Cabergoline in acromegaly: a renewed role for dopamine agonist treatment?

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Abstract
Objective and design: Eighteen active acromegalics entered a prospective open study with cabergoline (CAB), a dopaminergic drug much more potent than bromocriptine (Br).
Methods: CAB was administered for 6 months at doses ranging between 0.5 mg twice weekly and 0.5 mg/day. Clinical-anamnestic characteristics of the patients were: (i) sensitivity to dopamine agonist drugs (10 patients); (ii) resistance to somatostatin analogs (SAs) (8 patients); (iii) intolerance to SA (3 patients). In 2 patients marked hyperprolactinemia was present.
Results: Basal GH was 6.6 μg/l (2.2–50) (median (range)), and on treatment it was 3.5 μg/l (1.2–34) (P=0.013). The corresponding IGF-I values were 720 μg/l (410–1438) and 375 μg/l (167–1260) respectively (P=0.00001). Individual GH levels decreased below 2 μg/l in 5 patients, and between 2 and 5 μg/l in another 5 patients. IGF-I levels were suppressed below 50% of baseline in 8 patients and normal age-adjusted IGF-I values were reached in 5 patients (27% of the series). The retrospective comparison with previous chronic treatment with Br in the 10 suitable patients showed a greater effectiveness of CAB (IGF-I decrease on CAB treatment, 46.8%, on Br treatment, 31%, P=0.02).
Adenoma shrank in the 3 patients whose pituitary imaging was repeated during CAB.
Conclusions: These results envisage that CAB may represent a worthy therapeutic tool in acromegalic patients, inducing a degree of IGF-I and GH suppression comparable to SAs, administered by the oral route and much less expensive.

European Journal of Endocrinology 139 516–521

Introduction
Somatostatin analogs (SAs), such as octreotide (OC) and the newer long-acting molecules, are currently considered the first choice option for the medical treatment of acromegaly (1). However, in some patients SAs do not achieve a satisfactory hormonal response or cannot be used because of side effects or poor compliance owing to the injection regimen.
Dopamine agonist drugs (DAs) are an alternative pharmacological option. However, these drugs are effective only in a minority of patients and often are poorly tolerated (2).
Cabergoline (CAB) is a very potent DA with very prolonged duration of action (3) and an inhibitory potency on prolactin (PRL) secretion significantly greater than that of bromocriptine (Br) (4). As far as acromegalic patients are concerned, data concerning CAB treatment are still scanty.
The aim of this study was to evaluate the effects of chronic CAB treatment on growth hormone/insulin-like growth factor-I (GH/IGF-I) levels in a large series of acromegalic patients in the active stage of the disease; in a few of these patients tumor size changes were also assessed.

Subjects and methods
Patients
Eighteen patients (11 females, 7 males, aged 43–74 years) with active acromegaly (defined by GH levels higher than 2 μg/l, not suppressible by oral glucose load to less than 1 μg/l, and high IGF-I levels for age) entered the study. Individual demographic and clinical data are reported in Table 1. Eight patients had previously been treated by neurosurgery and eight had been irradiated 1.5–20 years before the study started. At neuroradiological pituitary imaging 6 had macroadenoma, 1 had a microadenoma, 4 had remnants of pituitary adenoma invading the cavernous sinus, and 7 had empty sella, with no or slight evidence of adenoma on the floor of the sella turcica. Clinical-anamnestic characteristics of the patients were: (i) ‘sensitivity to DA’, evaluated as a decrease of GH levels by more than 50% of baseline after oral acute administration of 2.5 mg Br (n=10, patients 1, 3, 5, 6, 8, 11, 14, 15, 17, 18); (ii) ‘resistance to SA’, defined as the lack of significant hormonal suppression during SA treatment (n=8, patients 1–4, 10, 12, 14, 15); (iii) ‘intolerance to SA’, defined as the occurrence of serious side effects or poor compliance (n=3, patients...
Patient #9 had never been treated previously with DAs or SAs. Six patients (#2, 3, 5, 6, 13, 14) had mild hyperprolactinemia, and two (#7, 17) had PRL levels greater than 100 μg/l.

Any drug treatment aimed at lowering GH hypersecretion or potentially capable of interfering with GH secretion was withdrawn at least eight weeks before the start of the study as part of the periodic off-treatment evaluation of the disease, with the exception of patient #2, who was switched directly to CAB owing to OC ineffectiveness. Substitutive treatment with levothyroxine and cortisone acetate was regularly carried on in two patients (#4, 12).

CAB was kindly supplied on a compassionate basis by Pharmacia-Upjohn (Milan, Italy).

Each patient gave informed consent after full explanation of the purpose of the study. The study was approved by the ethical committee of our hospital, and the procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983.

**Protocol**

**Baseline evaluation** Blood samples were collected in the morning hourly for three hours, after an overnight fast and rest, while the patients were supine and awake, with an indwelling needle inserted in an antecubital vein and kept patent by slow saline infusion. GH and PRL levels were assayed in each sample (in the Results section the reported value is the mean of the three samples) and IGF-I in the first sample.

**Chronic study** CAB was administered orally at bedtime for 6 months at increasing doses, starting from 1 mg/week in a twice weekly schedule (0.5 mg on Monday and Thursday). Hormonal evaluation was repeated as in the baseline evaluation at monthly intervals on the farthest day from CAB intake, and the drug dose was increased if IGF-I values were still out of the normal range. The final dose was 1 mg/week in three patients (#4, 13, 17), 1.5 mg/week (on Monday, Wednesday and Friday) in three patients (#1, 9, 16), and 3.5 mg/week (one tablet every day) in the remaining twelve patients. Drug dose was not increased in 4 patients (#4, 9, 13, 16) for poor compliance and in another one (#1) for the occurrence of side effects. Data reported for each patient are those obtained at the last control at the maximal CAB dose reached.

In all 10 'DA sensitive patients' the degrees of GH and IGF-I suppression (calculated as percentage decrease of hormonal values during treatment vs basal levels) obtained during a previous Br treatment (2.5 mg b.i.d.-5 mg q.i.d. for at least 6 months) were compared with the results of the present study.

A complete physical examination and hematological and biochemical safety parameters were also evaluated both at the beginning and at the end of the study period.

MRI was performed with MRI Philips Gyroscan (ACS-NT) 1.5 Tesla and CT with Siemens Somatom HiQ and the images were evaluated by a neuroradiologist unaware of the ongoing treatment. Pituitary imaging was repeated at the end of the study period in three patients (#2, 14, 15).

### Table 1 Demographic and clinical data.

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1 Previous neurosurgical treatment; 2 previous radiotherapy (year); 3 μ = microadenoma; M = macroadenoma; E = empty sella; 4 previous treatment with DA: S, sensitive to DA (see Methods), N, not evaluated; 5 previous treatment with SA: S, sensitive to SA (see Methods), R, insensitive to SA, N, not evaluated, I, intolerant or non compliant.
Methods
GH, PRL and IGF-I were assayed in duplicate by immunoenzymatic, immunoochemiluminescence, and RIA respectively, after acid-ethanol extraction.

Reagents were purchased from Sorin (Saluggia, Italy) for GH, Chiron Diagnostics (East Walpole, MA, USA) for PRL, and Nichols (San Juan de Capistrano, CA, USA) for IGF-I.

Standards were calibrated against the First International Standard 80/505 (1 ng=2 μIU) for GH, and the Third International Reference Preparations WHO 84/500 for PRL, WHO 87/518 for IGF-I.

Intra- and interassay coefficients of variation were 3.5 and 5.5% for GH, 3.2 and 4% for PRL, 3.7 and 7.2% for IGF-I.

Normal values in our laboratory are: PRL, 3–20 μg/l; IGF-I, 114–492 μg/l in patients 25–39 years old, 90–360 μg/l in patients 40–54 years old, and 71–290 μg/l in patients older than 55 years. The detection limit for GH levels was 0.1 μg/l.

Plasma IGF-I during Br treatment had been measured by the Nichols kit whose upper reported limit of the normal range was 2.2 U/ml.

Statistical analysis
Values are expressed as median and range, due to non normal distribution. IGF-I changes with CAB treatment were expressed both as percentage absolute variations compared with baseline levels and as percentages of the upper limit of the normal age-adjusted range.

Data were analyzed by Student’s t-test, Mann-Whitney test, Friedman analysis of variance followed by Student-Newman-Keuls test, Fisher exact test, as appropriate. A value of P less than 0.05 was considered significant.

Results
Baseline evaluation
Baseline values were: GH, 6.6 μg/l (2.2–50) (median (range)); IGF-I, 720 μg/l (410–1438); PRL, 14 μg/l (3–1600).

Chronic study
During the chronic study GH values fell to 3.5 μg/l (1.2–34) (P=0.013 vs baseline), with a percentage GH decrease of 41.9% (–95.5/+13.6). The analytical evaluation shows that GH levels decreased below 2 μg/l in 5 patients (# 6, 8, 14, 17, 18), and to between 2 and 5 μg/l in another 5 patients (# 1, 5, 9, 15, 16) (Fig. 1a).

IGF-I values decreased to 375 μg/l (167–1260, P=0.00001). Median IGF-I values decreased by 40.5% (–80/+3) when evaluated as absolute percentage change and decreased from a pretreatment value of 248% (range 114–400) to 114% (46–358) when expressed as a percentage of the upper limit of the normal range. The analytical evaluation shows a reduction of IGF-I levels (by percentage absolute changes) greater than 50% in 8 patients (# 2, 6, 8, 13–17) and below 141% of the upper normal values in 13 patients (Fig. 1b). Normal age-adjusted IGF-I values were reached in 5 patients (# 2, 6, 8, 14, 17).

In 12 patients (# 1, 2, 5, 6, 8, 9, 12, 14–18) CAB administration resulted in a decrease in both GH and IGF-I levels of more than 30% (arbitrarily taken as cutoff) of baseline; in three patients (# 3, 4, 13) a decrease in IGF-I of more than 30% was observed while the GH decrease ranged from 1.1 to 16%. In three patients (# 7, 10, 11) the IGF-I level did not change.

In the patients arbitrarily considered as sensitive, i.e. after discounting data of the ‘resistant patients’, and splitting them according to the different dosage of the drug, a significant GH and IGF-I suppression was obtained at a dose of 1.5 mg/week (data not shown).

There was a significant correlation between GH and IGF-I response to CAB (r=0.6, P=0.00753) and between basal and final hormonal values (for GH r=0.698, P=0.00126, and for IGF-I r=0.53, P=0.025).

There was no difference in response to CAB between patients bearing macroadenoma or microadenoma/empty sella, or between sexes, or between patients previously treated or not with neurosurgery or radiotherapy, or between patients with normal or high PRL levels.

The retrospective comparison of the degree of GH and IGF-I suppression during Br and CAB treatment in the 10 ‘DA responder patients’ showed that the GH decrease was similar (percentage decrease vs baseline 52.6% (–95.5/+14%) with CAB, 42.6% (–96/+5.9%) with Br, P=0.82), whereas the IGF-I decline was significantly greater during CAB treatment (percentage decrease vs baseline 46.8% (–80/+19%) with CAB, 31% (–68/+17%) with Br, P=0.02). There were significant correlations between hormonal responses to CAB and Br (for GH r=0.68, P=0.0144 and for IGF-I r=0.63, P=0.0261).

As regards PRL levels (data not reported), a marked suppression was always observed. In patient # 7 with very high PRL levels CAB treatment induced a marked reduction in PRL (from 1600 to 100 μg/l at a dose of 3.5 mg/week), even though it was unable to change GH and IGF-I levels.

A shrinkage of the macroadenoma was observed in the three patients whose pituitary imaging was repeated during treatment. The other patients were not reevaluated by neuroradiological imaging either for logistic reasons or because of very small remnants in those already treated by neurosurgery and/or radiotherapy.

Side effects
No variation in the safety laboratory data was observed (data not reported) and in only one patient (# 1) was
CAB withdrawn at the 5th month owing to gastric intolerance. Another patient (# 11) complained of nightmares during CAB treatment.

Discussion

DAs were the first effective drugs for the medical treatment of acromegaly. Br was the first used (5), later on data were reported on chronic treatment with depot preparations of Br (6) and other DAs, such as lysuride (7), pergolide (8), terguride (9), and quinagolide (10). DAs normalize GH/IGF-I levels only in a few patients and reduce GH levels below 5–10 μg/l in 15–30% of cases, even though an inhibition greater than 50% of pretreatment values following the acute administration of Br is observed in nearly 50% of patients (11). Considering the present more restrictive criteria of cure in acromegaly (1), pointing to the normalization of IGF-I values and to GH levels at least below 2 μg/l, chronic treatment with DAs is nowadays considered effective only in a minority of patients. Their efficacy is greater mainly in patients with concomitant PRL hypersecretion, owing to the expression on adenomatous GH-secreting cells of membrane dopaminergic D₂ receptors similar to those on lactotrope cells (12). DAs have to be taken three or four times daily to maintain a stable GH suppression in sensitive patients and no further GH decline is observed using doses of Br higher than 20 mg/day. DAs are often poorly tolerated, so that high doses can be given only in a few patients. Newer DA drugs (pergolide, terguride, Br-LAR, quinagolide) do not provide more significant results (6, 8–10).

Cabergoline is a very potent DA with prolonged duration of action (3). It was shown in experimental studies in rats that CAB inhibitory potency on PRL secretion was 34 times greater than that of Br (4). Moreover, CAB plasma half-life ranges between 62 and 115 h and has a long persistence at the pituitary dopaminergic receptor D₂ (up to 3 days in the rat and 7 days in the monkey) (13). It was shown in hyperprolactinemic patients that CAB is more effective and better tolerated than Br; normalizes PRL levels in most patients (14) and shrinks the adenoma in many (15).

In acromegaly, the few reported data on CAB treatment are conflicting. The first study by Ferrari...
et al. (16) showed that CAB administration (at a dose of 0.3–1.2 mg/week) normalized GH and IGF-I levels in three out of six selected patients. These results were confirmed later by Muratori and colleagues (17) in three selected acromegalic patients (treated with 1–3 mg/week), but not by other reports. No normalization in hormonal data was observed by Colao and colleagues (18) in eleven patients treated with 1–2 mg/week for 6 months, whereas in only two out of ten unselected acromegalics studied by Jackson et al. (19) were hormonal values normalized during CAB treatment (at 0.5 mg/day). However, recently Abs et al. (20) have shown a marked GH/IGF-I decrease in 43 out of 64 unselected acromegalics with the normalization of hormonal values in 25 of them treated with individualized CAB doses.

Our study showed that CAB treatment induced a marked suppression in GH and IGF-I levels. GH levels decreased below 2 μg/l in 5/18 patients (27%) and IGF-I levels were normalized in 5/18 patients (27%). In particular, in 4 patients (22%) CAB treatment resulted in both the normalization of IGF-I levels and a decrease in GH levels below 2 μg/l. As shown in Fig. 1b, besides the 5 patients with completely normal IGF-I levels that could be considered ‘cured’, there are another 8 patients whose IGF-I values fell below 141% of the upper limit of the normal range. Thus, in most patients of the series (i.e. in 13 out of 18) this treatment provided a control of disease activity that can be regarded as very satisfactory.

This marked sensitivity to CAB might be due to the clinical-anamnetic characteristics of these patients, since 10 out of 18 were considered ‘DA sensitive’. Indeed, IGF-I normalization was found in 4 ‘DA sensitive’ patients. However, the term ‘sensitivity to DA’ should be used with care, because GH suppression during chronic DA administration is sometimes lower than the GH response to acute Br test (11).

The comparison of the results of chronic Br and CAB treatments showed the better efficacy of CAB. The greater degree of IGF-I suppression compared with the similar inhibition of GH may be due to the tighter control on GH secretion throughout 24 h, i.e. by lowering the number and/or the width of GH fluctuations. Alternatively, a role may be played within the low GH group by the heterogeneity between the patients with normal or slightly pathological IGF-I levels, due to the fact that the modern GH assays assess only the 22 K fraction. In addition, a putative peripheral direct effect of CAB on IGF-I synthesis may be hypothesized.

As far as the dosage used is concerned, a significant GH/IGF-I suppression was already obtained with 0.5 mg administered three times weekly, i.e. a tablet every 48–72 h. In one very sensitive patient (no 17, with high PRL levels) even the twice weekly schedule resulted in the normalization of IGF-I levels. A daily dose of 0.5 mg was the maximal used: owing to the very good tolerability of the drug, higher doses might be used in order to gain further suppression of GH hypersecretion. However, literature data on DA doses and their efficiency are conflicting: in our experience with Br no further suppression of GH values was obtained at doses greater than 20 mg/day (11), whereas Besser & Wass (21) reported a greater GH decline by increasing Br up to 60 mg/day.

The comparison of our data on CAB with the results obtained by OC and the newer long-acting SAs shows that SAs provide a far better control of hormonal hypersecretion, since IGF-I levels are normalized in up to 65% of the treated patients (22–24). However, it should be considered that these high figures have sometimes been obtained in a series of patients selected on the basis of previously demonstrated sensitivity to OC. Moreover, very strict criteria of evaluating IGF-I results were adopted in our series, i.e. age-adjusted normal values.

CAB treatment resulted in tumor size reduction in the three patients in which neuroradiological imaging was repeated. The effect of CAB on the size of the pituitary tumor was studied in a large series of patients bearing macroprolactinoma and the results were comparable with those obtained by Br treatment (25). Tumor size reduction was reported in 13 out of 21 patients by Abs et al. (20), with a mass reduction greater than 50% in 5 GH-PRL cosecreting tumors.

The long-lasting experience with DA treatment in PRL- and GH-secreting pituitary tumors suggests that complete suppression of tumoral hypersecretion is a prerequisite to obtain a decrease in tumor size (i.e. the tumor never shrinks without hormone suppression), whereas in some patients the size does not change even in the presence of hormone suppression. As far as GH tumors in particular are concerned, our group (26) has reported the occurrence of tumor size reduction during DA treatment in only a few patients, whereas another study (11) in a larger series stressed that tumoral shrinkage occurred mainly in patients with mixed GH-PRL tumors. It is too early to draw conclusions after the performance of only three imaging studies in our CAB-treated patients: we can speculate that CAB treatment resulted in tumor shrinkage owing to the much more potent suppression of GH/IGF-I hypersecretion with CAB compared with Br and the other DA drugs. Our very promising results need further evaluation in a larger series of previously untreated patients with GH-secreting pituitary adenoma to verify the effects of the drug on tumor size and/or a hypothetical antiproliferative effect on the adenoma mediated by the decrease in IGF-I concentrations.

In conclusion, the normalization of IGF-I levels and the tumor size reduction found in some patients during chronic treatment with CAB suggest that long-acting DAs could still play a role in the treatment of acromegalic patients. CAB is a relatively inexpensive, orally effective drug that can be administered in a single dose every 24–72 h, thus improving acromegalic patients’ compliance. Owing to the very good
tolerability of the drug, higher doses might be used to gain further suppression of GH hypersecretion.

Acknowledgements
We are indebted to Pharmacia-Upjohn for the generous gift of cabergoline and to all the nursing staff of the outpatient division of our hospital.

References

Received 5 August 1998
Accepted 21 August 1998