THE IRAQI JOURNAL OF
VETERINARY MEDICINE

eISSN:2410-7409
pISSN: 1609-5693

OPEN ACCESS

Effect of P-glycoprotein Inhibitor (Carvedilol) on Developmental Outcome Methotrexate are Given Alone and in Combination of Pregnant Rats

Zaid K Shnawa*[1], Duraid A Abass[2]

[1]Department of Community Health Techniques, Baquba Technical Institute, Middle Technical University, Baquba, Iraq, [2]Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq

***Correspondence**:
zaidalazawy@yahoo.com

Received: 08 June 2022
Accepted: 31 August 2022
Published: 29 December 2022

DOI:
https://doi.org/10.30539/ijvm.v46i2.1410

Cite:
Shnawa ZK, Abass DA. Effect of P-glycoprotein inhibitor (Carvedilol) on developmental outcome methotrexate are given alone and in combination of pregnant rats. Iraqi J. Vet. Med. 2022;46(2):36-42.

A B S T R A C T

This study was performed according to FDA protocol to evaluate the developmental effects of carvedilol (P-glycoprotein inhibitor), methotrexate (P-glycoprotein substrate) and their combination at therapeutic doses on pregnant rats. Sixty Albino Wistar rats (40 female rats and 20 males) were allocated randomly into four groups orally administered 0.72 mg/kg carvedilol (Cv-treated group [TG]), 0.36 mg/kg methotrexate (MTX-TG), combined doses carvedilol+methotrexate (Cv+MTX-TG), and distilled water (control group) for 2 months in male and 2 weeks in female rats before mating and after copulation, then approval of pregnancy; dosing continued in female groups during pregnancy and lactation periods. Half of the animal groups were euthanized one day before parturition to study prenatal effects, while the other half left for parturition and lactation to study postnatal effect. The results of fertility index recorded in Cv-TG (71.43%), MTX-TG (42.46%) and Cv+MTX-TG (38.47%) was markedly lower than that in control (83.33%) group with lower gestation index was recorded in MTX-TG (80%) and Cv+MTX-TG (60%) than that in Cv-TG (100%) and the control group (100%). The result of resorbed and fetal death recorded a higher percent in Cv-MTX-TG in comparison with MTX-TG and Cv-TG; Cv-MTX-TG fetuses also recorded more anomalies, including hemorrhagic placenta, curved legs, and microcephaly during prenatal period. The postnatal effects showed that the Cv+MTX-TG group recorded a higher decrease in number of pups born, their weight, and increase in number of stillbirths in comparison with methotrexate followed by carvedilol groups in comparison with control group, while the result of viability index recorded (Cv-TG=98.15%, MTX-TG=93.93% and Cv+MTX-TG=76.19%) and lactation index (Cv-TG=77.36%, 83.87% and Cv+MTX-TG=75%). The postnatal anomalies were only recorded in Cv+MTX-TG included skull defect and ulceration, blindness, skin lesion, and alopecia in lactating pups. It is concluded that inhibition of P-gp by carvedilol might increase the placental passage and increase methotrexate concentration in fetal and pups' tissue with consequence of increase toxic effect of methotrexate both in fetus and pups of Cv+MTX-TG group which might explain the present results of teratogenic study.

Keywords: methotrexate, carvedilol, P-glycoprotein inhibitor, teratogenesis, rat

INTRODUCTION

Developmental toxicity is caused by exposure to teratogenic chemicals before conception, during pregnancy, or after birth, and may result in the death of the developing organism as well as morphological abnormalities, growth alteration, and functional deficiencies (1). The fetus is exposed to several xenobiotic substances throughout pregnancy, and these substances may transplacentally enter its blood (2)

P-glycoprotein (P-gp) is anticipated to play a role in fetal defense against harmful xenobiotics based on placental expression. Vincristine absorption by P-gp in membrane vesicles are made from human placenta trophoblast which

is considered the first study of demonstrating functional activity of P-gp in the placenta (3).

The dihydrofolate analogue methotrexate inhibits the dihydrofolate reductase enzyme (4). The hydrophobicity of all known P-gp substrates may reflect the requirements for their entry into the lipid bilayer rather than how they interact with P-gp (5). P-gp resists some hydrophobic methotrexate-related antifolates, such as trimetrexate, from entering cells through passive diffusion (6). Adrenergic receptor (AR) antagonist carvedilol inhibits a variety of AR types (7). Since P-gp inhibition can raise the levels of chemotherapeutic drugs that are counteracted and carvedilol exerts significant protective effects against chemotherapy-induced cardiotoxicity, the potential increase in doxorubicin's cytotoxicity caused by P-gp inhibition by carvedilol is likely to be insignificant clinically (8,9).

Important clinical evidence that is interaction between methotrexate and carvedilol for P-gp may occur in pregnant woman that suffers from chronic diseases treated with such drugs, with possible teratogenic and toxic consequences. The latter may occur, hence in this study it was tried to explore the such effect and to modulate the role of P-gp. Inhibitors on inducing such effects by their combination.

MATERIALS AND METHODS

Ethics

All procedures used in this study were reviewed and approved by The Scientific Committee of the Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Baghdad, and the Ethics Committee of the College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq in compliance with the ethical principles of animal welfare.

Animals

A total of sixty Albino Wistar rats, consisting of forty females and twenty males, were used in this study. They aged between 14 to 16 weeks and weighed 200- 250 g. They were fed standard pellets and water *ad libitum*. The animals were kept in special cages with optimal conditions two weeks before the experiment and maintained with the standard condition at 12-hour light-dark cycle, (20-25 °C) in an air-conditioned room. The bed was wood shaves that continuously changed, and the cages were cleaned twice per week. The female was separated from the male one month before the study for acclimatization and synchronization. After that, the animals were kept in a ratio of 2:1 female to male rats in each cage.

Developmental Study

The animals were orally treated with therapeutic doses of carvedilol, methotrexate (Cayman Chemical, USA) and in combination for two months in males and two weeks in females before mating and after conception. The pregnant female rats were examined daily after conception for five days. Vaginal smears stained with methylene blue (Promega, USA) were prepared to detect di-estrus phase. Pregnancy was detected by observation pale mucous membrane of vagina in the third day after conception (26)

The pregnant female rats were randomly assigned to one of four groups of ten each based on their treatment regimen as follows: Carvedilol-treated group (Cv-TG), pregnant females were orally administered the therapeutic dose of Cv at 0.72 mg/kg BW/week during pregnancy, with dosing continuing throughout lactation (10); methotrexate-treated group (MTX-TG), pregnant females were administered the therapeutic dose of MTX at 0.36 mg/kg BW/week with the same regimen as in Cv-TG; carvedilol-methotrexate combination group; carvedilol-methotrexate combination group (Cv+MTX-TG), pregnant females were administered in combination the therapeutic doses of Cv and MTX following same regimen; and control group (C), pregnant females administered same regimen dosing with distilled water. Half of the animals were euthanized by anesthesia each group one day before delivery for prenatal study while the other half was kept to parturition study postnatal effects in their pup's group (during the lactation period).

Prenatal and Postnatal Effects

Assessment of the following prenatal and prenatal parameters were performed according to (12, 25).

$$\text{Fertility Index (\%)} = \frac{\text{No. females conceiving}}{\text{No. females d to fertile males (mating)}} \times 100$$

$$\text{Gestation Index (\%)} = \frac{\text{No. females giving full term births}}{\text{No. females with evidence of pregnancy}} \times 100$$

$$\text{Viability Index (\%)} = \frac{\text{No. live offspring through days } 1-4)}{\text{Total No. of live offspring born}} \times 100$$

$$\text{Lactation Index (\%)} = \frac{\text{No. survival neonates (days } 4-21)}{\text{Total No. live offspring after 4 days}} \times 100$$

Statistical Analysis

IBM SPSS Statistics (Version 26) was used for the statistical analysis of the data. A one-way analysis of variance (ANOVA) and a post hoc test using Fisher's Least Significant Differences (LSD) at a significance level of $P \leq 0.05$ were used to assess statistically significant differences in means (13).

RESULTS

Prenatal effect

Body weight and percent of alive, dead and resorbed fetuses at one day before parturition of treated female rats

Treatment of animals with different doses of carvedilol alone and combined with methotrexate caused changes in

weight gain, total number of alive, dead, and resorbed fetuses in uterus of euthanized animals one day before parturition as listed in Table 1. The results showed that there were marked decrease in the percentage of alive fetuses of females of both MTX-TG and Cv-MTX-TG treated groups that recorded 90.9% and 73.33% while Cv-TG recorded 100% as in control group.

The weight of live fetuses showed a significant decrease (P<0.05) of all treated groups recording (2.04±0.02, 1.90±0.082 and 1.35±0.11) for Cv-TG, MTX-TG, Cv-MTX-TG, respectively in comparison with the control one (3.44±0.07). There also were a significant decrease in weight of fetuses of Cv-MTX-TG, MTX-TG and Cv-TG (1.35, 1.90 and 2.04) respectively. The percentage of dead fetuses of MTX-TG and Cv-MTX-TG treated groups recorded (5.88% and 11.76%) in comparison with the control one (0%). While carvedilol treated group (Cv-TG) recorded no dead fetuses (0%) as in control group. Same result also recorded for percentage of resorbed fetuses for the females of MTX-TG and Cv-MTX-TG recording (35.29% and 55.88%) respectively in compression with the control and Cv-TG groups that recorded 0% (Figure 1A, B).

Table 1. Effect of P. glycoprotein inhibitor carvedilol on body weigh, total number of alive, dead, and resorbed fetuses at one day before parturition

		Fetuses						
			Alive		Dead		Resorbed	
Groups	Total No. fetuses	Body weight (g)[1]	Number	%	Number	%	Number	%
Control, distilled water	57	3.44±0.07 [a]	57	100	0	0.00	0	0.00
Cv-TG, 0.72 mg/kg/BW	52	2.04±0.02 [b]	52	100	0	0.00	0.	0.00
MTX-TG, 0.36 mg/kg/BW	34	1.90±0.08 [b]	20	90.9	2	5.88	12	35.29
Cv+MTX-TG, 0.72+0.36 mg/kg BW	34	1.35±0.11 [b]	11	73.3	4	11.76	19	55.88
LSD		1.113						

[1]Mean±SEM, n=10, [a-b]Means within a column lacking a common superscript differ significantly (P≤0.05). Cv-TG, carvedilol-treated group; MTX-TG, methotrexate-treated group; Cv+MTX-TG, carvedilol-methotrexate combination group

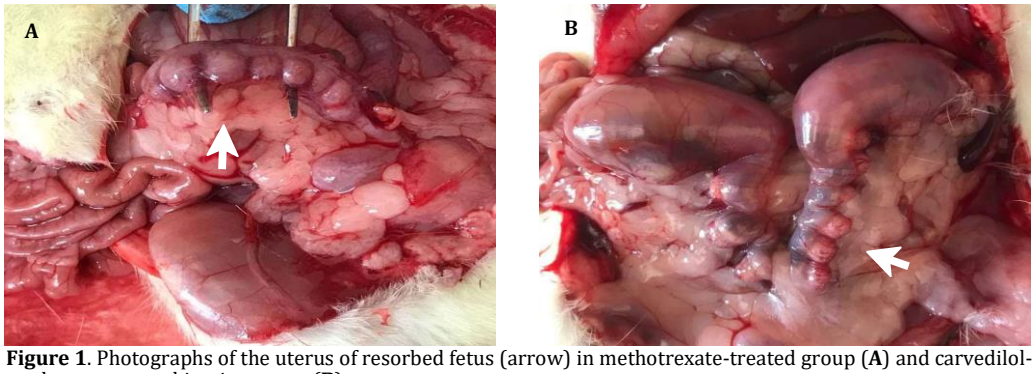

Figure 1. Photographs of the uterus of resorbed fetus (arrow) in methotrexate-treated group (**A**) and carvedilol-methotrexate combination group (**B**)

Table 2. Number and percentages anomalies of alive fetuses of euthanized treated pregnant rat groups with carvedilol, methotrexate alone and combined at one day before parturition

Groups	Total No. fetuses	Hemorrhagic placenta (%)	Cured legs (%)	Microcephaly (%)
Control, distilled water	57	0	0	0
Cv-TG, 0.72 mg/kg/BW	52	0	0	0
MTX-TG, 0.36 mg/kg/BW	22	0	0	0
Cv+MTX-TG, 0.72+0.36 mg/kg BW	15	46.66	13.33	0

Cv-TG, carvedilol-treated group; MTX-TG, methotrexate-treated group; Cv+MTX-TG, carvedilol-methotrexate combination group

Anomalies effect in the alive treated group fetuses at one day before parturition

The anomalies observed in current study are listed in Table 2. The results showed that the total number of fetuses (alive, dead and resorbed) was lower than that of control recording (57) according to their mother treatment with carvedilol, methotrexate, and their combination recording 52, 22, and 15 respectively while only combined treated group (Cv+MTX-TG) recorded higher percent of the following anomalies (hemorrhagic placenta 46.66%, curved leg 13.33%, Microcephaly 20%) (Figure 2 A, B, C).

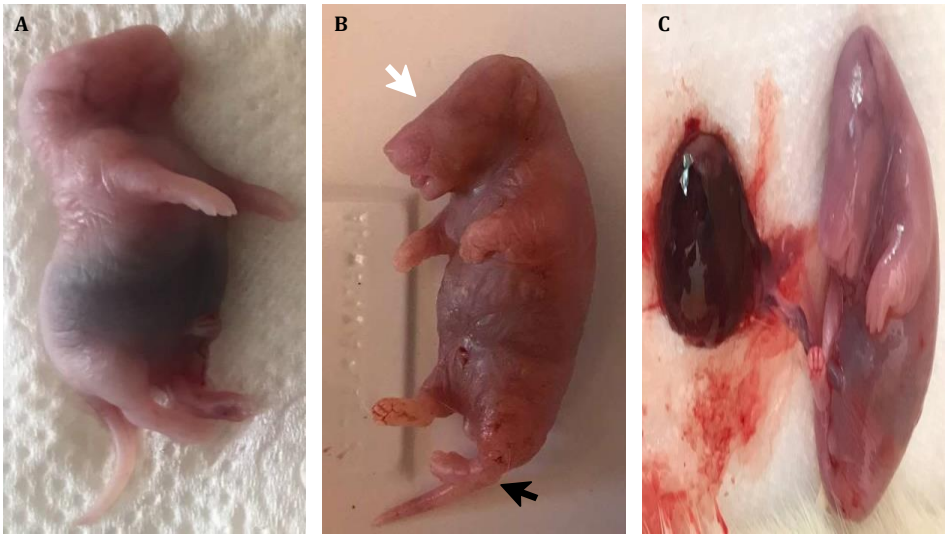

Figure 2. Photographs of rat fetuses from control group (**A**), received distilled water; carvedilol-methotrexate combination group (**B**), showing microcephaly (white arrow) and curved legs (black arrow); carvedilol-methotrexate combination group (**C**), showing hemorrhagic placenta

Effect of treatment with carvedilol, methotrexate alone and combined on fertility index and gestation index

Fertility index (FI) in Cv-TG (71.43%), MTX-TG (45.46%), and Cv+MTX-TG (38.47%) was markedly lower than that in control (83.33%) group (Table 3). Lower gestation index (GI) was recorded in MTX-TG (80%) and Cv+MTX-TG (60%) than that in Cv-TG (100%) and the control group (100%).

Table 3. Effect of carvedilol alone and in combination with methotrexate on fertility index (FI) and gestation index (GI) of female rats

Groups	FI (%)	GI (%)
Control, distilled water	83.33	100
Cv-TG, 0.72 mg/kg/BW	71.43	100
MTX-TG, 0.36 mg/kg/BW	45.46	80
Cv+MTX-TG, 0.72+0.36 mg/kg BW	38.47	60

Cv-TG, carvedilol-treated group; MTX-TG, methotrexate-treated group; Cv+MTX-TG, carvedilol-methotrexate combination group

Table 4. The number of alive, stillbirth body weight of parturated pups of carvedilol, methotrexate alone and in combination

	No. parturiated		No. pups	
Groups	Females	pups	alive	stillborn
Control, distilled water	5	55	55	0
Cv-TG, 0.72 mg/kg/BW	5	54	54	0
MTX-TG, 0.36 mg/kg/BW	5	33	32	1
Cv+MTX-TG, 0.72+0.36 mg/kg BW	5	21	19	2

Cv-TG, carvedilol-treated group; MTX-TG, methotrexate-treated group; Cv+MTX-TG, carvedilol-methotrexate combination group

Postnatal Effects

Total number of alive, stillborn parturiated pups

Table (4) shows that animals in the Cv+MTX-TG and MTX-TG had a marked decrease in the number of parturiated pups when compared to the control and Cv-TG, which had 55 and 54 parturiated pups, respectively, with no stillbirth effect. The Cv+MTX-TG had the highest number of stillborn pups, with two stillborn out of 21 parturiated pups, while the MTX-TG had one stillborn out of 33 parturiated pups.

Viability index and lactation index

The results treated groups Cv+MTX-TG and MTX-TG showed a marked decrease in viability index (VI) in comparison with Cv-TG and control groups. There was a marked decline in the VI of Cv+MTX-TG (76.19%) as compared with other treated groups. MTX-TG recorded a noticeable decline at 93.93%, while lactation index (LI) showed a marked decrease in pups of Cv+MTX-TG, MTX-TG, and Cv-TG in comparison with control group. The highest decline values in LI were recorded in the Cv+MTX-TG (75%) group as compared with MTX-TG and Cv-TG (83.87%, 77.36%, respectively) (Table 5).

Table 5. The effect of cavedilol alone and combined with methotrexate on viability index (VI) and lactation index (LI) of newborns rats

Groups	Total No. newborn	VI (%)	LI (%)
Control, distilled water	55	100.0	92.73
Cv-TG, 0.72 mg/kg/BW	54	98.15	77.36
MTX-TG, 0.36 mg/kg/BW	33	93.93	83.87
Cv+MTX-TG, 0.72+0.36 mg/kg BW	21	76.19	75.00

Cv-TG, carvedilol-treated group; MTX-TG, methotrexate-treated group; Cv+MTX-TG, carvedilol-methotrexate combination group

Anomalies in lactating pups

The results of deformities of lactating pups displayed in the Table 6 recorded only that the combined pups group showed different deformities including (skull defect and ulceration, blindness, skin lesion, and alopecia) as shown in Figure 3, Figure 4 shows the comparison with control, MTX-TG and Cv-TG that recorded non-observed defects

Table 6. The number of alive, stillbirth body weight of parturated pups of carvedilol, methotrexate alone and in combination

Groups	Skull defect, ulceration	Blindness	Skin ulceration	Alopecia
Control, distilled water	5	55	55	0
Cv-TG, 0.72 mg/kg/BW	5	54	54	0
MTX-TG, 0.36 mg/kg/BW	5	33	32	1
Cv+MTX-TG, 0.72+0.36 mg/kg BW	5	21	19	2

Cv-TG, carvedilol-treated group; MTX-TG, methotrexate-treated group; Cv+MTX-TG, carvedilol-methotrexate combination group

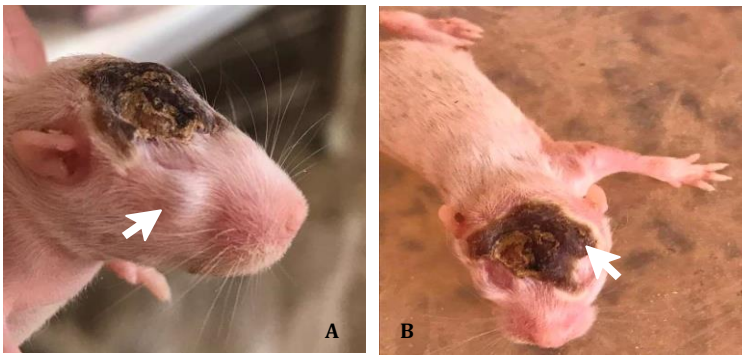

Figure 3. Photographs of rat pupies from carvedilol-methotrexate combination group, showing blindnes (**A**), skull defect and ulceration (**B**)

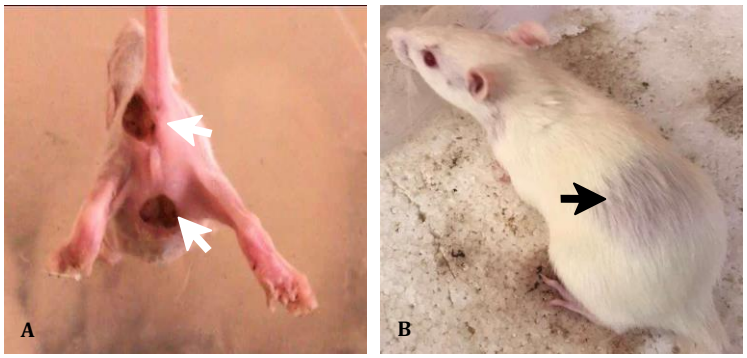

Figure 4. Photographs of rat pupies from carvedilol-methotrexate combination group, showing skin ulceration (**A**), alopecia (**B**)

DISCUSSION

The current study aimed to evaluate the effect of p.gp. inhibitor drug (carvedilol) that may be used in a pregnant woman as an antihypertension drug on the developmental effect of methotrexate (p-gp substrate) which is commonly used in the treatment of neoplastic and autoimmune diseases like rheumatoid arthritis and psoriasis, therefore, in this study, their possible teratogenic outcome was studied. When used together with carvedilol during both prenatal and postnatal periods throughout this study several parameters including prenatal and postnatal effects on the mothers, fetuses, and pups. The prenatal study, the percentage of the dead, weight of fetuses, and live & resorbed fetuses were recorded in all groups and mainly recorded in the first trimester and second trimester may be due to genetic disorders in a germ cell. Regarding the results of the current study, it was found that the Cv-MTX-TG group (combined) in the present study, it was recorded more reduction in weight of fetuses, percentage of the dead (11.76%), resorbed of fetus (55.88%), and the higher percentage of anomalies (hemorrhagic placenta, curved legs, microcephaly) and this may be due to carvedilol which was a potent inhibitor of P-gp (14, 15). This led to several, potentially significant drug-drug interactions of carvedilol, and methotrexate as P-glycoprotein substrates (14, 16). This study in agreement with (17) in which it was evaluated the developmental and cytogenic effects of ivermectin (P-gp substrate) and its interaction with P-glycoprotein inhibitor (verapamil) reported that drugs induced teratogenesis through alteration of expression of P-gp gene which has been found in the maternal/fetal placental barrier. The fertility index was measured at the first trimester (zygote formation and implantation) in treated groups. The present study reported that Cv-MTX-TG recorded more reduction in fertility index (38.47%) than MTX-TG (42.46%) and CV-TREATED GROUP (71.43%) groups which may be resulted from the possible accumulation effect of methotrexate in the fetal body due to inhibition of P-gp that effects the kinetics during P-gp inhibitors by carvedilol and increasing the placental transfer of methotrexate during pregnancy (18), it has been

noticed that the inhibitory effect of some MRP1 inhibitors is enhanced by the presence of methotrexate that causes harmful complications, impairment of fertility and oligospermia (19). The present study agrees with (20) who reported that Methotrexate causes teratogenic effects, impairment of fertility, oligospermia, and menstrual dysfunction in humans. The Gestation index was measured to study both fetus development and teratogen etic effects. The main effect was recorded in the Cv-MTX-TG treated female group (60%) also in MTX-TG ecording 80% which means that the main effect was concentrated in the second gestation stage (teratogenic period) as well as other gestation stages, carvedilol cause P-gp inhibition leading to increase the teratogenic effects of methotrexate. The present study agrees with (21) who found that some of the transporters prevent the entry of xenobiotics into the feto-placental unit. The most well-known of these is the P-glycoprotein or the MDR1 gene product. In the postnatal study, viability index was measured recording a higher percent (76.19%) in Cv-MTX-TG treated group and less effect in MTX-TG (93.93%) while the C_V-TG group recording (98.15%), these effects may be due to functional defects and hidden structural cellular in the third stage or second (teratogenic stage), this result may also be due to the accumulation effect of methotrexate and carvedilol due to the remnant of the drugs in milk from lactating mother. This study agrees with (22) who reported that methotrexate was detected in breast milk and serum following oral administration of MTX with peak breast milk level being 5.0 nM at9 h. The present study reported that all drug-treated groups of the experiment were affected by lactation index reported mainly in the 2nd and 3rd trimester, CV-TREATED GROUP & MTX-TG groups recorded that effects on lactation index due to their effects on structural and functional of cellular organs and tissues of developing fetus which result in organs dysfunction. This study agreement with (23) suggest that risks of neonatal hypoglycemia and bradycardia are associated with maternal exposure to β blockers at the time of delivery, a result from There were 10 585 (0.5%) pregnancies exposed to β blockers at the time of delivery. The risk of neonatal hypoglycemia was 4.3% in the β blocker–exposed neonates versus 1.2% in the unexposed; the risk of neonatal bradycardia was 1.6% in the exposed versus 0.5% in the unexposed. After controlling for confounders, the risk remained elevated for both neonatal hypoglycemia and bradycardia among exposed pregnancies versus unexposed interval, While the Cv-MTX-TG (combined) group reported more lactation index than other groups due to inhibition of P-gp that allows enhancing passage of methotrexate into a fetus that cause structural or functional abnormalities that might affect the viability and threaten the life of the growing pups during the lactation period. Postnatal anomalies which have been recorded in the present study in the Cv-MTX-TG group only according to skull defect and ulceration, blindness, skin lesion, and alopecia in pups as a result of fetal exposure to methotrexate that cause more teratogenic effects due to inhibition of P-GP. Causing an increase in placental transfer, and kinetic and teratogenic effects of methotrexate, and might pass from lactating mother to the pups of Cv-MTX-TG. This result agrees with (24) who recorded anomalies of methotrexate including hypoplasia of skull bones, growth deficiency, wide fontanels, microcephaly, coronal or lambdoidal craniosynostosis, and upswept frontal scalp hair. The outcome of such interaction could result in additive, accumulation, potentiation and synergism effects. Since inhibition of P-gp by carvedilol might increase the placental passage and increase methotrexate concentration in fetal and pups' tissue with consequence of increase toxic effect of methotrexate both in fetus and pups of Cv-MTX-TG group which might explain the present results of teratogenic study.

ACKNOWLEDGEMENTS

Authors would like to express their special thanks to the College of Veterinary Medicine, University of Baghdad for providing facilities for this work to be done.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Duong A, Steinmaus C, McHale C, Vaughan C, Zhang L. Reproductive and developmental toxicity of formaldehyde: a systematic review. Mutat Res.2011;728(3):118-138.
2. Garcia-Bournissen F, Feig DS, Koren G. Maternal-fetal transport of hypoglycaemic drugs. Clin Pharmacokinet. 2003;42(4):303-313.
3. Nakamura Y, Ikeda S, Furukawa T, Sumizawa T, Tani A, Akiyama S, et al. Function of P-glycoprotein expressed in placenta and mole. Biochem Biophys Res Commun. 1997;235(3):849–583.
4. Chapa JB, Hibbard JU, Weber EM, Abramowicz JS, Verp MS. Prenatal diagnosis of methotrexate embryopathy. Obstet Gynecol.2003;101(5 Pt 2):1104-1107.
5. Stein WD, Cardarelli C, Pastan I, Gottesman MM. Kinetic evidence suggesting that the multidrug transporter differentially handles influx and efflux of its substrates. Mol Pharmacol. 994;45(4):763-772.
6. Sharma RC, Assaraf YG, Schimke RT. A phenotype conferring selective resistance to lipophilic antifolates in Chinese hamster ovary cells. Cancer Res.1991;51:2949-2959.
7. Lymperopoulos A, McCrink KA, Brill A. Impact of CYP2D6 genetic variation on the response of the cardiovascular patient to carvedilol and metoprolol. Curr. Drug Metab.2015;17(1):30–36.
8. Običan S, Scialli AR. Teratogenic exposures. Am J Med Genet C Semin Med Genet. 2011;157C(3):150-169.
9. Takara K, Sakaeda T, Okumura K. Carvedilol: a new candidate for reversal of MDR1/P-glycoprotein-mediated multidrug resistance. Anti-Cancer Drugs. 2004; 15(4):303–309.
10. McNeil JJ, Louis WJ. Clinical pharmacokinetics of labetalol. Clin Pharmacokinet.1984;9(2):157-167.
11. Bello AE, Perkins EL, Jay R, Efthimiou P. Recommendations for optimizing methotrexate treatment for patients with rheumatoid arthritis. Open Access Rheumatol. 2017;9:67-79.
12. Klaassen CD, Amdur MO, Doull T. Cassaret and Doull's Toxicology: The Basic Science of Poisons (9th Ed.): Macmillan (Ed) Publishing Company, New York. 2019.
13. Snedecor GW, Cochran WG. Statistical methods. 7th ed. Iowa State Unv. Press., Ames., Iowa, U.S.A. 1980.

14. Bachmakov I, Werner U, Endress B, Auge D, Fromm MF. Characterization of β-adrenoceptor antagonists as substrates and inhibitors of the drug transporter P-glycoprotein. Fundam. Clin. Pharmacol. 2006; 20(3):273–282.
15. Wessler JD, Grip LT, Mendell J, Giugliano RP. The P-glycoprotein transport system and cardiovascular drugs. J Am Coll Cardiol. 2013;61(25):2495-502.
16. Baris N, Kalkan S, G¨uneri S, Bozdemir V, Guven H. Influence of carvedilol on serum digoxin levels in heart failure: is there any gender difference? Eur. J. Clin. Pharmacol.2006; 62(7):535–538.
17. El-Ashmawy IM, El-Nahas AF, Bayad AE. Teratogenic and cytogenetic effects of ivermectin and its interaction with P-glycoprotein inhibitor. Res Vet Sci.2011; 90(1):116-23.
18. Daud AN, Bergman JE, Bakker MK, Wang H, Kerstjens-Frederikse WS, de Walle HE, et al. P-glycoprotein-mediated drug interactions in pregnancy and changes in the risk of congenital anomalies: A case-reference study. Drug Saf.2015;38(7):651-659.
19. Rahi M, Heikkinen T, Härtter S, Hakkola J, Hakala K, Wallerman O, et al. Placental transfer of quetiapine in relation to P-glycoprotein activity. J Psychopharmacol.2007;21: 751-756.
20. Ponticelli C, Moroni G. Fetal toxicity of immunosuppressive drugs in pregnancy. J Clin Med. 2018;7(12):552.
21. Myllynen P, Pienimäki P, Vähäkangas K. Human placental perfusion method in the assessment of transplacental passage of antiepileptic drugs. Toxicol Appl Pharmacol. 2005;207(2 Suppl):489-494.
22. Thorne JC, Nadarajah T, Moretti M, Ito S. Methotrexate use in a breastfeeding patient with rheumatoid arthritis. J Rheumatol. 2014;41(11):2332.
23. Bateman BT, Patorno E, Desai RJ, Seely EW, Mogun H, Maeda A, et al. Late pregnancy β blocker exposure and risks of neonatal hypoglycemia and bradycardia. Pediatrics. 2016;138(3):e20160731.
24. Hyoun SC, Običan SG, Scialli AR. Teratogen update: methotrexate. Birth Defects Res A Clin Mol Teratol. 2012;94(4):187-207.
25. Amin FA, Alwan AF. Prenatal Study of testes growth and histological development 2-fetal goat. Iraqi J. Vet. Med. 2010;34(1):177-185.
26. Ajayi AF, Akhigbe RE. Staging of the estrous cycle and induction of estrus in experimental rodents: an update. Fertil Res Pract. 2020; 6: 5.

تأثير مثبط البروتين النافذ (كارفيدلول) على التأثيرات المسخية للميثوتركزيت التي تعطى بمفردها ومشتركة للجرذان الحوامل

زيد خلف شناوه[1]، دريد عبد الهادي[2]

[1]قسم صحة المجتمع، المعهد التقني بعقوبة، الجامعة التقنية الوسطى، بعقوبة، العراق، [2]فرع الفسلجة والكيمياء الحياتية والأدوية، كلية الطب البيطري، جامعة بغداد، بغداد، العراق

الخلاصة

تم إجراء الدراسة وفقًا لبروتوكول منظمة الغذاء والدواء (FDA) لتقييم التأثيرات المسخية والدوائية للكارفيديلول (مثبط البروتين النافذ) والميثوتريكزيت الدواء النافذ (سبستريت) ومزيجه في الجرعات العلاجية على الجرذان الحوامل والأمهات المرضعات وصغارهن. تم تخصيص جرذان مختبرية عدد (60 جرذا: 40 من الاناث و 20 ذكراً) مقسمة الى أربع مجاميع حيث اعطيت عن طريق الفم لمجموعة الكارفيديلول (0.72) ((Cv-TG ملغ / كم) ، مجموعة ميثوتركزيت 0.36) ((MTX-TG ملغ / كم)، جرعات مجمعة (Cv-MTX-TG) (كارفيديلول + ميثوتركزيت) ومجموعة السيطرة (ماء مقطر) لمدة شهرين للذكور وأسبوعين للإناث قبل التزاوج وبعد الجماع والتأكد من الحمل ، استمر العلاج للإناث خلال فترتي الحمل والرضاعة, تم قتل نصف الإناث من كل مجموعة بطريقة القتل الرحيم قبل يوم واحد من الولادة لدراسة تأثير ما قبل الولادة ، بينما ترك النصف الأخر للولادة والرضاعة لدراسة تأثير ما بعد الولادة. سجلت نتائج مؤشر الخصوبة (F.I)) في 71.43)%) Cv-TG و42.46%)) MTX-TG و Cv-MTX-TG 38.47%)) بينما سجل مؤشر الحمل (G.I)) في 100) %)Cv-TGو 80) %) MTX-TG و 60%) Cv-MTX-TG) وسجلت نتيجة الإرتشاف ووفيات الأجنة أعلى نسبة (55.88%) (11.76%) في Cv-MTX-TG بينما سجلت مجموعة 35.29 (% MTX-TG و 5.88%) على التوالي بمقارنه مع Cv-TG ومجموعة السيطره حيث لم يُسجل أي تأثير واضح، كما سجلت أجنة مجموعة Cv-MTX-TG المزيد من التشوهات التي تضمنت (نزف في المشيمة ، انحناء في الساق ، صغر الرأس) خلال فترة ما قبل الولادة. بينما اظهرت تأثيرات ما بعد الولادة أن مجموعة Cv-MTX-TG سجلت انخفاضًا حاداً في عدد ولادة الجراء ووزنها وزيادة في عدد حالات الولادة الميتة مقارنة بمجموعة الميثوتركزيت تليها مجموعة الكارفيديلول مقارنة بمجموعة السيطرة، كذلك سجلت نتيجة مؤشر الحيوية V.I) في 98.15)%) Cv-TG و 93.93)%) MTX-TG و 76.19)%) Cv-MTX-TG ومؤشر الرضاعةL.I)) في 77.36%) Cv-TG) و 83.87)%) MTX-TG و 75)%) Cv-MTX-TG. اما حالات ما بعد الولادة فسجلت فقط في Cv-MTX-TG التي تضمنت (تقرحات في الجمجمة ، عمى ، تقرحات في الجلد ، تساقط الشعر) في الجراء. نستنتج أن تثبيط البروتين النافذ (P-gp)) بواسطة دواء الكارفيديلول يؤدي إلى زيادة مرور المشيمة وزيادة تركيز الميثوتريكزيت في أنسجة الجنين والجراء نتيجة لزيادة التأثير السام للميثوتركزيت في كل من الجنين والجراء من مجموعة Cv-MTX-TG مما قد يفسر النتائج الحالية للدراسة المسخية.

الكلمات المفتاحية: ميثوتريكزيت، كارفيديلول، تركيبة، مثبط البروتين النافذ، المسخ