Endocrine Effects of Acute and Chronic Cimetidine Administration

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In normal men, acute oral administration of 300 mg cimetidine or intravenous injection of 50 mg of the drug had no effect on prolactin release. In contrast, intravenous injection of 150 or 300 mg led to substantial increments in serum prolactin. Peptic ulcer patients were randomly assigned to treatment with either cimetidine or antacid. Serial blood sampling until ulcer healing showed no significant changes in serum prolactin, testosterone, free testosterone, estradiol, LH, or FSH in either group. It is likely that the impotence and breast changes occasionally seen during cimetidine therapy are due to peripheral antagonism of androgen action rather than to alterations in circulating hormone levels.

Cimetidine, an H_2-histamine receptor antagonist, has been widely used in the treatment of peptic ulcer. Some male patients receiving chronic cimetidine therapy have developed impotence, gynecomastia, or galactorrhea (1–4); these side effects may be related to hyperprolactinemia or to an antiandrogenic effect of the drug. Although the acute intravenous administration of cimetidine increases serum prolactin levels, there are conflicting data regarding the endocrine effects of oral cimetidine administration (2, 5–11). In animal studies, cimetidine has a direct antiandrogenic effect on rat prostate and seminal vesicle, antagonizes the effect of exogenous testosterone, and inhibits dihydrotestosterone binding to its cytoplasmic receptor in rat prostate (12, 13).

The purposes of this study were (1) to compare serum testosterone, FSH, LH, estradiol, free testosterone, and prolactin levels before and after 2–6 weeks of treatment with cimetidine or with antacid in patients with duodenal ulcer, and (2) to determine the threshold dose for serum prolactin release in response to cimetidine.

Manuscript received July 13, 1980; revised manuscript received October 7, 1980; accepted October 10, 1980.

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Supported by funds from the Medical Research Service of the Veterans Administration and Smith, Kline and French Laboratories.

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MATERIALS AND METHODS

Acute Administration of Cimetidine. Nine normal male volunteers (ages 27–69, mean age 48 years) participated in the study of acute oral cimetidine administration and the intravenous dose–response study. None of the subjects was obese and none was receiving any medication at the time of the studies. After an overnight fast, a butterfly needle was inserted into an antecubital vein and kept patent with a slow infusion of 0.9% saline.

Single-Dose Oral and Intravenous Administration. Following the collection of two baseline blood samples (−15 and 0 min) from 6 subjects, 300 mg of cimetidine was given orally, and further blood samples collected every 30 min for 3 hr. After the 3-hr blood sample was collected, an additional 300 mg of cimetidine was injected rapidly as an intravenous bolus, and blood samples were collected every 15 min for 1 hr.

Intravenous Dose–Response Study. In 7 normal male subjects, prepared as above, graded intravenous doses of cimetidine were administered. After the collection of the baseline blood samples, 50 mg of cimetidine were slowly infused over a 2-min period using a Harvard infusion pump; at 30 and 60 min after this injection, 150 and 300 mg of cimetidine, respectively, were infused using the same technique. Blood samples for prolactin and cimeti-

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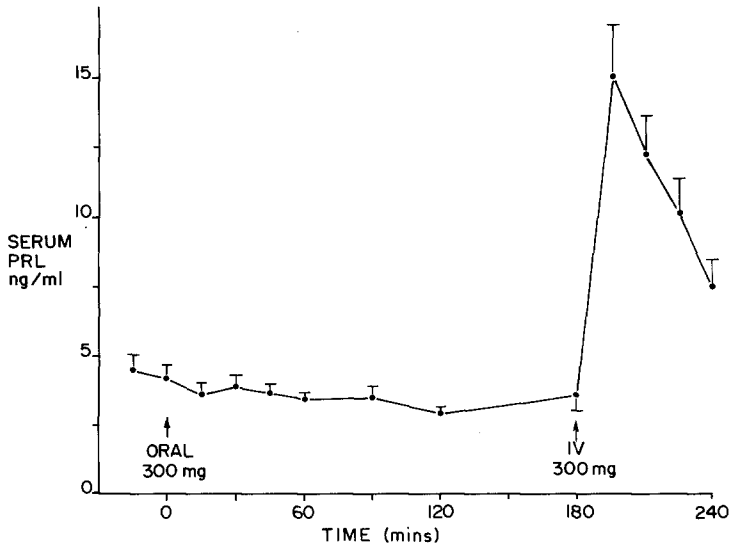

Fig 1. Serum prolactin (PRL) response to a 300-mg oral dose of cimetidine followed by 300 mg intravenously in 6 normal men; mean ± SE is shown.

dine measurement were collected every 10 min for 90 min following the start of the initial injection.

Chronic Oral Administration. Twenty-three male patients with endoscopically proven active duodenal ulcer disease were studied. These patients were consecutively entered from one hospital as part of a randomized, double-blind multicenter trial comparing cimetidine with antacid treatment of duodenal ulcer. Ten men (ages 30–81, mean 54 years) received cimetidine 300 mg orally qid and placebo liquid, while 13 subjects (ages 30–70, mean 55 years) were given placebo capsules plus Mylanta II, 7 oz daily. Subjects were seen before drug administration and at 2-week intervals until ulcer healing, up to 6 weeks. At each clinic visit, subjects were questioned about their sexual functioning and subjective breast discomfort; breasts and testes were examined (by the same examiner on each occasion), and a pooled blood sample (3 specimens drawn at 6-min intervals) was obtained for serum hormone measurements.

Assays. For each hormone, all samples from the same subject were measured in a single assay. Generally, 2 or 3 assay runs were needed to analyze samples from all the subjects; cimetidine and antacid patients were randomly distributed among these 2 or 3 assay runs for each hormone. Serum prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and estradiol were measured by standard radioimmunoassay methods (14–18). In normal men under 50 years of age, values for the various measurements are: prolactin 5.7 ± 3.0 (SD) ng/ml, LH 11.2 ± 4.6 mIU/ml, FSH 4.38 ± 2.67 mIU/ml, testosterone 464 ± 137 ng/dl, and estradiol 2.86 ± 0.98 ng/dl. Intraassay and interassay coefficients of variation for prolactin were 5% and 10%, respectively; for LH, 6.6% and 10.7%; for FSH, 3.3% and 12.1%; for testosterone, 5.1% and 10.7%; for estradiol, 5.7% and 12.4%. Reagents for the PRL, LH, and FSH assays were kindly provided by the National Pituitary Agency, NIAMDD. Serum levels of free testosterone were assessed with an equilibrium dialysis technique (19); normal men have a mean value of 9.5 ± 3.5 ng/dl. Serum cimetidine levels were measured by Smith, Kline and French Laboratories using high-pressure liquid chromatography (20). Student's paired *t* test was used for statistical analysis.

RESULTS

Acute Oral Cimetidine Administration. The acute ingestion of 300 mg cimetidine did not alter serum PRL concentrations in any of the subjects (Figure 1). Three hours after oral dosing, the intravenous injection of an additional 300 mg bolus of the drug acutely raised serum PRL levels, demonstrating the responsiveness of serum PRL in these subjects.

Intravenous Dose–Response. Infusion of an intravenous dose of 50 mg cimetidine over 2 min did not alter serum PRL; however, infusion of 150 mg provoked a small but significant ($P < 0.02$) rise in serum PRL, while a dose of 300 mg led to a substantial PRL increment, as before (Figure 2). Serum cimetidine levels reached 1.12 ± 0.14 (SE), 2.37 ± 0.17, and 7.76 ± 0.65 μg/ml after each dose of the drug. The increment in serum PRL following a 2-min infusion of 300 mg cimetidine was slightly less than that seen with rapid intravenous injection of the same dose, probably reflecting the lower serum cimetidine concentrations achieved with the slow infusion.

Chronic Oral Administration. Serum PRL was not altered by the chronic oral administration of cimetidine or placebo over a 2 to 6 week period in these duodenal ulcer patients. Total and free serum testosterone levels were slightly but not significantly increased in both groups; estradiol, LH, and FSH were unaltered (Table 1). No subject reported changes in sexual functioning or breast tenderness, and breasts and testes remained objectively unchanged in all.

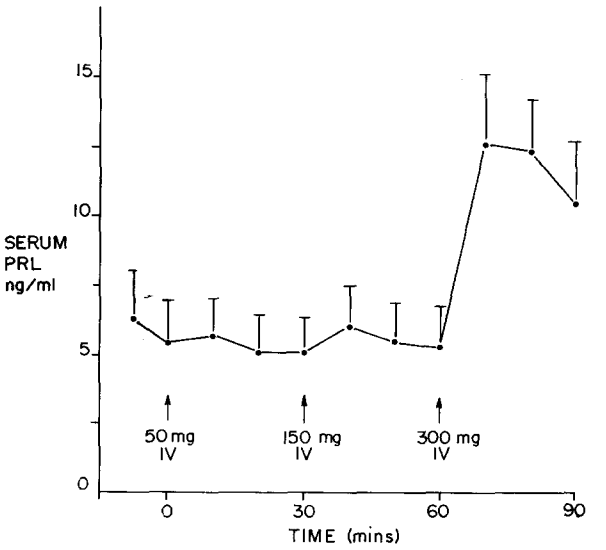

Fig 2. Serum PRL responses to graded intravenous doses of cimetidine in 7 normal men; mean ± SE is shown.

DISCUSSION

The present results demonstrate that the stimulation of PRL secretion by cimetidine appears to be confined to the acute intravenous administration of large doses of the drug. We found no change in serum PRL with either acute or chronic oral administration of cimetidine, in agreement with others (8–11, 21–24). It is probably necessary to achieve substantial elevations of serum cimetidine concentrations to release prolactin, perhaps due to poor penetration of cimetidine into the central nervous system sites responsible for the histaminergic regulation of prolactin secretion (25). Indeed, serum cimetidine levels only reach values of 1–1.5 μg/ml after a single 300 mg oral dose (26), while we found values 5 to 10-fold higher after slow intravenous drug administration; even higher plasma levels have been reported by Burland et al, using rapid intravenous injection (22). In the present study, the threshold intravenous dose for PRL release was about 150 mg. Similar findings have been recorded by Caldara et al, who determined an intravenous threshold dose of around 100 mg (27). In agreement with other studies, we found no change in serum gonadotropins, estradiol, or sex-steroid binding globulin following chronic oral administration (4, 7, 21, 24, 28). Similarly, intravenous administration of the drug does not alter these parameters (7, 27, 29).

It is thus likely that the production of gynecomastia and impotence in some men receiving cimetidine is due to other mechanisms, perhaps involving the antagonism of testosterone action at tissue receptor sites for testosterone or 5α-dihydrotestosterone. Such an antiandrogenic effect of cimetidine has recently been demonstrated (12, 13). Thus, blockade of androgen action in the presence of normal circulating estrogen concentrations could lead to a predominant estrogen effect, producing breast enlargement and impotence. In this respect, cimetidine would be similar to spironolactone, which is thought to produce a similar clinical picture through this mechanism (30). A blockade of

TABLE 1. SERUM HORMONE CONCENTRATIONS IN ULCER PATIENTS TREATED WITH CIMETIDINE OR ANTACID*

	Cimetidine			*Antacid*		
	Pretreatment	*2 weeks*	*Last day*	*Pretreatment*	*2 weeks*	*Last day*
Testosterone (ng/dl)	503 ± 34	525 ± 33	578 ± 56	450 ± 49	513 ± 55	531 ± 46
Free testosterone (ng/dl)	10.8 ± 0.87	11.3 ± 0.95	13.0 ± 2.0	9.4 ± 0.98	12.2 ± 2.3	11.5 ± 0.98
Estradiol (ng/dl)	3.6 ± 0.47	3.8 ± 0.42	3.6 ± 0.32	3.7 ± 0.42	4.1 ± 0.49	4.5 ± 0.47
FSH (mIU/ml)	5.2 ± 1.2	4.7 ± 0.94	4.9 ± 0.98	5.2 ± 0.63	5.0 ± 0.72	5.1 ± 0.72
LH (mIU/ml)	10.0 ± 1.5	11.8 ± 2.3	11.2 ± 1.9	10.8 ± 1.9	10.1 ± 1.8	10.4 ± 1.7
Prolactin (ng/ml)	4.4 ± 0.60	4.5 ± 0.44	4.7 ± 1.0	3.7 ± 0.4	3.6 ± 0.3	3.7 ± 0.3

*Mean ± SE values are shown for sera obtained before treatment, after 2 weeks of therapy, and on the last day of treatment (at ulcer healing, which could be at 2, 4, or 6 weeks of therapy).

androgen action might also affect the feedback regulation of gonadotropins, leading to a transient rise in serum LH, FSH, and subsequently, testosterone, with establishment of a new equilibrium at a higher serum testosterone level. In fact, a small but statistically nonsignificant increase in serum testosterone was observed in our subjects. However, a similar rise of serum testosterone was seen in the antacid-treated patients, suggesting that this change may be related to amelioration of peptic ulcer disease and not to any specific drug-related mechanism. In uncontrolled studies, Van Thiel et al found a small rise in serum testosterone in cimetidine-treated ulcer patients (11), while Bohnet et al (7), Barber and Hoare (21), and Sharpe and Hawkins (28) found no change. Additionally, Valk et al noted no change in serum testosterone in normal volunteers given cimetidine for 6 weeks (24). Taken together, these results suggest that serum testosterone is probably not altered by cimetidine administration in any predictable fashion. The failure to affect testosterone feedback on gonadotropin secretion is not unexpected, since cimetidine enters the central nervous system poorly (25) and thus may affect peripheral androgen receptor binding in a preferential fashion. Such a selective peripheral antagonism of androgen action without secondary gonadotropin hypersecretion could also explain the failure to demonstrate an increase in serum estradiol levels, which is commonly seen in states of congenital androgen insensitivity (31).

In summary, it appears that the only effect of cimetidine on the secretion of reproduction-related hormones is stimulation of prolactin secretion; this occurs only with intravenous administration of the drug. The occurrence of gynecomastia, breast tenderness, or impotence in patients receiving chronic oral cimetidine therapy is not due to diminished concentrations of serum total or free testosterone or to increased serum estradiol. While the pathophysiologic basis remains uncertain, cimetidine-associated impotence and breast changes are more likely to be related to an antagonism of androgen action in peripheral tissues.

ACKNOWLEDGMENTS

The authors wish to thank Inger Pearce and Linda Hagie for collecting the blood samples, and Nancy Meyer, Peggy Peterson, and Carol Madding for assistance in performing the hormone determinations.

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