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DETERMENTAL EFFECTS OF FLUNIXIN MEGLUMINE ON THE RAT FOETAL DEVELOPEMENT

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ABSTRACT

In pregnant female rat, the cyclooxygenase inhibitor; flunixin meglumine administered intramuscularly in the therapeutic dose and its two fold evoked red patches on different parts of the body . The most frequently observed internal malformations in response to flunixin meglumine injection (0.4 mg/kg B.wt.) were dilated brain ventricles, thickning of the ventricular wall of the heart and dilatation of the renal pelvis . Flunixin meglumine injection at a dose of 0.8 mg/kg B.wt. evoked dilatd brain ventricles, cerebral, intrathoracic and abdominal haemorrhages, marked thickning of ventricular wall of the heart and dilatation of renal pelvis. Skeletal malformation or response to both doses of the drug were absence of last caudal vertebrae, pronounced rudimentary or missing sternebrae and xiphisternam and absence of phalanges of both fore and hined limbs .

INTRODUCTION

Flunixin meglumine is a potent non narcotic analgesic, belonging to the non steroidal antiprostaglandin with anti-inflammatory and antipyretic activities [1,2]. Premature closure of ductus arterious secondary to administration of salicylates to dams is well documented [3]. Mofezolac, new NSAID, elicits a significantly decrease faeti weight, increased number of immature foeti and a significant retarded assification of sternbare and coccygeal vertebrate [4].

The present study was designed to delve into the possible detetrious effects of cyclo oxygenase inhilbitor, flunixin meglumine on the foetal developement, eventually to question the validity of its prolonged administration in pregnant females .

MATERIAL AND METHODS

Drug :

Flunixin meglumine (Finadyne Shering . Co., USA) . The effect of flunixin meglumine on foetal developement during the organogenesis period (from the 6th through the 15 day of gestation) was investigated on three equal groups of mature female albino rats, each of 10 animals .

The first group was intramuscularly injected , once a day, with therapeutic dose of the drug; 0.4 mg/kg body weight [therapeutic dose in rabbits converted to rat dose according to surface area [5,6]].

The second group was i.m. injected once a day, with the drug in double therapeutic dose. The third group was left as control . The female rats were daily examined using vaginal smear method to ensure regular oestrus cycle[7].

Every two females were placed with a male in a separate cage, in the following mornings , a vaginal smear was taken to verify the first day of gestation Pregnancy was confirmed by the persistance of diestrus state for 5 days after mating and palpable fetal masses in the abdomen on the 5th day of gestation, [7].

On the 20th day of gestation, the females were anaesthetized by ACE mixture and a caeserian section was performed to determine the effect of the drug on foetal development. The method used for morphological examination was performed [8] .

Two thirds of the foeti obtained from each female were kept in Bouin' Solution for one week to examine visceral abnormalitis [8] . The last third was eviscerated and kept in 95% ethanol for detection of skeletal malformation [9] .

Statistical analysis was performed according to standard method [10]. The different variables were analyzed using Student's (T) test .

RESULTS

The obtained data clearly demonstrated that flunixin meglumine evoked no foetal death and insignificant increase in foetal resorption rate (7.54 and 10% for 0.4 and 0.8 mg/kg B.wt . respectivity), Table (1) .

Morphological examination :-

Flunixin meglumine did not evoke any significant reduction in both foetal body weight and length . Red patches were externally seen on different parts of the body (16.43% and 55.5% of the foeti from mothers treated with flunixin meglumine, 0.4 and 0.8 mg/kg B.wt. respectivily), Fig. (3 & 4) .

Visceral examination :

The pregnant dames injected with 0.4 and 0.8 mg flunixin meglumine / kg B. wt., displayed the following percentage of visceral abnormalities in their foeti, Brain 48.15 and 62.5%, Heart 46.30 and 54.16% and kidney 37.03 and 43.75% respectivily.

Detailed examination of the pervious visceral abnormalities revealed dilated brain ventricles (Fig. 5& 6), echomosis of blood arround the brain and ventricles (Fig., 7), thickening of the ventriculer wall of the heart (Fig. 8 & 9), dilatation of renal pelvis of the kidney (Fig., 10 & 11) and intrathoracic and abdominal haemorrhages .

Skeletal examinations :

It is found that flunixin meglumine administered to pregnant rats at doses of 0.4 and 0.8 mg /kg. B.wt. resulted is abnormalities of vertebral column in 75 and 83.3% of examined foeti, ribs in 7.14 and 12.5%, sternebrae in 64.3 and 75% , fore limbs 32.1 and 41.6% and hined limb in 67.8 and 75% respectivily .

Detailed examination of the pervious visceral abnormalities revealed dilated brain ventricles (Fig. 5& 6), echomosis of blood arround the brain and ventricles (Fig., 7), thickening of the ventriculer wall of the heart (Fig. 8 & 9), dilatation of renal pelvis of the kidney (Fig., 10 & 11) and intrathoracic and abdominal haemorrhages .

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Detailed examination of previous skeletal abnormalities revealed absence of the last coccygeal vertebrae, shortening of the Last ribs, hypoplasia or missing of both sternebrae and xiphisternum and absence phalanges in both limbs . (Table 3 and Figs 12,13,14) .

DISCUSSION

In the present study, it has been shown that, in pregnant female rats the intramuscular administration of both therapeutic and two fold doses evoked multiple difference subcutaneous haomorrhages, which were mirrored as red patches that came in different shapes and distribution all over the bodies of the foeti .

It is documented that cyclooxygenase inhibitors including flunixin meglumine, aspirin and phenylbutazone, do inhibit serum thromboxane, which causes platelet aggregation and vasoconstriction, thus having a major impact on platelet aggregation and haemostasis [11]. On similar ground, cyclooxygenase inhibitors, reduce plasma prothrombin level and prolong bleeding time [12-14] .

Interestingly enough, intramuscular administration of flunixin meglumine into female rats induced a marked thickening of the ventricular wall of the heart . This effect is mediated by decreasing the circulatory and intramuscular produced levels of prostaglandins [15].

Therefore, placental transfer to prostaglandin synthetase inhibitors may block foetal prostaglandin synthetase and decrease foetal prostaglandin necessary to keep vascular smooth muscle relaxed and the ductus arteriouses patent [16]. Because the ductus is the a major channel through which about 90% of the right ventricular output flows to the descending aorta in the foetus [17], foetal ductal constriction causes increased pulmonary arterial and right ventricular pressure and increased right ventricular after load . Because foetal cardiac reserve is very limited [18,19], increase of after load causes decreased output, increased right ventricular diastolic and right arterial pressures and increased right ventricular volume [20].

Because of free communication through the foramen ovale cordis more blood flows to the left atrium and left ventricle, causing dilation of left ventricle. However, adequate compensatory increase in left ventricular output is not achieved and signs of congestive cardiac failure such as pericardial effusion appeared[21]. The right and left ventricles showed concentric hypertrophy with diminshed cavities [22]. Given this tapestry it is most likely that the reported marked thickening of the ventricular wall could be viewed as a straight forward sequel of a constricted ductus arteriosus .

Our findings did clearly demonstrat a marked dilatation of renal pelvis in response to intramuscular administration of both doses of flunix in meglumine. Our results are in harmony with that previously reported [23]. The authors documented that the therapeutic dose of salicylate given on both the 11th and 12th day of gestation has produced a high incidence of dilated pelvis is the term rat foeti .

PGE_2 is synthesized within the kidney by vascular smooth muscle compartment, small quantities of PG cause renal vasodilatation and can increase salt and water excretion independently on blood flow changes [24,25] This vasodilating action of rend PGE cauld be important as a local regular in minimizing renal ischemia. [26] demonstrated a significant decrease in renal blood flow induced by indomethacin induced inhibition of prostaglandin synthetase. It was previously [27] reported that a decreased glomerular filtration rate, renal blood flow, and PGE in indomethacin treated rabbits has been noticed. These findings were accoupamied by periglomerular inflammation and fibrosis .

In the light of the pervious notion, it is intriguing to_surmise that the reported dilated fetal renal pelvis is highly attributed to inflammation and fibrosis encountered in the renal cortex curiously enough, the intramuscular administration of flunixin meglumine induced a marked dilation of brain ventricles .

The present finding echoed the fact that salicylate could produce deformity in the foeti affecting chiefly the area of the central nervous system, [28] It seems that possible alterations in the maternal vascular functions especially those in the placenta, affected by cyclooxygenase inhibitors, could lead non specifically to the reported CNS deformities [29] .

Intramuscular administration of flunixin meglumine into dams resulted in rudimentary or absent sternbrae and coccygeal vertebrae and incomplete ossification of phalanges . Nearly similar findings have been demonstrated with the cyclooxygenase inhibitors, given during the period of organogenesis in pregnant rats

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Table (1) Morphological changes in faeti from Dam rats intramuscularly injected with flunixin meglumine (F.M.) 0.4 and 0.8 mg/kg B. wt. given once a day from the 6th through 15th day of gestation . mean ± S.E. (n =10).

Drug	Dose mg/kg B.wt.	Number /Mother								Foetal B.wt. (g)	Foetal length (cm)	Pre.-implantation death	Post implantation death
		Corpus luteum	Implantation sites	Viable foeti		Dead foeti		Resorbed foeti					
				Mean	%	Mean	%	Mean	%				
Control	0	10.8 ± 0.21	10.0 ± 0.25	9.6± 0.50	96	0	0	0.40± 0.10	4	4.0± 0.35	3.9± 0.24	1.08± 0.03	4.0 ± 1.26
F.M.	0.4	10.8 ± 0.32	8.8 ± 0.34*	8.2 ± 0.53	93.18	0	0	0.60± 0.16	6.82	3.43± 0.12	3.1± 0.03	1.23± 0.02	6.80 ± 1.3
F.M.	0.8	9.6 ± 3.16	8.2 ± 0.65	7.2± 0.89**	88.8	0.10± 0.1	1.23	0.1± 0.29	10	3.32± 0.11	3.21± 0.05	1.17± 0.03**	12.2 ± 1.43

* Significant at P < 0.01 ** Significant at P < 0.001

Table (2) Visceral malformations in faeti from mother rats intramuscularly injected with flunixin meglumine (F.M.) 0.4 and 0.8 mg/kg B. wt. given once a day from the 6th through 15th day of gestation . mean ± S.E. (n =10).

Drug	Dose mg/kg B.wt.	Number of examined faeti	Malformations																	
			Palate		Eye		Brain		Thumus		Heart		Lung		Liver		Kidney		Intestine	
			No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Control	0	46	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0
F.M.	0.4	54	-	0	-	0	26	48.2	-	0	25	46.3	-	0	-	0	20	37.3	-	0
F.M.	0.8	48	-	0	-	0	30	62.5	-	0	26	54.2	-	0	-	0	21	42.8	-	0

Table (3) Skeletal malformations in faeti from mother rats intramuscularly injected with flunixin meglumine 0.4 and 0.8 mg/kg B.wt. given once a day from the 6th through 15th day of gestation .

Drug	Dose mg/kg B.wt.	Number of examined faeti	Malformations															
			Skull		Vert. column		Scapula		Ribs		Sternebrae		Fore limb		Pelvic girdle		Hind limb	
			No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Control	0	23	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0
F.M.	0.4	28	-	0	21	75	-	0	2	7.12	18	64.3	9	32.1	-	0	19	67.8
F.M.	0.8	24	-	0	20	83.3	-	0	3	12.5	18	75	10	41.6	-	0	18	75

Fig. (1): Pregnant female rat administered Flunixin meglumine 0.4 mg/kg B.wt 6th day through the 15th displaying one late foetal resorption.

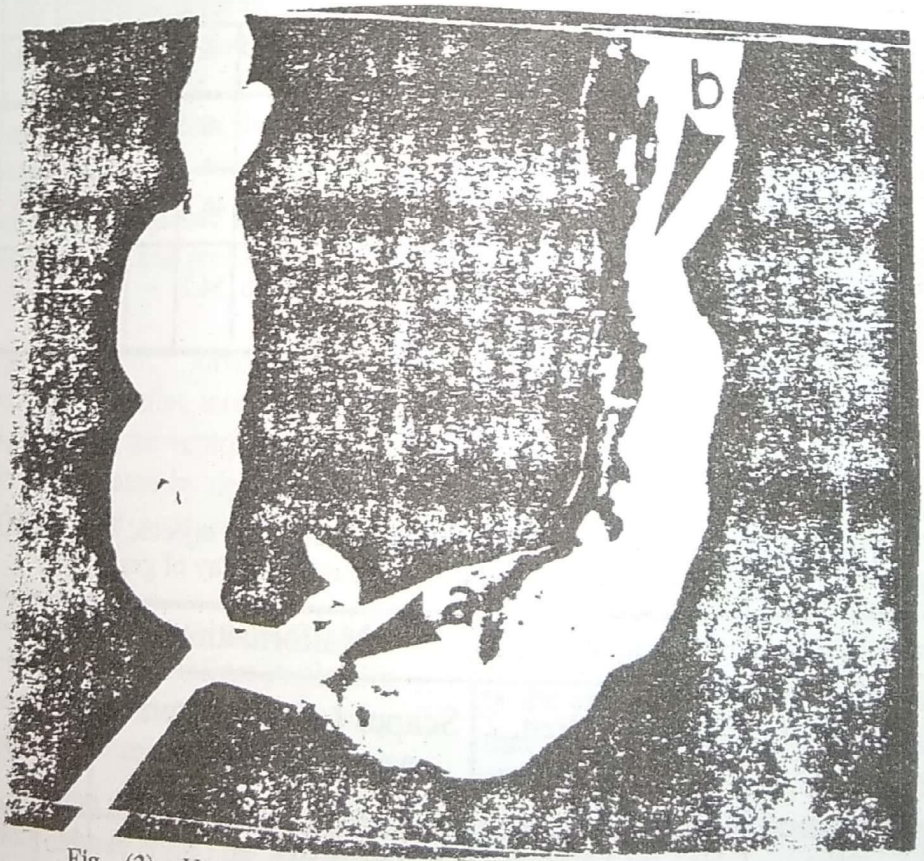

Fig. (2): Uterus of pregnant female rat intramuscularly administered Flunixin meglumine, 0.8 mg/kg B.wt. from 6th day through the 15th day of gestation demonstrating one early (A) and one late (B) foetal resorption .

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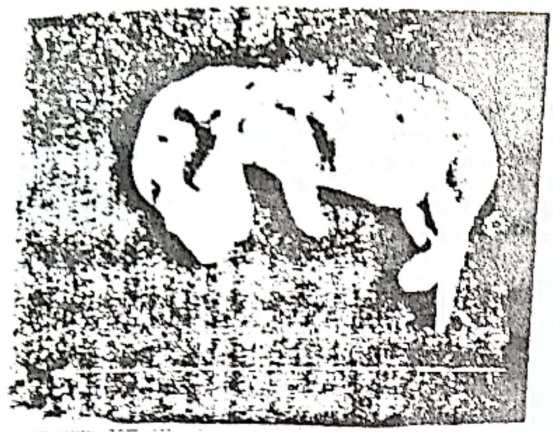

Fig. (3): A foetus from dam rat intramuscularly administered Flunixin meglumine, 0.4 mg/kg B.wt. from the 6th through the 15th day of gestation. The animal demenstrates haematomas in the head both fore and hind limbs and the shoulder regions .

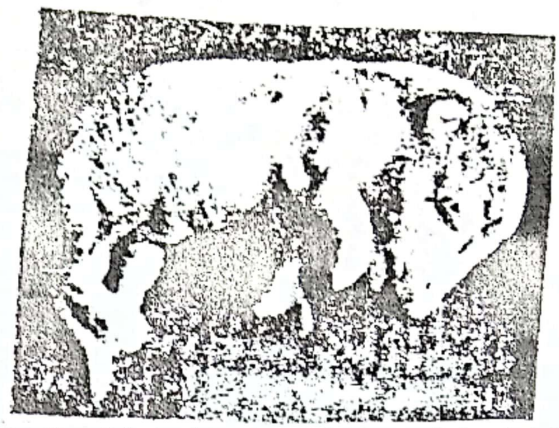

Fig. (4) : A foetus from dam rat intramuscularly administered Flunixin meglumine, 0.8 mg/kg B.wt. from the 6th through the 15th day of gestation. The animal demenstrates haematomas in the head both fore and hind limbs and the shoulder regions .

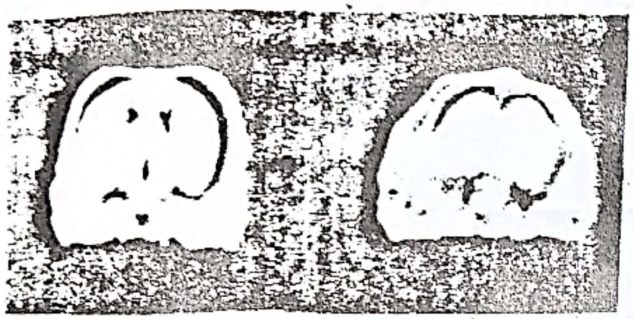

Fig. (5) : Cross section in the head of rat foetus demonstraung marked dilatation of both the lateral and central cerebral ventricles compared with the control (c) . The dam was intramuscularly injected with Flunixin meglumine, 0.4 mg/kg B. et. from the 6th through the 15th day of gestation .

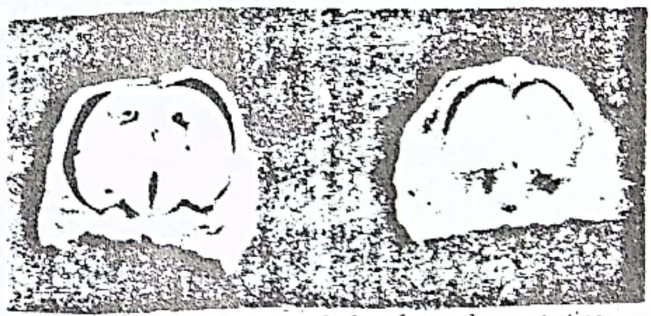

Fig. (6) : Cross section in the head of rat foetus demonstrating marked dilatation of both the lateral and central cerebral ventricles compared with the control (c). The dam was intramuscularly injected with Flunixin meglumine, 0.8 mg/kg B. wt. from the 6th through the 15th day of gestation .

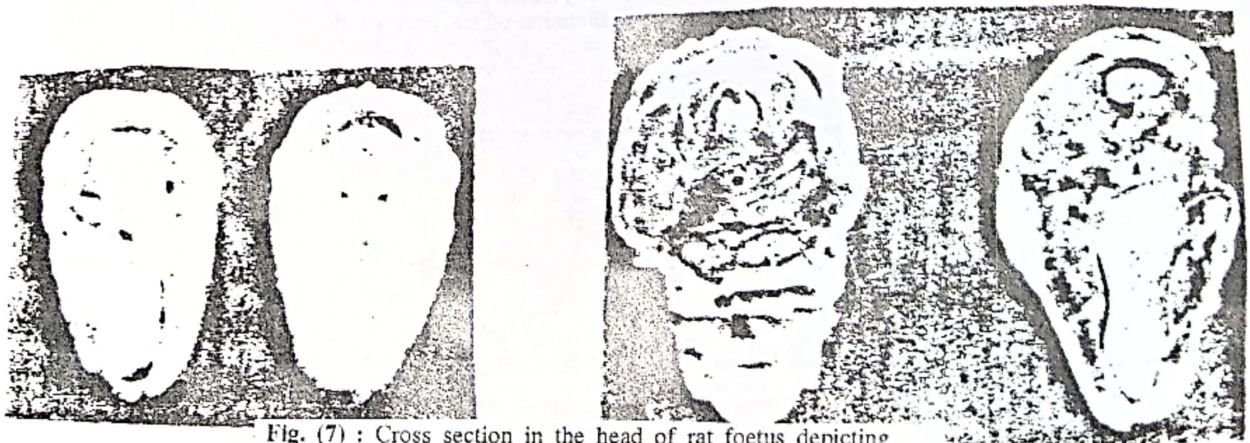

Fig. (7) : Cross section in the head of rat foetus depicting marked suborbital and periglossal interstitial haemorrhages compared with the control (c). The dam was intramuscularly injected with Flunixin meglumine, 0.8 mg/kg B.wt. from the 6th through the 15th day of gestation .

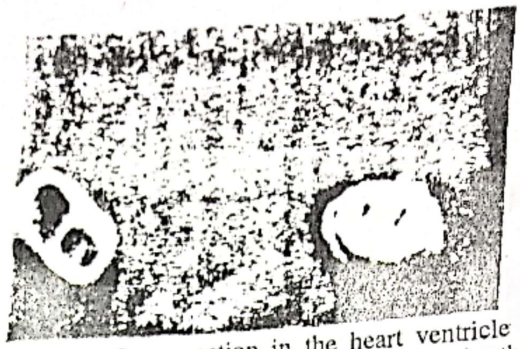

Fig. (8) : Cross section in the heart ventricle of rat foetus disclosing marked thickening in the ventricular wall compared with the control (c). The dam was intramuscularly injected with Flunixin meglumine, 0.4 mg/kg B.wt. from the 6th through the 15th day of gestation .

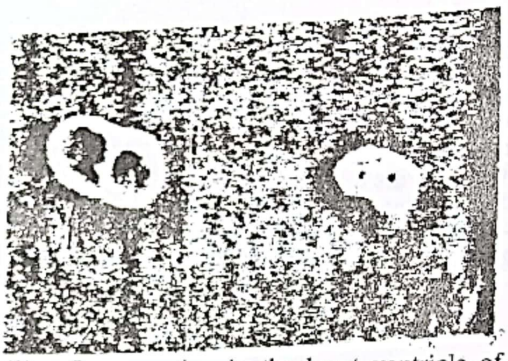

Fig. (9) : Cross section in the heart ventricle of rat foetus disclosing marked thickening in the ventricular wall compared with the control (c). The dam was intramuscularly injected with Flunixin

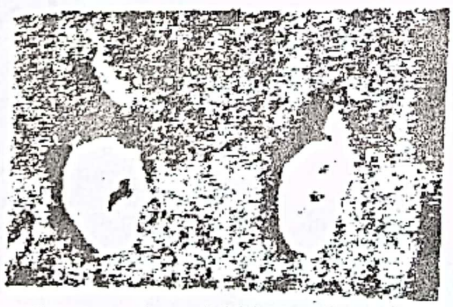

Fig. (10) : Cross section of kidney of rat foetus from dam intramuscularly given Flunixin meglumine, 0.4 mg/kg B.wt. from the 6th through the 15th day of gestation revealing dilatation of the renal pelvis with the control (c).

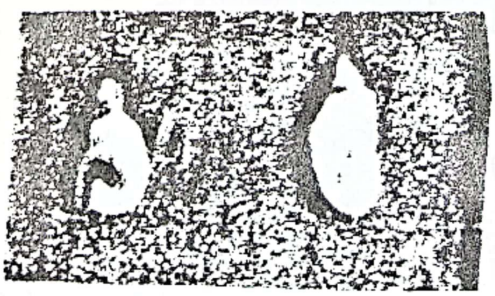

Fig. (11) : Cross section of kidney of rat foetus from dam intramuscularly given Flunixin meglumine, 0.8 mg/kg B.wt. from the 6th through the 15th day of gestation revealing dilatation of the renal pelvis with the control (c).

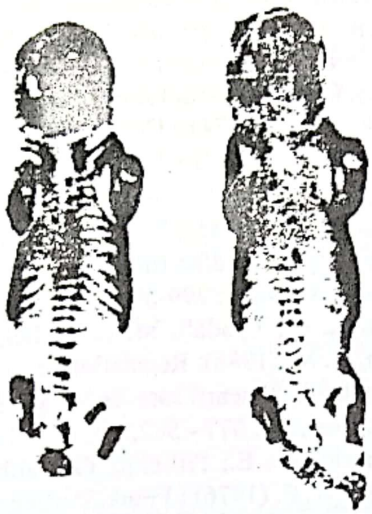

Fig. (12) : A rat foetus (b) from a dam intramuscularly injected with Flunixin meglumine; 0.4 mg/kg B.wt. given once a day from the 6th through the 15th day of gestation. Notice the rudimentary of second and fifth sternebrae compared with the control (c).

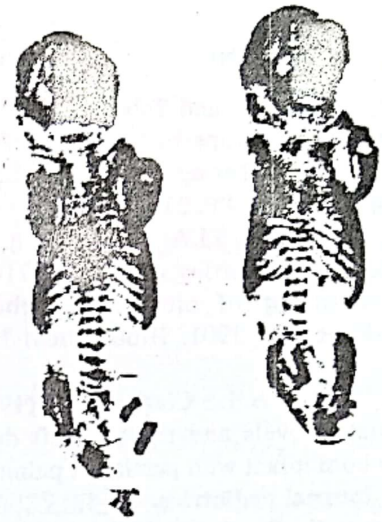

Fig. (13): A rat foetus (b) from a dam intramuscularly injected with Flunixin meglumine; 0.8 mg/kg B.wt. given once a day from the 6th through the 15th day of gestation. Notice the absence of both fifth sternebrae and xiphisternum compared with the control (c).

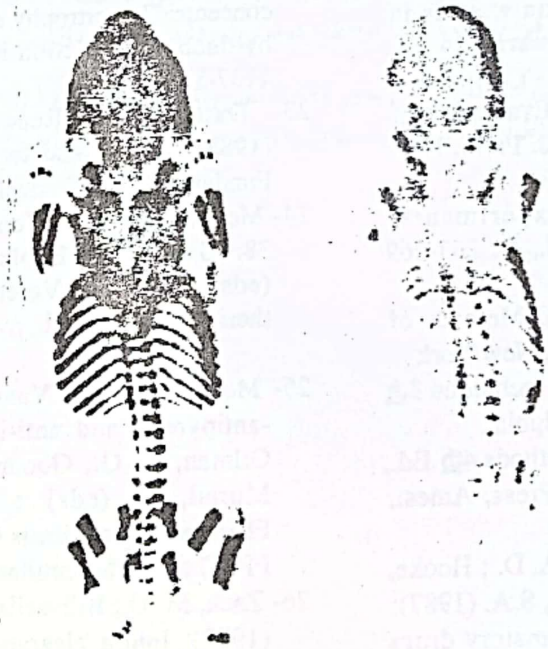

Fig. (14): A rat foetus (b) from a dam intramuscularly injected with Flunixin meglumine; 0.4 and 0.8 mg/kg B.wt. given once a day from the 6th through the 15th day of gestation. Notice the absence of both the last coccygeal vertebrae and phalanges compared with the control (c).

[4,30] . The cyclooxygenase inhibitor, Mofezolic induced a significantly retarded ossification of the 5th sternebrae and coccygeal vertebrae .

The previously documented deveoped malformations could be explained on the grounds that the production of sulphated mucopolysaccharides is reduced under the influence of cyclooxygenase inhibitors [31].

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تأثير الفلونكسن مجلومين على الخصوبة فى أناث الفئران

نجاح السيد أدريس ، نعيمه عفيفى*، ومها زين العابدين جابر*
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اجريت هذه الدراسة لمعرفة تأثير مضاد الالتهاب اللاستيرودى (فينادين) على التطور الجنينى لاناث الفئران البيضاء بعد اعطائها الدواء المختار من اليوم السادس حتى اليوم الخامس عشر من الحمل .

استعمل لهذا الغرض عدد ٣٠ من اناث الفئران الحوامل قسمت الى ثلاث مجموعات متساوية اعطيت المجموعة الاولى الدواء المختار (فينادين) بتركيز الجرعة الدوائية المعالجة ٤ر٠ مجم / كجم من وزن الجسم . أما المجموعة الثانية اعطيت الدواء بتركيز مزدوج للجرعة الدوائية المعالجة ٨ر٠ مجم / كجم من وزن الجسم وذلك عن طريق الحقن العضلى ابتداءا من اليوم السادس حتى اليوم الخامس عشر من الحمل واستخدمت المجموعة الاخيرة كمجموعة ضابطة . واستخرجت الأجنة من أرحام الفئران فى اليوم العشرين من الحمل ثم فحصت ظاهريا كما فحصت الأعضاء الداخلية لثلثى عدد الأجنة المأخوذة من كل أم وكذا الهياكل العظمية للثلث الاخر ودلت النتائج على ما يأتى :-

اعضاء دواء فينادين جرعتى ٤ر٠ - ٨ر٠ مجم / كجم من الوزن تسبب زيادة غير ملحوظة فى عدد الاجنة الممتصه ، كما لوحظ وجود بقع كبيرة حمراء موزعة على أجزاء الجسم المختلفة في عدد كبير من الاجنة وبفحص الاعضاء الداخلية للأجنة شوهد اتساع فى تجاويف المخ وحوض الكلى، زيادة فى سمك جدار البطين فى القلب وايضا لوحظ وجود نزيف داخل تجويف الصدر والبطن .

وبفحص الهيكل العظمى وجد اختفاء الفقرات الذيلية ، ضمور قطع القص واختفاء بعض منها بالاضافة الى ضمور غضروفة القص أو اختفائها فى حالات أخرى ، اختفاء السلاميات للأطراف الأمامية والخلفية وذلك فى نسب عالية من الاجنة المفحوصة .