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Research Article

Cimetidine at therapeutic dose induces derangements in serum levels of some sex hormones: ameliorative effect of Vitamin C

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Keywords:
Cimetidine, testosterone, follicle stimulating hormone, luteinizing hormone, estradiol and Vitamin C.

ABSTRACT

Background: Cimetidine is a potent histamine H_2-receptor antagonist widely used in treatment of peptic ulcer disease. The aim of this study was to evaluate the effect of chronic cimetidine treatment at therapeutic dose of 30 mg kg^{-1} on serum levels of testosterone, FSH, LH and estradiol and possible ameliorative effect of vitamin C on any derangements induced by cimetidine treatment. **Methods:** Forty adult male Wistar rats were divided into four groups (n = 10) and treated orally for 60 days. Group 1 (control) received distilled water; group 2 received cimetidine (30 mg kg^{-1}); group 3 received cimetidine (30 mg kg^{-1}) + vitamin C (25 mg kg^{-1}) and group 4 received cimetidine (30 mg kg^{-1}) + vitamin C (50 mg kg^{-1}). At the end of the study each animal was anaesthetized by chloroform inhalation in a gas chamber and blood was collected by heart puncture. Serum testosterone, FSH, LH and estradiol levels were determined using ELISA kits. **Results:** Serum levels of testosterone (5.11 ± 0.89), FSH (4.07 ± 0.16) and estradiol (3.13 ± 0.08) of the cimetidine-treated group were higher than that of the control (1.94 ± 0.53, 1.96 ± 0.04 and 1.52 ± 0.23, respectively) at $P \leq 0.05$ while the value for LH of the two groups were not significantly different. Treatment with vitamin C reversed the cimetidine-induced increase in the levels of some of these hormones. **Conclusion:** It was concluded that chronic cimetidine administration at therapeutic dose increased serum levels of testosterone, FSH and estradiol, but not LH and vitamin C at the dose of 25 mg kg^{-1} co-administered with cimetidine ameliorated the increase in serum concentration of testosterone and FSH.

INTRODUCTION

Cimetidine is a potent histamine H_2-receptor antagonist (Hamid *et al.*, 2010) that is widely prescribed worldwide (Al-Nailey, 2010), and is also available without prescription (Luangpirom and Komnont, 2011; Aprioku *et al.*, 2014). Cimetidine is an important drug commonly used in the treatment of gastric and duodenal ulcers (Aprioku *et al.*, 2014). Because it is a H_2-receptor antagonist it has the ability to block the actions of histamine on H_2-receptors (Winters *et al.*, 1979; Katzung, 1989; Ronald and Ashley, 2003) in the parietal cells of the stomach, thereby preventing the production of acid (Rang *et al.*, 2012; Altman, 1998). Thus, it promotes the healing of these ulcers and can also be used for prophylaxis of stress ulcers (Schupp *et al.*, 2003). However, cimetidine has been reported to be a reproductive toxicant (Franca *et al.*, 2000; Sasso-Cerri *et al.*, 2001; Sasso-Cerri and Cerri, 2008). Previous works on cimetidine were carried out using both acute and chronic high doses of the drug to demonstrate its effect on the reproductive system. However little is known about such effects of the drug at therapeutic doses (Aprioku *et al.*, 2013), as the most common use of cimetidine is over long duration (Hamid *et al.*, 2010) at therapeutic doses. Despite its known side effects at higher doses than the therapeutic dose, cimetidine is still widely used, hence the need for a remedy to the potentially serious side effects. This study sought to evaluate the effects of chronic cimetidine administration at therapeutic doses on testosterone, follicle stimulating hormone (FSH),

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leutinising hormone (LH) and estradiol and the possible ameliorative effects of vitamin C.

MATERIALS AND METHODS

Animals and Conditions

A total of forty adult male Wistar rats weighing between 110-130g, at 90 days old were obtained from the animal house of the Department of Human physiology, Bayero University, Kano, where the study was carried out. They were housed in plastic cages with plastic bottom and maintained under adequate ventilation in the animal house. They were also allowed access to standard laboratory rat chow and tap water *ad libitum* throughout the study. Experimental protocols were in accordance with the guidelines for animal research, as stated in the NIH Guidelines for the Care and Use of Laboratory Animals (National Academy of Sciences and National Institute of Health Publications, 2011).

Preparation of Administered Drugs

Five tablets (1000mg) of cimetidine 200 mg (Gasrol, Sam Pharmaceuticals, Nigeria) were crushed into powder using pestle and mortar and dissolved in 100mls of distilled water to make a stock solution containing cimetidine, at a concentration of 10 mg ml^{-1}. This was stored at room temperature, protected from light and used up within 3 days. Similarly, a stock solution containing vitamin C at a concentration of 10 mg ml^{-1} was prepared from pure grade vitamin C powder (Ascorbic Acid, Bulk supplements, Nevada, U.S.A) and stored at room temperature, protected from light and used within 3 days.

Grouping and Treatments

The animals were randomly divided into 4 groups of 10 rats each. They were administered with either drugs or distilled water orally using metallic cannula at 10:00am daily for 60 days. Group 1 (Control) received distilled water; group 2 received cimetidine at a dose of 30 mg kg^{-1}; group 3 received cimetidine (30 mg kg^{-1})+ vitamin C (25 mg kg^{-1}); and group 4 received cimetidine 30 mg kg^{-1} + vitamin C (50 mg kg^{-1}). The rats were weighed at the beginning of the experiment and every week subsequently. Doses of administered drugs were adjusted according to the body weights of the animals.

Sacrifice of Animals and Samples Collection

At the end of the experiment, the live weight of each rat was assessed before sacrifice. Subsequently each rat was anaesthetized by chloroform inhalation in a gas chamber. The chest was then opened and blood samples aspirated by heart puncture using 10ml syringe. Blood collected was quickly discharged into plain bottles for determination of hormonal levels.

Hormonal Assays

Whole blood collected in a plain bottle was allowed to clot by leaving it undisturbed at room temperature for a period of 15-30 minutes. The clot was then removed by centrifuging at 2000 revolutions per minute for 10 minutes in a centrifuge (Jenalab Medical, England). The resulting supernatant known as serum was immediately transferred into a clean plain sample bottle using a Pasteur pipette and immediately stored in a freezer at –20°C and freeze-thaw cycles avoided (Henry, 1979; Thavasu *et al.*, 1992; Adediran and Kolapo, 2014). This was subsequently used to determine the levels of testosterone, FSH, LH and estradiol. Assay for these hormones was carried out using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Fortress diagnostics, Antrim, U.K.) according to manufacturer's instructions.

Statistical Analysis

Data were presented as mean ± SEM and analyzed using Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS Inc, Chicago, United States). One-way ANOVA and Tukey post-hoc tests were used to compare means. Values of $P \leq 0.05$ were considered significant.

RESULTS

Testosterone (ng/ml)

Figure 1 shows serum concentration of testosterone (ng/ml) of rats following 60 days of administration. Serum testosterone concentration of group 2 rats (5.11 ± 0.89) was significantly higher compared to group 1 (1.94 ± 0.53) (P = 0.011). This shows that administration of 30 mg kg^{-1} cimetidine increased serum testosterone concentration in the treated rats. There was no significant difference in serum testosterone concentration between group 3 rats (4.39 ± 0.51) and group 1 (1.94 ± 0.53) (P = 0.070), indicating that 25 mg kg^{-1} vitamin C reversed (reduced) the increase in testosterone concentration caused by cimetidine administration. Serum testosterone levels of group 4 rats (4.54 ± 0.71) was significantly higher compared to group 1 (1.94 ± 0.53) (P = 0.049) indicating that 50 mg kg^{-1} vitamin C did not reverse (reduce) the effect of cimetidine. There was however no significant difference in serum testosterone concentration between group 4 (4.54 ± 0.71) and group 3 rats (4.39 ± 0.51) (P = 0.999).

Follicle stimulating hormone (mIU/ml)

Figure 2 shows serum concentration of FSH following 60 days of administration. The serum concentration of FSH in group 2 rats (4.07 ± 0.16) was significantly higher compared to group 1 (1.96 ± 0.04) (P = 0.001). This shows that administration of 30 mg kg^{-1} cimetidine

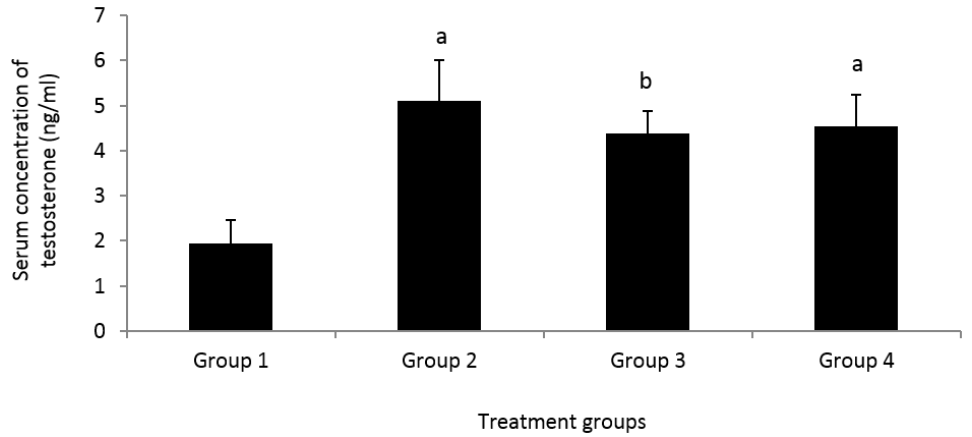

Fig. 1: Serum concentration of testosterone following 60 days of administration (Mean ± S.E.M., n = 10). [a] = Significant ($P \leq 0.05$) compared to group 1 (control group). [b] = Not significant ($P > 0.05$) compared to group 1 (control group)

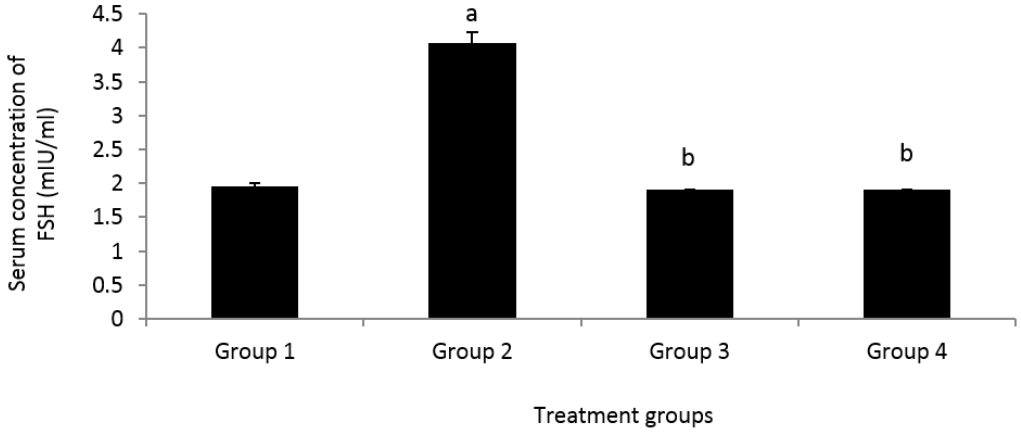

Fig. 2: Serum concentration of FSH following 60 days of administration (Mean ± S.E.M., n = 10). [a] = Significant ($P \leq 0.05$) compared to group 1 (control group). [b] = Not significant ($P > 0.05$) compared to group 1 (control group)

increased serum FSH concentration in the rats. There was no significant difference in serum FSH concentration of group 3 (1.90 ± 0.01) and group 4 rats (1.90 ± 0.01) compared to group 1 (1.96 ± 0.04) ($P = 0.962$ and $P = 0.947$, respectively) suggesting that vitamin C at both doses reversed the raised FSH concentration caused by 30 mg kg^{-1} cimetidine back to normal. There was no significant difference in serum FSH concentration of group 4 (1.90 ± 0.01) and group 3 rats (1.90 ± 0.01) ($P = 1.000$).

Leutinising hormone (mIU/ml)

Serum LH concentration of group 2 (2.77 ± 1.05), group 3 (0.49 ± 0.39) and group 4 rats (0.05 ± 0.05) were not significantly different compared to group 1 (1.38 ± 0.60) ($P = 0.423$, $P = 0.753$ and $P = 0.457$, respectively) as shown in figure 3. This shows that 30 mg kg^{-1} cimetidine, or its co- administration with 25 mg kg^{-1} vitamin C and 50 mg kg^{-1} vitamin C did not significantly affect LH concentration. There was also no significant difference in serum LH concentration of group 4 (0.05 ± 0.05) and group 3 rats (0.49 ± 0.39) ($P = 0.961$). Though the differences between the groups in LH values were not significant, a similar trend was observed in which cimetidine 30 mg kg^{-1} increased the hormonal level compared to control, while administration of both doses of vitamin C decreased the levels towards the normal.

Estradiol (pg/ml)

Figure 4 shows serum estradiol concentration following 60 days of administration. Serum estradiol concentration of group 2 (3.13 ± 0.08), group 3 (2.72 ± 0.04) and group 4 rats (2.70 ± 0.04) were significantly higher compared to group 1 (1.52 ± 0.23) ($P = 0.001$, $P = 0.001$ and $P = 0.001$, respectively), indicating that serum estradiol levels were significantly increased in these groups due to cimetidine administration alone as well as in combination with vitamin C. This also suggests that vitamin C at both doses did not reverse the cimetidine-induced increase in estradiol back to normal. There was also no significant difference in serum estradiol levels of group 4 (2.70 ± 0.04) and group 3 rats (2.72 ± 0.04) ($P = 0.999$).

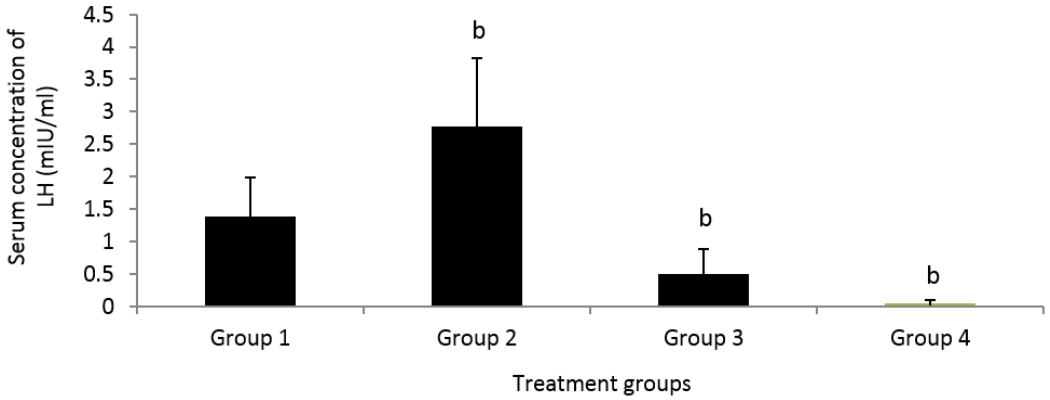

Fig. 3: Serum concentration of LH following 60 days of administration (Mean ± S.E.M., n = 10). [b] = Not significant ($P > 0.05$) compared to group 1 (control group).

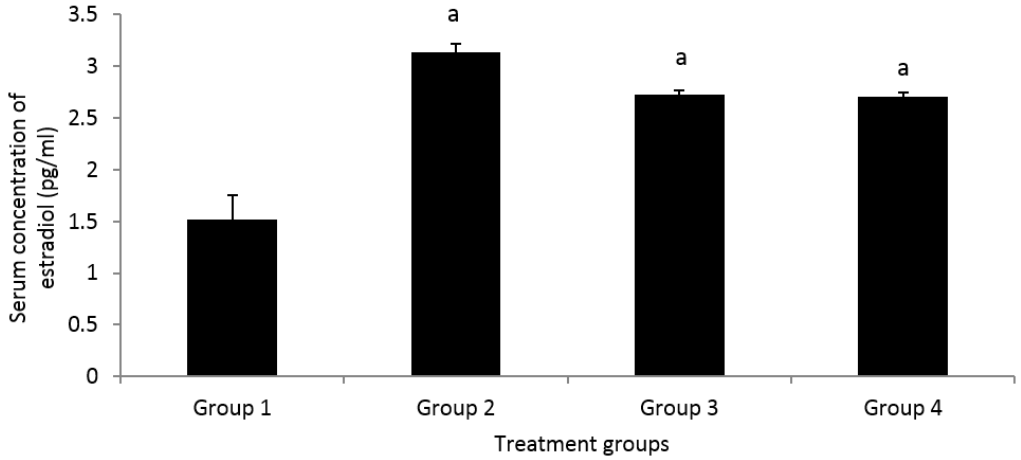

Fig.4: Serum concentration of estradiol following 60 days of administration (Mean ± S.E.M., n = 10). [a] = Significant ($P \leq 0.05$) compared to group 1 (control group)

DISCUSSION

Cimetidine has caused a significant increase in serum testosterone. The mechanism of this effect may be related to the anti-androgenic properties of cimetidine which acts as a non-steroidal anti-androgen by inhibiting testosterone transformation to dihydrotestosterone (Baba *et al.*, 1981) as well as inhibiting dihydrotestosterone from binding to the androgen receptor (Winters *et al.*, 1979; Funder and Mercer, 1979) thereby preventing its action. This in turn may result in accumulation of testosterone due to its decreased conversion to dihydrotestesterone. The decrease activity of dihydrotestosterone because of its inability to bind on the androgen receptors may result in increased release of gonadotrophin in order to facilitate the release of more testosterone to bind to the androgen receptors to maintain spermatogenesis. Also, the toxic effect of cimetidine on testicular structures with subsequent affectation of its function as reported by Sawyer *et al.* (1981) as well as Kaman and Kazerouni (2002) may result in a feedback mechanism that will increase testosterone level in an effort to enable the testis function properly. In addition, cimetidine which is similar to other anti–androgens such as flutamide and cyproterone (Walsh *et al.*, 1972; Neuman *et al.*, 1977) have been shown to cause an increase in gonadotrophin levels by antagonizing the negative feedback control of gonadotrophin secretion by androgens, thus resulting in increased testosterone concentration (Wang *et al.*, 1982; Knigge *et al.*, 1983).

The findings of this study is in agreement with that of Van Thiel *et al.* (1979), Penden *et al.* (1981) as well as Wang *et al.* (1982) who reported increased testosterone level. The findings however, disagree with those of Baba *et al.* (1981) and Parker *et al.* (1984), who reported a decrease in testosterone levels; and others (Leslie *et al.*, 1981; McGivern 1987; Pinelli *et al.*, 1987; Franca *et al.*, 2000; Hammodi *et al.*, 2011; Luangpirom and Komnont, 2011) who reported no change in serum testosterone level.

Treatment with vitamin C at 25 mg kg^{-1} reversed the effect of cimetidine. This may be related to the

antioxidant effect of vitamin C (Sharma and Bhattacharya, 2010), and may indicate oxidative stress as the possible mechanism of the cimetidine-induced increase in serum testosterone level. To support this, treatment with vitamin C at 50 mg kg^{-1} did not reverse the effect of cimetidine. This may be related to the pro-oxidant effect of vitamin C on testes as reported previously (Yarube *et al.*, 2014).

The increase in serum levels of FSH caused by cimetidine may be a compensatory response to impaired spermatogenesis (Rosen and Weintraub, 1971; Leonard *et al.*, 1972; Franchimont *et al.*, 1972; Van Thiel, *et al.*, 1972 and De Kretser *et al.*, 1974) resulting from toxic effect of cimetidine on testicular structures (Franca *et al.*, 2000), inadequate testosterone available for spermatogenesis due to its inability to bind to receptors (Sivelle *et al.*, 1982), and the antagonizing effect of cimetidine on the negative feedback control of gonadotrophin secretion by androgens (Wang *et al.*, 1982). The findings of this study is in agreement with that of Bélisle *et al.* (1982), Spona *et al.* (1987), Franca *et al.* (2000) and Hammodi *et al.* (2011). These findings however, disagreed with those of Barber and Hoare (1979), Nelis and Van de Meene (1980), Valk, England and Marshall (1981) and Hayakawa *et al*. (1982) who reported that there was no change in serum FSH level, while Van Thiel *et al*. (1979) reported inadequate FSH response. Treatment with 25 mg kg^{-1} and 50 mg kg^{-1} of vitamin C restored serum FSH level showing that vitamin C has protected the testicular structures from the toxic effect of cimetidine, resulting in normalization of FSH levels.

Though increase in FSH level due to cimetidine treatment was observed, it was without significant increase in LH. This may be due to the pulsatile nature of LH secretion, thus a single LH blood measurement may not adequately reflect the exact LH level (Wang *et al.*, 1982). The findings of this study is in agreement with that of Barber and Hoare (1979), Nelis and Van de Meene (1980), Bélisle *et al.* (1982), Hayakawa *et al.* (1982), Spona *et al.* (1987). The findings however, disagreed with those of Mahmud and Akhter (1995) who reported a significant increase in LH level, while Valk *et al.* (1981) reported a decrease in LH level after cimetidine treatment was discontinued. Treatment with 25 mg kg^{-1} and 50 mg kg^{-1} of vitamin C had a reversal effect on the insignificant increase caused by cimetidine. Again, this effect may be due to the antioxidant properties of vitamin C (Angulo *et al.*, 2011).

The increase in serum estradiol levels caused by cimetidine may be the result of inhibition of the degradation of estradiol following the inhibition of estradiol 2-hydroxylation by cimetidine in the liver (Galbraith and Jellinck, 1989) leading to increased serum estradiol level. An additional mechanism may be due to increased conversion of testosterone to estrogen (Hall, 2011) in the presence of high level of testosterone caused by treatment with cimetidine in this study. The findings of this study is in agreement with that of Valk *et al.* (1981), Galbraith and Jellinck (1989) and Michnovicz and Galbraith (1991) who reported an increase in estradiol levels. These findings however, disagreed with those of Barber and Hoare (1979), Bélisle *et al.* (1982) and Hayakawa *et al*. (1982) who reported no change in serum estradiol level. Treatment with vitamin C at 25 mg kg^{-1} and 50 mg kg^{-1} did not reverse the increase in serum estradiol level. Vitamin C, apparently did not interfere in the inhibition of estradiol 2-hydroxylation by cimetidine in the liver –the suggested mechanism of increased serum estradiol as described by Galbraith and Jellinck (1989).

CONCLUSION

Chronic administration of cimetidine at therapeutic dose caused a significant increase in serum levels of testosterone, FSH and estradiol, but not LH. Vitamin C at the dose of 25 mg kg^{-1} co-administered with cimetidine ameliorated the serum increase in testosterone and FSH while vitamin C at the dose of 50 mg kg^{-1} only ameliorated the serum increase in FSH. Study highlights potential serious side effects on male sex hormones associated with chronic cimetidine therapy and the beneficial effect of cimetidine co-treatment therapy with Vitamin C.

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