Prolactin secretion in man following acute and long-term cimetidine administration

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Abstract. In 20 patients with duodenal ulcer we measured serum prolactin levels following acute and long-term cimetidine administration. In addition, in 20 healthy volunteers we studied the effect of pre-treatment with bromocriptine, metergoline, nomifensine and cyproheptadine on cimetidine-induced prolactin release. Intravenous cimetidine stimulated prolactin secretion in patients and in normal subjects. In the latter, bromocriptine and metergoline pre-administration blunted the release of prolactin in response to iv cimetidine whereas nomifensine and cyproheptadine were ineffective. Long-term treatment with cimetidine (1.2 g daily for 3 months) had no effect on prolactin secretion in the 20 patients studied. No incidence of gynaecomastia, galactorrhoea or disorders of the menstrual cycle was observed.

It has been shown that cimetidine, an H2 receptor blocking agent, releases prolactin in man (Carlson & Ippoliti 1977; Bohnet et al. 1978). Moreover, side effects such as gynaecomastia and galactorrhoea have been reported in patients treated with the drug (Hall 1976; Delle Fave et al. 1977; Bateson et al. 1977).

We studied the effects of both acute and chronic cimetidine treatment on serum prolactin levels in 20 patients with duodenal ulcers. Additional studies were carried out on 20 normal subjects in order to elucidate the mechanism(s) responsible for cimetidine-induced prolactin secretion.

Materials and Methods

Studies were performed on 20 healthy volunteers, medical students and technicians, aged 19 to 36 years and 20 patients with duodenal ulcer, aged 23 to 38 years. In each group 50 per cent were male. All the patients had an endoscopic diagnosis of duodenal ulcer requiring treatment with cimetidine. An informed consent was obtained prior to the study. The experiments started at 08.00 h after an overnight fast with the subjects in a recumbent position. A venous cannula was inserted in a forearm vein at least 45 min prior to beginning the study; patency was maintained by a slow infusion of normal saline. After collection of three baseline samples (−30, −15 and 0 min) all subjects received an iv bolus of 200 mg cimetidine (Tagamet®, Smith Kline & French, Milan, Italy). Blood was collected 15, 30, 60 and 120 min later. In the volunteers, cimetidine administration was repeated 60 min after giving the following drugs: bromocriptine (2.5 mg p.o.), metergoline (2 mg p.o.), nomifensine (200 mg p.o.) and cyproheptadine (8 mg p.o.). A 3 day interval elapsed between each test which was performed exactly as described above. The patients were treated with cimetidine, 400 mg p.o., t.i.d. for 3 months. Blood samples were obtained weekly from each patient, at 08.00 h, prior to the administration of the first daily dose.

Blood samples for hormone assay were centrifuged and serum specimens stored at −20°C until assayed. All samples from each subject were processed in duplicate in the same assay. Prolactin release was measured by a specific double-antibody radioimmunoassay (McNeill 1973). Standard, antiserum and 125I-labelled human prolactin were obtained by Biodata, Milan, Italy. One ng Biodata antigen corresponds to 23 μU WHO 71/222. The method is sensitive to about 1 ng/ml. Intra- and inter-
assay variations were 3% and 7%, respectively. The results are reported in ng/ml. In our laboratory fasting prolactin levels in normal male and female subjects were found to be less than 10 ng/ml and 22 ng/ml, respectively. All the results are reported as means ± SEM. The two-tailed, paired and unpaired Student's t-tests were used for a statistical analysis of the data.

Results

The results are reported in Fig. 1 and Table 1.

Under control conditions serum prolactin levels measured in male and female volunteers were not significantly different from those observed in patients. Cimetidine injection induced a prompt, significant increase of prolactin in all the subjects studied. Serum prolactin, which had risen significantly above baseline 15 (P < 0.01) and 30 (P < 0.01) min following cimetidine administration, had returned to near baseline values at time +60 min. The prolactin response to iv cimetidine was greater in female than male subjects. No difference was observed between patients and controls in the prolactin response to cimetidine (P > 0.05).

In normal subjects, pre-treatment with bromocriptine and metergoline completely suppressed the cimetidine-induced prolactin release, the differences between values recorded under control

![Graph](image)

**Fig. 1.**

Serum prolactin behaviour in responses to iv cimetidine (200 mg) in male (filled circles) and female (open circles) volunteers and patients with duodenal ulcer. Means ± SEM are reported. Asterisks: (P < 0.01) with respect to values at time 0.

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Table 1.

Effect of pre-treatment with bromocriptine, metergoline, nomifensine and cyproheptadine on serum prolactin response to iv cimetidine in 10 male and 10 female volunteers. Average baseline values and peak values are reported. See Methods for full details on the experimental protocol.

<table>
<thead>
<tr>
<th></th>
<th>Serum Prolactin (ng/ml)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Peak</td>
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<tr>
<td><strong>Bromocriptine</strong></td>
<td></td>
<td></td>
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<tr>
<td>Males</td>
<td>mean 3.31 SEM 0.26</td>
<td>4.13 SEM 0.79</td>
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<tr>
<td>Females</td>
<td>mean 5.38 SEM 1.16</td>
<td>6.49 SEM 1.33</td>
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<tr>
<td><strong>Metergoline</strong></td>
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<td></td>
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<tr>
<td>Males</td>
<td>mean 4.45 SEM 1.10</td>
<td>6.06 SEM 1.45</td>
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<tr>
<td>Females</td>
<td>mean 6.26 SEM 1.30</td>
<td>8.11 SEM 2.07</td>
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<tr>
<td><strong>Nomifensine</strong></td>
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<td></td>
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<tr>
<td>Males</td>
<td>mean 6.03 SEM 0.90</td>
<td>11.67 SEM 3.06</td>
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<tr>
<td>Females</td>
<td>mean 8.21 SEM 1.79</td>
<td>20.45 SEM 3.56</td>
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<td><strong>Cyproheptadine</strong></td>
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<tr>
<td>Males</td>
<td>mean 6.78 SEM 0.87</td>
<td>15.23 SEM 2.06</td>
</tr>
<tr>
<td>Females</td>
<td>mean 11.18 SEM 2.20</td>
<td>23.95 SEM 2.50</td>
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conditions and following pre-treatment with bromocriptine and metergoline being highly significant \( (P < 0.01) \) for either agent. Conversely, the reduction induced by nomifensine was not statistically significant \( (P > 0.05) \). Administration of the antiserotonin agent cyproheptadine, either as a single 8 mg oral dose or at a daily dose of 16 mg for three days (data not reported here) had no effect on the prolactin response to cimetidine. In the patients with duodenal ulcer, chronic treatment with cimetidine had no appreciable effect on prolactin. Male patients had an average basal prolactin level of 6.71 ± 0.76 ng/ml. This was not statistically different from the values observed after 30, 60 and 90 days of treatment: 7.03 ± 1.23, 6.98 ± 0.96, 6.84 ± 1.13 ng/ml, respectively. Female patients had an average basal prolactin level of 10.37 ± 1.25 ng/ml. Values following 30, 60 and 90 days of treatment were 11.76 ± 2.13, 11.03 ± 1.45 and 10.38 ± 1.31 ng/ml, respectively \( (P > 0.05) \).

Both acute and long-term treatment with cimetidine were free from side effects. In no instance were gynaecomastia, galactorrhoea or disorders of the menstrual cycle observed in any of the patients.

**Discussion**

The present data confirm that cimetidine does release prolactin when given iv to male and female subjects. On the contrary, we were unable to demonstrate any significant change in serum prolactin levels in the 20 patients given oral cimetidine for 3 months to treat their duodenal ulcers. The finding of normal prolactin levels in patients receiving oral cimetidine is consistent with previously reported data (Majumdar et al. 1978; Spiegel et al. 1978). However, elevated prolactin levels have been found by other investigators under the same experimental conditions (Delle Fave et al. 1977; Bateson et al. 1977). I have been shown that an iv bolus of cimetidine is able to trigger comparable prolactin responses before and after its chronic oral administration (Bohn et al. 1978). Therefore, the failure of chronic oral cimetidine to stimulate prolactin secretion is presumably not due to an organismic adaptation to the agent. This confirms the hypothesis that cimetidine-induced prolactin release is dose-related. When given orally, the drug cannot reach blood levels sufficient to trigger prolactin secretion (Burland et al. 1979).

As for the mechanism of cimetidine-induced prolactin secretion, previous reports have suggested that this may be due to an effect on H2 central receptors (Carlson & Ippoliti 1977). In agreement with this interpretation, both histamine and the H2 antihistamine drug metiamide have been shown to be able to interfere with prolactin secretion in the rat (Libertun & McCann 1976; Arakelian & Libertun 1977). Data obtained in man have shown that the administration of dopaminergic agents can inhibit prolactin secretion induced by cimetidine (Bohn et al. 1978; Burland et al. 1979). The present data confirm this finding since pre-treatment with bromocriptine and metergoline, a drug that lowers prolactin presumably by its dopaminergic action (Delitala et al. 1977; Müller et al. 1977), completely inhibited prolactin secretion. In addition, we have previously obtained identical results following the administration of the highly specific dopaminergic agent apomorphine (Masala et al. 1979). These data indicate that the dopaminergic system is involved in the release of prolactin induced by cimetidine. However, since the DA pathway is the main inhibitory system controlling prolactin release (MacLeod & Lehmeyer 1974), it is possible that stimulation of dopaminergic receptors may specifically compete with the releasing stimulus produced by cimetidine. The lack of effect of nomifensine is difficult to explain since this inhibitor of endogenous DA re-uptake (Hunt et al. 1974; Schacht et al. 1977) reaches maximum blood levels within an hour after oral administration (Chamberlain & Hill 1977) and can inhibit prolactin secretion in normal subjects and in patients with hyperprolactinaemia (Müller et al. 1978; Masala et al., in press). However, it may be that bromocriptine and metergoline inhibit the prolactin-releasing action of cimetidine by acting directly at the pituitary level, a site of action that is not shared by nomifensine (Schacht et al. 1977). This explanation is consistent with reports demonstrating that nomifensine does not blunt the prolactin release in response to synthetic TRH which acts directly on pituitary lactotropes (Scanlon et al. 1977). The failure of cyproheptadine to interfere with prolactin secretion confirms previous data (Delitala et al. 1975; Ferrari et al. 1976) and indicates that a serotoninergic pathway does not participate in the release of prolactin in response to cimetidine. The present study demonstrates that long-term treatment with cimetidine, at the dosage schedule employed, had no effect on prolactin secretion in man. Presumably, this does not represent the me-

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mechanism responsible for the onset of gynaecomastia and galactorrhoea. As a possibility, it should be mentioned that recent reports attribute an antiandrogenic effect to cimetidine in rats that could be responsible for the side effects in question (Winters et al. 1979). The safety of long-term treatment with cimetidine in humans needs further investigation.

References


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