Journal of Pharmaceutics and Drug Research
JPDR, 1(1): 23-27
www.scitcentral.com

Original Research Article: Open Access

Comparative Safety Profile of Artemisinin-Based Combination Therapies in Patients with Uncomplicated Malaria

Aghahowa SE[1*], Ozolua RI[1], Bafor EE[1], Obarisiagbon P[1] and Isah AO[2]

*[*1]Department of Pharmacology and Toxicology, University of Benin, Benin City, Nigeria*

[2]College of Medicine, University of Benin, Benin City, Nigeria.

Received August 28, 2018; Accepted September 19, 2018; Published September 29, 2018

ABSTRACT

Comparative adverse effects of artemether-lumefantrine (AL), artesunate-amodiaquine (AA), artesunate-mefloquine (AM), artesunate-sulphadoxine-pyrimethamine (ASP) and dihydroartemisinin-piperaquine (DHP) in patients were investigated. ACTs were administered to systematically randomized patients in conventional doses/regimen. Blood samples were collected from the ante-cubital vein of participants before and after completion of therapies were assessed for common toxicity markers such as weights, glucose, lipids, renal electrolytes, liver enzymes and haematological indices. Seventeen were significantly altered by ACTs ($p<0.05$). Blood glucose significantly increased due to AL, DHP but decreased due to AA, AM, ASP. Total cholesterol significantly increased due to ASP but decreased due to AL, AA, AM, DHP. High Density Lipoprotein decreased significantly due to AA. LDL increased significantly due to ASP. Urea increased significantly due to AA. Creatinine decreased significantly due to AL, ASP but increased due to AM, DHP. ALP increased significantly due to AM, but decreased due to DHP. ALT increased significantly due to AL, AA, AM, ASP. Conjugated bilirubin increased significantly due to AL AA, ASP, DHP but decreased due to ASP. Total bilirubin increased due to AL, AM but decreased due to ASP. Altered haematological indices were lymphocytes and monocytes. Artemether-Lumefantrine seems most safe. Discrete selection of ACTs is recommended in co-morbid states.

Keywords: ACTs, Safety, Indices, Malaria

INTRODUCTION

Due to resistance, malaria remains a burden in the sub-tropical Africa. This has necessitated the introduction of newer agents to replace older ones whose resistances have been reported. Following the introduction of ACTs in 2005 by the Federal Ministry of Health, Nigeria, there has been an increase in the use of ACTs [1]. Several shortcomings were observed in the adverse event profile reported in past studies [2]. One of these is the limitation in pre-clinical safety evaluation using monotherapies to predict the fate of combination therapies [3]. Results from monotherapies cannot be used to directly extrapolate what may occur in combination therapies because there may be adverse synergy due to the contributory effects of individual drugs in combination therapies. It has also been observed that only hematological indices or liver enzymes were evaluated in some past studies [2]; without taking into cognizance other organ systems. Following the Federal Ministry of Health adoption of AL as first-line drug and AA as alternative [4], it has been observed that the use of five ACTs has been on the increase. Recent studies have shown objective report [5,6]. Without evaluating the inherent effect in biological systems. Only one or two ACTs have been compared [2]. When animal models were used [3,7] full reflection on what may happen in humans may be lacking. The aim of the study was to comparatively evaluate the safety profile of five commonly used ACTs and to rank the order of safety of the ACTs as a clue to drug selection in malarial therapy.

Corresponding author: Aghahowa SE, Department of Pharmacology and Toxicology, University of Benin, Benin City, Nigeria, Tel: +234 805 5219550; E-mail: se-aghahowa@uniben.edu

Citation: Aghahowa SE, Ozolua RI, Bafor EE, Obarisiagbon P & Isah AO. (2018) Comparative Safety Profile of Artemisinin-Based Combination Therapies in Patients with Uncomplicated Malaria. J Pharm Drug Res, 1(1): 23-27.

MATERIALS AND METHODS

The study centre was the University of Benin Teaching Hospital, Benin City, Nigeria. Ethical approval (EC/FP/015/05) was obtained prior to study. The ACTs were procured directly from the registered pharmacies in Benin City, Nigeria. Total sample size was adapted for common toxicity studies [8]. The patients recruited were those that had uncomplicated malaria as specified by systematic randomization [6,9]. These patients were randomly allotted into five groups according to the five ACTs resulting in (n=5) for each group. The ACTs were given freely to all the participants to be administered orally according to three days dosing regimen [10]. Insecticide Treated Nets and ACTs were also given freely as incentive to participants. Before and after the completion of therapy, about 5-7 ml was collected from the ante-cubital vein of each patient. These were Day 0 prior to drug administration, Days 1, 2, 3 and 4 after drug administration. All information about the patients that participated was kept confidential.

Collected blood samples introduced into plain and lithium heparin bottles were assayed for biochemical and hematological parameters respectively according to specifications [11]. Samples in the plain bottles were allowed to clot at room temperature before centrifugation using the Hettich centrifuge (Rototix 32A, Germany) at 4000 rpm for 10 min. The sera were further withdrawn into plain containers using a sterile syringe. Standard diagnostic kits specified [12]. were used and Automated Clinical System (VIS-7220G, Biotech Engineering Management Company Limited, UK; Analyzer ISE 4000 SFRI, France) was used to assay for the following biochemical parameters: Pancreatic index (Blood Glucose), Renal indices (creatinine, sodium, potassium, urea, bicarbonate), Liver indices (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, conjugated bilirubin, total bilirubin, albumin and total protein) and Lipids (Total cholesterol, low-density lipoprotein, high-density lipoprotein and total triglycerides). The samples in lithium heparin bottles were assessed for hematological parameters using the automated hematological multichannel analyzer (ERMA PCE 210, Japan).

DATA ANALYSES

The data were first entered into Microsoft Excel and SPSS version 11.0 (SPSS, Inc. Chicago, IL). They are presented as mean ± SEM. Inferential analysis was done using ANOVA with Tukey's and Fisher's post hoc tests, odds ratio and relative risks (GraphPrism Version 6, San Diego, USA). $p<0.05$ was regarded as significant.

RESULTS

Out of the thirty-seven toxicity markers evaluated, seven of the parameters were significantly altered ($p<0.05$). Weight did not change significantly due to the ACTs. Blood glucose was significant increased by AL and DHP but decreased by AA, AM, ASP ($p<0.05$). Total cholesterol significantly increased due to ASP but decreased due to DHP. Potassium ion decreased significantly due to AA but increased due to AM. Creatinine decreased significantly due to ASP but increased due to AM. Conjugated bilirubin increased significantly due to AL but decreased due to ASP. Percentage lymphocytes decreased significantly due to AL and AA, increased due to DHP. Percentage monocytes increased significantly due to DHP but decreased due to AL, AA, ASP. None of the participants died and none degenerated to severe malaria in the study. Relative risk and odd ratio of the ACTs was found to be 0.75 and 0.70, respectively. Rank order of safety of ACTs was AL ≥ AA>AM>ASP>DHP.

DISCUSSION

The study has shown a wide variation in the safety profile ACTs in uncomplicated malaria. Following the introduction of ACTs into the malaria treatment policy in 2005 there has been an increase in their prescription [1]. This initially necessitated the initiative of National Agency for Food Drug administration and Control (NAFDAC) in collaboration with the Federal Ministry of Health [4]. to conduct a pilot program of Cohort Event Monitoring (CEM) program in the six geopolitical zones of Nigeria on patients using AL and AA to assess safety in the treatment of uncomplicated malaria [5]. This study represents a gold standard in guiding the selection of ACTs in the treatment of uncomplicated malaria in human. This study has also validated the safety profile of the conventional doses as recommended in humans [10]. In other words, the safety of recommended doses has been confirmed in humans and these doses can be extrapolated in other future studies. It is interesting to note that some of these agents have been assessed singly during pre-clinical studies and have proven to have one or two peculiar adverse effects during acute and chronic toxicity testing [3]. This study has shown a wider scope, thus providing more reliable information of the five commonly used ACTs.

It was observed that there were no significant changes in weight due to ACTs in humans. This seems contrary to the reports noticing an increase in body weight after oral administration of artemether/lumefantrine in rats [13]. Meanwhile, Utoh-Nedusa et al. [3] have also reported an increase in body weight after oral administration of dihydro-artemisinin alone. The changes reported may be due to longer duration of exposure of the ACTs in these past studies. Findings in this study agree with the work in which artesunate administration caused no significant effect on body weight [14,15]. The reason for no changes in body weight may be due to short duration of administration as adopted in the study. Reduction in the human serum glucose level by some of the ACTs in humans is similar to earlier monotherapic effect seen with amodiaquine and sulphadoxine/pyrimethamine in the potentiation of

hypoglycemic symptom in both complicated and uncomplicated malaria [16]. Similar reduction due to amodiaquine alone has also been reported in patients [17]. The suppression of glucose resulting in hypoglycemia can be possibly linked to a common upstream event and over production of superoxide by electron transport chain mechanism which may be due to ACTs [18]. Also the reduction in the expression of glucose as seen with AA, AM and ASP could be due to the claimed prevention glycolytic enzyme function, leading to the accumulation of the upstream intermediate compounds of the glycolytic pathway [19]. These ACTs may have also interfered with the intermediates such as fructose-6-phosphate, dihydroxyacetone phosphate and glucose as known substrates/activators in the glycolytic pathways, thus leading to reduction in glucose [19]. Results from this study suggest that prescription of AA, AM, ASP may be more suitable for hyperglycemic patients and AL seems more suitable for hypoglycemic individuals. The mechanism of ACT interfering with glucose parameter is not completely understood, however it can be proposed that reduction in glucose level as seen with AA, AM, ASP could be due to interference of the superoxide dismutase (SOD) is a family of enzymes involved in the conversion of superoxide to H_2O_2 as a reactive oxygen species [19]. The overall benefit in glucose levels altered by AA, AM, ASP may be of fit for patients that have diabetes while AL and DHP should be avoided in diabetes. Also the weakness commonly reported due to ACTs, may be linked to drop in glucose AA, AM, ASP as seen in this study [5,6].

Little or no renal derangement due to ACTs was seen in the study. Malarial infection in man can potentiate adverse effects of ACTs [20]. It is worthy to note that malaria pathogens induced can cause oxidative stress on the kidney [21]; thus potentiating the effect of ACTs in the renal system as seen with AM increasing creatinine levels. The rare ionic derangement as characterized by fatigue, muscle weakness, diarrhea, and dehydration that are known features of hypokalemic and hypochloremic effects may be linked with fewer side effects seen with AL subjectively [5,6,22]. Since ASP decreased creatinine level, it may be an essential tool in the management of malaria where increase renal creatinine has been observed. On the other hand, AM can also mask serum creatinine level in individual whose levels are normal.

Total cholesterol level decreased proportionally in DHP but increased in ASP combinations. From the foregoing, it can be deduced that ASP may cause more cardiovascular risk. Therefore caution needs to be taken in ASP combinations in subjects that have high cholesterol. In situation of comorbidity; such as malaria co-existing with cardiovascular disease, choice of adequate DHP combination may be beneficial rather than ASP. Meanwhile, artemether, dihydroartemisinin and artesunate as representatives of artemisinin derivative have been reported to cause dose dependent increase in TG [23], although significant changes were not observed. Despite no significant changes in other lipid parameters, it is of importance to note that High-density lipoprotein (HDL) levels are negatively correlated with risk of CVD while low-density lipoprotein (LDL) levels are positively correlated with CVD risk [24] when treating malaria with ACTs. Meanwhile, for individuals that may be dose sensitive to any of the ACTs, low or high levels of high-density lipoprotein cholesterol (HDL-C), triglycerides and lipoproteins levels may be seen; thus cardiovascular morbidity and mortality as influencing markers [25].

It was observed that essential liver enzymes (ALT, ALP and AST) were not significantly altered. Meanwhile, there had been reported opposite effect of artemisinin in elevating the activities of serum aspartate aminotransferase, alanine aminotrasferase and serum alkaline phosphatase significantly at higher doses, this represent possible hepatic toxicity [3,26,27]. The reports of no significant changes in enzyme level in this study showed a good safety profile in co-morbid hepatocellular damage. Note that, chronic administrations of the drugs can cause negative changes than short duration administration. It was also reported that dihydroartemisinin had no effect on serum level of alanine aminotransferase, serum alkaline phosphatase and serum aspartate aminotransferase activities [3]. Amodiaquine is a 4-aminoquinoline that has been identified to generate free radicals in form of amodiaquine immine and semi quinine immine and it is implicated in lipid peroxidation of the membranes of the hepatocyte cells [28]. Total bilirubin (TB) is also a biomarker associated with altered bile homeostasis and/or hepatobiliary injury [29]. The increase in level of total bilirubin with most ACTs except AL is a clear indication that bile homeostasis may have been altered. Its increase observed in the ACTs may be related to the individual drug in the combination. It has been documented that total bilirubin (TB) is a composite of unconjugated (extrahepatic) and conjugated (hepatic) bilirubin [30]. Since there were no significant changes in liver enzymes, it is a clear proof of safety of ACTs when used in conjunction with patients that may have hepatocellular disorders or drugs that may have the potential to alter liver enzymes. There can be dose sensitivity of the enzymes due to ACTs even in a short period. It should also be noted that some ACTs can mask the enzyme level in individuals that may be dose sensitive with existing hepatocellular damage.

It is interesting to note that percentage lymphocyte and monocytes were the only altered hematological indices due to ACTs. Anemia as a main feature of severe malaria is also believed to occur due to hemolysis of parasitized and non-parasitized RBCs, peripheral removal/sequestration of RBCs and ineffective erythropoiesis [31,32]. Therefore the reduction in some of the hematological indices as in percentage lymphocyte and monocytes could be due to the effect of individual drug in the combination.

The observed significant reduction in percentage lymphocyte and monocytes due to AL and AA may be attributed to the contributory effects of the individual drug in the component of ACT. Percentage lymphocytes and monocytes were elevated due to DHP. The slight increase in percentage lymphocytes as observed with DHP may also be due to presence of malaria parasite in the blood stream. It can be predicted that these anomalies observed some ACTs even on short-term therapy can return to normal after stopping therapy.

Previous studies have described artemisinin and its derivatives alone to be generally safe and well tolerated [33]. Therefore changes observed in artemisinin combination treatment may be due to the partner agents such as amodiaquine, lumefantrine, mefloquine and piperaquine. Hematologic abnormalities as features in *P. falciparum* infection causing anemia are inevitable in most malaria cases. This study has further proven the safety of ACTs in a confirmed *P. falciparum* infection as proposed [34]. Conventional doses of milligram per kilogram body weight as recommended. WHO [10] suggest a good safety range; since no subject died in the course of the study. The order of safety was confirmed as AL ≥ AA>AM>ASP>DHP; meaning AL was most safe while ASP combination was least safe in patients that presented with uncomplicated malaria.

CONCLUSION

The commonly used ACTs in the treatment of uncomplicated malaria have been compared in malaria patients by assessing the common toxicity markers as gold standard in safety research. Following the results, discrete selection of these drugs should be ensued in patients with co-existing disorders with malarial infection to avoid adverse synergy.

ACKNOWLEDGEMENT

We wish to appreciate all that assistance during the course of the work; most especially staff of the Department of Pharmacology and Toxicology, University of Benin, Benin City, Nigeria. Staff of the Department of Pharmacy, University of Benin Teaching Hospital, Benin City, Nigeria. Physicians in the General Practice Clinic, Family Medicine Unit, University of Benin Teaching Hospital, Benin City, Nigeria.

CONFLICT OF INTEREST DECLARATION

We wish to certify that there is no conflict of interest in this study.

REFERENCES

1. Aghahowa SE, Obianwu HO, Isah AO (2013) Prescription pattern of anti-malarial pre and post 2005 policy in a tertiary institution. J Pharm Health Serv Res 5: 75-78.
2. Falade C, Manyando C (2009) Safety profile of Coartem®: The evidence base. Malaria J 8: S6.
3. Utoh-Nedusa PA, Akah PA, Okoye TC, Okoli CO (2009) Evaluation of toxic effects of dihydroarteminisin on vital organs of Wistar albino rats. Am J Pharmacol Toxicol 4: 169-179.
4. Federal Ministry of Health Nigeria (FMOH) (2005) National Drug Policy on malaria treatment 2005: 1-20.
5. Bassi PU, Osakwe AI, Isah A, Suku C, Kalat M, et al. (2013) Safety of artemisinin-based combination therapies in Nigeria: A cohort event monitoring study. Drug Saf 36: 747-756.
6. Aghahowa SE, Obianwu HO, Isah AO (2014) Tolerabilities of artemisinin-based combination drugs among patients with uncomplicated malaria in a tertiary institution Benin City, Nigeria. J Clin Pharmacol Biopharma 3: 2.
7. Obianime AW, Apirioku JS (2009) Comparative study of artesunate, ACTs and their combinants on the hormonal parameters of the male guinea pig. Niger J Physiol Sci 24: 101-103.
8. World Health Organization (2007) Relationship between sample size and probability of observing an adverse event (AE). A practical handbook on the pharmacovigilance of antimalarial medicines. WHO Press, p: 27.
9. World Health Organization (1990) Practical chemotherapy of malaria. Report of a WHO Scientific Group. Geneva, WHO, (WHO Technical Report Series, No. 805), pp: 1-50.
10. World Health Organization (2001) Antimalarial Drug Combination therapy: Report of a WHO technical consultation, Geneva. World Health Organization, pp: 1-36. Accessed from: http://www.who.int/malaria/world-malaria-report-2010/en/index.html
11. Want EJ, O'Maille G, Smith CA, Brandon TR, Uritboonthai W, et al. (2006) Solvent-dependent metabolite distribution, clustering, and protein extraction for serum profiling with mass spectrometry. Anal Chem 78: 743-752.
12. http://www.randox.com
13. Tijani SA, Ukwenya VO, Fakunle JB (2011) Acute administration of co-artemisiane induced oxidative stress in the testes of adult Wistar rats. Biosc Res Comm Mol 22: 5-12.
14. Izunya AM, Nwapora AO, Aigbiremolen A, Oaikhena GA (2010) Body and testicular weight changes in adult Wistar rats following oral administration of artesunate. Res J Appl Sci Eng Technol 2: 302-306.

15. Nwanjo HU, Oze G (2007) Hepatotoxicity following administration of artesunate in male guinea pig. Internet J Toxicol 1: 7.

16. World Health Organization (2000) Severe falciparum malaria. Trans R Soc Trop Med Hyg 94: 1-90.

17. Ewenighi CO, Ukwa BN, Dimkpa U, Onyeanusi J, Onoh LU, et al. (2013) Comparative evaluation of the effects of artemisinin-based combination therapy and amodiaquine monotherapy in G6PD activity, fasting glucose level and parasite clearance rate in malaria-infected adults in Abakaliki, Nigeria. J Biol Agric Healthc 3: 39-44.

18. Brownlee M (2001) Biochemistry and molecular cell biology of diabetic complications. Nature 414: 813-820.

19. Brownlee M (2005) The pathobiology of diabetic complications: Aunifying mechanism. Diabetes 54: 1615-1625.

20. Aghahowa SE, Obianwu HO, Isah AO, Arhewoh MI (2010) Possible mechanism, relevant factors and treatment approach of chloroquine-induced pruritus - A review. Indian J Pharm Sci 72: 283-408.

21. Dendooven A, Ishola DA, Nguyen TN, Van der Giezen DM, Kok RJ, et al. (2011) Oxidative stress in obstructive nephropathy. Int J Exp Pathol 92: 202-210.

22. Grosser T, Smyth E, FitzGerald GA (2011) Anti-inflammatory, anti-pyretic and analgesic agents; pharmacotherapy of gout. In: Goodman and Gilman's Pharmacological Basis of Therapeutics (Eds. Brunton LL, Chabner BA, Knollmann BC) (12th Edn) Cap 34. McGraw-Hill, p: 972.

23. Georgewill G, Ebong O (2012) Artemisinin combination therapies: Safe or not safe? Int J Pharmacol 10: 1-6.

24. Maranville JC, Di Rienzo A (2014) Combining genetic and non-genetic biomarkers to realize the promise of pharmacogenomics for inflammatory diseases. Pharmacogenomics 15: 1931-1940.

25. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, et al. (2012) Plasma HDL cholesterol and risk of myocardial infarction: A Mendelian randomisation study. Lancet 380: 572-580.

26. Aprioku JS, Obianime AW (2011) Structure activity - Relationship of artemisinin on some biological systems in male Guinea pigs. Insight Pharm Sci 1: 1-10.

27. Aniefiok U, Edoho JE, Olurufemi E, Etim EI (2009) Effect of artemisinin with folic acid on the activities of aspartate aminotransferase, alamin aminotransferase and alkaline phosphate in rat. Asian J Biochem 4: 55-59.

28. Maggs JL, Kitteringhan NR, Park BK (1988) Drug protein conjugate - XIV. Mechanism of formation of protein - arlating intermediate for amodiaquine, a myelotoxin and hepatotoxin in man. Biochem Pharmacol 37: 303-311.

29. Bjornsson E, Olsson R (2005) Outcome and prognostic markers in severe drug-induced liver disease. Hepatology 42: 481-489.

30. Wintrobe MM, Greer JP (2009) Wintrobe's clinical hematology. 12th Edn. Lippincott Williams & Wilkins, Philadelphia.

31. Akhtar S, Gumashta R, Mahore S, Maimoon S (2012) Hematological changes in malaria: A comparative study. J Pharm Biol Sci 2: 15-19.

32. Abdalla SH, Pasvol G (2004) Malaria: Hematological perspective. Imperial College Press, London, p: 75.

33. Nosten F, White NJ (2007) Artemisinin-based combination treatment of falciparum malaria. Am J Trop Med Hyg 77: 181-192.

34. Maina RN, Walsh D, Gaddy C, Hongo G, Waitumbi J, et al. (2010) Impact of Plasmodium falciparum infection on hematological parameters in children living in Western Kenya. Malaria J 9: S4.