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EVALUATION OF TERATOGENIC POTENTIALS OF DICLOFENAC IN PREGNANT FEMALE RATS

El-Sayed, M.G.A.[1]; El-Komy, A.A.A.[1] and Dalia, D.I.A. Ebied[2]

[1]*Department of pharmacology, faculty of veterinary medicine, Benha university, Egypt.*

[2]*Nile Company for Pharmaceutical and Chemical Industries, Cairo, Egypt.*

ABSTRACT

Cyclooxygenase (COX) inhibitors are one of the most often ingested drugs during pregnancy. The aim of the experiment was to evaluate the teratogenic potentials of diclofenac potassium in Wister albino rats. Fifty pregnant rats were divided into five groups; group (1) behaved as control received normal saline. Group (2) and group (3) administered 6.75 and 13.50 mg/kg b.wt. of diclofenac potassium orally once daily from 1st to 4th day of pregnancy respectively while group (4) and group (5) administered 6.75 and 13.50 mg/kg b.wt. of diclofenac potassium orally once daily from 6th to 15th day of pregnancy respectively. The study revealed no death or abortions in dams. Treated groups showed significant decrease in litter size, weight, length and retarded growth in fetuses. Fetal resorption significantly increased in all treated groups. The incidences of skeletal and visceral abnormalities were increased in treated groups.

Keywords: Diclofenac, pregnancy, visceral and skeletal abnormalities.

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1. INTRODUCTION

The use of non-steroidal anti-inflammatory drugs increased because these remain first–line during therapy for a wide range of rheumatic conditions and they are the drugs of choice for the treatment of inflammatory arthritis. It is well known that non-steroidal anti-inflammatory drugs provide analgesia and suppress inflammation by inhibiting the enzyme cyclooxygenase, resulting in decreased prostaglandin synthesis (Urban, 2000). Studies have shown that both therapeutic and side effects of non-steroidal anti-inflammatory drugs are dependent on cyclooxygenase inhibition (Warner et al., 1999). A few reports have demonstrated that non-steroidal anti-inflammatory drugs exerted embryo toxicity and teratogenicity among experimental animals including isopropyl antipyrine (Burdan, 2000), diclofenac (Chan et al., 2001), acetylsalicylic acid (Espiridiao et al., 2002), ibuprofen and tolmetin (Burdan, 2004) and piroxicam (Burdan, 2005) on rats. Diclofenac is a non-steroidal anti-inflammatory drug used commonly by women of reproductive age for treatment of dysmenorrhoea and menorrhagia (Dawood, 1993). Siu et al., (2000) reported that diclofenac crosses the human placenta readily during the first trimester. Some case studies have linked aspirin (acetylsalicylic acid) and indomethacin use with a higher risk of congenital abnormalities and low birth weight, whereas others have not found an association (Nielsen et al., 2001). The aim of the present study was to evaluate the teratogenic potentials of diclofenac

potassium in pregnant rats during the period of pre-implantation (1st to 4th day of pregnancy), (Sahu, 2009) and the period of organogenesis (6th to 15th day of pregnancy), (Chan et al., 2001).

2. MATERIALS AND METHODS

2.1. Materials:

2.2. Animals::

Fifty healthy and sexually mature primiparous female white albino rats (Rattus norvegicus. Bork), Wistar strain (200-250 grams and 6-8 months) were obtained from Animal House, Department of Nile Company for Pharmaceutical and Chemical Industries, (Cairo, Egypt). Animals were housed in stainless steel cages and maintained at a temperature of 25±2 ˚C, relative humidity of 50±5% and photoperiod at 12 h dark/12 h light. Animals were fed on commercial standard locally prepared rat pellets and water free from antimicrobials to withdraw any antibacterial residues.

Female rats were examined periodically using vaginal smear technique to ensure that they were in regular estrous cycle (Cahen, 1966). Each female rat in estrous phase was paired with a male of proven of fertility in a separate cage. Mating is confirmed in the next morning by the presence of spermatozoa in the content of the vaginal smear and / or the observation of the copulatory plug in situation; these findings designate first day of presumed gestation (Prakash and Arora, 1998; Christian, 2001).

2.3. Drugs:

Diclofenac as the potassium salt, is a benzeneacetic acid derivative, designated chemically as benzeneacetic acid, 2-[(2,6-dichlorophenyl) amino], monopotassium salt. It is available in a glass bottle contain 100 ml. Each one milliliter of diclofenac contains 2 mg of diclofenac potassium. It was bought from a local pharmacy and manufactured by Novartis Pharmaceutical Company, Egypt, under trade name Catafly ®. Diclofenac was used orally by using oro-gastric tube as therapeutic dose 6.75 mg/kg b.wt. and double therapeutic dose 13.50 mg / kg b.wt. of rat. These doses were calculated from human therapeutic dose according to Paget and Bernes, (1964).

2.4. Experimental design:

Five groups contained ten pregnant female rats were used in this study as the following:

Group (1): Ten pregnant female rats were used as control group and received only normal saline according to the method of the administration used.

Group (2): Ten pregnant female rats were received the diclofenac potassium at a dose of 6.75 mg/kg b.wt.(therapeutic dose) orally once daily from 1st to 4th day of pregnancy and sacrificed at 20th day of pregnancy.

Group (3): Ten pregnant female rats were received diclofenac potassium at a dose of 13.50 mg/kg b.wt. (double-therapeutic dose) orally once daily from 1st to 4th day of pregnancy and sacrificed at 20th day of pregnancy.

Group (4): Ten pregnant female rats were received diclofenac potassium at a dose of 6.75 mg/kg b.wt. (therapeutic dose) orally once daily from 6th to 15th day of pregnancy and sacrificed at 20th day of pregnancy.

Group (5): Ten pregnant female rats were received the diclofenac potassium at a dose of 13.50 mg/kg b.wt.(double- therapeutic dose) orally once daily from 6th to 15th day of pregnancy and sacrificed at 20th day of pregnancy.

2.5. Teratogenical design:

Ten pregnant female rats of all groups were sacrificed at the 20th day of gestation and dissected to examine the effect of the administrated drugs on fetal development by morphological (Hayes, 1986), visceral (

Wilson, 1965) and skeletal examinations (Staples and Schnell, 1986 and Prakash and Arora, 1998).

2.6. Statistical analysis:

The Statistical analysis was carried out using ANOVA with two factors under significance level of 0.05 for the whole results using SPSS (ver. 19). Data were treated as complete randomization design according to (Steel *et al.,* 1997). Multiple comparisons were carried out applying LSD.

3. RESULTS

3.1. Effect of diclofenac potassium on female pregnant rats during the pre-implantation period of pregnancy:

Diclofenac potassium was used at a dose of 6.75 (therapeutic dose) and 13.5 mg/kg b.wt. (double therapeutic dose) in the pregnant female rats given orally, once daily from days 1st to 4th of pregnancy which recorded highly significant decrease in the number of viable feti per female rat at dose of 6.75 mg/kg b.wt. and 13.50 mg/kg b.wt. The resorption rates were significantly higher in the double therapeutic dose than the therapeutic dose (Table1). At a dose of 6.75 mg/kg b.wt., there were dead feti obtained from a group of pregnant female rat.

Contrarily to the control group, delivered newborns maternally-treated with the tested drug showed a significant decrease in both fetal body lengths and weights which increased in the double therapeutic doses of diclofenac potassium in pregnant female rats (Table 2).

Visceral abnormalities of feti obtained from pregnant female rats given a dose 6.75 and 13.5 mg/kg b.wt. of diclofenac potassium from 1st to 4th day of pregnancy resulted in some abnormalities such as diverticulum dilatation of the brain in 50% and 57.1%; thymus aplasia or hypoplasia in 59% and 71.4%; cardiac enlargement in 77.2% and 85.7%; pulmonary hypoplasia in 63.6% and 71.4%; hepatomegaly in 54.5% and 57.1% and kidney enlargement in 31.8% and 42.8% respectively. No abnormalities in the size of the suprarenal gland were recorded (Table 3).

Skeletal abnormalities of feti obtained from pregnant female rats given orally diclofenac potassium at a dose 6.75 (therapeutic dose) and 13.5 mg/kg b.wt. (double therapeutic dose) from 1st to 4th day of pregnancy showed impaired ossification of skull in 33.3 % and 75%, absence of sternebra or reduction of size of sternebrae's bones in 50% and 50%. No abnormalities in the number and shapes of ribs after administration of both therapeutic and double therapeutic doses of diclofenac potassium. Absence of some metacarpal bone in 58.3% and 75%; absence of some metatarsal bone in 41.6 % and 50%; absence of digit's bone of fore and hind limb in 66.6 % and 75%, and absence some bones of coccygeal vertebra in 66.6% and 75%of examined feti , respectively (Table 4).

3.2. Effect of diclofenac potassium on female pregnant rats during the organogenesis period of pregnancy:

Diclofenac potassium administered at a dose of 6.75 mg/kg b.wt.(therapeutic dose) to pregnant female rats during 6th to 15th days of pregnancy which caused marked decrease in the number of viable feti per rat. There were no dead feti but the resorption rate of feti was moderately present while pregnant female rats administered diclofenac potassium at a dose of 13.50 mg/kg b.wt. (double-therapeutic dose) had highly significant decrease in the number of viable feti per rat and highly increased in the resorption rate of feti (Table 5).

During administration the therapeutic dose of diclofenac potassium to pregnant female rats, it was noticed that decrease in the fetal body length and weight in comparison to those of the feti of control group but there were highly significance after administration of the

double therapeutic dose of diclofenac potassium (Table 6).

Diclofenac potassium caused visceral abnormalities in the feti obtained from pregnant female rats administered the drug at 6.75 (therapeutic dose) and 13.5 mg/kg b.wt. (double therapeutic dose) from 6th to 15th day of pregnancy. The resulted visceral abnormalities included diverticulum dilatation of the brain in 46.8% and 50%; thymus hypoplasia or aplasia in 53.1% and 62.5%; cardiac enlargement in 62.5% and 68.75%; pulmonary hypoplasia in 56.25% and 62.5%; hepatomegaly in 59.3% and 68.75% and kidney enlargement in 37.5% and 43.75% (Table 7).

Skeletal examinations of feti obtained from pregnant female rats given orally diclofenac potassium at a dose of 6.75 and 13.5 mg/kg b.wt. from 6th to 15th day of pregnancy showed impaired ossification of skull in 27.7% and 36.3% and absence of sternebrae's bones, or absence or small size of some of them in 33. 3% and 45.4%. Absence of some metacarpal bone in 50% and 63.6%; absence of some metatarsal bone in 33.3% and 54.5%; absence of digit's bone of fore and hind limb in 50% and 63.6% were recorded . Absence of some bones of coccygeal vertebra in 66.6% and 72.7%. of examined feti , respectively (Table 8).

Table (1): Effects of diclofenac potassium on number of feti, viable, dead and resorbed feti per rat obtained from rats administered diclofenac potassium at a dose of 6.75 mg/kg b.wt. and 13.50 mg/kg b.wt. orally once daily from 1st to 4th day of pregnancy (n=10).

Parameter	Control (G1)	Diclofenac (mg/kg)		LSD at 0.05
		6.75 (G2)	13.50 (G3)	
No. of feti/rat	8.80±0.36^{b}	7.60±0.54^{ab}	6.40±0.60^{a}	1.48
No. of viable feti/rat	8.80±0.36^{b}	3.40±1.41^{a}	1.10±0.55^{a}	2.60
No. of dead feti/rat	0±0^{a}	0.40±0.40^{a}	0±0^{a}	0.67
No. of resorbed feti/rat	0±0^{a}	3.80±1.29^{b}	5.30±0.96^{b}	2.69

a & b: There is no significant difference (P>0.05) between any two means, within the same row have the same superscript letter.

Table (2): Morphological assessments of control and experimental delivered newborn feti obtained from rats administered diclofenac potassium at a dose of 6.75 mg/kg b.wt. and 13.50 mg/kg b.wt. orally once daily from 1st to 4th day of pregnancy (n=10)

Parameter	Control (G1)	Diclofenac (mg/kg)		LSD at 0.05
		6.75 (G2)	13.50 (G3)	
Fetal body length (cm)	4.19±0.13^{b}	1.21±0.49^{a}	1.10±0.45^{a}	1.14
Fetal body weight (g)	3.98±0.11^{b}	1.04±0.43^{a}	0.89±0.37^{a}	0.96

a & b: There is no significant difference (P>0.05) between any two means, within the same row have the same superscript letter.

Table (3):Visceral abnormalities in the fetuses obtained from rats administered diclofenac potassium at a dose of 6.75 mg/kg b.wt. and 13.50 mg/kg b.wt. orally once daily from 1st to 4th day of pregnancy(n=10).

Abnormalities	Diclofenac potassium	
	6.75 mg/kg b.wt. (G2)	13.50 mg/kg b.wt. (G3)
Brain	50%	57.1%
Thymus	59%	71.4%
Heart	77.2%	85.7%
Lungs	63.6%	71.4%
Liver	54.5%	57.4%
kidney	31.8%	42.8%
Suprarenal glands	-	-

Table (4): Skeletal abnormalities in the fetuses obtained from rats administered diclofenac potassium at a dose of 6.75 mg/kg b.wt. and 13.50 mg/kg b.wt. orally once daily from 1st to 4th day of pregnancy(n=10).

Abnormalities	Diclofenac potassium	
	6.75 mg/kg b.wt. (G2)	13.50 mg/kg b.wt. (G3)
Skull	33.3%	75%
Sternebrae	50%	50%
Ribs	-	-
Metacarpal bone	58.3%	75%
Metatarsal bone	41.6%	50%
Digit's bones	66.6%	75%
Coccygeal vertebrae	66.6%	75%

Table (5): Effects of diclofenac potassium on number of feti per rat and viable, dead and resorbed feti per rat obtained from rats administered diclofenac potassium at a dose of 6.75 mg/kg b.wt. and 13.50 mg/kg b.wt. orally once daily from 6th to 15th day of pregnancy (n=10)

Parameter	Control	Diclofenac (mg/kg)		LSD at
	(G1)	6.75 (G4)	13.50 (G5)	0.05
No. of feti/rat	8.80 ± 0.36^{b}	8.30 ± 0.21^{b}	6.90 ± 0.31^{a}	0.88
No. of viable feti/rat	8.80 ± 0.36^{b}	5.00 ± 1.37^{a}	2.70 ± 1.13^{a}	3.04
No. of dead feti/rat	0 ± 0^{a}	0 ± 0^{a}	0 ± 0^{a}	0.00
No. of resorbed feti/rat	0 ± 0^{a}	3.30 ± 1.35^{b}	4.20 ± 1.16^{b}	2.99

a & b: There is no significant difference (P>0.05) between any two means, within the same row have the same superscript letter.

Table (6): Morphological assessments of control and experimental delivered newborn feti obtained from rats administered diclofenac potassium at a dose of 6.75 mg/kg b.wt. and 13.50 mg/kg b.wt. orally once daily from 6th to 15th day of pregnancy (n=10)

Parameter	Control	Diclofenac (mg/kg)		LSD at
	(G1)	6.75 (G4)	13.50 (G5)	0.05
Fetal body length (cm)	4.19 ± 0.13^{b}	2.03 ± 0.55^{a}	0.96 ± 0.39^{a}	1.16
Fetal body weight (g)	3.98 ± 0.11^{b}	1.54 ± 0.42^{a}	0.62 ± 0.25^{a}	0.85

a & b: There is no significant difference (P>0.05) between any two means, within the same row have the same superscript letter.

Table (7):Visceral abnormalities in the fetuses obtained from rats administered diclofenac potassium at a dose of 6.75 mg/kg b.wt. and 13.50 mg/kg b.wt. orally once daily from 6th to 15th day of pregnancy (n=10).

Abnormalities in	Diclofenac potassium	
	6.75 mg/kg b.wt. (G4)	13.50 mg/kg b.wt. (G5)
Brain	46.8%	50%
Thymus	53.1%	62.5%
Heart	62.5%	68.75%
Lungs	56.25%	62.5%
Liver	59.3%	68.75%
kidney	37.5%	43.75%
Suprarenal glands	-	-

Table (8): Skeletal abnormalities in the fetuses obtained from rats administered diclofenac potassium at a dose of 6.75 mg/kg b.wt. and 13.50 mg/kg b.wt. orally once daily from 6th to 15th day of pregnancy(n=10).

Abnormalities in	Diclofenac potassium	
	6.75 mg/kg b.wt. (G4)	13.50 mg/kg b.wt. (G5)
Skull	27.7%	36.3%
Sternebrae	33.3%	45.4%
Ribs	-	-
Metacarpal bone	50%	54.5%
Metatarsal bone	33.3%	63.6%
Digit's bones	50%	63.6%
Coccygeal vertebrae	66.6%	72.7%

4. DISCUSSION

Diclofenac potassium was administered a dose of 6.75 and 13.5 mg/kg b.wt. to the pregnant rats given orally from the first to the fourth day of pregnancy also from 6th to 15th day of pregnancy. The pre-implantation stage revealed highly significant decreased in the number of viable feti per female rat. The period of organogenesis induced marked significant decrease in the number of viable fetuses per rat while a dose of 13.50 mg/kg b.wt. during the 6th to 15th days of pregnancy produced highly significant decrease in the number of viable fetuses per rat. This results agreed with Okamoto *et al.*, (1988), who administered Wistar-KY rats aspirin (62.5, 125,187.5 or 250 mg/kg) suspended with 0.5% CMC-Na. The live birth rate was significantly lower at 187.5 mg/kg than that in controls. Also, Randall *et al.*, (1991) observed the effect of ibuprofen

on alcohol-induced teratogenesis in mice. The results showed that maternal alcohol treatment resulted in significantly decreased fetal weight implantation sites and prenatal mortality was not affected. The obtained results of both doses was dose-dependent and partially consistent with data reported by Carp *et al.*, (1988),which recorded that rat blastocysts were cultured in diclofenac *in vitro* then implanted to host mothers rats on day 5 of pseudo pregnancy. It was clear that diclofenac had a profound effect preventing implantation as 72% of control embryo developed compared to only 35-41% after diclofenac treatment. It was probable that prostaglandin is produced by the blastocyst.

Prostaglandin appeared to be necessary throughout the process of implantation and placentation, which continues up to day 12 in the rat. When this process was disturbed by diclofenac, the number of growth-retareded embryos increased. Also, Tuchmann-Duplessis, (1975) cleared the decrease in the number of feti per mother to the direct toxic effect of the drug on the early developed fertilized ovum or the lack of oval production. Carp *et al.*, (1988) proved that prostaglandin inhibitors impaired implantation and due to a decrease in the synthesis of prostaglandins (Maathuis and Kelly, 1978; Abel *et al.*, 1980). During the first four days of pregnancy and the period of organogenesis, the resorption rates were significantly higher in the double therapeutic dose of diclofenac potassium than the therapeutic dose. This result agreed with O'Grady *et al.*, (1972) in rabbits after treatment with 8 or 16 mg/kg/day of subcutaneous indomethacin from the day of mating. Increased resorptions of developing embryos with no increase in birth defects in the survivors were reported. Also, Shapiro *et al.*, (1976) demonstrated perinatal mortality in relation to aspirin taken during pregnancy in woman. Also, Fuchigami *et al.*, (1990) performed a teratogenic study on mofezolac in New Zealand White rabbits to examine the effect on the dams and the teratogenic potentiality. Administration of 200 mg/kg produced a decrease in food consumption of the dams' concomitant with the embryocidal effects as shown by an increase in the early resorption rate. Also, Sahu, (2009) concluded that ibuprofen treatment of mice at pre-implantation phase showed no sign of continuing of pregnancy, suggesting an interference and possibly ibuprofen may have a lethal effect in early pregnancy.

The increase in the number of resorbed foeti might be attributed to the interference of the used drug to the placental transmission of some essential elements as leucin and magnesium, which are responsible for fetal growth, (Tuchmann-Duplessis, 1975). Siu *et al.*, (2000) showed that the drug cross first-trimester human placenta readily. Its relatively low molecular weight of 318.15 Daltons probably explained why diclofenac crossed trophoblastic membranes easily. So maternal administration of diclofenac resulted in a rapid accumulation of the drug in the fetus during the first trimester of pregnancy. This result wasn't agreed with that reported by Shafiq *et al.*, (2004), who showed that indomethacin caused a longer gestation period. .

A dose of 6.75 mg/kg b.wt. of diclofenac potassium from the first to the fourth day of pregnancy induced dead feti in pregnant female rat of the present study while during the period of organogenesis, there were no dead fetuses in both therapeutic and double therapeutic doses of diclofenac potassium. Larsson and Eriksson, (1966) proved that salicylate-induced fetal death and malformations in two mouse strains. The incidence of fetal death and resorption was estimated on the 18^{th} day of pregnancy. Deirdre *et al.*, (1976) indicated that the alkaloid solanine was embryotoxic when administered parenterally to pregnant mice and that its toxicity was potentiated by aspirin. Tátrai *et al.*, (1979) recorded experimental model for the study of the teratogenic interaction of chemical agents and drugs (toluene and acetylsalicylic acid). It was established that the fetal toxicity increased, i.e. increased the mortality rate of fetuses and the rate of the loss of the body weight. Jackson *et al.*, (1980) investigated fenbufen in rats, rabbits and mice after oral administration during organogenesis. Okamoto *et al.*, (1988) proved that aspirin induced fetal mortality.

Contrarily to the control group, delivered newborns maternally-treated with the tested drug, a significant decrease in both fetal body lengths and weights as a result of administration of diclofenac potassium to pregnant female rats orally once daily from the first to the fourth day of pregnancy in a

therapeutic dose and a double therapeutic dose but it increased in the double therapeutic doses of diclofenac potassium in pregnant female rats during the 6th to 15th days of pregnancy than the therapeutic dose. The decrease in body weight and length of fetuses from pregnant female rats treated during gestation with non-steroidal anti-inflammatory drugs were supported by Ungváry *et al.*, (1983) after administration of acetylsalicylic acid alone or with toluene inhalation; (Greenaway *et al.*, 1984) following salicylates through three major metabolites of salicylate; and (Bergman *et al.*, 1990) after supplementation of sodium selenite for 8 weeks prior to and throughout gestation with salicylate. Okamoto *et al.*, (1988) administered Wistar-KY rats orally with 62.5, 125,187.5 or 250 mg/kg aspirin suspended with 0.5% CMC-Na on days 9-11 of gestation. The fetal weight was lowered at and over 125 mg/kg. Carp *et al.*, (1988) proved that diclofenac administration to rats inhibited the ongoing process of implantation and placentation. It might be attributed to direct toxic effect of drug on fetal cell as it easily pass through placenta due to its low molecular weight (less than 1000 dalton), (Gerald, 2004).

On other hand, Fuchigami *et al.*, (1990) studied the teratogenicity of mofezolac in New Zealand White rabbits to examine the effect on the dams and the teratogenic potentiality. All pregnant females were sacrificed on day 28 of gestation and their fetuses were examined. There were no growth retardation and teratogenic effects on fetuses from the dams administered mofezolac. Toteno *et al.*, (1990) administered mofezolac orally to pregnant rats of the Jcl: Wistar strain (30 rats per group) at dose levels of 10, 50, 100 and 150 mg/kg/day from days 7 to 17 of gestation at 150 mg/kg. Significant decrease of fetal weight, increased number of immature fetuses as well as depressed body weight gain of female offspring was observed. According to Manson and Kang, (1994), the body weight and the crown length of the fetuses were considered sensitive indicators of animal's response to xenobiotics. It is well known that maternal toxicity reflects adversely on the offspring (Chahoud *et al.*, 1999; Burdan *et al.*, 2009) and consequently, similar findings were also noticed among the newborn rats, where the body parameters and bone ossification were adversely affected. These adverse effects would be exemplified by the magnitude of weight gain reduction, which is a symbol of the overall drastic change of these drugs.

Diclofenac potassium induced visceral abnormalities in the fetuses when administered therapeutic and double therapeutic dose in pregnant rats from the first to the fourth day of pregnancy and the period of organogenesis. The obtained results were dose-dependent. Klein *et al.*, (1981) administered a dose of aspirin to rats. The drug induced predominantly right-sided polydactyl of the hind limbs and preaxial digit formation. . Also, Guy and Sucheston, (1986) recorded significant external and visceral malformations after aspirin pretreatment in mice. Okamoto *et al.*, (1988) administered Wistar-KY rats orally with 62.5, 125,187.5 or 250 mg/kg aspirin suspended with 0.5% CMC-Na on days 9-11 of gestation. The internal anomalies tended to increase at and over 187.5 mg/kg. (Randall *et al.*, 1991) observed the effect of ibuprofen on alcohol-induced teratogenesis in mice. The results showed that maternal alcohol treatment resulted in an increased number of fetuses with limb and kidney defects. Di Sessa *et al.*, (1994) studied cardiac function in fetuses and newborns exposed to low-dose aspirin during pregnancy. Throughout gestation ductus arteriosus flow velocity, right ventricular output and diastolic area, and left ventricular output and diastolic area all increased and were similar in both aspirin- and placebo-exposed fetuses. Padmanabhan and Pallot, (1995) demonstrated aspirin–alcohol interaction in the production of cleft palate

and limb malformations in the TO mouse. Alcohol induced arched palate, cleft palate and deformities of the digits with haematomas in a modest number of embryos. Cappon *et al.*, (2003) studied relationship between cyclooxygenase 1 and 2 selective inhibitors and fetal development when administered to rats and rabbits during the sensitive periods for heart development and midline closure. In rabbits, diflunisal induced diaphragmatic hernia, ventricular septal defect, and midline defect (omphalocele) and single incidences of ventricular septal defect and midline defect (gastroschisis) were noted in the ibuprofen group; no other developmental findings were associated with treatment. In rats, ibuprofen, diflunisal, and ketorolac induced increases in the incidence of ventricular septal defect.

Diclofenac potassium induced skeletal abnormalities in the feti when administered orally in pregnant rats at therapeutic and double therapeutic doses from the first to the fourth day of pregnancy and the period of organogenesis. The obtained result obtained of both doses was dose-dependent. Guy and Sucheston, (1986) recorded teratogenic effects on the CD-1 mouse embryo exposed to concurrent doses of ethanol and aspirin. Larsson and Eriksson, (1966) studied salicylate-induced fetal death and malformations in two mouse strains. Anomalies of ribs and vertebrae showed the highest incidence after injection on the 9th day. Cekanova *et al.*, (1974) observed interactions between salicylic acid and pyridy;-3-methanol: anti-inflammatory and teratogenic effects. Salicylate-induced skeletal malformations were obtained after treatment in early organogenesis. This result was consistent partially with the data reported by (Kusanag *et al.*, 1977) after treatment of pregnant mice with 7.5 mg/kg of indomethacin orally on days 7-15 and produced an increased incidence of fused ribs and other skeletal defects in the offspring. These findings are in agreement with the report of (Brent, 2001) who gave leflunomide to pregnant rats and rabbits in doses equivalent to human doses induced skeletal malformations in the offspring. Decrease in alizarin staining, as a qualitative sign of mineralization reduction, was observed in bones whose development occurred slowly and / or late in fetal life e.g. cranial, phalanges, metacarpal and metatarsal (Zoetis *et al.*, 2003). However, according to available data (Fritz, 1975; khera, 1981; Beck, 1990 and Solecki *et al.*, 2003) proved that growth restriction and most of the skeletal variations, including treatment-related decrease of bone ossification, after administration of non-steroidal anti-inflammatory drugs.

The current investigation concluded that oral administration of diclofenac potassium in the therapeutic and double therapeutic dose to pregnant rats during the pre-implantation stage and the period of organogenesis induced marked significant results on viable, dead, resorbed feti as well as body weight and length. Also significant visceral and skeletal abnormalities in the fetuses were reported. The results were dose-dependent. It is advised to restrict the use of diclofenac potassium during pregnancy.

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تقييم الامكانات التشوهية للديكلوفيناك فى إناث الفئران الحوامل

مسعد جمال الدين احمد السيد[1] – أشرف عبدالحكيم الكومى[1]-داليا دسوقى إبراهيم أحمد[2]
[1]قسم الفارماكولوجيا- كلية الطب البيطرى- جامعة بنها
[2]شركة النيل للأدوية و الصناعات الكيماوية, القاهرة , مصر.

الملخص العربي

تعتبر مثبطات إنزيمات الأكسدة الحلقية (كوكس) واحدة من أكثر الأدوية التي تؤخذ أثناء الحمل لذلك تم إجراء هذه الدراسة لتقييم إمكانات التشوهية الناتجة من ديكلوفيناك البوتاسيوم في الجرذان البيضاء. تم تقسيم خمسون من الفئران الحوامل إلى خمس مجموعات؛ المجموعة (1)هى المجموعة الضبطية حيث تم تبليع الفئران الحوامل بالمحلول الملحي. المجموعة (2) والمجموعة (3)أعطيت 6.75 و 13.50مللى /كجم من وزن الفأر من ديكلوفيناك البوتاسيوم عن طريق الفم مرة واحدة يوميا من اليوم الأول إلى اليوم الرابع من الحمل على التوالي، بينما المجموعة (4) والمجموعة (5) تدار 6.75 و 13.50مللى /كجم من وزن الفأر من ديكلوفيناك البوتاسيوم عن طريق الفم مرة واحدة يوميا من اليوم السادس إلى اليوم الخامس عشر من الحمل على التوالي .كشفت الدراسة عدم وجود وفاة أو حالات الإجهاض في الأمهات وأظهرت المجموعات المعالجة انخفاضا كبيرا في حجم الأجنة، والوزن، والطول، وتأخر في النمو في الأجنة . و لقد وجد زيادة كبيرة فى الأجنة الممتصة في جميع المجموعات المعالجة كما زادت حالات تشوهات الهيكل العظمي والأحشاء الداخلية في المجموعات المعالجة.

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