Bromocriptine therapy in acromegaly. A long-term review of 35 cases

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Summary

Bromocriptine (CB-154, Parlodel, Sandoz) was given to 35 acromegalic patients for a period of 6-36 months. Basal and post-therapy endocrine functions including estimation of serum growth hormone (GH) profile; and GH kinetics during oral glucose tolerance test, augmented insulin tolerance test and thyrotrophin releasing hormone test were determined. The pituitary tumour size was delineated by a pneumoencephalogram. The mean GH levels ranged from 14 $\mu\text{g/l}$ to 316 $\mu\text{g/l}$. Bromocriptine suppressed GH values to 5 $\mu\text{g/l}$ or less in 16 patients and less than 10 $\mu\text{g/l}$ in a further 6 patients. In 33 patients GH values fell to 50% of the basal value or less. There was no significant GH reduction in 2 'non-responders'. Bromocriptine did not block the stress-induced GH secretion. It did not disturb pituitary functions other than prolactin which was suppressed much earlier and was maintained with smaller doses. GH suppression on the other hand was shortlived and rebounded when the drug was omitted. It had no adverse effect on tumour size in 2 patients having suprasellar extension of the tumour. Bromocriptine improved carbohydrate tolerance and sexual function although it did not affect insulin and gonadotrophin values. It seems reasonable to offer a trial of bromocriptine in all patients with acromegaly where therapy is deemed necessary as it is well tolerated, has insignificant side effects and no adverse drug interactions. Its high cost and prolonged course are obvious disadvantages. Caution should be exercised in cases with suprasellar extension and visual field involvement.

Introduction

Growth hormone (GH) is responsible for most of the clinical and biochemical features of acromegaly. Pituitary irradiation or surgical removal of the

tumour is usually recommended for its treatment. Recently bromocriptine, a semi-synthetic ergot alkaloid consisting of a lysergic acid residue and a cyclic tripeptide moiety (Griffith and Fluckiger, 1972), has been effective in the treatment of some acromegalic patients (Thorner *et al.*, 1975; Sachdev *et al.*, 1975; Summers *et al.*, 1975; Belforte *et al.*, 1977; Wass *et al.*, 1977). It works by suppression of growth hormone secretion. In this study further experience is reported of management of acromegaly with bromocriptine. The endocrine results before and during treatment are described.

Materials and methods

Thirty-five acromegalic patients (30 M, 5 F) aged 22-60 years were treated with bromocriptine for 6-36 months. Thirty-three patients had not received any treatment before the study but 2 had received external irradiation (3500-4500 rad) more than 2 years previously. All patients had the classical features of acromegaly and they all showed persistently elevated GH levels which could not be suppressed below 5 $\mu\text{g/l}$ during a standard oral glucose tolerance test (OGTT). Two had visual field defects caused by suprasellar extension of the pituitary as demonstrated by air encephalography. The following additional features were present: diabetes mellitus 9 (overt 3, chemical 6), carpal tunnel syndrome (5), galactorrhoea (5), hypertension (4), congestive cardiac failure (3), hypercalcaemia (2) and thyroid nodule with toxic manifestations in one patient. Four patients were on replacement therapy with hydrocortisone and 2 with thyroxine.

Two patients with overt diabetes mellitus were controlled with oral hypoglycaemic drugs (tolbutamide 3 g and glybenclamide 10 mg daily), and the

third required insulin (protamine zinc insulin 60 units).

Serial serum samples for GH (GH profile) were taken at 2-hourly intervals through an indwelling venous cannula starting at 8 a.m. The first sample was taken with the patient fasting and recumbent and subsequent samples with the patient ambulant and not fasting. An OGTT with 100 g glucose was carried out to assess carbohydrate tolerance. An insulin tolerance test (ITT) using 0.3 units crystalline insulin per kg body weight was performed. Blood sugar, plasma GH and cortisol were measured. Basal plasma luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured in all patients (Shaw *et al.*, 1974). Thyroid status was assessed by measurement of protein bound iodine (PBI) (Foss, Hankers and Van Slyke, 1960), thyrotrophin (TSH) (Hall, Amos and Ormston, 1971) triiodothyronine (T_3) (Chopra, Solomon and Beall, 1971) and thyroxine (T_4) (Chopra, 1972). An intravenous thyrotrophin releasing hormone (TRH) test (Ormston *et al.*, 1971) for GH and TSH response was carried out on each patient.

Serum GH (Hartog *et al.*, 1964), TSH, T_3 , T_4 , LH, FSH, prolactin (Sinha *et al.*, 1973) and insulin concentrations (IRI) (Herbert *et al.*, 1965) were estimated by radioimmunoassays. The following reference standards were used: National pituitary agency (NIAMDD) standards HS 2160 E for growth hormone; HS-RP-1 for TSH; LER-907 for

FSH and LH; PRL AFP-1582 C for prolactin and International Reference Preparation (IRP) London standard No. HIRI 66/304 for insulin. T_3 and T_4 were obtained from M/S Sigma Chemical Corporation, St Louis, in the free acid form and were used as standards without further purification. Blood sugar concentration was measured by modified Folin and Wu method (1920) and plasma cortisol by competitive protein binding (Murphy, 1967). Liver function tests, full blood count, blood urea and electrolytes were measured every 3 weeks. Radiological studies included antero-posterior and lateral skull X-rays, coned views and tomography of the pituitary fossa; heel pad and skin thickness measurements. Hand volumes were measured by displacement of water from a container with water maintained at a constant temperature of 30°C. Tattoo marks were made on the wrists to measure the exact displacement.

Bromocriptine was given orally in an initial dose of 2.5 mg with lunch. GH was estimated at 2, 4, 6 and 8 hr after the drug. Twenty-four hours later it was increased to 2.5 mg at 12-hr intervals. The dose was further increased in a step-wise manner at intervals of 7–10 days to 2.5 mg $\times$ 8 hourly; 2.5 mg $\times$ 6 hourly; 5 mg $\times$ 6 hourly and 10 mg $\times$ 6 hourly. Clinical assessment and GH profile were repeated at each dose increment and full biochemical and radiological reassessment at 3-month intervals. Thirty-four patients have been treated for a minimum

FIG. 1. Mean pre-therapy (●) and minimum post-therapy (▼) growth hormone values for 35 patients.

period of 6 months, 31 up to 12 months and 21 for a total period of 36 months. One patient discontinued therapy after 6 weeks.

The following criteria were applied to assess the response to treatment:

- (a) Full response
 - (i) Obvious clinical remission.
 - (ii) Mean GH during GH profile $< 5 \mu\text{g/l}$.
 - (iii) GH suppressed to $< 5 \mu\text{g/l}$ during OGTT.
- (b) Partial response
 - (i) Some improvement in clinical features.
 - (ii) GH values 50% or less of basal value but still $> 5 \mu\text{g/l}$.
 - (iii) GH suppressed but still $> 5 \mu\text{g/l}$ during OGTT.
- (c) No response

Where no change in clinical features or GH values was found.

Results

Mean GH levels during the GH profile ranged from $14 \mu\text{g/l}$ to $316 \mu\text{g/l}$ before bromocriptine therapy. GH values fell in all but 2 patients in whom the decrease in GH levels was not significant even with doses of up to 60 mg daily (Fig. 1). One patient left the study after 6 weeks. The maximum fall in GH was noted when the daily dose of bromocriptine was 20 mg or less, thereafter GH reduction was only marginal (Table 1). In 33 patients, the GH concentrations fell to 50% or less of their pre-treatment level, irrespective of the initial concentrations; in 22 the value of GH was reduced to less than $10 \mu\text{g/l}$ and in 16 patients it was suppressed to $5 \mu\text{g/l}$ or less.

Growth hormone reduction was accompanied by subjective changes in soft tissue texture and thickness of the skin. Paraesthesiae resolved in early stages of therapy. Galactorrhoea disappeared in

TABLE 1. Basal and post-therapy GH values

Case no.	Age (years) and sex	Pre-therapy	Mean serum GH levels ($\mu\text{g/l}$) During bromocriptine therapy for 3 months						Mean serum GH levels ($\mu\text{g/l}$) During maintenance therapy 10–20 mg.			
			2.5 mg	5 mg	10 mg	20 mg	30 mg	40 mg	5 months	12 months	24 months	36 months
1	27 M	234	206	223	144	112	144	88	25	20	20	17
2	56 M	128	118	123	109	84	80	78	48	26	10	8
3	36 M	95	84	72	67	40	41	48	36	21	15	7
4	33 M	89	74	43	38	24	30	20	5.8	3.0	5	3.2
5	27 M	48	34	25	21	17	14	17	7.0	3.0	2.5	2.9
6	31 M	43	24	22	17	15	14	13	12	3.2	3.7	4.1
7	54 M	42	33	29	18	19	20	18	11	4.5	3.0	3.1
8	38 M	41	39	37	30	21	19	16	10	3.4	2.7	3.2
9	22 M	41	33	—	31	21	18	16	6	3.4	3.6	2.6
*10	27 M	37	30	21	19	15	—	—	—	—	—	—
11	42 M	35	28	25	21	17	14	17	9.0	1.9	2.3	2.6
12	39 M	32	26	22	17	12	9.0	8.0	7.0	2.2	2.1	1.6
13	36 M	32	29	23	17	15	13	12	7.0	2.9	3.1	2.6
14	33 M	31	28	21	17	15	—	11	10.0	2.7	2.5	3.2
†15	26 M	26	24	26	24	22	—	24	22.5	—	—	—
16	25 M	21	21	18	13	13	—	8.0	5.0	3.5	2.5	2.7
17	30 M	20	14	16	8.0	5.0	—	3.0	6.0	3.0	2.1	1.9
†18	60 F	17	16	15	16	14	16	15.0	14	—	—	—
19	42 M	316	298	280	234	198	152	78	38	18	10	6
20	36 M	19	19	17	12	10	8	7	7	5.3	3.7	3.5
21	33 M	18	15	13	14	7	8	6	4.2	4.4	3.2	—
22	32 M	30	27	25	23	17	12	12	5.7	5.5	4.2	—
23	27 M	50	49	53	48	36	30	21	24	27	24	—
24	26 M	21	17	18	12	10	—	—	5.0	3.8	—	—
25	22 M	15	19	12	14	8	7	—	6	3.3	3.2	3.4
26	23 M	14	12	12	11	6	—	—	5	5.2	—	3.7
27	25 M	31	27	23	17	14	—	—	10	10	—	—
28	40 M	42	38	35	27	19	21	17	15	12	10	8.3
29	27 M	37	31	23	17	18	—	—	17	9.6	—	—
30	29 M	30	27	25	18	15	13	—	11	7.9	—	—
31	31 M	27	23	21	16	12	—	—	10	5.3	2.9	—
32	37 M	29	27	21	16	15	—	—	12	13	10	—
33	26 M	59	43	34	31	29	—	—	20	16	14.2	10.1
34	28 M	116	110	114	92	79	87	69	53	32	1	—
35	23 M	137	123	117	107	103	87	79	57	—	—	—

* Partial response but opted out of study. † Non-responders.

TABLE 2. Basal and post-therapy insulin values during standard glucose tolerance test

Time (min)		0	30	60	90	120
Pre-therapy	mean	6.20	52.0	46.8	31.8	16.2
	s.d.	5.49	31.73	35.29	30.38	20.83
	s.e.	2.46	14.19	15.78	13.59	9.32
Post-therapy	mean	3.70	49.8	26.30	16.90	9.4
	s.d.	3.43	25.38	16.76	10.97	6.34
	s.e.	1.00	8.03	5.30	3.47	2.0

TABLE 3. Basal and post-therapy GH values during i.v. TRH test (200 µg)

Time (min)		0	20	30	60	90	120
Pre-therapy GH values (µg/l)	mean	99.3	117.7	115.8	118	96.8	101.5
	s.d.	140.51	138.36	143.85	162.13	140.52	106.25
Post-therapy GH values (µg/l)	mean	59.3	72.3	88.8	68.0	58.3	60.5
	s.d.	93.35	68.2	142.85	97.19	76.2	74.04

TABLE 4. Basal and post-therapy GH values during augmented insulin tolerance test (0.3 u./kg)

Time (min)		0	15	30	45	60	90	120
Pre-therapy GH (µg/l)	mean	85.8	146.3	162.5	133.8	129.5	107.8	95.8
	s.d.	100.9	181.1	210.2	156.4	130.9	136.2	118.5
Post-therapy GH (µg/l)	mean	14.0	17.5	22.0	19.0	17.0	15.3	13.5
	s.d.	10.8	10.7	10.7	8.5	7.0	5.9	6.0

5–7 days. Sexual performance improved in all subjects. LH and FSH values, however, were unaffected. The secretion of other pituitary hormones also remained unchanged (Table 2). The pattern GH response to TRH and ITT remained unaltered (Tables 3 and 4). There was no TSH response to TRH in 45.7% of clinically euthyroid patients. Toxic nodular goitre, which was present in one patient, was not affected and radio-iodine therapy was needed. Congestive cardiac failure improved with decongestive treatment and there were no adverse drug interactions.

Carbohydrate tolerance improved in all diabetic patients (Table 5). Chemical diabetes disappeared in

all 6 patients while in overt diabetic subjects, the dose of hypoglycaemic therapy could be reduced. Blood pressure readings were unaffected and anti-hypertensive therapy continued unchanged in hypertensive patients. Radiological reduction in heel pad thickness greater than 5 mm was noted independently by a radiologist in 22 patients having GH values < 10 µg/l.

Transient nausea was reported by some patients in the initial stages and disappeared in 3–4 days. Seven patients complained of constipation and 2 of them required bulk-fibre laxatives. There were no symptoms suggesting peptic-ulcer-like syndrome. One patient complained of spasm and blanching of

TABLE 5. Basal and post-therapy blood sugar values during standard glucose tolerance test (mg/dl)

Time (min)		0	30	60	90	120
Pre-therapy	mean	120.2	174.3	197.5	189.3	170.2
	s.d.	23.9	36.1	32.5	24.2	19.4
Post-therapy	mean	90.6	136.3	131.0	100.3	80.4
	s.d.	15.5	9.6	42.2	43.8	26.7

toes with a daily dose of 40 mg bromocriptine. His complaints disappeared on reduction of the dose. Hypotension was not recorded in any of the patients. Haematological and hepatic status, serum electrolytes and blood urea remained unchanged. The patient (No. 10) who left the study after 6 weeks was given external irradiation (4500 rad). Nine months thereafter, she developed spontaneous pituitary necrosis and at present she is hypoadrenal, hypothyroid and amenorrhoeic.

Discussion

The GH secretion in a healthy subject fluctuates throughout the day. The GH pulses coincide with the onset of slow wave sleep (Takahashi, Kipnis and Daughaday, 1968). It increases in response to hypoglycaemic stress, physical exertion and certain amino acid (e.g. arginine) loads. It is suppressed by hyperglycaemia and by large doses of steroids. In acromegaly, GH levels are persistently elevated and pulsation during sleep is blunted. Raised GH levels fail to suppress in response to hyperglycaemia and this finding has been used as a diagnostic test. GH secretion in acromegaly is however not entirely autonomous. It may rise still further in response to hypoglycaemic stress (Table 4). It has been proposed that in acromegaly a central defect may be the lack of growth hormone release inhibitory hormone (GH-RIH) (Lawrence *et al.*, 1970; Besser *et al.*, 1974). The pituitary somatotroph in acromegaly is also abnormal in that GH secretion occurs in response to TRH and gonadotrophin-releasing hormone (Gn-RH) an increase which is not seen in normal subjects (Mortimer *et al.*, 1973; Gomez-Pan *et al.*, 1975).

Bromocriptine is a specific inhibitor of prolactin secretion and has been effectively used to control prolactin secretion and galactorrhoea (Lutterbeck *et al.*, 1971; Besser *et al.*, 1972; Rolland, Schellekens and Lequin, 1974). In normal subjects it did not lower GH levels (Camanni *et al.*, 1975a). Liuzzi *et al.* (1974) used a single dose of 2.5 mg of bromocriptine in 7 acromegalic patients and observed significant GH decrease 2–5 hr later. In the 'responders' in this study there was a significant decrease in GH levels 2–6 hr after oral administration of 2.5 mg bromocriptine. In 'non-responders' no significant GH reduction was noticed even when the dose was increased to 60 mg daily. This difference could be due to an inherently different biological response to dopaminergic stimulation. The dopamine receptor sites controlling the tonic inhibition of prolactin are more sensitive to bromocriptine than are those concerned with GH suppression. Thus the elevated serum prolactin concentrations were reduced in early stages with smaller doses in spite of persistently raised GH. The subjective feeling of well-being and

general improvement in facial features, hands, feet, hyperhidrosis and sexual performance might be due to reduction in serum prolactin. In some patients metabolic improvement was noticed earlier than any significant GH reduction. Thus it may be that bromocriptine acts preferentially on biologically active GH (in the monomeric form) or it may have a direct suppressive effect on somatomedin production by the liver or it may affect the peripheral tissues' response to GH or somatomedin.

In this study bromocriptine was fully effective in 16 patients (45.7%), partially effective in 17 (48.6%), and ineffective in 2 patients (5.7%). The optimum therapeutic dose was found to be 10–20 mg/day. The GH reduction was best sustained when bromocriptine was given 6-hourly.

Bromocriptine does not effect the secretion of pituitary hormones other than GH and prolactin. The subjective feeling of well-being and general improvement in facial features, hands, feet and hyperhidrosis occurred early and were reported by all patients irrespective of the change in GH levels. The improvement in carbohydrate tolerance was associated with a fall in GH levels and was due in part at least to decreased insulin antagonism.

Nausea during bromocriptine therapy is known to be due to the central effect on the drug chemotriggered zone. It is markedly reduced when the medicine is taken with meals and the dose is increased gradually. The untoward effects of bromocriptine in the doses and regimen used offered no serious problems and all biochemical measurements remained unaffected. It appears that bromocriptine mainly inhibits the release of GH and does not impair its synthesis, as a prompt overswing of GH values has been observed on sudden withdrawal of the drug (Chiodini *et al.*, 1975; Sachdev *et al.*, 1975; Belforte *et al.*, 1977). Unlike the response of prolactin, the increase in GH response to TRH is not blocked by bromocriptine. Insulin-induced hypoglycaemia, which acts at hypothalamic level, is also able to bypass bromocriptine-induced GH suppression. Therefore it is not clear whether bromocriptine acts at the pituitary or hypothalamic level, although its action on prolactin is directly on the pituitary cells where it acts as a functional analogue of dopamine (Fluckiger and Wanger, 1968; Yanai and Nagasawa, 1970; Pasteels *et al.*, 1971; Hokfelt and Fuxe, 1972; Leading Article, 1977).

From the present study it has not been possible to be sure whether bromocriptine has any effect on tumour growth although some workers (Quadri, Lu and Meites, 1972; Macleod and Lehmeyer, 1973; Corenblum *et al.*, 1975; Vaidya, Aloorkar and Sheth, 1977) have reported its beneficial effect on the size of tumour. The present authors have used it in 2 cases having suprasellar extension of the

tumour involving visual fields. The therapy did not result in any appreciable change in the tumour size over a period of 18 months but there was definitely no deterioration in visual fields. Bromocriptine is considered superior to other dopaminergic agents such as L-dopa, apomorphine and 1-2 pyrimidil 4-pyerohyl-piperazine because it has longer and more sustained action (Belforte *et al.*, 1977; Camanni *et al.*, 1975b). It has advantages over GHRH as it can be given orally, has a longer action and is free from haematological side effects and its actions on other hormones are less widespread (Hall *et al.*, 1973). GHRH, unlike bromocriptine, acts directly on the somatotrophin and blocks the TRH-induced GH release in acromegaly (Gomez-Pan *et al.*, 1975). Compared with other forms of available treatment, bromocriptine is expensive, has to be continued indefinitely in repeated doses and does not yield the definite results obtained by transphenoidal surgery (Williams *et al.*, 1975) but has less morbidity. The results of this therapy compare favourably with those achieved by irradiation and are much more rapid.

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