RESULTS AND DISCUSSION

Piroxicam and Pirprofen are anti-inflammatory drugs in common clinical use. Also these compounds showed a surprising results in the treatment of rheumatic diseases and inflammatory syndromes (Alvart, 1983 and Kummer and Nekora, 1984). On the other hand, these compounds have some toxic effects as any other medication.

The following experiments were conducted with the aim to illucidate the toxicity of the alone mentioned drugs on both acute single dose treatment and chronic administration. Also, a comparison was done between the toxic effects of the anti-infllamatory drugs given alone and with an anabolic agent, i.e., methyl androstenolone acetate. This was accomplished in an attempt to inhibit or minimize the harmful side effects of these compounds.

IV.1. Acute toxicity studies:

The results of acute toxicity determination indicated that the oral LD_{50}, Ld_{16} and LD_{84} for piroxicam in adult female rats were 220, 190 and 250 mg/kg respectively (Table 1). On the other hand in case of utilization of piroxicam (Feldene) with (primobolan)

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

Type of animals	Lethal doses (mg/kg piroxicam)			Lethal doses (mg/kg piroxicam) with MAA before treatment		
	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
Adult male	570 (393.1-826.5)	330	970	230 (176.9-299.0)	120	280
Immature female	230 (127.28-414.0)	180	290	-	-	-
Immature male	550 (443.6-688.0)	430	680	-	-	-

methyl androstenolone acetate (M.A.A.), the results were 250, 210 and 290 mg/kg, respectively. These data indicate that a slight changes in acute toxicity occurred.

In adult male rats, the oral LD_{50}, LD_{16} and LD_{84} for piroxicam were 570, 330 and 970 mg/kg and for piroxicam with M.A.A. were 230, 120 and 280 mg/kg, respectively. The LD_{50}, and Ld_{16} value of piroxicam alone equal about two times that of piroxicam with M.A.A. While its LD_{84} was 3.5 times that of the combined treatment. These results showed that there is an enhancement in the acute toxicity of piroxicam by the anabolic compound 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_{50} values of females were about one half those of the males. Furthermore the LD_{16} 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. This

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 M.A.A. While its LD_{50} in absence of M.A.A. was lesser than in presence of the anabolic agent. On the other hand, its LD_{84} in the absence of M.A.A. was greater than the combined treatment (Table 2).

In adult male rats the oral LD_{50}, LD_{16} and LD_{84} for pirprofen were 650, 490 and 850 mg/kg, while those of pirprofen with M.A.A. were 850, 710 and 990 mg/kg, respectively. These results illustrate that there is a slight reduction in the acute toxicity of pirprofen in adult male rats by M.A.A.

The results in table (2) indicate that there is no marked variations in acute toxicity parameter of pirprofen between males vs. females, adults vs. immature.

IV.2. Short term chronic toxicity studies:

IV.2.1. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on mortalities of rats:

The recorded deathes during the 8 weeks period in response to the different treatments are shown in table (3)

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

Type of animals	Lethal doses (mg/kg pirprofin)			Lethal doses (mg/kg pirprofin) with MAA before treatment		
	LD_{50} (fiducial limit)	LD_{16}	LD_{84}	LD_{50} (fiducial limit)	LD_{16}	LD_{84}
Adult female	690 (547.6-869.0)	510	910	610 (621.1-1159.5)	250	1300
Adult male	650 (528.5-799.5)	490	850	850 (472.2-1530.0)	710	990
Immature female	510 (414.6-627.3)	410	640	-	-	-
Immature male	450 (298.0-679.5)	210	990	-	-	-

Table (3) Cummulative percentage mortalities in rate 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.

Treatment	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
Piroxicam (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 M.A.A. (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 cummulative percentage mortality of 40%. Piroxicam (1.8 mg/kg) given with M.A.A. (1.8 mg/kg) showed deathes on the 4th week and a final cummulative 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 cummulative percentage mortalities 50%. Rats receiving pirprofen (8 mg/kg) with M.A.A. showed no mortalities during the experimental period, while the rats receiving pirprofen (24 mg/kg) with M.A.A. (1.8 mg/kg) showed 10% mortality on the first week and no further mortalities occurrred till the end of the 8th week.

The obtained results indicate that the administration of the anabolic M.A.A. compound reduced the toxicity of pirprofen to a marked extent but did not affect piroxicam

toxicity.

Also, the above results showed that piroxicam in its normal dose (1.8 mg/kg) did not accumulate in patients with normal renal function. On the other hand pirprofen in its normal dose (8 mg/kg) has the ability to accumulate in different organs with a state concentration. These results are in agreement with those reported by Jansen (1981) and Piricin (1983).

IV.2.2. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on the body weight of rats:

A follow up of the body weight of treated animals is shown in figures (1 and 2). The average weekly body gains are shown in tables (4 and 5). It has been observed that the growth rates of rats receiving the piroxicam or the anabolic M.A.A. or their combination, were less than that of controls receiving the vehicle (table 4, Fig. 1). the effect was more clear 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 M.A.A. or their combinations, were less than that of controls receiving the vehicle (table 5 & Fig. 2). The effect was improved by the anabolic compound this imporvement was pronounced in the

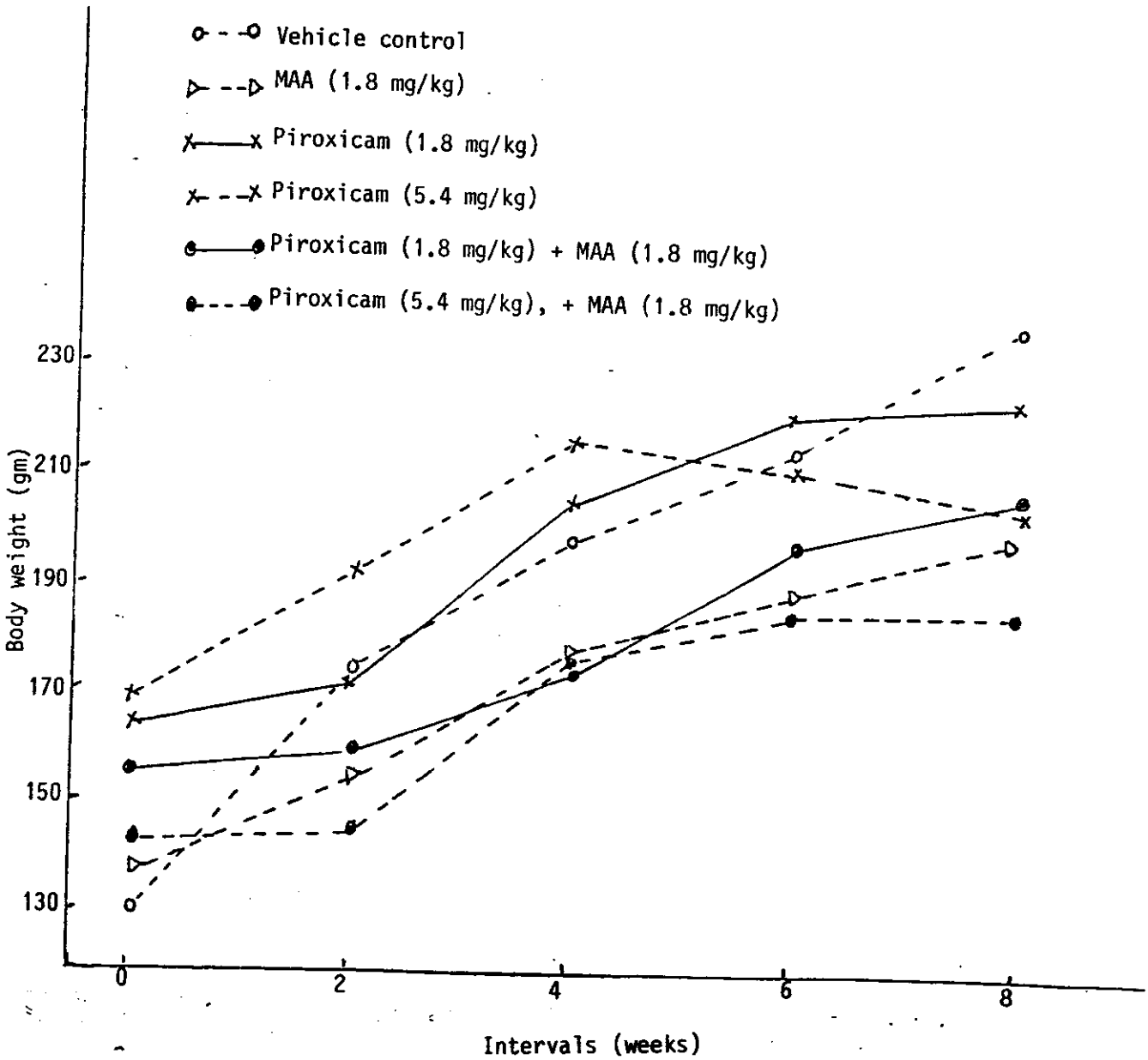

Fig. (1) Growth Curve of rats receiving orally piroxicam (1.8 or 5.4 mg/kg) given with or without methyl androsterolone acetate; MAA (1.8 mg/kg), daily for 8 weeks

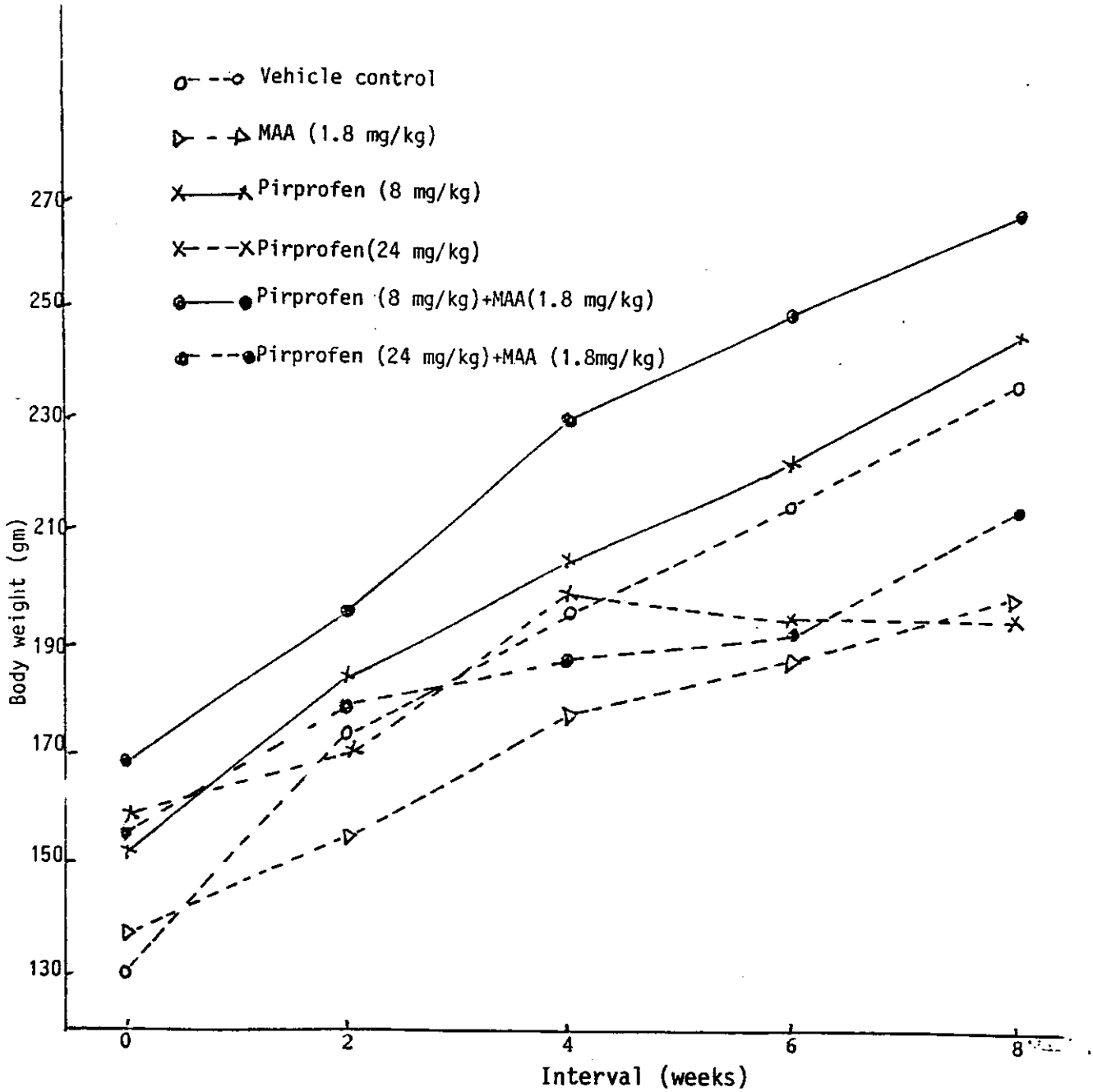

Fig. (2) Growth curve of rats receiving orally pirprofen (8 or 24 mg/kg) given with or without methyl androstenolone acetate; MAA (1.8 mg/kg) daily for 8 weeks.

Table (4) Weekly body gains of rats receiving orally piroxicam (1.8 or 5.4 mg/kg) given with or without methyl androstenolone acetate; MAA (1.8 mg/kg), daily for 8 weeks.

Treatment	Weekly body gain %(1)
Vehicle control	10.29
MAA (1.8 mg/kg)	5.46
Piroxicam (1.8 mg/kg)	4.27
Piroxicam (4.5 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

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

Table (5) Weekly body gains of rats receiving orally pirprofen (8 or 24 mg/kg) given with or without methylandrostenolone acetate; MAA (1.8 mg/kg), daily for 8 weeks.

Treatment	Weekly body gain %(1)
Vehicle control	10.29
MAA (1.8 mg/kg)	5.46
Pirprofen (8 mg/kg)	6.93
Pirprofen (24 mg/kg)	2.8
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 = $\frac{\text{Mean final body weight - Mean initial body weight}}{\text{Mean initial body weight x 8}}$

case of pirprofen than in piroxicam.

IV.2.3. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on the weight of internal organs of rats:

Tables (6 and 7) 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.

IV.3. Serum biochemical studies:

IV.3.1. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on serum glucose and bilirubin levels of rats:

Table (8) shows serum glucose and bilirubin levels as affected by piroxicam and pirprofen given alone and in the presence of methyl androstenolone acetate (MAA) daily for 8 weeks during the experiment. The mean (± SEM) initial serum glucose and bilirubin levels of rats before the treatment were 71.3 (± 7.6) and 0.85 (± 0.12) mg/dL,

Table (6) 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 methylandrostenolone 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)	8.1±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
Piroxican (5.4 mg/kg) + MAA (1.8 mg/kg)	8.6±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)	7.2±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)	7.1±0.4	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
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	7.0±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 $P < 0.05$

Table (7) Internal organs weight as percent of body weight of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/g), 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±0.035	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)	3.2±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)	3.6±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)	3.1±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

Table (8) Serum glucose and bilirubin levels of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg) given with or without methyl androstenlone acetate, MAA (1.8 mg/kg), daily for 8 weeks.

Treatment	Mean (± SEM) serum glucose and bilirubin (mg %)			
	After 4 weeks of treatment n = 6		After 8 weeks of treatment n = 6	
	Glucose	Bilirubin	Glucose	Bilirubin
Vehicle control	75.27±6.8	0.80±0.11	68.3±8.2	0.89±0.13
MAA (1.8 mg/kg)	83.78±7.1	1.04±0.21	80.1±5.2	0.79±0.22
Piroxicam (1.8 mg/kg)	72.85±5.51	1.37±0.13**	69.0±6.3	0.95±0.11
Piroxicam (5.4 mg/kg)	83.8±5.8	1.46±0.14**	69.11±5.9	0.80±0.28
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	76.18±4.93	1.15±0.18	83.2±8.1	0.86±0.14
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	89.2±6.1	1.16±0.16	88.2±7.3	0.42±0.24
Pirprofen (8 mg/kg)	86.45±7.6	0.91±0.09	61.53±6.8	0.98±0.17
Pirprofen (24 mg/kg)	100.81±8.7	0.79±0.26	59.26±7.4 (a)	1.29±0.04* (a)
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	75.79±6.58	1.07±0.23	73.46±5.4	0.89±0.23
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	90.92±7.20	1.05±0.54	67.9±7.05	0.64±0.24

(a) n = 5

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

respectively. Control rats receiving the vehicle did not show any change in either serum glucose or bilirubin levels after 4 or 8 weeks of treatment from initial values. Neither the anabolic nor the anti-inflammatory drugs alone or together had no significant effect on serum glucose level during the experimental period.

Serum bilirubin was not significantly affected by the anabolic compound. The anti-inflammatory drug piroxicam (1.8 or 5.4 mg/kg) induced marked elevation in serum bilirubin after four weeks of treatment. The increment amounted to 71.25% and 82.5% from the control values respectively. However, the effect was not observed at the end of treatment period. The results indicated that the presence of anabolic compound with piroxicam did not cause any change in serum bilirubin at 4 or 8 weeks of treatment.

The low dose of pirprofen did not cause any change in serum bilirubin. However, the high dose level of 24 mg/kg induced a marked increment in serum bilirubin i.e. 61.25% over control values. This effect was observed after 8 weeks of treatment. The combined treatment of pirprofen with the anabolic showed normal serum bilirubin values over the experimental period.

The obtained results are in agreement with those reported by Aly *et al.* (1992 b) during their experiments on piroxicam and pirprofen.

IV.3.2. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on serum proteins level of rats:

The results in table (9) show serum proteins levels of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg), given alone and in the presence of methyl androstenolone acetate; MAA (1.8 mg/kg), daily for 8 weeks. The mean (± SEM) initial serum total protein, albumin and globulin of rats before the treatment were 7.31 (± 0.74), 3.26 (±0.21) and 4.05 (±0.43), respectively. The initial albumin/globulin ratio (A/G) was 0.8 (± 0.09). The results of 4 and 5 weeks indicate that there is no change in serum total protein, albumin, globuline or A/g ratio of control rats after 4 or 8 weeks of treatment from the initial values. All treatments MAA (1.8 mg/kg), piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg), given alone or together with MAA showed no significant change in serum proteins for 4 or 8 weeks. The lack of any changes in serum proteins indicates that the treatments had no effect on the biosynthesis of the protein function of the liver

Table (9) Serum proteins levels 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	Mean (± SEM) serum proteins (g/dL)							
	After 4 weeks of treatment				After 8 weeks of treatment			
	Total protein	Albumin	Glubulin	A/G ratio	Total protein	Albumin	Glubulin	A/G ratio
Vehicle control	7.5±1.15	3.1±0.57	4.3±0.75	0.7±0.11	7.4±1.02	3.2±0.61	4.2±0.58	0.7±0.08
MAA (1.8 mg/kg)	5.6±0.77	2.9±0.47	0.9±0.51	0.9±0.21	6.29±1.6	2.7±0.71	3.5±0.84	0.7±0.04
Piroxicam (1.8 mg/kg)	5.1±0.73	2.3±0.3	2.8±0.5	0.8±0.09	5.53±1.09	2.7±0.29	3.6±0.53	0.8±0.07
Piroxicam (5.4 mg/kg)	4.3±0.55	2.0±0.26	2.3±0.35	0.9±0.1	4.47±1.06	1.4±0.58	2.9±0.95	0.8±0.18
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	5.8±0.55	2.8±0.32	3.0±0.38	1.0±0.15	7.15±0.52	3.3±0.43	3.7±0.36	0.9±0.14
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	6.5±0.97	3.1±0.58	3.3±0.39	0.8±0.1	5.61±0.74	2.7±0.14	2.8±0.62	0.9±0.15
Pirprofen (8 mg/kg)	8.0±0.7	3.0±0.19	4.9±0.59	0.6±0.04	6.54±0.39	3.4±0.21	3.1±0.5	1.2±0.27
Pirprofen (24 mg/kg)	9.3±0.37	3.0±0.18	6.4±0.18	0.4±0.04	7.5±0.59 (a)	2.9±0.85 (a)	4.5±0.45 (a)	0.6±0.16 (a)
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	7.8±0.69	2.8±0.05	4.9±0.55	0.6±0.07	7.57±0.48	3.5±0.74	4.0±0.44	1.0±0.22
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	6.2±0.63	2.7±0.33	3.5±0.63	0.8±0.16	6.73±0.87	2.8±0.42	3.8±0.68	0.8±0.15

(a) n = 5

hepatocytes since the latter is the sole site of protein production (Grant, *et al.*, 1987). The consistancy of normal serum proteins levels over the 8 weeks period indicates the dietary adequacy of the ratios employed and is in harmony with the earlier observation that the treatment in general retarded the growth rates but did not cause body weight loss. This observation is in agreement with that mentioned by Ross (1982).

IV.3.3. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on serum enzymes (GOT, GPT and ALP) of rats:

The effect of piroxicam and pirprofen drugs in absence and presence of methyl androstenolone acetate compound on serum enzymes, i.e. transaminases (GOT, GPT) and alkaline phosphatase (ALP) is shown in table (10). The obtained results illustrate that the mean (± SEM) initial serum transaminases (GOT and GPT) and alkaline phosphatase (ALP) levels of rats before the treatment were 40.01 (± 3.76), 6.59 (± 0.83) and 39.4 (± 7.3) IU/L, respectively. Control rats receiving the vehicle did not show any change in their serum GOT, GPT or ALP levels after 4 or 8 weeks of treatment from initial values. Treatment with the anabolic did not induce any change in GOT, GPT or ALP. It was also observed that the serum transaminase GOT level

Table (10) Serum enzymes levels 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	Mean (± SEM) serum enzymes (Iu/L)					
	After 4 weeks of treatment (n = 6)			After 8 weeks of treatment (n = 6)		
	GOT	GPT	ALP	GOT	GPT	ALP
Vehicle control	35.5±2.18	6.0±0.71	32.6±3.65	50.2±5.16	7.1±0.42	31.0±5.4
MAA (1.8 mg/kg)	41.0±0.45	6.6±1.36	34.4±4.01	44.3±3.26	5.8±0.46	28.3±0.34
Piroxicam (1.8 mg/kg)	33.1±1.19	4.9±0.83	58.5±5.7**	39.2±3.18	4.8±0.36**	30.9±0.97
Piroxicam (5.4 mg/kg)	35.8±1.92	7.0±0.65	45.0±10.78	44.2±9.04	3.13±0.13***	30.7±2.32
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	39.5±0.55	7.1±0.65	47.0±9.1	45.6±7.13	6.9±0.92	29.6±7.47
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	39.5±1.79	9.5±0.82**	38.6±6.95	50.2±8.16	4.8±0.46**	30.5±3.01
Pirprofen (8 mg/kg)	31.6±0.24	7.8±0.64	45.5±87	52.8±4.31	8.8±0.91	50.3±5.4*
Pirprofen (24 mg/kg)	36.7±3.71	6.7±0.59	59.7±6.78**	58.2±4.25 (a)	8.0±2.0 (a)	52.6±4.3* (a)
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	39.3±3.4	9.0±1.11	62.5±2.24***	49.5±3.76	8.8±1.02	58.3±4.9**
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	36.1±2.09	6.8±1.11	70.2±7.0***	47.1±3.55	9.4±0.93	64.2±6.1**

(a) n = 5

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

was not modified in response to any of the given treatments over the 8 weeks experimentation period. Rats receiving piroxicam (1.8 or 5.4 mg/kg) for 4 weeks showed no change in GPT. However after 8 weeks of treatment they showed significant decrease in the activity of these enzymes. These values reached 33.15% and 56.4% below control values, respectively. Piroxicam (1.8 mg/kg) given with MAA (1.8 mg/kg) did not change GPT serum level. The higher dose of piroxicam (5.4 mg/kg) given with the anabolic agent showed a significant elevation in serum GPT after 4 weeks but induced a significant decrease after 8 weeks. These fluctuations though significant statistically are within the range of normal values (Melby and Altman, 1974). On the other hand pirprofen did not induce any change in serum GPT level.

Rats receiving piroxicam (1.8 mg/kg) showed a noticeable increment in serum level of alkaline phosphatase amounting to 79.06% over control value after 4 weeks of treatment. This effect was not observed at the subsequent estimation or with the higher dose level of piroxicam or its combination with the anabolic. Rats receiving the low dose of pirprofen (8 mg/kg) showed no significant change in serum alkaline phosphatase after 4 weeks of treatment, but showed a marked increase i.e.

61.79% after 8 weeks. The high dose level (24 mg/kg) induced marked increase at both examined periods i.e. 82.89% and 69.4% over contorl values, respectively. The administration of the anabolic MAA compound along with low or high doses of pirprofen induced a marked elevation in ALP at both 4 and 8 weeks observation periods.

According to Wise and Cockayne (1985) serum GOT levels are elevated in diseases of the heart, lung, skeletal muscles and in severe acute hepatocellular disorders. The lack of any changes in this enzyme in response to any of the forementioned treatments indicate the occurrence of no such disorders.

The lack of any marked increment in serum GPT in response to the given treatments confirms, in particular, the lack of hepatocellular disorders (Johnson and Fody, 1985).

Moss *et al.* (1987) mentioned that serum alkaline phosphatase is elevated in hepatobiliary and bone disorders. Treatment with anti-infllamatory drugs induced increment in serum ALP. This increment was slight in response to piroxicam but marked and persistant in response to pirprofen or its combination with the anabolic. It is more likely to attribute this increment to

hepatobiliary affection rather than to bone disorders-since these treatments were shown to elevat serum bilirubin cholestasis and increased synthesis of ALP (Wise and Cockayne,1985). The obtained results are in consistant with those obtained by Hartmann *et al.* (1984). Consequntly, the chronic treatment with anti-inflammatory drugs, in particular, pirprofen may cause intrahepatic cholestasis (Johnson and Fody, 1985). Increment levels of ALP may be arise from bone growth and healing (Wise and Cockayne, 1985). This interpretation may explain the synergistic increase in ALP after the combined treatment with pirprofen and MAA. The anabolics are known to enhance bone ossificatlon (Kastrup, 1986).

IV.3.4. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on serum non protein levels of rats:

The results in table (11) illustrate the effect of piroxicam and pirprofen in absence and presence of anabolic agent on serum non protein, i.e. urea and creatinine levels of rats. The obtained results illucidate that the mean (± SEM) initial serum creatinine and urea levels of rats before the treatment were 0.56 (± 0.05) and 36.09 (± 4.75) mq/dL, respectively. Control rats receiving the vehicle did not show any change in their serum

Table (11) Serum non-protein nitrogen levels 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	Mean (± SEM) serum non-portein nitrogen (Creatinine and urea) mg/dL			
	After 4 weeks of treatment n = 6		After 8 weeks of treatment n = 6	
	Creatinine	Urea	Creatinine	Urea
Vehicle control	0.54±0.19	47.8±2.9	0.57±0.04	31.64±4.67
MAA (1.8 mg/kg)	0.72±0.14	43.3±5.59	0.48±0.12	23.48±2.58
Piroxicam (1.8 mg/kg)	0.61±0.13	42.22±3.19	0.52±0.14	20.6±1.62
Piroxicam (5.4 mg/kg)	0.66±0.12	50.2±7.3	0.54±0.14	24.3±4.39
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	0.61±0.1	46.65±4.93	0.52±0.16	24.0±2.6
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	0.39±0.05	45.57±3.3	0.57±0.11	22.8±1.62
Pirprofen (8 mg/kg)	0.52±0.1	37.5±5.36	0.62±0.09	26.23±2.25
Pirprofen (24 mg/kg)	0.43±0.04	28.9±1.09***	0.58±0.29 (a)	32.07±5.17 (a)
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	0.29±0.06	29.29±1.32***	0.48±0.06	24.42±1.9
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	0.35±0.05	31.65±2.19**	0.53±0.09	25.05±2.05

(a) n = 5

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

creatinine or urea levels. Rats receiving MAA (1.8 mg/kg) or piroxicam (1.8 and 5.4 mg/kg) or their combination did not show any change in their creatinine or urea serum levels over the 8 weeks period.

Treatment with pirprofen or its combination with the anabolic did not cause any increase in either creatinine or urea serum levels. On the contrary, a significant decrease in serum urea levels was observed after 4 week treatment with the high dose of pirprofen. The effect was not observed at the 8 week point of examination. The obtained results are in agreement with that opinion of Uthman (1985), who mentioned that the anti-inflammatory drugs and the anabolic agent would not hinder the excretory function of the kidney.

Smith (1985) mentioned that serum urea levels are decreased in cases of pregnancy, severe liver disease and decreased protein intake. The observed decrease in serum urea may be related to a degree of liver affection rather than any of the two other cases. It was shown earlier that these treatments caused increment in serum bilirubin and alkaline phosphatase. Besides, the analysis of serum proteins and body growth follow up confirmed the dietary adequacy of the given ration. In harmony with the present

finding. Aly *et al.* (1992 a) reported renormalization of elevated blood urea by piroxicam.

IV.3.5. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on prostaglandin serum levels of rats:

The estimated serum levels of prostaglandin PGF_2 at the end of treatment period i.e. 8 weeks are shown in table (12). The results indicate that the two different doses of piroxicam caused a great decrease in $PGF_2\alpha$ serum concentration, i.e. 40%. The effect was more pronounced when piroxicam was given along with the anabolic drug. By using the latter agent alone there is no change in $PGF_2\alpha$ level. On the other hand, pirprofen did not induce any change by its higher dose level given along with the anabolic which induced a 37% decrease in $PGF_2\alpha$ serum level. The obtained results are in hormony with Tavares *et al.*, (1985), who reported that piroxicam is a mild inhibitor of prostaglandin synthesis.

Maier *et al.*, (1981) mentioned that pirprofen was shown to be as a cyclooxygenase inhibitor and hence it is expected to reduce PG levels. Consequently, the use of anti-inflammatory e.g. piroxicam and pirprofen in medication purpose, is accompanied with lowering of

Table (12) Serum prostaglandins $F_{2}\alpha$ levels of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), piroprofen (8 or 24 mg/kg) given with or without methyl androstenolone acetate; MAA (1.8 mg/kg), daily for 8 weeks.

Treatment	Mean PG (± SEM) Pg (n=6)	Percent change from control
Vehicle control	3867±328	-
MAA (1.8 mg/kg)	3750±320	-3.03
Piroxicam (1.8 mg/kg)	2300±245*	-40.52
Piroxicam (5.4 mg/kg)	2300±245*	-40.52
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	1535±465**	-60.31
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	1933±371	-50.01
Pirprofen (8 mg/kg)	3900±230	+0.85
Pirprofen (24 mg/kg)	2828±641(a)	-26.87
Pirprofen (8 mg/kg) + MAA (1.8mg/kg)	3225±337	-16.61
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	2425±249**	-37.29

a n = 5

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

prostaglandin level.

Administration of the anabolic potentiated the PG inhibiting effect on the anti-inflammatory (piroxicam) and unmasked the effect of the high dose of pirprofen. Several workers attributed the anti-inflammatory, and other effects of anti-inflammatory drugs to its cyclooxygenase or prostaglandine synthetase inhibition (Carty *et al.*, 1978, Mallarkey and Smith, 1984; Ward *et al.*, 1984 and Tavares *et al.*, 1985). It may be concluded that the anabolic drug will enhance the medical effects of the anti-inflammatroy drugs or at least will not antagonise them.

IV.4. Liver biochemical studies:

IV.4.1. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on serum and liver triglycerides of rats:

The results in table (13) shows triglycerides (TG) levels in the liver and serum at the end of experiment periods. Rats receiving MAA (1.8 mg/kg) showed significant decrease in serum TG i.e. 64.2% below control values. However, liver triglycerides did not change. Piroxicam (1.8 mg/kg) caused a decrease in both liver and serum

Table (13) Triglyceride levels in liver and serum 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) Triglycerides in liver and serum mg/dL (n=6)	
	Triglycerides in liver	Triglycerides in serum
Vehicle control	1460.15±192.13	202.78±42.69
MAA (1.8 mg/kg)	1760.97±88.0	* 72.6±12.9
Piroxicam (1.8 mg/kg)	** 979.87±44.33	** 53.7±10.76
Piroxicam (5.4 mg/kg)	1710.67±160.95	134.3±13.5
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	1823.90±70.05	150.47±9.9
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg	*** 2792.44±75.47	** 49.26±5.52
Pirprofen (8 mg/kg)	1152.0±56.61	151.57±32.99
Pirprofen (24 mg/kg)	2228.83±434.5	183.13±18.2
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	1037.75±320.75	144.15±17.8
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	1203.97±100.99	234.6±39.3

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

triglycerides i.e. 32.19% and 73.5% below control values. The higher dose of piroxicam did not induce any change in either liver or serum T.Gs. Piroxicam (5.4 mg/kg) given in the presence of anabolic agent orginated a great decrease in serum TG i.e. 75.71% below control value. On the other hand, the same treatment increased liver TG by 91.24% over control. The increment of liver TG reflects a degree in liver fatty deposition, (Gorman, 1985). The decrease in serum TG may be attributed to the deposition of TG in liver.

Pirporofen given alone or with MAA showed no significant change in serum or liver triglycerides.

This effect may be due to suppression of pituitary hormones (Tietz, 1976). The latter may cuase a decrease in serum TG (kastrup, 1986).

IV.4.2. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on liver, nucleic acid (RNA-DNA) and total protein:

The effect of piroxicam and pirprofen on liver nucleic acid (RNA-DNA) and total protein contents are shown in table (14). The obtained results illustrate that liver RNA content of rats receiving the anabolic agent MAA for 8 weeks did not differ from control. While the rats

Table (14) Liver nucleic acid (RNA-DNA) and total proteins of rats receiving orally piroxicam (1.8 or 5.4 mg/kg), pirprofen (8 or 24 mg/kg) given with or without methyl androstenolone acetice; MAA (1.8 mg/kg) daily for 8 weeks.

Treatment	Mean (± SEM) liver nucleic acids (RNA-DNA) and total proteins (n = 6)		
	RNA (mg/g protein)	DNA (mg/g protein)	Total protein (g/g weight tissue)
Vehicle control	18.116±0.461	7.011±0.469	0.321±0.07
MAA (1.8 mg/kg)	18.978±0.627	7.059±0.206	0.390±0.008***
Piroxicam (1.8 mg/kg)	20.29±0.465**	6.836±0.44	0.349±0.006**
Piroxicam (5.4 mg/kg)	21.203±0.384**	6.955±0.351	0.332±0.006
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	19.328±0.682	7.006±0.131	0.364±0.003***
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	18.479±0.265	7.139±0.185	0.346±0.006**
Pirprofen (8 mg/kg)	21.515±0.232***	6.571±0.166	0.383±0.008***
Pirprofen (24 mg/kg)	20.862±0.384***	6.59±0.283	0.355±0.004**
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	21.520±0.22***	6.751±0.1210	0.404±0.004***
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	21.592±0.215***	6.802±0.171	0.412±0.011***

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

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 controls. On the other hand pirprofen with anabolic agent had RNA content greater than controls. Since, liver RNA content are concerned with protein synthesis. Consequently, the serum proteins were found un-changed. Besides, the anti-inflammatory drugs are subjected to the protein binding, this might stimulate excessive need for protein. And hence, the increment of cellular RNA individuals level occurred (Davis *et al.*, 1968).

The obtained results in table (14) indicate that piroxicam and pirprofen alone and in the presence of the anabolic did not induce any change in liver DNA content. Analogous results were reported by Hurley *et al.* (1990).

The total liver protein of rats treated with MAA was 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

proteins 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).

IV.4.3. The efect of piroxicam and pirprofen with or without methyl androstenolone acetate on total and released liver lysosomal enzymes of rats:

Table (15) shows the obtained results of the total and released liver lysosomal marker enzyme (Acid phosphatase, ACP) of different treatments at the end of experimenal period. These results illustrates that the anabolic MAA, the anti-inflammatory piroxicam alone and together caused a slight changes on the total lysosomal, ACP. The anabolic drug did not affect 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

Table (15) Liver lysosomal enzyme (Acid phosphatase, ACP) in rats receiving orally piroxicam (1.8 or 5.4 mg/kg), priprofen (8 or 24 mg/kg) given with or without methyl androstenolone acetate; MAA (1.8 mg/kg) daily for 8 weeks.

Treatment	Mean (± SEM) liver lysosomal enzyme (ACP) nmol/gm protein and percentage change from control. (n = 6)	
	Total	Released
Vehicle control	5644.45±119.876	3133.33±85.180
MAA (1.8 mg/kg)	5544.22±120.87 -1.8%	3122.22±105.242 -0.35%
Piroxicam (1.8 mg/kg)	5564.35±79.64 -1.4	* 3422.22±88.114 +9.2
Piroxicam (5.4 mg/kg)	5423.24±146.82 -3.9	** 3600.00±79.937 +15%
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	5744.44±177.52 +1.8	* 3388.85±112.178 +8.2
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	5633.33±121.70 -0.2	3201.15±68.896 +4.7
Pirprofen (8 mg/kg)	* 6000.00±116.236 +6.3	** 3555.56±188.76 +13.5
Pirprofen (24 mg/kg)	* 6114.00±119.874 +8.3	*** 3833.33±112.172 +22.3
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	5814.78±114.820 +3.0	* 3505.56±102.404 +11.9
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	5866.67±111.064 +3.9	* 3333.33±112.170 +6.4

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

to the role of anabolic agent in releasing ACP. Consequently, the increment released ACP was accompained with lysosomal membrane stability. the obtained results are in agreement with those obtained by Abd El Gawad *et al.* (1989).

IV.5. Blood haematological studies:

IV.5.1. 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 picture of rats after 4 and 8 weeks of treatment are shown in tables (16) and (17) 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 at the end of the experiment period.

The tested anti-inflammatory drugs had no noticeable affect 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

Table (16) 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.

Treatment	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±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±10.8	13.9±0.3	38.5±0.65	7.2±0.58	55.0±5.89	19.7±2.45	36.6±0.5
Piroxican (1.8 mg/kg)	65.8±8.98	14.7±0.7	38.2±1.17	8.9±0.4	43.1±1.32	16.6±0.81	38.1±0.9
Piroxican (5.4 mg/kg)	* 97.0±10.07*	** 17.0±0.9	41.8±0.75	7.2±0.42	*** 59.1±2.5	** 23.2±1.45	41.2±2.0
Piroxican (1.8 mg/kg) + MAA (1.8 mg/kg)	68.3±7.15	14.8±0.4	40.2±1.5	8.2±0.6	49.2±2.3	18.2±1.36	36.1±1.8
Piroxican (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±1.5
Pirprofen (8 mg/kg)	67.5±15.5	13.6±0.9	39.5±2.06	7.2±0.81	54.0±5.2	19.1±2.65	34.5±1.0
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±1.0
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	55.0±14.17	15.7±0.8	40.2±0.4	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±17.4	13.5±0.2	*** 33.5±0.99	7.3±0.54	46.1±4.0	18.5±1.22	* 41.0±1.0

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

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 = $\frac{HB}{HCT}$

Table (17) 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.

Treatment	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±16.6	12.5±0.4	34.2±1.46***	7.0±0.18	46.6±1.3	17.5±0.6	38.1±0.5
Piroxican (1.8 mg/kg)	50.2±11.03	13.1±0.3	42.4±1.5	8.2±033	51.7±2.97	15.8±1.0	31.1±1.4
Piroxican (5.4 mg/kg)	80.5±15.4	13.5±0.7	33.7±1.49***	7.5±0.28	44.0±0.9	18.0±0.4	39.0±2.0
Piroxican (1.8 mg/kg) + MAA (1.8 mg/kg)	90.4±17.8	14.0±0.7	44.8±6.11	7.6±0.37	57.8±1.2***	18.3±0.8	32.3±2.0
Piroxican (5.4 mg/kg) + MAA (1.8 mg/kg)	87.1±20.3	13.7±0.2	34.6±1.21***	6.9±0.53	50.6±4.0	20.2±1.3	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±3.3
Pirprofen (24 mg/kg)	27.5±8.07	13.5±0.5	35.0±3.0	7.9±0.29	44.4±5.44	17.1±1.26	39.0±2.8
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	72.5±11.6	14.5±0.9	36.2±1.55	7.6±0.33	44.3±3.02	19.1±1.07	44.1±3.0*
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±2.7	17.2±0.8	39.0±1.0

*, **, *** Denote significant differences from controls at P < 0.005, 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 = $\frac{HB}{HCT}$

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 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 signes 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 a 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.

IV.5.2. The effect of piroxicam and pirprofen with or without methyl androstenolone acetate on leucocytic counts of rats:

Tables (18) and (19) show leucocytic counts after 4 and 8 weeks of different treatments, respectively. These

Table (18) Blood total and differential leucocytic counts of rats receiving orally piroxican (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.

Treatment	Mean (± SEM) total and differential leucocytic counts (n = 6)			
	Total leucocytic count ($x10^3/mm^3$)	Lymphocytes %	Neutrophils %	Monocytes %
Vehicle control	7.90±0.52	63.58±1.38	35.31±1.27	0.94±0.39
MAA (1.8 mg/kg)	8.56±0.79	65.0±2.16	33.0±1.88	2.0±1.46
Piroxicam (1.8 mg/kg)	8.80±0.69	52.0±2.89**	50.0±3.54**	0.4±0.2
Piroxicam (5.4 mg/kg)	8.9±0.66	43.75±4.2***	54.5±4.27***	1.75±0.55
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	8.25±0.6	56.75±2.13*	42.0±1.68*	1.25±0.2
Piroxicam (5.4 mg/kg) + MAA (1.8 mg/kg)	8.96±0.45	50.75±2.1**	47.75±2.01**	1.50±0.29
Pirprofen (8 mg/kg)	7.09±0.4	49.0±1.53***	49.66±1.33***	1.33±0.33
Pirprofen (24 mg/kg)	7.05±0.37	48.5±1.6***	50.5±1.7***	1.0±0.21
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	7.54±0.25	55.0±1.44**	44.0±1.63**	1.0±0.21
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	7.56±0.24	52.3±1.32**	46.66±1.76	1.0±0.22

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

Table (19) 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.

Treatment	Mean (± SEM) serum total and differential leucocytic counts (n = 6)			
	Total leucocytic count ($x10^3/mm^3$)	Lymphocytes %	Neutrophils %	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	65.5±1.85	33.25±1.65	1.25±0.63
Piroxicam (1.8 mg/kg)	7.28±0.29	49.5±1.19**	49.5±1.19**	1.0±0.41
Piroxicam (5.4 mg/kg)	7.89±0.48	52.5±2.33**	46.25±2.93**	1.25±0.63
Piroxicam (1.8 mg/kg) + MAA (1.8 mg/kg)	8.43±0.28	54.5±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	39.0±1.0	1.15±0.29
Pirprofen (8 mg/kg)	7.36±0.3	50.25±2.39**	48.5±2.72**	1.25±0.11
Pirprofen (24 mg/kg)	7.14±0.02	47.0±1.0***	52.0±1.0***	1.0±0.29
Pirprofen (8 mg/kg) + MAA (1.8 mg/kg)	8.028±0.3	52.0±1.68**	44.5±1.93**	1.0±0.22
Pirprofen (24 mg/kg) + MAA (1.8 mg/kg)	7.56±0.25	50.1±2.12**	44.0±2.25**	1.25±0.31

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

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

The mechanism involved in the etiology of agranulocytosis by drugs is not clearly known. It might be due to its sensitivity to the drug (Frankel and Reitman, 1963) or an effect on bone marrow (Woodbury, 1968).

The spleen is the biggest lymph node of the body possessing a major role in the formation and activation of lymphocytes. 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).

General Conclusion:

From the forementioned results it could be concluded that the acute toxicity of piroxicam is dependent on the sex. This should be taken in concern during its use in females. Both piroxicam and pirprofen caused toxic effects on chronic repeated administrations. The main hazard effects observed were; reduction in the weight of the spleen, retarded growth rate, liver affection manifested by elevated serum bilirubin and increment in serum alkaline phosphatase activity; which is an indicator of drug induced cholestatic jaundice and agranulocytoses. Hepatic ribonucleic acid content was elevated in response to anti-inflammatory drugs. The effect is related to increased requirement to proteins needed for drug protein binding. These toxic effects were related to labilization of lysosomal membrane.

The anabolic drug was able to minimize some of the side effects induced by the above-mentioned anti-inflammatory drugs without antagonizing their action. The anabolic drug (MAA) reduced the mortality rate of pirprofen on chronic administration. Also, the effect of

anti-inflammatory drugs on serum bilirubin was abolished by the anabolic compound. On the other hand, the anabolic agent was able to antagonize the effect of piroxicam on serum alkaline phosphatase activity rather than that of pirprofen. Also, this compound antagonized the elevation of hepatic RNA which was induced by the anti-inflammatory drugs. Liver lysosomal studies 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.

It may be recommended that serum bilirubin estimation as well as haematological examination of leucocytes should be carried out during prolonged therapy with piroxicam or pirprofen. The concurrent administration of anabolic steroid may be important in reducing the side effects of these anti-inflammatory drugs from the therapeutic point of view.