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Augmentation of gastric acid secretion by chloroquine and amodiaquine in the rat stomach

[1]Ajeigbe K.O, [2]Emikpe B.O and [1*]Olaleye S.B

[1]Gastrointestinal Research Unit, Department of Physiology, College of Medicine, [2]Department of Veterinary Pathology, University of Ibadan, Ibadan

Summary: Gastrointestinal mucosal integrity has been shown to be altered by chloroquine and amodiaquine, although the exact mechanism is not clear. Since Gastric Acid Secretion (GAS) plays significant role in the etiology of ulcer, the present study was aimed at investigating the effect of chloroquine and amodiaquine on GAS, Parietal Cell Mass (PCM) and Gastric Mucous Cell Population (GMP) in rats. Male albino wistar rats were randomly assigned into three groups viz: control, chloroquine (CQ, 3 mg/kg), amodiaquine (AQ, 10 mg/kg). Basal GAS as well as secretion in response to histamine and carbachol was measured by continuous perfusion of the stomach with normal saline (1ml/minute) under urethane anaesthesia (0.6 mg/100 g). After obtaining a steady basal output response to normal saline in all animals, the antimalaria drugs were administered intramuscularly and the peak responses to each drug obtained. Further assessment of the roles of histaminergic and muscarinic receptors were done using ranitidine (H_2 antagonist) and atropine (M antagonist) in the treated animals. PCM and GMP were determined in the stomach samples by histometry. The basal acid output was 0.70 ± 0.01 mmol/10 mins. Chloroquine and amodiaquine produced increase in acid output to a peak of 1.35 ±0.03 mmol/10 mins (92.9%, $p<0.001$) and 1.40 ± 0.03 mmol/10 mins (100%, $p<0.001$) respectively. Histamine and carbachol elicited 107% and 100% increase acid secretion when compared with the basal output respectively. CQ and AQ potentiated histamine-induced secretory rate which peaked at 1.60 ± 0.02 mmol/10 mins and 1.70 ± 0.03 mmol/10 mins respectively. Similarly, the carbachol-induced acid secretory response was potentiated by CQ and AQ to a peak of 1.45 ± 0.02 mmol/10 mins and 1.50 ± 0.03 mmol/10 mins ($p<0.05$). Ranitidine and atropine attenuated histamine and carbachol induced acid secretion, but did not abolish it. CQ and AQ increased significantly the parietal cell numbers in the gastric mucosa (21±0.7 and 24±0.7 versus 15.2±0.8 control; $p<0.05$). On the other hand, mucus cell population was significant decreased by CQ and AQ (15±0.3 and 13±0.85 versus 17.4±0.5 control; $p<0.05$) respectively. Chloroquine and amodiaquine increased gastric acid secretion in rats. They stimulated histamine (H_2) and muscarinic (M_3) receptors, and enhanced parietal cell mass.

Keywords*:* Chloroquine, Amodiaquine, Gastric acid secretion, Histamine, Parietal cell mass

**Address for correspondence:* sbolaleye@yahoo.com

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INTRODUCTION

In the intact animal, gastric acid secretion is influenced by the interplay of stimulatory and inhibitory factors arising from both the central nervous system and within the gastrointestinal system (Yao and Forte, 2003). In addition to these regulatory processes are factors arising from daily assaults on the gastrointestinal tract such as food and drugs. Hydrochloric acid produced by the parietal cells in the stomach, is facilitated by the activity of H^+ K^+-ATPase in the apical membrane (Davies, 1951). It is finely regulated by overlapping neural, hormonal, paracrine pathways (Yao and Forte, 2003), and when levels of the acid and proteolytic enzymes overwhelm the mucosal defense mechanisms, ulcers occur.

Chloroquine (CQ) and amodiaquine (AQ) are 4-Aminoquinoline derivatives and are prototype antimalarial drug most widely used in the chemotherapy of *Plasmodium falciparum* malaria (Webster, 1992). This class of antimalarial drugs inhibits parasite growth (Wellems, 1992); blocks the production of cytokines inhibits cell proliferation in monocytes, macrophages and lymphocytes (Weber and Levitz, 2000). Although the relative popularity of the 4-Aminoquinoline derivatives is being compromised by resistance from the parasites, it remains a preferred antimalarial medication in most sub-Saharan African countries due to its affordability and availability (Olliaro and Taylor, 2003; Sweetman, 2005).

Apart from malaria, chloroquine has also been effective in the management of diseases such as rheumatoid arthritis, lupus erythematous, light eruptions and various inflammatory conditions (Ngaha *et al.*, 1982; Onigbogi *et al.*, 2000). In

therapeutic doses, chloroquine has been shown to interfere with a number of physiological processes. These include interference with blood biochemistry (Obi *et al.*, 2003; Mbajiorgu *et al.*, 2009), inhibition of cytochrome P450-mediated oxidation reactions (Farombi *et al.*, 2000) and the induction of oxidative stress in animals and man (Magwere *et al.*, 1997). The mutagenicity and genotoxicity of chloroquine have been reported in a number of cells (Obaseiki-Ebor and Obasi, 1986). In previous studies, we reported that chloroquine and amodiaquine potentiated experimental gastric ulceration induced by indomethacin and HCl/Ethanol mixture respectively (Ajeigbe *et al.*, 2008a, b). Although oxidative stress has been implicated in the observed effects of these drugs in gastric mucosal damage, the role of other factors determining mucosal integrity such as gastric acid secretion has not been well investigated. Barth *et al.* (1975) and Etimita *et al*. (2005) suggested an increase in acid secretion by amodiaquine and chloroquine respectively. In the present study, a holistic approach was employed in an attempt to investigate gastric acid secretory changes as well as parietal and mucous cell populations after chloroquine and amodiaquine treatments in rat.

MATERIALS AND METHODS

Animals

Male albino rats of Wistar strain weighing between 180-200 g and obtained from the Central Animal House, College of Medicine University of Ibadan, were used in the study. They were housed under standard conditions of temperature (23 ± 2^{o}C); humidity (55 ± 15%) and 12 h light (7.00 am-7.00 pm). They were kept in wire meshed cages and fed with standard commercial rat pellets (Ladokun Feeds Limited, Nigeria). Each animal was deprived of food 24-36 hours before the start of the experiment but allowed water *ad libitum.*

Drugs

Chloroquine phosphate tablets were purchased from Evans Medical Plc, Lagos. Amodiaquine hydrochloride tablets were purchased as Camoquin from Pfizer, Lagos. Histamine, carbachol and other analytical grade chemicals used were obtained from the British Drug Houses, UK.

Experimental Design

Animal grouping

Albino wistar rats used for the study were randomly divided between the groups of chloroquine (CQ) and amodiaquine (AQ). Each group has forty rats distributed evenly among eight subgroups.

Chloroquine group: The rats in the subgroups were administered as follows: Normal saline (1 ml/kg, control), chloroquine (3 mg/kg), histamine (1 mg/kg) + chloroquine (3 mg/kg), ranitidine (4 mg/kg) + histamine (1 mg/kg) + chloroquine (3 mg/kg), histamine (1 mg/kg); carbachol (50 µg/kg) + chloroquine (3 mg/kg), atropine (1 mg/kg) + carbachol (50 µg/kg) + chloroquine (3 mg/kg), carbachol (50 µg/kg).

Amodiaquine group: The rats in the subgroups were administered as follows: Normal saline (1 ml/kg, control), amodiaquine (10 mg/kg), histamine (1 mg/kg) + amodiaquine (10 mg/kg), ranitidine (4 mg/kg) + histamine (1 mg/kg) + amodiaquine (10 mg/kg), histamine (1 mg/kg); carbachol (50 µg/kg) + amodiaquine (10 mg/kg), atropine (1 mg/kg) + carbachol (50 µg/kg) + amodiaquine (10 mg/kg), carbachol (50 µg/kg).

Acid secretion studies.

The gastric acid secretion was measured using the continuous perfusion method of Ghosh and Schild (1958), modified by Amure and Ginsburg (1964). The animals were anaesthetized with 25% urethane (ethyl carbamate) at a dose 6 ml/kg body weight. A tracheal cannula was inserted via an incision on the neck to ensure normal breathing throughout the course of the experiment. An abdominal incision through the *linea alba* was made to expose the stomach and a semi-transection made at the junction of the pylorus with the duodenum. A pyloric cannula was inserted and tied to collect gastric contents. An orogastric cannula was inserted for perfusion of pre-warmed (at temperature 37^{0}C) 0.9% normal saline (pH 7.00) at a rate of 1ml/minute using a perfusion pump. The animals were kept warm by a 100 watts electric lamp to prevent hypothermia. Gastric acid was collected via the pyloric cannula at 10 minutes intervals. In order to determine acidity, 10ml of the stomach perfusate was titrated against 0.01M sodium hydroxide (NaOH) solution with phenolphthalein as indicator. Titrable acidity was expressed in mmol/10mins after calculation in each sample. At the 50th minutes of effluent collection, histamine and carbachol were administered via a femoral cannula vein for the stimulated acid secretory response, and ranitidine and atropine also introduced correspondingly to block the H_2 and muscarinic receptors. The route of administration of the antimalarials is intramuscular.

Determination of gastric parietal cell mass and mucus cell population.

The animals were sacrificed and the stomach removed as quickly as possible into normal saline. The stomach was opened along the greater curvature, washed and transferred into a beaker containing 10% formalin. Sections were prepared from strips removed from the fundic area of the stomach and stained using the method of Marks and Drysdale (1957) as

modified by Oluwole *et al.* (2007), using the Hematoxylin and Eosin stain. The various gastric mucosal secretory cells were clearly differentiated, taking up different colours. The nuclei of the parietal cells were stained deep blue while the mucous cells were clearly vacuolated.

Parietal cell mass index was calculated as described by Perraso *et al.* (1991) as the number of cells per mm^2 multiplied by the thickness of the glandular layer. Five counts from randomly selected fields were made on each section and the average count per unit area was calculated for each stomach by dividing the number of cells seen by the number of counts made.

Statistical Analysis

Data were analyzed by Microsoft Excel's XL Toolbox statistical package (2.60 version) using descriptive statistics, ANOVA and Bonferroni-Holm posthoc test at $p<0.05$.

RESULTS

Effects of chloroquine and amodiaquine on basal and stimulated acid secretion.

The basal gastric acid secretion in the control animals was 0.70 ± 0.01 mmol/10 mins. In the animals administered chloroquine and amodiaquine, the basal secretions were 1.35 ± 0.03 mmol/10 mins (92.9% increase; $p<0.001$) and 1.40 ± 0.03 mmol/10 mins (100% increase; $p<0.001$) respectively. The time-response relationship is shown in Fig. 1.

Table 1 shows the gastric acid secretory responses of rats to chloroquine and amodiaquine after histamine stimulation. Histamine significantly increased the gastric acid secretion from the basal value of 0.70 ± 0.01 mmol/10 mins to 1.45 ± 0.04 mmol/10 mins. CQ and AQ potentiated the histamine-induced secretion to 1.60 ± 0.02 mmol/10 mins and 1.70 ± 0.03 mmol/10 mins.

Carbachol significantly increased the gastric acid secretion from the basal value of 0.70 ± 0.01 mmol/10 mins to 1.40 ± 0.02 mmol/10 mins. CQ and AQ potentiated the carbachol-induced secretion to 1.45 ± 0.02 mmol/10 mins and 1.50 ± 0.02 mmol/10 mins.

Effect of Ranitidine on peak gastric secretory response to CQ and AQ

The effect of ranitidine, an H_2 antagonist, on gastric secretory response to chloroquine and amodiaquine is shown in Fig. 2. Ranitidine blocked the potentiation of histamine-induced secretion by CQ and AQ but did not abolish it.

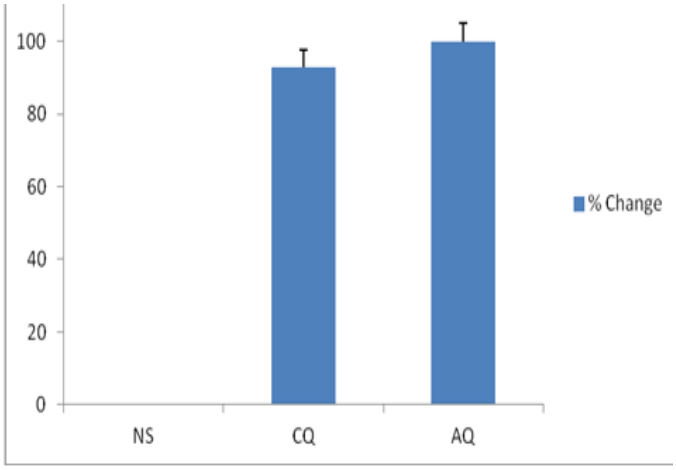

Figure 1: Percentage change in basal gastric acid secretion after treatment with chloroquine (CQ) and amodiaquine (AQ)

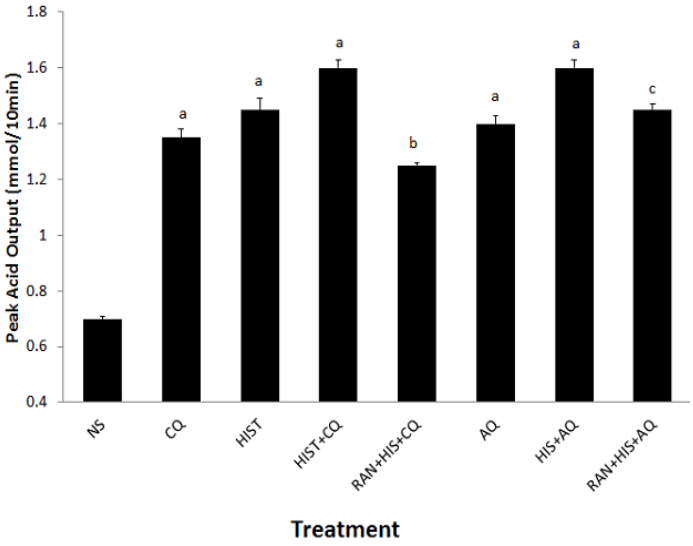

Fig. 2. Effect of histamine receptor blockade by ranitidine on peak gastric secretory response to CQ and AQ. Each vertical bar represents mean ± SEM of five rats per group. $^{a}P < 0.05$ (c.f. NS), $^{b}P<0.05$ (c.f. HIST+CQ), $^{c}P<0.05$ (c.f. HIST+AQ).

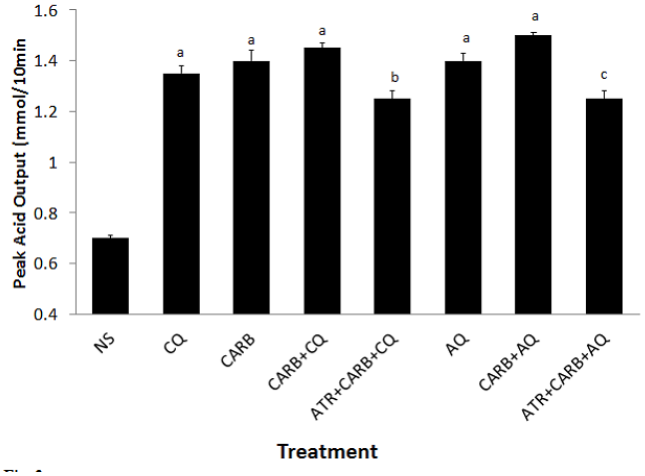

Fig. 3. Effect of muscarinic receptor blockade on peak gastric secretory response to CQ and AQ. Each vertical bar represents mean ± SEM of five rats per group. $^{a}P < 0.05$ (c.f. NS), $^{b}P<0.05$ (c.f. CARB+CQ), $^{c}P<0.05$ (c.f. CARB+AQ).

Table 1: Effect of chloroquine and amodiaquine on gastric acid secretion in rats.

Drugs	Basal Acid Output	Peak Responses to: Histamine	% change	Carbachol	% change
Normal Saline	0.70 ± 0.01	1.45 ± 0.04	107%	1.40 ± 0.02	100%
Chloroquine	1.35 ± 0.03	1.60 ± 0.02	18.5%	1.45 ± 0.02	7.4%
Amodiaquine	1.40 ± 0.03	1.70 ± 0.03	21.4%	1.50 ± 0.02	7.1%

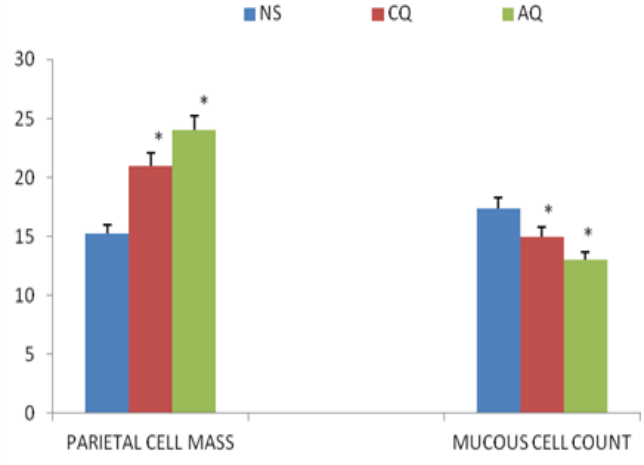

Figure 4. Effect of chloroquine and amodiaquine on parietal cell mass and gastric mucous cell population in the rat's gastric mucosa. Each vertical bar represents mean ± SEM value of five microscopic views. (*p<0.05 cf NS).

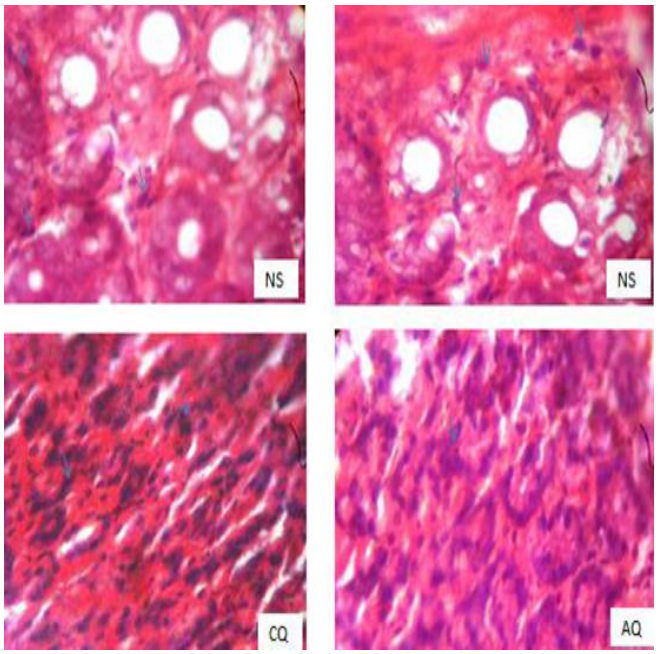

Plate 1. Photomicrographs of gastric mucosal sections from control rats (NS) and those treated with Chloroquine (CQ) and amodiaquine (AQ) showing relative densities of deep-blue-stained parietal cells and vacuolated mucous cells.

Effect of Atropine on peak gastric secretory response to CQ and AQ

Fig. 3 shows the effect of atropine, a muscarinic antagonist, on gastric secretory response to chloroquine and amodiaquine. Atropine inhibited the potentiation of carbachol-induced secretion by CQ and AQ but did not abolish it.

Effect of CQ and AQ on parietal and mucus cell count

CQ and AQ increased the parietal cell numbers significantly when compared with the normal gastric mucosa (21±0.7 versus 15.2±0.8 control) and (24±0.7 versus 15.2±0.8 control). On the other hand, mucus cell population was significant decreased by CQ and AQ (15±0.3 versus 17.4±0.5 control) and (13±0.85 versus 17.4±0.5 control) respectively. This is shown in Fig. 4.

DISCUSSION

In this study, we presented the descriptive events involved in the exacerbation of gastric acid secretion by chloroquine and amodiaquine. It was observed that chloroquine and amodiaquine significantly increased gastric acid secretion in rats; and the data also suggest that both histamine (H_2) and muscarinic (M_3) receptors play vital roles in this activity. In addition, the parietal cell numbers were increased and mucus cell population reduced significantly on chloroquine and amodiaquine administration.

It is well known that gastric acid secretion is mediated through interplay of neural, hormonal, paracrine pathways (Schubert, 2005). Histamine has been reported to stimulate acid secretion through H_2 receptors (Garrison, 1992) and carbachol M_3 receptors. Though gastrin stimulates acid secretion (via CCK_2 receptors); but indirectly by inducing the release of histamine by ECL cells; its direct effect on parietal cells plays a lesser role.

The results of the study indicated that both chloroquine and amodiaquine effect on gastric acid secretion may be due to histamine and muscarinic receptors; supported by the potentiation of acid secretion when chloroquine and amodiaquine were administered following histamine, and carbachol. Etimita *et al*. (2005) suggested chloroquine to be a weak stimulant of gastric acid secretion, and inhibits histamine stimulated acid secretion probably by occupying histamine H_2-receptors. However, the possibility of involvement of other receptors such as muscarinic receptors was not investigated by them.

Corroborating the involvement of the H_2 and muscarinic receptors activation as observed in the present study, ranitidine (H_2-antagonist), and atropine

(M-antagonist) administration before chloroquine and amodiaquine led to reduction in acid output but still significantly higher than the control level. This suggests that chloroquine and amodiaquine cause increase in gastric acid secretion by stimulating both histamine and muscarinic receptors. It lends much credence to our previous findings where chloroquine and amodiaquine were reported to elaborate the indomethacin and acidified ethanol induced effects on gastric juice volume, pH and consequently acid output (Ajeigbe *et al.*, 2008a, b). Barth *et al.* (1975) had even earlier suggested that amodiaquine may enhance the histamine stimulated gastric secretion by an inhibition of gastric histamine methyltransferase.

Gastric acid secretion is known to be linearly related with the parietal cell mass, and its attacking effect on the mucosa to be inversely related with the mucus cell population (Brunton *et al.*, 2005). Chloroquine and amodiaquine increased parietal cell mass and reduced gastric mucous cell count. This explains the elaboration of acid output by the parietal cells, and the mucosal injury-facilitating tendencies due to diminished defensive system of the gastric mucosa caused by abridged mucous cell population.

Besides oxidative stress (Perry *et al.*, 1986) and a number of other factors, gastric acid secretion still remains an important force to reckon with in the pathogenesis of inflammatory disorders of the GIT especially peptic ulceration. This is evidenced by the action of many anti-ulcerogenic drugs which reduce the acid secretion (Schmassmann, 1998). It has equally been shown that the anti-ulcer properties of some spices and herbs are mediated by antisecretory effects (Al Mofleh, 2010). The high prevalence of peptic ulceration in Africa and Asia, which are also malaria endemic regions, has long been related (Amure and Elegbe, 1975; Sonnerberg, 1985). Despite various side effects attributed to the use of antimalarials in the tropics, misuse is still widespread (White, 2004). Recent reports from our laboratory have also revealed that chloroquine and amodiaquine aggravate existing indomethacin and acidified ethanol induced gastric mucosa injury in rats by enhancing lipid peroxidation and/or diminishing endogenous antioxidants (Ajeigbe *et al.*, 2008a, b). Considering the crucial role gastric acid plays in the development and healing of ulcer, the present study investigated the effect of the antimalarials on basal and secretagogue-induced secretion. Parietal cell mass and mucus cell population were also undertaken as corroborating studies.

In conclusion, chloroquine and amodiaquine increase gastric acid secretion in the rat by stimulating histamine (H_2) and muscarinic (M) receptors. Besides, they increase parietal cell mass and decrease mucus cell population in the gastric mucosa. If extrapolated to man, these findings further underscore the mucosa-injury potentiating tendencies of chloroquine and amodiaquine.

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