The effect of oral cimetidine on the basal and stimulated values of prolactin, thyroid stimulating hormone, follicle stimulating hormone and luteinizing hormone

G. F. NELIS
M.D.

J. G. C. VAN DE MEENE
Ph.D.

*Department of Medicine and Chemical Pathology
Sophia-Ziekenhuis, Zwolle, The Netherlands*

Summary

The effect of cimetidine on the basal values of PRL, TSH, FSH and LH and on the TRH/LHRH-stimulated values of these hormones was investigated in patients with peptic ulcer. No difference was found between the values before, during or after cimetidine maintenance treatment. To evaluate whether a rise in PRL occurs during the early phase of cimetidine treatment, daily estimations were made of basal PRL values during the first week of cimetidine administration in volunteers. No significant difference was found. It is concluded that oral cimetidine treatment has no influence on the basal and stimulated values of PRL, TSH, FSH and LH.

Introduction

Cimetidine is one of the successes of this decade. Its potency to lower basal and stimulated gastric acid output had been documented; it presents an effective treatment for peptic ulcer, peptic oesophagitis and the Zollinger-Ellison syndrome and it has deepened our understanding of gastric physiology and pathophysiology.

The drug has been reported as safe and, apart from minor subjective complaints and minor elevations of serum creatinine, most of which are transient, no definitive side effects have been documented (Burland and Simkins, 1977).

Hall (1976) drew attention to the development of gynaecomastia in 2 male patients during cimetidine treatment, while Delle Fave *et al.* (1977) reported on elevated plasma prolactin concentrations in all of 7 patients on oral cimetidine maintenance treatment. At the time that the present investigations were started, the only definite study on cimetidine and prolactin reported a significant increase in plasma prolactin concentration after acute intravenous administration of cimetidine (Carlson and Ippoliti, 1977). Since then, several reports have been published in which no increase after single dose or maintenance dosage of oral cimetidine was found (Rowley-Jones, 1978; Spiegel *et al.*, 1978; Valcavi *et al.*, 1978),

while the significant rise after i.v. administration was confirmed (Cavallini *et al.*, 1978; Daubresse, Meunier and Ligny, 1978; Rowley-Jones, 1978).

The aim of this study was to investigate whether oral cimetidine treatment has an effect on the basal levels of prolactin (PRL), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) or on the response after stimulation with the releasing hormones thyrotropin (TRH) and luteinizing hormone-releasing hormone (LHRH).

Methods

Design of the study

Thirteen male patients with duodenal and/or gastric ulcer entered the study. Active peptic ulceration was proved by endoscopy in all patients, most of whom had had a barium meal.

In all patients with gastric ulcer repeat endoscopy was performed, but in patients with duodenal ulcer only if considered necessary. All patients were prescribed oral cimetidine 1000 mg daily (3 times 200 mg at meals and 400 mg at bedtime) from day 1 to day 28 inclusively. Endoscopy was performed on day -1 or -3. Tests were performed on day 0, 28 and 56; plasma levels of PRL, TSH, FSH and LH were measured before stimulation and 10, 20, 60 and 90 min after stimulation with 200 µg TRH and 150 µg LHRH intravenously.

Fifteen male volunteers were studied according to another protocol; the reason for this study will be discussed below. The volunteers took cimetidine orally 1000 mg for 7 days; administration of the drug started on day 1 at 1 p.m. Blood samples for PRL were withdrawn on days 1, 2, 3, 4, 5, 8 and 15 between 11 a.m. and 1 p.m.

Reasons for exclusion of patients and volunteers were: pregnancy, lactation, use of hormone-containing drugs (including oral contraceptives), Zollinger-Ellison syndrome, disorders or past surgery of hypothalamus, pituitary, thyroid gland or gonads,

use of drugs known to be associated with hyperprolactinaemia (Lamberts, Klijn and Brikenhäger, 1978). On account of these criteria one patient with choriocarcinoma of the testis was accepted for the TSH study only.

All patients and volunteers gave informed consent and the study was conducted in accordance with the Declaration of Helsinki.

Analysis

All blood samples in volunteers were taken between 11 a.m. and 1 p.m., all stimulation tests in patients started between 11 a.m. and noon. Sera were separated and stored at -20°C until assay. All samples from the volunteers were run in the same assay, as were all samples from a given patient.

Serum PRL, TSH, FSH and LH were estimated by radio-immuno-assay using CEA-IRE-SORIN (CIS) kits (Fleurus, Belgium) and corresponding to the following standards: MRC 71/222 (PRL), MRC 68/38 (TSH), MRC 69/104 (FSH) and MRC 68/40 (LH). PRL and TSH were expressed as $\mu\text{u./ml}$, FSH as $\mu\text{g/l}$ (one $\mu\text{g/l}=4\text{ u./l}$) and LH as $\mu\text{g/l}$ (one $\mu\text{g/l}=3\text{ u./l}$).

For statistical evaluation, Student's *t*-test for paired observations was used.

Results

The results are presented in Table 1–5. The basal and stimulated values of PRL, TSH, FSH and LH before, during and after cimetidine were compared, each patient serving as his own control. The values of any of the hormones at any time after stimulation during (day 28) or after cimetidine treatment (day 56) were not significantly different from those before cimetidine (Tables 1–4).

The only exception concerns FSH. FSH blood levels at 10 min after stimulation with LHRH were slightly but significantly higher at day 56 (3.38 ± 0.47) than at day 1 (3.00 ± 0.36) and day 28 (2.87 ± 0.40).

In the volunteers no statistically significant difference was found between the PRL values on any day.

Discussion

Prolactin shows a sleep-related circadian rhythm with one or more peaks between 2 and 5 a.m.

TABLE 1. PRL blood levels ($\mu\text{u./ml}$) ($\bar{x}$ s.e. mean) (at 0, 10, 20, 60, and 90 min) after TRH i.v. in patients with peptic ulcer ($n=12$) before, during and after cimetidine

<i>t</i> (min)	0	10	20	60	90
Before (day 1)	296.8 (22.6)	1201.1 (187.6)	1247.1 (236.9)	663.3 (76.4)	495.7 (40.2)
During (day 28)	273.5 (36.1)	1080.0 (108.0)	1089.6 (108.7)	615.4 (49.5)	417.3 (46.7)
After (day 56)	261.4 (32.4)	969.6 (97.9)	1015.8 (112.1)	613.8 (60.5)	434.5 (47.1)

TABLE 2. TSH blood levels ($\mu\text{u./ml}$) ($\bar{x}$ s.e. mean) (at 0, 10, 20, 60, and 90 min) after TRH i.v. in patients with peptic ulcer ($n=13$) before, during and after cimetidine

<i>t</i> (min)	0	10	20	60	90
Before (day 1)	5.87 (0.31)	10.38 (0.82)	12.99 (1.20)	10.02 (0.78)	8.41 (0.62)
During (day 28)	6.35 (0.37)	10.24 (0.89)	12.45 (1.09)	9.99 (0.84)	8.28 (0.56)
After (day 56)	6.59 (0.39)	12.53 (1.25)	13.20 (1.30)	10.71 (1.08)	9.04 (0.83)

TABLE 3. FSH blood levels ($\mu\text{g/l}$) ($\bar{x}$ s.e. mean) after LHRH i.v. in patients with peptic ulcer ($n=12$) before, during and after cimetidine

<i>t</i> (min)	0	10	20	60	90
Before cim. (day 1)	2.39 (0.29)	3.00 (0.36)	3.88 (0.49)	4.35 (0.52)	4.20 (0.50)
During cim. (day 28)	2.35 (0.29)	2.87 (0.40)	3.61 (0.54)	4.33 (0.69)	4.28 (0.73)
After cim. (day 56)	2.63 (0.33)	3.38 (0.47)	4.36 (0.66)	4.73 (0.74)	0.44 (0.68)

TABLE 4. LH blood levels ($\mu\text{g/l}$) ($\bar{x}$ s.e. mean) after LHRH i.v. in patients with peptic ulcer ($n=12$) before, during and after cimetidine

<i>t</i> (min)	0	10	20	60	90
Before cim. (day 1)	2.24 (0.16)	6.81 (0.66)	10.22 (1.14)	10.18 (1.17)	8.21 (0.98)
During cim. (day 28)	2.18 (0.17)	6.63 (0.65)	10.19 (1.38)	10.56 (1.54)	8.63 (0.97)
After cim. (day 56)	2.56 (0.20)	7.34 (0.68)	11.70 (1.42)	11.00 (1.34)	8.82 (0.92)

TABLE 5. PRL blood levels ($\mu\text{u./ml}$) in volunteers on cimetidine

	Cimetidine						
	Before	During					After
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15
$\bar{x}$	384.4	350.5	360.7	323.9	417.9	320.0	339.2
s.e. mean	73.7	67.4	64.8	58.8	94.9	90.2	78.1
n	15	14	14	15	12	14	12

(Parker, Rossmas and Van der Laan, 1973); a stabilization for several hours occurs after 10 a.m. (Finkelstein *et al.*, 1978). These observations made the authors perform their studies between 11 a.m. and 1 p.m. The maximal PRL values in response to TRH i.v. are seen after 10–20 min, the maximal TSH values after 20 min (Jacobs *et al.*, 1971); the maximal PRL response is obtained with a TRH dose between 100 and 400 μg and the authors' standard dose for testing in thyroid disease is 200 μg . Therefore they chose one of 200 μg TRH with sampling times after 10 and 20 min.

This study showed that oral cimetidine treatment does not influence the basal and stimulated values of PRL, TSH, FSH and LH after TRH and LHRH i.v. The fact that the values were not different at any moment after stimulation suggests that neither the initial nor the delayed response changed during and after cimetidine. Comparison with earlier results concerning the stimulated values of PRL, TSH, FSH and LH is not possible as the authors are not aware of any similar studies reported previously. Comparison of their basal values of PRL with those obtained by other workers after single dose or maintenance cimetidine treatment are in accordance with the reported results (Rowley-Jones, 1978; Spiegel *et al.*, 1978; Valcavi *et al.*, 1978). The rise in PRL after oral cimetidine reported by Delle Fave *et al.* (1977) remains unconfirmed and is not explained by the higher dose or prolonged administration, for the present authors did not find any rise in PRL on the 1600 mg regimen during 8 weeks in patients with oesophagitis. Whether there is a bias by the circadian rhythm of PRL secretion in Delle Fave's (1977) results remains speculative.

After having obtained the first results, the authors could not exclude the possibility of their having missed a peak in PRL during the initial stage of treatment. Because all the patients were treated on an out-patient basis and daily return to the laboratory was hardly possible, the authors studied the short-time effect on basal PRL values in healthy volunteers and failed to show any effect of cimetidine. The higher FSH blood level at 10 min after stimulation at day 56 (4 weeks after stopping cimetidine treatment) was probably a chance happening. With a 5% confidence

limit 2 abnormal results were to be expected in the total of 40 comparisons made.

The high PRL level after i.v. administration of cimetidine ($1480 \mu\text{u./ml} \pm 112.3$ s.e. mean in 8 patients) was in accord with other workers (Carlson and Ippoliti, 1977; Cavallini *et al.*, 1978; Daubresse *et al.*, 1978; Rowley-Jones, 1978).

It seems likely that the animal study of Arakelian and Libertun (1977), on H1 and H2 histamine receptor participation in the brain control of PRL secretion in lactating rats, presents the link between i.v. cimetidine and hyperprolactinaemia. Although interesting from the physiological point of view, there do not seem to be any major clinical consequences to these observations.

During the final preparation of this manuscript Funder and Mercer (1979) presented experimental evidence suggesting competitive binding of cimetidine to androgen receptors which might supply some explanation for cimetidine-associated gynaecomastia.

Acknowledgments

We kindly acknowledge the technical assistance by Miss N. Holtslag and the helpful criticism of the manuscript by Professor H. Doorenbos and Dr W.D. Reitsma (Department of Medicine, State University, Groningen, The Netherlands).

References

- ARAKELIAN, M.C. & LIBERTUN, C. (1977) H1 and H2 histamine receptor participation in the brain control of prolactin secretion in lactating rats. *Endocrinology*, **100**, 890.
- BURLAND, W.L. & SIMKINS, M.A. (1977) In: *Proceedings of the Second International Symposium on Histamine H2-receptor Antagonists*. Excerpta Medica, Amsterdam.
- CARLSON, H.E. & IPPOLITI, A.F. (1977) Cimetidine, an H2-antihistamine, stimulates prolactin secretion in man. *Journal of Clinical Endocrinology and Metabolism*, **45**, 367.
- CAVALLINI, G., LO CASCIO, V., ANGELINI, G., BOVO, P., VAONA, B., ADAMI, S., ZUNIGA, G., GALVANINI, G., MANFRINI, C. & SCURO, A. (1978) Effect of acute and chronic cimetidine administration on human serum prolactin. Abstracts VI World Congress of Gastroenterology, Madrid, 5–9 June 1978, p. 18.
- DAUBRESSE, J.C., MEUNIER, J.C. & LIGNY, G. (1978) Plasma-prolactin and cimetidine. *Lancet*, **i**, 99.
- DELLE FAVE, G.F., TAMBURRANO, G., DE MAGISTRIS, L., NATOLI, C., SANTORO, M.L., CARRATU, R. & TORSOLI, A. (1977) Gynaecomastia with cimetidine. *Lancet*, **i**, 1319.

- FINKELSTEIN, J.W., KAPEN, S., WEITZMAN, E.D., HELLMAN, L. & BOYAR, R.M. (1978) Twenty-four-hour plasma prolactin patterns in prepubertal and adolescent boys. *Journal of Clinical Endocrinology and Metabolism*, **47**, 1123.
- FUNDER, J.W. & MERCER, J.E. (1979). Cimetidine, a histamine H₂ receptor antagonist, occupies androgen receptors. *Journal of Clinical Endocrinology and Metabolism*, **48**, 189.
- HALL, W.H. (1976) Breast changes in males on cimetidine. *New England Journal of Medicine*, **295**, 841.
- JACOBS, L.S., SNIJDER, P.J., WILBER, J.F., UTIGER, R.D. & DAUGHADAY, W.H. (1971) Increased serum prolactin after administration of synthetic thyrotropin releasing hormone (TRH) in man. *Journal of Clinical Endocrinology and Metabolism*, **33**, 996.
- JACOBS, L.S., SNIJDER, P.J., UTIGER, R.D. & DAUGHADAY, W.H. (1973) Prolactin response to thyrotropin-releasing hormone in normal subjects. *Journal of Clinical Endocrinology and Metabolism*, **36**, 1069.
- LAMBERTS, S.W.J., KLIJN, J.G.M. & BRIKENHÄGER, J.C. (1978) Prolactine. *Nederlands Tijdschrift voor Geneeskunde*, **122**, 1327.
- PARKER, D.C., ROSSMA, L.G. & VANDERLAAN, E.F. (1973) Sleep-related nyctohemeral and briefly episodic variation in human plasma prolactin concentration. *Journal of Clinical Endocrinology and Metabolism*, **36**, 1119.
- ROWLEY-JONES, D. (1978) Cimetidine and serum-prolactin. *Lancet*, **ii**, 635.
- SPIEGEL, A.M., LOPATIN, R., PEIKIN, S. & MCCARTHY, D. (1978) Serum-prolactin in patients receiving chronic oral cimetidine. *Lancet*, **i**, 881.
- VALCAVI, R., BEDOGNI, G., DALL'ASTA, A., DOTTI, C. & PORTIOLI, I. (1978) Single oral dose of cimetidine and prolactin. *Lancet*, **ii**, 528.