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Toxicological fate of Artemether-lumefantrine after exposure to enzyme inducer (Phenobarbitone) and inhibitor (Omeprazole) of Cytochrome P450 in Wister rats

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ABSTRACT

Background: Due to lack of toxicological fate information of artemether-lumefantrine (AL) after exposure to Cytochrome P450 inducer (phenobarbitone) and inhibitor (omeprazole) this research work was undertaken to assess the AL toxicological fate after exposure to phenobarbitone and omeprazole in Wister rats.

Methods: Phenobarbitone (10 mg/kg) and omeprazole (20 mg/kg) were administered orally to albino rats for twenty-eight days. Artemether-lumefantrine was administered on the day 29, 30 and 31. The rats were euthanized under chloroform anesthesia on day 32. Blood samples collected from abdominal aorta were assessed for toxicity markers such as weights, glucose, lipids, renal electrolytes, liver enzymes and hematological indices.

Results: Out of the thirty-seven toxicity markers assessed, twenty-three showed significant differences ($P<0.05$). Phenobarbitone and omeprazole increased weight significantly after 14 days and 28 days. Phenobarbitone, omeprazole, artemether-lumefantrine, phenobarbitone-artemether-lumefantrine (PAL) and omeprazole-artemether-lumefantrine (OAL) increased weight between day 28 and 32. Glucose was increased by PAL and OAL. Cholesterol, Triglyceride, High Density Lipoprotein and Low-Density Lipoprotein were significantly decreased by PAL and OAL. Except LDL, other lipids were decreased significantly $P<0.05$ by AL. Urea, creatinine, and chloride ion increased due to AL and PAL, but decreased by OAL. Alkaline phosphatase, conjugated bilirubin and total bilirubin were altered by PAL and OAL. Eleven haematological indices also changed significantly.

Conclusion: Phenobarbitone and omeprazole altered the toxicological potential of artemether-lumefantrine after exposure. Artemether-lumefantrine may be recommended to be used with caution among patients which are chronic users of phenobarbitone in epilepsy and omeprazole in gastric ulcers.

Key words: **CYP450, artemether-lumefantrine, omeprazole, phenobarbitone, toxicological**.

1. INTRODUCTION

Cytochrome P450s (CYP540s) enzymes remain the cornerstone in pharmacogenomic studies. They are important heme-containing proteins that play important roles in the metabolism of xenobiotics and endogenous compounds [1]. The pharmacogenomics of antimalarial agents are poorly known and lack clinical studies most especially in low resource settings [2] and the application might be critical in optimizing treatment [3]. The changes due to concomitant use with other drugs can be used to predict fate of drugs. Therapeutic success of artemether-lumefantrine as a first-line drug [4,5] in the treatment of uncomplicated malaria therapy may depends on the enzyme induction or inhibition [6-9] and it may be influenced by other previously administered agents in a biological system.

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Most clinically relevant interactions result from changes in drug elimination has been observed to be caused by inhibition or induction of metabolic enzymes present in the liver and extrahepatic tissues [10,11]. The mechanisms involved in inhibition of CYP activity have been reviewed by several authors [8,9]. These may be categorized as reversible, quasi-irreversible and irreversible inhibition, among these, reversible inhibition has been shown to be the most common cause of drug-drug interactions [12]. Competition for the CYP active site is the underlying mechanism of reversible inhibition. The inhibitors may bind to the prosthetic heme iron, lipophilic part of the protein, or both sites as potent inhibitors [9]. Classes of compounds that are potent reversible CYP inhibitors include nitrogen-containing drugs, imidazoles, pyridines and quinolones [12]. Since there is lack of pharmacogenomics in antimalarial studies [2] and the polymorphic forms of cytochrome P450 enzymes responsible for the development of adverse drug reactions (6), it became necessary to assess the toxicological fate of artemether-lumefantrine after exposure to cytochrome P450 enzyme inducer (phenobarbitone) and inhibitor (omeprazole) in Wister rats.

2. MATERIALS AND METHODS

2.1 Materials

Phenobarbitone (Ferozsons Laboratories Ltd, Pakistan), Omeprazole (Dr. Reddy's Labs. UK), Artemether-lumefantrine (India)

2.2 Methods

Prior to the study, ethical approval was obtained from the Animal Ethics Committee of the Faculty of Pharmacy University of Benin Nigeria. Healthy albino rats were selected and allowed to acclimatize for two weeks. During this period, the rats were fed with pelletized grower's mash and allowed access to drinking water *ad libitum*. All the albino rats that were within weight range of 250 g and 300 g were selected and administered phenobarbitone (10 mg/kg) and Omeprazole (20 mg/kg) orally for twenty-eight days. After the simulated exposure, artemether-lumefantrine was administered on days 29, 30, 31 in mg/kg body weight as described by Aghahowa and co-authors 2018[13]. The rats were euthanized using chloroform anesthesia on day 32. Collected blood samples were assessed for common toxicity markers such as weights, glucose, lipids, renal electrolytes, liver enzymes and haematological indices as described [13].

2.3 Statistical analysis

The data collected from the various assays were entered into Graph Prism Version 6, San Diego, USA. They were computed as mean ± SEM. Suitable statistics were applied using Analysis of Variance, Tukey's and Fisher's *post hoc* tests. Statistical significances were rated as *P*-values equal to or less than 0.05 was regarded as significant.

3. RESULTS

Out of the thirty-seven toxicity markers assessed, twenty-three showed significant differences. Phenobarbitone and omeprazole increased weight significantly $P<0.05$ after 14 days and 28 days after exposure of the drugs. Phenobarbitone, omeprazole, artemether-lumefantrine, phenobarbitone-artemether-lumefantrine (PAL) and omeprazole-artemether-lumefantrine (OAL) increased weight significantly between day 28 and 32. Glucose as a biochemical parameter, increased significantly due to PAL and OAL. Cholesterol, triglyceride, high density lipoprotein and low-density lipoprotein were significantly decreased due to PAL and OAL. Apart from LDL, other lipids decreased significantly due to AL. Renal indices such as urea, creatinine, and chloride ion increased significantly $P<0.05$ due to AL and PAL, but decreased due to OAL. Liver parameters such as alkaline phosphatase, conjugated bilirubin and total bilirubin were altered significantly due to PAL and OAL. Eleven haematological indices also changed significantly, while others were did not change significantly.

Table 1. Lipids parameters after day 32 after Artemether-lumefantrine administration

GROUPS	CHOL(mg/dl)	TG(mg/dl)	HDL(mg/dl)	LDL(mg/dl)
CON	113.6±6.24	100.2±3.13*	36.80±1.20*	56.60±4.68
OME	113.1±3.33	84.60±3.55	31.80±1.07	64.20±1.92
PHE	113.6±4.69	98.00±7.36	38.80±3.21$^{\#}$	55.80±4.52
AL	98.80±4.65	74.40±4.57	26.40±1.00	57.40±4.52
OAL	97.40±4.48	77.20±3.95$^{\#}$	28.00±1.94	54.00±2.21
PAL	91.40±2.66*	86.20±6.72	26.40±0.93	47.20±3.79*

CHOL: *$P<0.05$ Vs CON, OME, PHE.TG: *$P<0.05$ Vs CON, PHE. $^{\#}P<0.05$ Vs OAL. HDL: *$P<0.05$ Vs AL, OAL, PAL. $^{\#}P<0.05$ Vs AL, OAL, PAL. LDL: *$P<0.05$ Vs OME. CON: Control, OME: Omeprazole, PHE: Phenobarbitone, AL: Artemether-lumefantrine, OAL:Omeprazole-Artemether-Lumefantrine, PAL: Phenobarbitone-Artemether-Lumefantrine. CHOL: Cholesterol, TG: Triglyceride, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein. Values =Mean±SEM

None of the albino rats died at any stage of the experiment which showed the drugs were not fatal at therapeutic doses since phenobarbitone and omeprazole altered the toxicological potential of artemether-lumefantrine after exposure.

Table 2: Renal indices on day 32 after Artemether-lumefantrine administration

GROUPS	Urea(mg/dl)	Na^+ (mMol/L)	K^+ (mMol/L)	$HCO3^-$(mMol/L)	Cl^- (mMol/L)	Creatinine(mg/dl)
CON	31.00±1.48	137.0±0.56	5.98±0.15	19.40±0.98	96.60±1.29	0.70±0.04
OME	29.00±1.48	136.8±0.39	6.42±0.23	19.40±0.27	100.8±0.25	0.70±0.02
PHE	34.40±1.75	137.8±0.68	6.56±2.00	19.20±0.65	101.4±2.02	0.66±0.03
AL	39.00±1.17*	138.0±0.42	6.50±0.23	19.20±0.39	99.40±0.72	0.92±0.03*
OAL	28.60±1.80	137.6±0.50	6.78±0.19	19.00±0.52	94.80±2.76*	0.66±0.05
PAL	32.40±1.05	136.8±0.57	6.78±0.35	19.60±0.50	102.2±0.53	0.74±0.07

Urea: *P<0.05 Vs CON, OME, PHE, OAL, PAL. Chloride ion: *P<0.05 Vs PHE, PAL. Creatinine: *P<0.05 Vs CON, OME, PHE, OAL. CON: Control, OME: Omeprazole, PHE: Phenobarbitone, AL: Artemether-lumefantrine, OAL: Omeprazole-Artemether-Lumefantrine, PAL:Phenobarbitone-Artemether-Lumefantrine. Values =Mean±SEM

Table 3: Liver indices on day 32 after Artemether-lumefantrine administration

GROUPS	ALP(U/L)	AST(U/L)	ALT(U/L)	TB(mg/dl)	CB(mg/dl)	TP(mg/dl)	ALB(g/dl)
CON	65.20±1.60	153.4±5.17	76.60±4.67	0.48±0.03	0.18±0.03	7.28±0.18	3.42±0.08
OME	80.00±3.66	159.0±4.95	69.00±5.28	0.44±0.02	0.14±0.02*	7.56±0.16	3.68±0.12
PHE	80.40±4.97	140.2±7.03	76.80±3.67	0.46±0.03	0.16±0.03	7.06±0.18*	3.58±0.12
AL	64.00±2.77	137.4±7.78	72.40±3.19	0.56±0.03	0.24±0.03	7.32±0.17	3.64±0.07
OAL	76.40±4.84	162.4±10.08*	73.80±2.51	0.52±0.03	0.20±0.02	7.82±0.13	3.82±0.07
PAL	76.80±6.51	130.2±5.66	70.20±3.71	0.46±0.05	0.18±0.03	7.360±0.24	3.52±0.11

AST: *P<0.05 Vs PAL. CB: *P<0.05 Vs AL. TP: *P<0.05 Vs OAL.
CON: Control, OME: Omeprazole, PHE: Phenobarbitone, AL: Artemether-lumefantrine, OAL: Omeprazole -Artemether-Lumefantrine, PAL: Phenobarbitone-Artemether-Lumefantrine. Values =Mean±SEM

Table 4: Haematological indices on day 32 after Artemether-lumefantrine administration

	WBC	LY	MO	GR	LYY	MOO	GRR	RBC	HGB
CON	4.90±1.23#	3.22±1.00	0.66±0.16#	1.22±0.27#	60.72±6.41	17.08±1.42	31.96±5.03	7.70±0.19	15.34±0.39
AL	8.22±0.89	4.03±0.29	2.01±0.31	2.60±0.46	49.58±6.18	18.78±0.97	33.64±4.44	7.23±0.33	12.56±0.54
OME	10.38±0.91	3.32±0.89	0.24±0.05	4.01±0.54	42.23±3.32	18.94±1.74	38.83±1.89	8.39±0.16	15.58±0.29
PHE	4.46±1.04*	4.280±0.97	1.32±0.20*	0.88±0.17*	69.14±6.22*	18.78±0.97	23.32±4.65	7.59±0.54	12.78±0.81
OAL	9.42±1.75	6.16±1.56	1.20±0.23	2.24±0.54	64.02±6.89	11.92±2.49	24.02±4.73	6.79±0.90	12.66±1.60
PAL	10.34±1.53	5.62±0.92	1.68±0.40	3.02±0.67	58.82±5.55	14.58±2.09	27.00±3.35	7.36±0.30	13.84±0.68

CON Vs OM, CON Vs PAL, OM Vs PHE, PHE Vs PAL. … PHE Vs PAL, AL, OM ….CON Vs OM. WBC: #P<0.05 Vs OM, PAL. *P<0.05 Vs OM, PAL. MO: #P<0.05 Vs OM, *P<0.05 Vs PAL, AL, OM..GR: #P<0.05 Vs OM, *P<0.05 Vs PAL, OM. LYY: *P<0.05 Vs OM. WBC×103µl, LY×103µl, MO×103µl, GR×103µl, LYY%, MO%, GR%, RBC×106µl , HGB, g/dl, CON: Control, OME: Omeprazole, PHE: Phenobarbitone, AL:Artemether-lumefantrine, OAL:Omeprazole -Artemether-Lumefantrine, PAL:Phenobarbitone-Artemether-Lumefantrine. Values =Mean±SEM

Table 5: Haematological indices on day 32 after Artemether-lumefantrine administration

	HCT	MCV	MCH	MCHC	RDM	PLT	PCT	MPV	PDW
CON	41.24±0.67	51.04±0.54	17.64±0.67	36.32±0.26	18.50±0.30	252.4±33.5	0.16±0.03	6.36±0.16	6.88±0.82
AL	37.82 ±1.87	52.06±0.49*	17.34±0.13	33.36±0.33	19.76±0.16*	251.2±42.93	0.17±0.03	6.34±0.17	7.70±0.73
OME	42.79±0.91	51.41±0.12	34.81±3.64*	45.46±3.03*	18.71±0.14	294.0±17.94	0.20±0.01	6.86±0.07	9.60±0.37
PHE	37.08±2.40	49.06±0.57	16.90±0.22	34.46±0.15	18.12±0.32	235.0±38.4	0.11±0.02	6.02±0.11*	6.72±0.65*
OAL	33.92±4.58	48.96±0.85	19.12±0.45	38.92±1.36	18.14±0.26	314.0±49.0	0.22±0.03	7.52±0.44	8.72±0.76
PAL	37.52±1.47	51.90±1.29	18.64±0.32	36.64±0.40	16.50±1.39	267.0±28.04	0.42±0.10*	6.16±0.64	9.44±0.68

MCV : *P<0.05 Vs OAL. MCH: *P<0.05 Vs CON, AL, PHE, OAL, PAL. MCHC: *P<0.05 Vs CON, AL, PHE, OAL, PAL. RDM: *P<0.05 Vs PAL. PCT: *P<0.05 Vs CON, OME, AL, PHE, OAL. MPV: *P<Vs. OAL. PDW: *P<Vs. OME. HCT%, MCV fl, MCH pg, MCHC g/dl, RDW %, PLT×103µl, PCT%, MPV fl, PDW%.CON: Control, OME: Omeprazole, PHE: Phenobarbitone, AL: Artemether-lumefantrine, OAL: Omeprazole -Artemether-Lumefantrine, PAL: Phenobarbitone-Artemether-Lumefantrine. Values =Mean±SEM

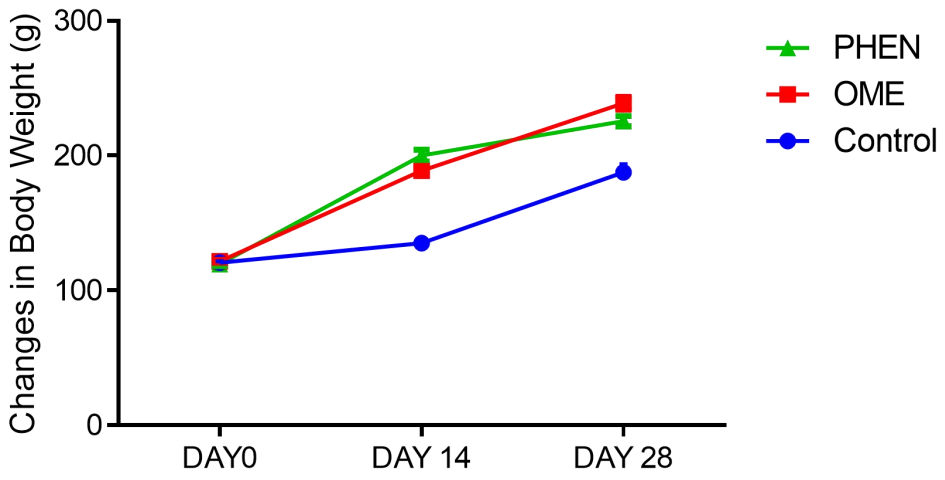

Fig 1: Significant changes in weight after 28 days *P<0.05 Vs OME. PHE. CON: Control, OME: Omeprazole, PHE: Phenobarbitone. Values =Mean±SEM

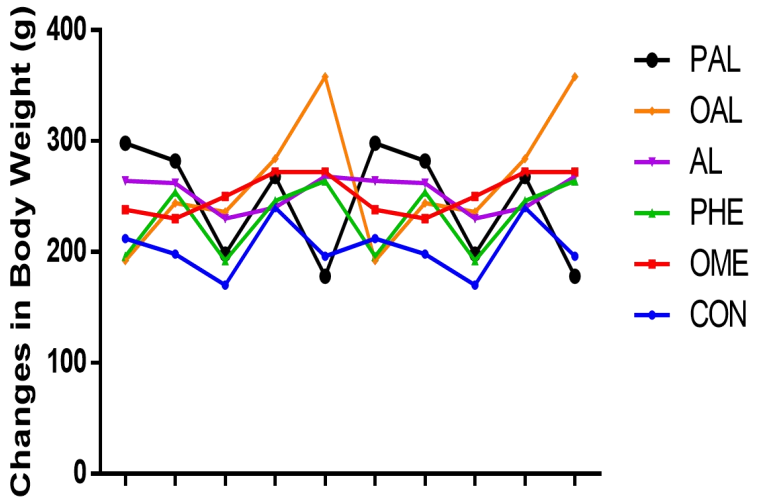

Fig 2: Significant changes in weight per group between 28th and 32nd day of administration of Artmether-lumefantrine administration *P<0.05 Vs OME, AL, OAL. CON: Control, OME: Omeprazole, PHE: Phenobarbitone, AL: Artemether-lumefantrine, OAL: Omeprazole -Artemether-Lumefantrine, PAL: Phenobarbitone-Artemether-Lumefantrine. Values =Mean±SEM

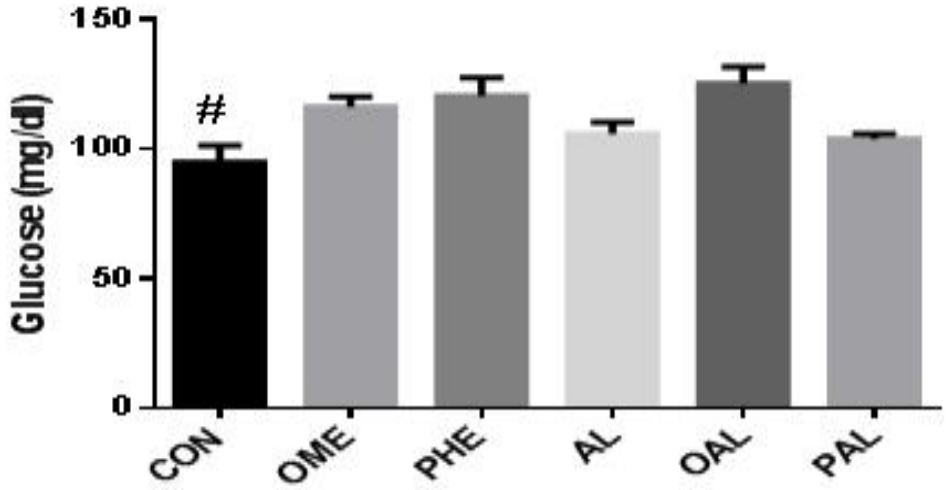

Fig 3: Significant changes in glucose after days 28 and 32 of Artemeter-lumefantrine administration *P<0.05 Vs PAL, OAL. CON: Control, OME: Omeprazole, PHE: Phenobarbitone, AL: Artemether-lumefantrine, OAL: Omeprazole -Artemether-Lumefantrine, PAL: Phenobarbitone-Artemether-Lumefantrine. Values =Mean±SEM

4. DISCUSSION

Changes in some of the parameters as seen in this study could be of clinical significance in therapeutics during long term therapies prior to the use of artemether-lumefantrine. Out of the thirty seven toxicity markers assessed, twenty-three showed significant differences. Phenobarbitone and omeprazole increased weight significantly after day 14 and 28 of exposure. Higher increase weight between days 28 and 32 as in figure 3 may be due to the contributory effect of artemether-lumefantrine as earlier reported in previous studies [14]. It can be however deduced that this combination can be of benefit deserving weight increase. Since glucose increased significantly due to combination of artemether-lumefantrine between days 28 and 32, hypoglycaemic individuals may also benefit from the combination. The hypoglycemic effect may be due to phenobarbital as reported [15]. This effect may have been potentiated artemether-lumefantrine as seen in figure 4. This effect seems to be more pronounced in phenobarbitone-artemether-lumefantrine co-administration. Most clinical studies have also reported that omeprazole improved glycemic control with decreased blood glucose levels [16-18]. The effect of phenobarbitone- artemether-lumefantrine and omeprazole- artemether-lumefantrine combination may pose a similar phenomenon in glucose level. Although there have been conflicting reports of no significant changes in serum glucose by proton pump inhibitors from other studies conducted [19,20]. The use of phenobarbitone may be an advantage because it may reduce the epileptogenic property of *Plasmodium falciparum* [21,22]. Since all lipids were significantly altered, it provides a clue for caution to be taken when phenobarbitone and omeprazole were used together with AL. As seen in the study, most of the lipids decreased in levels and this can be of benefit to individuals that may have existing lipid disorders in clinical certain. This benefit may be however seen with phenobarbitone- artemether-lumefantrine concurrent utilization as seen in Table 1, since the Low Density Lipoprotein (LDL) poses more implicated in cardiovascular risk [23]. On renal indices, PAL significantly increased urea and creatinine but showed no significant alteration of renal electrolytes (Potassium, Sodium and Hydrogen carbonate ions). Meaning PAL may worsen existing increase levels of urea and creatinine. Therefore PAL may pose a greater risk in individual with existing kidney disease. The induction of cytochrome P450s as seen with phenobarbitone as reported in most studies may lead to drug–drug interactions or decreased exposure in clinical certain, liver enlargement in preclinical species due to hepatocellular hypertrophy, and increased production of deleterious reactive intermediates and reactive oxygen species [24] may be linked to OAL increasing AST, CB and TB liver markers. Meanwhile, artemether-lumefantrine combination has been reported to be one of the most successful malaria treatment regimen which is highly effective and well-tolerated [25,26]. Although this advantage may be prominent, there may be drawback when the combination is used con-currently along with other drugs in co-morbid condition as in epilepsies and ulcers. The Artemisinin and its derivatives could have also influenced the activity of omeprazole, phenobarbitone and

lumefantrine. It has been reported that artemisinin is mainly metabolized to dihydro-artemisinin by CYP2B6 [27]. This resultant metabolite may have been influenced by phenobarbitone as inducer of the enzyme. The fate may also be linked to other metabolizing enzymes involved in the metabolism of artemisinin are CYP3A4 and CYP2A6 [28]. The enzyme CYP2A6 also play a major role in metabolizing artesunate to its active metabolite, dihydro-artemisinin [29,30]. Meaning, there seems to be no selectivity among the Artemisinin derivatives.

There was a significant increase in urea observed with AL. This significant increase was observed in this study is contrary to that reported [13], where there was a significant decrease in urea due to AL alone. Creatinine levels significantly decreased due to OAL but increase due to PAL. Slight increase which was not significant was observed with PAL compared to the control. Elevated levels of creatinine and urea in serum are an indication of risk to kidneys [31]. Systemic rise in blood creatinine is observed only with marked damage to functioning nephrons [32]. This study revealed a marked increase in urea and creatinine levels due to PAL. No significant change was observed with sodium, and hydrogen carbonate. There was a significant increase in Chloride ions due to PAL but a slight decrease was observed with OAL; which suggests hypochloremia and can lead to symptoms such as fatigue, muscle weakness, diarrhea, and dehydration [33]. Total cholesterol level was significantly reduced with AOL, and PAL suggesting that there is decreased propensity for cardiovascular risks in cases of concomitant use of AL with Phenobarbital or Omeprazole in epileptic or ulcer patient respectively, cardiovascular damage is reduced in clinically recommended doses. Previous report [13] has supported the above observation. Meanwhile artemether, dihydro-artemisinin and artesunate as representatives of artemisinin derivatives increase in TG [34]. Significant reduction in HDL levels was seen with AL, OAL, PAL with slight increase seen with PHE as in Table 1. LDL level was significantly reduced with PAL indicating that AL concomitant administration for malaria infected patients on Phenobarbital is beneficial lipid-cardiovascular risk patients. It has been documented that HDL levels are negatively correlated with risks of cardiovascular disease while LDL levels are positively correlated with CVD risk [35]. Lipid indices significantly reduced by AL after initial exposure to phenobarbital and omeprazole. Therefore, its use is recommended in managing malaria infection in hyperlipidemic patients on therapy with omeprazole or phenobarbital. There was also significant increase in total bilirubin due to AL, PAL, OAL. The increase in AST and TB observed in some of the treated animal groups suggests liver damage possibility. There was slight decrease in AST due to PAL suggesting hepatoprotective mechanism for patient that may have existing liver disease rather than risk. This finding is contrary to that reported by Aniefiok, Aprioku and their co-authors [36,37] which showed that artemisinin derivatives increased serum levels of ALT and AST at significantly high doses. This non-significant change in ALT, ALP, TB, ALB parameters also showed some levels hepato-safety properties. Antiepileptics, such as phenobarbital is a potent hepatic enzyme inducers [38] and increase in serum ALP, ALT, AST, and TP has also been indicated for liver injury [39]. The alteration of the integrity of the liver [40], may have led to the increase in serum levels of ALT, AST and ALP as observed in some cases in Table 3. Some of the variations seen in this study with respect to other studies may be due to difference in route of administration, dosage and duration of the drug administration. Eleven haematological indices were significantly altered as in Tables 4, 5. The results indicated that AL significantly elevated white blood cells (WBC) counts but no significant alteration in red blood cells and platelet counts. It was observed that there was a non-significant changes in RBC levels, and hemoglobin levels. No significant changes in RBC, HB and HCT values showed a reliability of the combinations in patients prone to anaemia or ulcerative bleeding. This result is similar to reports [41]. It is however essential to note that induction as seen with original principle of phenobarbitone can also influence the pharmacodynamical fate of quinine [42] which may also influence the clinical significance of artemether-lumefantrine. Caution should be ensured in the use of artemether-lumefantrine in epileptic patients undergoing phenobarbitone therapy. It may be interesting to note that certain disease condition may also induce or inhibit cytochrome P450 enzymes which will ultimately influence drug therapy [43,44]. Fundamental differences have been seen in rats and man, as omeprazole and rifampicin were shown to be potent inducers of CYP1A2 and CYP3A in humans respectively, but not in rats [45,46]. The fate of enzyme induction may not be the same in both species. Also the outcome can vary since all proton pump inhibitors are extensively metabolized by CYP2C19 and CYP3A4, except for rabeprazole, which primarily undergoes nonenzymatic metabolism agents [2]. Their use in conjunction with other agents can alter the pharmacodynamic fate of co-administered drugs. All proton pump inhibitors have been found useful clinically and the vary in their metabolism [47,48]. Since the major metabolic pathways for antimalarial agents include CYP2A6 for artesunate, CYP2B6 and CYP3A4 for other artemisinins, CYP2C8, CYP1A1 and CYP1B1 for amodiaquine, and CYP2C19 for biguanides [29], it shows thus how these agents toxicological potential will be determined by the individual inducers of the cytochrome P450 isoforms. Other studies showed no association between *CYP2C19* polymorphisms and breakthrough parasitemia, treatment failure, *ex vivo* antimalarial activity or mild adverse events, possible reflecting compensatory metabolism by CYP3A4 [30]. The complexity of cytochrome P450 lies on the isoforms. In a low resource centre, identification of such isoforms may be difficult. The ultimate activity may have been influenced by artemether as inducer of CYP450 2C19 and 3A4 [29]; meaning there may be competition with omeprazole in

enzyme induction. Artemether is metabolized quickly via CYP450 2B6, CYP450 3A4 and possibly CYP450 2A6 (49,50) to the more potent antimalarial metabolite DHA, which in turn is converted to inactive metabolites primarily by glucuronidation via UGT1A1, 1A8/9 and 2B7 [50]. Lumefantrine is metabolized by N-debutylation mainly by CYP450 3A4 [49,50] to desbutyl-lumefantrine with 5–8-fold higher antiparasitic effect than lumefantrine. Lumefantrine inhibits CYP450 2D6 (49). Artemether, lumefantrine, and nevirapine are all primarily metabolized by the cytochrome P450 (CYP) isoenzyme CYP3A4, and nevirapine is a known inducer of CYP3A4 [49,51,52]. All these may create the potential for important drug interactions with concomitant therapy as seen in this study. The induction of hepatic metabolizing enzymes, in particular the cytochrome P450s, could complicate the development and intended therapeutic use of a drug [1] as seen in some cases with phenobarbitone. This induction of drug metabolism suggests variable expression of a constant genetic constitution. Whether induction or inhibition phenomenon of CYP450 system, it has proven to influence important causes of drug–drug interactions (7). This study support an insight that pharmacogenomics of lumefantrine and other newer antimalarials [2] requires to be explored to give a better clue that may arise in safety and therapeutically resolution issues. Despite the few studies of pharmacogenomic of antimalarials even some ACTs in human subject [3] and the insufficient report on the fate of ACTs with other drugs even in large populations [3], this study has proven the possible interference of phenobarbitone and omeprazole by artemether-lumefantrine in albino rats. This also gave an insight in predicting what may happen in humans. Since artemether-lumefantrine has altered the toxicological fate of phenobarbitone and omeprazole after four weeks exposure, this combination should be used with caution in chronic therapies as in epilepsy and gastric ulcers.

5. CONCLUSION

The study has proven relevance in knowing the toxicological fate of Artemether-lumefantrine therapy in patients that may be treating epilepsy for a long time. In other words, patients that may have had epilepsy as an existing illness can present with malaria infection suddenly, therefore this will necessitate the use of antimalarial such as Artemether-lumefantrine. In this disposition, the fate of Artemether lumefantrine (efficacy/toxicity) will now be influenced by cytochrome P450 inducer like phenobarbitone. The same principle can also be predicted with omeprazole as cytochrome P450 inhibitor when artemether-lumefantrine is given to patient that may have had gastric ulcers.

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