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Research Article

Quinine Stimulates Gastric Acid Secretion in Rats

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Abstract

Quinine remains an important anti-malarial drug. However, the effects of quinine on many gastrointestinal functions are not known. This study was aimed at investigating the effect of quinine on gastric acid secretion, which might be important in peptic ulcer patients. Forty albino Wistar rats were randomly divided in 8 groups. Gastric acid output was measured by the continuous perfusion method in animals anaesthetized with urethane (6ml/100g). After consistent basal gastric output were obtained, the animals were treated as follows: group 1, normal saline (1ml/kg); group 2, quinine (10mg/kg); group 3, carbachol (50µg/kg); group 4, quinine + carbachol; group 5, atropine (1mg/kg) + quinine; group 6, histamine (20mg/kg); group 7, quinine + histamine and group 8, ranitidine (4mg/kg) + quinine. Values were expressed as mean ± SEM and compared by student t-test. Result showed that peak acid secretion (PAS) in rats treated with normal saline was 1.26 ± 0.04mEq/L/10min. Quinine significantly increased PAS to 2.00 ± 0.18mEq/L/10min ($p < 0.01$). Injection of quinine before carbachol did not affect the PAS as compared with carbachol alone ($p > 0.05$) and atropine administration did not reduce the PAS to quinine ($p> 0.05$). Histamine significantly increased the PAS to 8.08 ± 0.26mEq/L/10min ($p <0.001$). Injection of quinine before histamine significantly reduced the PAS to 3.42 ± 1.12mEq/L/10min ($p < 0.01$) and ranitidine blocked the secretory response of the stomach to quinine. In conclusion, quinine increased gastric acid secretion in rats by stimulating histamine H_2 receptors.

Keywords: Gastric acid secretion, quinine, H_2 receptor

INTRODUCTION

The hydrochloric acid secreted by the stomach is important for protecting the body against pathogens ingested with food or water; activating enzyme pepsin needed for protein digestion and facilitating the absorption of calcium, iron, and vitamin B12 (Smith, 2003). However, gastric acid has long been associated as a causative factor of gastric and duodenal ulcer. The normal rate of acid secretion may cause ulceration in the breached mucosa when some gastroprotective factors are lost. Furthermore, its corrosive property and increased peptic activity is sufficient to aggravate the ulcer (Wallace and Muscara, 2001).

In an attempt to protect the gastric mucosa from gastric acid, enhance ulcer healing, and prevent ulcer recurrence, pharmacological control of gastric acid secretion has long represented a desirable goal (Aihara *et al*., 2003; Tuorkey and bdul-Aziz, 2009; Tuorkey and Karolin, 2009). Various drugs, such as histamine H_2 receptor antagonists and H^+/K^+-ATPase (acid pump) inhibitors have been developed and utilized for the treatment of acid-related peptic diseases (Black, *et al*, 1972).

The treatment of malaria with quinine marked the first successful use of a chemical compound to treat an infectious disease (**Achan et al., 2011)**. Quinine remained the mainstay of malaria treatment until the 1920s, when more effective synthetic anti-malarials became available. The most important of these drugs was chloroquine. However with increasing resistance to chloroquine, quinine again played a key role, particularly in the treatment of severe malaria (Bloland, 2001).

Based on trials, intravenous artesunate was recommended to be used for the treatment of severe falciparum malaria in adults and children, in preference to quinine (Dondorp *et al*., 2005). However, the 2010 World Health Organisation guidelines recommend a combination of quinine plus doxycycline, tetracycline or clindamycin as second-line treatment for uncomplicated malaria (to be used when the first-line drug fails or is not available) and quinine plus clindamycin for treatment of malaria in the first trimester of pregnancy (WHO, 2010).

There is a dearth of information on the effects of quinine on gastric acid secretion. This would become important in actually knowing the effects of this drug on acid secretion and also in ulcer patients who are being treated for malaria, so that medical practitioners could be better advised when prescribing drugs to malaria patients. Therefore the aim of this work is to investigate the action of quinine on gastric acid secretion and the possible mechanism of action.

MATERIALS AND METHODS

Animals : Male albino rats of Wistar strain weighing between 180-200g were used for the study. They were obtained from the Animal House, College of Health Sciences, Benue State University, Makurdi. They were housed under standard conditions of temperature (23 ± 2°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. The care and use of the animals and the experimental protocol of this study were in accordance with Experimental Animal

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Care and Use Regulation of the Animal House, College of Health Sciences, Benue State University, Makurdi, Nigeria which were also in accordance with the internationally accepted principles for laboratory animal use (EEC Directive of 1986; 86/609/EEC). Each animal was deprived of food 18 hours before the start of the experiment but allowed water *ad libitum.* The animals were divided into 8 groups, with each group consisting of 5 animals each.

Gastric acid secretion study: The gastric acid secretion was measured using the continuous perfusion method of Gosh and Schild, modified by Amure and Ginsburg (Ghosh and Schild, 1958; Amure and Ginsburg, 1964). The animals were anaesthetized with 25% urethane (ethyl carbamate) at a dose 0.6ml/kg body weight. A tracheal canula 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, through which a pyloric canula was inserted and tied to collect gastric contents. An oro-gastric canula was inserted for perfusion of pre-warmed (at temperature 37^0C) 0.9% normal saline (pH 7.00) at a rate of 1ml/minute. The animals were kept warm by a 100watts electric lamp to prevent hypothermia.

Gastric acid was collect via the pyloric cannula at 10 minutes intervals. In order to determine acidity, 5ml of the stomach perfusate was titrated against 0.01M sodium hydroxide (NaOH) solution with phenolphthalein as indicator. Titrable acidity was expressed in mEq/L/10mins.

After obtaining consistent basal gastric output, the different groups of animal were administered with various drugs as follows:

Group 1 – was administered 1ml/kg normal saline intraperitoneally.

Group 2 - The animals in the second group was given human therapeutic dose of quinine (10 mg/kg) intramuscularly.

Group 3 - The third group of animals received carbachol (50µg/Kg i.p).

Group 4 - Animals received 10 mg/kg quinine followed by 50µg/kg (i.p) carbachol.

Group 5 – Animals were administered atropine (1mg/kg, i.p) followed by quinine

Group 6 - Animals were administered histamine (20mg/kg, i.p)

Group 7 – Animals in this group were given 10mg/kg quinine followed by 20mg/kg histamine

Group 8 – Animals received ranitidine (4mg/kg, i.p) followed by 10mg/kg quinine

Statistical Analysis: Results were expressed as mean ± SEM. Student t-test was used to assess the statistical difference of results obtained between the two groups. Confidence interval of 95% was taken as statistically significant using SPSS version 17 statistical package

RESULTS

Effect of Normal saline and quinine on gastric acid secretion

Result showed that the basal acid secretion in animals in Control group was 1.20 ± 0.06mEq/L/10min. After administration of normal saline, the peak gastric acid secretion, 1.26 ± 0.04 was not significantly different ($p < 0.05$) from the basal secretion.

The basal gastric acid secretion in animals in group 2 was 1.22 ± 0.07mEq/L/10min. Administration of quinine significantly increased ($p < 0.01$) the peak acid secretion to 2.00 ± 0.18mEq/L/10min as shown on Fig. 1.

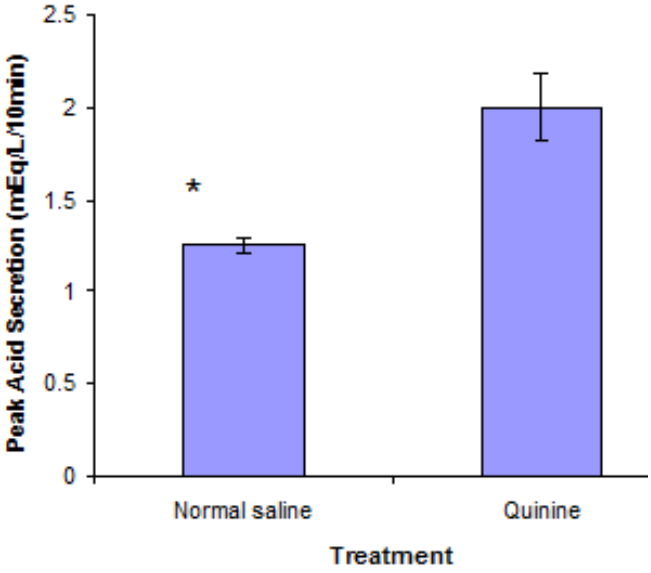

Figure 1:
Effects of quinine on gastric acid secretion. N = 5; * significant compared with quinine alone treatment at $p < 0.05$.

Effect of carbachol, atropine and quinine on gastric acid secretion

Carbachol alone significantly ($p < 0.001$) increased the acid secretion from basal level of 2.44 ± 0.69mEq/L/10min to peak secretion of 9.38 ± 1.33mEq/L/10min. This peak acid secretion in carbachol treated animals is significantly higher ($p < 0.001$) than the peak acid secretion in the control group (Fig. 2). Injection of quinine before carbachol increased the peak acid secretion 10.86 ± 0.85mEq/L/10min, but the value was not significantly different ($p > 0.05$) from the peak acid secretion in animals given carbachol alone. However, quinine potentiated gastric acid secretion in animals treated with carbachol as shown in Fig 2.

Result also showed that the peak acid secretion in animals administered atropine followed by quinine was 1.68 ± 0.02mEq/L/10min. This value was not significantly different ($p > 0.05$) from animals given quinine alone, 2.00 ± 0.18mEq/L/10min.

Effect of histamine, quinine and rantidine on gastric acid secretion

Administration of histamine significantly increased ($p < 0.001$) the peak acid secretion from 1.24mEq/L/10min to 8.08 ± 0.26mEq/L/10min, which is significantly higher ($p < 0.001$) than the peak acid secretion in control animals (Fig. 3).

Injection of quinine before histamine significantly reduced ($p < 0.01$) the peak acid secretion to 3.42 ± 1.12mEq/L/10min as compared with that cause by histamine alone as shown in Fig. 3. However, the peak acid secretion in rats treated with quinine before histamine is significantly higher ($p < 0.01$) than that in control animals.

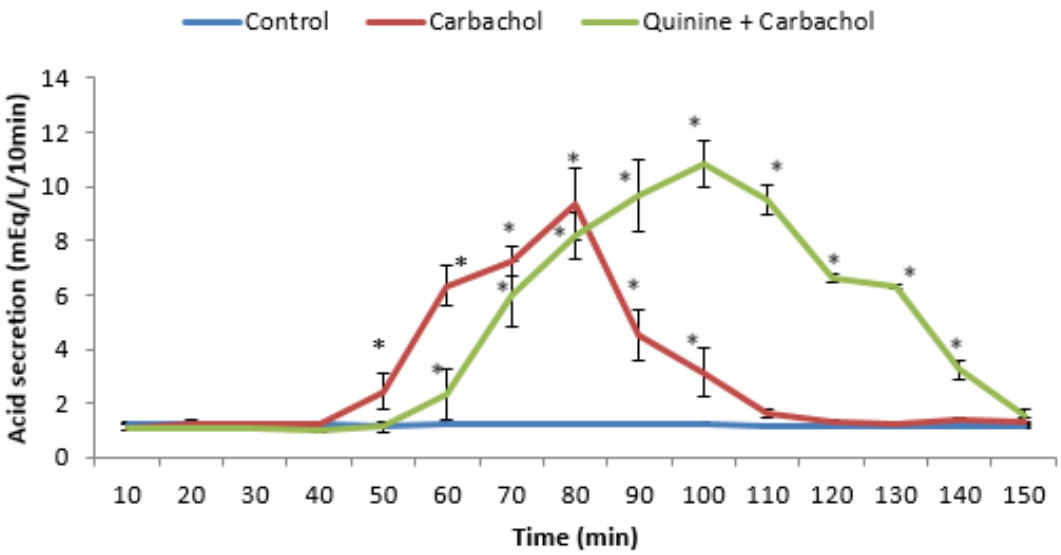

Figure 2:
Effect of carbachol alone and quinine + carbachol on gastric acid output in rats. N = 5,
* Significant compared with control treatment at $p < 0.01$

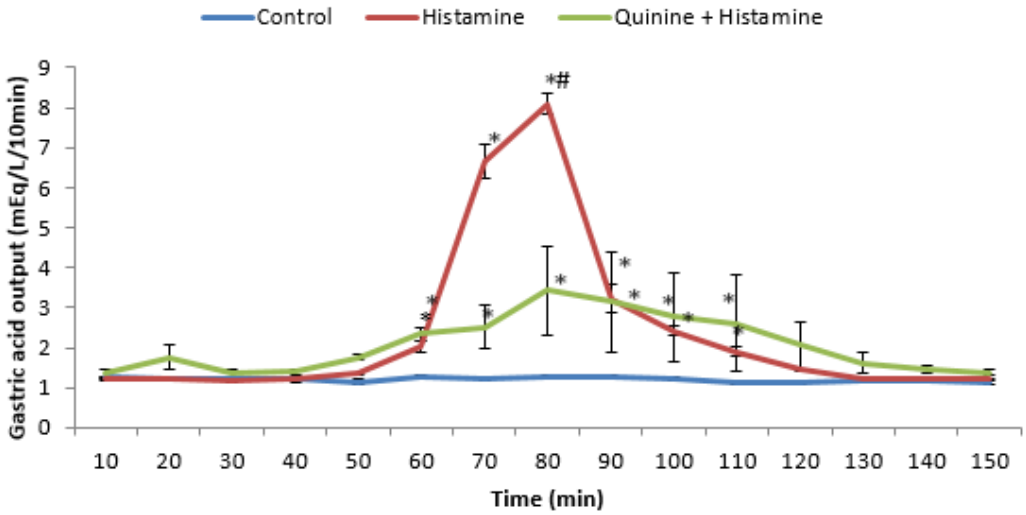

Figure 3:
Effect of Histamine alone and quinine + Histamine on gastric acid output in rats. N= 5,
* significant compared with control treatment at $p < 0.01$, # = significant compared with Quinine + Histamine at $p < 0.01$.

Result also showed that administration of ranitidine before quinine blocked the acid secretion in response to quinine. The peak acid secretion in animal given ranitidine before quinine was 0.82 ± 0.06 mEq/L/10min, which was significantly lower ($p < 0.001$) than animal given quinine alone (2.00 ± 0.18mEq/L/10min).

DISCUSSION

The result of this research revealed that administration of human therapeutic dose of quinine in rats significantly increased gastric acid secretion when compared with animals given normal saline, which served as control animals. This is similar to the effect of chloroquine and amodiaquine on gastric acid secretion as previously reported by Etimita *et al*., (2005) and Ajeigbe *et al*., (2012) respectively. The stimulatory effect of quinine of gastric acid secretion might be by stimulating the H_2 receptors or by release of histamine. Our result revealed that histamine alone caused a high increase in gastric acid output while when quinine was administered before histamine, the secretory response of the stomach was significantly lower. This suggests that quinine acts through the same receptor and histamine and therefore competitively blocked histamine stimulated output.

Our finding showed that quinine did not significantly change the peak acid response to carbachol. Furthermore the two drugs appear to potentiate the action of each other as shown in Fig. 2. Atropine did not significantly reduce the secretory effect of quinine. This also suggests that quinine does not act through the muscarinic receptors. This is contrary to the report of Ajeigbe *et al*,. (2005) that reported that chloroquine and amodiaquine, which are also antimalaria drugs, increase acid secretion by stimulating muscarinic M_3 receptors.

The role of acid in gastroduodenal pathogenesis has been extensively studied. Gastric acid has long been associated as a causative factor of gastric and duodenal ulcer, for instance,

about 50% of gastric ulcer patients are pepsin and acid hypersecretors and duodenal ulcer patients usually secrete more acid (Szabo, 1988; Wolfe and Soll, 1988). In fact, "no acid, no ulcer" is the dictum for duodenal ulcer. Although the secreted acid itself is not sufficient for ulcer formation, its corrosive property and increased peptic activity is sufficient to aggravate the ulcer (Wallace and Muscara, 2001**)**. Hence, acid suppression is a common practice to control gastroduodenal lesions (Wolfe and Sachs, 2000). Histamine H_2 receptor antagonists and proton pump inhibitors such as omeprazole, lansoprazole, pantoprazole, and rabeprazole are extensively used for therapeutic control of acid-related disorders including gastroesophageal reflux disease and Zollinger-Ellison syndrome and for peptic-ulcer disease caused by stress (stress-related erosive syndrome), nonsteroidal antiinflammatory drugs, and *Helicobacter pylori* infection (Wolfe and Sachs, 2000; Horn, 2000).

By 2009, 31 African countries recommended quinine as second-line treatment for uncomplicated malaria, 38 as first-line treatment of severe malaria and 32 for treatment of malaria in the first trimester of pregnancy (WHO, 2009). In most of African countries, quinine is still used as monotherapy, contrary to the WHO recommendations (WHO, 2009; 2010). Quinine continues to play a significant role in the management of malaria in sub-Saharan Africa and other malaria endemic areas, and its use in routine practice may not be restricted to the stated WHO recommendations. It is important to note that WHO in the year 2011 estimated 216 million cases of malaria in Africa, which is 81% of malaria cases worldwide and in Nigeria, there are an estimated 100 million malaria cases with over 300,000 deaths per year. This compares with 215,000 deaths per year in Nigeria from HIV/AIDS (Nigeria Malaria Fact Sheet, 2011). Reports also revealed that chloroquine and amodiaquine, which increase gastric acid secretion also 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). Therefore the use of quinine might also have the same adverse effect on peptic ulcer formation and healing.

In conclusion, quinine increased gastric acid secretion in rats by stimulating H_2 receptors. This fact might be important during treatment of malaria, especially in individuals who have history of peptic ulcer as it could further aggravate the symptoms

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