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Research article

COMPARATIVE EVALUATION OF GASTRIC AND BLOOD ANOMALIES IN COARTEM, CHLOROQUINE, FANSIDAR, LONART AND IN EXPERIMENTAL MALARIA

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ABSTRACT

Study on the effects of some antimalaria drugs; coartem, fansidar and lonart on gastric acid secretion was carried out for 14 days on thirty albino male and female mice infected with Plasmodium berghei berghei malaria parasite. The results showed that coartem at a dosage of 33.6mg/kg decreased red blood cells count as compared with control $P<0.05$, same with chloroquine at a dosage of 14.3mg/kg. But Lonart at a dosage of 32.1mg/kg increased red blood cells count ($P<0.05$) compared with control. In the white blood cells count, coartem increased its count ($P<0.05$) compared with control, similar effect but with slight increase was observed with fansidar. However, Lonart and chloroquine drugs have high significant increase in white blood cells counts as compared with control. Significant gastric acid output ($P<0.05$) was obtained with chloroquine administration same with lonart as compared with control whereas coartem and fansidar groups had reduced values as compared with control. All the mice infected with malaria parasites had elevated gastric acid output. It is concluded that both antimalaria drugs and malaria disease affect the gastric and blood physiology.

Keywords: Antimarials, malaria, gastric, blood anomalies.

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INTRODUCTION

The stomach, a J. Shaped structure is an important organ of the digestive system which main functions are storage secretion, mixing of food and digestion e.g. protein (Guyton 2006). The stomach secrets hydrochloric acid which is pivotal in the digestion of protein with its proteolytic influence in converting pepsinogen to pepsin. It secret hydrochloric acid through gastrin, histamine receptors parietal mechanism and such regulated by nervous and hormonal pathways. Apart from its natural secretions in the presence of food in the stomach in various physiologic phases; cephalic, gastric and intestinal, gastric secretions are also stimulants related e.g. tea, Jimmy et al 2013. Others are drugs; chloroquine, Etimital, 2005. The ultimate effect of the acidic secretions is peptic ulcer, such ulceration often are the interactions of reaction oxygen species on the gastric mucosa and often increased in disease situations e.g Helicobacter pylori (Yamaguchi, 2001). Malaria is also incriminated in the formation of reaction oxygen species (ROS), Sanjeve, 20003. There are scanty documentation on the gastric status in malaria and its chemotherapy.

Malaria is an endemic disease in Africa affecting young and old but the children and pregnant women are the most vulnerable about 2500 children die yearly in Nigeria due to malaria attacks, (Malaria consortium 2013). The death tolls increase is basically due to the fact that nearly all the drugs are resisted by the resistant strains e.g *Plasmodium falciparum* Ibrahim, 2009, Cally, 2004, Tim, 2004 Slater, 1992, Peters, 1987. Other strains that attack man are *P. Vivax*, *P. Ovale* and *P. malaria*e. Those that thrive well in animals are *P. berghei berghei*, *P. Yoeli, P. Chabaudi, P. Vinckei*, *P. Knowlesi. P. Simium, P. gallinaleum*, *P. Lophurae*, *P. agamae*, and *P. Cymolgi*, Abildgraad, 1975, Aikawa, 1975.

In experimental malaria research it is the *P. berghei berghei* that is mostly utilized as it proliferates well in both the young and old blood cells in culture medium both invitro and invivo particularly in mice. Malaria is caused by female anophiles mosquitoes because its only the type that sucks blood for its reproduction requirements. The sporozoites in the mosquitoe's salvia via its glands enter the blood stream and migrate into the liver and infect the hepatocytes for its asexual reproduction. This result in the formation of merozoites. The merozoites developed through its dependency on amino acids from the broken down haemoglobin cause by itself in the red blood cells, Sherman, 1997. The merozoites multiply to torphozoites then to schizonts leading to the sexual form; gametocytes Sindin, 1981, that will enter the mosquitoes by its feeding on blood and cycle continues, (Pasvol, 1982). The effects of the parasites sojourning in the human body affects every facets but often death comes from anaemia due to effects on red blood, white cells and platelets, Essien 1979. Malaria symptoms include fever, vomiting, joint pains, anaemia, hemoglobinuria, retinal damage, convulsion, Beare, 2006. Others are splenomegaly; severe headache cerebral ischaemia, hepatomegaly, renal failure, Tran 1992, hypoglycemia, diarrhoea and cough. Information in malaria and its gastric associated anomalies are scanty and not taken alongside in the clinical management of malaria hence, the relevance of this study. Both chloroquine and fansidar are not very effective in the treatment of malaria as a result of the emergence of resistance species, *Plasmodium falciparum.* However, the alternative drugs meant to tackle resistance malaria; Lonart and coartem are very potent but expensive. The gastric associated anomalies of these new drugs have not been fully documented, which is the main objective of this study as compared with the old drugs but chloroquine is observed to stimulate gastric secretion, Etimital, 2005. Chloroquine is a curative drug, very cheap highly available, and highly prescribed, (Ollian, 2003). It is also widely misused (Anne, 2011) and wrongly medicated, Jimmy 2000. The aim of the study is to assess associated gastric and blood anomalies in the antimalaria drugs and such in malaria disease which double jeopardy is unprevented but a choice of a physiologic friendly antimalaria drugs could prevent the double scourge.

MATERIALS AND METHODS

A total of thirty 30 albino mice, male and female were used in the study. The consent for their use was not obtained as there is no animal right committee where the study was done. However, the animals were not tortured in the course of the study. The albino mice were grouped into five experimental areas; with six (6) mice in each group; Group 1 was control group without malaria parasite (*P. berghei berghei*), group 2 had malaria parasite without treatment. Groups 3 mice were inoculated with malaria parasites and treated with Fansidar, group 4 had malaria parasites and treated with coartem, group 5 had malaria parasites and treated with chloroquine while group 6 also had malaria parasites and treated with Lonart.

INOCULATION OF MALARIA PARASITES INTO THE ALBINO MICE AND PARASITE DETERMINATION

Each adult mouse in groups 3-6 infected intraperitoneally with 0.15ml of *P. berghei berghei* from infected mouse diluted 1:3 with sterile saline (Essien, 1984). Daily parasite determination was done by peripheral blood collection from the mouse tail. The mouse red blood cells were collected during acute rise in the infection as observed through the count. Thick blood films were made and stained with giemsa stain and studied under the microscope using x 100 oil immersion objective to determine the parasites species. The species of parasites were identified by the stages of development and malaria parasites identified were those of *P. berghei berghei*.

BLOOD CELLS COUNTS: The red blood, white blood cells and platelets were counted based on the methods of Imelda, Lewis, 2007 and Essien et al 1984, 1979.

Preparation and Administration of Antimalaria Drugs

The drugs were prepared and administered according to the methods of Jimmy et al 2007, Bertram, 2004, Robert et al 1979. The drugs were prepared by the weight of the animals based on the average weight of man as follows;

(a) **Chloroquine:** 4 tablets of 250mg for the first day of 2 tablet each for the next three days dissolved in 100ml of distilled water and given 1mg/ml to the animals

(b) **For fansidar group:** 3 tablets of 525mg were dissolved in 100ml of distilled water and 1mg/ml given as single dosage.

(c) **Coartem:** 140mg being a tablet weight was dissolved in 50ml of distilled water; 33.6mg/kg of drug dosage was given to each mouse i.e after first dosage the 2nd dosage is given after 8 hours then repeated morning and evening for 2 days.

(d) **Lonart:** A tablet of 560mg was dissolved in 100ml of distilled water with 32.1mg/kg was given first dosage and 2nd dosage after eight hours, and after that once daily for 3 days.

(e) **Route of administration of drugs:** The drugs were administered orally using canula, by-passing the oesophagus and delivered into the stomach, Jimmy et al, 2007 Robert et al 1979.

(f) **Determination of Gastric Secretion:**
(Silverton & Baker 1982)

The stomach was removed from each mouse after chloroform anaesthesia. It was cut opened vertically and content squeezed into petridish and 5ml of distilled water added. The content was filtered and the solution titrated against 0.02N NaOH using 2 drugs phenolphthalein indication. The titrable acidity was calculated

to arrive at total acid output using the formular, X = initial gastric content without addition of 5ml of distilled water diluted water

Y = volume after adding 5ml of dilute water

$$\frac{X.Y.\ 20\ mmoL/L.}{}$$

RESULTS

(a) Gastric acid Secretion

The mean acid output in control group, group 2, 3, 4, 5, 6 with malaria parasite, fansidar, chloroquine, lonart and coartem were, 11.67 ± 0.16, 12.27 ± 0.18. 10.80 ± 0.12, 14.89 ± 0.19, 13.05 ± 0.06 and 11.47 ± 0.05. The mean value of chloroquine group 14.89, Lonart group, 13.05 and the malaria group 2; 12.27 were significantly higher (P <0.001) than control group (11.67) while control was higher than group 6 (Coartem); 11.67 and group 3; (fansidar); 10.80. P < 0.001. Table 3

(b) **The RBC Counts:** The values of the mean

RBC count in the control, malaria, fansidar, chloroquine, coartem and lonart groups were 6.77 ± 0.3, 6.54 ± 0.23, 6.53 ± 0.3, 6.48 ± 0.09, 6.93 ± 0.27 and 7.59 ± 0.09 respectively Table 1. The mean values of group 6 (coartem) and group 5 (Lonart) with values of 7.59 and 693 were significantly (P < 0.05) higher than control group (6.77), group 2, (malaria) 6.54, fansidar group 3, 6.54 and chloroquine (4) 6.48. Among the antimalaria group, Lonart had the highest mean value (16.76) while group 3 (fansidar) had the least mean value (10.29). However, lonart group was significantly higher (P < 0.001) than group 4, group 6 and group 3, Table 2.

(c) **WBC Count:** The results showed this varied values in the groups; control, malaria, fanisdar, chloroquine, lonart and coartem; 10.6 ± 0.34, 10.14 ± 0.03, 10.29 ± 0.42, 16.08 ± 0.12, 16.76 ± 0.22 and 11.04 ± 0.10, table 2 mean values of group 5, (Lonart), group 4, (chloroquine, group 6, coartem and group 3 (fansidar) were significantly higher (P. < 001) than the control group, while the entire group was slightly higher than the malaria group.

TABLE 1: RED CELLS COUNTS

S/N	GROUPS	RBC
1.	Control	6.77 ± 0.3
2.	Malaria	6.54 ± 0.23

3.	Fansidar	6.53 ± 0.3
4.	Chloroquine	6.48 ± 0.09
5.	Lonart	6.93 ± 0.27
6.	Coartem	7.59 ± 0.09

TABLE 2: WBC COUNTS

S/N	GROUPS	WBC
1.	Control	10.16 ± 0.34
2.	Malaria	10.14 ± 0.03
3.	Fansidar	10.29 ± 0.42
4.	Chloroquine	16.08 ± 0.12
5.	Lonart	16.76 ± 0.22
6.	Coartem	11.04 ± 0.10

TABLE 3: GASTRIC ACID SECRETION

S/N	GROUPS	GASTRIC SECRETION
1.	Control	11.67 ± 0.16
2.	Malaria	12.27 ± 0.18
3.	Fansidar	10.80 ± 0.12
4.	Chloroquine	14.89 ± 0.19
5.	Lonart	13.05 ± 0.06
6.	Coartem	11.47 ± 0.05

DISCUSSION

The results from the study had shown significant variations in the gastric and blood parameters values. The gastric secretion values in different drug groups has indicated the pharmacologic interplay in gastric physiology and the altered aspect of it. For instance, a high acid output is associated with chloroquine treatment confirming its ulcerogenic potentials, Etitimal, 2005. The observed ulcerogenic effects on the most widely available, cheap and affordable antimalaria is quite worrisome. The implications are obviously many; majority of patients on this drug as many are on self-medication will be prone to ulcer. That means the malaria morbidity will be extended to a more complicated aspect involving the gastric. This means more of the malaria patients on chloroquine treatment being

candidates for gastric ulcer. The gastrin; histamine, parietal cells, nervous and hormonal systems as per hydrochloric acid output need be re-examined in chloroquine as it mediates acid by acting on gastrin-histamine pathway, (Sanduk, et al, 2001). It is also worried that malaria disease as observed in the study enhanced increase gastric output. Malaria is said to cause gastritis and gastritis is associated with peptic ulcer, Guyton, 2006. Though parasite counts per the drug groups were not done, it appears that the high acid output may also be associated with the low potency of chloroquine which is the drug resistant by malaria. This is because coartem a combination of arthemeter and lumefantine had show how acid output as compared to chloroquine and it is the most potent of the antimalaria for now i.e. as alternative drug for drugs that are ineffective in the treatment of malaria. However, fansidar has also shown remarkable low acidity meaning that it has antiulcerogenic properties, (Schmassman, 1998). But there is a likely negative implication in the consumption of this drug as preventive therapy in the digestive of protein which requires range of hydrochloric acid for metabolism of protein vis, a vis the conversion of pepsinogen to pepsin which hydrochlororic acid plays a pivotal role. A disease condition achlorhydria may therefore result as it is not known if the low acid output associated with fansidar is the result of damage to parietal cells which could also lead to pernicions anaemia as parietal cells produce intrinsic factor for the absorption of vitamin B_{12} necessary for blood development, Guyton, 2006. However, the efficacy of the drug could be associated with low acid output as in the case of coartem but the likely gastric anomalies in observed low acid output requires further investigation. The high acid output with lonart therapy could also be associated with its ulcerogenic properties as in chloroquine but it also underscores its efficacy of such tallies with high acid output. This is because it is claimed to be of the same constituents; Artemeter and lumen-fantrine which coartem also comprised. And if potency is here judged by the acid output then it is likely that the claimed combination may not be real. The acid output could be therefore used as marker to identity potencies of antimalaria drugs as some antimalaria drugs are old drugs in new packets. But the issue of fake drugs in this case could not be ruled out. In the study, the varied blood values are associated with agents that directly affect the blood cells. For instance, low RBC is observed in malaria group without treatment as malaria parasites live within the red cells and feed on its haemoglobin, and its component DNA thus lowering its development, Sherman 1997. Parasites stay in the red cells causes damage to the red cell membrane, lowers it metabolism and make such vulnerable to reticulo endothelial cells which remove them from the circulation as foreign cells, Hoffbrand 1991. The low RBC in chloroquine treated group indicates the low potency of the drug which could not parasite eliminate the parasites and hence affects the red cells number. Lonart recorded the highest RBC count indicating its boosting to red cells development. The good values of the RBC within the normal range prove its potency against malaria parasite though its high acid output was initially hung on its potency too as compared with coartem with same pharmacologic constituents. Lonart may possess a trigger factor that affect the bone marrow to produce red blood cells through it may lack high antimalarial potency. The mechanism of its boosting potentials on RBC need be further examined even as such is observed with coartem though slightly lower. If lonart affects the haematology of the body positively then its stand as a good drug of choice in malaria management as what kills mostly in malaria is anaemia. The white blood cells were low in malaria group without treatment which is due to its consumption in the attacks of the parasites. The high white blood cells in the lonart and chloroquine could be attributed to the myeloid response (Nikoli 2013), but it is also an indication of low potency of the drugs which the parasites rates had increased stimulating increase in white blood cells in response to the parasites. Increase in white blood cells in malaria may lead to maglignancy of the cells as in B-lymphocytes proliferation which may result in blood cancer, lymphocytic leukaemia, Jimmy 1996.

RECOMMENDATION

This study recommends appropriate malaria parasite screening in association with potent drugs that are physiologically friendly. Such will avert the double jeopardy likely to be envisaged with the malaria disease and the antimalaria drugs used in the treatment of malaria disease particularly in self medication.

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