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EFFECT OF CIMETIDINE, RANITIDINE AND TIOTIDINE ON PLASMA TESTOSTERONE AND LUTEINIZING HORMONE LEVELS IN RATS

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ABSTRACT

This investigation was carried out to study the comparative effects of cimetidine, ranitidine and tiotidine on the plasma levels of testosterone and luetinizing hormone under local conditions. The three H_2-blocking drugs were injected to the adult male albino rats twice daily at the recommended therapeutic dose levels for six weeks. The data obtained showed that only tiotidine caused a significant (<0.05) increase in the level of testosterone. However, all the three drugs caused a significant rise in the levels of luteinizing hormone with the most active ranitidine administration.

Introduction

The histamine H_2 receptor-blocking agents have been extensively used in these times for the treatment of peptic ulcer disease. Especially, cimetidine and ranitidine have come in more prevalent use. Thus reports of their side effects have also appeared which include disturbance of plasma hormone levels. For example, cimetidine has caused gynaecomastia in the males (Hall, 1976), a rise in the plasma levels of testosterone (Van Thiel et al., 1979) and even antiandrogenic effects (Winters et al., 1979). Similarly, ranitidine has been observed to cause gynaecomastia (Tosi and Cagnoli, 1982) and an increase in the serum level of prolactin (Edwards et al., 1982).

However, ranitidine has not been reported to alter the levels of prolactin, luteinizing hormone, thyroid stimulating hormone, growth hormone and adrenocorticotrophic hormone (Yeo et al., 1980). In another study, ranitidine has not showed any effects on the serum levels of testosterone, luteinizing hormone and follicle stimulating hormone (Wang et al., 1983). As far as ascertained studies on the effects of tiotidine on the levels of said hormones were not available. Therefore, an investigation was carried out to study the comparative effects of the three antiulcer drugs on testosterone and luteinizing hormonal levels under local environmental conditions.

Materials and Methods

Animals:

Male adult albino Sprague-Dawley rats weighing between 250-300 grams were used. Animals were kept under local environmental conditions and were fed on a locally prepared rat feed. Tap water was allowed ad *libitum.*

Drugs:

Cimetidine HCL of S.K. & F., ranitidine HCI of Gino and tiotidine HCI of I.C.I. were used. Ether anesthetic was of the commercial grade. The hormonal radioimmunoassay kits were prepared by Serena Diagnostics and Amersham, England.

Groups of Rats and Drug Administration:

Four groups each containing 10-14 adult male rats, aging four months were used randomly. The control group received 2 ml of normal saline intramuscularly twice daily with an interval of 12 hours for six weeks. The cimetidine group was treated with cimetidine HCl, 5.71 mg/kg (Heading, 1984). It was given intramuscularly to the rats twice daily with 12 hours interval for six weeks. Rantidine group was injected with ranitidine HCl, 2.14 mg/kg (Burkhalter and Frick, 1982) intramuscularly twice daily with 12 hours interval for six weeks. Similarly, the tiotidine group was injected with tiotidine HCl, 1.4 mg/kg (Kaojaren et al., 1979) intramuscularly to the rats twice daily with 12 hours interval for six weeks.

Sampling of Blood

Animals were anaesthetizied under ether anesthesia (Williams, 1976) and blood (1-2 ml) was collected through cardiac puncture using disposable syringes. Serum was separated by centrifugation.

Determination of Plasma Testosterone Levels:

The radioimmunoassay kit was used to determine the amount of testosterone in the scrum samples. The method described by (James et al., 1973) was followed for the estimation of serum testosterone.

Determination of Plasma Luteinizing Hormone Levels:

Radioimmunoassay method as described by (Wide et al., 1973) was followed by using the kit for the estimation of luteinizing hormone.

Statistical Analysis:

For the statistical analysis Student's "t" test described by Walpole (1982) was followed.

Results

Plasma Testosterone Levels:

The control value of plasma testosterone was 157 ± 0.6 ng/ml.

Plasma testosterone level in the control group was 157 ± 0.6 ng/ml. In the cimetidine group, level of plasma testosterone was 0.80 ± 0.8 ng/ml which is ($P>0.05$) similar to the control group. In the ranitidine group the mean value of plasma testosterone was 0.65 ± 0.1 ng/ml and is also similar to the control. However, after tiotidine treatment the plasma testosterone level was 7.2 ± 1.6 ng/ml which is higher ($P<0.05$) than the control group (Table 1).

Plasma Luteinizing Hormone Levels:

Mean plasma luteinizing hormone (LH) level in the control group was 6.0 ± 0.9 mIU/ml. In the cimetidine group, mean plasma LH level was 7.9 ± 0.6 mIU/ml which is higher ($P <0.05$) than the value of the control group. In the ranitidine group, the plasma LH level was 93 ± 05 mIU/ml which is highly significant ($P <0.001$) from the control. However, in the tiotidine group, mean plasma LH level was 8.3 ± 0.4 mIU/ml which is higher ($P <0.05$) than the control group (Table 2).

Discussion

Regarding plasma levels of testosterone and luteinizing hormone (LH), Van Thiel et al. (1979) have reported that after cimetidine therapy in duodenal ulcer patients there was no change in the plasma levels of testosterone and LH. Winters et al. (1979) have also demonstrated that after one week administration of cimetidine to rats there was no change in the plasma levels of testosterone and LH. In addition, Yeo et al. (1980) have shown that rantidine does not alter the plasma levels of LH, TSH and ACTH in man and Peden et al. (1981) have observed that plasma levels of testosterone and LH remained unchanged in patients taking ranitidine. However, Wang et al. (1982) have reported elevations in the plasma levels of testosterone in patients taking cimetidine, but there was no change in the levels of LH. Wang et al. (1983), in another study, have observed that ranitidine does not affect the plasma levels of testosterone, LH and FSH.

The present study, correlates with those observations in which cimetidine and ranitidine does not alter the plasma levels of testosterone. However, Wang et al. (1982) noticed a rise of plasma testosterone with cimetidine but in this investigation such effect was seen with tiotidine. Cimetidine has caused a rise of plasma testosterone in humans (Wang et al., 1982) and not in the rats (Winters et al., 1979). This indicates that this difference or response is due to variation of species.

In our study all the three drugs have caused in rise in the plasma levels of luteinizing hormone which is contrary to the above quoted previous reports. One possible explanation of this can be that human patients usually take some other drugs alongwith the H_2-blockers and in our study only the H_2-blockers were given which have caused a rise in the luteinizing hormone levels. The study carried out by Winters et al. (1979) showed that there was no effect of a dose of 50 mg/kg/day for one week of cimetidine on the plasma levels of luteinizing hormone, while our study shows a rise of LH which may be due to the fact that our study was carried out for six weeks at the dose levels of 5.71 mg/kg body weight twice daily. Although the dose level in our case is lower but the time period is longer which might also be responsible for this rise of LH level in plasma.

Moreover, in our study ranitidine has caused a significant rise in the LH levels, therefore, it is recommended that the local physicians should be watchful of this effect on the patients taking this drug. In conclusion, ranitidine has been found to be a safer drug as compared to cimetidine because it did not disturb the plasma levels of testosterone which is the main cause of gynaecomastia as explained by Winters et al. (1979). The gynaecomastia caused by ranitidine, as reported by Tosi and Cagnoli (1982) needs further evaluation as no other workers has reported a similar finding.

Table 1
Effect of H_2-blocking drugs on the serum level of testosterone in rats

Group No.	Treatment	Testosterone* (ng/ml)	P
1.	Normal saline 2.0 ml i/m	1.57 ± 0.6 (II)	-
2.	Cimetidine HCL 5.71 mg/kg i/m	0.8 ± 0.08 (10)	P > 0.05
3.	Ranitidine HCL 2.14 mg/kg i/m	0.65 ± 0.1 (11)	P > 0.05
4.	Tiotidine HCL 1.4 mg/kg i/m	7.22 ± 1.6 (14)	P < 0.01

*The values shown represent the mean ± SEM with number of determinations shown in parenthesis underneath each value.

Table 2
Effect of H_2-blocking drugs on the serum level of LH in rats

Group No.	Treatment	Testosterone* (ng/ml)	P
1.	Normal saline 2.0 ml i/m	6.02 ± 0.9 (II)	-
2.	Cimetidine HCL 5.71 mg/kg i/m	7.9 ± 0.6 (10)	P < 0.01
3.	Ranitidine HCL 2.14 mg/kg i/m	9.3 ± 0.5 (11)	P < 0.01
4.	Tiotidine HCL 1.4 mg/kg i/m	8.3 ± 0.4 (14)	P < 0.01

*The values shown represent the mean ± SEM with number of observations shown in parenthesis underneath each value.

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