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# Evaluation of biochemical indices following administration of artemether, halofantrine and a combination of artemether and lumefantrine in guinea pigs

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**ABSTRACT**

Combination of artemether and lumefantrine (artemether-lumefantrine) is an orally effective artemisinin-based combination therapy, used widely in the treatment of *Plasmodium falciparum* infections. The present study investigates the comparative effects of artemether, halofantrine and artemether-lumefantrine on biochemical indices in the male guinea pig. Half, normal and double therapeutic doses of the drugs were given to different groups of animals (n=5) by oral gavage. After the drug treatments, serum levels of biochemical parameters were measured using standard methods. Artemether significantly ($p<0.05$) reduced uric acid (UA) level (10.44%), but produced no significant effects on the other parameters measured. Halofantrine and artemether-lumefantrine significantly increased acid phosphatase- ACPT (56.13 and 26.45%) and prostatic acid phosphatase-ACPP (100.00 and 78.95%) respectively, while alkaline phosphatase (ALP) was not affected. In addition, halofantrine and artemether-lumefantrine significantly and dose-dependently decreased UA, while urea and creatinine levels were increased. UA was decreased by 12.15 and 17.92%; urea was increased by 84.42 and 53.25%; and creatinine was increased by 42.15 and 30.25%, respectively. Furthermore, both drugs had no significant effects on serum levels of total protein and cholesterol. The results show that halofantrine and artemether-lumefantrine may cause toxicity to renal and reproductive functions in the male guinea pig, halofantrine likely to cause more of these effects.

## INTRODUCTION

Effective treatment of malaria has been a major challenge to medicine. This is majorly due to resistance of the Plasmodium parasite (the causative organism of the disease) to antimalarial agents (Yeung *et al.,* 2004; Sharma, 2005) and partly due to the prevalence and endemicity of the disease, especially in the tropical regions (Sachs and Malaney, 2002). Artemether-lumefantrine, a fixed-dose combination drug, containing artemether (an artemisinin derivative) and lumefantrine (an aryl amino alcohol), is one of the approved artemisinin-based combination therapies (ACTs). Artemether-lumefantrine and its component drugs are potent blood schizontocidal antimalarial agents which are used increasingly in the treatment of Plasmodium infections (Katzung**,** 2004; Price *et al.,* 2006). Artemether-lumefantrine and other ACTs have been shown to have high efficacy against malaria parasite because of their high killing rates (Adjuik *et al.,* 2004; Mueller *et al.,* 2006; van Vugt *et al.,* 2006). They are therefore recommended as the choice drugs for the treatment of uncomplicated and multiple-drug resistant malaria (Olliaro and Taylor, 2004; Nosten and White, 2007). Halofantrine is a phenanthrene methanol and a structurally related compound to lumefantrine. It is active against all forms of human malaria parasites, including chloroquine and multi-drug–resistant *P. falciparum* (Katzung, 2004; Price *et al.,* 2006).

Artemisinins and ACTs (including artemeter-lumefantrine) are considered to be relatively safe drugs (Adjuik *et al.,* 2004; Nosten and White, 2007), however, there have been recent concerns on their anti-fertility and anti-androgenic effects in experimental animals (Nwanjo *et al.,* 2007; Aprioku and Obianime, 2011). Halofantrine has also been reported to alter male reproductive function (Didia *et al.,* 2002; Orisakwe, *et al.,* 2003) as well as being cardiotoxic (Nosten *et al.,* 1993; Katzung, 2004). In addition, artemisinins, halofantrine and artemether-lumefantrine have been shown to adversely affect hepatic enzymes in animal

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models (Obi *et al.,* 2004; Adaramoye *et al.,* 2008) and not much is known about their effects on other biochemical parameters. Furthermore, most of the previous studies did not show dose-dependent relationships and there are limited reports on the biochemical effects of these drugs in the guinea pig system, which has better drug metabolism, compared to the other animal models previously used (Gregus *et al.,* 1988; Turpeinen *et al.,* 2007). The present study is thus intended to investigate the comparative dose-related effects of artemether-lumefantrine and its combinant drugs: artemether and lumefantrine (represented by halofantrine) on the serum levels of phosphatase enzymes, urea, creatinine, uric acid, total cholesterol and total protein in male guinea pigs.

## MATERIALS AND METHODS

### Chemicals

The drugs used: artemether (Paluther$^R$) injection (Aventis InterContinental, France), halofantrine (Halfan$^R$) tablets (Glaxo SmithKline, UK) and artemether-lumefantrine (Coartem$^R$) tablets (Norvatis Pharmaceuticals Corporation, USA) were obtained from the Pharmacy unit of the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria. Alkaline phosphatase kits (QCA, S.A, Amposta/Spain); acid phosphatase, uric acid, urea, total protein, creatinine and cholesterol kits (Randox Laboratory Ltd. UK) were also obtained from the Department of Chemical Pathology of the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria. All other chemicals were of reagent grade. The tablets were powdered in a glass mortar and administered as aqueous suspension by oral gavage. The drug suspensions were continuously agitated during administration in order to deliver the drugs homogeneously to the animals. Artemether was administered intramuscularly, using a 1 ml syringe.

### Animals

Outbred strains of adult male guinea pigs (*Cavia porcellus*) weighing between 650-670 g and aged 20-21 weeks were obtained from the animal house of the Department of Pharmacology, University of Port Harcourt, Nigeria. The animals were allowed to acclimatize for 14 days in a well ventilated room at a room temperature of 28.00±2.00$^o$C under natural lighting condition. They were housed in shoebox cages with wire bar lids. Bedding was provided to allow absorption of urine. The animals were fed with standard rodent chow (Topfeeds Ltd, Sapele, Nigeria) and allowed free access to tap water *ad libitum*. All the animals used in this study were handled in accordance with the international, national and institutional guidelines for Care and Use of Laboratory Animals as promulgated by the Canadian Council of Animal Care (2009).

### Methods

Fifty (50) adult male guinea pigs were randomly distributed into ten groups (A, B, C, D, E, F, G, H, I and J) containing five animals per group. The animals in group A were given 3.2 mg/kg of artemether on the first day, followed by 1.6 mg/kg twice daily for two consecutive days. This is equivalent to its therapeutic dose for the treatment of uncomplicated malaria (Khan *et al.,* 2006). Group B animals were given 1.6 mg/kg of artemether on the first day, followed by 0.8 mg/kg twice daily for two consecutive days (half therapeutic dose). Group C received 6.4 mg/kg of artemether on the first day, followed by 3.2 mg/kg twice daily for two consecutive days (double therapeutic dose). The animals in group D were given 8 mg/kg of halofantrine, every six hours x 3 doses, which is equivalent to its therapeutic dose for the treatment of uncomplicated malaria (Khan *et al.,* 2006). The animals in group E were given 4 mg/kg of halofantrine, every six hours x 3 doses (half therapeutic dose), while Group F received 16 mg/kg of halofantrine, every six hours x 3 doses, equivalent to double its therapeutic dose. The animals in group G were given 2.2/13.6 mg/kg of artemether-lumefantrine at 0, 8, 24, 36, 48 and 60 hrs, which is equivalent to its therapeutic dose for the treatment of uncomplicated malaria (van Vugt *et al.,* 2006). Group H received 1.1/6.8 mg/kg artemether-lumefantrine at 0, 8, 24, 36, 48 and 60 hrs (half therapeutic dose). Group I had 4.4/27.2 mg/kg artemether-lumefantrine at 0, 8, 24, 36, 48 and 60 hrs (double therapeutic dose). Group J animals were given only distilled water for 3 days to serve as the control.

Animals were sacrificed after drug treatments. Blood samples were collected, allowed to clot and centrifuged for 15 min at 3,000 rpm. Clear serum was then separated from the cells and assayed for biochemical parameters.

### Biochemical assays

Serum alkaline phosphatase level was measured by the phenolphthalein method as described by Babson et al. (1966), total and prostatic acid phosphatases by colorimetric method (Fishman and Davidson, 2006); urea by urease-Berthelot method (Weatherbum, 1967); uric acid by enzymatic colorimetric method (Fossati *et al.,* 1980); and creatinine was measured by alkaline picrate method (Tietz *et al.,* 1986). Furthermore, the biuret method was used for serum total protein assay as described by Henry et al. (1974), while total cholesterol was assayed using the enzymatic endpoint method (Roeschlau *et al.,* 1974).

### Statistical analysis

Data were expressed as means ± standard errors of mean. Comparisons between control values and values obtained in experimental guinea-pigs were performed with one-way analysis of variance (ANOVA). Statistical significance was set at $p<0.05$.

## RESULTS

### Effects on serum levels of phosphatase enzymes

Artemether produced no significant ($p>0.05$) effects on phosphatase enzyme levels (Figures 1, 2 and 3). On the contrary, the serum levels of total acid phosphatase (ACPT) and prostatic acid phosphatase (ACPP) were significantly ($p<0.05$) increased by halofantrine and artemether-lumefantrine, while there was no significant ($p<0.05$) effect on serum alkaline phosphatase (ALP)

levels (Figures 1, 2 and 3). While the effect of halofantrine on ACPT was dose-dependent, that of artemether-lumefantrine was biphasic (Figure 2). The maximum serum level of ACPT in halofantrine-treated animals (24.20±1.30 IU/L) was obtained at the double therapeutic dose, while the maximum serum level in artemether-lumefantrine-treated animals (19.60±1.10 IU/L) was obtained at the therapeutic dose. Compared to 15.50±1.00 IU/L obtained in the control animal group, these values represented 56.13 and 26.45% increases, respectively (Figure 2). Furthermore, the effects of halofantrine and artemether-lumefantrine on ACPP were dose-dependently higher than the control, with maximum serum levels of 7.60±0.25 IU/L and 6.80±0.30, respectively, compared to 3.80±0.30 IU/L in the control animal group (Figure 3). These values were equivalent to 100.00 and 78.95% increases, respectively.

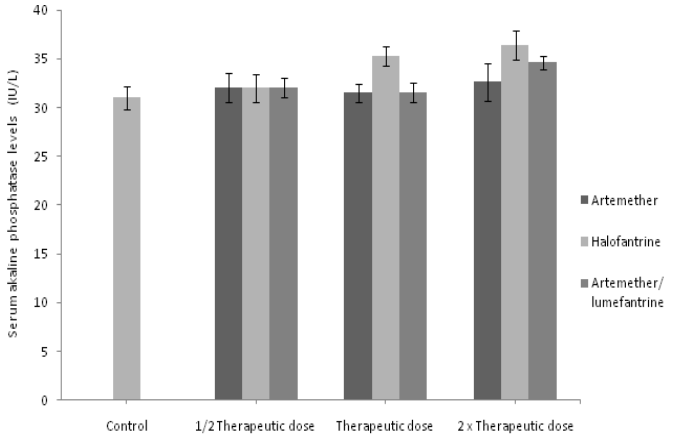


**Fig. 1:** Artemether-, halofantrine- and artemether-lumefantrine-induced serum levels of alkaline phosphatase in guinea pigs. Data are expressed as mean ± SEM.

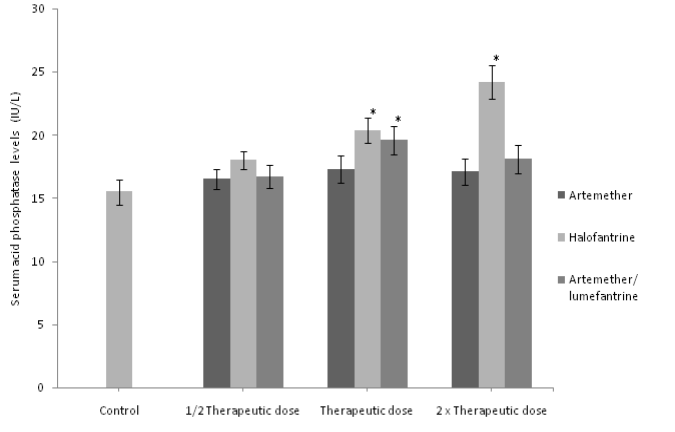


**Fig. 2:** Artemether-, halofantrine- and artemether-lumefantrine-induced serum levels of acid phosphatase in male guinea pigs. Data are expressed as mean ± SEM. * Significant at p<0.05 ANOVA.

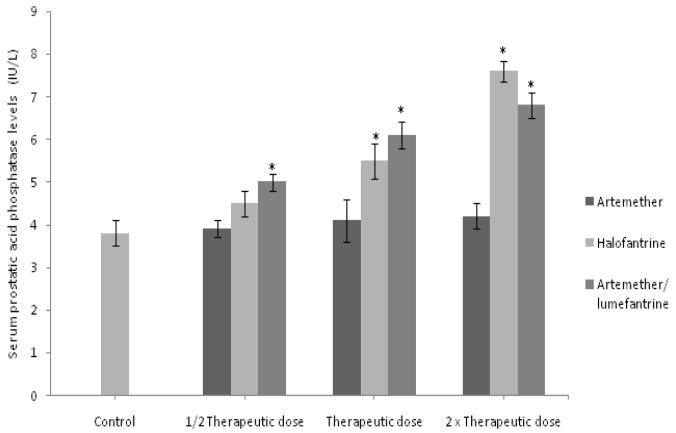


**Fig. 3:** Artemether-, halofantrine- and artemether-lumefantrine-induced serum levels of prostatic acid phosphatase in male guinea pigs. Data are expressed as mean ± SEM. * Significant at p<0.05 ANOVA.

**Effects on serum levels of other biochemical parameters**

Artemether significantly (p<0.05) reduced uric acid (UA) level by 10.44% (Figure 6) and had no significant effects on urea, creatinine, total protein and cholesterol (Figures 4, 5, 7 and 8). In addition, serum urea and creatinine levels were significantly (p<0.05) and dose-dependently increased in halofantrine and artemether-lumefantrine administered animals (Figures 4 and 5). The serum levels of urea and creatinine in animal groups that were given double therapeutic dose of halofantrine were 14.20±1.10 g/L and 86.00±5.00 µmol/L, respectively, while the values obtained in artemether-lumefantrine-treated animals were 11.80±1.00 g/L and 78.80±5.30 µmol/L, respectively (Figures 4 and 5). Compared to their control serum levels (7.70±0.60 g/L and 60.50±4.70 µmol/L, respectively), halofantrine increased urea and creatinine by 84.42 and 42.15, respectively; while artemether-lumefantrine increased same parameters by 53.25 and 30.25 %, respectively (Figures 4 and 5).

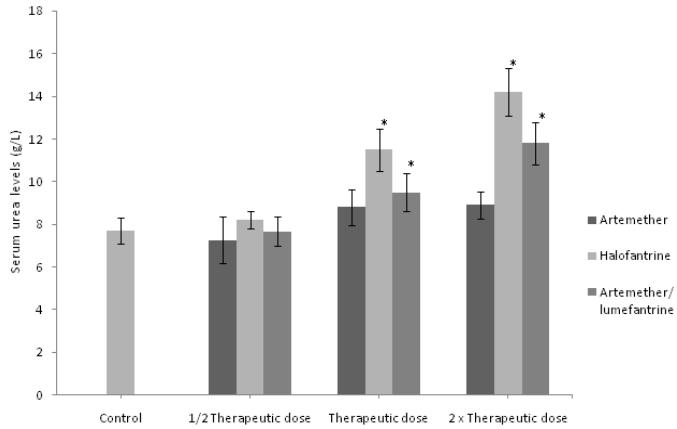


**Fig. 4:** Artemether-, halofantrine- and artemether-lumefantrine-induced serum levels of urea in male guinea pigs. Data are expressed as mean ± SEM. * Significant at p<0.05 ANOVA.

Furthermore, both drugs significantly ($p<0.05$) and dose-dependently decreased the serum concentration of uric acid (Figure 6). The serum uric acid level induced by double therapeutic dose halofantrine (324.00±6.10 mmol/L) and double therapeutic dose artemether-lumefantrine (302.70±6.80 mmol/L) were lower than (368.80±7.10 mmol/L) obtained in the control animals (Figure 6).

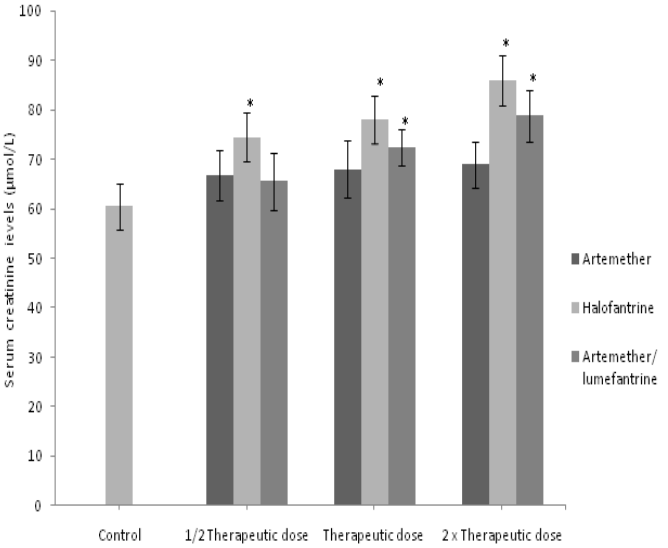


**Fig. 5:** Artemether-, halofantrine- and artemether-lumefantrine-induced serum levels of creatinine in male guinea pigs. Data are expressed as mean ± SEM. * Significant at $p<0.05$ ANOVA.

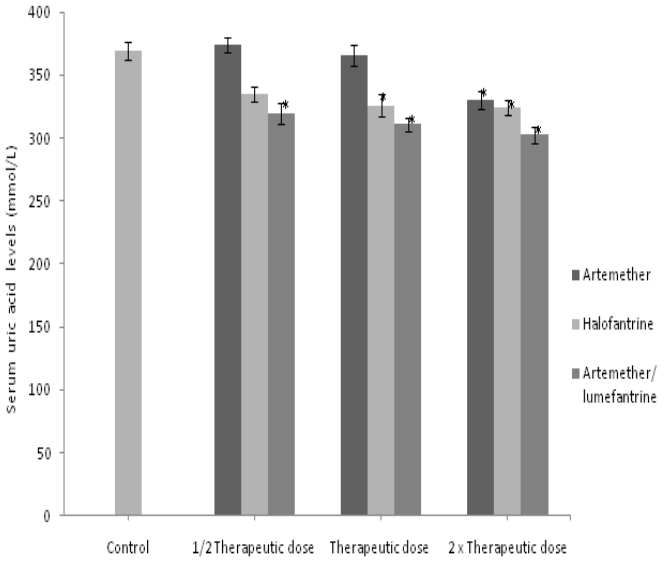


**Figure 6:** Artemether-, halofantrine- and artemether-lumefantrine-induced serum levels of uric acid in male guinea pigs. Data are expressed as mean ± SEM. * Significant at $p<0.05$ ANOVA.

These vales represented percentage decreases of 12.15 and 17.92 %, respectively. Furthermore, halofantrine and artemether-lumefantrine caused no significant ($p>0.05$) effects on total protein and total cholesterol serum levels (Figures 7 and 8).

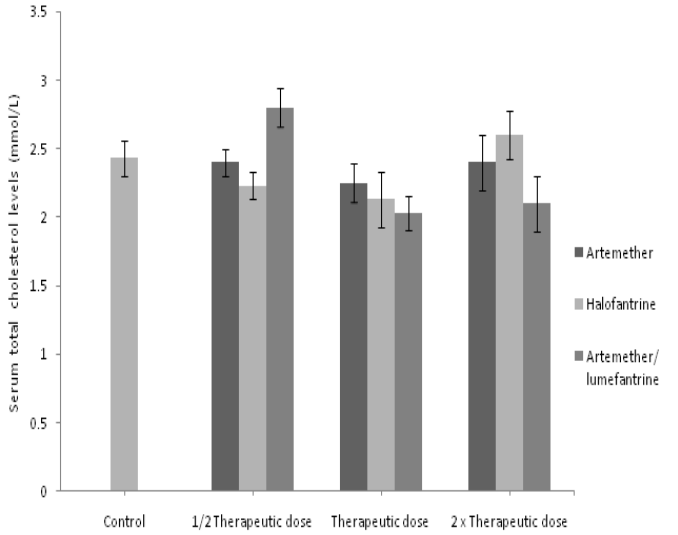


**Fig. 7:** Artemether-, halofantrine- and artemether-lumefantrine -induced serum levels of total cholesterol in male guinea pigs. Data are expressed as mean ± SEM.

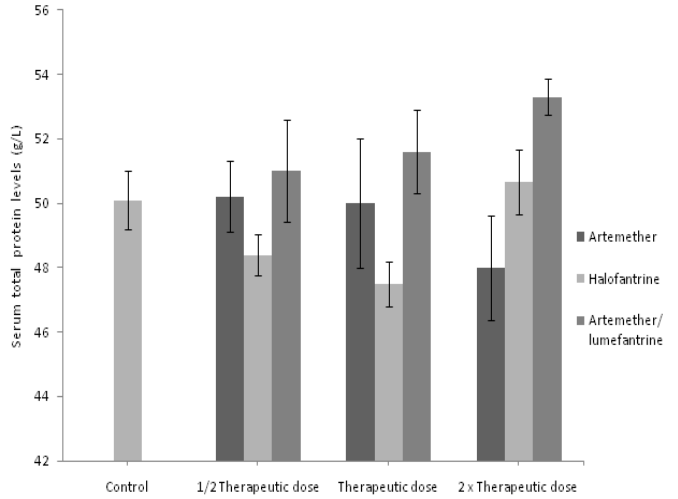


**Fig. 8:** Artemether-, halofantrine- and artemether-lumefantrine -induced serum levels of total protein level in male guinea pigs. Data are expressed as mean ± SEM.

## DISCUSSION

The present study is aimed at evaluating the relative biochemical effects of artemether-lumefantrine, an artemisinin-based combination therapy (ACT) and its component drugs, artemether and lumefantrine in male guinea pigs. Lumefantrine is represented with its chemically related drug, halofantrine in this study and the biochemical parameters investigated are: phosphatase enzymes, urea, creatinine, uric acid, cholesterol and total protein.

Alkaline phosphatase (ALP) and total acid phosphatase (ACPT) are produced in the liver, kidney and bone, where they play vital roles in normal biochemical processes in the body. In addition, human prostatic acid phosphatase (ACPP) and ACPT are major phosphatase enzymes and their serum concentrations are differentiation markers in normal, well-differentiated prostate

epithelial and testicular cells (Lin *et al.*, 1980; Wetterauer, 1986; Chu and Lin 1998). These enzymes exist in the serum at specific concentrations, but may be secreted excessively into the blood when there is tissue injury, resulting in elevations of their serum concentrations. The serum levels of these enzymes are therefore used as surrogate markers of toxicities of the appropriate tissues/organs (Yam, 1974; Wetterauer, 1986; Chu and Lin 1998). In the present study, while artemether caused no ($p<0.05$) significant effects on phosphatase enzymes, halofantrine and artemether-lumefantrine significantly ($p<0.05$) increased the serum levels of ACPT and ACPP, without significant effects on ALP. The effects of halofantrine on ACPT and ACPP were dose-dependent and their serum levels were increased by 56.13 and 100.00 %, respectively. The effect of artemether-lumefantrine on ACPP was dose-dependent, while it was biphasic on ACPT. Maximum reduction in serum ACPT concentration (26.45%) was obtained at the therapeutic dose, while similar effect on ACPP (78.95%) was obtained at the double therapeutic dose of the drug. The results indicate that artemether-lumefantrine and halofantrine may be toxic to testicular tissues. This is consistent with previous findings (Orisakwe *et al.,* 2003; Nwanjo *et al.,* 2007; Obianime and Aprioku, 2009; Aprioku and Obianime, 2011). Furthermore, while there were no significant ($p<0.05$) changes between the serum levels of artemether-treated and control animals, serum urea and creatinine levels were significantly ($p<0.05$) and dose-dependently elevated by artemether-lumefantrine (53.25, 30.25 %) and halofantrine (84.42, 42.15 %). These results are consistent with the findings of Adaramoye et al. (2008), although the previous study did not show any dose-response relationship, because only single doses of halofantrine and artemether-lumefantrine were used. Additionally, artemether-lumefantrine, halofantrine and artemether caused significant ($p<0.05$) dose-dependent reductions in the serum concentration of uric acid, without significant ($p<0.05$) effects on total protein and cholesterol levels.

Urea and creatinine are metabolic waste products that are freely filtered by the glomeruli of the kidneys and their serum concentrations are commonly used to screen for renal or cardiovascular diseases (Nankivell, 2001). Artemether-lumefantrine - and halofantrine-induced elevations in these parameters in this study is highly suggestive of renal toxicity (Perrone *et al.,* 1992; Nankivell, 2001; Traynor *et al.,* 2006)**.** In addition, uric acid is an antioxidant which scavenges reactive oxygen radicals in the blood (Hooper *et al.,* 2000; Knapp *et al.,* 2004). Significant reduction of serum uric acid levels by artemether-lumefantrine, halofantrine and artemether suggests that the drugs may cause reduction in the antioxidative activity of the animal and cause increase in oxidative stress. This is consistent with the findings of Adaramoye et al. (2008).

The biosynthesis of most of the biochemical parameters measured in this study involves oxidation-reduction (redox) processes (Wyss and Kaddurah-Daouk, 2000). Furthermore, the antiplasmodial mechanisms of action of artemisinins and halofantrine have been shown to involve generation of oxidative free radicals (Robert *et al.,* 2002; de Villiers *et al.,* 2008). Thus, the observations in this study may be due to increase in oxidative stress on the affected tissues or organs by the antimalarial agents.

## CONCLUSION

The present study shows that artemether may have little effect on the serum levels of biochemical markers of renal and testicular function, while halofantrine and artemether-lumefantrine alter their levels and may cause toxicity to the organs. Furthermore, the biochemical effects of halofantrine are more than artemether-lumefantrine, suggesting that the biochemical effects of the ACT may be less than the sum of the individual biochemical effects of its combinant drugs.

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