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Renal Toxicity and Haematological Effect of Luter (An Antimalarial Drug) in Albino Rats

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ABSTRACT

Background and Objective: Malaria is a common disease in tropical and developing countries that affects humans and other animals. Several antimalarial drugs have been reported to cause various side effects on various body organs. This study investigated the effect of luter, an antimalarial drug, on some renal function and haematological parameters in albino rats. **Materials and Methods:** Sixteen adult male albino rats were dived into four groups of four rats each. Group A was the normal control, while groups B, C and D were administered 8.0, 16.0 and 24.0 mg kg^{-1} b.wt., of luter solution, respectively, through oral intubation for 7 days. After 7 days, blood samples were collected from the rats for the assessment of the concentrations of creatinine, urea and uric acid, including Haemoglobin (Hb), Packed Cell Volume (PCV), White Blood Cell (WBC), Red Blood Cell (WBC) and Platelets (PLT) counts. **Results:** A decrease in feed and water intake accompanied by a decrease in physical activities and body weights was observed in the test animals compared to the control. Also, the result of blood assessments showed significantly ($p<0.05$) increases in the levels of creatinine, urea, uric acid and platelets, with significant ($p<0.05$) decreases in haemoglobin, packed cell volume, white blood cells and red blood cells' levels in the test groups compared to the control in a dose-dependent manner. **Conclusion:** Findings suggest that the antimalarial drug, luter may possess both renal and haematological adverse effects. Hence, luter may not be suitable for patients already having renal and haematological disorders.

KEYWORDS

Plasmodium, malaria, luter, artemisinin, renal parameters, haematological parameters, morbidity

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INTRODUCTION

Malaria is a common tropical mosquito-borne infection of which the pathogen is the protozoa in *Plasmodium* species[1]. The vector for *Plasmodium* species is a female A*nopheles* mosquito that inoculates sporozoites contained in her salivary glands into the host's puncture wound when feeding[2]. The *plasmodium* affects blood cells and malaria symptoms are associated with fever, shaking chills, pains, weakness, headache, loss of appetite, nausea and vomiting, among others. About 300 million people are infected word wide yearly by malaria, causing around 1.5 million deaths every year, being the major cause of death morbidity and mortality in West Africa[3]. It is endemic in Sub-Saharan Africa and the greatest burden of the disease is suffered by children below the age of five[4]. The majority of deaths by malaria are caused by *P. falciparum*. Other species of malaria parasites-*P. vivax, P. malariae*, *P. ovale* and *P. knowlesi*

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are less effective in causing mortalities to their hosts[5,6]. Several antimalarial drugs have been developed for both prophylaxis and treatment of *Plasmodium* infections, yet malarial remains one of the deadliest tropical diseases.

Aminoquinolines were the earliest drugs used in the treatment and prevention of malaria, with chloroquine taking the lead from 1934[7]. However, the emergence and spread of resistance of *Plasmodium* parasites in a large population of the African continent had led to the introduction of Artemisinin-based Combination Therapy (ACTs) in the 21st century, of which Zambia was the first African country to adopt ACT treatments in its policy[8]. Artemisinin is a natural anti-malarial derived from the Chinese medicinal plant *Artemisia annua*. The artemisinin derivatives such as artemether, artesunate, etc., are the most effective anti-malarial drugs available today and they have been used with success in areas with multidrug-resistant *Plasmodium falciparum* malaria[9,10]. Luter is among the ACT drugs used in Africa for the treatment of malaria, similar to Coartem and other artemether-lumefantrine (AL) antimalarial drugs.

Luter (80 mg artemether+480 mg lumefantrine) tablet is an artemisinin-based combination drug used for the treatment of malaria in both children and adults. However, it is not suitable for the prevention or treatment of severe/complicated malaria affecting when the brain, lungs or kidneys are affected. Artemether and lumefantrine have different modes of action and act at different points in the parasite life cycle. Oral formulations of AL are available as a tablet and dispersible formulations with similar pharmacokinetic properties[11,12].

Artemether is a lipid-soluble methyl ether of dihydroartemisinin, having a rapid effect against the schizont stage of *P. falciparum* with a parasitemia clearance rate of 30-84 hrs[13]. It functions by interfering with parasite transport proteins, disrupting parasite mitochondrial function, inhibiting angiogenesis and modulation of host immune function[14]. Lumefantrine is aryl-amino alcohol[15] that prevents detoxification of heam, such that toxic heam and free radicals induce parasite death[16]. Absorption of lumefantrine occurs 2 hrs after oral intake, reaching peak plasma concentration after 3-4 hrs[17]. It has a half-life of 3-6 days and is responsible for preventing recurrent malaria parasitemia[18].

Like some other drugs, the use of luter in malarial treatment may be associated with some possible side effects on the kidney during elimination/excretion and the blood cells. Therefore, this study aimed to determine the effect of oral administration of luter on some renal and haematological parameters in albino rats.

MATERIALS AND METHODS

Study Area: This study was carried out in May, 2020 at the animal house and the Laboratory of the Biochemistry Department of Ebonyi State University, Abakaliki, Nigeria.

Materials

Drug: One pack of luter (artemether 80 mg+lumefantrine 480 mg) containing six film-coated tablets (by Hovid Company) was purchased from Clanol Pharmacy, Abakaliki, Ebonyi State, Nigeria.

Chemicals/reagents: All reagents used in this research were of analytical grades and included: Uric acid reagent, diacetyl monoxide, 4-aminoantiprine, uricase, peroxidase and buffer. The assay kits were products of Randox Laboratories Limited, BT29 4QY, United Kingdom.

Apparatus/equipment: Spectrophotometer (LKB, Bechion), weighing balance (Merek, England), microhematocrit centrifuge (Haematospin 1400, Hawkey England).

Methods

Animal management: Twenty male healthy outbred albino rats weighing between 126 and 162 g were purchased from the Department of Zoology, University of Nigeria, Nsukka and transferred to the animal house, Department of Biochemistry, Ebonyi State University, Nigeria in steel cages. The rats were acclimatized for 7 days at room temperature and maintained *ad libitum* on water and feed. Their weights were checked with a weighing balance before the experiment and daily till the end of the experiment. Their weights were used to determine the actual volume of drug solution to be administered and the effect of the drug on the rats.

Preparation of drug: Luter 80/480 mg, 6 tablets were dissolved in 200 mL of distilled water to obtain 0.2 g mL^{-1} of drug solution.

Experimental design: The animals were randomly selected and placed in four (4) groups: A, B, C and D with four animals in each group. Group A was given only distilled water the normal control group, while groups B, C and D were administered 8.0, 16.0 and 24.0 mg kg^{-1} b.wt., of luter solution, respectively, through oral intubation for 7 days. They were allowed free access to feed (growers mash) and water before and throughout the experiment.

Collection of blood sample: After treatment for 7 days, the animals were fasted overnight and sacrificed under anaesthesia using chloroform and blood samples were collected by cardiac puncture into both sterile anticoagulant-free bottles and EDTA bottles for renal and haematological parameters, respectively. The blood samples in the anticoagulant-free bottles were allowed to clot before they were centrifuged at 3000 rpm for 10 min to obtain the serum for renal function assessments.

Renal parameters: Serum urea, creatinine and uric acid concentrations were determined according to the standard procedure in the manual of Randox kits.

Haematological parameters: The levels of Haemoglobin (Hb), White Blood Cell (WBC), Red Blood Cell (RBC) and Platelet (PLT) counts were determined according to the method described by Ochei and Kolhatkar[19].

Statistical analysis: Statistical analysis was performed using One-way Analysis of Variance (ANOVA) followed by Ducan's multiple range test procedures of SAS software version 9.1. All the results obtained were expressed as Mean±Standard Deviation (SD) of three replicates of each sample and the differences between means were regarded as significant at $p<0.05$.

RESULTS

Physical activity: Within the 7 days of administration of the luter drug solution, there were obvious decreases in physical activities by the rats such as a reduction in food and water intake, compared to that of the control.

Body weight: The changes in the average body weights of the rats in each group during the 7 days of treatment are shown in Table 1. There was a gradual decrease in the body weights of the luter-administered groups B (141.25-129.63 g), C (152.50-135.50 g) and group D (153.75-128.00 g) in a dose-dependent manner, while the control group A (146.88-156.00 g) gained weight.

Renal parameters: Table 2 shows the result of serum urea, creatinine and uric acid levels in rat groups after 7 days of oral administration of luter. It was observed that the serum levels of urea, creatinine and uric acid increased significantly ($p<0.05$) in a dose-dependent fashion, in the test animals, when compared

Table 1: Changes in average body weight (g) of animals after 7 days of administration of luter solution

	Body weight (g)			
Days	Group A	Group B	Group C	Group D
1	146.88±8.10	141.25±3.63	152.50±5.56	153.75±7.87
2	146.90±7.20	140.25±5.67	149.50±9.98	150.80±6.96
3	150.75±9.96	138.38±7.32	146.00±7.78	146.75±8.10
4	151.13±6.24	135.00±7.58	144.50±8.24	144.75±4.19
5	153.70±6.58	133.13±5.50	141.50±5.58	140.00±3.90
6	154.38±9.25	132.00±21.81	139.00±4.99	134.38±6.10
7	156.00±8.10	129.63±11.96	135.50±4.90	128.00±9.27

Values are Mean±Standard deviation, n = 4, Groups A-D = Normal control, 8.0, 16.0 and 24.0 mg kg^{-1} b.wt., of luter, respectively

Table 2: Serum levels of urea, creatinine and uric acid in albino rats administered with different doses of luter for 7 days

Groups	Urea (mg dL^{-1})	Creatinine (mg dL^{-1})	Uric acid (mg dL^{-1})
A	$21.91±1.43^{a}$	$2.96±0.39^{a}$	$0.82±0.20^{a}$
B	$28.91±3.04^{b}$	$3.83±0.62^{b}$	$1.07±0.31^{b}$
C	$36.21±1.06^{c}$	$4.26±0.89^{c}$	$1.42±0.32^{c}$
D	$47.55±2.02^{d}$	$7.14±0.82^{d}$	$1.94±0.32^{d}$

Mean values with different letters as superscripts down the columns are considered significant ($p<0.05$), values are Mean±Standard deviation, n = 4, Groups A-D = Normal control, 8.0, 16.0 and 24.0 mg kg^{-1} b.wt., of luter, respectively

Table 3: Effect of oral administration of different doses of luter for 7 days onhaematological parameters of albino rats

Groups	WBC ($\times10^{3}$ μL^{-1})	RBC ($\times10^{6}$ μL^{-1})	PLT ($\times10^{6}$ μL^{-1})	PCV (%)	Hb (g dL^{-1})
A	$58.09±3.82^{d}$	$10.43±0.10^{d}$	$4.01±0.24^{a}$	$56.54±2.56^{d}$	$14.27±0.32^{d}$
B	$44.70±1.24^{c}$	$9.31±2.36^{c}$	$5.07±0.34^{b}$	$48.31±2.36^{c}$	$11.43±0.10^{c}$
C	$35.41±1.77^{b}$	$8.01±2.36^{b}$	$6.11±0.66^{c}$	$40.89±1.10^{b}$	$10.34±0.59^{b}$
D	$28.23±2.98^{a}$	$6.31±2.36^{a}$	$7.43±0.80^{d}$	$31.33±3.29^{a}$	$8.58±0.34^{a}$

Mean values with different letters as superscripts down the columns are considered significant ($p<0.05$), values are Mean±Standard deviation, n = 4, Groups A-D = Normal control, 8.0, 16.0 and 24.0 mg kg^{-1} b.wt., of luter, respectively

to that of the control group. Urea level increased from 28.91±3.04 to 36.21±1.06 and 47.55±2.02 mg dL^{-1} in groups B, C and D, respectively, while it was lower in the control group A (21.91±1.43 mg dL^{-1}). Likewise, creatinine level increased from 3.83±0.62 to 4.26±0.89 and 7.14±0.82 mg dL^{-1} in groups B, C and D, respectively, whereas it decreased in the control group A (2.96±0.39 mg dL^{-1}). Also, the level of uric acid increased from 1.07±0.31-1.42±0.32 and 1.94±0.32 mg dL^{-1}, respectively in groups B, C and D compared to 0.82±0.20 mg dL^{-1} in the control group A. Thus, the administration of luter solution affected the serum levels of urea, creatinine and uric acid in albino rats, signifying renal impairment.

Haematological parameters: The result of the effect of luter onhaematological parameters of rats administered with different doses of luter for 7 days is represented in Table 3. There were significant ($p<0.05$) decreases in the levels of White Blood Cell (WBC) count, Red Blood Cell (RBC) count, Packed Cell Volume (PCV) and Haemoglobin (Hb), with a significant ($p<0.05$) increase in the Level of Platelets (PLT) after 7 days of oral administration of luter in albino rats, in a dose-dependent manner, when compared to the normal control. Thus, WBC decreased from 44.70±1.24-35.41±1.77 and 28.23±2.98 ($\times10^{3}$ μL^{-1}) in groups B, C and D, respectively, when compared to 58.09±3.82 ($\times10^{3}$ μL^{-1}) of the normal control group A. The RBC decreased from 9.31±2.36-8.01±2.36 and 6.31±2.36 ($\times10^{6}$ μL^{-1}), respectively in groups B, C and D compared to 10.43±0.10 ($\times10^{6}$ μL^{-1}) of the normal control group A. Likewise, PCV and Hb level decreased from 48.31±2.36% and 11.43±0.10 g dL^{-1} to 40.89±1.10% and10.34±0.59 g dL^{-1} and finally to 31.33±3.29% and 8.58±0.34 g dL^{-1}, respectively in groups B, C and D compared to 56.54±2.56% and 14.27±0.32 g dL^{-1}, of the normal control group A. Whereas, the level of Platelets (PLT) increased from 5.07±0.34-6.11±0.66 and 7.43±0.80 ($\times10^{6}$ μL^{-1}), respectively in groups B, C and D when compared to 4.01±0.24 ($\times10^{6}$ μL^{-1}) of the normal control group A.

DISCUSSION

Luter is an artemisinin-derived antimalarial drug with high efficacy in eliminating *Plasmodium* species. It is associated with known common side effects such as headache, loss of appetite, weakness, joint pain or muscle pain. The decrease in physical activities such as feed and water intakes displayed by the rats, especially those in groups C and D administered with 16.0 and 24.0 mg kg^{-1} b.wt., of luter, respectively could be a result of the aforementioned common side effects. Likewise, there was a gradual decrease in weight observed in the luter-administered rats while there was a gradual normal weight gain in the normal control rats (Table 1). The same mechanism causing loss of appetite could be responsible for weight loss. A decrease in body weight was observed in mice infected mice after prolonged exposure to *P. berghei,* whereas anincrease in weight after treatment with antimalarial drugs was observed after a few days[20]. The weight reduction effect of *P. berghei* and weight recovery after parenteral antimalarials support an earlier report of an increase in body weight after oral administration of artemether/lumefantrine in rats[21]. Also, there was a report of increased body weight in rats after oral administration of dihydroartemisinin (an artemisinin derivative)[22]. In contrast, artesunate administration was reported to have no significant effect on body weight other[23]. Samuel *et al.*[24] reported that treatment of male rats with both artesunate-amodiaquine (ats-amq) and artemether-lumefantrine (art-lum) for 3 and 6 days caused no statistically significant difference in the body weight of the treatment group when compared with the control. The reduction in body weight observed after oral administration of luter in the rats could be due to drug-induced alteration of fuel metabolism.

In this study, there were significant ($p<0.05$) increases in the serum concentrations of urea, creatinine and uric acids in groups B, C and D administered with 8.0, 16.0 and 24.0 mg kg^{-1} b.wt., of luter, respectively when compared to the normal control group A (Table 2). The result showed that prolonged administration of luter could hurt the kidney, by affecting the glomerular filtration of the nephrons, although they are still within tolerable levels. Our report is in tandem with that of Li *et al.*[25], who reported reversible nephrotoxicity on albino rats administered with artesunate. Decreased glomerular filtration rate with increased kidney blood flow and urinary excretion of Na, Cl and K caused by artesunate was also reported[26].

The result of the effect of luter onhaematological parameters of rats administered with different doses of luter for 7 days (Table 3) showed significant ($p<0.05$) decreases in the levels of White Blood Cell (WBC) count, Red Blood Cell (RBC) count, Packed Cell Volume (PCV) and Haemoglobin (Hb), with a significant ($p<0.05$) increase in the level of Platelets (PLT) after 7 days of oral administration of luter in albino rats, in a dose-dependent manner, when compared to the normal control. Similar effects of chloroquine and coartem on haematological parameters in rats have been Ofem *et al.*[27]. Also, Osonugal *et al.*[3] reported a significant ($p<0.05$) decrease in the PCV, Hb, RBC and WBC of Albino rats treated with different doses of artemether after 1, 2 and 3 days, respectively, in a dose-dependent manner, whereas discontinuation of the drug use showed gradual recovery of the depressed indices of the blood parameters.

CONCLUSION

Luter has moderate adverse effects on the renal and haematological systems. These alterations are seen to be within tolerable limits since there will be a possible recovery of the assessed indices on discontinuous use of the drug. However, luter may not be suitable for malaria treatment in patients with serious renal and/or haematological problems.

SIGNIFICANCE STATEMENT

This study discovers that the antimalarial drug, luter can cause renal toxicity and altered haematological effects in albino rats. This research will help researchers to uncover some of the bioactive compounds in this drug that is responsible for its effects on the renal and haematological parameters and use them in

other toxicological studies, which many researchers have not explored. Also, such active compounds could be of pharmacological importance as a tool for new targets in *Plasmodium* species for malaria treatment.

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