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Effect of artesunate and amodiaquine alone and in combination on plasma biochemical parameters in mice

Abstract

Albino mice are considered a comparable genetic model to humans and it is well established that they also exhibit natural differences in susceptibility to malaria infection. The study was aimed at determining and comparing the effects of artesunate, artesunate+amodiaquine combination, on biochemical parameters such as plasma pH, plasma glucose and plasma cholesterol in the course of administering antimalarial drugs. The effects of artesunate, amodiaquine and a combination of artesunate-amodiaquine on some hematological and biochemical parameters were assessed in this study. Twenty albino mice of eight weeks old were randomly divided into 4 groups based on a specific antimalarial drug administered and one group served as control. Blood sample was obtained at the end of the study and assay was done for glucose concentration, plasma pH, and plasma cholesterol concentrations. Data were expressed as mean±standard errors of mean. Comparisons between control and treated groups of albino mice were performed with one-way analysis of variance (ANOVA), followed by Tukey Kramer *post hoc* test for multiple comparisons. Statistical significance was set at $P<0.05$. Plasma pH was not significantly lower ($p<0.05$) in the antimalarials; artesunate, amodiaquine and artesunate+amodiaquine groups compared to the control group. Plasma glucose was significantly lower in the antimalarials; Artesunate, artesunate+amodiaquine but higher in Amodiaquine compared to the control group. Plasma cholesterol was significantly lower ($p<0.05$) in the treated groups, Amodiaquine, artesunate+amodiaquine groups compared to the control group. Hence, maximum reduction was seen in the combination group compared to the individual drugs.

Keywords: amodiaquine, antimalarials, artesunate, albino mice, plasma cholesterol

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Introduction

Malarial infection still stands out as one of the widespread parasitic diseases affecting mainly the third world countries yet causing a high morbidity and mortality.[1] The parasite has a unique mechanism of action through its invasion of red blood cells, liver and in some severe forms splenic and cerebral involvements.[2,3] The complications resulting from malaria could be in the acute or chronic phase mediated by direct parasitic invasion of tissues or distortions from altered biochemical processes.[4,5] The role of antimalarials in reducing morbidity and mortality resulting from malaria cannot be understated, especially in sub-Saharan Africa. However, the targets of most health bodies in mitigating the problem have not been met owing to the socio-economic factors affecting healthcare.[6] These factors are directly related to the endemicity of destitution in Africa. Erstwhile, malaria's morbidity and mortality rate were soaring owing to inefficient medications and irrational use of available medications which invariably led to high resistant strains of the *Plasmodium falciparum*.[7] Chloroquine-based drugs faced out after the introduction of the artemisinin-based combination therapies (ACTs) which proved effective, safe and economically sound[8] but currently remains in use in treating some autoimmune diseases such as discoid lupus erythematous.[9] Amodiaquine, a 4-aminoquinoline similar to chloroquine is used in the treatment of malaria currently in combination with the artemisinin, especially artesunate.[10] It acts by an intercellular mechanism halting and shutting down the DNA and RNA machinery.[11] Although, well tolerated compared to chloroquine, it results in several haematological and biochemical aberrations such as neutropenia and raised serum transferases.[12,13] Artesunate is an artemisinin derivative,[14] which is usually used solely or in various combinations. It has a wide therapeutic window,[15] leading to its widespread use in malaria. The malarial parasites have no resistance to the artemisinin as at now.[16] Notwithstanding, it has shortfalls such as increased rate of recrudescence owing to its short half-life[17] hence its sole administration can lead to resistance in future. Combination therapies are usually preferred to avert this unfavorable outcome.[18] Measurement of resistance is very difficult and usually recognized at a very latter stage, hence measures need to be put in place to avoid this. Artemisinin and its congeners can produce carbon-based radicals which can cause oxidative stress to surrounding tissues.[19] However, the effect of artemisinin compounds and their combinations on various plasma biochemical parameters have neither been evaluated nor compared to some of the older drugs.

Methods

Twenty imprint control (ICR) albino mice of both sexes (25-30g) were obtained and housed in a cage at ambient temperature. The albino mice were fed daily on experimental basis. Study was conducted in accordance with established guidelines for care and use of animals in research by the National Institute of Health (NIH).

Experimental design

The twenty-imprint control (ICR) albino mice were divided into four groups (n=5). Treatment is provided in all groups two times daily at therapeutic doses calculated on weight of the albino mice.

Group A: albino mice were treated with normal saline and served as a control group Group B: albino mice were given 1mg of Artesunate

suspension using normal saline Group C: albino mice were given 2.7mg of Amodiaquine suspension using normal saline Group D: albino mice were given 1mg of Artesunate and 2.7mg of Amodiaquine suspension using normal saline.

Treatment with specific drugs were done for three consecutive days as they were on their normal feed, for morning and evening in an 8 hrs time interval. Albino mice were sacrificed by cervical dislocation at the end of the third day and blood samples taken for biochemical analysis.

Statistical analysis

Data was presented in mean±SEM and was analyzed using GraphPad Prism for Windows Version 6.01 (GraphPad Prism Software, San Diego, USA). Results were presented as Mean values±standard error of mean (SEM), and the statistical differences between treatment groups compared using One–way analysis of variance (ANOVA) followed by Tukey Kramer *post hoc* test for multiple comparisons, with a 95% confidence interval. $P<0.05$ was considered statistically significant.

Results

Plasma pH concentration was reduced in all treatment regimen when compared to the control group. When compared with the saline control group 7.35±0.05, treatment with Artesunate, Amodiaquine and combination of Artesunate+Amodiaquine reduced plasma pH concentration to 7.36±0.01, 7.34±0.01 and 7.40±0.01 respectively (Table 1). None of the drugs resulted in a pH significantly different from the naive control ($p>0.05$).

Table 1 Effects of medications on plasma pH

Treatment	pH	P-value
Saline Control	7.35±0.05	
Artesunate	7.36±0.02	0.09
Amodiaquine	7.34±001	0.08
Artesunate+Amodiaquine	7.40±0.01	0.197

Table 2 Effects of medications on plasma glucose (g/dL)

Treatment	Glucose	P-value
Saline control	35.58±0.60	
Artesunate	31.81±0.31	0.04
Amodiaquine	37.06±0.36	<0.001
Artesunate+Amodiaquine	30.91±0.17	0.02

Table 3 Effects of medications on plasma cholesterol

Treatment	Cholesterol	P-value
Saline control	51.86±0.16	
Artesunate	39.45±0.09	<0.001
Amodiaquine	43.21±0.78	<0.001
Artesunate+Amodiaquine	32.10±0.52	<0.001

Treatment with Artesunate, Amodiaquine and combination of Artesunate+Amodiaquine therapy at the stated doses significantly reduced plasma glucose concentration to 31.81±0.31, 37.06±0.36 and 30.91±0.17 respectively when compared with 35.58±0.60 in the saline control albino mice (Table 2). All three drugs resulted in variable plasma glucose which was significantly different from the control ($p<0.05$).

Plasma cholesterol level was elevated to 51.86±0.16 in the saline control group compared to treatment with AR, AM and combination of AR+AM of 39.45±0.09, 43.21±0.78 and 32.10±0.52 respectively (Table 3). Artesunate, Amodiaquine and Artesunate+Amodiaquine decreased total cholesterol concentration to levels significantly different from the control group.

Discussion

Malaria endemic regions have seen several pharmacotherapeutic agents been administered and changed over the course of time. Resistance to treatment and recognition of unbearable side effects lead to sudden abolition of older drugs while newer agents are gradually incorporated into treatment protocols. There was a variable response to plasma biochemical parameters after the administration of antimalarials (artesunate, amodiaquine and artesunate-amodiaquine) in albino mice without malarial infestation.[20] The results on plasma pH depict an essential finding in the pharmacotherapeutic options in malarial treatment. It was realized that a 3-day post-treatment of antimalarials, resulted in no significant change ($p>0.05$) in plasma pH when compared to control. This shows that pH is not altered during treatment with artesunate, amodiaquine or artesunate-amodiaquine. Antithetical to this finding, malaria with high parasitemia presents with lactic acid build up leading to metabolic acidosis[21] hence drugs which do not precipitate this complication during treatment presents as a safe choice. Clinically, these drugs can be used in patients predisposed to metabolic acidosis such as in those with uncontrolled diabetes mellitus. The findings of this study showed amodiaquine and the control with higher blood plasma levels compared to the other groups. The study involved unparasitized albino mice which have a low level of glucose metabolism and hence minimal effect on plasma glucose. Amodiaquine's ability to induce hypoglycemia can then be considered as an augmentation of parasitic-induced hypoglycemia rather than a direct influence from the drug.[22] Quinine and other cinchona alkaloids can reduce plasma glucose irrespective of parasitemia.[23] In this study, the greatest reduction was seen in the combination therapy followed by the group treated with the Artesunate. Artesunate, however was realized to have reduced plasma glucose significantly in a chronic study of 45 days, where chronicity led to deranged liver functions and hence an aberration in its metabolic roles.[20] It was observed that the individual reduction of plasma glucose by the medications were less than the combination therapy in the acute phase. The phenomenon of potentiation could possibly explain the trend seen from both drugs in reducing plasma glucose. The level of serum cholesterol was seen to have been reduced after the 3-day therapy with the antimalarials. Artesunate, Amodiaquine and Artesunate+Amodiaquine decreased total cholesterol concentration, thus having cholesterol-lowering effects at their therapeutic doses. Maximum reduction was seen in the combination group compared to the individual drugs. These agents may therefore be used safely in dyslipidemia with possible benefits.

Conclusion

In this present study, the maximum reduction was seen in the combination group compared to the individual drugs**.** Following was the treatment with Artesunate which was found to reduce plasma glucose significantly. The introduction of the new agents in replacing previously used antimalarial drugs such as quinine and chloroquine was successful. Untoward effects from cinchona alkaloids which was mainly hypoglycemia and allergic reactions were averted with the

introduction of artesunate, amodiaquine and its congeners. In depth toxicological studies of these agents in humans are lacking owing to the specious perception of these agents having any untoward effects. This study, however, sets the premise for further research with respect to antimalarials in human subjects and focusing on chronic exposure as compared to acute exposure in this study.

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Conflicts of interest

The authors declare that this article content has no conflict of interest.

References

1. Murphy SC, Breman JG. Gaps in the childhood malaria burden in Africa: cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia, and complications of pregnancy. *The American Journal of Tropical Medicine and Hygiene*. 2001;64(1-2 Suppl):57–67.
2. Kerb R, Fux R, Mörike K, et al. Pharmacogenetics of antimalarial drugs: effect on metabolism and transport. *The Lancet Infectious Diseases*. 2009;9(12):760–774.
3. Klonis N, Creek DJ, Tilley L. Iron and heme metabolism in Plasmodium falciparum and the mechanism of action of artemisinins. *Current Opinion in Microbiology*. 2013;16(6):722–727.
4. Markham LN, Giostra E, Hadengue A, et al. Emergency liver transplantation in amodiaquine-induced fulminant hepatitis. *The American Journal of Tropical Medicine and Hygiene*. 2007;77(1):14–15.
5. Zachary Y. Attitude of Mothers towards Complications of Malaria Case of Children Less than 5years Living in New Bell Ebolowa (Cameroon). *Malaria Control & Elimination*. 2016;5(2).
6. *Guidelines for the Treatment of Malaria*. World Health Organization: Geneva, Switzerland; 2010.
7. Snow RW. Global malaria eradication and the importance of Plasmodium falciparum epidemiology in Africa. *BMC Medicine*. 2015;13(1):23.
8. Itoh M, do Valle SN, Farias S, et al. Efficacy of Artemether–Lumefantrine for Uncomplicated Plasmodium falciparum Malaria in Cruzeiro do Sul, Brazil, 2016. *The American Journal of Tropical Medicine and Hygiene*. 2018;98(1):88–94.
9. Laurentius A Pramono, Suryo Anggoro, Sandra Langow, et al. Successful Treatment of Discoid Lupus Erythematosus with Chloroquine. *Acta Med Indones*. 2013;45(4):321–323.
10. Famin O, Ginsburg H. Differential effects of 4-aminoquinoline-containing antimalarial drugs on hemoglobin digestion in Plasmodium falciparum-infected erythrocytes. *Biochemical Pharmacology*. 2002;63(3):393–398.
11. Rosenblatt JE. *Antiparasitic agents*. Mayo Clinic Proceedings: Elsevier; 1992. 276–287 p.
12. Farombi EO. Influence of amodiaquine treatment on microsomal lipid peroxidation and antioxidant defense systems of rats. *Basic & Clinical Pharmacology & Toxicology*. 2000;87(6):249–254.
13. Yeka A, Lameyre V, Afizi K, et al. Efficacy and safety of fixed-dose artesunate-amodiaquine vs. artemether-lumefantrine for repeated treatment of uncomplicated malaria in Ugandan children. *PLoS One*. 2014;9(12):e113311.
14. Olurishe TO, Kwanashie HO, Anuka J, et al. Histopathological effects of sub-chronic lamivudine-artesunate co-administration on the liver of diseased adult Wistar rats. *North American Journal of Medical Sciences*. 2011;3(7):325–328.
15. Li Q, Xie LH, Johnson TO, et al. Toxicity evaluation of artesunate and artelinate in Plasmodium berghei-infected and uninfected rats. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2007;101(2):104–112.
16. Saifi MA, Beg T, Harrath AH, et al. Antimalarial drugs: Mode of action and status of resistance. *African Journal of Pharmacy and Pharmacology*. 2013;7(5):148–156.
17. LaCrue AN, Scheel M, Kennedy K, et al. Effects of artesunate on parasite recrudescence and dormancy in the rodent malaria model Plasmodium vinckei. *PLoS One*. 2011;6(10):e26689.
18. White N. Delaying antimalarial drug resistance with combination chemotherapy. *Parassitologia*. 1999;41(1-3):301–308.
19. Kavishe RA, Koenderink JB, Alifrangis M. Oxidative stress in malaria and artemisinin combination therapy: Pros and Cons. *The FEBS Journal*. 2017;284(16):2579–2591.
20. Ayogu E, Ugwuowo O, Amorha K, et al. Evaluation of ciprofloxacin effect on the antimalarial activity of some antimalarial drugs in plasmodium Berghei Infected Mice. *International Journal of Pharmaceutical Sciences and Research*. 2016;7(5):1896–1903.
21. Onaolapo AY, Onaolapo OJ, Awe EO, et al. Oral Amodiaquine, Artesunate and Artesunate Amodiaquine Combination Affects Open Field Behaviors and Spatial Memory in Healthy Swiss Mice. *Journal of Behavioral and Brain Science*. 2013;3(8):569–575.
22. Adeleye G, Nneli R, Nwozor C, et al. Effects of Coartem and Artesunate on Some Haematological and Biochemical Parameters in Albino Rats. *African Journal of Biomedical Research*. 2012;15(1):55–58.
23. Gomes AP, Vitorino RR, Costa AdP, et al. Severe Plasmodium falciparum malaria. *Revista Brasileira de Terapia Intensiva*. 2011;23(3):358–369.