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PROLACTIN RESPONSES TO CIMETIDINE

W.L. BURLAND, R.I. GLEADLE, R.M. LEE & D. ROWLEY-JONES
The Research Institute, Smith Kline & French Laboratories,
Welwyn Garden City, Hertfordshire

G.V. GROOM
Tenovus Institute, University Hospital of Wales,
The Heath, Cardiff, Wales

1 An intravenous injection of cimetidine 400 mg to four healthy male subjects resulted in high blood concentrations of cimetidine and a rapid three-fold increase in serum prolactin.

2 This effect was prevented by pretreatment with bromocriptine.

3 No increase in prolactin followed a single oral dose of cimetidine 800 mg administered to a different group of healthy male subjects. The mean peak blood concentration of cimetidine was < 20% of that achieved with 400 mg i.v.

4 Only isolated reports have been received of gynaecomastia or galactorrhoea occurring during cimetidine treatment. In three of seven cases studied there was associated hyperprolactinaemia. This may be an idiosyncratic response at the lower blood concentration of cimetidine associated with oral therapeutic dose regimens.

Introduction

Gynaecomastia or galactorrhoea has been reported in ten patients during treatment with cimetidine a histamine H_2-receptor antagonist used as treatment for peptic ulceration (Hall, 1976; Bateson, Browning & Maconnachie, 1977; Delle Fave, Tamburrano, de Magistris, Natoli, Santoro, Carratu & Torsoli, 1977; Sharpe & Hawkins, 1977). Serum prolactin was measured in seven of these patients and found to be increased above normal in only three (Hall, 1976; Bateson *et al.*, 1977; Delle Fave *et al.*, 1977; R. Spence, personal communication). Intravenous injection of cimetidine 300 mg caused a two to three-fold rise in serum prolactin in healthy male subjects but did not affect serum TSH, growth hormone, T3 or T4 (Carlson & Ippoliti, 1977). Patients with breast changes had normal circulating concentrations of testosterone, growth hormone, FSH and LH and oestradiol when all or some of these were measured (Hall, 1976; R. Spence, personal communication), as did unaffected duodenal ulcer patients treated with cimetidine 1.6 g/day for six weeks (Sharpe & Hawkins, 1977). Mean serum prolactin was unaltered in duodenal ulcer patients treated with 1 g/day for two months (Petrillo, Prada, Bianchi-Porro, Bevilacqua, Raggi & Norbiato, 1977).

We have investigated the effect of i.v. and orally administered cimetidine on serum prolactin in healthy male subjects. We also measured the resulting blood concentrations of cimetidine and studied the effect of pretreatment with bromocriptine, a dopamine receptor agonist, on the prolactin response to the i.v. injection of cimetidine.

Methods

Four healthy male subjects fasted overnight. At 08.30 h a cannula was inserted into a forearm vein in both arms with the subjects at rest. Sixty minutes later, 30 min after a standard breakfast of cereal, toast, marmalade and coffee, cimetidine 400 mg was administered by rapid i.v. injection. Venous blood samples were taken prior to injection and two and a half, five, 10, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210 and 240 min afterwards for determination of serum prolactin and blood cimetidine concentration. On a second occasion the same subjects took bromocriptine 2.5 mg orally 14 and 2 h prior to the injection of cimetidine.

Another four healthy fasting subjects took cimetidine 800 mg orally at 09.00 h, 30 min after a cannula had been inserted into a forearm vein. Blood samples were taken prior to ingestion of cimetidine and at the time intervals shown in Table 1 for the measurement of both serum prolactin and blood concentrations of cimetidine.

Serum prolactin was determined by radioimmunoassay (Groom, 1977) and blood cimetidine by HPLC (Randolph, Osborne, Walkenstein & Intoccia, 1977).

Results

Mean serum prolactin increased three-fold after an i.v. injection of cimetidine 400 mg (Figure 1). The mean peak concentration occurred at 10 min (at 15 min in one subject) and the mean level had returned to basal values by 75 min (range 60 to 120 min). No changes occurred in serum prolactin in response to an oral dose of cimetidine 800 mg and pretreatment with bromocriptine abolished the prolactin response to i.v. cimetidine. The highest mean blood cimetidine concentrations (± s.e. mean) were observed 2.5 min after i.v. injection, 84.6 ± 7.4 μmol/l after cimetidine alone and 110.4 ± 18.3 μmol/l after cimetidine and bromocriptine (3.9 μmol/l = 1 μg/ml) (Table 1). The blood concentration following cimetidine 800 mg orally increased to a mean peak concentration of 14 μmol/l, 105 to 120 min after administration, maximum concentrations for each subject ranged from 12.9 to 23 μmol/l.

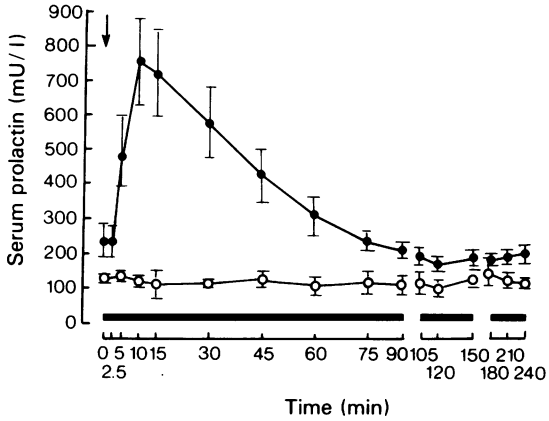

Figure 1 Serum prolactin values (mean ± s.e. mean) in response to oral and i.v. cimetidine (● cimetidine 400 mg i.v.; — cimetidine 400 mg i.v. plus bromocriptine 2.5 mg 2 and 14 h previously; ○ cimetidine 800 mg orally). Cimetidine was given at arrow.

Discussion

Dopamine is considered to be the inhibitor of prolactin release from the anterior pituitary. Administration of some medicines is associated with hyperprolactinaemia. Some, e.g., methyldopa, deplete the hypothalamus of dopamine whereas others, such as phenothiazines and metoclopramide, act as dopamine receptor antagonists. Their administration has also been associated with gynaecomastia, galactorrhoea, impotence etc. (Besser & Thorner, 1977; Martindale, 1977).

Cimetidine does not enter the rat brain after i.v. injection but is rapidly taken up and identifiable in the pituitary in autoradiographic studies (Cross, 1976). The rapid increase in prolactin concentration in response to an i.v. injection of cimetidine reported here and the evidence from autoradiographic studies in the rat may indicate that cimetidine is acting at the dopamine receptor site in the pituitary rather than depleting dopamine stores. The effect only appears to

Table 1 Mean ± s.e. mean blood concentrations of cimetidine (μmol/l)

Time (min)	*Cimetidine 400 mg i.v.*	*Cimetidine 400 mg i.v. + bromocriptine*	*Cimetidine 800 mg orally*
2.5	84.6 ± 7.4	110.4 ± 18.3	—
5	62.0 ± 1.6	70.2 ± 7.8	0
10	47.6 ± 7.0	46.4 ± 5.5	0
15	33.9 ± 6.2	30.4 ± 2.7	1.2 ± 0.4
30	16.4 ± 2.0	19.1 ± 2.0	8.2 ± 2.3
45	11.3 ± 1.6	14.0 ± 1.6	11.7 ± 1.6
60	9.8 ± 1.6	10.9 ± 1.2	11.7 ± 2.3
75	7.8 ± 1.2	10.1 ± 1.2	12.1 ± 2.3
90	6.2 ± 0.8	7.8 ± 1.2	13.7 ± 3.1
105	5.5 ± 0.8	7.0 ± 1.2	14.0 ± 3.5
120	4.7 ± 1.2	5.9 ± 1.2	14.0 ± 3.1
150	3.9 ± 0.8	—	13.3 ± 2.0
180	2.7 ± 0.8	—	13.3 ± 1.6
210	2.7 ± 0.4	—	12.5 ± 2.3
240	2.3 ± 0.8	—	10.1 ± 1.2
360	—	—	5.9 ± 0.8

occur in response to very high concentrations of cimetidine in the blood and not to those achieved with the more conventionally used oral doses of cimetidine. The cimetidine blood concentration achieved after a single 800 mg dose is unlikely to be exceeded during chronic oral administration of cimetidine (Bodemar, Norlander, Fransson & Walan, 1978).

Carlson & Ippoliti (1977) have proposed that cimetidine acts at H_2-receptor sites to cause the rise in prolactin since their *in vitro* studies have indicated a lack of antagonism of the effects of dopamine by cimetidine. Other possibilities are that histamine plays a permissive interacting role at the dopamine receptor site in the pituitary which may be blocked by cimetidine, or that cimetidine at high concentration blocks the uptake of prolactin in peripheral tissues such as the breast, leading to an accumulation in the general circulation.

Since we have shown hyperprolactinaemia only to occur in association with very high blood concentrations of cimetidine, it may be a rare idiosyncratic response at lower concentrations in patients taking conventional oral doses of cimetidine. Further studies are required to confirm the mode and site of action of cimetidine-induced increases in serum prolactin.

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