Effect of Cimetidine on Prolactin Secretion in Normal Controls and Hyperthyroid Patients

KEIICHI KAMIJO¹, AKIMITSU SAITO¹, TERUO KATO¹, KIMIO KAWASAKI¹, MITSUAKI SUZUKI¹, TSUYOSHI YABANA¹, AKIRA YACHI¹ and TAKEO WADA²

¹First Department of Internal Medicine and ²President, Sapporo Medical College, Sapporo 060

Abstract

Nine healthy female controls and 10 hyperthyroid female patients were studied. The intravenous administration of 200 mg cimetidine, an H₂-receptor antagonist, was followed by a significant and marked rise in serum prolactin levels in all control subjects. There was no significant difference in serum PRL response to cimetidine injection between the euthyroid controls and hyperthyroid patients. But max ΔPRL, the change from basal to peak values, is significantly lower in the hyperthyroid patients than in the controls. There was a significant negative correlation between max ΔPRL and serum T₄ or T₃ levels in hyperthyroid patients before and after treatment with MMI or PTU. It appears from our data that cimetidine induced PRL release was blunted in hyperthyroid patients.

Histamine and histamine-sensitive adenyl cyclase are present in the hypothalamus in high concentrations (Brownstein et al., 1974; Sato et al., 1974). It was suggested by Sato et al. (1974) that one of the biogenic amines, histamine, might play an important role in serving as a neurotransmitter in the medial hypothalamus, although it is not yet established that cyclic AMP is involved as a mediator in the regulation of releasing hormone secretion from the hypothalamus.

It was demonstrated in rats that brain histamine has a dual effect on prolactin (PRL) secretion. H₂ receptors (blocked by metiamide and cimetidine) mediate events related to the inhibition of PRL release and H₁ receptors (blocked by diphenhydramine) seem to be involved in a facilitary mechanism of PRL release (Arakelian et al., 1979). It has been also shown that i.v. cimetidine stimulates PRL secretion in normal controls (Delitala et al., 1979; Eversman et al., 1979; Neil et al., 1980).

In thyrotoxicosis, PRL responses to TRH and chlorpromazine are virtually blunted and also the exogenous administration of thyroid hormones appears to influence PRL response to TRH (Bowers et al., 1973; Yamaji et al., 1974; Onishi et al., 1975).

The present study was undertaken to assess the relationship between cimetidine induced PRL release and thyroid states.

Materials and Methods

Nine healthy female euthyroid volunteers (aged 21–28 years) and ten hyperthyroid women patients (aged 21–35 years) were studied.

After overnight fasting, the volunteers and hyperthyroid patients before and after treatment with methimazol (MMI) or propylthiouracil (PTU) were allocated to receive an i.v. bolus injection of 200 mg cimetidine at 9 a.m.

Blood samples for PRL assay were taken at 0, 30, 60 and 90 min after cimetidine administration. Serum PRL was measured by the radioimmunoassay, as
reported previously (Kamijo et al., 1971).

Serum triiodothyronine and thyroxine were also measured by the radioimmunoassay using a Dainabot kit. The sensitivities of T₃ and T₄ assay were 12.5 ng/ml and 3 μg/dl, respectively. Intra- and interassay coefficients of variants in T₃ assay were 5.3 and 8.9%, while in T₄ assay they were 7.0 and 4.5%, respectively.

Statistical analysis was performed using the Student's test for paired and nonpaired data. The results were expressed as a mean±SEM.

Results

A) *The Euthyroid Group* (Fig. 1 and 2)

The mean (±SEM) PRL levels at 0 time and 30, 60 and 90 min after bolus injection of cimetidine in normal females were 6.5±0.8, 25.2±3.9 (significant from basal levels, p<0.001), 13.2±2.8 (p<0.02) and 8.2±1.1 (p<0.05), respectively. Intravenous cimetidine injection was followed by a significant and marked rise in serum prolactin levels in all subjects, as shown in Fig. 1.

B) *The Hyperthyroid Group*

Basal PRL levels in the hyperthyroid group, 11.7±1.9 ng/ml, were slightly but significantly (p<0.05) higher than those in the euthyroid group. Following cimetidine, serum PRL levels rose to 18.5±3.9 (p<0.02). There was no significant difference in serum PRL response to cimetidine injection between the euthyroid and hyperthyroid group, as shown in Fig. 2. But max ΔPRL, the change from basal to peak values, is significantly lower in the hyperthyroid group than in the euthyroid group (Fig. 3).

There was a significant negative correlation between max ΔPRL and serum T₄ levels (Fig. 4) or T₃ levels (Fig. 5) in hyperthyroid patients before and after treatment with MMI or PTU.

Discussion

The present study confirmed the fact that intravenous administration of cimetidine induced a marked and significant increase in serum prolactin concentration in healthy subjects, while in hyperthyroid patients serum PRL response to cimetidine injection was blunted.

It was reported by Marcon et al. (1979) that unlike the TRH-mediated PRL release, cimetidine-induced PRL release is independent...
of thyroid hormone levels. This conclusion differs from our data. In our results, although there was also no statistically significant difference in serum PRL response to cimetidine between the euthyroid and hyperthyroid group, max ΔPRL is significantly decreased in the hyperthyroid group compared with the normal controls.

Delitala and his coworkers (1979) reported that cimetidine induced PRL release is dose-related and 200 mg cimetidine is the minimum dose which induces a definite PRL release when given in an intravenous bolus injection. For this reason we used 200 mg cimetidine

Fig. 2. Changes in serum PRL levels (ng/ml) before and after bolus injection of cimetidine in normal controls (○--○) and hyperthyroid patients (●--●).
while Macaron et al. (1979) used 300 mg cimetidine.

It is known that cimetidine does not readily cross the blood-brain barrier (Cross et al., 1977). The drug may, however, penetrate into the brain when high blood concentrations are attained, as observed by bolus injection but not by oral administration (Burland et al., 1979). Such a mechanism might be involved in the lack of prolactin-secreting activity in orally administered or infused cimetidine. (Burland et al., 1979; Delitala et al., 1979).

The serum PRL response to cimetidine was abolished by dopamine infusion and almost completely suppressed by L-DOPA plus carbidopa administration (Ferrari et al., 1979).

In addition, cimetidine, when given by infusion at a dose of 100 mg/h for 5 hr or bolus injection at a dose of 300 mg, did not alter serum PRL response to TRH (Delitala et al., 1979; Carlson et al., 1980). Furthermore, in the pituitary cell culture system histamine as much as 10 mg did not show any effect on prolactin release (River et al., 1977).

These findings suggest that the drug acts on the central nervous system, possibly at the hypothalamic level, to stimulate prolactin release.

It has been demonstrated that the drug does not act on dopamine receptors (Pontiroli et al., 1979).

On the other hand, the findings that thyroxine increased anterior pituitary PRL concentrations without changes in hypothalamic PIF content (Chen et al., 1969) and that basal PRL values are slightly higher in hyperthyroid patients than in normal controls suggest that thyroid hormones may not decrease PRL synthesis and release (Onishi et al., 1975).

It is suggested from our data that thyroid hormones, to some extent, suppress cimetidine induced PRL release. A possible mechanism may lie in changes in H2-receptor concentrations in the hypothalamus or sensitivity of lactotrophes in thyrotoxicosis, although the mechanism involved in hyperthyroid patients remains unclarified at present.

References


