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Short Communication

Effect of Artemisinin-Based Combination Therapy on some Selected Liver Function Indices of Pregnant Wistar Albino Rats

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ABSTRACT

In the risk assessment of the effect of administration of artemisinin-based combination therapy on some selected liver function indices of pregnant wistar albino rats. Fifteen (15) pregnant wistar albino rats were divided into three groups and were allowed to acclimatize to laboratory condition for seven (7) days. Rats in group A served as the control and were administered with normal saline throughout the experimental period of seven (7) days, while rats in group B and C were administered intra-peritoneally with 3 and 6mg/kg body weight of artemisinin-based combination therapy respectively throughout the experimental period. Twenty four (24) hours after the last administration, the pregnant wistar albino rats were sacrificed. Blood was obtained by cardiac puncture for analysis of serum ALP, AST, ALT and bilirubin using standard methods and enzyme kits. The result showed that the drug at both 3and 6mg/kg body weight produced a significant ($P<0.05$) dosage increase in serum AST, ALT and ALP. The ratio of AST: ALT and AST: ALP showed a significant ($P<0.05$) increase. Similar pattern was also displayed by serum bilirubin concentration. These results are clear manifestations that artemisinin-based combination therapy might pose hepatic injury, hepatobilliary toxicity or complete hepatic damage in pregnant wistar albino rats. Thus, it is suggested that special precaution needs to be exercised on the usage of artemether-lumefantrine in pregnancy.

INTRODUCTION

Malaria is a vector-borne infectious disease caused by different strains of the protozoan parasites of the genius plasmodium. Malaria still remains one of the most deadly infections in the tropical and subtropical regions of the world despite various control programmes (Okafor *et al.*, 2013). Each year, there are about 216 million episode of acute malaria illness, 655,000 mortality and 91% occurred in the African region (CDC, 2012).The increasing resistance to the available pharmacological agents with antimalarial potentials call for more findings on malarial control in endemic countries (Ridley, 2002). One of the chemotherapeutic drugs recommended by the World Health Organization (WHO) in the management of malaria are artemisinin-based combination therapy which prevents the development of gametophyte in *Plasmodium vivax, Plasmodium ovale, Plasmodium malarae* and the early stage *of Plasmodium falciparium*.

The most widely used artemisinin derivatives are arte sunate, artemether and dihydro-artemisinin (DHA). Based on the available safety and efficacy data, different therapeutic options of the artemisinin-based combination treatments (ACTs) are now available which include artemether-lumefantrine, artesunate-amodiaquine, artesunate -sulfadoxine/pyrimethamine, artesunate-mefloquine, dihydroartemisinin-piperaquine phosphate among others (WHO, 2011).

Therefore, since relevant information about the effect of artemisinin-based combination therapy on the hepatobilliary system of pregnant women have not been fully elucidated, hence, this present research is focussed on the effect of artemisinin-based therapy on some selected liver function indices of pregnant wistar albino rats.

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MATERIALS AND METHODS

SAMPLES

The drug sample (Coartem) was obtained from Rabana pharmacy, Calabar while other samples and reagents used were of analytical grade.

Animals and treatment protocols:

Fifteen (15) pregnant wistar albino rats weighing 200-220g were used for this work. The animals were obtained from the animal holding unit of the Department of Biochemistry, University of Calabar, Calabar, Cross River State. The animals were housed in plastic cages and were allowed acclimatization period of Seven (7) days in a well-ventilated room with a temperature and pressure of 29±2 ^{O}C and70% respectively. The pregnant wistar albino rats were maintained with rat chow (vital feeds Ltd) and water *ad libitum*.

The animals were exposed to 12 hours light-dark cycle and handled according to standard protocols. At the end of acclimatization period, they were divided into three groups A, B and C of five (5) pregnant rats each. Group A served as control while B and C were the test groups. The control group was treated with 0.5mls of normal saline while B and C were treated with 0.5mls corresponding to 3 and 6 mg/kg body weight of the drug respectively and were administered intra-peritoneally for seven (7) days.

The pregnant wistar albino rats were sacrificed 24 hours after the last administration in accordance with the guide lines of the European Convention for the protection of vertebrate animals and other scientific purposes-ETS-123 (European Treaty Series, 2005).

Preparation of Serum

The animals were anaesthetized in a jar containing cotton wool soaked in ether. When the animals became unconscious, they were brought out quickly of the jar, the abdominal region was opened along the linear Alba and diaphragm cut with scalpel blade to expose the organs and blood was collected into a sterile sample container by cardiac puncture. Blood was collected into a clean, dry centrifuge tube and allowed to clot for 30 minutes before centrifuging at 300rpm x 10min using Uniscope Laboratory Centrifuge.

The serum was thereafter aspirated into clean, dry, sample bottles using Pasteur pipette and was kept or stored in sample bottles and used within 12hours of preparation as described by (Malomo, 2000). Later it was transferred into specimen bottles before being used for biochemical analysis.

Statistical Analysis

Statistically analysed data used was presented as mean ± SD of five (5) determinations. Statement analysis was carved out using one way analysis of variance (ANOVA). Differences were statistically significant at P<0.05 (Mahajan, 1997).

RESULTS

The results below depict the effect of administration of artemsinin-based combination therapy on some selected liver function indices of pregnant wistar albino rats. Table 1 showed a significant increase (P<0.05) in serum ALT, AST and ALP. The ratio of AST: ALT and AST: ALP produced a significant (P<0.05) increase following the administration of the drug to the pregnant wistar albino rats (Table2). More so, artemisinin-based combination therapy produces a significant (P<0.05) elevation on both total and conjugated serum bilirubin level at both 3mg and 6mg per kg body weight when compared with control (Table 3).

Table. 1: Effect of artemisinin-based combination therapy on serum enzymes.

Group	ALT (IU/L)	AST(IU/L)	ALP(IU/L)
A (Control)	73.6±9.0	79.8±38.8	93.2 ±23.4
B(Treated with 3mg/kg b.w of the drug	87.8 ±20.3	303.6 ±23.7*	134±6.8
C(Treated with 6 mg/kg b.w of the drug)	196±67.1*	386.8±24*	154±3.2*

Results are expressed in mean ± SEM (n=5).* Significant at P<0.05 compared with the control

Table. 2: Effect of artemisinin-based combination therapy on serum enzyme ratio

Group	AST/ALT (IU/L)	AST:ALP(IU/L)
Control (A)	1.08±4.3	0.85±0.2
B(Treated with 3mg/kg b.w.of the drug	3.46±2.1*	2.26±1.2*
C(Treated with 6mg/kgb.w of the drug	1.97±3.22	2.44±2.1*

Results are expressed in mean ± SEM (n=5).* Significant at P<0.05 compared with the control.

Table. 3: Effect of artemisinin-based combination therapy on serum bilirubin concentration.

GROUP	Total Bilirubin (IU/L)	Conjugated Bilirubin (IU/L)
A (Control)	41±10.2	54±1.3
B (Treated with 3mg/kg b.w of the drug)	39.5 ±2.2*	65±2.1*
C (Treated with 6mg/kg b.w of the drug)	118.2±3.3*	129.4±3.4*

Results are expressed in mean ± SEM (n=5).* Significant at P<0.05 compared with the control

DISCUSSION

The hepatocyte membrane distortion is associated with membrane leakage of the hepatocyte cytosolic contents which is manifested by significant elevation of serum/plasma enzymes of acute hepatocellular damage namely ALT, AST and ALP as a marker of hepatocellular damage (Bhaltacharyya *et al.*, 2003). However of this marker enzymes, ALT is the most reliable. AST is known to be abundant in the cardiac muscles, skeletal muscles, kidneys and testes. Thus, any disease state affecting any of these extra hepatic tissues, significantly elevates the serum level of enzymes (Olayinka and Ore, 2013).Therefore, the observed significant increase in serum ALT, AST and ALP when compared with the control at both dosages of the treated animals suggest that the drug might induce hepatic damage or hepatotoxicity in the pregnant albino rats. These findings are similar to the findings of other researchers (Farombi *et al.*, 2000; Obi *et al.*, 2004; Pari and

Anuli, 2005). Researchers have shown that other antimalarial drugs such as chloroquine, amodiaquine, quinine and halofrantrine were also reported to elevate serum ALT and ALP and may induce hepatic damage (Nwanjo and Oze, 2007; Adaramoye *et al*., 2008; Udobre *et al*., 2009). The observed elevation AST: ALT and AST: ALP ratios, are indications of hepatic injury (Nyblom *et al*., 2004; Nyblom *et al*., 2006) .

Likewise, the significant increase in the serum level of both total bilirubin and conjugated bilirubin is an indication that the drug (ACTs) might induce injury to the hepatic tissue or caused conjugated hepatobilliary injury on the pregnant wistar albino rats which might also signal an inimical effect on the foetus.

Though pregnancy itself induces some abnormalities on the liver, including cholestasis (resulting in raised conjugated bilirubin and ALP) and in cases of pre-eclampia, the HELLP Syndrome (Haemolysis elevated liver enzymes and low platelet) Jamjute *et al*., 2009*).* It might thus become necessary to exercise special caution in the usage of artemether-lumefantrine in the management of malaria in pregnancy. Artesunate -sulfadoxine/pyrimethamine might thus continue to remain the drug of choice in the intermittent prevention of malaria in pregnancy (Schantz *et al*., 2009). Thus, it is logical to conclude that various alterations in the selected biochemical parameters studied above showed that artemisinin-based combination therapy might induce hepatotoxicity or hepatobilliary injury in pregnancy.

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