

Cabergoline in the Treatment of Acromegaly: A Study in 64 Patients

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ABSTRACT

Cabergoline is a new, long acting, dopamine agonist that is more effective and better tolerated than bromocriptine in patients with hyperprolactinemia. Because dopamine agonists still have a place in the medical management of acromegaly, cabergoline might be a useful treatment.

We, therefore, evaluated the effect of long term administration of cabergoline in a large group of unselected acromegalic patients. Sixty-four patients were included in a multicenter, prospective, open labeled study. A subgroup of 16 patients had GH-/PRL-cosecreting pituitary adenomas. Cabergoline was started at a dose of 1.0 mg/week and was gradually increased until normalization of plasma insulin-like growth factor I (IGF-I) levels, occurrence of unacceptable side-effects, or a maximal weekly dose of 3.5 mg (7.0 mg in 1 case) was reached.

Treatment with cabergoline suppressed plasma IGF-I below 300 $\mu\text{g/L}$ in 39% of cases and between 300–450 $\mu\text{g/L}$ in another 28%. With pretreatment plasma IGF-I concentrations less than 750 $\mu\text{g/L}$, a suppression of IGF-I below 300 $\mu\text{g/L}$ was obtained in 53% of cases, and a suppression between 300–450 $\mu\text{g/L}$ was obtained in another 32%. By contrast, with pretreatment plasma IGF-I concentrations above

750 $\mu\text{g/L}$, only 17% of cases showed a suppression of IGF-I below 300 $\mu\text{g/L}$, and there was IGF-I suppression between 300–450 $\mu\text{g/L}$ in another 21%. In GH-/PRL-cosecreting adenomas, 50% of cases suppressed plasma IGF-I levels below 300 $\mu\text{g/L}$, and another 31% did so between 300–450 $\mu\text{g/L}$, in contrast to only 35% and 27%, respectively, in GH-secreting adenomas.

Similar results were obtained concerning the secretion of GH. Tumor shrinkage was demonstrated in 13 of 21 patients, with a mass reduction by more than half in 5 GH-/PRL-cosecreting adenomas. Except for slight gastrointestinal discomfort and orthostatic hypotension in a few patients at the beginning of therapy, cabergoline treatment was well tolerated. Only 2 patients stopped medication because of nausea. The weekly dose of cabergoline ranged between 1.0–1.75 mg. A further increase in the dose was only effective in 1 GH-/PRL-cosecreting adenoma.

The results of this study suggest that cabergoline is an effective, well tolerated therapy that should be considered in the management of acromegaly, especially if the pituitary adenoma cosecretes GH and PRL or if pretreatment plasma IGF-I levels are below 750 $\mu\text{g/L}$. (*J Clin Endocrinol Metab* 83: 374–378, 1998)

GH-SECRETING pituitary adenomas are the most common cause of the acromegalic syndrome (1). About one third of these adenomas are plurihormonal acidophil cell-derived tumors and cosecrete PRL in addition to GH (2). In view of the increased mortality associated with acromegaly, successful management is of utmost importance, as reduction of the GH concentration below 2.5 $\mu\text{g/L}$ produces a shifting of the mortality rate into the normal range (3). Selective resection of the adenoma by the transsphenoidal approach is the treatment of choice for acromegaly (4). However, when stringent standards of cure, such as serum GH levels below 2 $\mu\text{g/L}$ and normalization of plasma insulin-like growth factor I (IGF-I) levels, are used, the global rate of success of surgery is less than 50% (5). Effects of pituitary radiation are usually not measured against these criteria and, moreover, are slow to develop (6). These findings clearly indicate the necessity for adequate adjunctive drug treatment.

The most efficient drugs are currently the somatostatin

analogs, given either by multiple daily sc injections (7, 8) or as a depot preparation once monthly (9, 10). A larger experience has been obtained with dopamine agonists, but comparative studies have shown that bromocriptine is less effective in the suppression of GH and IGF-I secretion than octreotide (11, 12). Cabergoline is a new ergot derivative with a prolonged duration of action and pronounced activity. In the treatment of hyperprolactinemia it is superior to bromocriptine in terms of efficacy and tolerability (13–15). As cabergoline has not yet been tried in a large group of acromegalics, we, therefore, conducted an open labeled, multicenter study in 64 acromegalic patients.

Subjects and Methods

Subjects

Sixty-four patients with active acromegaly, 27 men and 37 women, aged 17–75 yr, were enrolled in this prospective, open labeled study. Informed consent was obtained from all patients. Diagnosis of acromegaly was established by the demonstration of elevated serum GH levels not suppressible below 2 $\mu\text{g/L}$ after a 75-g oral glucose load and elevated plasma IGF-I levels above 300 $\mu\text{g/L}$. As cosecretion of PRL has been shown to be associated with a better clinical response to dopamine agonist therapy (16), the patients were divided into 2 groups.

Group I consisted of 16 acromegalic patients, 9 men and 7 women, aged 17–67 yr, with elevated serum PRL levels. Twelve patients had

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previously been treated. Surgery was performed in 7 and was followed by radiotherapy in 1, bromocriptine in 2, and octreotide in 1 patient. As primary treatment, bromocriptine was given to 3, and octreotide to 2 patients. Four patients had never received any treatment. A microadenoma was present in 4 subjects, and a macroadenoma in 9 cases, whereas in 3 cases no tumor remnants could be found due to the anatomical rearrangement after surgery. Cosecretion was established by immunohistochemistry in 10 operated patients, as 3 more underwent surgery after closure of the study. Cosecretion was assumed in the 6 other patients in the presence of a basal serum PRL level above 30 $\mu\text{g/L}$, which, in addition, was not responsive to the administration of TRH. Moreover, this assumption was supported in the 4 microadenomas by the absence of a pituitary stalk compression that might have been responsible for hyperprolactinemia and in the remaining 2 macroadenomas by a pronounced increase in the basal serum PRL levels, at 61 $\mu\text{g/L}$ in a 19-mm large tumor without stalk compression and at 879 $\mu\text{g/L}$ in a 30-mm large tumor, respectively.

Group II comprised 48 acromegalic patients, 18 men and 30 women, aged 30–75 yr, with normal serum PRL levels. Primary treatment consisted of surgery in 25 patients and radiotherapy in 2 others. Surgery was followed by radiotherapy in 8, bromocriptine in 6, and octreotide in 12 patients. As primary treatment, bromocriptine was given to 1, and octreotide to 2 patients. The remaining 18 patients had never received any treatment. A microadenoma was present in 8 cases, and a macroadenoma in 16 cases, whereas in 24 cases treated by surgery or radiotherapy no tumor remnants were found.

Study design and drug administration

Cabergoline was proposed as an adjunctive treatment to patients not cured by prior therapy and also as a primary treatment. Administration of cabergoline was started at least 3 months after surgery or 3 yr after radiotherapy, and 1 month after discontinuation of medical therapy. It was initiated at a dose of one tablet of 0.5 mg twice weekly (1 mg/week) given with the evening meal. The plasma IGF-I concentration was used as parameter for adaptation of the dose because it reflects the integrated GH secretion of the previous day. Hence, a normalization of the plasma IGF-I level was considered to express a normalization of the GH production (17). In case of insufficient therapeutic response, defined as a plasma IGF-I level above 300 $\mu\text{g/L}$, the frequency of administration was increased stepwise to a 0.5-mg dose every 2 days (1.75 mg/week), daily (3.5 mg/week), and in one patient twice daily (7 mg/week). Plasma IGF-I, serum GH, and PRL concentrations were measured randomly before the start of the treatment, every 1–3 months during the dose-establishing period, and every 4–6 months after normalization of the IGF-I level. The treatment period varied between 3–40 months. In the case of a lack of therapeutic efficacy, the study was discontinued after 3 months.

Evaluation of treatment efficacy

The criteria used to determine the efficacy of cabergoline were arbitrarily chosen. A good response was defined as a value less than 300 $\mu\text{g/L}$ for IGF-I, less than 2 $\mu\text{g/L}$ for GH, and less than 20 $\mu\text{g/L}$ for PRL. A moderate response was considered a value between 300–450 $\mu\text{g/L}$ for IGF-I, between 2–5 $\mu\text{g/L}$ for GH, and between 20–50 $\mu\text{g/L}$ for PRL. A poor response was specified as a value more than 450 $\mu\text{g/L}$ for IGF-I, more than 5 $\mu\text{g/L}$ for GH, and more than 50 $\mu\text{g/L}$ for PRL. Furthermore, pretreatment cut-off levels of 750 $\mu\text{g/L}$ for plasma IGF-I and 20 $\mu\text{g/L}$ for serum GH were used as predictive values to assess the efficacy of treatment.

Magnetic resonance imaging of the pituitary region was performed at baseline, after 6 months of treatment, and then yearly. Reduction by half of one of the diameters of the adenoma was defined as tumor shrinkage by at least 50%.

Assays

Plasma IGF-I was measured by RIA (SM-C-RIA-CT, Medgenix Diagnostics, Fleurus, Belgium). Plasma concentrations are influenced by age, but may be considered normal below 300 $\mu\text{g/L}$ for the age group of our patients. The interassay coefficient of variation was 10.2% at 38 $\mu\text{g/L}$, 6.7% at 169 $\mu\text{g/L}$, and 6.5% at 472 $\mu\text{g/L}$. Serum GH was measured

using a two-site immunoradiometric assay (Pharmacia Diagnostics hGH RIA, Pharmacia, Uppsala, Sweden). The interassay coefficient of variation is 2.7% at 3.0 $\mu\text{g/L}$, 2.7% at 7.8 $\mu\text{g/L}$, and 2.1% at 15.8 $\mu\text{g/L}$. Serum PRL was measured using a two-site immunoradiometric assay (RIA-gnost Prolactin, Behringwerke, Marburg, Germany). Normal values are less than 10 $\mu\text{g/L}$ (350 mU/L) in males and less than 20 $\mu\text{g/L}$ (700 mU/L) in females. The interassay coefficient of variation is 3.5% at 6.7 $\mu\text{g/L}$, 2.7% at 15.7 $\mu\text{g/L}$, and 3.2% at 39.6 $\mu\text{g/L}$.

Results

The treatment with cabergoline was well tolerated. Only seven patients mentioned gastrointestinal discomfort or orthostatic hypotension at the start of treatment. Two patients, both taking a dose of 1.75 mg/week, discontinued the treatment because of nausea. No serious adverse events were recorded.

For each patient individually, the plasma IGF-I concentration at the end of treatment is depicted in relation to the basal value in Fig. 1. A pretreatment plasma IGF-I level less than 750 $\mu\text{g/L}$ corresponds to a more consistent therapeutic success. For all patients, evaluated as a single group, the hormonal responses to the treatment are summarized in Table 1.

Prior medical treatment with bromocriptine or octreotide did not have a large impact on the therapeutic efficacy of cabergoline when the plasma IGF-I level was used as criterion. In the pretreated group, 36% of patients were considered good responders, 36% moderate responders, and 28% poor responders, whereas in the nontreated group, the response was good in 42% of patients, moderate in 22%, and poor in 36%.

Group I

The global responses in GH-/PRL-cosecreting adenomas are summarized in Table 1. The results for PRL were considered good in 14, moderate in 1, and poor in 1 patient. The individual responses to the administration of increasing doses of cabergoline are shown in Fig. 2.

Magnetic resonance follow-up studies were performed in 9 of 13 patients who initially presented radiological signs of tumoral mass. A small regression in volume was observed in 1 microadenoma. A distinct shrinkage was found in 7 of 8

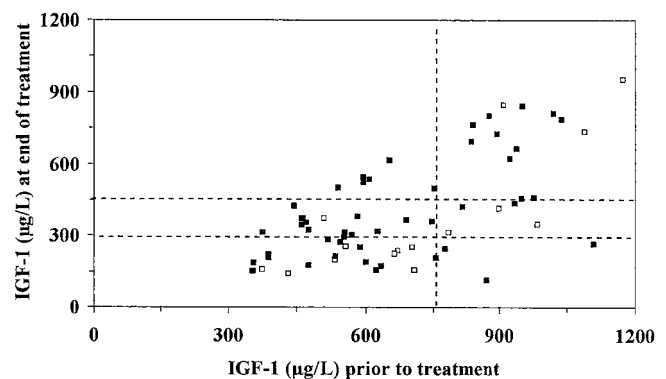


FIG. 1. Plasma IGF-I concentration for each patient individually at the end of treatment in relation to the pretreatment concentration. Open squares correspond to GH-/PRL-cosecreting adenomas in group I; closed squares correspond to GH-secreting adenomas in group II.

TABLE 1. Therapeutic response according to pretreatment IGF-I and GH concentrations

	IGF-I response			GH response		
	Good <300 µg/L	Moderate 300–450 µg/L	Poor >450 µg/L	Good <2 µg/L	Moderate 2–5 µg/L	Poor >5 µg/L
All adenomas						
All (n = 64)	25 (39)	18 (28)	21 (33)	30 (46)	17 (27)	17 (27)
IGF-I <750 µg/L (n = 40)	21 (53)	13 (32)	6 (15)	24 (60)	12 (30)	4 (10)
IGF-I >750 µg/L (n = 24)	4 (17)	5 (21)	15 (62)	6 (25)	5 (21)	13 (54)
GH <20 µg/L (n = 48)	23 (48)	15 (31)	10 (21)	29 (61)	15 (31)	4 (8)
GH >20 µg/L (n = 16)	2 (12)	3 (19)	11 (69)	1 (6)	2 (13)	13 (81)
Group I (GH/PRL-secreting)						
All (n = 16)	8 (50)	5 (31)	3 (19)	9 (56)	4 (25)	3 (19)
IGF-I <750 µg/L (n = 10)	8 (80)	2 (20)	0 (0)	8 (80)	2 (20)	0 (0)
IGF-I >750 µg/L (n = 6)	0 (0)	3 (50)	3 (50)	1 (17)	2 (33)	3 (50)
GH <20 µg/L (n = 13)	8 (62)	5 (38)	0 (0)	9 (69)	4 (31)	0 (0)
GH >20 µg/L (n = 3)	0 (0)	0 (0)	3 (100)	0 (0)	0 (0)	3 (100)
Group II (GH-secreting)						
All (n = 48)	17 (35)	13 (27)	18 (38)	21 (44)	13 (27)	14 (29)
IGF-I <750 µg/L (n = 30)	13 (43)	11 (37)	6 (20)	16 (54)	10 (33)	4 (13)
IGF-I >750 µg/L (n = 18)	4 (22)	2 (11)	12 (67)	5 (28)	3 (17)	10 (55)
GH <20 µg/L (n = 35)	15 (42)	10 (29)	10 (29)	20 (58)	11 (31)	4 (11)
GH >20 µg/L (n = 13)	2 (15)	3 (23)	8 (62)	1 (8)	2 (15)	10 (77)

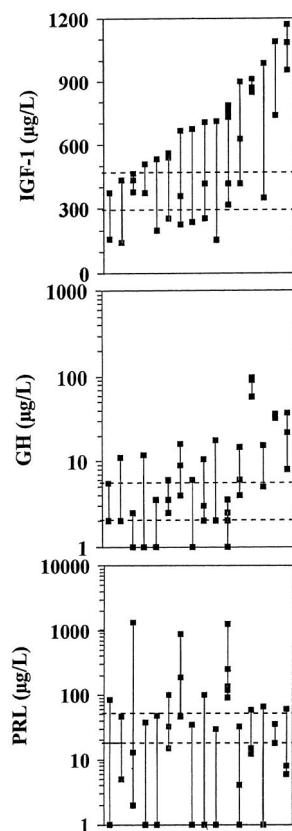


FIG. 2. The *upper squares* indicate the pretreatment plasma IGF-I, serum GH, and PRL concentrations in the GH/PRL-cosecreting adenomas in group I. The *lower squares* correspond to the concentrations obtained by progressively increasing the weekly dose of cabergoline, *i.e.* 1.0, 1.75, 3.5, and 7.0 mg, respectively. Note the log scale for GH and PRL.

macroadenomas, and in 5, the mass reduction was at least 50%.

The weekly dose of cabergoline was 1.0 mg in eight patients and 1.75 mg in seven patients. Only in a 17-yr-old man

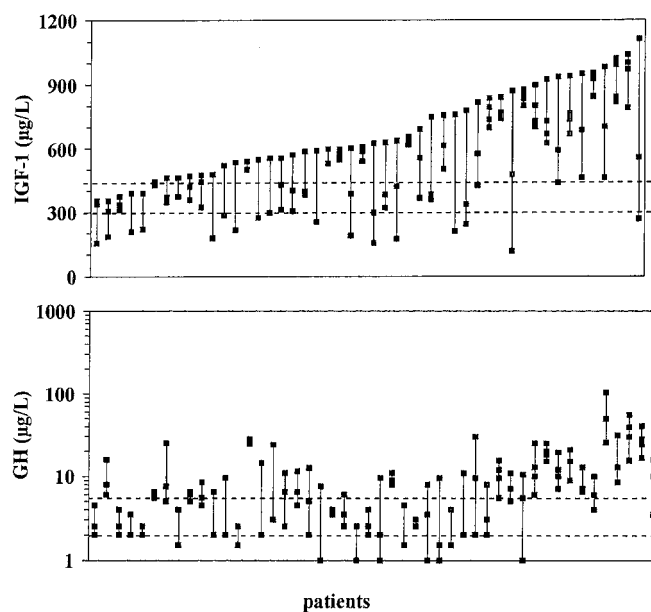


FIG. 3. The *upper squares* indicate the pretreatment plasma IGF-I and serum GH concentrations in the GH-secreting adenomas in group II. The *lower squares* correspond to the concentrations obtained by progressively increasing the weekly dose of cabergoline, *i.e.* 1.0, 1.75, and 3.5 mg, respectively. Note the log scale for GH.

with gigantism and hyperprolactinemia since the age of 9 yr was the dose progressively increased to 3.5 and 7 mg/week. This resulted in a further amelioration of the hormonal parameters and necrosis of the adenoma.

Group II

The global responses in pure GH-secreting adenomas are summarized in Table 1. The individual responses to the administration of an increasing dose of cabergoline are shown in Fig. 3.

Magnetic resonance follow-up studies were performed in 12 of 24 patients showing radiological signs of tumoral mass.

No reduction in volume was observed in 3 microadenomas. A distinct shrinkage was found in 5 of 9 macroadenomas, but none reached a 50% mass reduction.

The weekly dose of cabergoline was 1.0 mg in 13 patients and 1.75 mg in 28 patients. A further increase in the dose to 3.5 mg/week in 7 poorly responding patients could not suppress the IGF-I secretion more efficaciously.

Discussion

Dopamine agonists have been widely used in the treatment of acromegaly since the availability of bromocriptine in 1974, and more than 30 clinical studies have been published evaluating the effect of this medication (18). However, ambiguous criteria used to define therapeutical efficacy, mostly a more than 50% reduction of the GH concentration, make interpretation of the available data difficult. In general, suppression of GH secretion to a serum concentration of less than 5 $\mu\text{g/L}$ and normalization of the plasma IGF-I level, which are more stringent criteria of adequate therapy, are only obtained in 20% and 10% of acromegalic patients, respectively. Compared to prolactinomas, the treatment of acromegaly usually requires a more frequent daily intake and a higher dose of bromocriptine. Some of the constraints could be avoided by using the long acting and repeatable im form of bromocriptine or apomorphine derivatives such as quinagolide. However, the few reports concerning the efficacy of these two drugs in the treatment of acromegaly also emphasize that normalization of plasma IGF-I levels is only obtained in a limited number of patients (19, 20).

This is the first multicenter trial with cabergoline, a long acting, orally administered dopamine agonist, in a large series of unselected acromegalic patients. We showed that a decrease in IGF-I below 300 $\mu\text{g/L}$ can be obtained in 39% of patients, and a decrease in GH below 2 $\mu\text{g/L}$ can be obtained in 46% of patients. In addition, a suppression of IGF-I between 300–450 $\mu\text{g/L}$ is obtained in another 28% of patients, and a suppression of GH between 2–5 $\mu\text{g/L}$ is obtained in another 27% of patients. These results are much better than the data previously reported for bromocriptine. This can be explained to some extent by a superior pharmacological profile of cabergoline. Compared to bromocriptine, cabergoline has a more specific D2 receptor-binding capacity and possesses a much longer half-life than bromocriptine. This avoids large fluctuations in dopamine agonist activity and both enhances clinical efficacy and reduces side-effects, as has been shown in a double blind study of patients with hyperprolactinemia (14). This pharmacological advantage may be of even greater importance in acromegaly than in hyperprolactinemia, as much higher doses of dopamine agonist activity are required.

Similar to bromocriptine therapy (16), two factors were predictive for the ultimate therapeutic response to cabergoline in our study. First, the activity of acromegaly, as reflected by IGF-I or GH levels, is a negative factor, as normalization was less frequently obtained in patients with initial values above 750 or 20 $\mu\text{g/L}$, respectively. Second, a more pronounced inhibitory response was found in patients cosecreting PRL. Although immunohistochemical evidence of cosecretion could not be demonstrated in each patient, the

therapeutic response, assessed by determination of hormone levels and radiological examination, was clearly superior in group I.

The high number of acromegalic patients with normalized IGF-I levels during cabergoline treatment in our study must probably also be explained by a bias in patient selection. Indeed, some of our patients had been treated by surgery and/or radiotherapy and had only moderate elevations of IGF-I. Also, some patients included in the present study had initial GH levels below 5 $\mu\text{g/L}$ and would have been considered cured in earlier studies. However, even when patients with high IGF-I levels (>750 $\mu\text{g/L}$) were considered, 17% of normalized IGF-I values meant a doubling of success compared to the effect of bromocriptine therapy.

Until now, the therapeutic effect of cabergoline in acromegaly has been reported in 3 smaller studies. In the first, normal plasma IGF-I levels were obtained in 3 of 6 patients with a weekly dose of 0.3–0.6 mg (21). An increase in the dose to 1.2 mg in the 3 other patients was insufficient to reach normalization of IGF-I. In the second study, 11 patients were treated with a weekly dose of cabergoline between 1.0–2.0 mg (22); this resulted in a significant decrease in plasma IGF-I levels, but without normalization in any of the patients. In the last study, 10 patients each received a dose of 3.5 mg cabergoline/week (23). Substantial decreases in plasma IGF-I and GH were observed in 7 patients, and biochemical remission was achieved in 2 of them. An increase in the dose to 7.0 mg did not improve the efficacy, but induced intolerability.

Therapy with cabergoline was well tolerated, even at the higher doses. Only two patients (3%) stopped treatment because of side-effects. This confirms data from comparative studies using bromocriptine, in which 12% of patients discontinued therapy, whereas this was the case in only 3% of patients treated with cabergoline (14). In analogy to other dopamine agonists, rare cases of pleuropulmonary disease have been reported with large doses of cabergoline (up to 10 mg daily) for Parkinson's disease (24), but this seems unlikely to occur with the dose employed in our study.

In conclusion, cabergoline represents a valuable new tool in the therapeutic arsenal for acromegaly. Although not formally proven by a double blind study, its superiority to bromocriptine seems clear, as is the case in the treatment of prolactinomas. Cabergoline will, therefore, reinforce the role of dopamine agonists in the treatment of acromegaly, particularly in patients with moderately elevated plasma IGF-I levels and/or in the case of cosecretion of PRL.

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