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Biochemical Implications of Administration of Halofantrine Hydrochloride (Halfan) on Estradiol Levels of Female Wistar Rats

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Abstract:-This study determines the effects of doses of halofantrine hydrochloride, a phenanthrene methanol drug used in the therapeutic treatment of malaria on the estradiol levels of female wistar rats. Twenty (20) Female Wistar rats were used and divided into four groups. Group A being the control, Group B, Group C and Group D, all containing 5 rats in each group. A suspension of drugs at a dose of 0.1ml/kg body weight three times at six hourly intervals was administered orally to different groups of mature female rats for 2 weeks, 4 weeks and 6 weeks duration, control group was given normal saline. The animals were sacrificed on the 14th day, 28th day and 42nd day respectively after the last drug administration by cardiac puncture. Whole blood samples were collected for white blood count. From the plasma, the hormonal level was determined by radio-immunoassay and enzyme activities were also determined. The estradiol level following 2 weeks, 4 weeks and 6 weeks treatment was higher significantly ($p<0.05$) in all the groups compared to the control. The activities of the AST, ALT, and ALP increased significantly ($P < 0.05$) in all the groups compared with the control. The white blood cell count also increased significantly($p<0.05$) in all the groups compared with the control. These findings could signify the toxicity of the drug.

Keywords:-Halofantrine Hydrochloride, Malaria, Estradiol Levels, Female Wistar Rats, Radioimmunoassay.

I. INTRODUCTION

Malaria has been one of the most prominent and ancient disease which has been profiled and studied. It has been one of the greatest burdens to mankind, with a mortality rate that is unmatched by any other modern disease other than tuberculosis. This dreadful disease, caused by four different agents (Plasmodium falciparum, Plasmodium vivax, Plasmodium malariaeandPlasmodiumovale) of the same genus, is a major health problem in most of the countries in the Tropics (Adjene and Agoreyo, 2013). Halfan (Pharmacological name Halofantrine) is an anti-malaria drug chemically related to mefloquine and quinine. Halfan emerged from the US Army's huge post-Vietnam anti-malaria drug discovery program. There is no question that safe and effective anti-malaria drugs were needed in the second half of the twentieth century, once it became apparent that the *Plasmodium* had developed resistance to the mainstay of anti-malaria therapy, namely chloroquine (WHO, 1988). Halofantrine is schizonticidal and exerts its action at the erythrocytic stage of the life cycle (trophozoite and schizont). It is not effective against exo-erythrocytic (hepatic) schizonts or against the sporozoite, merozoite or gametozoite stages of the life cycle of Plasmodium species investigated (Singh *et al.,* 1978). In the treatment of acute uncomplicated malaria due to Plasmodium falciparum and Plasmodium vivax, including those strains resistant to chloroquine. Administration of halofantrine in the treatment of malaria caused by P. vivax should be followed up by treatment with an 8-aminoquinoline derivative to eliminate hepatic forms (Parkinson *et al*., 1989). Estradiol is the steroid hormone that is produced by the cells lining the ovarian follicles in response to FSH, and the very high levels of estradiol within the leading follicle nourish and mature the egg (Wiselogle, 1986).Some estradiol reaches the blood to cause the lining of the uterus to grow, the secretion of ovulatory cervical mucus, and to provide feedback to the brain and pituitary that another cohort of follicles has been recruited and is growing (Wiselogle, 1986). Estradiol, or more precisely, 17β-estradiol, is a human sex hormone and steroid, and the primary female sex hormone. It is named for and is important in the regulation of the estrous and menstrual female reproductive cycles. Estradiol is essential for the development and maintenance of female reproductive tissues but it also has important effects in many other tissues including bone (Ugochukwu *et al.*, 2008). Estradiol is produced especially within the follicles of female ovaries, but also in other endocrine (i.e., hormone-producing) and non-endocrine tissues (e.g., including fat, liver, adrenal, breast, and neural tissues).

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II. MATERIALS AND METHODOLOGY

A. *Animal Maintenance and Grouping*

Twenty (20) female wistar rats were housed and fed until they weighed between 160-215g. They were acclimatized under standard housing conditions of an ambient temperature. The rats were randomly selected and divided into groups 1-4, with each group containing five rats. Group A serves as control while B, C and D serve as treatment groups.

B. *Drug Administration*

Halofantrine that was used in this research was produced by SmithKline and French Laboratories. The drug suspension was administered to the animals on the basis of their body weight. Usually, 5mls of the drug suspension contain 100mg of halofantrine hydrochloride (Halfan). The therapeutic dose for the experimental animals was thus 0.1ml/kg body weight as against the therapeutic dose of humans, which are 10ml/kg six hourly doses. The suspension of halofantrine was administered orally with the aid of an orogastric tube attached to needle and syringe.

C. *Statistical Analysis*

The statistical significance between groups was analyzed using one-way analysis of variance (ANOVA) to analyze the experimental groups and were considered as a level of significance followed by Fisher Least Significance Difference (LSD) post hoc test. Statistical tests were performed using SPSS (version 11) package.

III. RESULTS

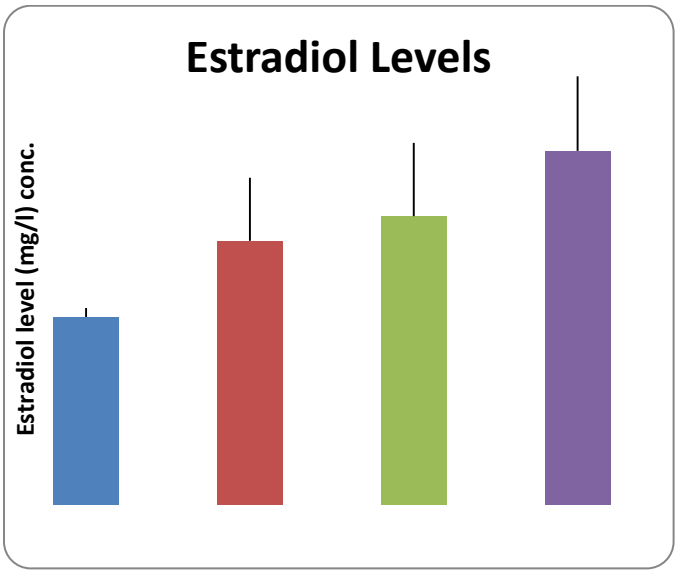

Fig. 1 Showed the Estradiol levels of female wistar rats treated with Halofantrine hydrochloride for 2 weeks, 4 weeks and 6 weeks respectively.

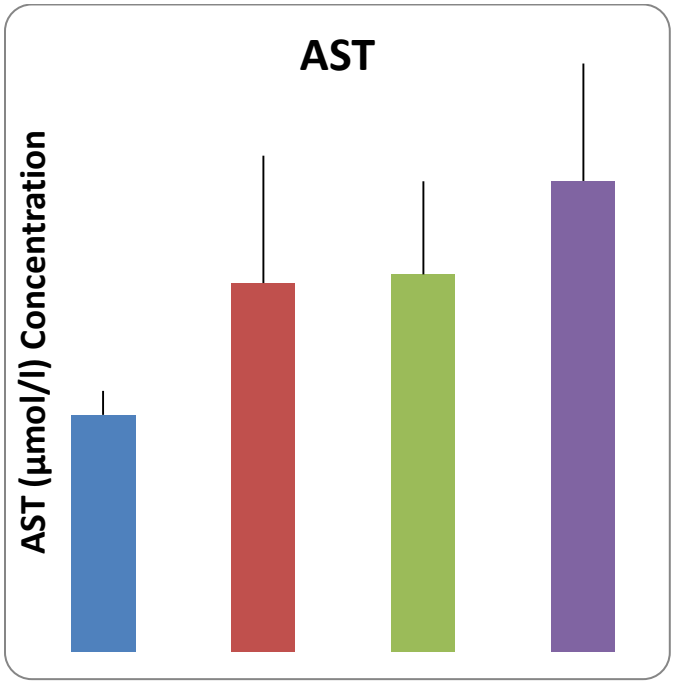

Figure 2: Showed the levels of AST of female wistar rats treated with Halofantrine hydrochloride for 2 weeks, 4 weeks and 6 weeks respectively.

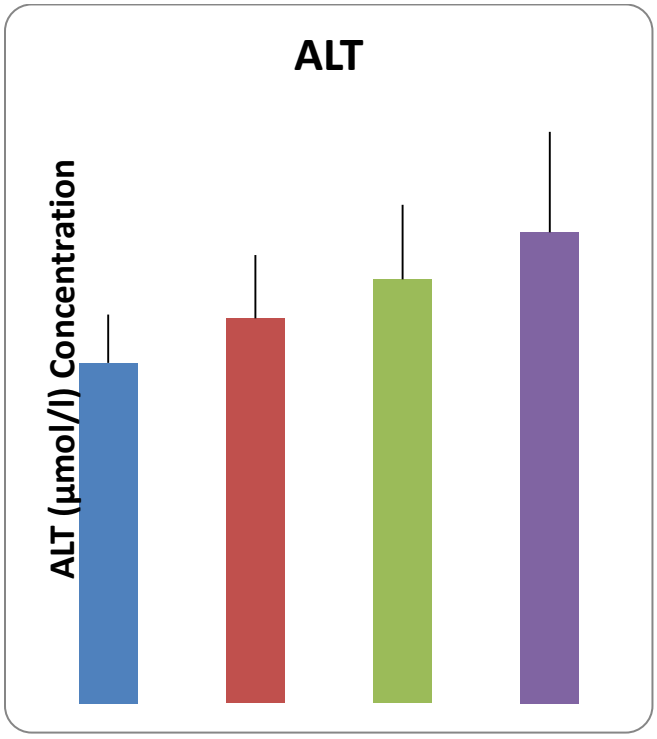

Figure 3: Showed the levels of ALT of female wistar rats treated with Halofantrine hydrochloride for 2 weeks, 4 weeks and 6 weeks respectively.

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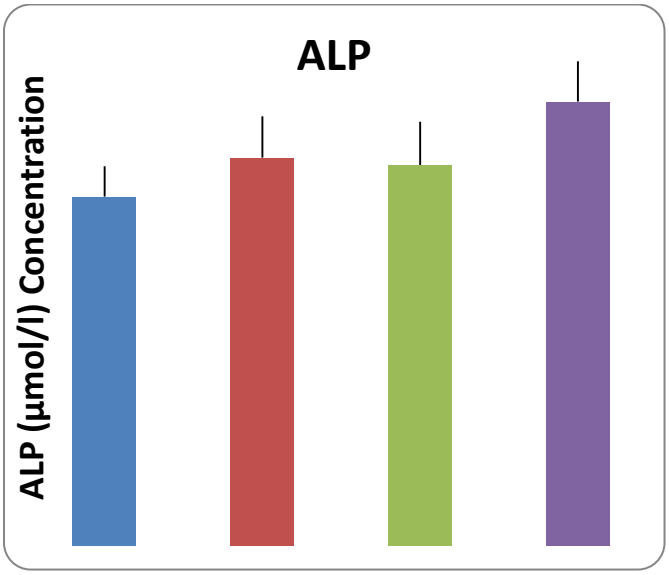

Figure 4: Showed the levels of ALP of female wistar rats treated with Halofantrine hydrochloride for 2 weeks, 4 weeks and 6 weeks respectively.

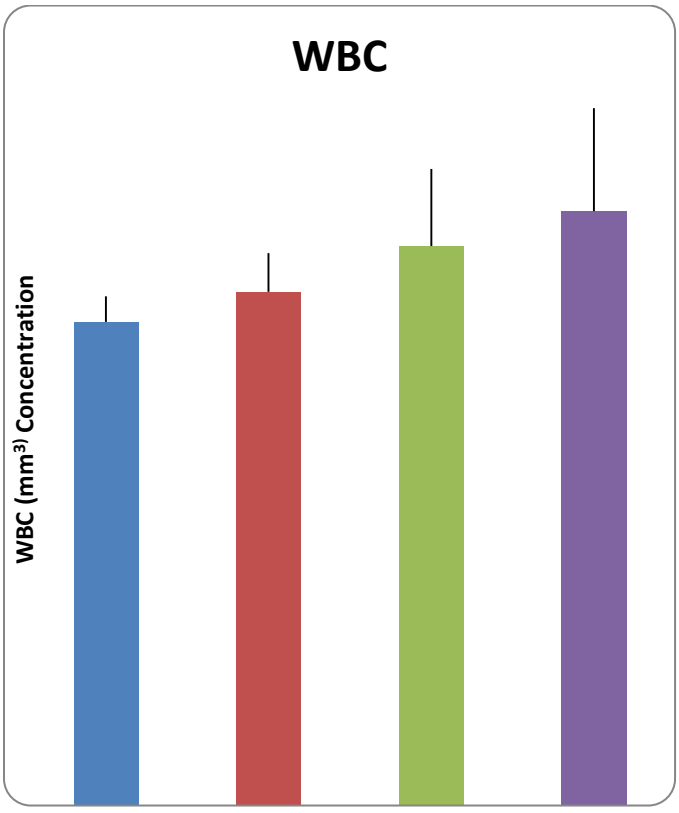

Figure 5: Showed the levels of white blood cell count of female wistar rats treated with Halofantrine hydrochloride for 2 weeks, 4 weeks and 6 weeks respectively.

IV. DISCUSSION

It was discovered from this study that halofantrine hydrochloride caused a significant increase in the liver function test and full blood count of the treated female wistar rats. This could signify toxicity of the drugs on the bone marrow of the rats, the increase in the full blood count indicates a pathological condition. The result therefore appears to suggest that Halfan may be inducing the steroidogenic enzymes thereby causing high levels of estradiol. This would influence both endocrine balance and reproductive activities, thereby affecting both anatomical and physiological functions of the ovary. Evidence from female users of this drug has shown that the drug administered at a normal human therapeutic dose induces menstrual flow which could probably be attributed to increase estradiol levels.

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