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CONDENSED REPORT

Long-term treatment of acromegaly with bromocriptine

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Summary

Seventy-three patients with active acromegaly were treated for three to 25 months with bromocriptine 10-60 mg/day. Seventy-one patients showed symptomatic and objective clinical improvement. This included reduction in excessive sweating, hand and foot size, and the number of headaches; improved facial appearance; and increased energy and libido. Abnormal visual fields became normal in two patients, one of whom had concomitant radiotherapy. Mean circulating growth hormone levels, obtained by averaging serial samples through the day, fell by more than 7 µg/l or became undetectable in 58 patients (79%) but did not reach normal values: only 15 patients had mean levels on treatment of 5 µg/l or less. Twenty-three patients were diabetic before treatment, and glucose tolerance became normal in 15 and improved in a further five. Provided the drug was started slowly side effects were minor when compared with the considerable clinical benefit obtained.

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Two patients died while they were taking bromocriptine, but the deaths were not thought to have been caused by the drug.

Bromocriptine offers a major advance in the medical management of acromegaly, but further careful follow-up is required to determine whether serious side effects will be a problem with the long-term use of high doses.

Introduction

Bromocriptine is a long-acting dopamine agonist which raises serum growth hormone (GH) levels in normal subjects but, paradoxically, lowers them in acromegalic patients.^{1,2} We have described the short-term biochemical and clinical benefits of bromocriptine in acromegaly,³ and these early results have been confirmed by others.⁴⁻⁶

We report here our experience of treating 73 patients with bromocriptine for 3 to 25 months (mean 12.8 months). Forty-five were treated for 12 months or more. We examined the clinical changes on treatment and how these related to GH suppression during long-term management.

Patients and methods

Seventy-three acromegalic patients (48 men) aged 18-72 years were treated with bromocriptine. All gave their informed consent to the studies. Active acromegaly had been clinically diagnosed two weeks to 28 years before they started bromocriptine and was confirmed at the time of starting treatment by lack of suppression of circulating GH to less than 2 µg/l during a 50-g oral glucose tolerance test. Forty-two patients also had their pituitary tumours treated by external irradiation, which was carried out from 28 years before to five months after starting bromocriptine; in 15 patients irradiation had been performed at least three years earlier. Five patients had also been treated by partial hypophysectomy and one by yttrium implantation two to 12 years before drug treatment. Twenty-five patients had had no other

treatment for acromegaly. Six patients required appropriate replacement therapy with hydrocortisone, thyroxine, desmopressin, and gonadal steroids.

The patients were assessed clinically and biochemically as out-patients at least once every three months.

CLINICAL ASSESSMENT

Systematic inquiry into the symptoms of acromegaly and the subjective effects on bromocriptine treatment was made and the blood pressure taken. In 51 patients finger size was assessed by measuring the circumference of the fourth or fifth fingers of each hand using jeweller's rings. The pituitary fossa was radiologically assessed before and after 12 months' treatment.

LABORATORY ASSESSMENT

All blood samples were obtained through indwelling forearm venous cannulae. Before and every three to six months during treatment the following biochemical assessments were made.

Mean serum GH during day—In view of the known pulsatility of GH secretion a mean value during the day was calculated as an index of GH secretion. Blood samples were taken for GH assay at 0830 (fasting), 1300, 1700, and 1900 and the results averaged. On this basis patients whose mean GH concentration during the day either became less than 2 $\mu\text{g/l}$ or fell by 7 $\mu\text{g/l}$ or more on treatment with bromocriptine were arbitrarily defined as "responders"; 7 μg was used as a criterion because it represents twice the interassay variation at 30 $\mu\text{g/l}$ (the median circulating GH value before treatment). Similarly, if GH rose by more than 7 $\mu\text{g/l}$ on treatment this was considered significant.

Oral glucose tolerance test (GTT)—Two basal samples for GH and blood sugar were taken, a 50-g glucose load was given, and samples were taken every half hour for two and a half hours. Patients were considered to be diabetic when the peak blood sugar was 8.9 mmol/l (160 mg/100 ml) or more and the 120-minute level 6.1 mmol/l (110 mg/100 ml) or more.⁷

Thyrotrophin-releasing hormone (TRH) tests were performed in 35 patients before treatment and in 26 of these patients after one year's treatment. TRH 200 μg was given intravenously. Blood samples were taken at -60, 0, 20, and 60 minutes for GH, prolactin, and thyrotrophin estimation.

Blood and 24-hour urine samples were taken for routine full blood counts; calcium, electrolytes, and urea estimation; and liver function tests.

REGIMEN OF BROMOCRIPTINE

Patients were told to take all doses of bromocriptine with food to avoid nausea and dyspepsia. The initial dose of 2.5 mg was taken on retiring. This was increased after 72 hours to 2.5 mg every 12 hours. Further 2.5-mg increments were added every 48 to 72 hours up to a set daily dose of 10 mg in the 22 patients at the London Hospital and 20 mg in the 51 seen at St Bartholomew's Hospital. This amount was taken in divided doses every six hours. If side effects occurred the dose was reduced and subsequently increased more gradually. The dose requirement was reconsidered every three months in the light of the results of clinical and biochemical assessments and was increased as necessary to 20 to 60 mg/day in divided doses.

ASSAYS

Human GH (1 $\mu\text{g/l}$ = 2 mIU/l) was measured by radioimmunoassay using MRC 66/217 GH as standard and tracer and antihuman GH antiserum with double-antibody separation of bound and free hormone.⁸ Human prolactin was measured using human prolactin MRC 71/222 as standard and human prolactin (Dr P J Lowry) as tracer and a double-antibody separation.⁹ The human thyrotrophin assay used MRC 68/38 thyrotrophin as standard and tracer, using an antiserum raised against porcine thyrotrophin (Organon). The between-assay coefficient of variation for GH was 13-25%, for prolactin 8-15%, and for thyrotrophin 15-28%. All assays were subject to the quality control of the Supraregional Assay Service. Blood sugar was measured by a neocuproine method (Technicon).

Results

BIOCHEMICAL RESPONSES

Mean serum GH during day—Before treatment the mean serum GH varied from 6 to 400 $\mu\text{g/l}$. In 57 of the 73 patients mean serum growth hormone fell by 7 $\mu\text{g/l}$ or more and in another patient GH became undetectable (fig 1). Of the 58 responders (79% of the total) 15 (26%) had levels on treatment of 5 $\mu\text{g/l}$ or less, 10 (17%) had levels of 6-10 $\mu\text{g/l}$, 17 (29%) had levels of 11-20 $\mu\text{g/l}$, and 16 (28%) had levels above 20 $\mu\text{g/l}$ (range 21-120 $\mu\text{g/l}$) when last assessed. All patients who failed to respond with a fall in mean GH of at least 7 $\mu\text{g/l}$ on bromocriptine had pretreatment levels of under 30 $\mu\text{g/l}$. GH levels fell in 36 of the 45 patients who were treated for 12 months or more, usually in the first six months of treatment. This fall was usually maintained thereafter (figs a and b*). Three patients failed to maintain the initial reduction in serum GH on treatment, though none returned to pretreatment levels (fig a). One later showed a fall while continuing the same dose of bromocriptine.

FIG 1—Change in mean serum GH before (●) and during (○) bromocriptine treatment in 73 patients. Asterisks indicate non-responders. GH was plotted on logarithmic scale for convenience.

Effect of different doses of bromocriptine—Increasing the dose above 20 mg/day produced further improvement in mean serum GH in 12 out of 21 patients (fig c). Maximum GH suppression was, however, reached at doses that differed from patient to patient between 20 and 60 mg/day. Once this optimum effect was reached no further fall in serum GH was seen with time if patients were maintained on a constant dose of bromocriptine (fig d).

Blood sugar during GTT—Twenty-three patients (32%) had a diabetic GTT result before treatment. Two were on insulin and three on oral hypoglycaemic agents when bromocriptine was started. On bromocriptine the glucose tolerance improved in 20 diabetic patients (87%), becoming normal in 15 (65%). Sixteen diabetic acromegalics were treated for a year or more and the results in the 14 who did not need insulin are shown in fig 2. By six months glucose tolerance had improved in all but two patients, and this improvement was maintained at follow-up. Of the five patients whose carbohydrate tolerance was improved but not to normal, one could be managed by diet alone, and insulin requirements decreased in the other two; one patient, who had had 88 units/day, needed 56 and the other, who had had 120 units/day, needed only 40. Circulating GH levels did not fall significantly in three patients whose glucose tolerance became normal.

GH during GTT—The patients whose mean daily GH levels fell during treatment also had lower GH levels during the GTT. Fifteen of these patients showed GH suppression to less than 4 $\mu\text{g/l}$ and in 23 levels were suppressed to 4-10 $\mu\text{g/l}$. The pattern of GH responses to the glucose load also changed. Of the 45 patients treated for over 12 months 22 had had a paradoxical rise in GH (10 $\mu\text{g/l}$ or more) before bromocriptine, but this was abolished in 15 after 12 months' treatment.

Basal serum prolactin levels were measured in 51 patients before and during treatment. They were raised (over 18 $\mu\text{g/l}$) in 17 men and six women (32%). On treatment prolactin levels became undetectable in all.

TRH test—Among the 26 patients who were tested before and during treatment thyrotrophin increased normally in 15 before bromocriptine was started. During treatment 16 showed a reduced thyrotrophin response to TRH. GH responded to TRH—that is, the concentration rose over the mean basal level by more than 10 $\mu\text{g/l}$ —

*Copies of figs a-e may be obtained from the authors.

in 29 of the 35 patients who were tested before bromocriptine was started. Only 26 patients were tested during treatment, and 11 still showed an increase in GH concentrations after TRH, but seven patients who had previously responded in this manner no longer did so. Two patients who had initially failed to show a GH response to TRH showed a fall in GH concentrations on bromocriptine. Three patients who had responded to TRH with an increase in GH failed to show a clear fall on bromocriptine.

Serum calcium—Two patients were initially hypercalcaemic (2.80 and 2.78 mmol/l (11.2 and 11.1 mg/100 ml)). By six months the level had fallen in both to 2.65 mmol/l (10.6 mg/100 ml). There were no changes in serum calcium in the other patients.

Urinary calcium did not consistently change.

Liver function and electrolyte, urea, haemoglobin, white cell, and platelet levels were unchanged on treatment.

FIG 2—Change in carbohydrate tolerance before and during bromocriptine treatment in 14 acromegalic patients who did not need insulin. GTT: ● = diabetic result; △ = non-diabetic result; based on assessment of individual blood sugar values.

FIG 3—Change in finger circumference in 34 patients on bromocriptine for 12 months.

CLINICAL RESPONSES

Subjective evaluation—Sixty-three patients noted excessive sweating before treatment, and this symptom was abolished or improved in all except three. The skin became thinner or less greasy in 42 patients, facial features improved in 26, hand and finger sizes decreased in 58, and in two patients wedding rings fell off unexpectedly and were lost. The foot size decreased in 31 patients, and 17 could wear shoes at least one size smaller. Headaches were relieved in 15 of the 20 patients who had suffered them, usually within seven days of starting the drug. Libido and sexual performance were improved in 17 of the men, 12 of whom had complained of impotence before treatment; 15 of these had been hyperprolactinaemic. Improved energy and wellbeing were reported in 15 patients. In all, 71 (97%) of the 73 patients noted symptomatic improvement.

Objective evaluation—Ring size was measured in 51 patients and it decreased in all but four of the 34 patients in whom it was measured over a year or more (fig 3). The blood pressure was raised (diastolic pressure 95–120 mmHg) in 29 of the 73 patients (17 of the 45 treated for 12 months). At the end of a year the diastolic pressure had fallen to 90 mm Hg or below in eight patients, and in one patient anti-hypertensive treatment was stopped. No change was seen in diastolic pressure in the normotensive patients, but systolic pressure fell by an average of 14 mm Hg at the end of one year's treatment.

Visual fields—Two patients had bilateral upper quadrantic field defects for red vision. These disappeared within three months of starting treatment with bromocriptine, but one of these patients had also had concomitant external irradiation.

Radiological examination of pituitary fossa with plain films, and tomograms when indicated, showed abnormalities in all patients before treatment. No change was seen in the size of the fossa in 45 patients after one year's treatment.

WITHDRAWAL OF BROMOCRIPTINE

At the end of 12 months treatment was withdrawn in all patients. The results in 18 responsive patients are available (fig 4). After two months off treatment GH had increased in all but one patient, although the increased value was less than the pretreatment value in 12 patients. In association with the GH changes there were symptomatic changes, which included increased sweating, recurrence of headache, decreased potency, and decreased energy. In four diabetics glucose tolerance deteriorated.

SIDE EFFECTS

Provided the dose was increased gradually, early side effects of nausea, vomiting, and postural hypotension were not a major problem; if they did occur they were relieved by a reduction in the dose followed by a more gradual increase. Twenty-eight patients noted temporary nausea. Constipation was the most common long-term side effect, affecting 36 patients (49%). In 32 of these improvement was seen spontaneously or with the help of a bulk-fibre laxative. Dry mouth, alcohol intolerance, leg cramps, and hyperkinesia were also occasionally seen (see table).

Digital vasospasm induced by cold was noted in 29 patients who were receiving 10–60 mg/day. Five of these had suffered from Raynaud's phenomenon before treatment and only in one patient did this worsen. This symptom was mild in all but four patients, in whom the dose had to be lowered to alleviate it, and was not a problem in any patient in the warmer weather.

Four patients in this group developed peptic ulcers—two in the stomach and two in the duodenum. Two haematemeses from these ulcers occurred and one was fatal. A further patient died from septicaemia after surgical treatment of her prepyloric ulcer. These two deaths occurred in patients aged 69 and 63. The affected patients were taking bromocriptine in doses of 60 mg/day and 20 mg/day. Until seven weeks before death the patient who suffered the fatal haematemesis

Side effects noted by 73 patients on bromocriptine 10 to 60 mg/day

	Digital vasospasm	Hyperkinesia	Leg cramps	Alcohol intolerance	Nausea	Dry mouth	Constipation
No of patients with side effects	29	3	6	5	28	22	36
No of patients who improved on continued treatment	10		6	5	28	16	32

sis had been taking dexamethasone (2-8 mg/day) during irradiation of her large pituitary tumour, as she was unfit for hypophysectomy.

Discussion

Bromocriptine treatment produced considerable subjective and objective clinical improvement as well as reducing the circulating levels of GH and improving the glucose tolerance of the acromegalics who were initially diabetic. These beneficial effects were maintained throughout treatment for up to two years. Only rarely, however, were the GH levels reduced to normal. Only 15 of the responsive patients had mean serum GH levels of 5 μ g/l or less and the same number had their circulating GH levels suppressed to 2 to 4 μ g/l during oral glucose testing. Nevertheless, 43% had circulating levels of less than 10 μ g/l, and 72% had levels of less than 20 μ g/l. Generally the higher the starting GH levels the greater the fall (fig 1), and all patients with pretreatment values above 29 μ g/l showed GH reduction and clinical improvement. Twenty-one of the 35 patients with pretreatment values below this also benefited. Contrary to the suggestion of Liuzzi *et al*,¹⁰ we did not find that the presence of an increase in GH after TRH always predicted reliably the patients whose GH would fall on bromocriptine.

A higher proportion of patients showed a clinical improvement—97%. Excessive sweating, impotence, and headache improved first, followed by improvement in facial features and decrease in tongue size, skin thickness, and hand and foot size. The improvement in facial features was so great that we now start patients on bromocriptine three months before external irradiation; when the two were started together facial landmarks changed position during treatment. Soft tissue changes were confirmed objectively by improvement in ring size. Such improvements occurred occasionally in patients who did not show a reduction in GH levels, and many patients showed greater clinical and metabolic improvement than could have been predicted from the changes in total immunoreactive GH.

The reason for this discrepancy between the clinical and GH responses is not clear. We have reported¹¹ preliminary studies which suggest that acromegalic patients receiving bromocriptine show a change in the nature of the circulating GH. The most biologically active monomeric form of the hormone suffers a proportionately greater reduction, so that a greater amount of the total immunoreactive GH remaining in the circulation is in the larger, less biologically active, oligomeric form. If this is confirmed it might account for the occasionally greater clinical and metabolic efficacy of bromocriptine than could be expected from the reduction in GH. Three patients who had no significant fall in GH showed an improvement clinically as well as in glucose tolerance. We have shown that there is no change in glucagon or insulin concentrations on bromocriptine.³ Possibly, however, bromocriptine produces part of its clinical and biochemical effect by a direct action on peripheral mechanisms as well as any effect on circulating GH.

Though there was no evidence from the skull radiographs of any change in the size of the tumour, it is of particular importance that early visual field defects disappeared in two patients while they were receiving bromocriptine. We have also seen this occur in a hyperprolactinaemic woman with a pituitary tumour. This suggests that in man, as in rats,¹² dopamine agonists reduce pituitary cell division and tumour size.

We explored the use of bromocriptine in a dose range of 10-60 mg/day. The effect on serum GH of a given dose was apparent by three months, and patients varied in the dose at which maximum GH suppression was seen. Usually this lay between 20 and 40 mg/day. In patients whose serum GH is not maximally suppressed, the need for an increased dose should be assessed every three months. If a dose increment is not accompanied by a further fall in circulating GH or greater clinical improvement the patient should revert to the earlier dose at which maximal suppression was seen.

Side effects were not a major problem once patients were established on a full dose. The reported temporary initiating side effects were minimised by slow incremental introduction of the drug. The higher doses for acromegaly have been associated with mild constipation and the newly recognised side effect of digital vasospasm induced by cold.^{5, 13} These have not proved to be a serious problem. Two patients bled severely from peptic ulcers, and one died. This patient had, however, recently received high doses of dexamethasone to cover irradiation of a very large pituitary tumour, as she was unfit for hypophysectomy. We have no evidence that bromocriptine increases the incidence of peptic ulceration, but it might interfere with the local neuromuscular control mechanisms in the gut that terminate haemorrhage.^{14, 15} This needs further study. Until this question is answered any dyspeptic symptoms should be taken seriously and should be regarded as an indication for further gastrointestinal assessment. Patients should be advised always to take bromocriptine during meals, as this avoids dyspepsia.

As well as welcoming the reversal of the features of acromegaly many patients have appreciated the development of a strong sense of wellbeing and a clear increase in activity. Many men reported improved potency. This may have been related to a reduction in hyperprolactinaemia but sometimes occurred even when prolactin levels before treatment were normal and also in some patients who had not considered their potency to be impaired.

Bromocriptine suppresses GH levels only while it is being taken and does not have permanent effects. Thus GH rose in most patients once they stopped treatment. As GH concentrations did not rise in two patients after treatment had been withdrawn, however, it is important to assess the effect of the primary treatment by regularly withdrawing the drug. Attempts to lower GH levels by surgery or radiotherapy are often not completely successful, although the condition may continue to improve many years after radiotherapy. Medical treatment with bromocriptine is of great value to augment these methods, either as interim therapy until the full effects of treatment can develop or permanently if they are not adequate. It could be the sole treatment when patients are unfit for such primary therapy.

We have treated patients for hyperprolactinaemia safely with a lower dose of bromocriptine for up to six years, but it is too early to determine whether serious side effects will be a problem with the long-term use of higher doses for acromegaly. Nevertheless, bromocriptine seems to represent a major advance in the management of this chronic disabling disease.

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Copies of the figures may be obtained from Professor G M Besser, Department of Endocrinology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

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