91 ±0.17	0.82 ±0.04	1.23*** ±0.11	0.69 ±0.1	0.86 ±0.03	1.24* ±0.23	0.70 ±0.09	0.91 ±0.11	0.95 ±0.21	0.89 ±0.01

G1=control G2=Ibuprofen G3=Dexamethazone

Data are presented as mean ± S.E Significant at * (p≤ 0.05) ** (p≤ 0.01) and * (p≤ 0.001)**

Table (6) :Effect of Ibuprofen and Dexamethasone on plasma glucose and liver glycogen in rats after stopping injection.

Time / groups	1 day			7 days			15 day			45 day		
	1 G	**2G**	**3G**	**1G**	**2G**	**3G**	**1G**	**2G**	**3G**	**1G**	**2G**	**3G**
Glucose Mg\dL	85.30 ±5.21	101.10* ±3.82	119.11*** ±5.42	85.00 ±4.75	129.90*** ±9.56	139.90*** ±8.16	84.94 ±6.12	115.94*** ±6.12	118.94*** ±7.85	83.11 ±7.66	94.71 ±3.15	106.71 ±6.95
Glycogen gm\100mg	6.83 ±0.45	8.85*** ±0.26	10.69** ±0.95	7.51 ±0.57	10.88*** ±0.59	13.34*** ±1.04	7.61 ±0.46	9.45* ±0.46	10.10* ±0.72	7.42 ±0.41	7.11 ±0.91	10.15 ±0.72

G1=control G2=Ibuprofen G3=Dexamethazone

Data are presented as mean ± S.E Significant at * (p≤ 0.05) ** (p≤ 0.01) and * (p≤ 0.001)**

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