EFFECT OF PIROXICAM AND PIRPROFEN COMPOUNDS ON TOXICIETY, LIVER FUNCTION AND BLOOD PICTURE

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Effect of piroxicam and pirprofen compounds, which are anti-inflammatory drugs, on toxicity, liver function and blood picture were studied alone and with methyl androstenolone (MAA) as an anabolic agent.

The results of acute toxicity indicated that piroxicam drug was more toxic to female rats than males on acute basis, since the LD50 and LD84 of female were about one third those of males. Its acute toxicity was not antagonized by the anabolic grug. Pirprofen was equally toxic to male, female, adult, and immature rats. Its acute toxicity was reduced by 25%in adult male rats by the anabolic drug.

The obtained data short term chronic toxicity illustrated that the administration of anabolic (MAA) compound reduced the toxicity of pirprofen to a marked extent, but did not affect in the case of piroxicam drug.

The two antiinflammatory drugs reduced the growth rates, while the body weight was constant. The anabolic drug minimized the harmful effect of pirprofen but this effect was not observed in case of piroxicam. Both the antiinflammatory drugs caused a noticeable reduction in the weight of the spleen but the other internal organs i.e. liver, heart, brain, kideys, and testes were constant.

The obtained results indicated that piroxicam drug (1.8mg/kg) caused a decrease in liver triglycerides content i.e. 32.9% below control values. On the other hand, piroxicam (5.4mg/kg) treatment caused the highest increment of liver triglycerided i.e. 91.24% over control . This effect was not antagonized by the anabolic drug. Pirprofen drug given alone or with MAA compound showed no significant change in the liver triglycerides. Hepatic ribonucleic acid content was elevated in response to both piroxicam and pirprofen by 17 and 18.7%, respectively. The anabolic agent antagonized the effect of piroxicam drug. Hepatic DNA was not affected by both piroxicam and pirprofen drugs. While the both drugs caused an increment in the liver protein of rats.

Liver lysosoma; results indicated that chronic toxicity of both pirozxicam and pirprofen is related to excessive labilization of lysosomes. This toxic effect was minimized to a great extent by the anabolic drug.

Blood haematological data showed that both piroxicam and pirprofen caused agranulocytosis phenomena. This toxic effect was not accom-panied by any degree of anaemia. The anabolic agent was not able to correct this effect.

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By

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ABSTRACT

Effect of piroxicam and pirprofen compounds, which are anti-inflammatory drugs, on toxicity, liver function and blood picture were studied alone and with methyl androstenolone acetate (MAA) as an anabolic agent.

The results of acute toxicity indicated that piroxicam drug was more toxic to female rats than males on acute basis, since the LD_{50} and LD_{84} of female were about one third those of males. Its acute toxicity was not antagonized by the anabolic drug. Pirprofen was equally toxic to male, female, adult and immature rats. Its acute toxicity was reduced by 25% in adult male rats by the anabolic drug.

The obtained data of short term chronic toxicity illustrated that the administration of anabolic (MAA) compound reduced the toxicity of pirprofen to a marked extent, but did not affect in the case of piroxicam drug.

The two anti-inflammatory drugs reduced the growth rates, while the body weight was constant. The anabolic drug minimized the harmful effect of pirprofen but this effect was not observed in case of piroxicam. Both the anti-inflammatory drugs caused a noticeable reduction in the weight of the spleen but the other internal organs i.e. liver, heart, brain, kidneys and testes were constant.

The obtained results indicated that piroxicam drug (1.8 mg/kg) caused a decrease in liver

triglycerides content i.e. 32.9% below control values. On the other hand, piroxicam (5.4 mg/kg) treatment caused the highest increment of liver triglycerides i.e. 91.24% over control. This effect was not antagonized by the anabolic drug. Pirprofen drug given alone or with MAA compound showed no significant change in the liver triglycerides. Hepatic ribonucleic acid content was elevated in response to both piroxicam and pirprofen by 17 and 18.76%, respectively. The anabolic agent antagonized the effect of piroxicam drug. Hepatic DNA was not affected by both proxicam and pirprofen drugs. While both drugs caused an increment in the liver protein of rats.

Liver lysosomal results indicated that chronic toxicity of both piroxicam and pirprofen is related to excessive labilization of lysosomes. This toxic effect was minimized to a great extent by the anabolic drug.

Blood haematological data showed that both piroxicam and pirprofen caused agranulocytosis phenomena. This toxic effect was not accompanied by any degree of anaemia. The anabolic agent was not able to correct this effect.

INTRODUCTION

Anti-inflammatory drugs are one of the oldest medication used for relief, treatment of rheumatic diseases and inflammatory syndromes. Hayens and Murad (1985) mentioned that there are two types of drugs that are used to control inflammation i.e. steroidal anti-inflammatory drugs e.g. corticosteroids and non-steroidal anti-inflammatory drugs . Non steroidal anti-inflammatory drugs are heterogeneous group of compounds (Flower et al., 1985).

Piroxicam is one of the representative prototypes of the oxicam series of compounds distinguished from other non steroidal analgesic anti-inflammatory drugs "NSAIDS" (Zinnes et al., 1982). Also, Wiseman (1978) added that *piroxicam is relatively non-lethal in rodent on acute basis.*

Estimated oral acute medium lethal doses (LD_{50}) were 360 mg/kg in mouse, 270 mg/kg in rat and 700 mg/kg in dog.

Teleb et al. (1990) reported that renal lysosomal labilization indicator of nephrotoxicity evoked by short term oral piroxicam in rats.

Pirprofen is a potent antirheumatic agent, combining excellent analgesic properties with anti-inflammatory and also antipyretic activity. Its chemical structure possesses a propionic acid with amphoteric character. This compound acts as a strong inhibitor in the conversion of arachidonic acid into prostanoids, without interference with the formation of leucotrienes (Maier, 1984).

In acute toxicity studies (single administration) Pericin (1983) observed that pirprofen was much better tolerated by mice (LD_{50} = 125 mg/kg body weight). The species differences are even more pronounced and amplified following repeated daily oral administration over two weeks. The rats are more sensitive than other species, not only to pirprofen but also to other NSAIDs. These drugs are extensively recirculated in the entero hepatic cycle, particularly in rats and dogs and this offers an explanation for their low tolerability in these species.

Anabolic steroid agents are derived from or are closely related to the androgen testosterone and therefore have androgenic as well as anabolic activity (Kastrup, 1986). The same author stated that anabolics cause retention of calcium and are useful in the treatment of osteoporosis.

The aim of this research work is to elucidate the toxicological side effects of two commonly used non steroidal anti-inflammatory drugs i.e., piroxicam and pirprofen. Besides, an attempt was carried out to minimize these harmful side effects by using methyl androstenolone acetate as anabolic steroid compound.

MATERIALS AND METHODS

Materials:

a) Piroxicam was supplied from Pfizer company in capsule form. Each capsule contained 20.0 mg of piroxicam.

b) Pirprofen compound was obtained from Ciba Company in capsule form. Each capsule contained 400 mg of pirprofen.

Steroidal anabolic compound primoblan was supplied from Schering Company in tablet form and each tablet contained 5 mg of methyl androstenolone acetate (MAA).

Methods:

I. Acute toxicity studies:

Acute toxicity studies were carried out to determine the medium lethal dose (LD_{50}) for each of the two NSAIDs compounds according to the design of Litchfield and Wilcoxon (1949) , in adult , immature (4 weeks) , male or female as well as in those adults pretreated with MAA (1.8 mg / kg for 2 weeks . Several groups of 6 rats received increasing dose of the tested NSAID . Percent mortalities were recorded 7 days afterwards .

II. Short term chronic toxicity studies:

These studies were done on 100 adult normal male albino rats, weighing from 150 to 200 g. These rats were divided into 10 equal groups, each comprising 10 rats. The rats received daily the following treatments for 8 weeks.

Group 1:

This group received (1.0 ml/100 g body weight) of the vehicle (water and 2% Tween 80) and served as control.

Group 2:

This group received orally methyl androstenolone acetate (1.8 mg/kg body weight).

Group 3:

This group received piroxicam (1.8 mg/kg body weight). This dose is equivalent to human therapeutic dose (Paget and Barnes, 1964).

Group 4:

This group received piroxicam (5.8 mg/kg body weight). This dose level is equivalent to three times of the human therapeutic dose .

Group 5:

This group received simultaneously both piroxicam (1.8 mg/kg) and methyl androstenolone acetate (1.8 mg/kg).

Group 6:

This group received simultaneously both piroxicam (5.4 mg/kg) and methyl androstenolone acetate (1.8 mg/kg).

Group 7:

This group received orally pirprofen (8 mg/kg body weight), the effective dose in rats (Maier et al., 1981).

Group 8:

This group received orally pirprofen (24 mg/kg body weight). This dose level is three times of the effective dose in rats.

Group 9:

This group received simultaneously both pirprofen (8 mg/kg) and methyl androstenolone acetate (1.8 mg/kg body weight).

Group 10:

This group received pirprofen (24 mg/kg body weight) together with methyl androstenolone acetate (1.8 mg/kg body weight).

All compounds were given orally as homogeneous suspension in water by using Tween 80 (2%) as a suspending agent. Animals were fed on the ingredient of ration (crushed wheat 46%, shredded barley 40%, fish meal powder 9%, dried milk 3%, yeast 1% and minerals, vitamins 1%), according to Ahmed (1976). Animals were kept in air conditioned room housed 5 per cage. Food and drinking water were given adlibitum. All treatments were given at 10.00 A.M. Animal were weighed weekly for monitoring body growth changes.

After 4 and 8 weeks of treatment, blood samples for heamatological investigations, were taken from the retro-orbital plexus (Schermare, 1967) of 6 animals of each group, 24 hr after the last dose. Blood samples were taken at 10.00 A.M. to avoid any variations arising from circadian rhythm . At end of 8 weeks , animals were sacrificed , internal organs were weighed and liver were homogenized for analysis.

III. Biochemical analysis in the liver:

1. Liver triglycerides:

Liver triglycerides were determined according to Wieland (1974) by using liver homogenate in saline solution.

2. Determination of liver nucleic acids (RNA & DNA) and total proteins:

RNA and DNA concentration were determined by the method described by Wassemachar et al. (1965).

Protein was estimated by using biuret reagent according to Henry et al. (1974).

3. Liver lysosomal enzyme estimations:

Preparation of liver homogenate and isolation of the fractionated lysosomal was achieved according to the method described by Tanaka and Lisuka (1968).

The acid phosphatase A.P.; (Orthophosphoric monoester phosphohydrolase) was determined according to Van-Hoof and Hers (1968).

4. Blood haematological parameters:

The haematological parameters were carried out according to Frankel and Reitman (1963).

IV. Statistical analysis:

Standard error (S.E.) was determined according to standard statistical methods (Bernstein and Weatherall, 1952). Student (t) described by Goldstein (1964) was used for testing significancy of differentiated between two sample means.

RESULTS AND DISCUSSION

I. Effect of piroxicam and pirprofen compounds with or without the anabolic agent on toxicity and body weight of rats:

1. Acute toxicity:

The results of acute toxicity (Table, 1) indicate that there is an enhancement in the acute toxicity of

Table (1): Comparative acute toxicological data of piroxicam and pirprofen in absence and presence of methyl androstenolone acetate (MAA) pretreated (1.8 mg/kg orally for 2 weeks) rats.

Type of rats	*Lethal doses (mg/kg piroxicam)						Lethal doses (mg/kg pirprofen)					
	Without MAA			With MAA before treatment			Without MAA			With MAA before treatment		
	LD_{50} (fiducial limit)	LD_{16}	LD_{84}	LD_{50} (fiducial limit)	LD_{16}	LD_{84}	LD_{50} (fiducial limit)	LD_{16}	LD_{84}	LD_{50} (fiducial limit)	LD_{16}	LD_{84}
Adult female	220 (183.33-264.0)	190	250	250 (206.61-302.5)	210	290	690 (547.6-869.0)	510	910	610 (621.1-1159.5)	250	1300
Adult male	570 (393.1-826.5)	330	970	230 (176.9-299.0)	120	280	650 (528.5-799.5)	490	850	850 (472.2-1530.0)	710	990
Immature female	230 (127.28-414.0)	180	290				510 (414.6-627.3)	410	640			
Immature male	550 (443.6-688.0)	430	680				450 (298.0-679.5)	210	990			

* $LD_{50,\ 16,\ 84}$ = Lethal dose to 50%, 16% and 84% of the animals, respectively.

piroxicam by the anabolic in male rats. Also, the obtained results showed that female rats were more succeptible to the acute toxicity of piroxicam, since in both adult and immature rats the LD_{16} values of females were about one half those of the males. Furthermore the LD_{50} and LD_{84} of females were about one third those of males.

The LD_{50} and LD_{84} of piroxicam in the presence of M.A.A. in adult male rats were almost similar to those in adult females. While in case of LD_{16} the value of lethal dose of adult female was about double of adult male. This observation may be related to hormonal agonistic and antagonistic effect of the anabolic compound. These observation is in agreement with that obtained by Bennett and Wells (1985). In adult female rats the oral LD_{50} for pirprofen (Rengasil) was similar to that of pirprofen with MAA. While its LD_{50} in absence of MAA was less than those in presence of the anabolic agent. On the other hand, its LD_{84} in the absence of MAA was greater than the combined treatment (Table, 1).

These results illustrate that there is a slight reduction in the acute toxicity of pirprofen in adult male rats by the anabolic agent.

The results in table (1) indicate that there is no marked variations in acute toxicity parameter of pirprofen between males vs. females, adults vs. immature.

2. <u>Short term chronic toxicity studies</u>:

The recorded deathes during the 8 weeks period in response to the different treatments are shown in table (2).

Table (2): Cummulative percentage mortalities in rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg) given in absent and presence of methyl androstenolone acetate (MAA) (1.8 mg/kg), daily for 8 weeks.

Treatments	Cummulative % mortalities (weekly intervals)							
	1	2	3	4	5	6	7	8
Vehicle control	0	0	0	0	0	0	0	0
MAA (1.8 mg/kg)	0	0	0	0	0	0	0	0
Piroxicam (1.8 mg/kg)	0	0	0	0	0	0	0	0
Proxicam (5.4 mg/kg)	0	0	0	0	0	0	20	40
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	0	0	0	0	10	10	10	10
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	0	0	0	10	20	20	20	20
Pirprofen (8 mg/kg)	0	10	10	10	10	10	10	10
Pirprofen (24 mg/kg)	30	40	40	40	50	50	50	50
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	0	0	0	0	0	0	0	0
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	10	10	10	10	10	10	10	10

Rats receiving the vehicle (control) in absence and presence of MAA (1.8 mg/kg) showed no mortalities during the experiment period.

Male rats receiving piroxicam (1.8 mg/kg) showed no mortalities during the experiment period.

By increasing the piroxicam dose i.e. 5.4 mg/kg, the deathes of rats started by the 7th week only, and showed a final cumulative percentage mortality of 40%. Piroxicam (1.8 mg/kg) given with MAA (1.8 mg/kg) showed deathes on the 4th week and a final cumulative percentage of 20%. On the other hand, rats receiving pirprofen (8 mg/kg) showed deathes on the second weeks and a final mortality of 10%, while pirprofen (24 mg/kg) caused 30% mortality on the first week and cumulative percentage mortalities 50%. Rats receiving pirprofen (8 mg/kg) with MAA showed no mortalities during the experiment period, while the rats receiving pirprofen (24 mg/kg) with MAA (1.8 mg/kg) showed 10% mortality on the first week and no further mortalities occurred till the end of the 8th week.

The obtained results indicates that the administration of the anabolic MAA compound reduced the toxicity of pirprofen to a marked extent but did not affect in the case of piroxicam drug.

Also, the above results are in agreement with those reported by Jansen (1981) and Pericin (1983)

3. **Body weight of rats**:

The average weekly body gains are shown in table (3). It has been observed that the growth rates of rats receiving the piroxicam or the anabolic MAA or their combination, were less than that of controls receiving the vehicle. The effect was more clearly at the high dose level of piroxicam, than that caused by the low dose level. It was also observed that the growth rates of rats receiving the pirprofen or the anabolic MAA or their combinations, were less than that of controls receiving the vehicle (Table, 3). The effect was improved by the anabolic compound, this improvement was pronounced in the case of pirprofen drug than in piroxicam drug.

Tables (4 and 5) show the results of the mean weight of internal organs of rats receiving the different treatments for 8 weeks. The obtained data illustrated that there is no significant change in the weights of the liver, heart, brain, kidney or the testes. However, the spleen was found to be significantly and markedly decreased in response to both anti-inflammatory drugs. Also, the anabolic drug methyl androstenolone acetate (MAA) did not antagonize this effect.

II. Liver biochemical studies:

1- **The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on liver triglycerides of rats**:

Table (3): Weekly body gains of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg) given with or without methyl androstenolone acetate (MAA) (1.8 mg/kg), daily for 8 weeks.

Treatments	Weekly body gain % (1)
Vehicle control	10.29
MAA (1.8 mg/kg)	5.46
Piroxicam (1.8 mg/kg)	4.27
Proxicam (5.4 mg/kg)	2.52
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	4.13
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	3.64
Pirprofen (8 mg/kg)	6.93
Pirprofen (24 mg/kg)	2.80
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	7.21
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	4.76

(1) % Weekly body gain = $\frac{\text{Mean final body weight - Mean initial body weight}}{\text{Mean initial body weight x 8}}$

Table (4): Internal organs weight of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg), given with or without methyl androstenolone acetate (MAA) (1.8 mg/kg), daily for 8 weeks.

Treatment	Internal organs weight (±SEM) (n=6)					
	Liver	Heart	Brain	Kidney	Spleen	Testes
Vehicle control	7.46±0.43	0.95±0.03	1.93±0.05	1.30±0.01	1.12±0.06	2.60±0.04
MAA (1.8 mg/kg)	8.10±0.71	0.93±0.03	2.08±0.06	1.35±0.02	1.27±0.08	2.63±0.06
Piroxicam (1.8 mg/kg)	8.35±0.35	0.95±0.04	2.12±0.05	1.32±0.02	0.71*±0.07	2.93±0.03
Piroxicam (5.4 mg/kg)	7.76±0.42	0.95±0.03	2.12±0.08	1.40±0.02	0.62*±0.05	2.66±0.05
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	7.90±0.55	1.03±0.02	2.12±0.05	1.26±0.01	0.68*±0.05	2.54±0.07
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	8.60±0.53	0.85±0.07	1.84±0.07	1.53±0.03	0.57*±0.09	2.60±0.09
Pirprofen (8 mg/kg)	7.20±0.63	0.85±0.05	1.86±0.03	1.40±0.01	0.60*±0.03	2.64±0.05
Pirprofen (24 mg/kg)	7.10±0.40	0.79±0.03	1.79±0.06	1.46±0.01	0.68*±0.06	2.01±0.06
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	7.73±0.51	0.83±0.02	1.94±0.08	1.32±0.02	0.64*±0.07	2.05±0.08
Pirproten (24 mg/kg) + MAA (1.8 mg/kg)	7.00±0.61	0.82±0.04	2.06±0.06	1.49±0.01	0.69*±0.05	2.13±0.03

* Denote significant difference from control at $P < 0.05$.
n = number of samples.

Table (5): Internal organs weight as percent of body weight of rats recevinig orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg), given with or without methyl androstenolone acetate (MAA) (1.8 mg/kg) daily for 8 weeks.

Treatment	Internal organs weight as percent (%) (n=6)					
	Liver	Heart	Brain	Kidney	Spleen	Testes
Vehicle control	2.37±0.25	0.30±0.01	0.61±0.01	0.41±0.02	0.36±0.02	0.83±0.02
MAA (1.8 mg/kg)	2.66±0.35	0.30±0.02	0.68±0.03	0.44±0.02	0.42±0.01	0.86±0.01
Piroxicam (1.8 mg/kg)	2.76±0.27	0.31±0.02	0.70±0.04	0.45±0.01	0.23*±0.01	0.97±0.02
Piroxicam (5.4 mg/kg)	2.63±0.15	0.32±0.01	0.72±0.04	0.47±0.01	0.21*±0.02	0.90±0.02
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	2.28±0.23	0.30±0.01	0.61±0.02	0.36±0.02	0.20*±0.03	0.73±0.03
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	2.86±0.34	0.29±0.01	0.62±0.01	0.51±0.03	0.19*±0.01	0.87±0.01
Pirprofen (8 mg/kg)	3.20±0.35	0.30±0.02	0.86±0.01	0.45±0.02	0.27*±0.02	0.92±0.01
Pirprofen (24 mg/kg)	3.60±0.28	0.35±0.02	0.92±0.02	0.46±0.01	0.35±0.01	0.76±0.01
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	2.86±0.25	0.31±0.03	0.61±0.01	0.49±0.01	0.24*±0.01	0.78±0.03
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	3.10±0.32	0.29±0.01	0.93±0.06	0.59±0.02	0.32±0.02	0.93±0.02

* Denote significant difference from control at $P < 0.05$.
n = number of samples.

The results in table (6) show triglycerides (TG) levels in the liver at the end of experiment peroids . Liver triglycerides of rats received MAA (1.8 mg/kg) did not change. Piroxicam (1.8 mg/kg) caused a decrease in liver triglycerides i.e. 32.89% below control values. The higher dose of piroxicam did not induce any change in liver TG. Piroxicam (5.4 mg/kg) given in the presence of anabolic agent increased liver TG by 91.24% over control. The increment of liver TG reflects a degree in liver fatty deposition (Gorman, 1985).

2- **The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on liver, nucleic acid (RNA & DNA) and total proteins:**

The effect of piroxicam and pirprofen on liver nucleic acid (RNA & DNA) and total protein contents is shown in table (6). The obtained results illustrated that liver RNA content of rats receiving the anabolic agent MAA for 8 weeks were not different from control. While the rats treated with the anti-inflammatory drugs had RNA liver contents significantly greater than those receiving the vehicle. The group receiving the anabolic with piroxicam had a slight different values from control. On the other hand, pirprofen with anabolic agent had RNA content greater than control values.

The obtained results in table (6) indicate that piroxicam and pirprofen alone and in the presence of the anabolic did not induce any change in liver DNA content. Similar results were reported by Hurley et al. (1990).

Table (6): Liver lysosomal enzyme (Acid phosphatase, ACP), nucleic acid (RNA & DNA) and total protein contents of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg) given with or without methyl androstenolone acetate (MAA) (1.8 mg/kg) daily for 8 weeks.

Treatments	Mean (±SEM) (n=6)					
	Lysosomal enzyme		Nucleic acid		Total protein	Triglycerides in liver
	Total nmol/g	Released nmol/g	RNA mg/g protein	DNA mg/g protein	g/g weight tissue	mg/dl
Vehicle control	5644.5±119.9	3133.3± 85.2	18.12±0.46	7.01±0.47	0.321±0.070	1460.2±192.1
MAA (1.8 mg/kg)	5544.2±120.9 -1.8%	3122.2±105.2 -0.35%	18.98±0.63	7.06±0.21	0.390***±0.008	1761.0± 88.0
Piroxicam (1.8 mg/kg)	5564.4± 79.6* -1.4	3422.2± 88.1** +9.2	20.29±0.47**	6.84±0.44	0.349**±0.006	979.9±** 44.3
Piroxicam (5.4 mg/kg)	5423.2±146.8 -3.9	3600.0± 79.9** +15	21.20±0.38**	6.96±0.35	0.332±0.006	1710.7±161.0
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	5744.4±177.5 +1.8	3388.9±112.2* +8.2	19.33±0.68	7.01±0.13	0.364***±0.003	1823.9± 70.1
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	5633.3±121.7 -0.2	3281.2± 68.9 +4.7	18.48±0.27	7.14±0.19	0.346**±0.006	2792.4***± 75.5
Pirprofen (8 mg/kg)	6000.0*±116.2 +6.3	3555.6±188.8** +13.5	21.52***±0.23	6.57±0.17	0.383***±0.008	1152.0± 56.6
Pirprofen (24 mg/kg)	6114.0*±119.9 +8.3	3833.3**±112.2 +22.3	20.86***±0.38	6.59±0.28	0.355**±0.004	2228.8±434.5
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	5814.8±114.8 +3.0	3505.6*±102.5 +11.9	21.52***±0.22	6.75±0.12	0.404***±0.004	1037.8±320.8
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	5866.7±111.1 +3.9	3333.3*±112.2 +6.4	21.59***±0.22	6.80±0.17	0.412***±0.011	1204.0±101.0

*, **, ***: Denote significant differences from controls at $P < 0.05$, $P < 0.01$ and $P < 0.001$.

n = number of samples.

The total liver proteins of rats which treated with MAA were more than control value by 22%. However, the groups treated with piroxicam alone and in the presence of the anabolic MAA showed very slight increase in their liver proteins. On the other hand, those treated with pirprofen showed an increase in their liver protein. It might be noted that pirprofen alone or with anabolic elevated hepatic RNA. This may give further evidence that tissue protein are stimulated in response to such treatment. **Piroxicam behaved in a different way** , this may be due to some differentiations in mechanism of action. Such interpretation was in agreement with that obtained by Burch et al. (1983).

3. **The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on total and release liver lysosome enzyme of rats:**

Table (6) shows the obtained results of the total and relased liver lysosomal marker enzyme (Acid phosphatase, ACP) of different treatments at the end of experiment period. These results illustrates that the anabolic MAA, the anti-inflammatory piroxicam alone and together caused slight changes on the total lysosomal, ACP. The anabolic drug did not effect on the released enzyme. Piroxicam dose dependently elevated the released lysosomal ACP. This effect was reduced by the anabolic and a less marked increment was observed in response to piroxicam and MAA combined treatment.

Pirprofen significantly increased both total and released ACP. The concomittant administration of the

anabolic antagonised, this effect and the total ACP values were not varied from controls . This observation may be due to the role of anabolic agent in releasing ACP. Consequently, the increment in the released ACP was accompanied with the lysosomal membrane stability. The obtained results are in agreement with that obtained by Abd-El-Gawad et al. (1989).

III. Blood haematological studies:

1- The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on the blood picture of rats:

The effects of the different treatment on the blood picutre of rats after 4 and 8 weeks of treatment are shown in tables (7 and 8), respectively. The initial blood haematological parameters of the rats, as determined before starting the treatment, were within normal values (Melby and Altman, 1974). Control rats receiving the vehicle did not show any change in their haematological values over the experiment period. Rats receiving the anabolic drug MAA showed slight decrease in their HCT to the end of the experiment period.

The tested anti-inflammatory drugs had no noticeable effect on coagulation time. However, piroxicam at the high dose level of 5.4 mg/kg caused 42% prolongation after 4 weeks of treatment, the effect was not observed afterwards. This effect is probably related to inhibition of prostaglandin synthesis (Moncada and Van, 1979).

Piroxicam did not cause any sign of aneamia, on the contrary its high dose level after 4 weeks caused an

Table (7): Blood haematological parameters of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg) given with or without methyl androstenolone acetate (MAA) (1.8 mg/kg) daily for 4 weeks.

Treatments	Mean (±SEM) blood haematological parameter (n=6)						
	Coagulation time (sec)	HB[1] (g/100 ml)	HCT[2] %	EC[3] (x10/m³)	MCV[4] (cu)	MCH[5] (PG)	MCHC[6] %
Vehicle control	55.4± 2.31	13.6±0.5	39.6±0.60	8.3±0.45	46.8±2.22	16.6±1.30	35.0±0.02
MAA (1.8 mg/kg)	70.0±10.80	13.9±0.3	38.5±0.65	7.2±0.58	55.0±5.89	19.7±2.45	36.6±0.50
Piroxicam (1.8 mg/kg)	65.8± 8.98	14.7±0.7	38.2±1.17	8.9±0.40	43.1±1.32	16.6±0.81	38.1±0.90
Piroxicam (5.4mg/kg)	97.0*±10.07	17.0**±0.9	41.8±0.75	7.2±0.42	59.1***±2.50	23.2**±1.45	41.2±2.00
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	68.3± 7.15	14.8±0.4	40.2±1.50	8.2±0.60	49.2±2.30	18.2±1.36	36.1±1.80
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	90.0±11.18	14.7±0.4	41.7±1.08	6.9**±0.06	61.5*±5.36	21.3*±1.12	35.1±1.50
Pirprofen (8 mg/kg)	67.5±15.50	13.6±0.9	39.5±2.06	7.2±0.81	54.0±5.20	19.1±2.65	34.5±1.00
Pirprofen (24 mg/kg)	81.2±12.97	13.4±0.2	35.2**±1.25	8.1±0.15	43.4±1.75	16.2±0.56	38.0±1.00
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	55.0±14.17	15.7±0.8	40.2±0.40	7.4±0.43	55.5±4.62	21.1±2.58	39.1±1.01
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	75.0±17.40	13.5±0.2	33.5***±0.99	7.3±0.54	46.1±4.00	18.5±1.22	41.0*±1.00

*, **, ***: Denote significant difference from controls at $P < 0.05$, $P < 0.01$, $P < 0.001$.

1- Haemoglobin 2- Hamatocrit 3- Erythrocytic count

4- Mean corpuscular volume = $\frac{HCT}{EC}$ 5- Mean corpuscular haemoglobin = $\frac{HB \times 10}{EC}$

6- Mean corpuscular haemoglobin concentration = $\frac{HB}{HCT}$

n = number of samples.

Table (8): Blood haematological parameter of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg) given with or without methyl androstenolone acetate (MAA) (1.8 mg/kg), daily for 8 weeks.

Treatments	Mean (±SEM) blood haematological parameter (n= 6)						
	Coagulation time (sec.)	HB[1] (g/100 ml)	HCT[2] %	EC[3] (x10/mm³)	MCV[4] (Cu)	MCH[5] (PG)	MCHC[6] %
Vehicle control	55.4±12.31	13.6±0.5	39.6±0.60	8.3±0.45	46.8±2.22	16.6±1.30	35.0±0.02
MAA (1.8 mg/kg)	85.0±16.60	12.5±0.4	34.2±1.46***	7.0±0.18	46.6±1.30	17.5±0.60	38.1±0.50
Piroxicam (1.8 mg/kg)	50.2±11.03	13.1±0.3	42.4±1.50	8.2±0.33	51.7±2.97	15.8±1.00	31.1±1.40
Piroxicam (5.4mg/kg)	80.5±15.40	13.5±0.7	33.7±1.49**	7.5±0.28	44.0±0.90	18.0±0.40	39.0±2.00
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	90.4±17.80	14.0±0.7	44.8±6.11	7.6±0.37	57.8±1.20***	18.3±0.80	32.3±2.00
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	87.1±20.30	13.7±0.2	34.6±1.21***	6.9±0.53	50.6±4.00	20.2±1.30	40.0±2.0
Pirprofen (8 mg/kg)	78.3±11.37	15.9±1.3	37.5±1.04	7.8±0.33	48.0±0.97	20.5±1.99	42.1±3.30
Pirprofen (24 mg/kg)	27.5± 8.07	13.5±0.5	35.0±3.00	7.9±0.29	44.4±5.44	17.1±1.26	39.0±2.80
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	72.5±11.60	14.5±0.9	36.2±1.55	7.6±0.33	44.3±3.02	19.1±1.07	44.1*±3.00
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	56.6±15.09	13.6±0.0	35.2*±1.49	7.8±0.36	45.0±2.70	17.2±0.80	39.0±1.00

*, **, ***: Denote significant differences from controls at $P < 0.05$, $P < 0.01$ and $P < 0.001$.

1- Haemoglobin 2- Haematocrit 3- Erythrocytic count

4- Mean corpuscular volume = $\frac{HCT}{EC}$ 5- Mean corpuscular haemoglobin = $\frac{HB \times 10}{EC}$

6- Mean corpuscular haemoglobin concentration = $\frac{HB}{HCT}$

n = number of samples.

increase in blood haemoglobin accompanied by an increase in the MCV. The MCH and the MCHC remained constant. Its combination with the anabolic reduced the number of red blood cells but increased their volume (MCV) and haemglobin content (MCH). After 8 weeks of treatment, the low dose of piroxicam with the anabolic MAA, increased the MCV without changing the MCH or MCHC, and hence, causing no signs of aneamia. The high dose of piroxicam given alone or in combination with MAA induced a slight decrease in HCT. The haemoglobin MCH and MCHC were not changed indicating no anaemic effect.

Pirprofen likewise did not cause any sign of aneamia despite slight decrease in the HCT occurred after 4 weeks of the high dose. The effect is probably related to a slight decrease in red cell volume and counts.

2- **The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on leucocytic counts of rats:**

Tables (9 and 10) show leucocytic counts after 4 and 8 weeks of different treatments, respectively. These results indicate that the total count of white blood cells was not changed over the 8 weeks in all treatment groups. Consequently, this data illustrates no pathologic infection of the experiment animals. Control vehicle treated, as well as anabolic drug treated animals showed no changes in their total or individual white cell counts.

Both piroxicam and pirprofen caused decrease in lymphocytes and an elevation of neutrophils, this phenomena

Table (9): Blood total and differential leucocytic counts of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg) given with or without methyl androstenolone acetate (MAA) (1.8 mg/kg), daily for 4 weeks.

Treatments	Mean (±SEM) total and different leucocytic counts (n=6)			
	Total leucocytic count ($x10^3/mm^3$)	Lymphocytes %	Nuetrophils %	Nonocytes %
Vehicle control	7.90±0.52	63.58±1.38	35.31±1.27	0.94±0.39
MAA (1.8 mg/kg)	8.56±0.79	65.00±2.16	33.00±1.88	2.00±1.46
Piroxicam (1.8 mg/kg)	8.80±0.69	52.00**±2.89	50.00**±3.54	0.40±0.20
Piroxicam (5.4mg/kg)	8.90±0.66	43.75***±4.20	54.50***±4.27	1.75±0.55
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	8.25±0.60	56.75*±2.13	42.00*±1.68	1.25±0.20
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	8.96±0.45	50.75**±2.10	47.75**±2.01	1.50±0.29
Pirprofen (8 mg/kg)	7.09±0.40	49.00***±1.53	49.66***±1.33	1.33±0.33
Pirprofen (24 mg/kg)	7.05±0.37	48.50***±1.60	50.50***±1.70	1.00±0.21
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	7.54±0.25	55.00**±1.44	44.00**±1.63	1.00±0.21
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	7.56±0.24	52.30**±1.32	46.66**±1.76	1.00±0.22

*, **, *** Denote significant differences from controls at $P < 0.05$, $P < 0.01$ and $P < 0.001$.
n = number of samples.

Table (10): Blood total and differential leucocytic counts of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg), given with or without methyl androstenolone acetate (MAA) (1.8 mg/kg) daily for 8 weeks.

Treatments	Mean (±SEM) serum total and differential leucocytic counts (n=6)			
	Total leucocytic count ($x10^3/mm^3$)	Lymphocytes %	Meutrophils %	Monocytes %
Vehicle control	7.90±0.52	63.58±1.38	35.31±1.27	0.94±0.39
MAA (1.8 mg/kg)	8.46±0.42	65.50±1.85	33.25±1.65	1.25±0.63
Piroxicam (1.8 mg/kg)	7.28±0.29	49.50**±1.19	49.50**±1.19	1.00±0.41
Piroxicam (5.4mg/kg)	7.89±0.48	52.50**±2.33	46.25**±2.93	1.25±0.63
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	8.43±0.28	54.50*±2.33	44.25*±2.93	1.25±0.63
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	7.28±0.29	59.75±0.85	39.00±1.00	1.15±0.29
Pirprofen (8 mg/kg)	7.36±0.30	50.25**±2.39	48.50**±2.72	1.25±0.11
Pirprofen (24 mg/kg)	7.14±0.02	47.00***±1.00	52.00***±1.00	1.00±0.29
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	8.03±0.30	52.00**±1.68	44.50**±1.93	1.00±0.22
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	7.56±0.25	50.10**±2.12	44.00**±2.25	1.25±0.31

*, **, ***: Denote significant differences from controls at $P < 0.05$, $P < 0.01$ and $P < 0.001$.

n = number of samples.

is known as agranulocytosis. This effect was observed after 4 weeks of treatment and remainded till the end of 8 weeks of treatment. The concurrent administration of the anabolic improved, but did not abolish the effect of the anti-inflammatory drugs. The obtained results are in harmony with that obtained by (Hartmann et al., 1984).

The spleen is the biggest lymph node of the body prossessing a major role in the formation and activation of lymphohocytes. It was observed that both piroxicam and pirprofen decreased the weight of the spleen. Thus, the agranulocytosis may be related to their effects on the spleen (Frankel and Reitman, 1963).

From the forementioned results it may be recommended that haematological examination of leucocytes should be carried out during prolonged therapy with pirprofen or piroxicam drugs . The concurrent administration of anabolic steroid may be important in reducing the side effects of these anti-inflammatory drugs from the therapeutical point of view .

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تاثير مركبات البيروكسيكام والبيربروفين على السمية ، وظائف الكبد وصورة الدم

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** الهيئة القومية للرقابة الدوائية والبحوث ـ القاهرة ـ مصر .

تمت دراسة تاثير مركبات مضادات الالتهاب بيروكسيكام والبيربروفين كل على حده او مع خلات الميثيل اندروستينولون كمادة بناءه على السمية ووظائف الكبد وصورة خلايا الدم على مجموعات من الفئران البيضاء الكبيرة البالغة والغير مكتملة النمو.

اوضحت نتائج السمية الحاده ان البيروكسيكام كان اشد تاثيرا على الاناث عنها على الذكور حيث كانت الجرعة LD_{84} ، LD_{50} للاناث تلك تلك الجرعات الخاصة بالذكور ولم تتغير سميتها باضافة المادة البناءه . كانت سمية البيربروفين متساوية لكل من الذكور والاناث البالغة والغير مكتملة النمو وقد تناقصت سميتها بمقدار ٢٥٪ عند اعطاء المادة البناءه للفئران الذكور البالغة .

اوضحت نتائج دراسة السمية المزمنة ان اعطاء المادة البناءه خفض من سمية البيربروفين بدرجة ملحوظة بينما لم يؤثر فى حالة البيروكسيكام .

واوضحت النتائج ايضا ان مضادى الالتهاب انقصا معدلات النمو بينما كان وزن الجسم ثابتا وقد حسنت المادة البناءه من التاثير الضار للبيربروفين الا ان هذا التاثير لم يلاحظ فى حالة البيروكسيكام . وقد سببت المادتين المضادتين للالتهاب نقصا ملحوظا فى وزن الطحال الا ان الاعضاء الداخلية الاخرى (الكبد والقلب والمخ والكلية والخصية) كانت ثابتة .

وقد اشارت النتائج ان البيروكسيكام (١٫٨ ملجم/كجم) قد سببت نقص فى محتوى الكبد من الجلسريدات الثلاثية بمقدار ٩١٫٤٢٪ وهذا التاثير لم يتحسن باعطاء المادة البناءه . اعطاء مادة البيربروفين منفردا او مع المادة البناءة لم يظهر اى تغيير معنوى فى محتوى الكبد من الجلسريدات الثلاثية . وقد ارتفع محتوى الكبد من الاحماض النووية الريبوزومية باعطاء كلا من البيروكسيكام والبيربروفين بمقدار ١٧ ، ١٨٫٧٦٪ على التوالى ، وقد قللت المادة البناءه من التاثير الضار لمركب البيروكسيكام . لم يتاثر محتوى الكبد من الاحماض النووية الديزوكسية بكل من المضادين بينما تسبب الاثنان فى زيادة محتوى الكبد من البروتين . اظهرت نتائج الكبد الليزوزومية ان السمية المزمنة أدت الى التحليل الزائد لهذه الاغشية ، وقد امكن الاقلال من هذا التاثير السام الى حد ما باستخدام المادة البناءه .

اوضحت نتائج صور الدم بان البيروكسيكام والبيربروفين قد سببا ظاهرة granulocytosis. (اى خللا فى مكونات الدم الخلوية البيضاء) دون حدوث مرض الانيميا ولم يمكن معالجة هذا المرض بواسطة المادة البناءه .