IJPSR (2016), Vol. 7, Issue 5 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 17 November, 2015; received in revised form, 26 January, 2016; accepted, 07 February, 2016; published 01 May, 2016

EVALUATION OF CIPROFLOXACIN EFFECT ON THE ANTIMALARIAL ACTIVITY OF SOME ANTIMALARIAL DRUGS IN *PLASMODIUM BERGHEI* INFECTED MICE

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Key words:

Ciprofloxacin, artesunate, artemether-lumefantrine, artesunate-amodiaquine, drug interaction and malaria

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ABSTRACT: This study evaluates the effect of ciprofloxacin (CIP) on the antimalarial activity of artesunate (AS), artemether-lumefantrine (AL) and artesunate-amodiaquine using animal model. Some 120 albino mice infected with chloroquine sensitive *Plasmodium berghei* NK65 strain were used. The study was carried out in three phases. Phase 1 consisted of eleven groups treated with different doses of either AS, AL, ASAQ or CIP alone. Phase 2 consisted of nine groups treated with 7 mg/kg of CIP (CIP1) combined with different doses of AS, AL, ASAQ. Phase 3 consist of ten groups treated with 14 mg/kg of CIP (CIP2) with different doses of AS, AL, ASAQ. Thin blood films were used to assess parasitemia level daily after administration of drugs for 72 h. Results were analyzed using student t-test and analysis of variance (ANOVA). CIP alone showed antimalarial activity with 63 % parasitemia reduction. Antimalarial activities of AS and AL were significantly enhanced by both 7 and 14 mg/kg of CIP. The antimalarial effect of ASAQ was enhanced but not statistically significant. Low dose ciprofloxacin significantly enhanced the antimalarial activities of Artesunate, Artemether-Lumefanthrine and Artesunate-Amodiaquine This combination may be beneficial in the management of *Plasmodium falciparum* infection or co-infection with salmonellosis.

INTRODUCTION: Drug interactions have been recognized for over 100 years. The risk of drug interactions has been reported to increase from approximately 6 % in patients taking only two medications to 50 % in those taking five medications and 100% in those taking 10 medications [1]. Drug interaction occurs when the pharmacokinetics and/or the pharmacodynamics of a drug are altered by the presence of another drug, food, drink, or herb [2].

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.7(5).1896-03

Article can be accessed online on:
www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (5).1896-03

The co-administration of two or more drugs is usually accompanied by a variety of therapeutic implications ranging from opposition, alteration, synergism, potentiating as well as physical and chemical antagonism.

Ciprofloxacin (CPX) is a fluoroquinolone antibiotic used for treating respiratory, urinary tract, gastrointestinal and abdominal infections [3]. Ciprofloxacin is indicated for both Gram-negative and Gram-positive bacterial infections.The bioavailability of ciprofloxacin is approximately 70%. It is widely distributed to tissues after oral administration, where it often reaches higher concentrations than in plasma. It is partly metabolized in the liver and excreted as the unchanged drug in the urine to an extent of 40% to 50%, [4].

Malaria is a leading cause of morbidity and mortality in children and adults especially in developing countries [5]. According to Ughasoro et al., [6] in Nigeria, malaria accounts for approximately 40 % of hospital admissions and 30 % of mortalities with associated infections such as enteric fever, diarrhoea, Human Immuno-deficiency Virus (HIV), tuberculosis. Enteric fever is also a widely recognized major public health problem in most developing tropical countries, with estimated global burden of greater than 27 million cases per annum and clinical relapse rate of 5 % to 20 % [7]. There is also high incidence of malaria and enteric fever co-infection [8] which has led to the co-administration of an antimalarial and antibiotic by health care providers.

The chemotherapeutic arsenal for malaria treatment today is limited to three main families of compounds: quinolines, antifolates and Artemisinin derivatives [9]. Artemisinin combination therapies (ACTs) are the only antimalarial drugs with very minimal resistance recorded [10]. WHO Recommendation[5] for first line treatment of uncomplicated malaria includes: Artemether plus lumefantrine, Artesunate plus amodiaquine, Artesunate plus mefloquine, Artesunate plus sulfadoxine and pyrimethamine, Dihydroartemisinin plus piperaquine.

Fluoroquinolones have been found to be efficacious both intreatment of severe salmonella-associated illnesses [11]. The co-administration of ACTs derivatives and ciprofloxacin is a common practice in Nigeria in the treatment of malaria and enteric fever co-infection[12]. Ciprofloxacin inhibits CYP1A2 and have been reported to increase plasma theophylline levels. Another study has also shown that co-administration of ciprofloxacin and quinine is superior to quinine alone in reduction of parasitemia [13]. Ciprofloxacin forms complexes with multivalent cations that impair its oral absorption. Previous study [14] showed that combination of mefloquine or artesunic acid with ciprofloxacin was experimentally active against *P. falciparum.* Likewise, a study carried out by Ejikeme and her colleague [15], showed that 12.9 mg/kg body weight of quinine with 15 mg/kg body weight of ciprofloxacin achieved 87 % reduction in parasitaemia level and significantly reduced mortality in the infected animals compared with other treatment groups

Clinically important interactions may occur between ACTs drugs and ciprofloxacin compromising the treatment of either infection. Hence, this study evaluated the effect of ciprofloxacin (CIP) on the antimalarial activity of artesunate (AS), artemether-lumefantrine (AL) and artesunate-amodiaquine using animal model.

MATERIALS AND METHODS:

Materials:

Drugs:

Artesunate 50 mg tablets Artesunat® (Mekophar Chemical Pharmaceutical Joint-Stock Company, Vietnam), Artesunate and amodiaquine 100/270 mg Winthrop® (Sanofi Aventis), Artemether/ lumefantrine 20/120 mg Coartem® (Norvatis) and ciprofloxacin 500 mg Ciprotab® (Fidson Healthcare Plc, Nigeria). All drugs were purchased from a registered pharmacy in Nsukka, Enugu State, Nigeria.

Equipment and reagents:

Microscope and reagents used include 0.9 % normal saline sodium hydroxide, Oil Immersion, Giemsa stain solution (pH 7.2), methanol and chloroform. All the reagents were of analytical grade.

Animals:

One hundred and twenty (120) adult male and female Swiss albino mice (18-25 g) were used for this study. The mice were obtained and maintained in the Animal House of the Faculty of Vertinary Medicine, University of Nigeria, Nsukka, Enugu State. The mice were observed under light/dark cycle in metabolic, well ventilated rodent cubicle, fed with pelleted feed and provided with access to clean drinking water ad libitum. All the animals used in this study were handled in accordance with the recommendations from the Declaration of Helsinki as recorded by the Institute for laboratory Animal Research, Washington, DC[16].

Parasite*:*

Mouse-infective Chloroquine-sensitive strain of Plasmodium berghei NK-65 was obtained from the Institute of Advanced Medical Research and

Training (IAMRAT), College of Medicine, University College Hospital, Ibadan, Nigeria.

Methods:

Parasite inoculation:

A donor mouse was infected with cryopreserved chloroquine-sensitive parasite and thereafter allowed to develop parasitaemia. The presence of parasitemia was established by microscopic examination of a thin blood film. The infected blood (1ml) was diluted with normal saline to 25 ml, then 0.2 ml of the dilution containing about 1 x 10^7 *P. berghei* - parasitized erythrocytes was injected intra-peritoneally into each of the healthy mice [17].

Treatment of experimental animals:

Treatment of animals started 72 h after inoculation. One hundred and twenty (120) infected albino mice were randomly divided into thirty groups (n=4). This study was carried out in three phases.

Phase 1:

Eleven groups were used in this phase. Two groups were treated with ciprofloxacin alone at 7 mg/kg (CIP1) and 14 mg/kg (CIP2) doses respectively; three groups were treated with 3 mg/kg, 6 mg/kg and 12 mg/kg doses of Artesunate (AS) respectively; three groups received 16 mg/kg, 32 mg/kg and 64 mg/kg doses of Artemether-lumefantrine (AL) alone respectively and the last three groups were treated with 11 mg/kg, 22 mg/kg and 44 mg/kg of artesunate-amodiaquine (ASAQ) alone respectively.

Phase 2:

Nine groups of infected animals were used in this phase. Three groups received 3, 6, 12 mg/kg of AS co-administered with CIP1 respectively. Three other groups received 16, 32 and 64 mg/kg of AL with CIP1 respectively. The last three groups were treated with 11, 22 and 44 mg/kg of ASAQ with CIP1 respectively.

Phase 3:

Ten groups of animals were used in this phase. Three groups were given 3, 6 and 12 mg/kg AS co-administered with CIP2 respectively. Another three groups also received 16, 32 and 64 mg/kg of AL with CIP2 respectively. Three other groups received 11, 22 and 44 mg/kg of ASAQ with CIP2 respectively. The last group received 0.1 ml/kg of distilled water and served as the negative control.

All drugs administered were done by oral route once daily for three days based on the animal's body weight.

Determination of responses of infection to treatment:

The parasitaemia level was determined at 0, 24, 48 and 72 hours after drug administration by obtaining blood from the caudal vein for blood smearing[18]. Thin smears were prepared from each mouse, fixed with methanol and stained with Giemsa for 15 minutes. Parasite density was estimated from the thin smears and the level of parasitaemia was expressed as percentage (%) of erythrocytes infected with malarial parasites. In this method, 1,000 erythrocytes were examined and the number of parasitized Red Blood Cells (RBCs) among these were noted and percentage parasitaemia was then calculated.

$$\% \text{ Parasitaemia} = \frac{\text{Number of parasitized RBCs}}{\text{Total RBCs counted (1000)}} \times 100$$

Statistical Analysis:

Results were expressed as mean ± standard deviation. Student-test and one way analysis of variance (ANOVA) was used to analyze differences among the treated groups. All data were analyzed at a 95 % confidence interval and values were considered statistically significant at $p<0.05$.

RESULTS:

Effect of ciprofloxacin on parasitemia level:

Plasmodial infection in the mice was noticeable after 72 h of inoculation. The parasitaemia level increased in the control group that was treated with distilled water from 23.5 % to 27.5 % as the time progressed to 72 hr.

Ciprofloxacin administration at varied doses resulted in decrease in parasitaemia level in infected mice though the 14mg/kg dose caused lower parasitemia level reduction than the 7 mg/kg dose as shown in **Table 1**.

TABLE 1: THE EFFECT OF CIPROFLOXACIN ON THE PARASITAEMIA LEVEL

Drug	Dose(mg/kg)	% Parasitaemia				% Red.
		0hr	24hr	48hr	72hr	
Water	0.1 ml/kg	23.50±5.45	24.75±2.22	27.00±2.99	27.25±1.71	-
Ciprofloxacin	7	15.75±2.50	11.2±2.06	8.25±2.63	5.75±2.22	63
Ciprofloxacin	14	12.50±1.73	9.50±2.65	8.25±3.50	6.50±3.11	49

% Red. percentage reduction

Effect of 7 mg/kg Ciprofloxacin (CIP1) on artesunate clearance of parasitemia:

The parasitemia reduction of 3, 6 and 12 mg/kg of AS alone was 49, 64 and 71 respectively. Co-administration different doses of AS and CIP1 significantly ($p<0.05$) reduced parasitemia compared to equivalent doses of AS alone. Combination of 6 mg/kg of AS with CIP1 had the highest parasitemia clearance 100 % after 72 hr, when compared to 3 and 12 mg/kg that had 96 and 97 % respectively. The parasitemia value for each combination is shown in **Table 2**.

TABLE 2: EFFECT OF 7 mg/kg CIPROFLOXACIN (CIP1) ON ARTESUNATE CLEARANCE OF *P. BERGHEI* PARASITAEMIA IN MICE

Drug	Dose (mg/kg)	% Parasitaemia				% Max Reduction
		0hr	24hr	48hr	72hr	
AS	3	17.75±2.50	12.75±1.26	11.00±1.41	9.00±1.41	49
AS:CIP1	3 : 7	8.25±5.56	6.25±1.71	1.25±0.96	0.25±0.500	97
P value		0.000	0.001*	0.000*	0.000*	
AS	6	15.25±2.22	11.00±0.82	8.00±0.82	5.50±1.00	64
AS:CIP1	6: 7	6.00±1.83	6.50±4.04	1.00±0.00	0.00±0.00	100
P value		0.000	0.014*	0.000*	0.000*	
AS	12	8.75±1.50	8.00±1.63	4.00±0.82	2.50±0.58	71
AS:CIP1	12:7	6.75±2.75	3.25±3.59	1.50±2.38	0.25±0.50	96
P value		0.344	0.010*	0.053	0.005*	

* P value is significant at <0.05 when compared with AS alone
AS= Artesunate; AS: CIP1 = artesunate:ciprofloxacin 7 mg/kg

Effect of 14 mg/kg ciprofloxacin (CIP2) on artesunate clearance of parasitemia:

Co-administration of CIP2 with AS significantly ($p<0.05$) decreased parasiteamia level. The parasitemia reduction of CIP2 with 3 and 12 mg/kg of AS was 94 and 97 % respectively while that of 6 mg/kg AS was 67 %. The parasitemia values after 24, 48 and 72 hr are shown in **Table 3.**

TABLE 3: EFFECT OF 14 mg/kg CIPROFLOXACIN (CIP2) ON ARTESUNATE CLEARANCE OF *P. BERGHEI* PARASITAEMIA IN MICE

Drug	Dose (mg/kg)	% Parasitaemia				% Red.
		0hr	24hr	48hr	72hr	
AS	3	17.75±2.50	12.75±1.26	11.00±1.41	9.00±1.41	49
AS:CIP2	3 : 14	9.00±2.94	6.75±2.22	2.00±2.83	0.50±0.58	94
P value		0.000	0.002*	0.000*	0.000*	
AS	6	15.25±2.22	11.00±0.82	8.00±0.82	5.50±1.00	64
AS:CIP2	6: 14	6.00± 1.41	4.00± 2.94	2.50± 2.38	2.00±2.31	67
P value		0.000	0.014*	0.000*	0.000*	
AS	12	8.75±1.50	8.00±1.63	4.00±0.82	2.50±0.58	71
AS:CIP2	12:14	9.50 ±3.42	5.50 ±1.29	1.00 ±2.00	0.25 ±0.50	97
P value		0.721	0.154	0.022*	0.005*	

* P value is significant at <0.05 when compared with artesunate alone.
AS = Artesunate; AS:CIP2 = artesunate:ciprofloxacin14mg/kg; % Red.= percentage reduction

Effect of 7 mg/kg Ciprofloxacin on artemether-lumefantrine clearance of parasitemia:

The parasitemia reduction of 16, 32 and 64 mg/kg of AL alone was 69, 70 and 83 respectively, while that of AL in combination with CIP1 was 82, 84 and 91 % respectively. There was significant difference ($p<0.05$) in the parasitemia reduction by CIP1 and 16 or 32 mg/kg of AL when compared to AL alone as shown in **Table 4.**

TABLE 4: EFFECT OF CIPROFLOXACIN (7 MG/KG) ON ARTEMETHER-LUMEFANTRINE CLEARANCE OF *P.BERGHEI* PARASITAEMIA IN MICE

Drug	Dose(mg/kg)	% Parasitaemia				% Red
		0hr	24hr	48hr	72hr	
AL	16	17.75±2.65	13.25±1.26	10.00±2.00	5.50±2.38	69
AL:CIP1	16 : 7	7.00±2.94	4.00±3.37	1.50±1.29	1.25±1.50	82
P value		0.000	0.001*	0.000*	0.001*	
AL	32	11.00±1.83	9.25±0.96	7.75±1.26	3.25±0.96	70
AL:CIP1	32: 7	5.75 ±2.06	3.00 ±4.24	1.25 ±2.50	1.75 ±2.36	84
P value		0.057	0.018*	0.000*	0.191	
AL	64	7.25±0.96	6.50±0.58	3.50±0.58	1.25±1.50	83
AL:CIP1	64:7	5.75±7.14	2.50±2.52	1.00 ±1.15	0.50 ±0.58	91
P value		0.575	0.117	0.103	0.508	

* P value is significant at <0.05 when compared with Artemether-lumefantrine alone
AL= Artemether-lumefantrine; AL: CIP1= Artemether-lumefantrine: Ciprofloxacin7 mg/kg

Effect of 14 mg/kg Ciprofloxacin (CIP2) on artemether-lumefantrine clearance of parasitemia:

The parasitemia reduction of co-administration of CIP2 with 16, 32 and 64 mg/kg of AL was 85, 63 and 55 %. Increased doses of AL alone at 32 and 64 mg/kg had higher parasitemia reduction of 70 and 83 respectively compared to when co-administered with CIP2 as shown in **Table 5.**

TABLE 5: EFFECT OF 14 mg/kg CIPROFLOXACIN ON ARTEMETHER-LUMEFANTRINE CLEARANCE OF *P. BERGHEI* PARASITAEMIA IN MICE

Drug	Dose(mg/kg)	% Parasitaemia				% Red
		0hr	24hr	48hr	72hr	
AL	16	17.75±2.65	13.25±1.26	10.00±2.00	5.50±2.38	69
AL:CIP2	16 : 14	8.25±6.85	3.50 ±5.20	1.00 ±1.15	1.25 ±1.89	85
P value		0.002	0.001*	0.000*	0.001*	
AL	32	11.00±1.83	9.25±0.96	7.75±1.26	3.25±0.96	70
AL:CIP2	32: 14	8.00±3.56	3.00 ±3.46	1.50 ±1.91	0.25 ±0.50	63
P value		0.267	0.018*	0.000*	0.012*	
AL	64	7.25±0.96	6.50±0.58	3.50±0.58	1.25±1.50	83
AL:CIP2	64:14	14.00±2.00	6.25 ±5.68	5.00 ±4.40	1.50±1.29	55
P value		0.017	0.920	0.320	0.825	

* P value is significant at <0.05 when compared with Artemether-lumefantrine
AL= Artemether-lumefantrine; AL: CIP2= Artemether-lumefantrine: Ciprofloxacin14mg/kg

Effect of 7 mg/kg Ciprofloxacin on Artesunate-Amodiaquine clearance:

The parasitemia reduction of 11, 22 and 44 mg/kg of ASAQ alone was 72, 67 and 81 respectively, while that of ASAQ in combination with CIP1 was 52, 68, and 83 % respectively. There was no significant difference ($p<0.05$) in the parasitemia reduction by co administration of CIP1 and ASAQ when compared to ASAQ alone. The distributions of parasitemia at different hours are shown in **Table 6.**

TABLE 6: EFFECT OF 7 MG/KG CIPROFLOXACIN ON ARTESUNATE- AMODIAQUINE CLEARANCE OF *P. BERGHEI* PARASITAEMIA IN MICE

Drug	Dose (mg/kg)	% Parasitaemia				% Red
		0hr	24hr	48hr	72hr	
ASAQ	11	16.00±3.56	9.25±0.96	7.50±2.65	4.50±3.11	72
ASAQ : CIP1	11:7	10.50±1.00	10.00±0.82	5.50±3.51	5.00±4.69	52
P value		0.007	0.719	0.227	0.774	
ASAQ	22	15.25±0.96	8.50±1.29	6.25±2.06	5.00±1.83	67
ASAQ: CIP1	22:7	7.00 ±2.83	6.00 ±3.37	3.50 ±1.73	2.25 ±2.06	68
P value		0.000	0.235	0.101	0.202	
ASAQ	44	9.25±0.96	6.25±1.71	3.50±1.29	3.50±1.29	81
ASAQ: CIP1	44:7	4.75±2.99	4.50±2.89	3.00 ±0.00	0.75 ±1.50	83
P value		0.025	0.403	0.055	0.038*	

* P value is significant at <0.05 when compared with Artemether-lumefantrine
ASAQ=Artesunate-amodiaquine; ASAQ: CIP1=Artesunate-amodiaquine; ciprofloxacin (7mg/kg).

Effect of 7 mg/kg Ciprofloxacin on Artesunate-Amodiaquine clearance:

The parasitemia reduction of co-administration of CIP2 with 11, 22 and 44 mg/kg of ASAQ was 93, 93 and 85 %. There was significant difference ($p<0.05$) in the reduction at 48 and 72 hr by CIP2 and 22 mg/kg ASAQ compared to ASAQ alone. The data is shown in **Table 7**.

TABLE 7: EFFECT OF 14 mg/kg CIPROFLOXACIN ON ARTESUNATE- AMODIAQUINE CLEARANCE OF *P. BERGHEI* PARASITAEMIA IN MICE

Drug	Dose	% Parasitaemia				% Red.
	(mg/kg)	0hr	24hr	48hr	72hr	
ASAQ	11	16.00±3.56	9.25±0.96	7.50±2.65	4.50±3.11	72
ASAQ :CIP2	11:14	13.75±4.19	8.75±4.03	1.75±2.87	1.00±2.00	93
P value		0.245	0.810	0.001*	0.52	
ASAQ	22	15.25±0.96	8.50±1.29	6.25±2.06	5.00±1.83	67
ASAQ: CIP2	22:14	10.75±2.75	6.75 ±4.19	2.25 ±1.26	0.75 ±0.96	93
P value		0.025	0.235	0.020*	0.020*	
ASAQ	44	9.25±0.96	6.25±1.71	3.50±1.29	3.50±1.29	81
ASAQ: CIP2	44:14	6.50±2.65	3.00±4.08	1.50 ±3.00	1.50±3.00	85
P value		0.158	0.005*	0.227	0.667	

* P value is significant at <0.05 when compared with Artesunate-amodiaquine

ASAQ= Artesunate-amodiaquine; ASAQ: CIP1= Artesunate-amodiaquine: ciprofloxacin14mg/kg

DISCUSSION: With the increase in the co-infection of malaria and enteric fever [19], the use of more than one drug is required, raising the concern about potential drug interaction [20]. This drug interaction may be beneficial, harmful or have no significant effect. The assessment of treatment response in malaria rests on the clinical and parasitological outcome. In clinical setting, the level of parasitaemia is one of the criteria for defining *Plasmodium falciparum* malaria and to monitor the effect of antimalaria therapy [21].

The results of the study showed an increase in the parasitaemia in the control group from 0hr to 72hr. This may be as a result of rapid multiplication which occurs after the red blood cells are infected. This is in agreement with Breman et al., [22] who reported that parasitaemia increases progressively after inoculation until the point of death in the absence of a suitable treatment.

The administration of Artesunate, Artemether-lumefantrine and Artesunate-amodiaquine showed a significant reduction in the parasitaemia values. This is in consonance with expected outcome since ACTs are established antimalarials due to their ability to reduce the basal parasite multiplication rate [23]. Artemisinins are particularly active against the large ring stage of infection when parasites are beginning to become most metabolically active and also target tiny ring stages of infection (present only a few hours after red cells are invaded by merozoite stages). Our findings show that treatment with AL and ASAQ resulted in a higher percentage parasitaemia reduction than that of the artesunate alone indicating that ACTs improve therapeutic efficacy in malaria treatment. This is consistent with the report from Adjuik et al. [24], which stated that ACTs (Artesunate-amodiaquine) improved treatment efficacy in African children more than monotherapy (amodiaquine). It was also observed that AS and AL exhibited a dose dependent antimalarial activity as percentage reduction in parasitemia increased with increase in dose, while ASAQ activity was not dose dependent.

The results of this study revealed that ciprofloxacin treatment also resulted in a reduction in the parasitaemia levels. Our work agrees with a work done by Salmon and his colleagues [3] that showed that ciprofloxacin has antimalarial activities. It has been suggested that malaria parasites contain both mitochondrion and plastids that originate from bacterial symbionts [25] and that some antibacterial drugs, like ciprofloxacin, inhibit the growth of these parasites by targeting their bacterium-derived endosymbiotic organelles, the mitochondrion and plastids [26] but the stage of malaria parasite life cycle remains unknown [25]. Ciprofloxacin targets the *Plasmodium falciparum*a picoplast genome inhibiting DNA replication [27].

The combination of AS and AL with CIP significantly cleared the parasite more than AS and AL alone suggesting that CIP enhanced the antimalarial activity of AS and AL, this report

supports the study by Noedl et al.[28], which showed that antibiotics (azithromycin) combination with AS led to faster clinical and parasitological improvement in adults infected with *Plasmodium falciparum* and with another phase II clinical trial in Gabon children with uncomplicated *falciparum* malaria that demonstrated an improved efficacy with Artesunate when used in combination with (antibiotic) fosmidomycin as a short course regimen [29]. Our findings are in agreement with previous study by Andrade et al.[14] which showed that combination of mefloquine or artesunic acid with ciprofloxacin were experimentally active against *P. falciparum.*

Likewise, another study carried out by Ejikeme and her colleague [15] showed that 12.9 mg/kg body weight of quinine with 15 mg/kg body weight of ciprofloxacin achieved 87 % reduction in parasitaemia level and significantly reduced mortality in the infected animals compared with other treatment groups. The combined effects of different doses of AS and AL with 7 mg/kg of ciprofloxacin produced greater parasitemia reduction than the 14 mg/kg of ciprofloxacin, indicating that increased dose of CIP has no advantage over low dose in terms of potentiating antimalarial activity of AS. This observation is in congruent with a work by Olayemi et al.,[30] which suggests that the combination of CIP and antimalarial (chloroquine) at lower concentration possesses rapid parasite clearance rate compared to higher concentration.

However, when Artesunate-amodiaquine was administered concurrently with 7 mg/kg ciprofloxacin, there was no significant increase in rates of parasite clearance. On administration of 14 mg/kg dose of ciprofloxacin with ASAQ, there was significant antimalaria potentiation. The enhanced antimalarial activity observed with 14 mg/kg CIP and ASAQ confirms a recent finding by Falajiki et al., [31] which states that there is beneficial interaction between ciprofloxacin and artesunate-amodiaquine as the combination significantly enhanced response of infection in animal treatment.

CONCLUSION: Our study has demonstrated that ciprofloxacin enhanced the antimalaria effects of artesunate, artesunate-amodiaquine and Artemether-lumefantrine against the chloroquine sensitive *Plasmodium berghei* infection mice. This may be beneficial in the management of P*lasmodium falciparum* infection or co-infection with salmonellosis. However, this potentiation of activity could lead to increased toxicity in subjects especially in pediatrics and pregnant women, hence the need for close monitoring of biochemical markers in patients receiving this drug regimen.

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How to cite this article:
Ayogu EE, Ugwuowo O, Amorha KC and Okonta JM: Evaluation of Ciprofloxacin Effect on the Antimalarial Activity of Some Antimalarial Drugs in *Plasmodium Berghei* infected Mice. Int J Pharm Sci Res 2016; 7(5): 1896-03.doi: 10.13040/IJPSR.0975-8232.7(5).1896-03.