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## Protective Effect Of Ascorbic Acid On Cimetidine-Induced Reproductive Toxicity In Male Wistar Rats

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### ABSTRACT

The effects of the H<sub>2</sub> receptor antagonist, cimetidine on the male reproductive system have been well studied and shown to cause several untoward effects. The present study evaluates the influence of vitamin C (VTC) on the testicular effects of cimetidine in the rat. Different animal groups (n = 6) were orally administered cimetidine (30 or 60 mg kg<sup>-1</sup> day<sup>-1</sup>); VTC (50 mg kg<sup>-1</sup> day<sup>-1</sup>) plus cimetidine and vehicle (1 mL kg<sup>-1</sup> day<sup>-1</sup>) for 14 days. Animals were sacrificed and their testes were removed. Sperm was collected from the epididymis and analyzed. Histology of testis was also performed using standard methods. Cimetidine caused significant (p<0.05) and dose-dependent reductions in sperm count and motility, without an effect on sperm morphology and viability. Cimetidine also caused alterations in the histology of the testis with marked degeneration of seminiferous epithelium, vacuolization and maturation arrest of spermatogenic cells. Furthermore, cimetidine failed to produce any significant effect on semen parameters in VTC-treated animals. Also, there was no alteration in the histology of testis in VTC-treated animals, compared to control. From the results, cimetidine alters testicular function which may be inhibited or protected by VTC.

**Key words:** Ascorbate, cimetidine, spermatogenesis, testis, vacuolization

### INTRODUCTION

Cimetidine is a potent histamine 2 (H<sub>2</sub>)-receptor antagonist, extensively used for treatment of gastric and duodenal ulcers and the drug is available over the counter and by prescription. It is also used to relieve symptoms of various other gastrointestinal disturbances including, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, adenomas and in the prevention of gastrointestinal bleeding and cancer therapy (Eriksson *et al.*, 1995; Khoshbaten *et al.*, 2006). The actions of cimetidine have long been established to be mediated via inhibition of H<sub>2</sub> receptors, the receptors that mediate acid secretion by the parietal cells in the stomach (Ruoff *et al.*, 1979).

Cimetidine is the oldest and least potent among the other H<sub>2</sub> antagonists (e.g., ranitidine and famotidine) in inhibition of gastric acid secretion (Sewing *et al.*, 1981; Collen *et al.*, 1984). Being a potent inhibitor of hepatic cytochrome p450 enzyme (Martinez *et al.*, 1999), cimetidine is an important drug in toxicokinetics. This is because its concurrent administration with most drugs

results in increase in their plasma concentrations which can lead to toxicity. Furthermore, the toxicological effects of cimetidine on various organs in the body have been reasonably studied, including the testis.

The testis is the major male reproductive organ, which is primarily responsible for sperm production (spermatogenesis) and androgen synthesis (steroidogenesis). Spermatogenesis takes place primarily in the seminiferous tubules while steroidogenesis occurs in the Leydig cells of the testis and both processes are necessary for fertility in the male. Cimetidine has been demonstrated by Franca *et al.* (2000) to be a testicular toxicant and a number of studies have reported on its high potential of causing reproductive dysfunction in the male. Chronic use of cimetidine has been reported to cause gynaecomastia (Sawyer *et al.*, 1981; Hugues *et al.*, 2000) and hyperprolactinemia (Park and Selmanoff, 1991). The drug has also been shown to cause modest decrease in sperm count and motility (Wang *et al.*, 1982; Kazerouni and Nayeri, 2000) and impotence (Sawyer *et al.*, 1981) resulting in decrease in sexual desire and drive. Furthermore, high dose of cimetidine has been demonstrated to cause anti-androgenic effects in rodents (Winters *et al.*, 1979; Wang *et al.*, 1982; Gill *et al.*, 1991). In other studies, cimetidine has been shown to cause atrophy or shrinkage of the testis (Leslie and Walker, 1977; Sasso-Cerri *et al.*, 2001) and accessory organs (Winters *et al.*, 1979; Kaman and Kazerouni, 2002; Eilati, 2006), probably due to its anti-androgenic property. Importantly, however, cimetidine is clinically very valuable in the treatment of peptic ulcers and is widely used for this purpose globally. Additionally, the drug is used for long periods since peptic ulcer is a chronic disease that requires long term treatment. Thus, cimetidine-induced male reproductive dysfunction is a major concern and the amelioration of this adverse effect, particularly with the increasing reports of infertility among couples (Araoye, 2003; Bushnik *et al.*, 2012), has become even more of a concern.

Vitamin C or L-ascorbic acid is a potent antioxidant (Padayatty *et al.*, 2003). Vitamin C also enhances male reproductive function (Luck *et al.*, 1995) and protects male reproductive organs from most chemical- and/or drug-induced damages (MacKercher *et al.*, 1977; Sharma and Bhattacharya, 2010; Fernandes *et al.*, 2011; Mahdavi and Mozdarani, 2011; Ayinde *et al.*, 2012).

The present study investigates the effect of vitamin C on harmful testicular effects of clinically relevant dose levels of cimetidine in rats.

## MATERIALS AND METHODS

**Drugs:** Cimetidine tablet (Medrel pharmaceuticals, India) and vitamin C tablet (Emzor Pharmaceuticals, Nigeria) were obtained from the Department of Pharmacy of the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria.

**Methods:** Thirty adult male Wistar albino rats between the ages of 20 and 21 weeks, weighing 200-300 g were obtained from the animal house of the University of Port Harcourt, Nigeria for the study. They were supplied with diet pellets and water *ad libitum*. The animals were divided into five groups (I, II, III, IV and V) of six animals per group and administered the following drugs orally with a feeding tube: Group I, 30 mg kg<sup>-1</sup> of cimetidine daily (in 2 divided doses) for 14 days; group II, 50 and 30 mg kg<sup>-1</sup> of vitamin C and cimetidine daily, respectively (in 2 divided doses) for 14 days; group III, 60 mg kg<sup>-1</sup> of cimetidine daily (in 2 divided doses) for 14 days; group IV, 50 and 60 mg kg<sup>-1</sup> of vitamin C and cimetidine daily, respectively (in 2 divided doses) for 14 days;

group V (Control), 1 mL kg<sup>-1</sup> of distilled water daily (in 2 divided doses) for 14 days. The animals were sacrificed by cervical dislocation under diethyl ether anesthesia and the testes were carefully removed for sperm and histopathological analyses.

**Sperm analysis:** The method of Amelar *et al.* (1973) was used in collecting sperm cells from the epididymis. Briefly, the testis was excised and the caudal epididymis was carefully isolated and placed in a Petri dish containing 3 mL of NaHCO<sub>3</sub> buffered Tyrodes's Lactate solution. Several (1 mm) incisions were made on it and sperm was gently drawn into a plastic transfer pipette and transferred into 5 mL test tubes and was then vigorously shaken for homogeneity and dispersal of sperm cells. Sperm was then analyzed to determine sperm motility, sperm count, percentage of abnormal sperm cells (sperm morphology) and percentage of viable sperm cells (sperm viability) following standard procedures (WHO, 1999).

**Histopathological analysis:** The testis was fixed in 10 % buffered formalin. The testicular tissues were embedded in paraffin and tissue sections (5 µm) were stained with hematoxylin and eosin (H and E) and examined with light microscope (Nikon Eclipse E400). All alterations from the normal structure were registered and histopathological changes between control and experimental animals were noted. The images were photographed with an Olympus Model BX51 microscope at a magnification of 200x.

**Statistical analysis:** Data were expressed as mean±SE of mean. Statistical analyses were done by one way analysis of variance (ANOVA) using GraphPad Prism 5 Software. Values were considered significant at p<0.05.

## RESULTS

**Sperm parameters:** The sperm parameters measured were: sperm count, sperm motility, percentage of abnormal sperm cells (morphology) and percentage of viable sperm cells (sperm viability).

There was a significant (p<0.05) decrease in sperm count and sperm motility in cimetidine-treated animal groups, compared to control. Sperm counts obtained in cimetidine-treated animals were 285.00±9.88×10<sup>6</sup> and 235.20±10.50×10<sup>6</sup>, respectively, while the value in control group was 366.00±8.45×10<sup>6</sup> (Fig. 1a). These values were equivalent to 22.13 and 35.74% decreases, respectively, compared to the control. Sperm motility obtained in cimetidine-treated animals were 82.50±4.86 and 63.10±4.40%, respectively, which corresponded to 3.51 and 26.2% decreases, respectively, compared to the value (85.50±7.20%) obtained in control group (Fig. 1b). However, only 60 mg kg<sup>-1</sup> cimetidine produced significant effect. In addition, sperm morphology and viability values in animal groups that received cimetidine were not significantly (p>0.05) different, compared to the controls (Fig. 1c and d). Furthermore, values of sperm count, sperm motility, sperm morphology and sperm viability that were obtained in vitamin C-pretreated animal groups were all not significantly (p>0.05) different from the control values (Fig. 1a-d).

**Histopathology:** In different groups of animals (n = 6), the effect of vitamin C on cimetidine (30, 60 mg kg<sup>-1</sup>)-induced histopathological effects on the testis was investigated in the rat.

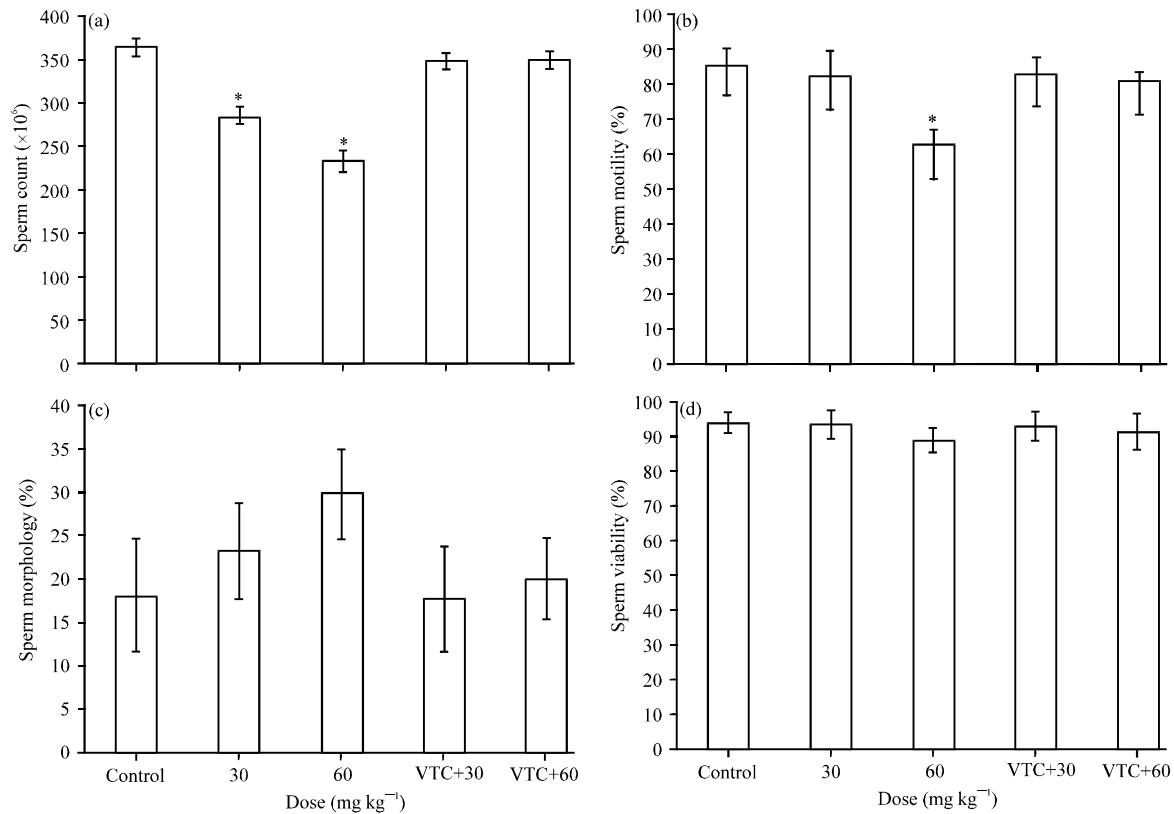


Fig. 1(a-d): Effects of 14 days administration of cimetidine (30, 60 mg kg<sup>-1</sup>) and vitamin C- VTC (50 mg kg<sup>-1</sup>) plus cimetidine on: (a) Sperm count, (b) Sperm motility, (c) Percentage of abnormal sperm cells (sperm morphology) and (d) Percentage of viable of sperm cells (sperm viability) in Wistar albino rats. Data expressed as mean±SEM. \* Significant at p<0.05

Histopathological analysis of testis in the control group showed normal architecture of testis with normal seminiferous epithelium, normal spermatogenic cell differentiation and numerous spermatozoa in the lumen (Fig. 2a). Histopathological analysis of testis in cimetidine-treated animal groups, revealed mild degeneration of seminiferous epithelium, vacuolization of spermatogonia and reduced number of spermatozoa in the lumen at 30 mg kg<sup>-1</sup> (Fig. 2b) and severe degeneration of seminiferous epithelium, vacuolization of spermatogonia, poor differentiation of spermatogenic germ cells, maturation rest and depressed spermatogenesis at 60 mg kg<sup>-1</sup> (Fig. 2c), compared to normal testis in the control group (Fig. 2a). Furthermore, histological analysis of vitamin C-pretreated animal groups revealed normal histology of testis with normal architecture and normal spermatogenesis (Fig. 2d-e), compared to the control group (Fig. 2a).

## DISCUSSION

Cimetidine is an example of H<sub>2</sub>-receptor antagonist widely used in the treatment of gastric and duodenal ulcers and in the symptomatic relief of other gastrointestinal disorders including gastroesophageal reflux disease (GERD), Zollinger ellison syndrome (Walt *et al.*, 1981;

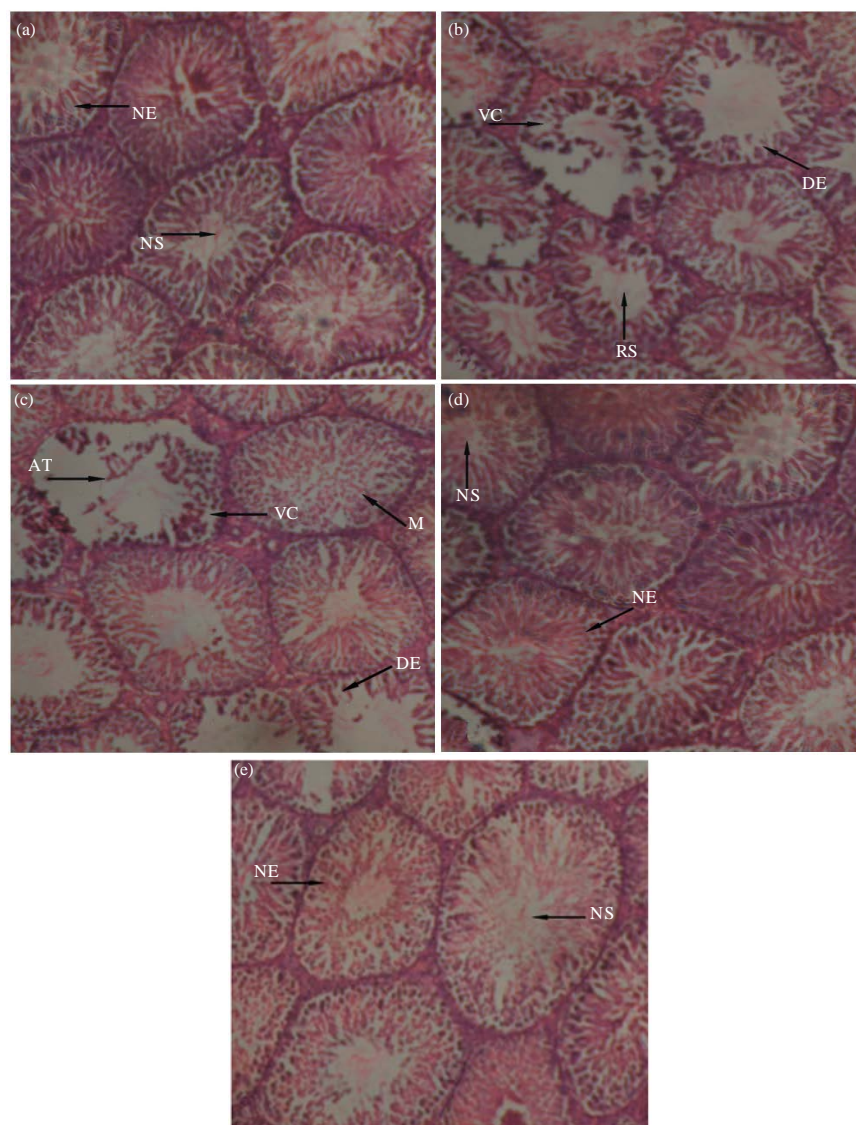


Fig. 2(a-e): Photomicrographs showing testis sections of rats following 14 days administration of cimetidine (30, 60 mg kg<sup>-1</sup>) and vitamin C -VTC (50 mg kg<sup>-1</sup>) plus cimetidine (200x), (a) Group V (Control) shows normal histology of testis with normal germinal epithelium and normal spermatogenic cell differentiation (NE), lumen contains numerous spermatozoa (NS), (b) Group I shows mild degeneration of germinal epithelium (DE), vacuolization (VC) and reduced number of spermatozoa in the lumen (RS), (c) Group II shows severe degeneration of germinal epithelium (DE) and vacuolization (VC). There is atrophy of germinal cells at the lumen (AT). There is interruption of differentiation (maturation arrest) of spermatogonia (MA), (d) Group III shows normal germinal epithelium (NE) and numerous spermatozoa in the lumen (NS), similar to control and (e) Group IV shows normal germinal epithelium (NE) and numerous spermatozoa in the lumen (NS) similar to control

Khoshbaten *et al.*, 2006). It has also been demonstrated to have beneficial effects in some cancers (Matsumoto *et al.*, 2002) and dermatological conditions (Scheinfeld, 2003). Like most other H<sub>2</sub>-receptor antagonists, cimetidine is well tolerated and generally considered to have minimal adverse effects. However, apart from its potential of hepatic cP450 inhibition (Michalets, 1998; Martinez *et al.*, 1999) and the consequent clinical and toxicological implications when concurrently administered with other drugs (adverse drug-drug interactions), there is a growing concern of its effect on the male reproduction system.

Cimetidine has been shown to adversely affect male reproductive structures and testicular function in previous studies (Sawyer *et al.*, 1981; Wang *et al.*, 1982; Franca *et al.*, 2000; Kaman and Kazerouni, 2002). As this may limit the clinical usefulness of the drug to a large extent, there are concerns on the amelioration of this effect. The possible protection of the toxicological effects of cimetidine on male reproductive function by ascorbic acid (vitamin C) was evaluated in this work. In most previous works, testicular effects of cimetidine were demonstrated with relatively high doses- often higher than clinically relevant doses of the drug. In the present study, we evaluated the effects of standard and double of the standard therapeutic dose equivalents of cimetidine on sperm parameters and histology of the testis in rats. To study the effects of vitamin C on the cimetidine-induced responses, we treated some groups of animals with vitamin C and cimetidine concurrently.

In this study, while cimetidine did not cause any significant ( $p>0.05$ ) effect on sperm morphology and viability, it significantly ( $p<0.05$ ) decreased sperm count and motility in a dose-dependent manner. Sperm count is a vital property of sperm and male fecundity decreases progressively with reduction in sperm concentrations (Maya, 2010). On the other hand, sperm motility is a critical indicator of semen quality and fertility potential (WHO, 1999; Zinaman *et al.*, 2000). The result thus indicates that cimetidine may cause impairment in seminiferous tubular function and alter normal spermatogenesis at clinical dose levels in the rat. Similar results have been reported, however using higher dose levels of the drug (Baba *et al.*, 1981; Kazerouni and Nayeri, 2000). Furthermore, the histological effects of cimetidine observed in this study were positively correlated to the results obtained in sperm analysis: degeneration of seminiferous epithelium with depressed spermatogenesis. This is consistent with the results of previous studies that experimented with higher dose levels of the drug (Al-Nailey, 2010; Hamid *et al.*, 2011). Our observations were also dose-dependent, which most previous studies failed to show.

Furthermore, our observation in the vitamin C-treated animals indicates that vitamin C may inhibit or protect cimetidine-induced toxicological responses in the testis. Our result is similar with reports in previous studies that vitamin C protects male reproductive organs from most chemical- and/or drug-induced damages (MacKercher *et al.*, 1977; Sharma and Bhattacharya, 2010; Fernandes *et al.*, 2011; Mahdavi and Mozdarani, 2011; Ayinde *et al.*, 2012). In addition, marked degenerative changes in the testes and accessory organs have been reported by Chinoy *et al.* (1983) and Sapra *et al.* (1987), as well as inhibition of steroidogenesis by Gombe *et al.* (1977) in scorbutic guinea pigs. Dawson *et al.* (1992) and Luck *et al.* (1995) had also shown in their studies that vitamin C enhances male reproductive function, which corroborates our result.

Vitamin C is a potent antioxidant (Padayatty *et al.*, 2003), essential for humans and certain other animal species as a nutrient for a range of key metabolic reactions. Additionally, testicular environment contains vitamin C (Colagar and Marzony, 2009) and a number of other antioxidant

molecules/systems for the maintenance of redox balance which is critical for optimal testicular function (Agarwal *et al.*, 2006; Turner *et al.*, 2008) and this may explain the protective and beneficial effects of the vitamin in the testis. In this study, the inhibition of cimetidine-induced testicular toxicity by vitamin C may be due to its antioxidant property. We therefore suggest that the effects of cimetidine may be due to direct deleterious effects to the seminiferous tubules, probably via alteration of the oxidative status of the testicular milieu.

## CONCLUSION

Cimetidine decreases sperm count and motility and alter histology of testis at standard therapeutic dose levels which can be protected by vitamin C. Concurrent administration of cimetidine and vitamin C could be encouraged to reduce the adverse reproductive effects of cimetidine.

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