LONG-TERM TREATMENT OF ACROMEGALY WITH BROMOCRIPTINE

By

Peter Claes Eskildsen¹, Per Aaby Svendsen², Lisbeth Vang² and Jørn Nerup²

ABSTRACT

Treatment with bromocriptine, 30–55 mg daily, in 13 acromegals for 1–15 months, resulted in a 60% decrease in growth hormone secretion, as judged from the excretion of growth hormone in 24-h urine. Normal excretion was obtained in 10 patients, while 1 patient showed no response. The plasma growth hormone response to O-GTT was improved, but not normalized, in 4 of 7 patients treated for more than 6 months, and marked glucosuria disappeared in two diabetics. While the secretion of TSH, LH and FSH was unchanged, the prolactin secretion was inhibited. The urine excretion of free cortisol showed a 30% decrease, possibly due to a direct effect of bromocriptine on the ACTH-secretion. Hypercalcaemia was never seen, but the initial hypercalcuria showed a modest decrease without measurable changes in the creatinine clearance. The subjective relief during long-term treatment was marked in 10 of 11 patients and the dominating symptoms disappeared in 40–67%, whereas heal-pad thickness, enlarged sellae, and visual fields remained unchanged. No serious side effects were observed. Treatment with bromocriptine seems effective and should be considered as a remedy amongst others, in suitable cases of acromegaly.

In 1974 a preliminary report was published about the acute suppressive effect of the semisynthetic secale alkaloid, bromocriptine, on the growth hormone level in the plasma of acromegals (Liuzzi et al. 1974). This finding was later confirmed, not only in short-term experiments, but also in long-term treatment of acromegals, following several studies (Thorner et al. 1975; Sachdev et al.)
Bromocriptine (2 brom-α-ergocryptine methane sulphonate, CB 154, Parlodel®, Sandoz) is a long-acting dopamine receptor agonist primarily produced to inhibit pituitary prolactin secretion (Pasteels et al. 1971). Secondarily it was found to interact with growth hormone secretion, stimulating this effect in normal man, but inhibiting this effect in acromegalics, presumably through a direct action on the pituitary growth hormone producing cells (Liuzzi et al. 1972).

Growth hormone secretion is difficult to assess from plasma samples since the plasma level fluctuates at a higher level during the night than during the day. In the kidney the hormone is filtered freely through the glomerular membrane, the main part being re-absorbed in the proximal renal tubules, and only a small but constant proportion of the secreted amount (0.01%) is excreted in the 24-h urine (Hanssen 1975).

In the present study, the excretion of human growth hormone (HGH) in the 24-h urine sample is used as a parameter of the daily pituitary secretion of the hormone, and this parameter together with the control of other pituitary hormones and repeated clinical examinations is used to evaluate the effectiveness of bromocriptine during long-term treatment of acromegalics.

MATERIALS AND METHODS

Fourteen acromegalic patients, 10 women and 4 men, were included in the study. All were out-patients. One, however, had a cerebral attack (pituitary apoplexy) just before bromocriptine was started leading to hypopituitarism, and one patient was treated for only 1 month. The remaining 12 acromegalics were treated for 3–15 months, on an average for 10 months.

Five patients had previously been treated with external irradiation (see Table 1) and during the study two further patients (No. 3 and 6) received pituitary external irradiation with 4000 R (circulating source). Acromegaly was judged to be active from the finding of elevated HGH-values in plasma and urine, no HGH-suppression during an oral glucose tolerance test (O-GTT, see Table 2) and clinical symptoms and signs (see Table 3). No patients had visual field defects.

The patients were examined before and every 6 months during the treatment by measuring glucose, insulin and HGH in plasma during O-GTT (100 g), and TSH, prolactin, FSH and LH after stimulation with 200 μg TRH and 200 μg LH-RH. HGH, cortisol, creatinine, calcium and glucose in plasma (fasting state) and in 24-h urine was measured together with serum prolactin before and every second month during the treatment. Simultaneously a clinical evaluation was undertaken, based on a special score system. X-rays of the sella turcica, hand, foot and heal-pat, and determination of the visual field were controlled every 6–12 months.

Treatment was started with 2.5 mg bromocriptine (Sandoz-Parlodel®) per day for the first week, followed by a stepwise increase in dosage at intervals of 2–3 weeks.
Table 1.
Clinical presentation of 14 patients with acromegaly.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Beginning of symptoms</th>
<th>Time of diagnosis established</th>
<th>Previous treatment</th>
<th>Months on bromocriptine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>♂</td>
<td>1968</td>
<td>1974</td>
<td>Irradiation</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>♂</td>
<td>1950</td>
<td>1950</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>♂</td>
<td>1971</td>
<td>1975</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>♂</td>
<td>1969</td>
<td>1975</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>♂</td>
<td>1974</td>
<td>1975</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>♂</td>
<td>1970</td>
<td>1976</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>♂</td>
<td>1966</td>
<td>1976</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>♂</td>
<td>1955</td>
<td>1957</td>
<td>Irradiation</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>♂</td>
<td>1965</td>
<td>1974</td>
<td>Irradiation</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>47</td>
<td>♂</td>
<td>1966</td>
<td>1974</td>
<td>Irradiation</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>57</td>
<td>♂</td>
<td>1965</td>
<td>1977</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>61</td>
<td>♂</td>
<td>1966</td>
<td>1975</td>
<td>Irradiation</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>69</td>
<td>♂</td>
<td>1958</td>
<td>1972</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>♂</td>
<td>1966</td>
<td>1975</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

until a daily dose of 30–55 mg, mean 40 mg, was reached. In 9 patients the treatment was started by measuring the plasma HGH and serum prolactin at 1–2 h intervals from 8 a.m. to 10 p.m. on 2 consecutive days, the second day after 2.5 mg bromocriptine at 9 a.m. Bromocriptine was discontinued after 6 months, and started again after 1–3 months withdrawal and then continued for another 6 months.

Laboratory methods

HGH was measured by a double antibody radioimmunoassay technique in plasma (Hanssen 1972a, after modification of this technique: normal range in fasting state: 1–7 ng/ml) and in urine after dialysis and concentration by lyophilization (Hanssen 1972b, after modification: normal range 40–100 ng/24 h).

Plasma insulin (fasting < 20 mU/l, after 100 g glucose max. 30–180 mU/l, Jørgensen 1969), serum TSH (basal < 2.0 mU/l), serum LH (women, fertile age 2–123 mIU/ml, post-menopausal 24–96 mIU/ml, men 2–16 mIU/ml), and serum FSH (women fertile age 4–43 mIU/ml, post-menopausal 98–288 mIU/ml, men 5–20 mIU/ml) were all measured by radioimmunoassays.

689

Acta endocr. 87, 4
Serum prolactin was determined by a double antibody radioimmunoassay (modified according to Mc Neilly 1973), using specific antibody and purified human prolactin, labelled with $^{125}$I, from NIAMD. The sensitivity limit was 2.5 ng/ml serum, the inter-assay variation 7.9 % (6–8 ng/ml) – 7.3 % (20–25 ng/ml), and the intra-assay variation 4.5–5.5 %. The basal level in women was 3–13.5 ng/ml, in men 1.5–13 ng/ml, and 20 min after stimulation with 200 μg TRH 10–72 and 10–31 ng/ml, respectively.

Total cortisol in plasma (normal range 10–32 μg/100 ml) and free cortisol in 24-h urine (normal range 17–170 μg) was measured by a competitive protein-binding technique. Blood glucose, calcium and creatinine in plasma and in urine were measured by routine methods in the Department of Clinical Chemistry.

For statistical evaluation, non-parametric methods were used for paired (Wilcoxon-Rank test) or unpaired samples (Mann-Whitney test).

**Ethical aspects**

All patients were thoroughly informed about the disease, the different ways of treating it, and the experimental nature of long-term bromocriptine treatment of acromegaly. They were further informed about the known side-effects of the drug, but all consented to participate in the study.

**Table 2.**

<table>
<thead>
<tr>
<th>No.</th>
<th>Plasma-HGH</th>
<th>Urine-HGH ng/24 h (40–100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal level ng/ml (1.0–7.0)</td>
<td>Suppression during O-GTT</td>
</tr>
<tr>
<td>1</td>
<td>40</td>
<td>Not perform.</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>Paradox incr.</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>Paradox incr.</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>Paradox incr.</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>13.5</td>
<td>Paradox incr.</td>
</tr>
<tr>
<td>7</td>
<td>14.5</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>11.5</td>
<td>Not perform.</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>9.5</td>
<td>Paradox incr.</td>
</tr>
<tr>
<td>14</td>
<td>34</td>
<td>No</td>
</tr>
</tbody>
</table>

690
RESULTS

1. Effects of bromocriptine on HGH in plasma and urine

Plasma (fasting) and 24-h urine HGH-levels were clearly elevated before treatment in all patients (Table 2), although no correlation existed between plasma- and urine-values.

The effect of the bromocriptine, 2.5 mg orally, was controlled in 9 patients (Fig. 1 A), showing a significant fall ($P < 0.05$) in plasma HGH after 3–4 h in 6 of the patients, and non-significant changes in 3. The 24-h urine excretion of HGH fell on the day of bromocriptine treatment as compared with the control day in 7 patients, but rose in 2 (Fig. 1 B).

By increasing the dose of bromocriptine to about 40 mg per day a persistent suppression of the HGH secretion was obtained. The urine excretion of HGH (Fig. 2) was significantly suppressed (mean 60 %) after 3–6 months in all but one patient – in 10 to normal values ($\leq 100$ ng/24 h). After withdrawal of bromocriptine HGH-excretion increased in all patients during the 1–3 months’ interval. When the treatment was resumed, the HGH-excretion fell again (Fig. 2).

![Fig. 1.](image)

A – The change in plasma HGH (ng/ml) in 9 acromegalic patients during day-time after 2.5 mg (po) bromocriptine, CB 154, at 8.30 a.m., when plasma HGH is expressed in per cent of the corresponding value from the preceding control day. The level of plasma HGH is significantly ($P < 0.05$) decreased in 6 patients (drawn lines), but unchanged in 3 (dotted lines) the day after CB 154.

B – The excretion of HGH in 24-h urine (ng/24 h) in the same 9 patients on the 2 days, control and after 2.5 mg CB 154. The excretion is decreased in 7 and increased in 2 (dotted lines). The time of the meals (M) is indicated by the arrows below.
The excretion of HGH in 24-h urine (ng/24 h) of 14 patients with acromegaly, before (○, n = 14), during treatment (●, n = 13→10), and after withdrawal of bromocriptine (○, n = 9). Two patients were externally irradiated after 9 months (asterisk). The normal range, 40–100 ng/24 h, is indicated by the dotted lines. The level of significance is shown below.

In contrast, the plasma HGH level, measured at the same time as the urine HGH by single samples taken under fasting conditions in the morning, showed no significant changes (Fig. 3) during the treatment with bromocriptine.

2. Effects of bromocriptine on glucose-, insulin- and HGH-response to O-GTT

In 7 non-diabetic acromegals, repeated O-GTTs (100 g) showed a diabetic response in 4 (30–60 min: 12.5–16 mmol/l, 120 min: 7–11 mmol/l) which was normalized in 2 (30–60 min: 9–11 mmol/l, 120 min: 5–6 mmol/l) and unchanged in 2 after 6–12 months on bromocriptine. Carbohydrate tolerance of the remaining 3 patients was unchanged in one and improved (30–40 %) in 2 patients.

One patient (No. 1) with manifest diabetes and marked glucosuria (1300–1500 mmol/24 h) in spite of treatment with glibenclamide (30 mg/day) initially
The levels of plasma HGH (ng/ml) in the fasting state of 13 patients with acromegaly before (○, n = 13), during (●, n = 13 → 10), and after withdrawal of bromocriptine (○, n = 9). Two patients were externally irradiated after 9 months (asterisk). The normal range, 1–7 ng/ml, is indicated by the dotted lines. The level of significance is shown below.

showed in response to repeated insulin injections (8 units iv) very small changes in blood glucose (22.2 → 15.3 mmol/l). After 6–12 months on bromocriptine marked hypoglycaemia began to occur after insulin injection (5.6 → 1.4 mmol/l) while plasma HGH-response still remained very high (max. 400 ng/ml). Simultaneously, glucosuria disappeared completely, even after discontinuing glibenclamide. A second acromegalic woman with diabetes, treated only for 3 months, had also showed a satisfactory regulation of her diabetes while on bromocriptine, but so far only in combination with glibenclamide.

The insulin-response to O-GTT was elevated in 4 (basal: 10–112 μU/ml, max: 200–650 μU/ml), 3 of these having had a diabetic glucose-response before treatment. After 6–12 months on bromocriptine the insulin-response was still elevated in 2, but normalized in 2 patients. No changes were found in the remaining 3 patients.

The HGH-response to O-GTT was characterized by high, unchanged or paradoxically increasing values (Table 2) before treatment. After more than 6 months on bromocriptine, the response was obviously diminished in 6 patients, but aggravated in 1 patient. Complete suppression of HGH was, however, not obtained.
Fig. 4.
The TRH-stimulated (200 μg iv) response of serum prolactin (ng/ml) in 11 acromegalic patients, 8 women (left) and 3 men (right), before treatment. The hatched area below shows the range of serum prolactin of the same patients exposed to repeated TRH-stimulation after 6 and 12 months on bromocriptine. The dotted lines indicate the range of serum prolactin in 8 normal women and 8 normal men.

SERUM - PROLACTIN

BROMOCRIPTINE

2.5 mg p.o.

ng/ml

30.0

20.0

10.0

<15

0 20 60

MIN

Fig. 5.
The level of serum prolactin (ng/ml) in 8 acromegalic patients during daytime the day before (o) and the day after 2.5 mg bromocriptine (●) at 8.30 a.m. The values are shown by the mean±s.d. The times of the meals (M) are indicated by the arrows below.

694
3. Effects of bromocriptine on different pituitary hormones

Stimulation with TRH (200 µg iv) and LH-RH (200 µg iv) was repeated in 8 of the patients after 6 months of treatment, and in 6 of these again after 12 months. While the TSH-response was normal in all the patients and unchanged during treatment (basal: 0.6 ± 0.5 (sp) µU/ml - max: 5.5 ± 3.3 (sp) µU/ml), the TRH-stimulated increase in serum prolactin was completely inhibited during the bromocriptine treatment (Fig. 4). Measurements of serum prolactin every to every second hour performed in 8 of the patients the day before and the day on the initial dose of 2.5 mg bromocriptine showed in all cases a significant fall (P < 0.05), lasting for 8–10 h (Fig. 5).

LH and FSH, basal (4–50 and 9–181 mIU/ml, n = 13) as well as after LH-RH (21–150 and 13–280 mIU/ml, n = 13), were initially within normal limits, and no change (P > 0.10) was found during treatment.

4. Effects of bromocriptine on cortisol and calcium excretion

Plasma cortisol was within normal limits (10–30 µg/100 ml) in all patients before as well as during the treatment. Free cortisol in 24-h urine was initially within normal limits in 9 and elevated in 5 patients (mean 158, range 91–287 µg/100ml). After 6 months on bromocriptine, a significant (P < 0.01) fall of about 30 % (10–47 %) occurred in 9 patients, and withdrawal from the treatment resulted in a similar and significant (P = 0.02) increase in free cortisol in the urine.

While hypercalcaemia was never seen, the excretion of calcium in 24-h urine (ref.: 3.8–5.0 mmol) was, however, increased in all the patients (on non-calcium standard diet) prior to treatment (mean 10.1, range 5.2–20 mmol/24 h, n = 14). Treatment with bromocriptine for 6 months in 9 patients resulted in a significant (P < 0.05) decrease of about 23 % (range 15–45 %), but normalization was only obtained in 2 patients. Withdrawal of bromocriptine was followed by an increase in calcium-excretion, and when the treatment was resumed up, an equal decrease was demonstrable. Creatinine-clearance was high (145 ± 44 (sp) ml/min, range 82–204 ml/min), but unchanged during treatment (P > 0.10).

5. The effect of bromocriptine on the clinical symptoms and signs

Clinical evaluations of the patients were performed before and at intervals of 1–3 months during treatment (Table 3). Besides acral changes and enlarged sella increased fatigue, headache, diffuse muscle- and joint-pain, and carpal tunnel syndrome were the most frequently occurring complaints. These symptoms were far more disabling for the patients than the acral changes, and were especially improved during the treatment. Changes of the acral enlargements,
Table 3.
Effect of bromocriptine in long-term treatment on clinical features of 11 patients with acromegaly.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. ptt. affected</th>
<th>Effect of CB 154</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Worse (%)</td>
</tr>
<tr>
<td>Acral changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>face</td>
<td>11/11</td>
<td>–</td>
</tr>
<tr>
<td>hands-finger</td>
<td>11/11</td>
<td>–</td>
</tr>
<tr>
<td>feet</td>
<td>11/11</td>
<td>–</td>
</tr>
<tr>
<td>incr. heal-pad</td>
<td>10/11</td>
<td>–</td>
</tr>
<tr>
<td>carp. tunnel syndr.</td>
<td>8/11</td>
<td>–</td>
</tr>
<tr>
<td>Weakness, fatigability</td>
<td>10/11</td>
<td>10</td>
</tr>
<tr>
<td>Mental instability</td>
<td>5/11</td>
<td>–</td>
</tr>
<tr>
<td>Headache</td>
<td>6/11</td>
<td>–</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>8/11</td>
<td>12</td>
</tr>
<tr>
<td>Joint pain</td>
<td>9/11</td>
<td>–</td>
</tr>
<tr>
<td>Enlarged sella</td>
<td>10/11</td>
<td>–</td>
</tr>
<tr>
<td>Nasal stenosis</td>
<td>4/11</td>
<td>–</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>9/11</td>
<td>–</td>
</tr>
<tr>
<td>Sexual insufficiency</td>
<td>2/11</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3/11</td>
<td>–</td>
</tr>
<tr>
<td>Struma</td>
<td>4/11</td>
<td>–</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2/11</td>
<td>–</td>
</tr>
<tr>
<td>Galactorrhoea</td>
<td>1/11</td>
<td>–</td>
</tr>
<tr>
<td>Visual defect</td>
<td>0/11</td>
<td>–</td>
</tr>
</tbody>
</table>

Mean change of symptoms pr. patient in per cent 1 47 28 24

loosening of the fingers and shoes, were also observed, while the heal-pad thickness remained unchanged.

Three patients were hypertensive, but only one showed a permanent fall in blood pressure and a reduced need for anti-hypertensive drugs. Regular control of blood pressure in 8 patients on the day before and on the day after the primary dose of bromocriptine showed in all patients a smaller fall in blood pressure, 15–20 % of the systolic and diastolic pressure, lasting for 4–6 h.
During prolonged treatment the blood pressure was not influenced by bromocriptine.

Diffuse atoxic goitres were diagnosed in 4 patients and a smaller reduction in volume was observed in one.

Defects of the visual field were never seen, either before or during the treatment.

6. Side effects of bromocriptine

Just after the primary dose transient nausea and dizziness were often recorded, but disappeared after 2–3 days of treatment. With administration of the tablets during or after the meals, gastric symptoms were never seen. Constipation frequently occurring initially, was aggravated in three cases, but in only one had bromocriptine to be stopped intermittently. Two patients with the carpal tunnel syndrome observed during treatment with doses of 40–55 mg a tendency to pallor and coldness of the fingers, which disappeared when the dose of bromocriptine was reduced. In one patient (No. 9) bromocriptine had to be discontinued after 3 months because of unspecific diffuse complaints difficult to relate to the treatment with bromocriptine, as several other drugs were taken simultaneously.

Altogether, severe side effects were not seen, even after more than a year of treatment.

DISCUSSION

The discovery of the growth release inhibiting hormone, somatostatin, seemed to increase the possibility of non-invasive treatment of acromegaly (Hall et al. 1973; Besser et al. 1974a). But for practical purposes it was, however, found to be ineffective (Besser et al. 1974b; Christensen et al. 1976).

External irradiation is widely used but is effective in only about half the cases and often not until a year or more after the treatment (Lamberg et al. 1976b). In fact only 1 of 5 previously irradiated patients in the present study showed any effect of this treatment, as determined clinically and by HGH-secretion. Proton-beam therapy is vastly more effective (Lawrence et al. 1970), but only possible in few places of the world. Hypophysectomy by the transsphenoidal approach (Hall et al. 1972; Williams et al. 1975), followed by cryoapplication (Lamberg et al. 1976a), or the pituitary ablation with implantation of radioactive seeds (Hartog et al. 1965; Kaufman et al. 1966) are relatively simple and effective invasive techniques with few complications in skilled hands, but leads to hypopituitarism in 25–30% of the cases. Transfrontal hypophysectomy (Lindholm et al. 1976) is especially indicated in case of rapidly growing tumours and in cases showing signs of pressuer from the tumour.
Bromocriptine has now been used for 3 years in the treatment of acromegaly, but some facts still have to be established: the category of acromegals suitable for this treatment, the effect of long-term treatment on HGH-secretion and symptomatology, the specificity of the drug, the frequency and type of side effects, and finally the duration of the treatment.

The patients in the present study belong to a less severe category of acromegals, although all in an active phase. HGH-secretion, determined in the urine excretion, was significantly reduced in 12 of 13 patients and normalized in 10 patients treated for 3 months or more. Only 1 patient was a non-responder. The finding of a significant decrease in plasma HGH in only 6 of 9 patients (66%) after the initial small dose of bromocriptine shows that it is not possible in this way to separate responders from non-responders, which is in agreement with the findings of Thorner et al. (1975). The changes in plasma HGH during the long-term treatment were quite insignificant, a fact which may be explained by the well-known fluctuations of HGH in plasma, and by the conditions of blood sampling. From a theoretical and practical point of view we find it preferable to use the 24-h excretion of HGH as a parameter of HGH-secretion instead of plasma HGH. Although we feel it unlikely it is possible that bromocriptine through a direct effect on the renal tubules, increases HGH-re-absorption, thereby lowering the urinary HGH-excretion relatively more than plasma HGH levels. This should be studied in normal man.

Plasma HGH is important to follow during O-GTTs since it was found to diminish after 6 and 12 months of treatment, but not to be completely suppressed, in 5 of 7 patients. It was unchanged in one patient, and aggravated in the non-responder. Cassar et al. (1976) were not able to find any change in the plasma HGH response to O-GTT. This discrepancy can possibly be explained by the higher dosage and the longer term of treatment in the present study.

The increased insulin sensitivity during the treatment was especially pronounced in the two diabetics, in one with a normalization of blood glucose values making possible the discontinuation of glibenclamide treatment.

The clinical response to bromocriptine was roughly correlated with the effects on HGH. All the symptoms taken together showed improvement in 52%, while 47% remained unchanged, and 1% deteriorated, which is quite as good as reported by other investigators (Joplin et al. 1961; Hartog et al. 1965; Roth et al. 1970; Lawrence et al. 1970; Wass et al. 1977).

While TSH, FSH and LH were unaffected by bromocriptine, the secretion of prolactin was completely inhibited, as expected. The small, but significant decrease in free cortisol in 24-h urine, a parameter for the ACTH-secretion, has not previously been described. This effect of bromocriptine may play a therapeutic role in cases of acromegaly with pituitary-dependent adrenal hyperfunction. Whether this is an effect of bromocriptine directly on the pituitary
ACTH-secretion or secondarily to the decreased HGH-secretion is not known. The lack of any positive correlation between the change in HGH in urine and free cortisol in urine, together with the reported lowering effect of bromocriptine on both plasma prolactin and plasma ACTH in Nelson's syndrome (Lamberts & Birkenhäuser 1976) may point to a direct action on the hypothalamus-pituitary axis.

The occurrence of hypercalcuria in acromegalics, sometimes combined with elevated calcium in the plasma is a wellknown finding (Lawrence et al. 1970). In this study treatment with bromocriptine resulted in a small, but significant, decrease in urine-calcium, which is in contrast to the findings of Wass et al. (1977).

In this study the observed side-effects of bromocriptine were mild and did not cause any interruption of the treatment, even when dosages as high as 55 mg daily were administered. It seems likely that tolerance to the drug is greater in acromegals than in normal subjects. The reported incidence of massive gastric bleeding during bromocriptine treatment (Wass et al. 1976) emphasizes, however, the importance of careful follow-up of the patients during long-term treatment. The average period of treatment was 10 months, and it cannot be excluded at present that side effects might occur later on.

In conclusion bromocriptine has to be considered an effective alternative treatment of acromegaly, when immediate surgical interference is not necessary. Since relapse of increased HGH-secretion was demonstrated at withdrawal, it is perhaps advisable to combine bromocriptine treatment with external irradiation thus aiming at permanent and complete normalization of the HGH-secretion.

ACKNOWLEDGMENTS

The investigators wish to thank Sandoz, Copenhagen, for the supply of bromocriptine (Parlodel®), Hoechst Denmark for LH-RH, and the National Pituitary Agency, National Institute of Arthritis, Metabolic and Digestive Diseases, for providing reagents used in the prolactin radioimmunoassay.

REFERENCES


Received Wass Sachdev Pasteéis Wass Roth Lamberts Liuzzi Lamberg Köbbcrling Kaufman Haussen Jorgensen Joplin Haussen Hartog Hall Hall Christensen Chiodini Cassar Cammani 8-Sulway 8- Se Stuart & 35 J. Radiology endocr. (Kbh.) Endocr. (1972)


Received on September 15th, 1977.


700