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Teratogenic Effects of Halofantrine on Sprague–Dawley Rat Foetuses

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ABSTRACT: This study was designed to examine the teratogenic effects of Halofantrine, an anti-malarial drug, on the foetuses of Sprague–Dawley rats. Groups of female rats in pro-estrous were mated overnight with fertile males of the same stock. Two experimental groups of 15 female pregnant rats in each group were given oral Halofantrine.

The first group received 24mg/kg/day of the drug on 13th, 14th and 15th day of gestation while the second group received 48mg/kg/day of the same drug on 13th, 14th and 15th day of gestation. The results showed foetuses with morphological anomalies. These include resorption of foetuses, and growth retardation evidenced by significant decrease ($P < 0.05$) in foetal weight, crown-rump length, tail length and placenta weight in the two experimental groups compared with the control.

Halofantrine is embryotoxic in rats and should be taken with caution in pregnancy.

Key words: Teratogenicity, Halofantrine, Rat foetuses, Antimalarial drugs.

Introduction

Malformation of foetus and growth retardation have been induced by lots of environmental factors exerting their teratogenic influence during the critical phase of embryogenesis in several animals (1,2,3). These drugs cross the placenta barrier to reach the foetus to produce marked cognitive and phsyiological deficits in their offsprings (3).

Halofantrine is a phenanthrenemethanol anti-malarial that is effective against asexual forms of multi-drug resistant plasmodium falciparum malaria. It has no action on gametocytes or hypnozoites in the liver (4). This drug has dose – dependent cardiotoxic effects causing prolongation of QTc interval and cardiac arrythmia (4). Besides a few nuances of kinetic nature observed in pregnant women, a good knowledge of teratogenous or embryotoxic effect is fragmentary (5).

Due to lack of experimentation of this drug on pregnant women, this investigation was carried out to determining whether artemether will induce foetal malformation and growth retardation when administered during susceptible period of teratogenesis.

Materials and Methods

A total of forty-five Sprague–Dawley rats weighing 150 – 180g were collected from the Animal House of the Faculty of Science of the University of Ilorin. They were acclimatized for one week in a ventilated house at the Department of Anatomy. They had access to feed and water *ad libitum*.

A daily vagina smears were taken with separate pipettes containing physiological saline (0.9 NaCl).

The smears were examined under light microscope to determine the epithelia cells predominantly present in the vaginal lavage. The predominant presence of uniformly large nucleated cells indicate pro-estrous stage, cornified cells indicate estrous (ovulation) and predominant presence of leucocytes with or without epithelial cells indicates the diestrous I or diestrous II stages.

Rats which exhibited two or more consecutive four – day estrous cycle were used. Proestrous females were mated with normal males of same stock. Presence of sperm plug in vagina smears obtained the following morning at estrous indicated successful mating, and this day was taken as day zero of gestation. The pregnant rats were weighed on day zero and twice a week till the end of the experiment.

The two experimental groups contained 15 rats each while the control group contained 10 rats. Group One rats were given 24mg/kg/day Halofantrine per oral on 13^{th}, 14^{th} and 15^{th} day of gestation. Group two rats were given 48mg/kg/day Halofantrine per oval on 13^{th}, 14^{th} and 15^{th} day of gestation.

On the 29^{th} day of gestation, the rats were sacrificed by gullotine decapitation and foetuses delivered by hysterotomy. The uteri were examined for number and placement of live, dead or resorbed foetuses, live foetuses were weighed, measured and examined for gross skeletal malfomations.

Statistical analysis was performed using paired students t – test where appropriate.

Results and Discussion

As shown in Table 1, there was a dose dependent decrease in foetal and placental weights, crown-rump and tail lengths. There were varied forms of placenta morphology with foetal resorption with the higher dose.

The result of this study showed that Halofantrine causes foetal resorption and growth retardation. Although nutritional, genetic and endocrine factors have been known to influence intrauterine growth and cause foetal resorption, several environmental agents can also induce growth retardiation depending on the dose and the stage at which the embryo is exposed to them.

Growth retardiation has now been accepted to be included within the scope of teratology (6).

Stunted growth was assessed using parameters like foetal weight, crown rump length, tail length and transumbilical distance (2, 7). But foetal weight alone was considered adequate in a study (8).

Body weight and crown rump length were used to assess growth retardation in other studies (9, 10).

The transumbilical distance is indicative of visceral growth (11). Additionally, the placenta weight was taken because a positive correlation between birth weight and placenta weight have been reported (12).

As shown in Table 1, a significant reduction ($P<0.05$) was observed in C.R. length, tail length, umbilical distance, foetal weight and placenta weight in foetuses of animal fed on 24mg/kg/day compared with the corresponding control, but a more significant reduction in the above parameters when a dose of 48mg/kg/day of the drug was given on similar days of gestation compared with the corresponding control.

Foetal resorption was also produced in 21.88% of foetuses administered 48mg/kg/day dose of the drug on 13^{th}, 14^{th} and 15^{th} day of gestation.

Small laboratory animals are more susceptible to teratogens than are higher primates. As such, anomalies observed in this study cannot be transferred by analogy to man.

In conclusion, Halofantrine should be taken with caution in pregnancy. However, further studies are necessary on higher primates.

Table 1: Effect of Halofantrine on the morphology of rat fetuses on the 13th, 14th and 15th Day of Gestation.

Parameters observed	Control	24mg/kg per oral	P-Value	48mg/kg per oral	P-Value
Number of Rats	10	15		15	
Number of Foetuses	78	105		96	
Weight of Viable Foetuses (G) (Mean ± S.D.)	4.6 ± 0.3	2.9 ± 0.15	P < 0.05	1.9 ± 0.5	P < 0.05
Weight of Placenta (G) (Mean ± S.D.)	1.3 ± 0.01	0.7 ± 0.02	P < 0.05	0.5 ± 0.05	P < 0.05
C.R. Length (mm) (Mean ± S.D.)	46.0 ± 1.0	41.0 ± 0.5	P < 0.05	35.5 ± 0.5	P < 0.05
Tail Length (mm) (Mean ± S.D.)	14.0 ± 1.0	12.0 ± 0.5	P < 0.05	10.0 ± 1.0	P < 0.05
Umbilical Length (mm) (Mean ± S.D.)	28.5 ± 0.5	26.0 ± 0.5	P < 0.05	21.5 ± 0.5	P < 0.05
Number of Resorbed Foetuses	NIL	NIL		21	P < 0.05
Number of Externally Malformed Foetuses	NIL	NIL		NIL	

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