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PERINATAL EFFECTS OF PYRANTEL PAMOATE IN MICE

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SUMMARY

Using pregnant NMRI mice, the perinatal effects (gestation period, litter size, stillbirth, neonatal mortality, fetal birth weight, and sex ratio) of the pyrantel pamoate suspension (Combantrine) were reported. When the drug was used during the first trimester of pregnancy, the gestation period was longer in the treated animals than in the control group ($P < 0.01$). Also, there was a decrease in the (litter size, and an increase in fetal birth weight if compared with the control ($P < 0.05$). However, when the drug was given during the third trimester of pregnancy, the percentage of stillborn was raised ($P < 0.05$).

The possible explanation of the associated between these perinatal effects and the pyrantel pamoate is that it might be due to its action on the pituitary, adrenals, placenta and myometrium-axis. It is concluded that clinical investigations should be carried out before the drug can be prescribed to pregnant mothers.

Key words: Perinatal, pyrantel, gestation period, litter size, fetal birth weight, mortality, mice, offspring.

INTRODUCTION

Pyrantel pamoate (Combantrin®, Antiminth®) is widely used in the treatment of ancylostomiasis, ascaris and enterobiasis. These parasitic infections have been reported to be commonly prevalent in Saudi Arabia (**Afifi et al., 1981**).

Many drugs have proved to be harmful to the fetus and are, therefore, contrainadicated during pregnancy (**Hassan et al., 1986**). The safety of these drugs is not known and it is advised not to give them to pregnant women without proper testing and knowing their effects. Pyrantel pamoate is one of those drugs whose safety is not yet tested and little information is available about its effects on pregnant women. This work investigates the perinatal effects of the drug since pregnant women may need to use it if they are infected with intestinal parasites.

This investigation is only a part of the research project concerned with the perinatal effects of pyrantel pamoate on post-natal development of the central nervous system, teratology, blood picture, visceral and body growth of offspring of mice receiving the drug during different weeks of pregnancy. Other reports have been published elsewhere (**Al-Hachim and Tayeb, 1984; Hashim et al.,1985; Noorwali and Al-Hachim, 1985 ; Noorwali et al., 1986**).

MATERIAL AND METHODS

Animals used:

Three months old virgin female and adult male

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NMRI mice weighing between 25 and 30g each, were used. One female and one male were housed together in an individual macrolone cage (27 x 21 x 14 cm) with saw dust bedding and received food and water *ad libitum*. the colony room was on a 12-h dark lightning cycle and the temperature was controlled at 26 ± 2°C throughout the experiment. The female animals were exchanged daily in the evening and checked for a vaginal plug the following morning. Each mated female was placed in its own cage with food and water *ad libitum*. The day on which the vaginal plug was observed was designated as the first day of pregnancy. The pregnant mice were divided randomly into 3 groups of at least 10 for each trimester.

Gestation periods:

The gestation period was divided into three stages; first began with the observation of the vaginal plug and continued for the sixth day of pregnancy and was designated the first trimes ter. The second stage extended from the seventh day of pregnancy until the twelfth day and was designated the second trimester. The thrid stage began on the 13th day of pregnancy and ended with delivery a was designated as the third trimester. Each moth gave birth in her own maternity cage.

Drug Administration

Pyrantel pamoate (Combantrin®, Pfizer Co., Ne York, USA) was administered to the experiment pregnant mice. The daily doses of the drug use for each trimester in the experiment were 10 m kg, 20 mg/kg, or 30 mg/kg as a base. Each do was diluted in 10 ml of physiological normal s line solution (0.90% sodium chloride). Contr groups of pregnant animals were given norm physiological saline solution, 10 ml/kg.

Route and Time of Administration

Each calculated dose of the drug was administere orally. Each dose was given daily for each pre nant mother per group and per trimester, estal lishing nine groups of experimental mothers a three groups of controls.

RESULTS

Table (1) : The mean ± SD of perinatal effects of prenatal pyrantel pamoate base or normal saline (control) administered daily during the first trimester

Treatment	N	Gestation period (days)	Litter size	Birth weight (gm)	% Mortality Stillborn	% Mortality Neonatal	Male/Female ratio
Control A	14	19.00±0.00	12.71±2.27	1.58±1.30	0.00	0.71±1.20	0.97±0.55
10 mg B	13	19.31±0.48	11.15±1.95	1.60±0.18	0.00	1.00±1.08	1.14±0.46
20 mg C	15	18.93±0.26	11.55±2.95	1.73±0.22	0.00	0.36±0.63	0.88±0.46
30 mg D	15	19.73±0.46	10.63±2.53	1.96±0.30	0.07±0.26	1.00±2.30	1.17±1.01
		T - test value					
Compared Treatment							
AxB		3.31*	1.92	0.40	0.00	0.65	0.86
AxC		1.00	1.09	2.20*	0.00	0.98	0.49
AxD		6.21**	3.37**	4.70**	1.00	0.44	0.64
BxC		3.51*	0.38	1.60	0.00	1.87	1.51
BxD		3.19*	0.65	4.10**	1.00	0.00	0.07
CxD		5.98**	0.86	3.60*	1.00	1.08	0.99

N Number of mothers per group
* significantly different from corresponding control ($p < 0.05$)
** Highly significantly different from corresponding control ($p < 0.01$)

Table (2) : The mean ± SD of perinatal effects of prenatal pyrantel pamoate base or normal saline (control) administered daily during the second trimester

Treatment	N	Gestation period (days)	Litter size	Birth weight (gm)	% Mortality		Male/Female ratio
					Stillborn	Neonatal	
Control A	15	20.30±0.60	11.20±2.50	1.64±0.14	0.20±0.40	0.73±0.90	0.84±0.79
10 mg B	15	19.30±0.70	13.00±2.10	1.60±0.10	0.70±2.70	1.40±1.40	1.05±1.02
20 mg C	15	19.30±0.70	10.90±3.10	1.70±0.30	1.30±0.52	1.40±1.40	1.00±0.50
30 mg D	15	19.70±1.10	11.70±2.02	1.70±0.30	0.00	2.10±3.10	1.20±0.80
			T - test value				
Compared Treatment							
AxB		3.90**	2.20	0.40	0.80	1.60	0.60
AxC		4.20**	0.30	0.20	0.40	1.60	0.80
AxD		1.70	0.60	0.90	1.90	1.70	1.40
BxC		0.30	2.10	1.10	0.90	0.00	0.05
BxD		1.20	1.80	1.60	1.10	0.80	0.60
CxD		1.40	0.80	0.60	1.00	0.80	0.90

N number of mothers per group

** highly significantly different from corresponding control ($p < 0.01$)

Table (3) : The mean ± SD of perinatal effects of prenatal pyrantel pamoate base or normal saline (control) administered daily during the third trimester

Treatment	N	Gestation period (days)	Litter size	Birth weight (gm)	% Mortality		Male/Female ratio
					Stillborn	Neonatal	
Control A	10	19.40±0.97	11.40±4.10	1.68±0.38	2.40± 7.40	13.90±11.34	0.76±0.59
10 mg B	10	19,40±0.52	12.90±2.23	1.65±0.19	0.65± 2.10	12.40± 8.70	0.88±0.57
20 mg C	10	19.40±0.52	11.00±3.20	1.70±0.30	10.50± 7.70	6.10± 7.30	0.60±0.16
30 mg D	10	19.50±0.71	10.00±4.40	1.55±0.53	20.20±30.90	14.60±22.10	1.51±1.47
			T - test value				
Compared Treatment							
AxB		0.00	1.01	0.45	0.70	0.33	0.27
AxC		0.00	0.24	0.12	2.40*	1.84	0.53
AxD		0.26	0.74	0.61	2.78*	0.10	0.95
BxC		0.00	1.54	0.38	3.93**	1.82	0.82
BxD		0.36	1.87	0.71	2.00	0.28	0.79
CxD		0.36	0.58	0.76	0.97	1.11	1.23

N number of mothers per group

* significantly different from corresponding control ($p < 0.05$)

** highly significantly different from corresponding control ($p < 0.01$)

The perinatal effects: gestation periods, litter size, stillborn (No. of born-dead offspring) and neonatal mortality (during the first month of age) of live births, birth weights and sex ratio for offsprings were reported for drug-treated and control groups of pregnant animals in each trimester of pregnancy. The statistical analysis of the results was carried out with the Student's t test.

At the first trimester (Table 1), the drug prolonged the gestation period ($p < 0.05$, $p < 0.01$), and reduced litter size and increased fetal birth weight ($p < 0.05$, $P < 0.01$). At the second trimester, the drug reduced the gestation period ($P < 0.01$) but had no effect on the other parameters (Table 2). During the last stage of pregnancy, the drug raised the percentage of stillborn ($P < 0.05$) without affecting other parameters (Table 3).

DISCUSSION

Gestation Period:

The gestation period was prolonged in the mice which received the pyrantel pamoate during the first trimester of pregnancy and was reduced in those which received the drug during the second trimester. On the other hand, there was no significant difference in the gestation period between animals which had the drug during the third week and the control gorup.

As the mechanism for the onset of labour is not yet certain, it is not possible to give a clear explanation of the effects of pyrantel pamoate on the duration of pregnancy.

The association of pyrantel pamoate and the longer duration of pregnancy when given during the first trimester of pregnancy could be attributed to the effect of pyrantel pamoate on progesterone level (Liggins, 1969) and/or to decrease in litter size. The drug might have increased the concentration and prolonged the action of progesterone when it was administered during the first trimester of pregnancy. Possible explanation of this effect could be a reduction of uterine content. The number of offspring in the mice treated during the first trimester was less than the control (Table 1). This might cause lesss uterine distension in the druging treated mothers and,therefore, the delay in uterine contraction and hence prolongation of the gestation period in the drug-treated mothers.

The association between the administration of the drug during the second trimester and shortening of the gestation period could be due to the action of pyrantel pamoate of the pituitary, adrenals, placenta and myometrium-axis (Howes, 1971; Liggins et al., 1966, Liggins, 1969). This possible action may influence uterine contraction. During the second trimester on pregnancy, one expects that the placental and the fetal pituitary and adrenals are more mature than during the first trimester, the pyrantel pamoate might act on one of these organs to release some hormones such as adrionocorticotrophin (ACTH), glucocorticoides and α-oestradiol. All these hormones are responsible for the production of prostaglandins (Liggins, 1969), which will sensitize the uterus and pave the way for the action of oxytocin. Hence, the drug might hasten the production of prostglandins and shorten the gestation period when given during the second trimester of pregnancy.

The drug did not cause significant change in gestaiton period when given during the third trimester as there may not have been enough time for the drug to act on different organs to hasten the production of different hormones necessary for influencing uterine contractions.

Litter Size:

The association between the administration of pyrantel pamoate during the first trimester of pregnancy and the reduction in the litter size might be due to the effect of the drug on the implantation of the zygote and/or on fetal resorption. Since the early conceptions are already implanted and differentiated during the third week, the drug may have had no effect on litter size when it was administered during these trimesters of pregnancy.

Fetal Birth Weight:

Prenatally administered pyrantel pamoate has had an effect on fetal body weight during first trimester only since it increased fetal body weight at birth (Table 1). This increase was very pronounced with the large dose which was large enough to reduce litter size during the first trimes-

ter only. It seems that there is inverse relationship between litter size and fetal body weight where smaller litter size can be nourished better than larger ones via placenta of their mothers.

Mortality

The percentage of stillbirths was raised when pyrantel pamoate was given during the third week of pregnancy. This effect may be due to the direct toxicity on the fetus. Another possiblity could be through variation in placental supply to the tissues. It is observed that there is no significant difference in neonatal mortality between the pyrantel treatment and control mice. This finding might indicate that there is no postnatal effect for pyrantel pamoate on the offspring from prenataly treated mothers.

Sex Ratio:

The male/female ratio of the off springs was not affected by the administration of pyrantel pamoate. This is not surprising because so far there are no reports on similar drugs having any effects on male/female ratio (Noorwali and Al-Hachim, 1985).

However, it is advisable that pyrantel pamoate should not be given to pregnant women because it might cause premature labour, increase the incidence of stillbirths of intrauterine fetal death by direct toxicity. It is recommended that clinical investigations should be carried out before the drug is prescribed during pregnancy.

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