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EFFECT OF MELOXICAM AND CEFOTAXIME ON FOETAL DEVELOPMENT IN RATS

BY

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ABSTRACT

This study was applied on forty female mature rats divided into four groups, to investigate the effect of meloxicam (NSAID), cefotaxime (third- generation cephalosporin) antibiotic and their combination on developing rat foeti through morphological, visceral, skeletal examinations, also the effect on oxidant and antioxidant activities in serum of mothers and amniotic fluid. The 1st group was kept as control (injected normal saline subcutaneously), while the 2nd group was injected meloxicam subcutaneously (1 mg/kg b.wt.), for three days, once daily, Meanwhile the 3rd group was injected cefotaxime Na intramuscularly (50mg/kg b.wt.), for five days, each 12 hour. The fourth group was received both the therapeutic dose of meloxicam and cefotaxime Na. The obtained results showed that, the therapeutic dose of each drug or their combination exhibited absence of any visceral or skeletal malformations. Cefotaxime revealed a slight increase in resorptions rate, a decrease in feotal body weight and crown rump length, and an increase in each of L- malondialdehyde (MDA), superoxide dismutase (SOD) and catalase levels in serum and in amniotic fluid, Whereas meloxicam and its combination with cefotaxime elicited a reduction in MDA, SOD and catalase levels than cefotaxime. We concluded that meloxicam can minimize the oxidative stress induced by cefotaxime Na.

Key words: Meloxicam / Cefotaxime Na / Genotoxicity / Teratogenicity / Oxidant anti-oxidant status.

INTRODUCTION

In recent years, there has been widespread and increasing concern that drugs, as well as environmental chemicals, may present a potential hazard to mankind by developmental malformations.

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually combined with antimicrobial agents in veterinary and human diseases to treat various infections associated with fever, pain and other inflammatory conditions **(Kumar et al., 2003).**

Meloxicam is an NSAID of the oxicam class, that acts by inhibiting prostaglandin synthesis and inducible COX-2, thereby exerting anti-inflammatory, anti-exudative, analgesic and antipyretic effects **(Hirsch et al., 2003).** Meloxicam crossed the placenta of pregnant rats and was detected in foetal tissue at levels similar to those found in the placenta **(Qstensen and Skomsvoll, 2004).**

Beta-lactams having a long history of use without significant deleterious effects on the fetuses and still are the safest choice during pregnancy. Cefotaxime is a wide-spectrum, semisynthetic, third- generation cephalosporin antibiotic (Beta-lactams). This antibiotic displays a high antimicrobial potency, high resistance against the action of beta-lactamases and lowered toxicity profile compared to other cephalosporins **(Nathwani, 2000). Fiol et al., (2005)** stated that cefotaxime can easily cross the placenta by passive diffusion reaching the fetus.

The purpose of the present study was to evaluate the effect of meloxicam, cefotaxime and their combination on developing rat foeti through morphological, visceral, skeletal examinations, Also to investigate the effect of the tested drugs; if any; on the oxidant and antioxidant activities in serum of mothers and amniotic fluid.

2. Materials and Methods

2.1. Drugs

A- Meloxicam:-Anti-Cox II (ADWIA Co. S.A.E. 10th of Ramadan City-Egypt). Each 3 ml ampoule contains the equivalent of 15 mg meloxicam. The current recommended dose for meloxicam is 1 mg/kg subcutaneously, once daily **(Roughan and Flecknell, 2003).**

B- Cefotaxime:- CEFOTAX (E.I.P.Co.) (Egyptian international Pharmaceutical industries Co. 10th of Ramadan City-Egypt). Each vial containing 500mg of cefotaxime as

cefotaxime sodium. Cefotaxime is given by intramuscular administration. The current recommended dose is 50 mg/kg, twice daily **(Kim, 1985).**

2.2. Experimental design:

The effects of meloxicam, cefotaxime and their combination on foetal development were investigated on fourty mature female albino rats, using twenty mature male albino rats for mating. Animals were kept under hygienic conditions housed in metal cages, fed on a balanced ration and watered ad-libidum. They were accommodated to the laboratory conditions for two weeks before experimentation.

Daily vaginal smears were examined and the female proved to be in oestrus was paired with a male in a separate cage. In the following morning a vaginal smear was taken to verify the first day of gestation. Presence of sperms in the obtained vaginal smear indicates zero day of gestation **(Barcellona et al., 1977).** Pregnancy was confirmed by microscopic examination of vaginal smears, presence of permanent dioestrus indicated pregnancy. Body weight was recorded and prominent increases were observed chiefly after 10 days from the expected day of pregnancy **(Cahen, 1966)**. The pregnant rats were divided into three equal groups each of 10**.**

Group I: received normal saline subcutaneously, on the 6th day of gestation as a control group.

Group II: received therapeutic dose of meloxicam (1mg/kg b.wt.) subcutaneously, on the 6th day of gestation, for three days, once daily.

Group III: received therapeutic dose of cefotaxime Na (50mg/kg b.wt.) I/M, on the 6th day of gestation for five days, each 12 hour.

Group IV: received meloxicam (1mg/kg b.wt.) subcutaneously, for 3 days, once daily and cefotaxime Na (50mg/kg b.wt.) I/M, for 5 days, each 12 hour on the 6th day of gestation.

I. Effects on developing foeti (Teratological examination):

Drugs were injected on the 6thday of gestation period during which the organs are more sensitive to the effect of the toxic substances **(Snell, 1982).** The possible effects of them on developing foeti were evaluated by **morphological, visceral** and **skeletal examination.**

On day 20 of gestation period, all pregnant females from each group were sacrificed, the uterine horns were opened and The number of implantation and resorption sites were counted as described by **Kopf and Salewski, (1964).**

The number of live and dead foeti, foetal body weight and foetal crown-rump length were recorded. The foeti were examined for any gross external malformations. Pre and post-implantation deaths were calculated according to **Hayes (1988).** Foeti preserved in Bouin's fixative were rinsed with cold water and examined grossly**.** Stained skeletons with alizarin red stain were examined by a hand lens for any abnormalities in shape or size or absence of bones**.**

II- Effects on oxidant and antioxidant activities:

A- Determination L- Malondialdehyde (MDA):

Plasma and amniotic fluid MDA were calorimetrically determined according to the method adapted by **Esterbauer et al., (1982).**

B- Determination of catalase activity :-

Plasma and amniotic fluid catalase activity were estimated according to the method described by **Sinha (1972).**

C- Determination of superoxide dismutase (SOD) activity:

Superoxide dismutase (SOD) activity in both serum and amniotic fluid were detected according to the method of **Packer and Glaezer (1990).**

Statistical analysis:

Data analyses were performed with the statistical software program **SPSS (1994).** The mean values and standard deviation for each assessed variable were calculated.

RESULTS

I- Effects on developing foeti :

The mean values of the different teratogenic variables are recorded in Table (1) and Figures (1-6). The results showed that, administration of meloxicam on the 6th day of gestation period evoked insignificant change in foetal resorption rate (0.40± 0.160 with a percent of 3.99± 1.66, while dams administrated cefotaxime Na displayed a significant

(P<0.05) increase (1.40± 0.40) with a percent of 14.45± 4.01. Dams received meloxicam/cefotaxime Na combination evoked insignificant increase in foetal resorption rate (0.60± 0.16) with a percent of 5.91 ± 1.67 versus (0.30± 0.15) with a percent of 3.02 ± 1.55 for the control group**.**

The obtained data clearly demonstrate that the administration of meloxicam, cefotaxime Na or their combination showed insignificant changes in the mean values of the viable foeti which were (8.50± 0.56) with a percent of 98.75± 1.25, (8.20± 0.51) with a percent of 97.84± 1.46 and (8.90± 0.55) with a percent of 98.75± 1.25 respectively versus (9.80± 0.39) with a percent of 99.09± 0.91 for the control group.

Dams received each of meloxicam, cefotaxime Na or their combination evoked insignificant changes in the mean values of the dead foeti (0.10 ± 0.10) with a percent of 1.25± 1.25, (0.20± 0.13) with a percent of 2.16± 1.46 and (0.10± 0.10) with a percent of 1.25± 1.25 respectively in comparison with the control group (0.10± 0.10) with a percent of 0.91± 0.91.

Administration of the therapeutic dose of meloxicam displayed insignificant changes (0.04± 0.02) in the mean values of pre-implantation death. Dams received cefotaxime Na elicited a significant (P<0.05) increase (0.14± 0.04), while Dams received drugs combination provoked slight significant (P<0.05) increase (0.07 ±0.04) in the mean values of pre-implantation death compared with the control group (0.03± 0.02).

The results also showed that dams given meloxicam, cefotaxime Na and their combination elicited insignificant changes in the mean values of the post-implantation death compared with the control group.

I.A- Morphological examination:

The obtained data clearly demonstrated that both meloxicam and the combination of meloxicam and cefotaxime Na induced insignificant changes in the mean values of the body weight of the obtained foeti (5.20±0.11 and 5.18± 0.10 respectively), While cefotaxime Na induced a significant (P<0.05) decrease in the mean values of the body weight of the obtained foeti, which was (4.84± 0.04) versus, 5.30± 0.14 for the control group **(Table 1 and Figure 2).**

Administration of meloxicam and the meloxicam with cefotaxime Na evoked insignificant changes in the mean values of the foetal crown-rump length of the obtained foeti

(4.16± 0.06 and 4.14± 0.01 respectively), while cefotaxime Na evoked a highly significant ($P < 0.01$) decrease in the mean values of the foetal crown-rump lenght of the obtained foeti (4.05± 0.02) versus the mean value 4.20 ± 0.03 of the control group foeti **(Table 1 and Figure 2).**

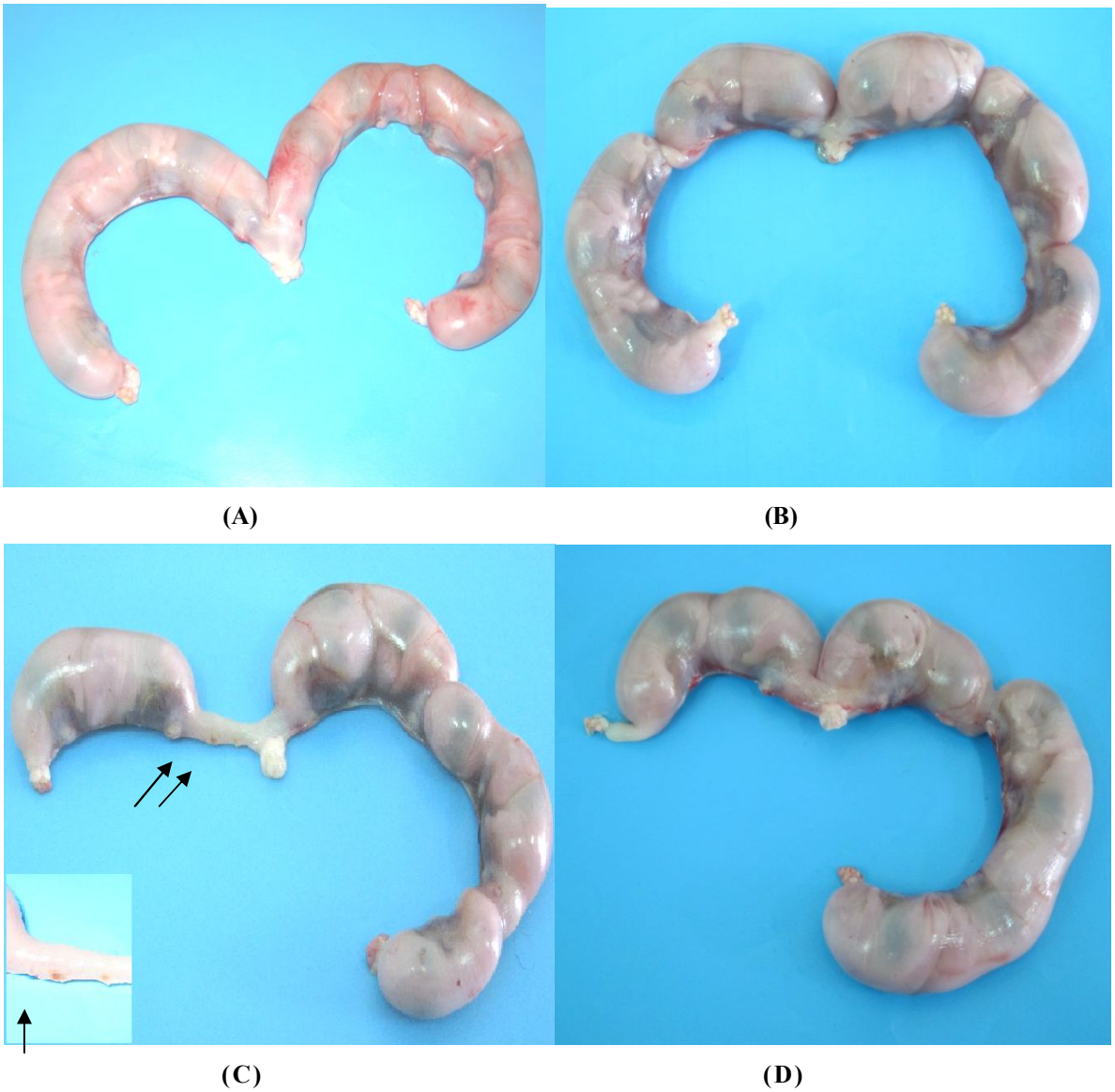


Fig. (1): A) Uterus of a pregnant rat (control), note the complete number of foeti that are normal in size. **B)** Uterus of a pregnant rat given meloxicam (1mg/kg b.wt) subcutaneously, exhibiting normal size of foeti that are complete in number. **C)**Uterus of a pregnant rat administered cefotaxime Na (50mg/kg b.wt.) I/M, exhibiting early foetal resorptions. **D)** Uterus of a pregnant rat received each of meloxicam (1mg/kg b.wt.) subcutaneously, and cefotaxime Na (50mg/kg b.wt.) I/M, evoked normal size of foeti that are complete in number.

Table (1): Morphological changes and mortality rate in foeti from dam rats administered therapeutic regimen of meloxicam (1mg/kg b.wt) subcutaneously, once daily for three days, cefotaxime Na (50mg/kg b.wt) I/M, each 12 hour. for five days, and their combination on the 6th day of pregnancy.

(Mean ± S.E) n=10

Group	No. of corpora lutea	No. of implantation sites	Viable feoti		Dead foeti		Resorbed foeti		Foetal b.wt. (gm)	Foetal length (cm)	Death	
			Mean ± S.E	%	Mean ± S.E	%	Mean ± S.E	%			Pre-implantation	Post-implantation
(G1) Control group injected with normal saline	10.2^{a}± 0.36	9.90^{a}± 0.41	9.80^{a}± 0.39	99.09± 0.91	0.10^{a}± 0.10	0.91± 0.91	0.30^{b}± 0.15	3.02^{b} ± 1.55	5.30^{a}± 0.14	4.20^{a}± 0.03	0.03^{b}± 0.02	0.01^{a}± 0.01
(G2) Group injected with meloxicam (1mg/kg b.wt)	9.4^{a}± 0.58	9.0^{a}± 0.54	8.50^{a}± 0.56	98.75± 1.25	0.10^{a}± 0.10	1.25± 1.25	0.40^{b}± 0.16	3.99^{b} ± 1.66	5.20^{a}± 0.11	4.16^{a}± 0.06	0.04^{b}± 0.02	0.01^{a}± 0.01
(G3) Group injected with cefotaxime Na (50mg/kg b.wt)	9.6^{a}± 0.39	8.40^{a}± 0.54	8.20^{a}± 0.51	97.84± 1.46	0.20^{a}± 0.13	2.16± 1.46	1.40^{a}± 0.40	14.45^{a} ± 4.01	4.84^{b}± 0.04	4.05^{b}± 0.02	0.14^{a}± 0.04	0.02^{a}± 0.01
(G4) Group injected with meloxicam(1mg/kg b.wt) and cefotaxime Na(50mg/kg b.wt)	9.5^{a}± 0.64	9.0^{a}± 0.52	8.90^{a}± 0.55	98.75± 1.25	0.10^{a}± 0.10	1.25± 1.25	0.60^{b}± 0.16	5.91^{b} ± 1.67	5.18^{a}± 0.10	4.14^{a}± 0.01	0.07^{ab}± 0.04	0.01^{a}± 0.01

The different letters in the same columns means significant at (p □ 0.05).

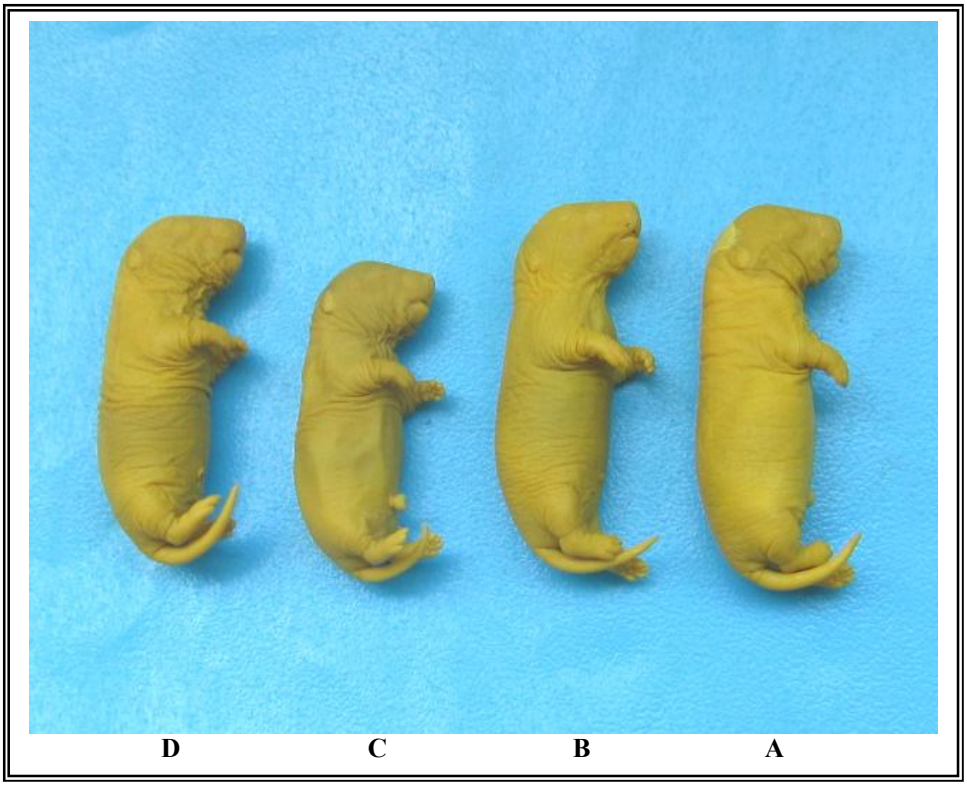


Fig.(2): (A) Rat foeti from dams received normal saline subcutaneously, as a control group. **(B)** Rat foeti from dams injected (s.c) with meloxicam (1mg/kg b.wt)**. (C)** Rat foeti from dams injected (I.M). with cefotaxime Na (50mg/kg b.wt.) : notice the decrease in the foetal size in group compared with (A), (B) and (D) **(D)** Rat foeti from dams received both meloxicam and cefotaxime Na: notice the decrease in the foetal size in group **(C)** compared with a foetus from control dams.

I.B- Visceral examination:-

Foeti obtained from the treated and control groups (which kept in Bouin's solution) were macroscopically examined by the aid of a magnifying hand lens.

The obtained results are revealed that injection with meloxicam (1mg/kg b.wt.) subcutaneously, and cefotaxime Na (50mg/kg b.wt.) I/M, or their combination to pregnant rats on the 6^{th} day of gestation period evoked no visceral malformations as in control group **(Figures 3-6).**

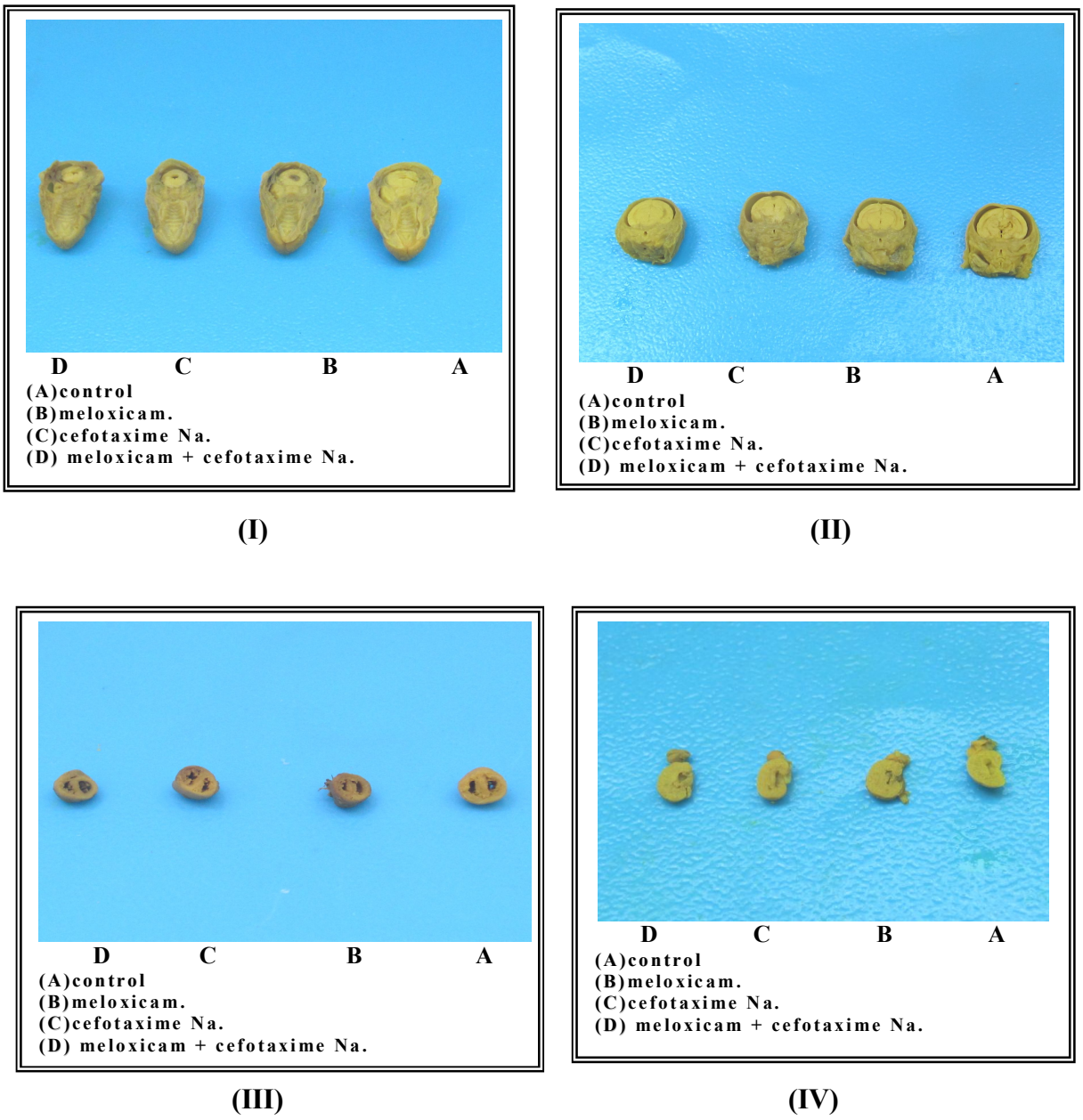
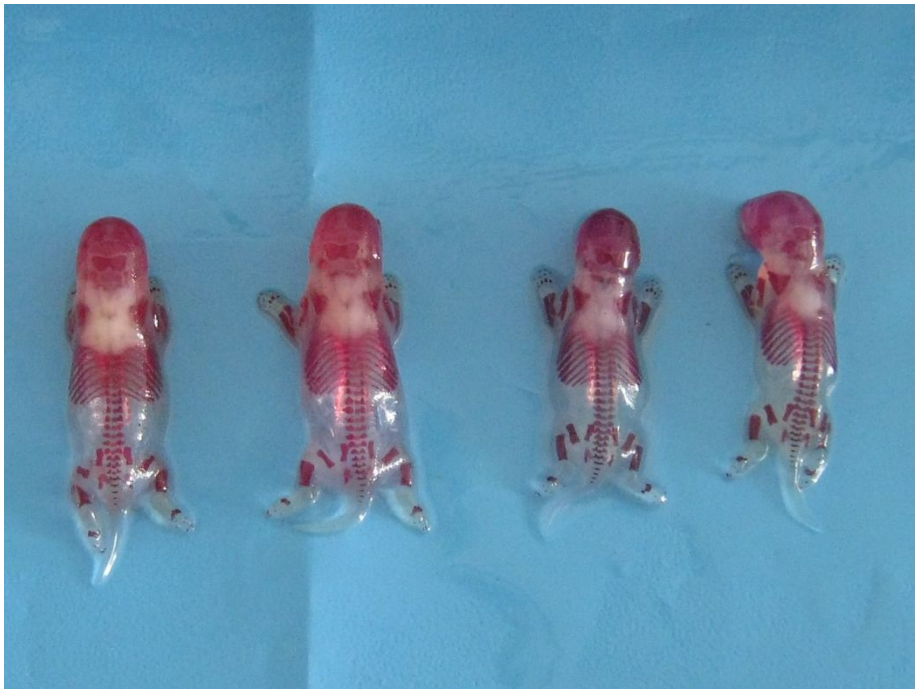


Fig. (3): **(I)** Saggital section in the head of rat foeti from treated dams groups **(B-C-D)** showing absence of any malformations compared with a foetus from control dams **(A). (II)** Cross section in the head of rat foeti from treated dams groups **(B-C-D)** showing absence of any malformations in the brain compared with a foetus from control dams **(A). (III)**Cross section in the heart ventricles of rat foeti from treated dams groups **(B-C-D)** disclosing absence of any thickening in the ventricular wall of the heart compared with the heart ventricles of rat foeti from control dams **(A). (IV)** Cross section in the kidney of rat foeti from treated dams groups **(B-C-D)** showing absence of any widening of the renal pelvis, compared with a kidney of the rat foeti from control dams **(A).**

I.C- Skeletal examination:-

Alizarin red stained skeletons of rat foeti obtained from both treated and control dams were macroscopically examined by the naked eye and a magnifying hand lens for detecting the possible skeletal malformations.

Under the influence of the drug injection with meloxicam (1mg/kg b.wt.) subcutaneously, and cefotaxime Na (50mg/kg b.wt.) I/M, or combination of both drugs to pregnant rats on the 6th day of gestation period there were no skeletal malformations as the observed in control group **(figure 4).**



A **B** **C** **D**

Fig. (4): (B) Rat foeti from dams injected with meloxicam (1mg/kg b.wt.) subcutaneously**,(C)**Rat foeti from dams injected with cefotaxime Na (50mg/kg b.wt.) I/M**, (D)**Rat foeti from dams received both the therapeutic dose of meloxicam and cefotaxime Na : notice that all foeti showing normal complete skeleton as a foetus from control dams **(A).**

III- Effects of drugs on oxidant and antioxidant activities:

(A) In the serum:-

Data presented in Table (2) depict the effects of the therapeutic regimen of meloxicam (1mg/kg b.wt subcutaneously, once daily for three days), cefotaxime Na (50mg/kg b.wt I/M, each 12 hour. for five days), and their combination on the 6th day of pregnancy on the serum L- Malondialdehyde (MDA) level, superoxide dismutase (SOD) and catalase activity.

1- L- Malondialdehyde (MDA) level:-

Administration of the therapeutic regimen of meloxicam, cefotaxime Na and their combination induced significant increase in the serum MDAlevel which were (12.37± 0.000, 17.86± 0.76 and 14.24± 0.08) respectively, compared with the level reached in serum of for the control group (9.515± 1.178).

2- Superoxide dismutase (SOD) level:

Pregnant rats administered meloxicam, cefotaxime Na, and their combination evoked a significant increase in the levels of serum superoxide dismutase (0.70± 0.02,0.99± 0.079and 0.75± 0.026 respectively), compared with the level reached in the control group (0.498± 0.01).

3- Catalase level :-

Pregnant rats given meloxicam revealed insignificant change in serum catalase activity, (1.18± 0.052), but dams received cefotaxime Na and their combination with meloxicam displayed a significant increase in the serum catalase activity (2.09± 0.21 and 1.95± 0.295 respectively), compared with the level reached in the control group (0.97± 0.19).

(B) In the amniotic fluid:-

Effects of the therapeutic regimen of meloxicam (1mg/kg b.wt subcutaneously, once daily for three days), cefotaxime Na (50mg/kg b.wt I/M, each 12 hour for five days), and their combination on the 6th day of pregnancy on the levels of L- malondialdehyde (MDA), superoxide dismutase (SOD) and catalase in amniotic fluid were recorded in **Table (3)**.

1- L- Malondialdehyde (MDA) level:-

Dams administered meloxicam, cefotaxime Na and their combination induced a significant increase in amniotic fluid MDA levels (4.78± 0.95, 6.46± 0.178 and 5.63± 0.51

respectively), compared with the level recorded in amniotic fluid of the control group (2.96± 0.32).

2- Superoxide dismutase (SOD) level:

Dams given meloxicam displayed insignificant change in amniotic fluid SOD level which were (0.28± 0.11) compared with (0.25± 0.06) in amniotic fluid of control group.

The levels of superoxide dismutase (SOD) in amniotic fluid of pregnant rats received cefotaxime Na and combination of meloxicam with cefotaxime Na were significantly increased (0.65± 0.017 and 0.54± 0.02 respectively), compared with that obtained in amniotic fluid of control group (0.25± 0.06).

3- Catalase level :-

Administration of meloxicam, and combination of meloxicam and cefotaxime Na induced insignificant increase in amniotic fluid catalase levels (4.42± 0.42 and 4.53± 1.08 respectively), while dams injected with cefotaxime Na displayed a significant increase in amniotic fluid catalase level (10.89± 0.50) compared with the control group (2.49± 0.27).

Table (2): The response of oxidant and antioxidant activities in serum of dams received meloxicam (1mg/kg b.wt subcutaneously , once daily for three days), cefotaxime Na (50mg/kg b.wt I/M, each 12 hour for five days), and combination of both drugs on the 6th day of pregnancy.

(Mean ± S.E) n=10

Group	L-Malondialdehyde (MDA)	superoxide dismutase (SOD)	catalase
(G1) Control group injected with normal saline	9.515^{c} ± 1.178	0.498^{c} ± 0.010	0.965^{b} ± 0.194
(G2) Group injected with meloxicam (1mg/kg b.wt)	12.370^{b} ± 0.000	0.703^{b} ± 0.023	1.183^{b} ± 0.052
(G3) Group injected with cefotaxime Na (50mg/kg b.wt)	17.863^{a} ± 0.761	0.990^{a} ± 0.079	2.090^{a} ± 0.212
(G4) Group injected with meloxicam(1mg/kg b.wt) and cefotaxime Na(50mg/kg b.wt)	14.238^{b} ± 0.083	0.745^{b} ± 0.026	1.950^{a} ± 0.295

Table (3): The response of oxidant and antioxidant activities in the amniotic fluid to the therapeutic regimen of meloxicam (1mg/kg b.wt subcutaneously , once daily for three days), cefotaxime Na (50mg/kg b.wt I/M, each 12 hour for five days), and combination of both drugs on the 6th day of pregnancy.

(Mean ± S.E) n=10

Group	L-Malondialdehyde (MDA)	superoxide dismutase (SOD)	catalase
(G1) Control group injected with normal saline	2.963^{b} ± 0.319	0.250^{b} ± 0.061	2.488^{b} ± 0.272
(G2) Group injected meloxicam (1mg/kg b.wt)	4.775^{a} ± 0.951	0.283^{b} ± 0.110	4.423^{b} ± 0.418
(G3) Group injected with cefotaxime Na (50mg/kg b.wt)	6.463^{a} ± 0.178	0.650^{a} ± 0.017	10.888^{a} ± 0.504
(G4) Group injected with meloxicam(1mg/kg b.wt) and cefotaxime Na(50mg/kg b.wt)	5.628^{a} ± 0.513	0.538^{a} ± 0.022	4.525^{b} ± 1.083

The different letters in the same columns means significant at (p ≤ 0.05).

DISCUSSION

Infections are common during pregnancy, and like anybody else, pregnant animal are susceptible to infections. Virtually all antibiotics cross the placenta and thus have the potential to affect the fetus adversely **(Dasheand Gilstrap, 1997).**

Cefotaxime is a third-generation cephalosporin antimicrobial agent (Beta-lactams) indicated for the treatment of many serious infectious diseases. Despite its extensive use, it remains a viable option because many micro-organisms remain susceptible to its antimicrobial activity**(Patel et al., 1995).**

Non-steroidal anti-inflammatory drugs (NSAIDs) as meloxicam are usually combined with antimicrobial agents in veterinary and human diseases to treat various infections associated with fever, pain and other inflammatory conditions **(Kumar et al., 2003).**

Briggs et al. (2001) showed that all drugs with a molecular weight less than 1000 daltons cross the placenta and those less than 600 crossing easily. **Friton et al. (2003)** demonstrated that meloxicam has molecular weight about 351 and can cross the placenta of pregnant rats, Moreover, **Fiol et al. (2005)** stated that cefotaxime can easily cross the placenta by passive diffusion reaching the fetus due to its molecular weight is about 477.

Strikingly enough, the obtained finding evinced no visceral or skeletal malformations in response to administration of either meloxicam, cefotaxime Na or their combination during early organogenesis. Assuredly, this data lend credence to those recorded by **Lehmann et al. (1996).** The authors illustrated that there was no evidence of mutagenic, clastogenic, teratogenic or tumorigenic activity on immunogenic potential in rats injected with the therapeutic dose of meloxicam.

Smilarly, cefotaxime has been reported to produce detectable concentrations in cord blood, amniotic fluid, and fetal blood, however the product information of the drug states that no evidence of fetal harm occurred in mice or rats **(Schwarz, 1981; Cho et al., 1982 and Fiol et al., 2005).**

In the present work, it has been recorded that the intramuscular administration of therapeutic dose of cefotaxime Na in pregnant rats on the 6^{th} day of pregnancy evoked a significant increase in foetal resorption rates and significant decrease in foetal body weight and lenght. Attractive clues for foetal resorption were provided by **Persaud &Henderson (1969) and Haschek & Rousseausc (1993).** The authors reported that during the first twelve

days of embryonic development, certain teratogenes may kill the embryo by damaging all or most of its cells by preventing implantation of the blastocyst or by producing several chromosomal changes and consequently its resorption.

In the same boat, it has been demonstrated that the therapeutic regimen of cefotaxime Na during early organogenesis induced significant increase in malondialdehyde (MDA) level in the serum and in the amniotic fluid of pregnant dams.

In this context, it is trustworthy to mention that lipid peroxidation is a chain reaction providing a continuous supply of free radicals as it involves the oxidation of polyunsaturated fatty acids in membranes causing oxidative cell damage. L- malondialdehyde (MDA) is formed as an end product of lipid peroxidation and acts as an indicator of it **(Devi et al., 2000).**

Of particular significance to this study, is the issue that lipopolysaccharide (LPS) has been associated with adverse developmental outcome, including embryonic resorption, intrauterine fetal death (IUFD), intra-uterine growth retardation (IUGR), and preterm delivery. Reactive oxygen species (ROS) **(Xu et al., 2005).**

In the glow of the previous notion, we are led to believe that both foetalresorptions and the decreased foetal body weight and length seen with cefotaxime could be a straightforward sequel to the increasing of L- Malondialdehyde (MDA) level reported in the current work which has been associated with LPS-induced developmental toxicity.

In the current work, it has been amply demonstrated that cefotaxime administered in therapeutic regimen during early organogenesis provoked a significant increase in superoxide dismutase (SOD) and catalase levels in serum of pregnant dams and in the amniotic fluid compared with other groups.

It has been stated that free radicals like superoxide anion are highly reactive and can cause both morphological and functional damage in the cell. The cells protect themselves against oxidative damage by enzymatic and non-enzymatic antioxidant system **(Deaciuc et al., 1999).**

Superoxide dismutase is the primary enzymatic antioxidant defense system in the cell. This scavenging enzyme plays an important role in protection of the cell against the potentially harmful effects of superoxide anion generated by a wide variety of biological processes **(Bhuvarahamurthy et al., 1996).**

Enzyme catalase seems to be the main regulator of hydrogen peroxide metabolism. Hydrogen peroxide at high concentrations is a toxic agent, while at low concentrations, it appears to modulate some physiological processes such as signaling in cell proliferation, apoptosis, carbohydrate metabolism, and platelet activation **(Góth et al., (2004).**

In a similar vein, **Fang (2002)** stressed that there is a dynamic balance between the amount of free radicals produced and the antioxidants to eliminate them from the body. The antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidases) act synergistically in scavenging free radicals.

Stemmed from the previous conceit that the elevation of superoxide dismutase (SOD) and catalase levels in serum and amniotic fluid in pregnant dams received cefotaxime corresponding to the significant increase of L- Malondialdehyde (MDA) level.

The recorded findings in this study revealed that, the administration of therapeutic regimen of meloxicam elicited to pregnant dams lowering in MDA and SOD levels than the levels recorded in cefotaxime administered group. In addition, it evoked a slight insignificant change in catalase level in serum and amniotic fluid of treated dams.

Without doubt, the previous results are in complete harmony with those reported by **Neve et al. (2001)** who stated that NSAIDs may play a role in the oxygen radicals scavenging and formation of less harmless molecules and consequently, some NSAIDs have been tested as potential free radical scavengers. Their capacity for preventing oxidative damage in vivo has also been comparatively determined.

In this frame of reference, it has been affirmed that recent drugs such as several compounds belonging to the oxicam family (tenoxicam, lornoxicam, piroxicam and meloxicam) were tested for interacting with the main reactive oxygen species **(Neve et al., 2001).**

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المخلص العربى

تأثير الميلوكسيكام والسيفوتاكسيم على التطور الجنيني في الفئران

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من المعروف انه في الغالب ما يتم الجمع بين الأدوية المضادة للالتهابات غير الستيرويدية (المسكنات) مع المضادات الحيوية لعلاج مختلف الأمراض المرتبطة الحمى والألم و حالات الالتهابات الأخرى. لذا كان الهدف من هذه الدراسة مقارنة آثار الميلوكسيكام (كمضاد الألتهابات) والسيفوتاكسيم (مضاد حيوى من الجيل الثالث من عائلة السيفالوسبورين) ومزيج من الاثنين معا على التطور الجنيني للفئران من خلال دراسة التشوهات الجنينية ، و فحص الأعضاء الداخلية والهياكل العظمية للأجنة، و أيضا دراسة تأثير هذه الأدوية على العوامل المؤكسدة ومضادات الأكسدة في مصل الأم و السائل الذي يحيط بالجنين. أجريت هذه الدراسة على عدد أربعين من الفئران الإناث ناضجة مقسمة إلى أربع مجموعات كلا منها يضم عشر فئران.

المجموعة الأولى: كمجموعة ضابطة (تم حقنها بمحلول ملحي عادي تحت الجلد) .

المجموعة الثانية : حقنت بالجرعة العلاجية للميلوكسيكام تحت الجلد (١ ملغ / كغ) ، لمدة ثلاثة أيام ، مرة واحدة يوميا.

المجموعة الثالثة: حقنت بالجرعة العلاجية للسيفوتاكسيم في العضل(٥٠ملغ / كغ) ، لمدة خمسة أيام كل ١٢ ساعة.

المجموعة الرابعة : تم حقنها بمزيج من الجرعة العلاجية لكل من الميلوكسيكام و السيفوتاكسيم .

وقد أظهرت النتائج أن الجرعة العلاجية من الميلوكسيكام أو السيفوتاكسيم أو حقن كلاهما معا أدى إلى عدم وجود أي تشوهات جنينية سواء في الأعضاء الداخلية أو الهياكل العظمية للأجنة. وكشفت الدراسة عن وجود زيادة طفيفة في معدل ارتشاف الأجنة في المجموعة التي حقنت بعقار السيفوتاكسيم مع وجود انخفاض بسيط في وزن وطول الأجنة ، بالإضافة إلى زيادة في معدل المالنداهايد وإنزيم سوبر أكسيد ديسموتاز وإنزيم الكاتلاز في مصل الدم و السائل الذي يحيط بالجنين مقارنة بالمجموعات الأخرى. بينما وجد أن الميلوكسيكام قد قلل معدل هذه الأنزيمات عندما حقن مع السيفوتاكسيم.

نستخلص من هذه الدراسة أن استخدام الجرعة العلاجية لكل من الميلوكسيكام أو السيفوتاكسيم يعتبر آمن في مرحلة تخليق الأعضاء، كما أن الميلوكسيكام يحد من الإجهاد التأكسدي الناجم عن السيفوتاكسيم .