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## **Evaluation of Nephrotoxic and Hepatotoxic Potential of Artesunate in Malaria Patients**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author UDN designed the study and wrote the protocol. Author HNO wrote the first draft of the work and performed the statistical analyses.*

*Authors UDN and CEU collected the samples and performed the biochemical analysis. Author CEU wrote the second draft of the work. Author CVN carried out the literature review. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Aim:** To evaluate the nephrotoxic and hepatotoxic potentials of artesunate in humans.

**Place and Duration of Study:** Department of Biochemistry, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria, between November and December 2019.

**Methodology:** 70 blood samples were collected from 35 normal individuals (control group), and 35 malaria patients treated with parenteral artesunate (treatment group). These were analyzed for biochemical parameters, including blood urea nitrogen (BUN), creatinine, total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP). The treatment group was further regrouped according to gender (19 males and 16 females), age (20 patients aged 20-29 and 15 patients aged 30-40 years) and duration of treatment (29 patients on 3<sup>rd</sup> or 4<sup>th</sup> day and 6 patients on 5<sup>th</sup> or 6<sup>th</sup> day of treatment). Biochemical tests were carried out using

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standard Randox test kits. One-way ANOVA was done on the parameters using statistical package for social sciences (SPSS), and comparisons were made.

**Results:** Compared to control group, the treatment group showed significant increases ( $p < 0.05$ ) in BUN ( $15.89 \pm 1.30$  against  $11.69 \pm 0.62$ ), Creatinine ( $0.96 \pm 0.62$  against  $0.82 \pm 0.03$ ) and AST ( $22.14 \pm 2.45$  against  $16.66 \pm 0.85$ ), a non-significant increase ( $p > 0.05$ ) in ALT ( $26.57 \pm 3.18$  against  $21.66 \pm 2.56$ ) and ALP ( $85.31 \pm 4.06$  against  $77.54 \pm 3.09$ ) and a non-significant decrease ( $p > 0.05$ ) in total bilirubin ( $0.59 \pm 0.06$  against  $0.65 \pm 0.06$ ). However, all parameters examined were within the normal ranges. There was no significant relationship found in any parameter in a comparison of gender, age and duration of treatment.

**Conclusion:** Since all parameters examined were in the normal ranges, administration of artesunate in the recommended dosage and the right duration may not have any significant toxic effect on the kidney and liver. However, further studies may be necessary to ascertain if the observed elevations could be attributed wholly to artesunate or other medications taken by the malaria patients.

**Keywords:** Artesunate; hepatotoxic; nephrotoxic; gender; age; duration.

## 1. INTRODUCTION

Artesunate is one of the chemosynthetic derivatives of artemisinin, a sesquiterpene lactone endoperoxide, derived from the *Artemisia annua* weed commonly called the annual wormwood [1]. Artemisinin derivatives are new generation antimalarial drugs effectively used to treat acute malaria, including chloroquine-resistant malaria. Artesunate has been used singly and in combination with other agents to treat malaria. Some of the popular artemisinin-based combination therapy (ACT) include artesunate/ sulfadoxine/ pyrimethamine, artesunate/amodiaquine and some combination of these [2]. These combinations, especially artesunate/amodiaquine has been very useful because they are quite affordable and efficacious in the treatment of uncomplicated, severe and multidrug-resistant falciparum malaria in most parts of Africa [1]. Hence, intravenous artesunate has become a preferred alternative to intravenous quinine in the treatment of severe malaria [3].

Artesunate is a water-soluble prodrug with different routes of administration including parenteral, oral and per rectal [4]. Malaria parasite causes metabolic acidosis through erythrocyte destruction. Artesunate is a rapidly acting blood schizonticide which exerts its antimalarial activity by generating reactive oxygen species (ROS) capable of destroying *Plasmodium* species. It is converted to active metabolite dihydroartemisinin which tightly binds to parasite-infected erythrocyte membrane then inhibits the sarcoplasmic/endoplasmic reticulum calcium ATPase encoded by *P. falciparum* [5],

thereby restoring erythrocyte numbers and thereby preventing malaria progression.

Some studies have reported artesunate capable of altering blood and other body parameters. In one study, artesunate reduced biochemical parameters like K, Cl,  $\text{HCO}_3$ , Na and the body's defence system like white blood cells (WBC) and Neutrophils [1]. In another study using rats and rabbits, artesunate was reported to induce abortion in rabbits, resorptions, low incidence of cardiovascular malformations and skeletal defect at artesunate doses close to embryolethal in both rat and rabbit newborns, but with no maternal toxicity observed. The same study reported no adverse drug-related developmental defects observed in a case of over 700 pregnant women treated with artesunate [6].

Other studies have investigated the potential of artesunate in the treatment of diseases other than malaria. In a study using collagen to induce arthritis in rat models, Ma et al. found artesunate capable of suppressing inflammation and preventing bone and cartilage destruction suggesting its potential as an anti-rheumatic drug for the treatment of rheumatoid arthritis [7]. Artesunate was also reported capable of inhibiting lysosomal function in cells. Since some cancer cells use lysosomal secretions to degrade drug, thereby forming a resistance to such drugs, this study suggests insight into the treatment of such cancer using artesunate [8]. Further, Kong et al. conducted an *In vitro* and *In vivo* study to evaluate the effect of artesunate on rats induced with liver fibrosis using carbon tetrachloride ( $\text{CCl}_4$ ). In this study, artesunate was found to alleviate liver fibrosis once more, suggesting its potential in the treatment of liver fibrosis [9].

In a study using rats to examine the effect of artemisinins on behavioural performance (auditory discrimination task – ADT) and neurotoxicity (brain histological examinations), no significant damage was observed for artesunate and arteether. However, arteether showed a severe progressive decline in ADT and marked damage in different parts of the brain [10]. In another study, several complications including liver failure, renal insufficiencies and finally death, were reported for a five years old boy administered rectal artesunate for treatment of malaria. However, this seems to be a case of overdosing, as he was administered adult doses totalling 88 mg/kg/day for four days against the recommended 4 mg/kg/day [11].

The effect of artesunate on biochemical parameters has also been studied. According to a report by Bigoniya et al. involving rats, administration of artesunate at 8 mg/kg/day for 45 days increased alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), triglycerides (TG), total cholesterol (TC), total bilirubin (TB), glucose, white blood cells (WBC), eosinophil, neutrophil, packed cell volume (PCV) and mean cell hemoglobin, but showed no significant effect on total protein (TP), albumin, creatinine, urea, hemoglobin, total red blood cells (RBC), lymphocytes, platelets, basophil, mean corpuscular hemoglobin concentration and mean cell volume [12]. On the contrary, a study by Hamman et al. also using rat models administered artesunate at 1, 2 and 5 mg/kg/day for five days reported no observed changes in serum AST, ALT, ALP and non-significant differences in RBC, WBC, and differential counts (DC) [13].

Given the wide acceptance of artesunate as first-line treatment for falciparum malaria, there is a need to study its effect on crucial body organs such as the kidney and liver. Although some studies have evaluated the effect of artesunate on biochemical parameters, some reports seem to contradict while still others varied based on the animal models used for the study, establishing a need for such studies using human models. Since it is recommended to administer parenteral artesunate for few days without exceeding seven days and continue treatment with oral ACT, there was a need to compare artesunate effect in the typical duration of administration (3-4 days) with the extreme duration (5-6 days). Also, people within an age bracket are generally exposed to

some underlying health conditions which may influence drug effect [14], posing a need to investigate artesunate effect based on age. Therefore, the present study evaluated the possible nephrotoxic and hepatotoxic effect of artesunate administered in humans for the treatment of malaria and made a comparison of effect based on gender, age and duration of administration.

## 2. MATERIALS AND METHODS

### 2.1 Chemicals and Equipment Used

Water bath (thermoshaake, S.W.B), Weighing balance (Ohaus's, cooperation, USA), Spectrophotometer (Ryan, Science and Instrument Company England), Mechanical Shaker, and Bench Centrifuge. Standard RANDOX kits were used to perform biochemical tests following instructions as outlined in the manual.

### 2.2 Sample Collection

Test group samples were collected from patients receiving malaria treatment at the Federal Medical Center (FMC), Umuahia, Abia State, Nigeria. Control group samples were collected from willing donors in Umuahia axis, mostly students of the Michael Okpara University of Agriculture, Umudike, Umuahia, Abia State, Nigeria.

### 2.3 Experimental Design

Blood samples were collected from 70 willful donors as follows:

Control group: 35 normal individuals

Treatment group: 35 malaria patients receiving treatment with parenteral artesunate.

The treatment group was further regrouped, according to:

Gender: 19 males and 16 females

Age: 20 patients aged 20-29 and 15 patients aged 30-40 years, and

Duration of treatment: 29 patients on 3<sup>rd</sup> or 4<sup>th</sup> day and 6 patients on 5<sup>th</sup> or 6<sup>th</sup> day of treatment.

## 2.4 Biochemical Tests

Urea, creatinine, total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) were determined using standard Randox test kits following the directions on the product manual.

## 2.5 Statistical Analysis

All data were analyzed statistically using the Statistical Package for Social Sciences (SPSS) (Version 20). The data were expressed as mean  $\pm$  standard error. Comparisons were made between the groups using the one-way Analysis Of Variance (ANOVA). The results were considered statistically significant at  $P < .05$ .

## 3. RESULTS

A comparison of treatment group against control group as shown in Table 1 indicates a significant increase ( $p > 0.05$ ) in Urea ( $15.89 \pm 1.30$  against  $11.69 \pm 0.62$ ), Creatinine ( $0.69 \pm 0.62$  against  $0.82 \pm 0.03$ ) and AST ( $22.14 \pm 2.45$  against  $16.66 \pm 0.85$ ), a non-significant increase ( $p > 0.05$ ) in ALT ( $26.57 \pm 3.18$  against  $21.66 \pm 2.56$ ) and ALP ( $85.31 \pm 4.06$  against  $77.54 \pm 3.09$ ) and a non-significant decrease ( $p > 0.05$ ) in total bilirubin ( $0.59 \pm 0.06$  against  $0.65 \pm 0.06$ ).

Table 2 shows that a comparison of men against women indicates a non-significant decrease ( $p > 0.05$ ) in urea and creatinine and a non-significant increase ( $p > 0.05$ ) in Total bilirubin, AST, ALT and ALP.

Table 3 indicates a non-significant increase ( $p > 0.05$ ) in all the parameters for people aged 30-40 against people aged 20-29.

A comparison of duration of treatment as in Table 4 shows a non-significant decrease ( $p > 0.05$ ) in all parameters for people receiving treatment for 5-6 weeks against 3-4 weeks, except ALP that showed a non-significant ( $p > 0.05$ ) increase.

## 4. DISCUSSION

Urea is a waste product of metabolism produced when proteins are broken down to produce ammonia which undergoes deamination by liver

enzymes [15]. It is produced in the liver and excreted by the kidney as a component of urine. It has a role in carrying waste nitrogen, and in the nephrons' exchange system, by which water and some critical ions are reabsorbed from excreted urine. Blood urea nitrogen (BUN) concentration depends on protein intake, the ability of the body to catabolize proteins and renal excretion through the kidneys. Elevated levels of BUN may be due to distortion in the glomerulus of the renal tubules, or a decrease in glomerular filtration rate and accumulation of waste products of metabolism that should be excreted in the urine. The typical human reference range for BUN is about 7 to 20 mg/dL. While there was a significant increase in the level of BUN of the artesunate treated group ( $15.89 \pm 1.30$ ) as compared to the normal group ( $11.69 \pm 0.62$ ), the value was very much within the reference range. Hence, the result does not suggest any damage to the kidney. However, the elevation in BUN with the increase in the duration of treatment, though non-significant, may suggest that prolonged use of artesunate above recommendation may lead to renal injuries as reported by Bigoniya et al. [12].

Creatinine is a product of the breakdown of muscle creatine produced at a rate that depends on muscle mass. It is removed from the blood chiefly by the kidneys, primarily by glomerular filtration, but also by proximal tubular secretion. Tubular reabsorption of creatinine rarely occurs. Serum creatinine is an indicator of renal health as its level correlates approximately to glomerular filtration rate (GFR) [16]. However, elevated creatinine is not always representative of a true reduction in GFR. A high reading may be due to increased production of creatinine [17], or decreased tubular secretion of creatinine from blockage, which can be caused by some medications [18]. The typical human reference range for serum creatinine is 0.5 to 1.1 mg/dL for women and 0.6 to 1.2 mg/dL for men. Although there was a significant increase in creatinine of the treatment group ( $0.96 \pm 0.62$ ) over the normal group ( $0.82 \pm 0.03$ ), the value was still within the reference range. This suggests that administration of artesunate at the recommended dosage may not pose a risk to the kidney. No significant relationship was noticed in creatinine levels for comparisons of gender, age and duration of treatment.

**Table 1. Result of biochemical parameters between treatment and control groups**

Groups	Sample size	Urea (mg/dl)	Crea (mg/dl)	T. Bil (u/l)	AST (u/l)	ALT (u/l)	ALP (u/l)
Treatment	35	15.89 ± 1.30 <sup>b</sup>	0.96 ± 0.62 <sup>b</sup>	0.59 ± 0.06 <sup>a</sup>	22.14 ± 2.45 <sup>b</sup>	26.57 ± 3.18 <sup>a</sup>	85.31 ± 4.06 <sup>a</sup>
Control	35	11.69 ± 0.62	0.82 ± 0.03	0.65 ± 0.06	16.66 ± 0.85	21.66 ± 2.56	77.54 ± 3.09

<sup>a</sup> non-significant from control,  $p > 0.05$

<sup>b</sup> significant from control,  $p < 0.05$

Mean ± S.E.M = Mean values ± Standard error of means

**Table 2. Comparison of biochemical parameters of patients in the treatment group based on gender: male versus female**

Groups	Sample size	Urea (mg/dl)	Crea (mg/dl)	T. Bil (u/l)	AST (u/l)	ALT (u/l)	ALP (u/l)
Male	19	15.37 ± 1.47 <sup>a</sup>	0.95 ± 0.08 <sup>a</sup>	0.66 ± 0.09 <sup>a</sup>	23.26 ± 3.34 <sup>a</sup>	30.63 ± 4.37 <sup>a</sup>	86.42 ± 5.42 <sup>a</sup>
Female	16	16.50 ± 2.28	0.96 ± 0.09	0.51 ± 0.09	20.81 ± 3.69	21.75 ± 4.46	84.00 ± 6.30

<sup>a</sup> non-significant from control,  $p > 0.05$

Mean ± S.E.M = Mean values ± Standard error of means

**Table 3. Comparison of biochemical parameters of patients in the treatment group based on age (Years): 20-29 versus 30-40**

Groups	Sample size	Urea (mg/dl)	Crea (mg/dl)	T. Bil (u/l)	AST (u/l)	ALT (u/l)	ALP (u/l)
20-29	20	15.60 ± 1.54 <sup>a</sup>	0.93 ± 0.06 <sup>a</sup>	0.54 ± 0.08 <sup>a</sup>	19.85 ± 3.13 <sup>a</sup>	24.10 ± 3.99 <sup>a</sup>	82.50 ± 5.26 <sup>a</sup>
30-40	15	16.27 ± 2.28	0.99 ± 0.11	0.66 ± 0.11	25.20 ± 3.88	29.87 ± 5.19	89.07 ± 6.45

<sup>a</sup> non-significant from control,  $p > 0.05$

Mean ± S.E.M = Mean values ± Standard error of means

**Table 4. Comparison of biochemical parameters of patients in the treatment group based on the duration of treatment (days): 3-4 versus 5-6**

Groups	Sample size	Urea (mg/dl)	Crea (mg/dl)	T. Bil (u/l)	AST (u/l)	ALT (u/l)	ALP (u/l)
3-4	29	16.14 ± 1.53 <sup>a</sup>	0.96 ± 0.07 <sup>a</sup>	0.60 ± 0.07 <sup>a</sup>	25.17 ± 2.91 <sup>a</sup>	27.59 ± 3.70 <sup>a</sup>	84.97 ± 4.53 <sup>a</sup>
5-6	6	14.67 ± 1.61	0.95 ± 0.07	0.55 ± 0.14	17.17 ± 1.85	21.67 ± 4.78	87.00 ± 9.86

<sup>a</sup> non-significant from control,  $p > 0.05$

Mean ± S.E.M = Mean values ± Standard error of means

Bilirubin is a product of the catabolic breakdown of heme which arises when aged red blood cells are normally destroyed. Elevated levels of serum bilirubin indicate improper liver functioning in clearing the bilirubin, suggesting liver disease or damage [19]. Typical range for adults is: 0.1-1.2 mg/dl. There was no significant increase observed in total bilirubin for all the comparisons, and all the values were within the normal range. This suggests that administration of artesunate poses no risk to the liver. Surprisingly, the total bilirubin level was lower, though non-significantly, in the treatment group ( $0.59 \pm 0.06$ ) than the normal group ( $0.65 \pm 0.06$ ), and the reasons for this decrease is not understood. This was unexpected as malaria parasite leads to the destruction of erythrocytes, and this should normally lead to more production of bilirubin in the catabolism of the erythrocytes.

Aspartate transaminases (AST) and Alanine transaminase (ALT) are liver enzymes used to tract liver damage and other liver diseases. Increased AST and ALT levels suggest damage to the parenchyma tissue of the liver. However, since AST is also a heart and muscle enzyme, it is not a specific marker of hepatic injury as cardiac tissue injury, hemolysis and muscle injury can also lead to elevations [20]. ALT is a more highly specific marker of hepatic injury since it is exclusively a liver enzyme. The normal level of AST in serum is 8 to 40 IU/L while that of ALT is 7 to 56 IU/L. While the levels of AST and ALT for both treatment and normal groups remained within the normal ranges, there was a significant increase in AST level of treatment group ( $22.14 \pm 2.45$ ) over that of the normal group ( $16.66 \pm 0.85$ ). However, this increase may not suggest significant hepatic injury as there was no significant concurrent increase in ALT, which is a more specific marker of liver injury. Nonetheless, the non-significantly increase ( $p > 0.05$ ) in ALT level of the treatment group ( $26.57 \pm 3.18$ ) over the normal group ( $21.66 \pm 2.56$ ), especially as a significant increase in AST accompanied this, may indicate that administration of artesunate above recommended dose and duration may lead to considerable harm. This is in harmony with the report of Omotuyi et al. They recorded elevations in AST and ALT of rats treated with high doses of artesunate and suggested damage to the liver [21]. Therefore, while artesunate administration at the right dosage may pose no significant harm to the liver, care must be taken to avoid overdosing as this may cause significant liver damage.

Alkaline phosphatase (ALP) is a hydrolytic enzyme that removes phosphates from all kinds of molecules such as proteins, nucleotides etc. It is found in cells lining the biliary system. Hence, elevation may indicate damage of the biliary tree due to cholestasis, extra-hepatic or intrahepatic obstruction, or inflammation of the biliary channels. The normal level of alkaline phosphatase is between 45 to 115 IU/L. The ALP level of the treatment group ( $85.31 \pm 4.06$ ) was within the normal range and showed no significant difference from the normal group ( $77.54 \pm 3.09$ ). This indicates there was no obstruction of bile flow and is in harmony with the report of Hamman et al. who observed no significant change in ALP at the right dose of artesunate.

A comparison of different genders, ages and duration of treatment revealed a non-significant difference in all the parameters examined. This could further confirm that artesunate used with the right dosage and to the right duration may pose no risk to the liver and kidneys, especially in average-aged people. There may be a need to examine this effect in people within the extreme age groups, which is children and the elderly.

## 5. CONCLUSION

Since the values of all parameters examined fell under the normal range, we concluded that artesunate might not pose any significant toxic effect to the liver and kidney when the right dose is administered and to the recommended duration. Hence, care should be taken to stick to the recommendations and directions when administering artesunate. Since the patients used for the study may have been on other medications apart from malaria drugs, further studies may be necessary to ascertain if the observed elevations could be attributed wholly to artesunate or the other medications, if any, taken by the malaria patients.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by

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## CONSENT AND ETHICAL APPROVAL

All authors hereby declare that all experiments and sample collections have been examined and approved by the appropriate ethics committee. Consent was given by all donors and approval was also given by the Head of Biochemistry Department, Michael Okpara University of Agriculture, Umudike and Head of Outpatient Department, Federal Medical Center, Umuahia.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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