RESULTS

RESULTS

IN VITRO STUDY

I. Isolated rabbits heart :

I.1 Effect of increasing doses of meloxicam on the isolated rabbit's heart:

Administration of meloxicam in the different dose levels (0.03, 0.1, 0.3 µmol/ml) induced a dose dependent increase in the amplitude of the rhythmic contractility of the heart *(Figure 3)*.

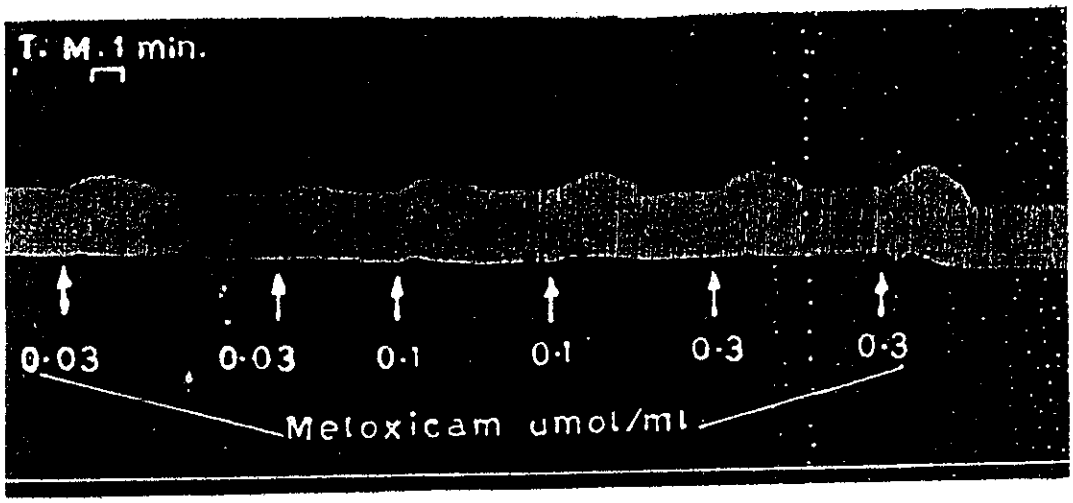
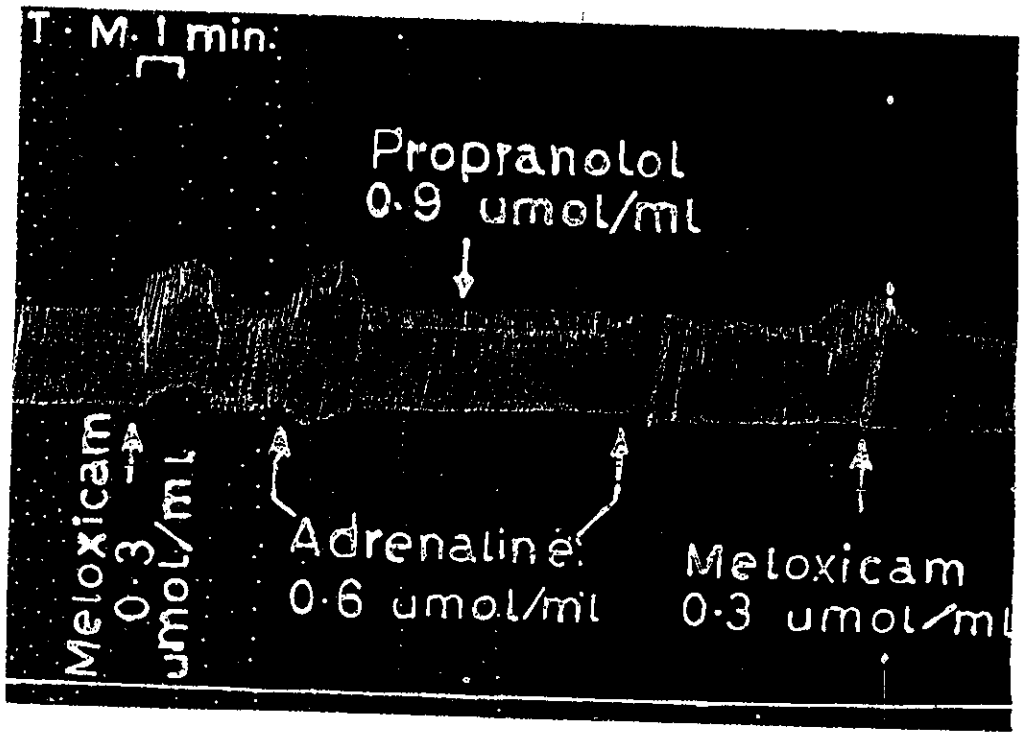


Figure (3) Effect of increasing doses of meloxicam on the isolated rabbit's heart.

I.2 the effect of meloxicam on different receptors in isolated rabbit heart :

A .**Effect of meloxicam on β receptors:**

Meloxicam was added in a dose of 0.3μmol/ml produced stimulation of cardiac contractility, after which adrenaline was added in a dose 0.6 μmol/ml that produced an increase in the amplitude of the heart's contractility. Preincubation of the heart by propranolol in a dose of 0.9 μmol/ml for three-min. duration abolished the stimulatory effect of adrenaline; however, it had no effect on meloxicam's stimulatory effect *(Figure 4)*.



(Figure 4) : Effect *of meloxicam on β receptors*

B Effect of meloxicam on dopaminergic receptors:

Addition of meloxicam in a dose of 0.3 µmol/ml induced stimulat on of heart's contractility, and then dopamine was added in a dose of 0.9 µmol/ml induced a similar increase in the amplitude of the heart's contractility. Preincubation of the heart with metoclopramide in a dose of 0.6 µmol/ml for three-min. duration abolished the stimulatory effect of dopamine; however, it had no effect on meloxicam's stimulatory effect *(Figure 5)*.

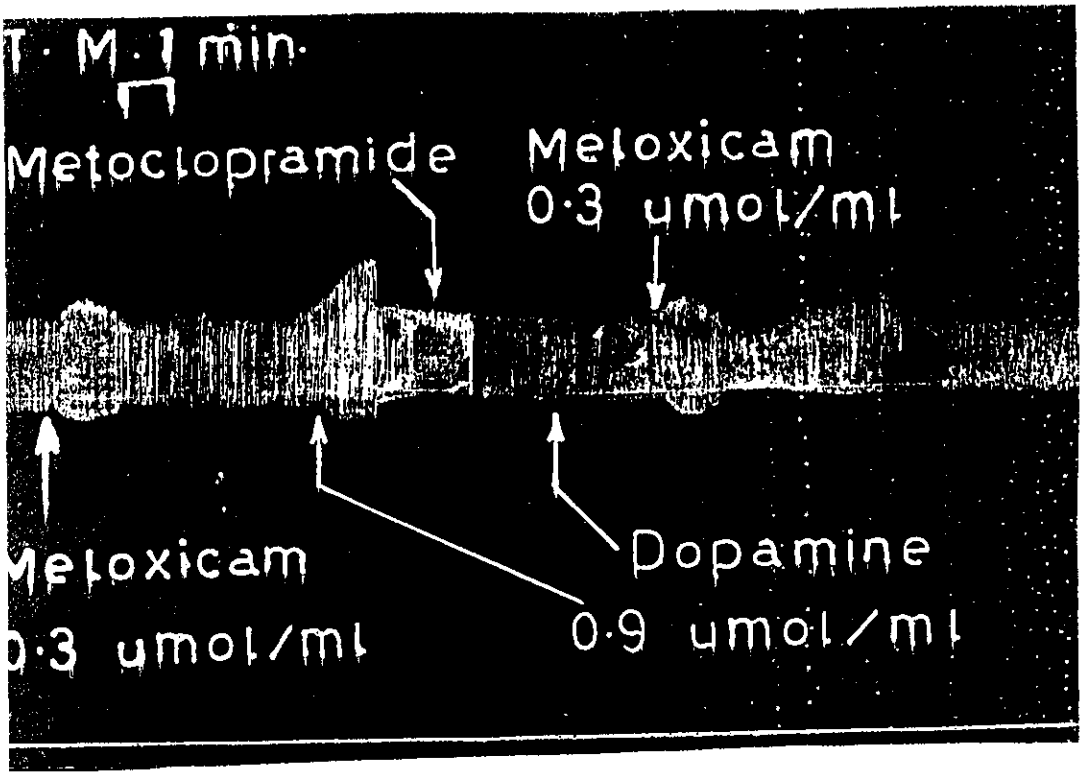


Figure (5)Effect of meloxicam on dopaminergic receptors

C. Effect of meloxicam on adenosine receptors:

Administration of Adenosine in the dose of 0.9 µmol/ml produced a decrease in the amplitude of the contractility of the heart; addition of the meloxicam in a dose of 0.3 µmol/ml induced an increase in the amplitude of the contraction. Preincubation of the heart with a dose of 0.6 µmol/ml of adenosine antagonist 8 SPT abolished the action of adenosine, while the action of meloxicam was not affected *(Figure 6)*.

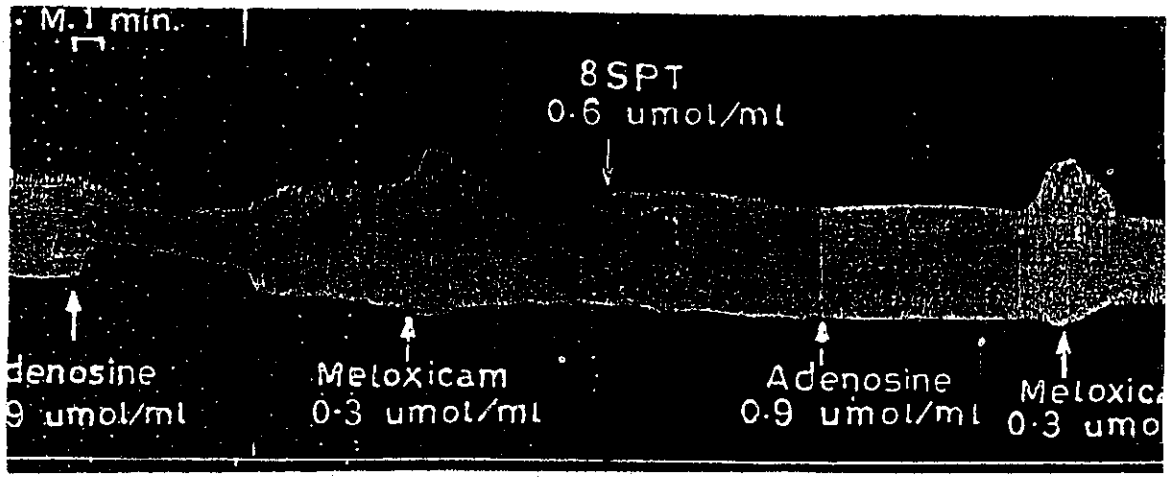


Figure (6) . Effect of meloxicam on adenosine receptors

II. Isolated aortic strip:

1. Effect of increasing doses of meloxicam on isolated aortic strip

Addition of different dose levels of meloxicam (ranging from 0.03 to 3 μmol/ml) to the isolated aortic strip had no effect on it's basal tone.*(Figure 7).*

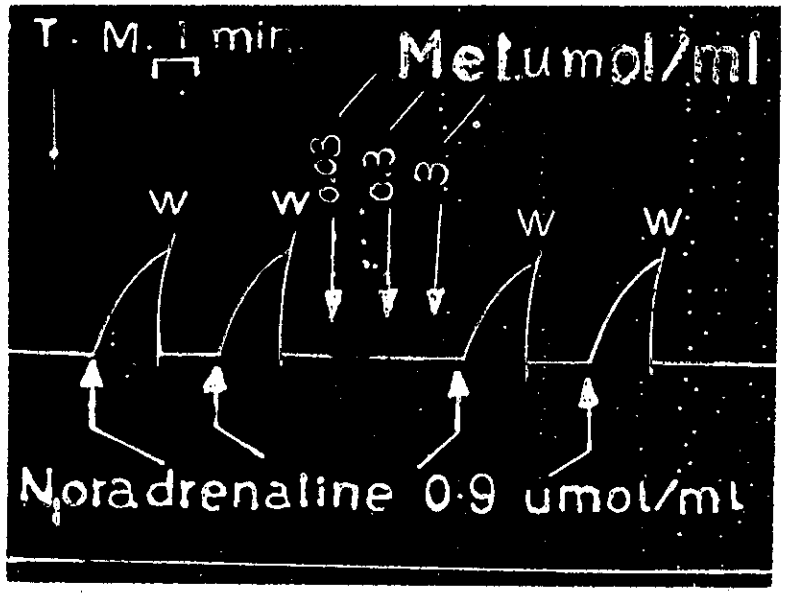


Figure (7) The effect of increasing doses of meloxicam on isolated aortic strip

2- Interaction of meloxicam with different vasopressor mediators

A .Interaction with noradrenaline:

Administration of noradrenaline in a dose of 0.9 µmol/ml induced contraction of the aortic spiral strip, preincubation with meloxicam in the dose of 0.3 µmol/ml had no effect on the pressor effect of noradrenaline on the aortic strip *(Figure 8)*.

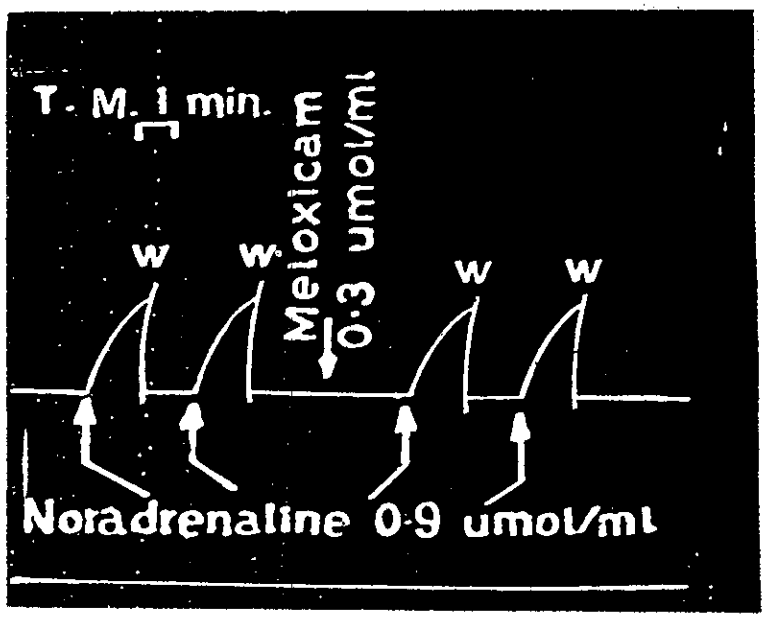


Figure (8) : **Interaction of meloxicam with noradrenaline**

B .Interaction with angiotensin :

Administration of angiotensin in a dose of 0.06 µmol/ml induced contraction of the aortic spiral strip, preincubation with meloxicam in the dose of 0.3 µmol/ml had no effect on the pressor effect of angiotensin on the aortic strip *(Figure 9).*

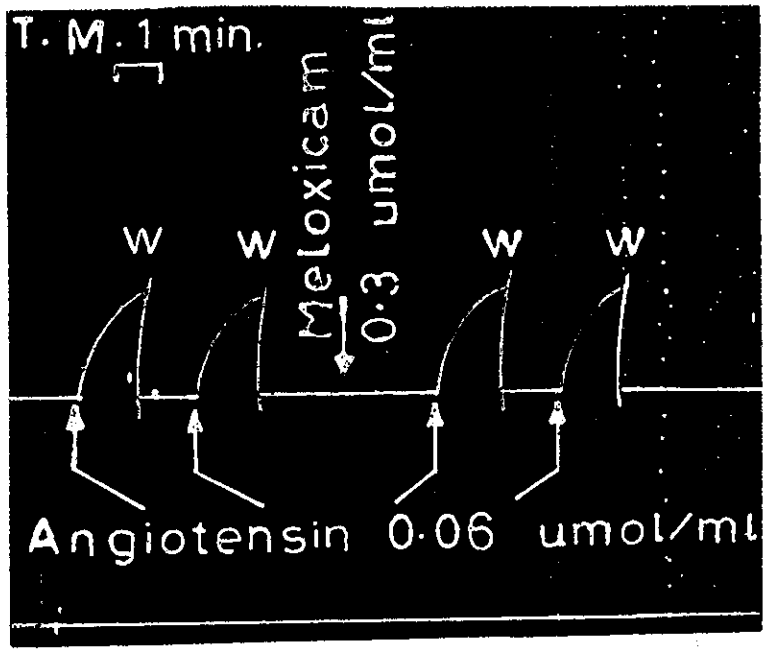


Figure (9) : Interaction of meloxicam with angiotensin

C .Interaction with serotonin :

Administration of serotonin in a dose of 0.3 µmol/ml induced contraction of the aortic spiral strip, preincubation with meloxicam in the dose of 0.3 µmol/ml had no effect on the pressor effect of serotonin on the aortic strip *(Figure 10)*.

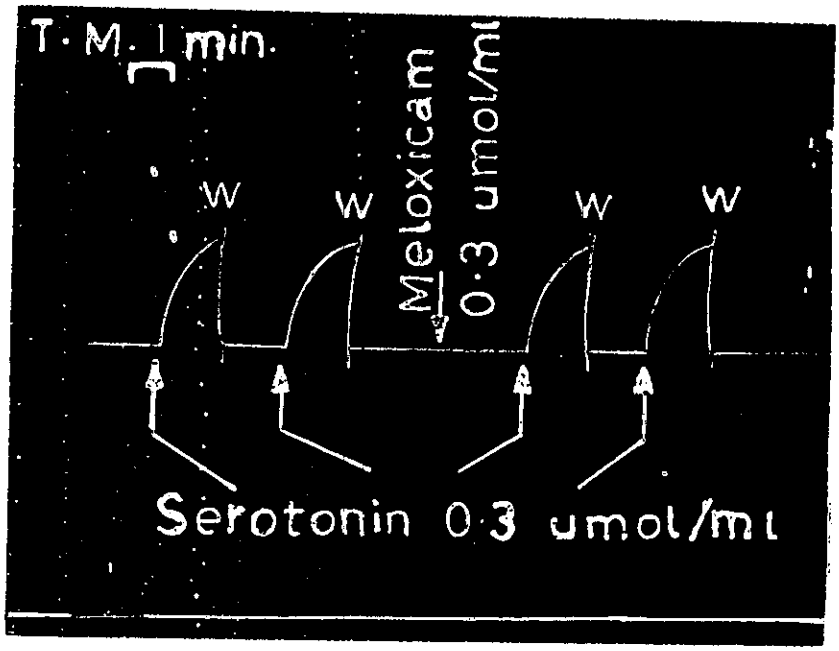
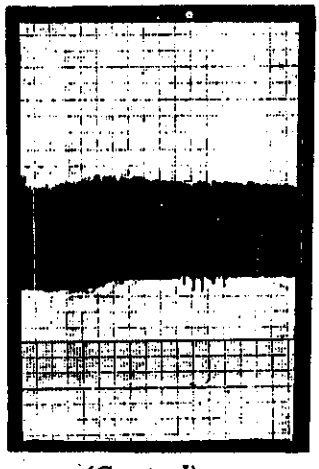


Figure (10) : . **Interaction of meloxicam with serotonin**

IN VIVO STUDY

1. Effect of increasing doses of meloxicam on mean arterial blood pressure:

The acute administration of meloxicam as IV bolus doses of 0.03, 0.1, 0.3 μg/kg, induced a dose dependent elevation of the blood pressure, as the basal MAP reading was 110 ± 8mmHg, the dose of 0.03 μg/kg increased the blood pressure to 118 ± 9 mmHg, and the doses of 0 1, 0.3 μg/kg increased the blood pressure to the values of 131 ± 11and 139 ± 12 mmHg respectively ***(Figure 11 A)***.



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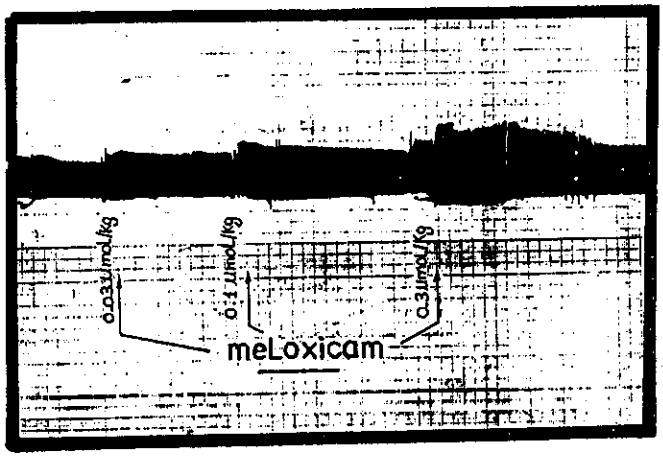
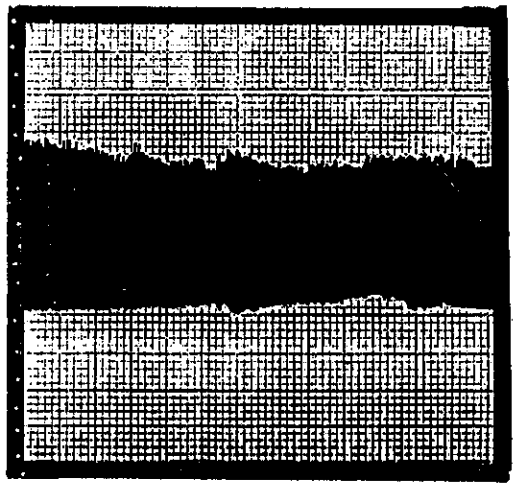


Figure (11 A) : **Effect of acute administration of different doses of meloxicam on mean arterial blood pressure**

The chronic intraperitoneal administration of meloxicam in a dose of 0.3 μg/kg, induced a non significant change in the blood pressure. *(Figure 11 B)*and control group.



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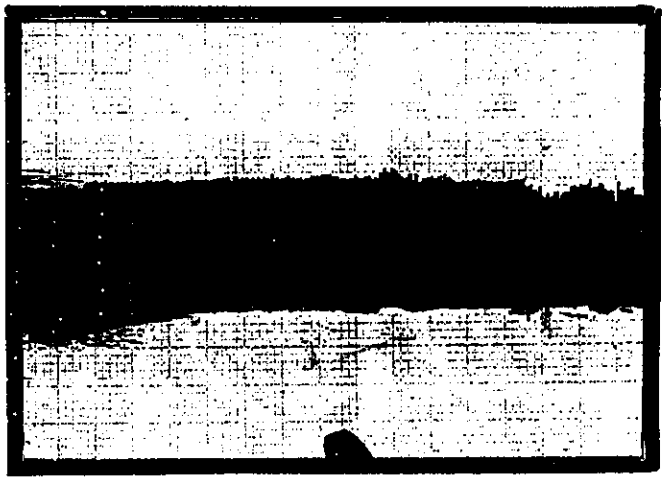
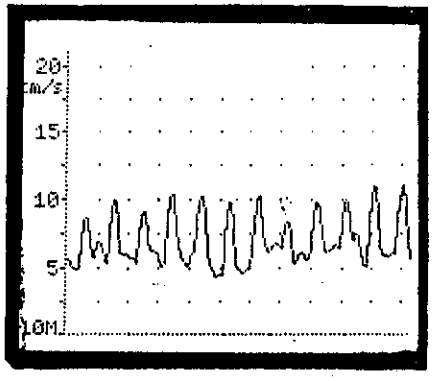


Figure (11 B) : Effect of chronic administration of meloxicam on MBP

II. Effect of meloxicam on the renal blood flow

Acute administration of meloxicam as IV bolus doses of 0.03, 0.1, 0.3 µg/kg produced significant dose related increase of RBF in values of '14±1.3*', '17±3' and '21±2' respectively ***(Figure 12 A i, ii, iii)***.



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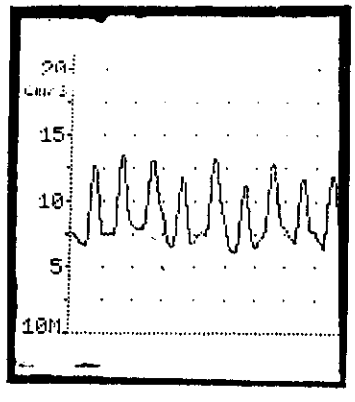
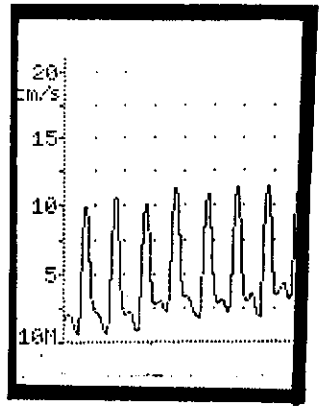


Figure (12 A i)Effect of acute IV injection of 0.03µg/kg meloxicam on RBF



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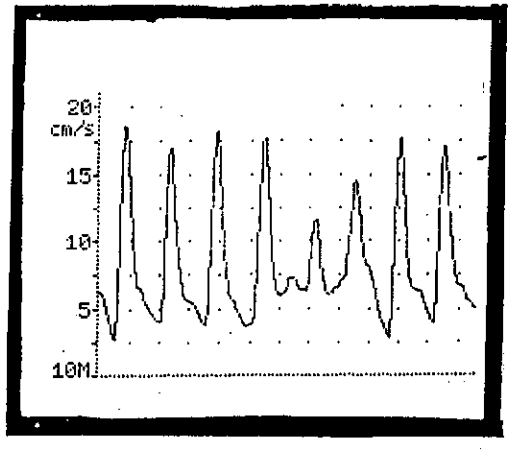
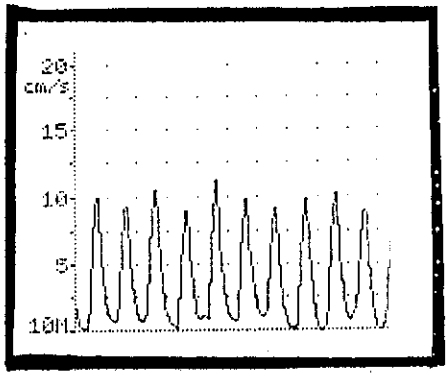


Figure (12 A ii)Effect of acute IV injection of 0.1µg/kg meloxicam on RBF



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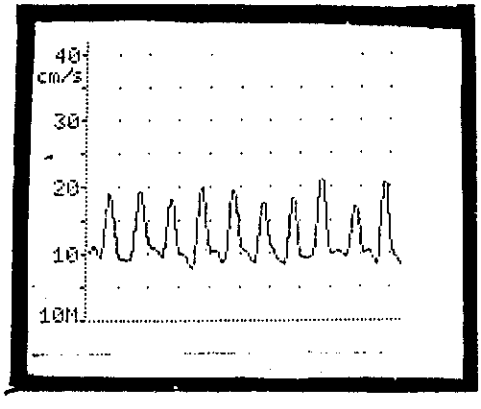


Figure (12 A iii)Effect of acute IV injection of 0.3µg/kg meloxicam on RBF

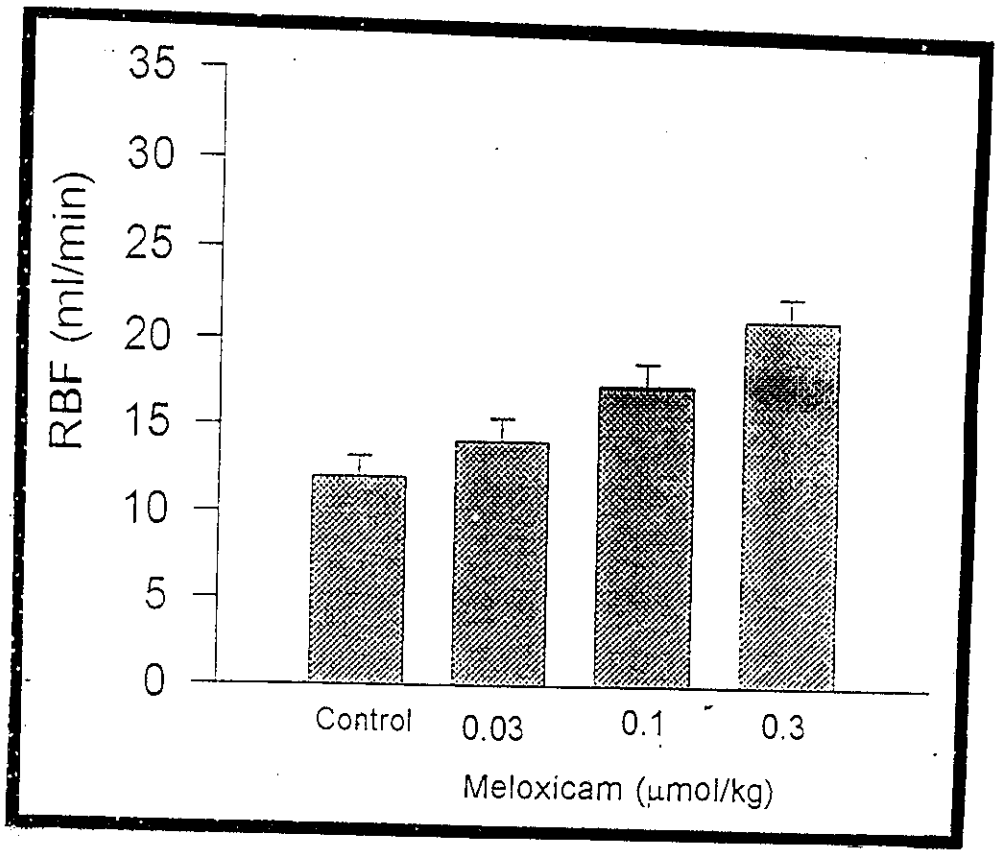
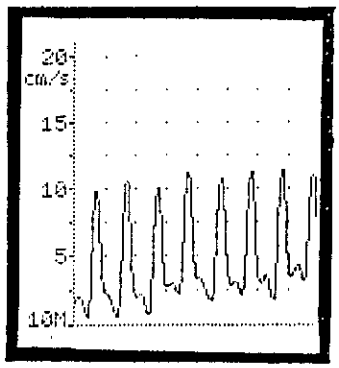


Figure (12 B) : **Effect of acute IV administration of meloxicam in doses of 0.03, 0.1 and 0.3 μg/kg on RBF.**

The Chronic administration of meloxicam in a dose of 0.1 µg/kg for a period of two weeks resulted in no significant change of the renal blood flow in treated rats (giving values of 11±1.9) in comparison to the control group (giving values of 10.5±2) ***(Figure 12 C i).***



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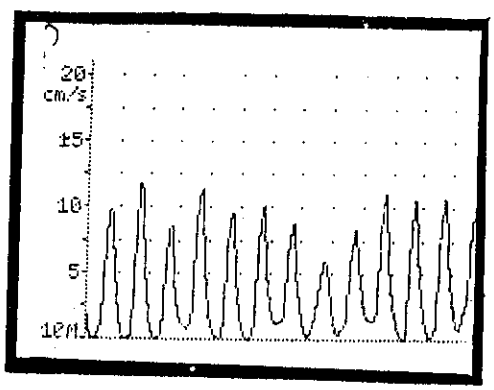


Figure (12 C i)Effect of chronic intraperitoneal injection of 0.3µg/kg meloxicam on RBF

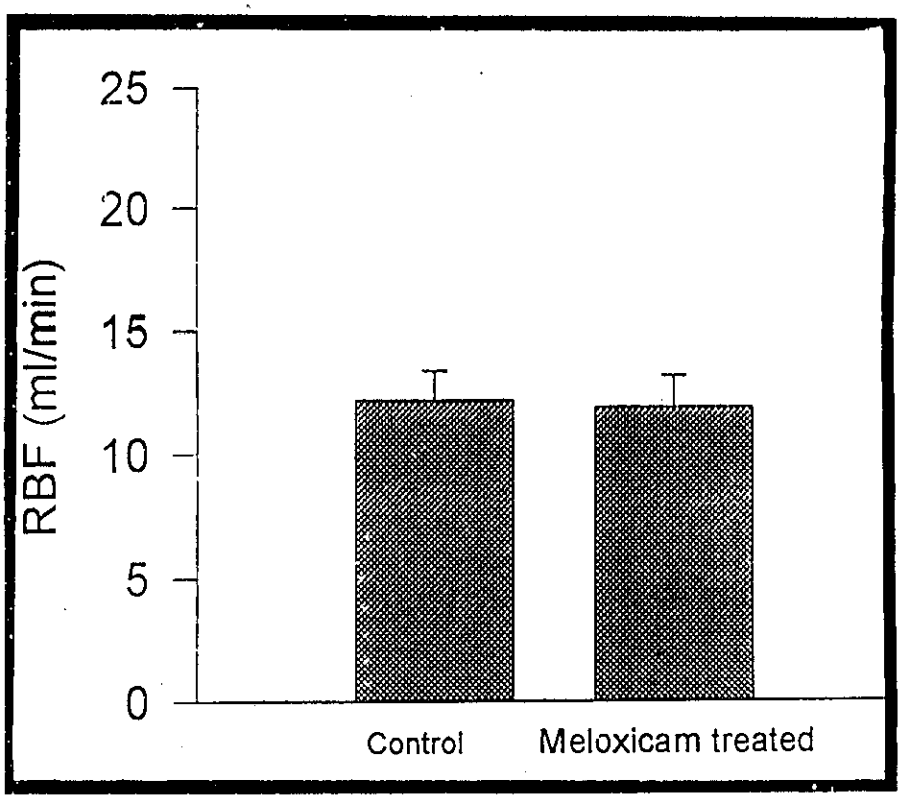
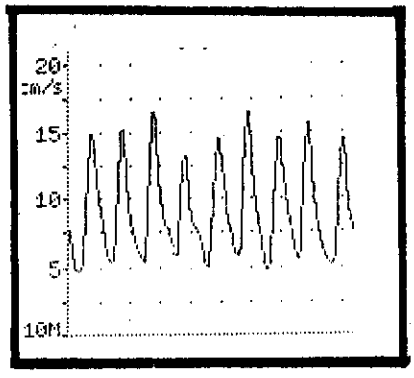


Figure (12 C ii)Effect of chronic intraperitoneal injection of 0.3µg/kg meloxicam on RBF

.III. Effect of meloxicam on mesenteric blood flow

Acute administration of meloxicam as IV bolus doses of 0.03, 0.1, 0.3 µg/kg, produces a dose dependent significant increase in the MBF(in values of '21±2', '25±1.5' and '30±3' respectively). *(Figure 13 A i, i, iii).*



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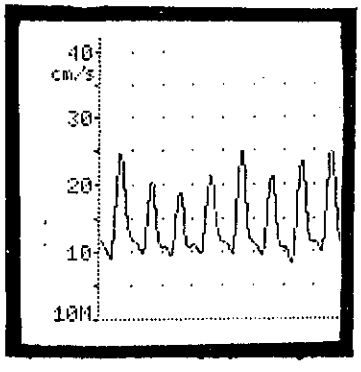
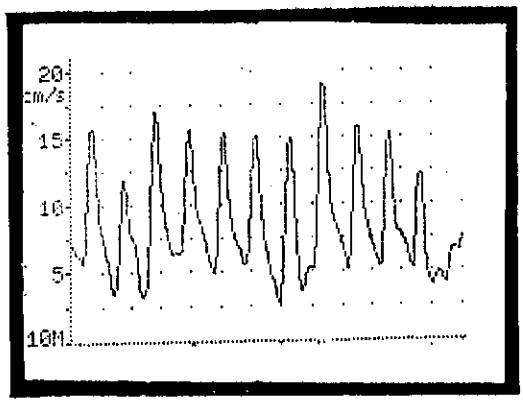


(Figure 13 A i)Effect of acute IV injection of 0.03µg/kg meloxicam on MBF



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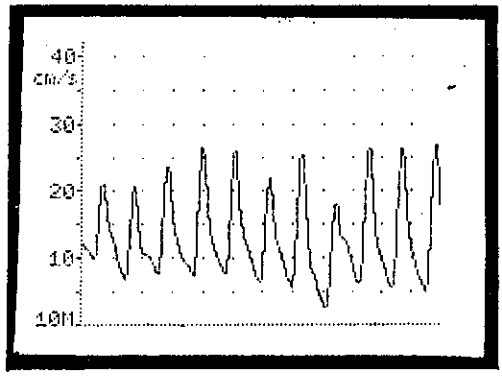
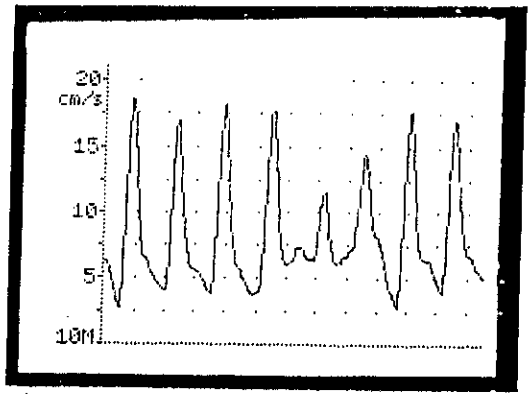


(Figure 13 A ii)Effect of acute IV injection of 0.1µg/kg meloxicam on MBF



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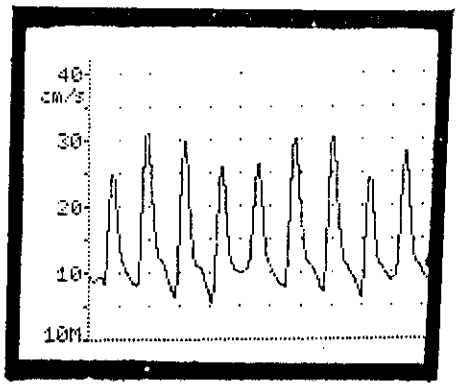


(Figure 13 A iii)Effect of acute IV injection of 0.3µg/kg meloxicam on MBF

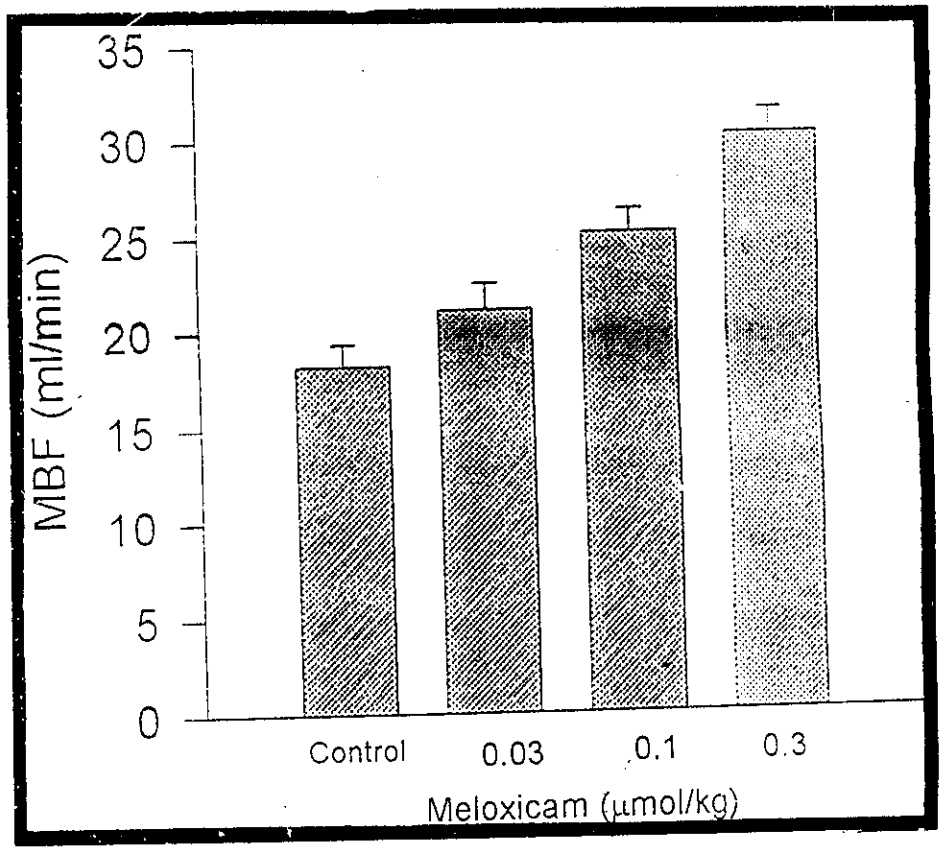
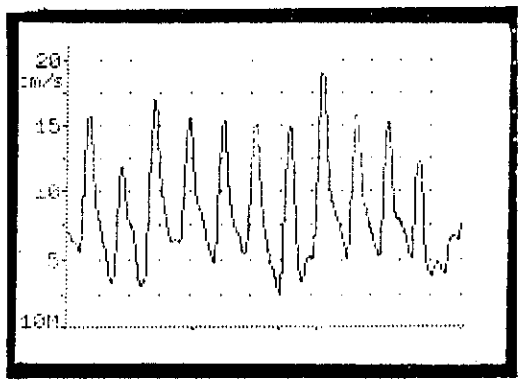


Figure (13 B) :Effect of acute IV administration of meloxicam in doses of 0.03, 0.1, 0.3 μg/kg on the MBF

Meanwhile, the chronic administration of meloxicam in a dose of 0.3 µg/kg for a period of two weeks resulted in non significant change of the mesenteric blood flow in treated rats in comparison to the control group *(Figure. 13 C i).*



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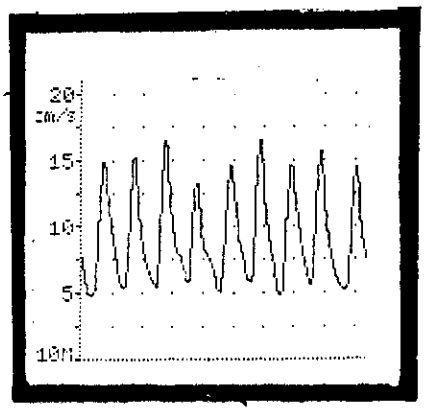


Figure (13 C i)Effect of chronic intraperitoneal injection of 0.3µg/kg meloxicam on MBF

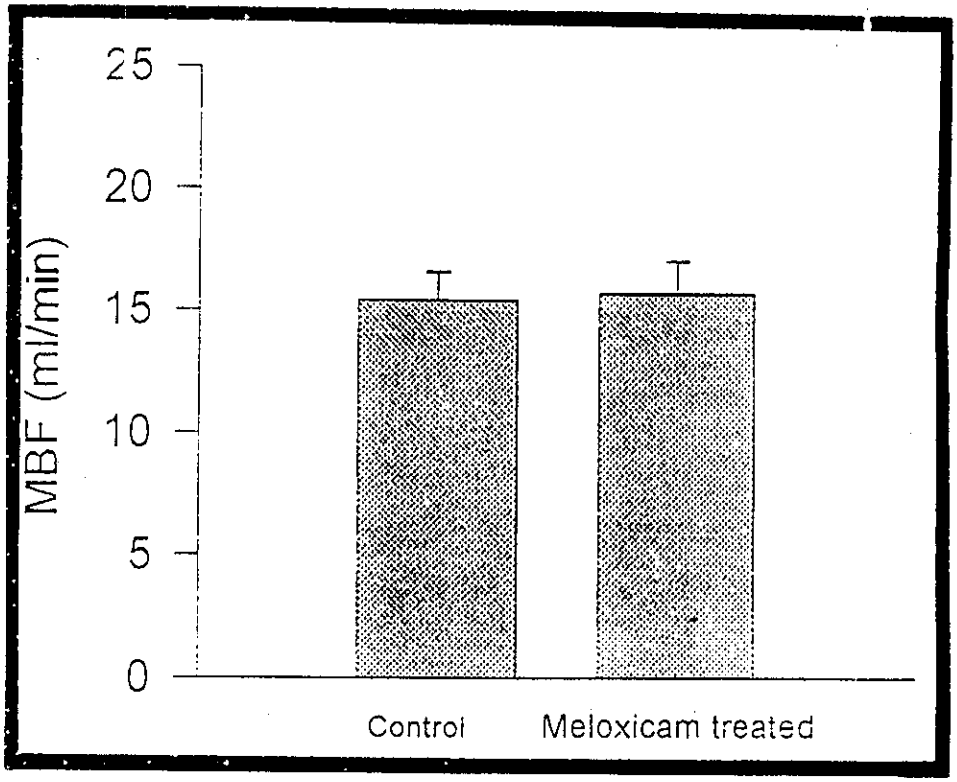
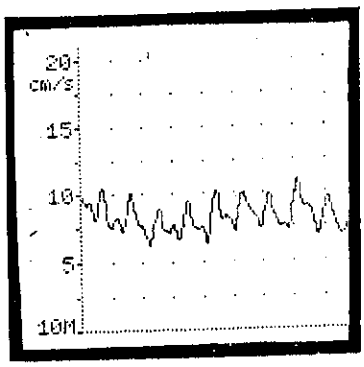


Figure (13 C ii):**Chronic intraperitoneal injection of 0.3µg/kg meloxicam on MBF**

IV. Effect of meloxicam on carotid blood flow

Acute administration of meloxicam as IV bolus doses of 0.03, 0.1, 0.3 µg/kg, produced no change in the CBF (to values of '10.5±1.2', '10±0.9', and '905 ±0.9' respectively). ***(Figure 14 A i, ii, iii).***



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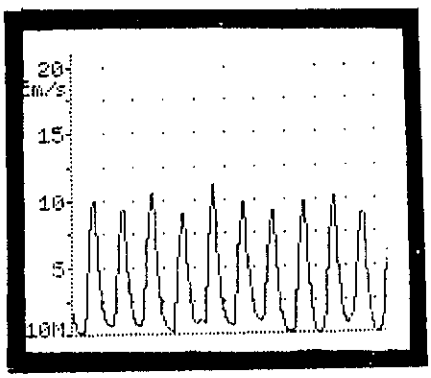
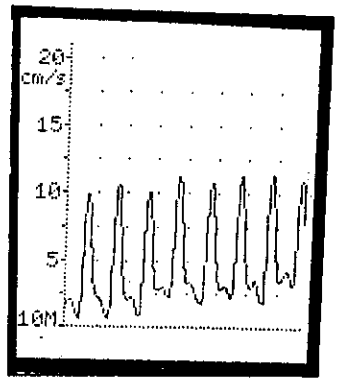


Figure (14 A i)Effect IV injection of 0.03µg/kg meloxicam on CBF



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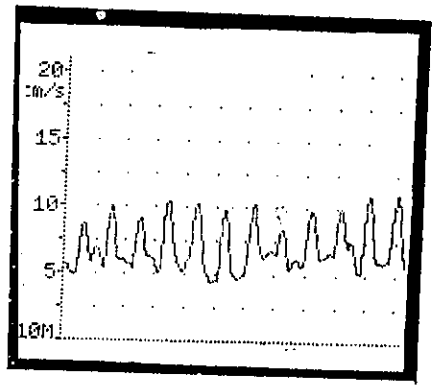
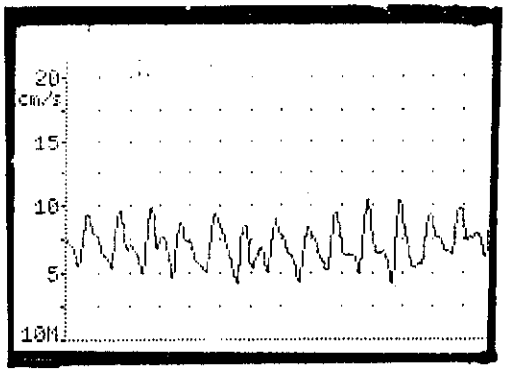


Figure (14 A ii)Effect IV injection of 0.1μg/kg meloxicam on CBF



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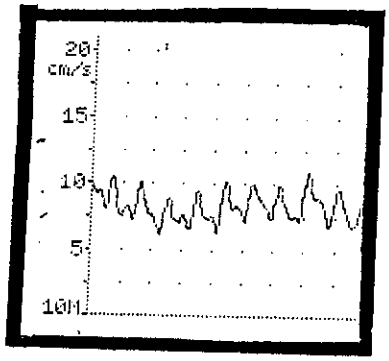


Figure (14 Aiii)Effect IV injection of 0.3µg/kg meloxicam on CBF

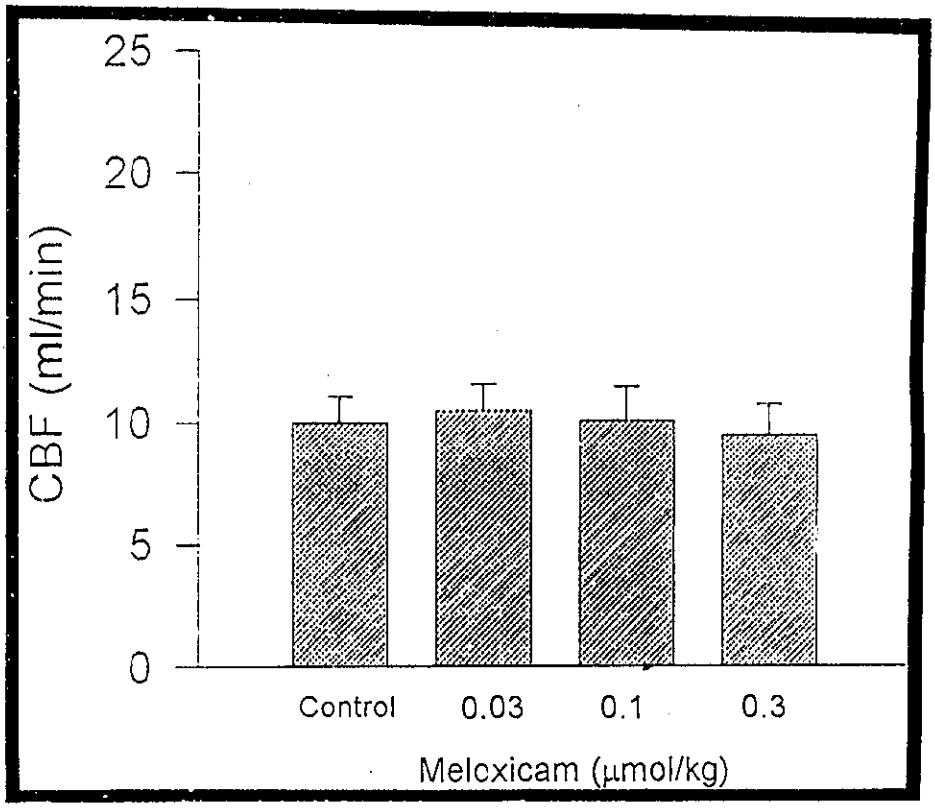
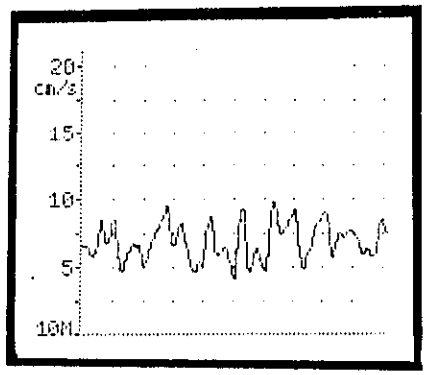


Figure (14 B) : Effect of acute IV administration of meloxicam in doses of 0.03, 0.1 and 0.3 ug/kg on CBF

Similarly, the chronic administration of meloxicam in a dose of 0.3 µg/kg for a period of two weeks resulted in no significant change carotid blood flow measurements in treated rats (8±1.6) in comparison to the control group (7.8+ 2)*(Figure 14 C i).*



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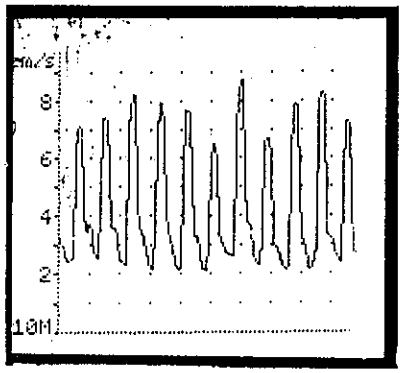


Figure (14 Ci)Effect of chronic intraperitoneal injection of 0.3µg/kg meloxicam CBF

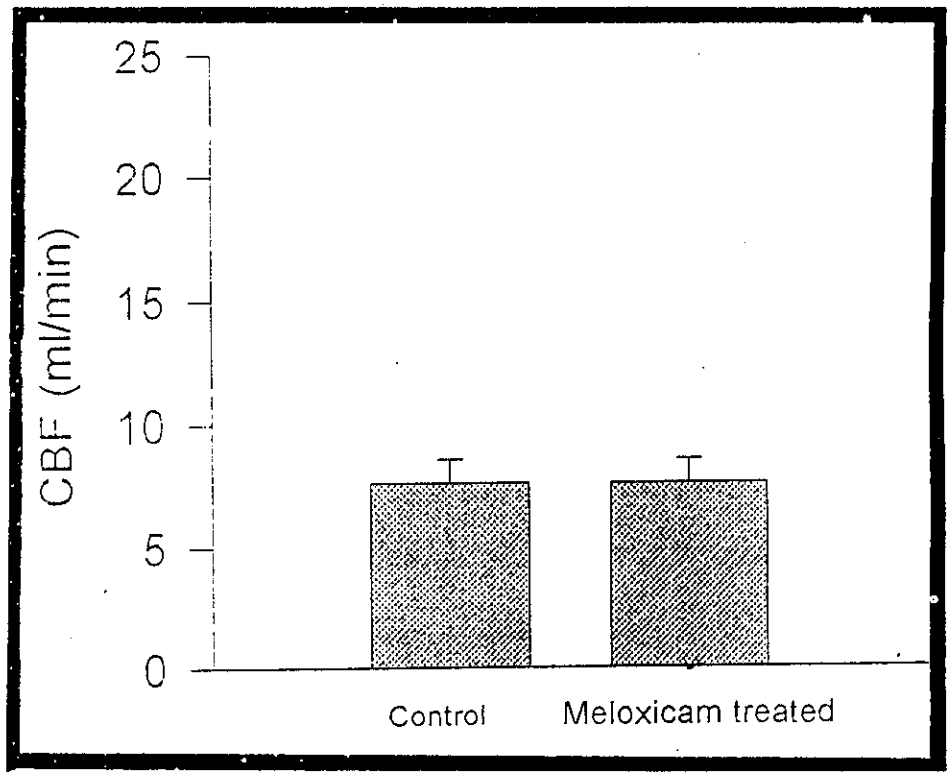
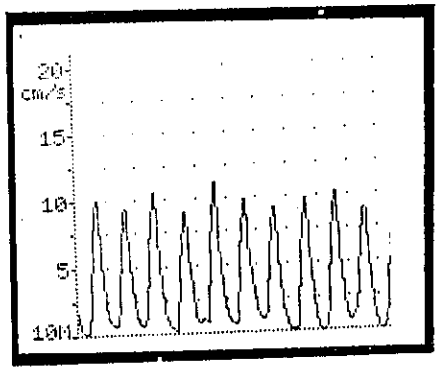


Figure (14 C ii): Effect of chronic intraperitoneal injection of 0.3µg/kg meloxicam on CBF

V. Effect of meloxicam on hindquarters blood flow

Acute administration of meloxicam as IV bolus doses of 0.03, 0.1, 0.3 µg/kg, produced no significant change in the HBF (to values of '101.5', '10 ± 1.2' and '91 1.8' respectively) *(Figure 15 A i, ii, iii)*.



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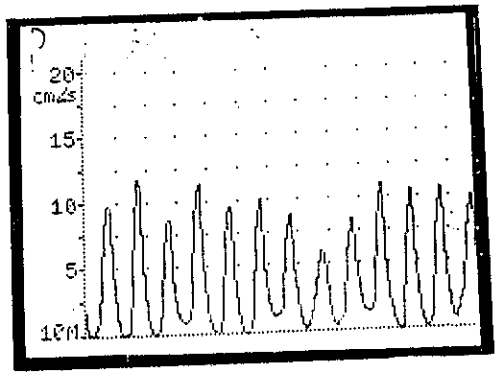
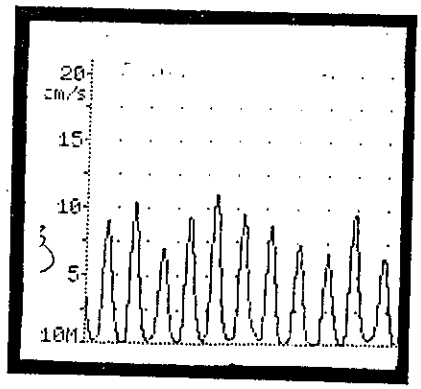
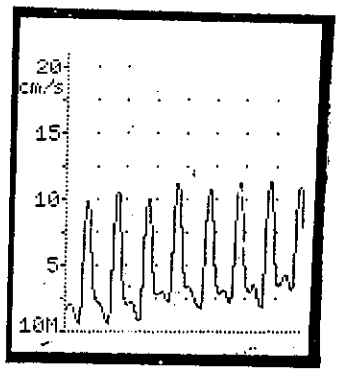


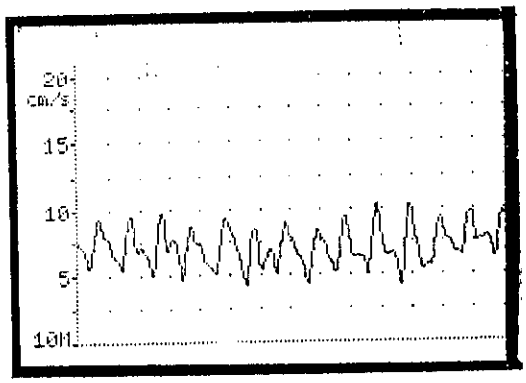
Figure (15 A i)Effect of IV injection of 0.03µg/kg meloxicam on HBF



(Control)



Figure(15 A ii)Effect of IV injection of 0.1µg/kg meloxicam on HBF



(Control)

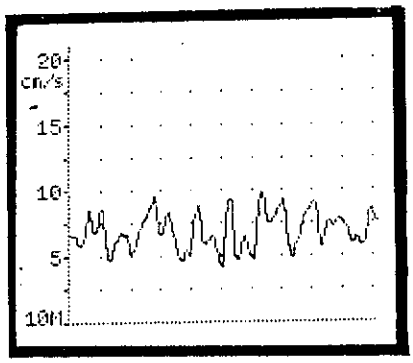


Figure (15 A iii)Effect of IV injection of 0.3µg/kg meloxicam on HBF

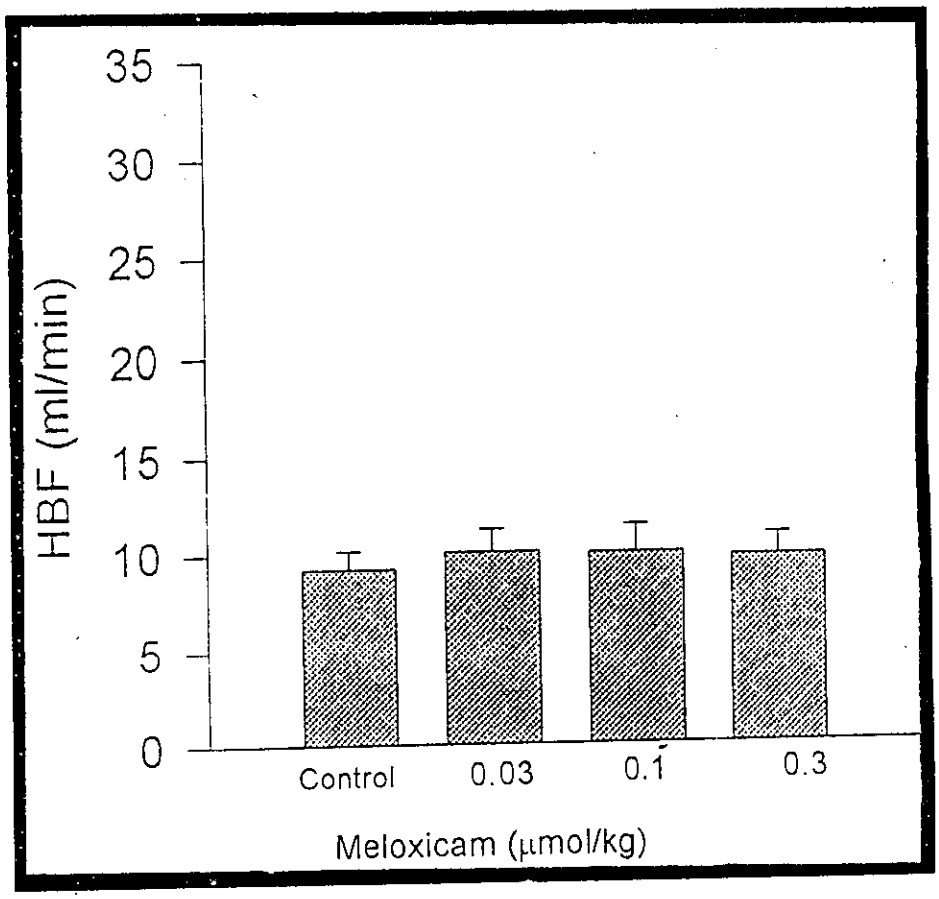
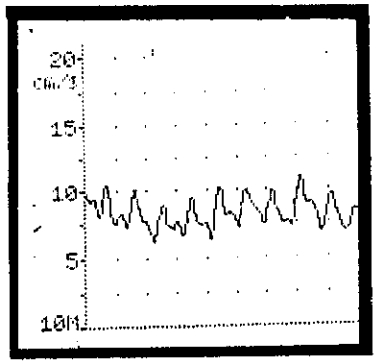


Figure (15 B) : Effect of acute IV administration of meloxicam in doses of 0.03, 0.1, 0.3 μg/kg on the HBF.

Similarly, the chronic administration of meloxicam in a dose of 0.3 µg/kg for a period of two weeks showed non significant change in HBF in treated rats (9±2.1)in comparison to the control group(10± 2) ***(Figure 15 C i)***.



(Control)

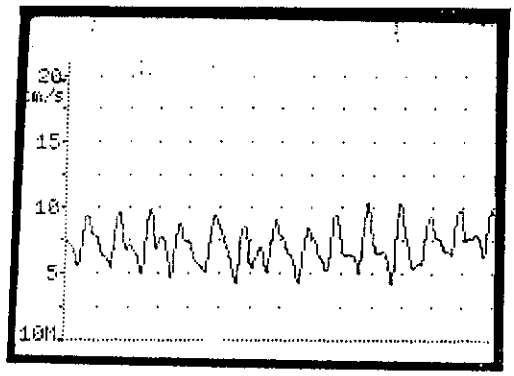


Figure (15 C i)Effect of chronic intraperitoneal injection of 0.3µg/kg meloxicam on HBF

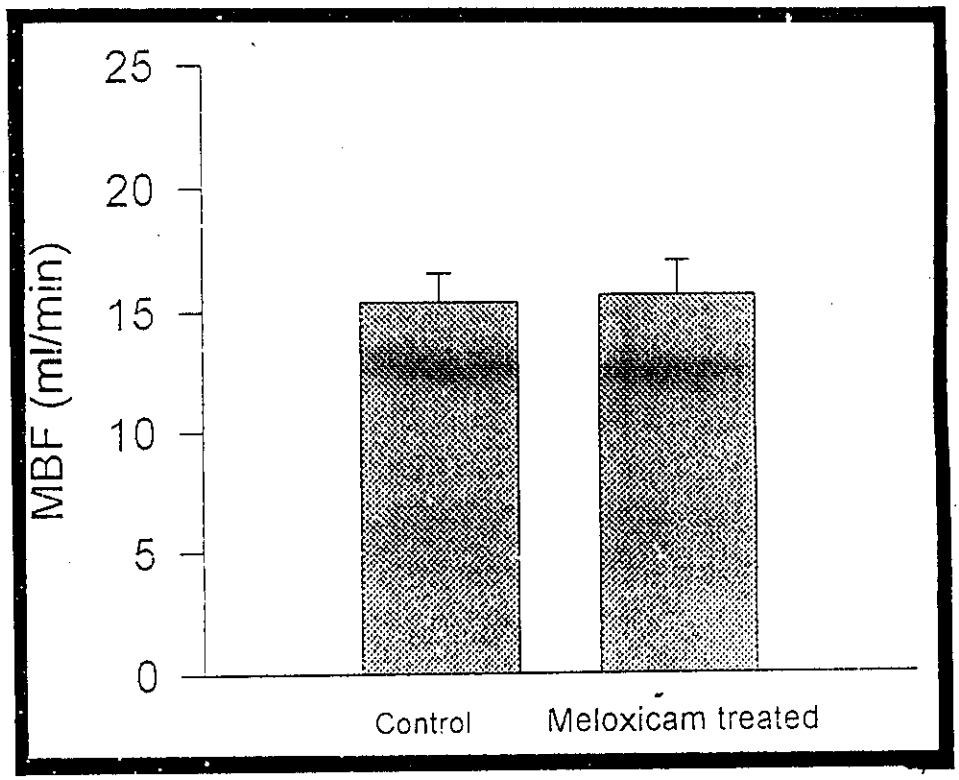


Figure (15 C ii) : Chronic intraperitoneal injection of 0.3µg/kg meloxicam on HBF.

(Table 2) :Effect of acute intravenous injection of meloxicam in doses of 0.03, 0.1, and 0.3 µg/kg on MAP, RBF, MBF, CBF and HBF.

Dose	Blood pressure	Renal blood flow	Mesenteri c blood flow	Carotid blood flow	Hindquar ter blood flow
Control	110±5	12±2	18±1	10±1.6	9±2
0.03 µg/kg	118±6	14±1.3	21±2	10.5±1.2	10±1.5
0.1 µg/kg	131±10	17±3	25±1.5	10±0.9	10±1.2
0.3 µg/kg	139±8	21±2	30±3	9.5±1.9	9±1.8

(Table 3) : Effect of injection of meloxicam in doses of 0.3 µg/kg on MAP, RBF, MBF, CBF and HBF.

Dose	Blood pressure	Renal blood flow	Mesente-ric blood flow	Carotid blood flow	Hindqua-rter blood flow
Control	118±10	12±2.1	17±2.1	9±1.1	10.5±1.3
Treated	114±14	11±1.9	15±3.5	8±1.9	9±2.1

BIOCHEMICAL STUDIES:

Biochemical studies were done to view liver function namely SGPT, SGOT, and alkaline phosphatase, renal functions namely, serum urea and creatinine.

Liver functions

In rats chronically treated with meloxicam for two weeks of intraperitoneal injection of 0.3μg/kg biochemical results revealed normal values, while those treated with ten fold the therapeutic dose (3μg/kg) showed elevated values. *(Table 4 A).*

Table (4) : Effect of chronic administration of meloxicam in the therapeutic dose (0.3μg/kg) and ten folds the therapeutic dose (3μg/kg)

Parameter	Control group	Group treated with 0.3μg/kg	Group treated with 3 μg/kg
ALP (U/L)	194 ± 59	193 ± 58	380±56*
SGOT (U/L)	170 ± 21	169 ± 15	257±61*
SGPT (U/L)	65 ± 10	72 ±10	118±13*

* significant at the level P< 0.05 compared to non treated group.

Kidney function

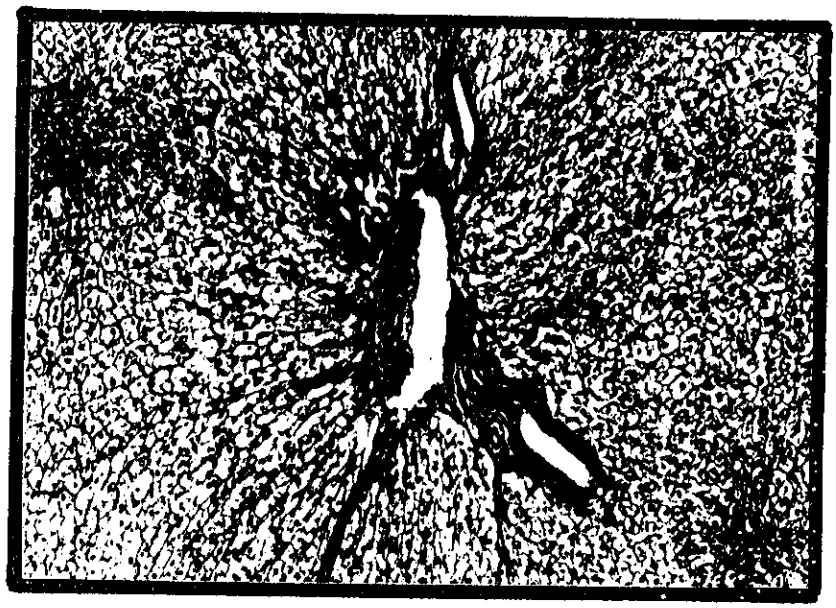
Kidney function tests (serum creatinine and blood urea) concentrations showed values within normal range in both groups treated with meloxicam in doses of 0.3 and 3µg/kg respectively **(Table 5).**

Table (5): Effect of chronic administration of meloxicam on kidney functions.

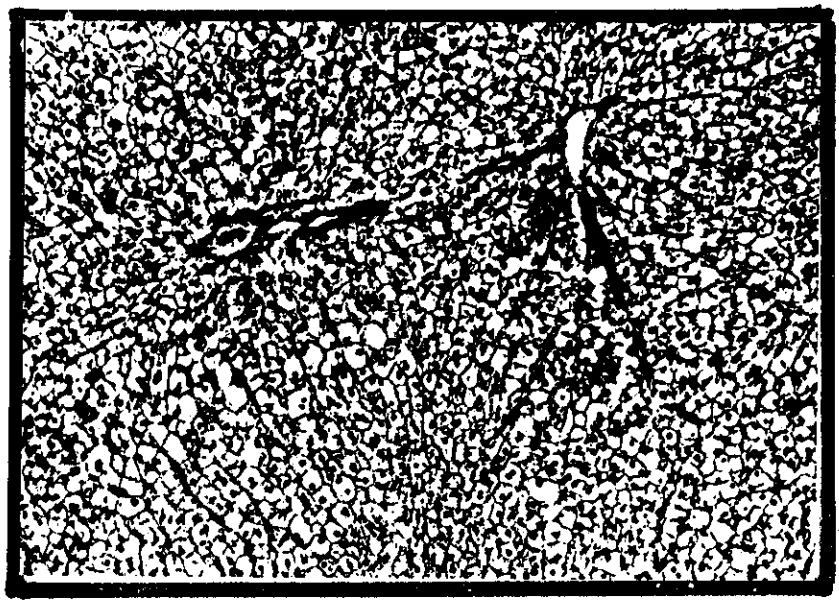
Parameter	Control group	Group treated with 0.3µg/kg	Group treated with 3µg/kg
Blood urea (mg/dl)	40 ± 9	42 ± 11	41 ± 10
Serum creatinine (mg/dl)	0.29±0.05	0.28 ± 0.07	0.30 ± 0.06

HISTOPATHOLOGICAL STUDIES:

Histopathological study of meloxicam in doses of 0.3μg/kg and 3 μg/kg (ten fold the therapeutic dose) was done on the following organs "testis, kidney, intestine, pancreas, and the spleen" showed insignificant changes. While effect of meloxicam on the hepatic tissue showed no change with treatment in the therapeutic dose ***(Figure 16 A)***.While in the dose of 3μg/kg it revealed preserved architecture, diffuse hydropic degeneration with increased binucleated hepatocytes, compressed sinusoids, focal infiltration of the portal tracts by lymphocytes and neutrophils as well as eosinophils, "spotty lobular necrosis"***(Figure 16 B)***.



(Figure 16 A)



(Figure 16 B)