The Combination Therapy with Bromocriptine and Cyproheptadine in Patients with Acromegaly

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Abstract

The therapeutic efficacy of the combination of cyproheptadine and bromocriptine was studied in 15 patients with active acromegaly showing incomplete GH suppression in response to bromocriptine therapy alone. The mean basal plasma GH was $31.3 \pm 5.5 \mu\text{g/L}$, and it decreased to $19.0 \pm 3.9 \mu\text{g/L}$ during the single bromocriptine therapy (10 to 20 mg for 2 to 21 months). When cyproheptadine (12 to 16 mg for 8 to 52 months) was added to bromocriptine therapy, plasma GH decreased further ($9.4 \pm 3.0 \mu\text{g/L}$: vs pretreatment, $P < 0.001$; vs bromocriptine treatment, $P < 0.005$), and GH normalization was obtained in 8 patients. The plasma somatomedin-C levels in these 8 patients ($0.3\text{--}1.8 \text{ U/ml}$) were within the normal range during the combination therapy. Plasma GH responses to TRH or GHRH were markedly suppressed in 6 patients during the combination therapy compared to pretreatment or during bromocriptine treatment. In addition, a clear reduction in the tumor size was observed in 4 of 7 previously untreated patients during the combination therapy. In conclusion, cyproheptadine has therapeutic efficacy in acromegalic patients who showed incomplete GH suppression in response to treatment with bromocriptine alone. Following the cyproheptadine and bromocriptine combination therapy tumor shrinkage was observed in some patients.

As a medical treatment for acromegaly, bromocriptine has been widely used (Daughaday, 1985; Frohman, 1987).

With this treatment, however, normalization of plasma GH is obtained in only about 20% of cases (Faglia *et al.*, 1985). We have already reported that dopaminergic agents, which can cross the blood brain barrier, might have a dual action on GH

secretion in acromegalic patients; one is a direct somatotroph inhibition and another is a indirect somatotroph stimulation via the CNS (Hanew *et al.*, 1987). Therefore, it seems likely that bromocriptine therapy is not effective in acromegalic patients whose hypothalamic GHRH secretions are stimulated by bromocriptine.

In such cases, the combination of hypothalamic GH suppressants with bromocriptine might be desirable (Hanew *et al.*, 1987).

Cyproheptadine is known to suppress GH secretion in normal and some acromegalic patients (Bivens *et al.*, 1973; Nakai *et al.*, 1974; Smyth and Lazarus, 1974; Nakai *et al.*, 1975; Chihara *et al.*, 1976; Feldman *et al.*, 1976; Dammacco *et al.*, 1977; Hainer *et al.*, 1981; Kato *et al.*, 1983), probably through the central anti-serotonergic actions (Bivens *et al.*, 1973; Nakai *et al.*, 1974; Smyth and Lazarus, 1974; Chihara *et al.*, 1976; Feldmen *et al.*, 1976; Dammacco *et al.*, 1977).

In this study, we have examined the therapeutic efficacy of the cyproheptadine and bromocriptine combination therapy in 15 patients with active acromegaly who did not show GH normalization in response to treatment with bromocriptine alone.

Materials and Methods

Fifteen patients with active acromegaly (8 males and 7 females, aged 23 to 73 yr) were studied (Table 1). These patients had increased plasma GH (8.7–73.4 $\mu\text{g/L}$; normal range $<6 \mu\text{g/L}$).

L), enlarged sella turcica by plain XP, pituitary adenomas by CT scan, and other clinical manifestations of GH excess. Among 15 cases, ten (#2, 3, 5, 6, 9, 11–15) were untreated and the remaining five (#1, 4, 7, 8, 10) were previously treated by an incomplete transsphenoidal adenomectomy. The adrenal and thyroid functions were normal in all cases. These patients received bromocriptine (Sandoz, Basel; 10–20 mg/day, every 6 hrs) for 2 to 21 months, and subsequently combined administration of bromocriptine and cyproheptadine (Banyu, Tokyo; 12–16 mg/day, every 6 hrs) for 8 to 52 months (Table 1). Blood sampling during the treatment was done 3 to 6 hours after the drug ingestion.

Before and during the treatment, TRH (Tanabe, Osaka; 500 μg , iv) and GHRH [GHRH (1–44) NH_2 , Sumitomo, Osaka; 100 μg , iv] tests were performed according to the methods previously reported (Hanew *et al.*, 1980; 1988), and blood samples were obtained at –30, 0 min before and 15, 30, 45, 60, 90, 120 min after the injection of each agent.

Plasma GH, prolactin (PRL), and somatomedin-C (Sm-C) were measured with commercial RIA kits (GH, Dainabot, Tokyo; PRL, Sorin, Gif-sur-Yvette; Sm-C, Nichols Institute, San Juan Capistrano, CA) and the minimal detectable

Table 1. Clinical and laboratory data in 15 patients with acromegaly

Subjects	Sex	Age	Plasma GH ^a (ng/ml)	Plasma PRL ^b (ng/ml)	Bromocriptine		Cyproheptadine ^c		Previous therapy ^d
					dose (mg)	duration (M)	dose (mg)	duration (M)	
1	F	32	8.7	11.5	10	10	12	18	TS
2	F	73	10.2	10.1	10	6	16	10	None
3	F	58	10.3	28.6	10	21	12	12	None
4	F	37	11.9	11.3	10	10	16	15	TS
5	M	55	12.2	5.5	10	4	16	11	None
6	M	57	17.1	5.0	10	16	16	18	None
7	M	26	17.5	12.0	10	4	16	12	TS
8	M	23	28.6	9.2	10	2	16	27	TS
9	M	58	35.0	6.0	20	7	16	37	None
10	F	25	37.0	11.7	20	2	16	37	TS
11	M	36	43.8	5.6	10	2	16	12	None
12	F	62	46.3	14.3	10	4	16	52	None
13	F	72	54.0	13.1	10	10	16	8	None
14	M	33	63.3	5.2	20	4	16	16	None
15	M	43	73.4	6.3	10	12	16	37	None

a, b: Mean value for several basal samples. c: Cyproheptadine was administered with bromocriptine. d: TS, Transsphenoidal pituitary adenomectomy.

levels were 0.2 $\mu\text{g/L}$, 1 $\mu\text{g/L}$, and 0.1 U/ml, respectively (Hanew *et al.*, 1980; 1988).

The pituitary CT-scan was examined before and during the combination therapy of bromocriptine and cyproheptadine. Student's *t*-test was used after log transformation of each datum, if necessary, for statistical evaluations.

Results

I) Plasma GH levels in 15 acromegalic patients before and during treatment with bromocriptine alone or combined treatment with bromocriptine and cyproheptadine.

Following bromocriptine treatment, 6 of 15 cases (40%) showed plasma GH decrease over 50% from the pretreatment values,

although each value was still higher than the normal ranges (6.3–60.5 $\mu\text{g/L}$) (Fig. 1a).

When cyproheptadine was added, plasma GH decreased further and 11 cases (73%) showed a decrease of more than 50% from the pretreatment values and normalization of plasma GH was obtained in 8 cases (# 1–3, 5, 8, 10, 11, 13) (Fig. 1a).

In 15 patients, the mean plasma GH value for the combined bromocriptine and cyproheptadine therapy ($9.4 \pm 3.0 \mu\text{g/L}$) was significantly lower than either that of the single bromocriptine therapy ($19.0 \pm 3.9 \mu\text{g/L}$; $P < 0.005$) or the pretreatment value ($31.3 \pm 5.5 \mu\text{g/L}$, $P < 0.001$) (Fig. 1b). In all 8 patients, who showed GH normalization during the combined treatment, the plasma

Fig. 1. Plasma GH levels in 15 acromegalic patients before and during the medical treatment. a, individual value: b, mean $\pm$ SEM of these values. BC: bromocriptine, Cypro: cyproheptadine

Sm-C level during the treatment was within the normal ranges ($0.3\text{--}1.8\text{ U/ml}$; Mean, $1.2\pm0.2\text{ U/ml}$; normal range $0.7\text{--}2.0\text{ U/ml}$) (Table 2).

Cyproheptadine administration was discontinued in two patients (#1 & 5). Their plasma GH rose to the level of the single

bromocriptine therapy, and fell again after the recommencement of cyproheptadine administration (Fig. 2). Plasma GH levels in one patient (#8) remained in the low normal ranges and the response to TRH disappeared (data not shown) even after the cessation of both agents, and this patient was considered to be cured completely (Fig. 2).

The levels of plasma PRL during the single bromocriptine treatment ($3.9\pm0.4\text{ }\mu\text{g/L}$) and the combined treatment ($2.8\pm0.3\text{ }\mu\text{g/L}$) were significantly lower than the pretreatment level ($10.4\pm1.5\text{ }\mu\text{g/L}$) (both $P<0.001$), and the value during the combined treatment was also slightly lower than for single bromocriptine treatment ($P<0.05$) (individual data not shown).

Fig. 2. Plasma GH profile in three patients (#1, 5, 8) before and during the bromocriptine and/or cyproheptadine therapy.

2) Plasma GH responses to TRH and GHRH in acromegalic patients before and during the single bromocriptine and the combined bromocriptine and cyproheptadine treatment.

Six of 15 patients received TRH (#3, 5, 6, 8, 11, 12) and GHRH tests (#2, 3, 5, 6, 11, 12) before and during the treatments. All patients except two (#6, 12) were the cases who showed GH normalization in response to the combination therapy (see Fig. 1a). After TRH injection, plasma GH increased markedly (peak=15 min, $322.2\pm100.7\text{ }\mu\text{g/L}$) before treatment, and the response was blunted modestly during the single bromocriptine treatment (peak=15 min, $161.2\pm63.6\text{ }\mu\text{g/L}$; $P=\text{NS}$) (Fig. 3a). After the addition of cyproheptadine, the GH response was further suppressed (pretreatment vs combined treatment, 15 min, 322.2 ± 100.7 vs 48.6 ± 18.3 , $P<0.02$;

Table 2. Plasma Sm-C values (U/ml) before and during the bromocriptine (BC) and cyproheptadine (Cypro) therapy in 8 GH normalized patients with combination therapy

Subjects	Before	BC	BC+Cypro
1	3.9	2.8	1.8
2	3.0	1.6	1.2
3	2.2	2.2	1.4
5	2.8	2.7	0.9
8	—	—	0.3
10	—	—	1.2
11	2.7	2.1	1.2
13	3.4	—	1.4

30 min, 316.8 ± 126.1 vs 47.5 ± 21.2 , $P < 0.05$; 60 min, 173.0 ± 77.6 vs 32.3 ± 18.8 $\mu\text{g/L}$, $P < 0.05$) (Fig. 3a).

Plasma GH response to GHRH was also slightly suppressed by the single bromocriptine therapy compared to the pretreatment response ($P = \text{NS}$). The response was marked-

ly suppressed by the addition of cyproheptadine (pretreatment vs combined treatment: 15 min, 62.4 ± 24.0 vs 15.5 ± 7.1 ; 30 min, 59.1 ± 20.7 vs 16.6 ± 7.0 ; 45 min, 61.1 ± 17.8 vs 17.7 ± 6.5 ; 60 min, 59.2 ± 15.4 vs 18.4 ± 6.0 ; 90 min, 53.5 ± 12.8 vs 16.1 ± 3.8 ; 120 min, 47.9 ± 14.5 vs 15.4 ± 3.6 $\mu\text{g/L}$, all $P < 0.05$) (Fig. 3b).

3) Pituitary adenoma size before and during the bromocriptine and cyproheptadine therapy in previously untreated acromegalic patients.

Seven acromegalic patients, who were previously untreated, received a pituitary CT-scan before treatment and during the bromocriptine and cyproheptadine treatment. The CT-scan during the combination therapy was performed 8 to 44 months after the start of the therapy. Four of seven patients showed a reduction in the tumor size (maximal height) exceeding the

Fig. 3. Plasma GH responses to TRH (a) and GHRH (b) in 6 acromegalic patients before and during the single bromocriptine (BC) or the combined bromocriptine and cyproheptadine treatment (BC+Cypro). vs pretreatment: *1, $P < 0.05$; *2, $P < 0.02$; *3, $P < 0.01$; *4, $P < 0.005$

Patient 13

Patient 11

Fig. 4. Pituitary CT-scanning in two patients before (a) and during (b) the combination therapy with bromocriptine and cyproheptadine. The marked and moderate shrinkages of the pituitary adenoma are observed in patient 11 (upper) and patient 13 (lower), respectively.

CT slice width (1.5–3 mm) (Table 3). CT changes in most representative cases (# 11, 13) are shown in Fig. 4.

Table 3. Adenoma size before and during the bromocriptine and cyproheptadine therapy in previously untreated acromegalic patients

Subjects	Adenoma Size (mm) ^a		
	Before	During (months) ^b	
3	12.3	9.9	(8)
5	7.0	2.5	(24)
9	15.3	15.3	(41)
11	16.5	11.2	(16)
12	14.1	13.3	(44)
13	16.7	11.8	(9)
14	16.8	16.7	(13)

a: Maximal height of the adenoma.

b: Duration of the combination therapy.

Discussion

In this study, eight out of 15 acromegalic patients, in whom GH normalization was not achieved with bromocriptine therapy alone, showed GH normalization after the combination therapy with bromocriptine and cyproheptadine. Plasma GH responses to TRH or GHRH were also significantly inhibited in these patients, and a clear reduction in the tumor size was observed in 4 of 7 patients, whereas consistent results have not yet been obtained regarding the effect of single bromocriptine therapy on tumor size in acromegalic patients (Faglia *et al.*, 1985, Besser and Wass, 1987).

Although bromocriptine is known to inhibit GH secretion in acromegalic patients by its direct action on the pituitary adenoma (Molinatti *et al.*, 1984), the possibility of simultaneous GH stimulation via the hypothalamus has been proposed by us (Hanew *et al.*, 1987) and Camanni *et al.* (1977). Cyproheptadine is reported to inhibit sleep-induced GH secretion and GH responses to several exogenous stimuli, which probably mediate the stimulation of

hypothalamic GHRH or the inhibition of hypothalamic somatostatin release in normal subjects (Bivens *et al.*, 1973; Nakai *et al.*, 1975; Smyth *et al.*, 1974; Nakai *et al.*, 1975; Chihara *et al.*, 1976; Dammacco *et al.*, 1977; Hainer *et al.*, 1981; Alba-Roth *et al.*, 1988). Cyproheptadine has anti-serotonergic, anti-histaminergic and weak anti-cholinergic actions (Williams and Martin, 1982). The GH inhibitory action of the cyproheptadine might be due to the anti-serotonergic action, since 5HTP (5-hydroxytryptophan: the precursor of serotonin)-induced GH release is inhibited by pretreatment with cyproheptadine (Nakai *et al.*, 1974). This action might take place at the level of the hypothalamus. However, because plasma GH response to TRH and GHRH was significantly blunted and pituitary tumor size was clearly reduced in 4 of 7 patients during the bromocriptine and cyproheptadine combination therapy, cyproheptadine might have a direct suppressive effect on pituitary adenomas.

Concerning this, Ishibashi *et al.*, (1985) have reported that cyproheptadine inhibited GH secretion from GH secreting tumors in vitro, probably through a non-serotonergic mechanism. In addition to such direct suppressive effects, we should consider the possibility that functional and morphological changes were caused by a chronic suppression of GHRH and/or chronic stimulation of somatostatin secretion from the hypothalamus.

Previous animal experiments revealed no direct effect of serotonin on basal GH secretion (Kato *et al.*, 1980; Hall, 1982; Hall *et al.*, 1984). With a histochemical technique, synaptic connections between serotonergic nerve endings and somatostatin neurons have been observed in the rat anterior periventricular nucleus (Kiss *et al.*, 1988). Although serotonin has been reported to have an inhibitory (Richardson *et al.*, 1981) or no effect (Chihara *et al.*, 1979; Peterfreund and Vale 1983) on basal

somatostatin secretion from the rat hypothalamus, anti-somatostatin serum does not inhibit 5HTP induced GH release (Kato *et al.*, 1980). In contrast, pretreatment with rabbit anti serum specific for rat GHRH abolishes the plasma GH increase induced by 5HTP or serotonin in rats (Murakami *et al.*, 1986).

These observations support the theory that cyproheptadine, at least in part, inhibits GH secretion in acromegalic patients via the inhibition of hypothalamic GHRH release. As for the effect of cyproheptadine on acromegalic GH secretion, Kato *et al.* (1983) observed GH lowering in 3 of 4 patients and GH normalization in one patient. However, the inhibitory effect of acute cyproheptadine administration on acromegalic GH secretion is generally weak (Feldman *et al.*, 1976; Chiodini *et al.*, 1976; Kato *et al.*, 1983), and seldom is the normalization of GH obtained with single cyproheptadine treatment (Faglia *et al.*, 1985; Kato *et al.*, 1983). We also could not find any acute GH suppressive effect of cyproheptadine in several acromegalic patients (unpublished data), and we did not try single cyproheptadine therapy. The effectiveness of the bromocriptine and cyproheptadine combination therapy seems to indicate that cyproheptadine might have an inhibitory effect on GHRH secretion if bromocriptine has dual actions on acromegalic GH secretory tumors; i. e. one is a directly suppressive effect and the other an indirect stimulatory effect via the hypothalamus (Camanni *et al.*, 1977; Hanew *et al.*, 1987).

With the combination therapy, we observed untoward effects in only one patient (# 10), who complained of increased appetite and body weight.

Four of 15 patients (# 2, 7, 9, 14) previously received treatment with somatostatin analogue (SMS 201-995, 200 µg/day bid-tid) for 3 to 8 weeks, and GH and Sm-C levels were normalized in 3 patients (# 2, 7, 9). However, these patients complained

of pain in the injection site, epigastric discomfort, anorexia, urinary irritation, troublesomeness of injection, and they preferred oral medication to SMS therapy.

In conclusion, we have observed clear GH suppression following the bromocriptine and cyproheptadine combination therapy in patients with acromegaly who did not show GH normalization when on single bromocriptine therapy. Such a combination therapy is recommended for acromegalic patients who have received incomplete pituitary adenomectomy, refused surgery or SMS therapy, and patients showing inadequate GH suppression in response to treatment with bromocriptine alone.

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