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Prolactinomas Resistant to Standard Dopamine Agonists Respond to Chronic Cabergoline Treatment

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ABSTRACT

Cabergoline (CAB), a new, potent, and long-lasting PRL-lowering agent, was shown to be effective in tumoral hyperprolactinemia. The aim of this study was to investigate the effectiveness of CAB in patients with prolactinoma proven to be resistant to bromocriptine (BRC) and quinagolide (CV 205–502).

Twenty-seven patients (19 macro- and 8 microprolactinomas) were treated with CAB at a weekly dose of 0.5–3 mg for 3–22 months. All patients were previously shown to be resistant to BRC, and 20 of them were resistant to CV 205–502 as well. Basal serum PRL levels before CAB treatment ranged from 108-3500 μg/L in macroprolactinomas and from 64–205 μg/L in microprolactinomas. Gonadal failure was present in all patients, whereas symptoms of tumor expansion, such as visual field defects and headache, were present in 10 of 27 patients. Eight macroprolactinomas had previously undergone surgery and/or radiotherapy.

CAB treatment normalized serum PRL levels in 15 of 19 macroprolactinomas and in all 8 microprolactinomas. In 3 of the remaining 4 patients it caused a notable decrease in prolactinemia (89%, 80.5%, and 68.7% of the baseline). Only 1 patient was withdrawn from CAB therapy after 3 months at the weekly dose of 2 mg due to the absence of any significant clinical, hormonal, or radiological improvement. Gonadal function was restored in 18 of 27 patients, galactorrhea disappeared in 5 of 6 women, and headache improved in 7 of 8 patients. A significant tumor shrinkage was detected by computed tomography and/or magnetic resonance imaging in 9 macroprolactinomas and 4 microprolactinomas. CAB was well tolerated by all patients, except 6 who referred slight and short-lasting nausea, postural hypotension, abdominal pain, dizziness, and sleepiness at the beginning of treatment. In particular, CAB was well tolerated by 19 patients previously shown to be poorly tolerant to BRC and CV 205–502.

In conclusion, CAB may represent, at the moment, the only successful therapy for prolactinoma-bearing patients resistant to BRC and CV 205–502, as it normalized PRL levels in 22 of 27 patients, reduced tumor size in 13 of 27 patients, and improved clinical symptoms in 25 of 27 patients in the present study. (*J Clin Endocrinol Metab* **82:** 876–883, 1997)

IT HAS BEEN widely recognized in the last 2 decades that medical therapy with dopamine agonists has become the first therapeutic option in prolactinomas (1, 2). Dopamine receptor agonists normalize serum PRL concentrations in about 90% of cases and cause tumor shrinkage in about 60% of prolactinomas (3, 4).

A minority of patients, however, do not respond satisfactorily to the most widely used dopamine agonist, bromocriptine (BRC) (5–7). It has been suggested that the failure of BRC to reduce PRL levels can be the consequence of abnormalities at the dopamine D_2 receptor or at a postreceptor level (7–9). On the other hand, the possibility that a reduction of these high affinity receptors occurs cannot be ruled out (7–9). In line with other reports, we previously observed that a nonergot dopamine agonist, namely quinagolide (CV 205–502), was effective in 24 patients shown to be resistant or intolerant to BRC (10). The effectiveness of this compound has been attributed both to its specific binding to the dopamine D_2 receptor (9), whereas BRC binds to D_1 and D_2 receptors, and to its higher potency that also allowed treatment of poorly tolerant patients.

In recent years, cabergoline (CAB), a synthetic ergoline, selective and long-lasting D_2 dopamine agonist that inhibits PRL secretion in both healthy and hyperprolactinemic subjects, has been developed. CAB is characterized by a duration of action as long as 21 days after a single oral dose of 0.3–1 mg (11–13). In a multicenter study, 95% of hyperprolactinemic women showed a decrease in serum PRL levels during chronic CAB administration at the dose of 1 mg twice weekly (14). Moreover, CAB has been shown to be more effective and better tolerated than BRC in a multicenter, randomized, 24-week trial in 459 hyperprolactinemic women (15) and in a few patients with macroprolactinoma as well (16).

The aim of the present study was to evaluate whether CAB could represent an effective therapy for patients with prolactinomas previously shown to be resistant to BRC and/or CV 205–502 treatment. The results of the present study showed that CAB is effective in reducing serum PRL levels, in restoring gonadal function and in shrinking tumor mass in the majority of patients.

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Subjects and Methods

Patients

Twenty-seven patients (9 men and 18 women; age, 15–64 yr) entered this open study after their informed consent had been obtained. Nineteen had macroprolactinoma; 8 had microprolactinoma. Eight macroprolactinoma patients had undergone previous surgery, but hyperprolactinemia and/or residual tumor persisted. Three patients (no. 2–4, Table 1) had been previously irradiated. Before starting CAB treatment, baseline serum PRL levels were 520.5 ± 176.6 μg/L (range, 180-3500 μg/L; mean ± SEM) in macroprolactinoma patients and 146 ± 18.9 μg/L (range, 64–212 μg/L) in microprolactinoma patients. All 27 patients had been treated with BRC, 20 of them had also been given CV 205–502, for 3–12 months before CAB treatment was started. The patient's profile at study entry and serum PRL responses to BRC, CV 205–502, and CAB treatments are shown in Table 1. In line with others (5–7), resistance to BRC, administered in daily doses of 15 mg for at least 3 months, was defined by an absent or poor response in the normalization of PRL levels, the lack of tumor mass shrinkage, or both. Similarly, resistance to CV 205–502 was defined by an absent or poor therapeutic response to a daily dose of 0.6 mg for at least 3 months. BRC and CV 205–502 were discontinued at least 3 weeks before starting CAB therapy in all patients except two (no. 18 and 19, Table 1), who had huge tumors on magnetic resonance imaging (MRI).

Seven men had loss of libido and impotence, whereas 17 women had menstrual disturbances. Six women had spontaneous or provocative galactorrhea. Four patients with macroprolactinoma (2 previously subjected to surgery and radiotherapy) had panhypopituitarism (Table 2).

Screening, follow-up, and drug treatment schedule

Routine clinical and hormonal evaluations showed no evidence of any thyroid or adrenal abnormalities, except for secondary hypothyroidism and hypocorticism in 4 patients with panhypopituitarism (Table 2). These patients received a standard replacement therapy with L-T_4 and cortisone acetate before starting CAB therapy. Before treatment, the average PRL levels was calculated on the basis of a 6-h time course with hourly sampling (0800–1400 h). After 15, 30, 60, 90, 180, and 360 days of treatment, serum PRL levels were assayed at 0800 h in a single sample. A general clinical examination was performed every month. CAB therapy was started at a dose of 0.25 mg once weekly for the first week, twice weekly during the second week, and then 0.5 mg twice weekly. Starting from the second month of treatment, adjustment of the dose was carried out on the basis of serum PRL suppression. Thus, the dose of CAB was progressively increased up to 1 mg twice weekly in seven patients and up to 1.75 mg (0.25 mg daily) in one patient (no. 12) after 6 months of treatment. In two other patients (no. 4 and 6) the dose was further increased up to 3 mg/week after 3 months of treatment; initially, the dose was given twice weekly and then 0.5 mg/day, 6 days/week.

Radiological imaging

The MRI was carried out using a superconductive magnetic resonance (0.5–1.0 Tesla) and superficial coil in axial, coronal, and sagittal sections. The acquisitions were spin echo with a 1000-msec repetition time and a 40- to 120-ms echo time of 21 msec. MRI was performed before and after 6 and 12 months of CAB administration. In two nonoperated macroprolactinomas, MRI was also carried out after 3 months of treatment. Tumor shrinkage, documented by MRI scan, was quantified in a semiquantitative way as follows: absent, less than 25% as not significant, 25–50% as moderate, and greater than 50% as notable tumor size reduction of pretreatment size.

Visual field

Visual field examination was performed with the Goldmann-Friedmann perimetry. Visual field assessment was carried out in all patients before CAB administration and again every 6 months in patients with visual field defects.

Assay

Serum PRL levels were assessed by RIA using commercial kits (Radim, Pomezia, Italy). The intra- and interassay coefficients of variation for PRL were 5% and 7%, respectively. The normal range for PRL was below 20 μg/L.

Statistical analysis

Data were expressed as the mean ± SEM. Statistical analysis was performed by ANOVA, followed by the Newman-Keuls test where appropriate. The significance was set at 5%.

Results

The responses of serum PRL to BRC, CV 205–502, and CAB in the 27 patients are reported in Table 1. Previous therapy with BRC and CV 205–502 significantly reduced serum PRL levels before CAB therapy was started; however, normoprolactinemia was never reached, although a significant tumor shrinkage was obtained in 4 patients (no. 1, 10, 16, and 19). In both macro- and microprolactinomas, BRC and CV 205–502 treatments induced a similar percent inhibition of serum PRL concentrations, whereas CAB treatment induced a significantly greater percent inhibition of serum PRL concentrations (Fig. 1).

Effect of CAB treatment on serum PRL levels (Table 1)

CAB administration for 1–6 months normalized serum PRL levels in 9 of 19 macroprolactinomas (Fig. 2) and in all 8 microprolactinomas (Fig. 3). Moreover, CAB notably decreased PRL levels in 9 of the remaining 10 patients. In the last patient (no. 18, Table 2), CAB therapy was withdrawn after 3 months because of the absence of any significant change in the clinical, hormonal, or radiological picture. After 1 yr of CAB therapy, serum PRL concentrations remained suppressed in all of these 17 patients and were normalized in three other patients (no. 6, 9, and 10, Table 2). Furthermore, serum PRL levels reached values close to the normal range in another three patients (no. 1, 5, and 12, Table 2). Two of these patients (no. 5 and 12) normalized serum PRL levels after 18 months of treatment. In all of the patients, the percentage of PRL decrease during CAB treatment was significantly greater than that during BRC or CV 205–502 treatment (Fig. 1).

Effect of CAB treatment on clinical symptoms (Table 2)

Improvement of gonadal failure and headache was observed in 18 of 27 patients and in 7 of 8 patients, respectively. Menses resumed in all women except 4; 2 (no. 4 and 23) remained oligomenorrheic, 1 with primary amenorrhea (no. 6) remained amenorrheic, and 1 (no. 26) had early menopause, as diagnosed by progressively increased FSH and LH levels. Galactorrhea disappeared in all 6 patients. Improvement of sexual potency was reported by 7 adult men after 1–6 months of treatment.

MRI results

CAB treatment induced a tumor shrinkage of 25% or more of the pretreatment size in six macroprolactinoma patients and one microprolactinoma patient and of more than 50% in two macroprolactinoma and three microprolactinoma patients that completely disappeared at MRI after 1 yr of CAB treatment. In two macroprolactinoma patients, shrinkage was evident after as early as 3 months of therapy (no. 6, Fig.

TABLE 1. Effect of chronic administration of bromocriptine, CV 205-502, and cabergoline on serum PRL levels and tumor mass in the 27 patients

Patient sex, age (yr)	Response to bromocriptine therapy			Response to CV 205-502 therapy			Response to cabergoline therapy		
	Serum PRL levels (μg/L)		Tumor shrinkage (% of pretreatment value)	Serum PRL levels (μg/L)		Tumor shrinkage (% of pretreatment value)	Serum PRL levels (μg/L)		Tumor shrinkage (% of pretreatment value)
	Basal	Nadir		Basal	Nadir		Basal	Nadir	
Macroprolactinomas									
1. M,15	150	61	>50	165	46	Absent	143	20	Absent
2. M,15^{S,RT}	1600	185	Absent	870	44	Absent	491	8.6	<25
3. M,16^{S,RT}	731	540	Absent	646	211	Absent	512	15	25–50
4. F,17^{RT}	563	234	Absent	685	279	Absent	473	50.7	<25
5. F,17^{S}	200	75	Absent	/	/	/	205	16.9	25–50
6. F,21	140	40	Absent	150	49	<25	110	16.7	25–50
7. F,23	241	68	Absent	273	40	<25	230	0.1	25–50
8. F,25^{S}	336	119	<25	497	58	Absent	293	19	25–50
9. M,26^{S}	380	130	Absent	222	174	Absent	265	19.9	Absent
10. F,28	1348	99	25–50	958	125	Absent	724	8.9	Absent
11. F,28	196	52	Absent	202	70	<25	271	0.2	>50
12. M,30^{S}	1346	370	Absent	443	67	Absent	632	19.5	Absent
13. F,31	193	76	Absent	135	66	Absent	241	47	25–50
14. F,34	93	50	<25	131	74	Absent	108	0.5	>50
15. F,35^{S}	138	100	Absent	136	170	Absent	180	56.3	Absent
16. M,41	210	31	>50	/	/	/	176	8	Absent
17. M,51^{S}	242	51	Absent	351	44	Absent	254	6.2	Absent
18. M,52	4000	2200	Absent	/	/	/	3500	2000	Absent
19. M,64	973	452	>50	/	/	/	1182	0.1	Absent
Mean ± SEM	688.4 ± 213.5	259.6 ± 112.9		388 ± 84.3	140.5 ± 32.1		520.5 ± 176.6	121.8 ± 104.4	
Microprolactinomas									
20. F,21	194	45	Absent	131	47	Absent	166	15.8	25–50
21. F,23	160	31	Absent	150	47	Absent	184	16.8	>50
22. F,24	95	27	Absent	/	/	Absent	93	2.1	>50
23. F,25	75	51	Absent	/	/	Absent	64	19	Absent
24. F,26	151	47	Absent	143	73	Absent	212	6.2	<25
25. F,33	120	53	Absent	230	96	Absent	131	4	<25
26. F,40	144	70	Absent	136	77	Absent	123	0.1	>50
27. F,52	250	35	Absent	/	/	Absent	205	16	Absent
Mean ± SEM	148.6 ± 19.6	44.9 ± 4.9		158 ± 18.3	68 ± 9.4		146 ± 18.9	10 ± 2.7	

Superscript labels: S, surgery; RT, radiotherapy. M, male; F, female. Tumor shrinkage at MRI was quantified semiquantitatively as follows: absent, <25% as not significant; 25–50% as moderate, >50% as notable.

TABLE 2. Time course of the effect of chronic cabergoline administration on PRL levels, tumor size, and clinical symptoms in the 27 patients

Patient no.	Response to cabergoline therapy				Radiological findings[a]			Symptomatology		
	Dose (mg/week)	Duration (months)	Nadir of PRL (μg/L)	Obtained after months	Before cabergoline	After cabergoline	Obtained after months	Before cabergoline	After cabergoline	Obtained after months
1	1	17	20	17	Empty sella	Unchanged	12	H	None	2
2	1	17	8.6	3	Residual tumor	Unchanged	12	PHP, VFD	PHP	6
3	2	24	15	16	Residual tumor	Shrinkage	12	PHP	PHP	/
4	3	8	50.7	7	Intrasellar MP	Unchanged	6	A	O	6
5	1	8	16.9	8	Residual tumor	Shrinkage	6	A**,G,H	A,H	3
6	3	12	16.7	5	Intrasellar MP	Shrinkage	6	A	None	3
7	1	14	0.1	6	Intrasellar MP	Shrinkage	6	A	None	2
8	1	14	19	5	Residual tumor	Shrinkage	9	A	None	2
9	2	21	19.9	14	Residual tumor	Unchanged	12	L-P failure	None	6
10	1	18	8.9	15	Intrasellar MP	Unchanged	12	A	None	5
11	1	13	0.2	6	Suprasellar MP	Shrinkage	6	H,A	None	3
12	1.75	15	19.5	15	Empty sella	Unchanged	12	L-P failure	None	5
13	2	14	47	8	Suprasellar MP	Shrinkage	3	A	None	5
14	1	13	0.5	7	Intrasellar MP	Shrinkage	6	A,G	None	6
15	2	7	56.3	3	Empty sella	Unchanged	6	A	None	3
16	1	12	8	6	Intrasellar MP	Unchanged	9	H	None	2
17	1	12	6.2	4	Empty sella	Unchanged	12	H, L-P failure	None	4
18	2	3	2000	0.5	Extrasellar MP	Unchanged	3	PHP, VFD	PHP, VFD	/
19	1	14	0.1	2	Extrasellar MP	Unchanged	12	PHP, VFD	PHP	6
20	1	18	15.8	16	7 mm mp	Shrinkage	12	A,G	None	6
21	1	14	16.8	6	7 mm mp	Shrinkage	9	H,A	None	6
22	0.5	10	2.1	2	5 mm mp	Shrinkage	6	A	None	2
23	0.5	13	19	12	3 mm mp	Unchanged	12	A,G	O	6
24	1	12	6.2	3	10 mm mp	Unchanged	12	A,G	None	3
25	0.5	16	4	8	6 mm mp	Unchanged	12	H,A	None	6
26	1	18	0.1	3	6 mm mp	Shrinkage	12	H,A,G	Menopause	12
27	1	7	16	6	8 mm mp	Unchanged	6	Menopausal age	/	/

[a] The maximal diameter of microadenomas is shown in millimeters.

MP, macroprolactinoma; mp, microprolactinoma; PHP, panhypopituitarism; VFD, visual field defects; A, amenorrhea; A**, primary amenorrhea; L-P failure, libido and potency failure; H, headache; G, galactorrhea.

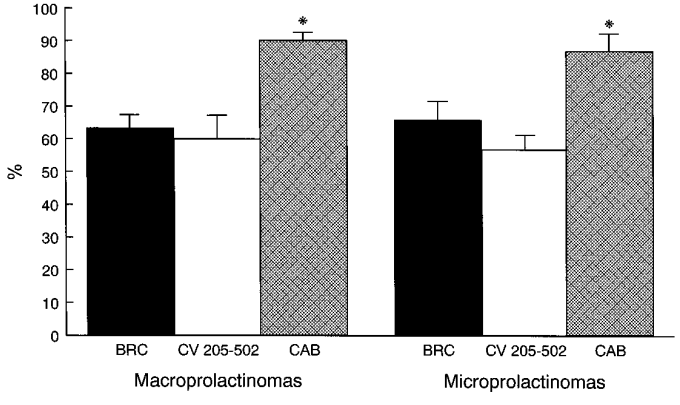

FIG. 1. Percentage of decrease in serum PRL during BRC, CV 205–502, and CAB therapies in macroprolactinoma and microprolactinoma patients. *, $P < 0.01$ *vs.* BRC and CV 205–502 treatments.

4, and 13) despite the persistence of moderate hyperprolactinemia. In addition, shrinkage was documented in a patient (no. 3) resistant to previous surgery, radiotherapy, and 5-yr treatment with BRC and CV 205–502.

Tolerability

As shown in Table 3, CAB was well tolerated. Six of 27 patients reported mild and short-lasting side-effects that consisted of nausea, postural hypotension, abdominal pain, sleepiness, and dizziness. These side-effects disappeared spontaneously during the second week of treatment. No patient was withdrawn from CAB therapy for side-effects. CAB was optimally tolerated by 16 patients who had reported side-effects during previous BRC and CV 205–502 treatments.

Discussion

The results of the present open study showed that prolactinomas hyporesponsive to standard dopamine agonists respond to chronic CAB treatment. Particularly, CAB brought down serum PRL to normal values and caused the restoration of gonadal function in 70% of patients in which BRC and CV 205–502 had been unable to normalize serum PRL levels and gonadal function despite long term and high dose treatments. Furthermore, CAB induced a significant shrinkage in tumor mass in eight macroprolactinoma patients and four microprolactinoma patients in which BRC and CV 205–502 treatment had failed.

At present, the molecular mechanism underlying the resistance to BRC and/or CV 205–502 is not fully elucidated. Pellegrini *et al.* (8) showed that in some patients bearing BRC-resistant macroprolactinomas there was a marked decrease in the density of high affinity D_2 dopamine receptor-binding sites in tumor lactotrophs. As CAB

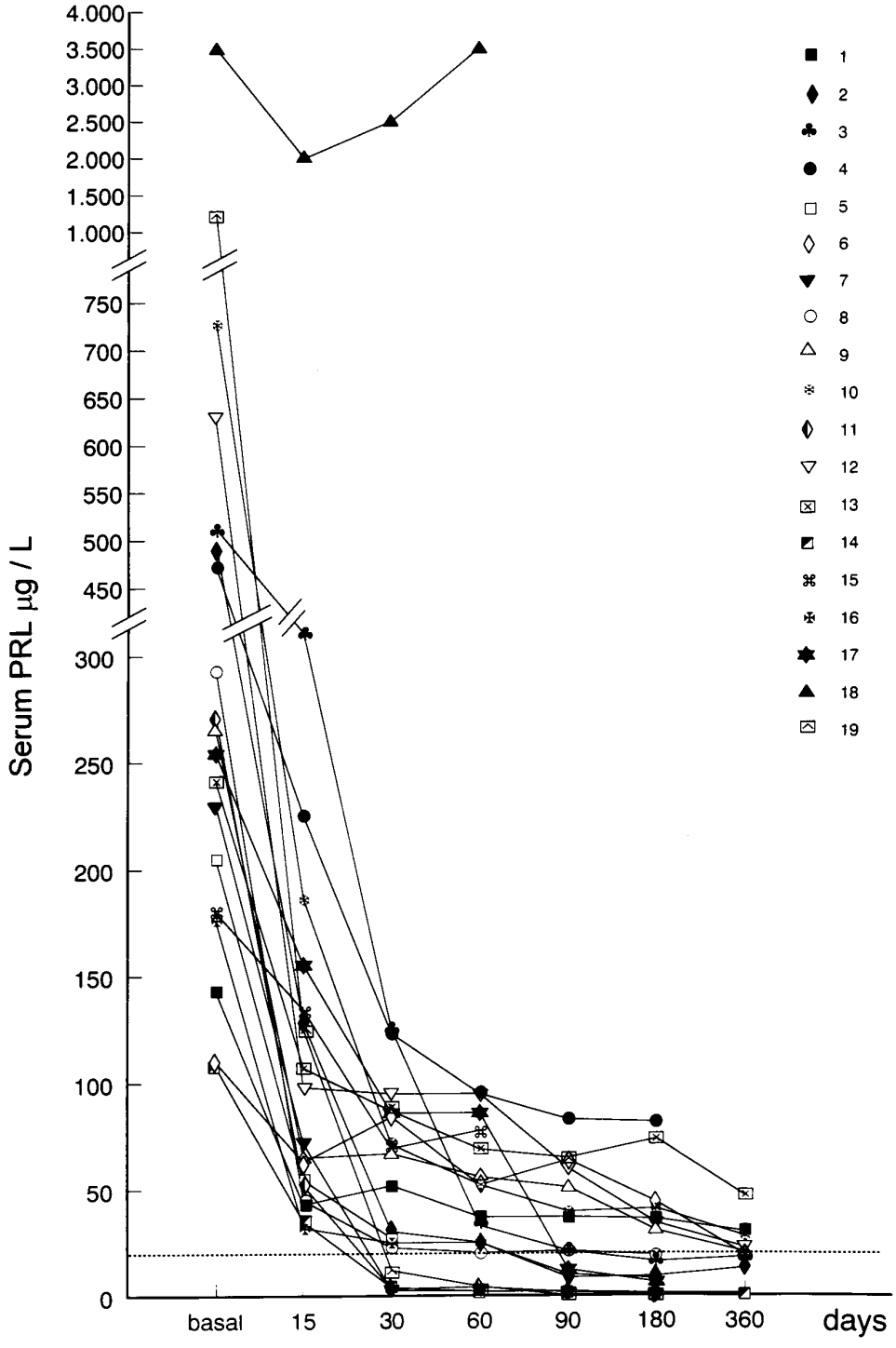

FIG. 2. Serum PRL profile before and during CAB therapy in the 19 macroprolactinoma-bearing patients. Patients are numbered in line with tables. The *broken line* indicates the upper limit of the normal range.

has been shown to possess a higher affinity for dopamine-binding sites in rat striatum compared to BRC (16), it is possible that a higher affinity in resistant prolactinomas may account for CAB effectiveness. Moreover, the comparative time-course analysis of the regional inhibition of [^{3}H]*N-n*-propylnoramorphine-binding receptors in different rat brain areas, such as striatum, olfactory tubercules, thalamus and hypothalamus, and adeno- and neurohypophysis, showed that CAB occupied D_2 receptor for a longer time than did BRC (16). Further studies in the rat striatum and adenohypophysis showed that CAB receptor occupancy was dose dependent and still detectable 72 h after iv administration (16). Another important finding is that CAB reduces the size of the estradiol-induced PRL-secreting tumor in the rat (17) and *de novo* PRL synthesis (18) to a greater extent than does BRC. On the other hand,

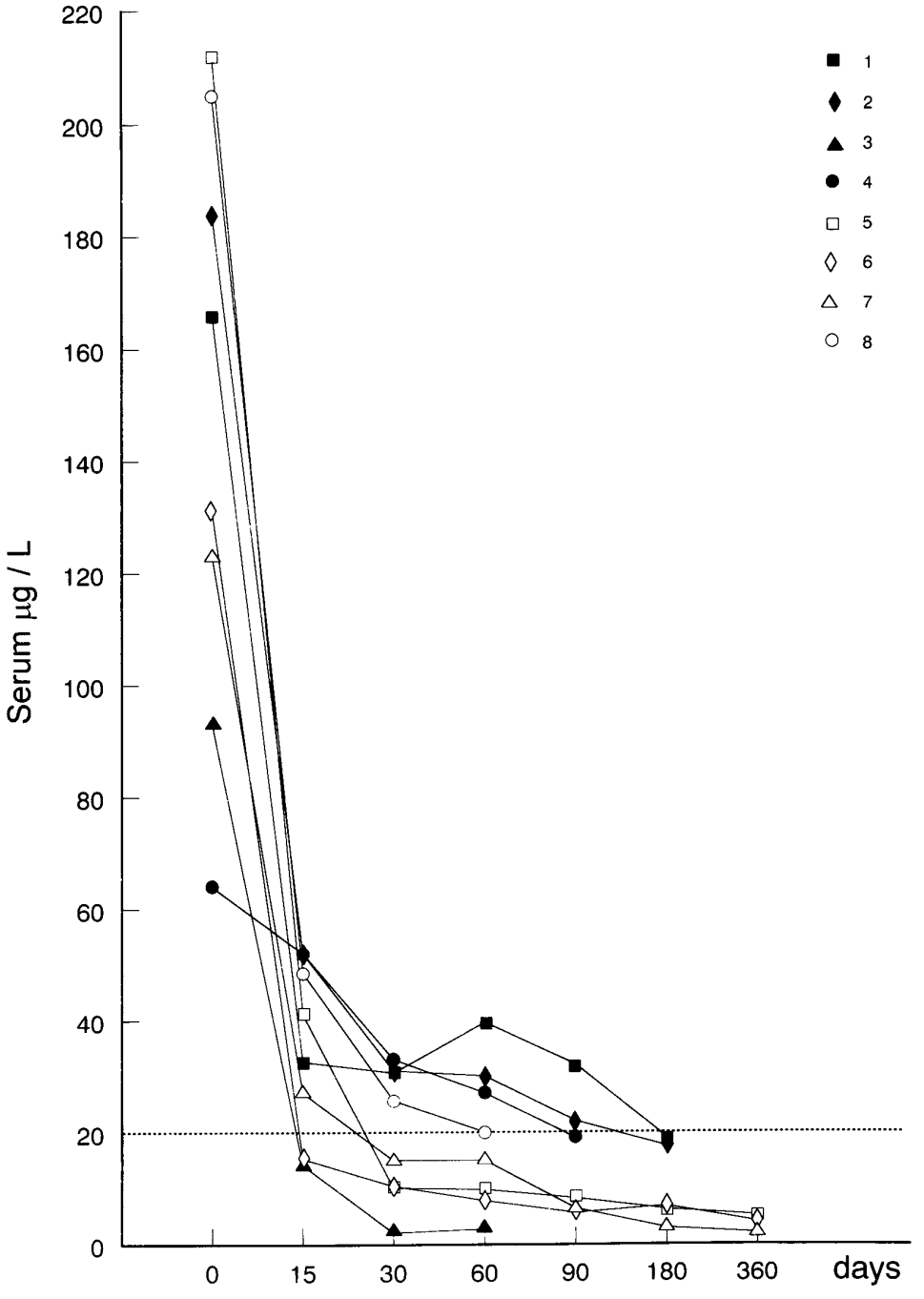

FIG. 3. Serum PRL profile before and during CAB therapy in the eight microprolactinoma-bearing patients. Patients are numbered in line with tables. The *broken line* indicates the upper limit of the normal range.

the possibility exists that the peculiar pharmacokinetic profile of CAB, characterized by a prolonged half-life and a notably slow elimination from highly perfused tissues such as the pituitary (11), could be responsible at least in part for the effectiveness of CAB in resistant patients. Finally, another point not to disregard when explaining the effectiveness of CAB compared to those of BRC and CV 205–502 is the greater tolerability of this new ergoline derivative. In fact, this pharmacological property made it possible to increase the weekly dose of CAB in 40% of hyporesponsive macroprolactinomas and consequently enhanced the success rate of this therapy. This aspect is of crucial relevance in the chronic treatment of prolactinomas, because the appearance of side-effects can preclude the achievement of an effective dose with consequent persistence of the hyperprolactinemic syndrome.

In conclusion, the results of this study indicate that CAB might be a valid, safe, and well tolerated therapy in patients proven to be resistant or even hyporesponsive to high doses of other dopaminergic agents, including BRC and CV 205–502.

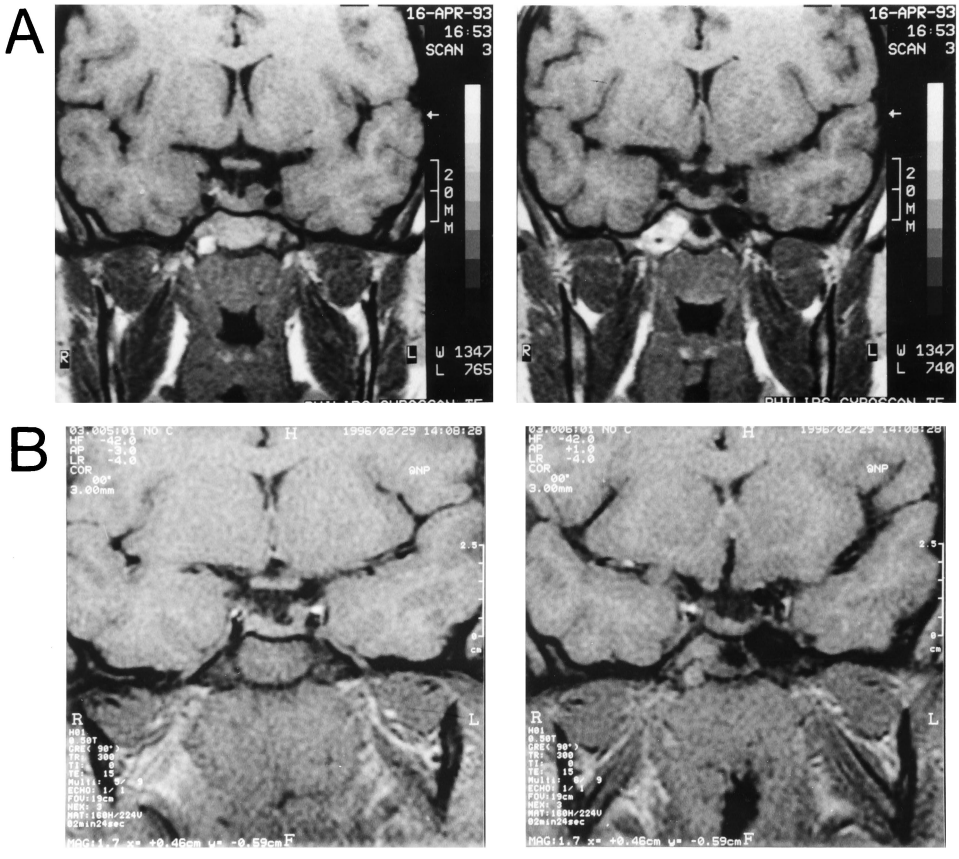

FIG. 4. MRI before (A) and after 3 months of CAB treatment (B) in a patient with macroprolactinoma (no. 6, Tables 1–3). Shrinkage was evident in two different coronal sections.

TABLE 3. Comparison of tolerability to the chronic bromocriptine, CV 205-502 and cabergoline treatment in the 27 patients

Patient no.	Bromocriptine	CV 205-502	Cabergoline
1	V^2	V^2	None
2	N^1, V^2	AP^1, N^2	D^1
3	P^2, AP^2	AP^1	AP^1
4	V^2	AP^1, D^1	None
5	N^1	N^1	None
6	V^2, P^2	P^2	S^2
7	P^2	A^2	None
8	N^1, V^1, P^1	N^1, A^2	None
9	N^1, V^1, P^2	P^1	None
10	None	None	None
11	N^1	None	None
12	N^1, V^1, S^1	S^1	None
13	N^1	None	None
14	V^2, P^1	V^1	None
15	N^1, V^2	N^1	P^1
16	N^1, V^2	D^2, P^1, S^1	None
17	P^2, N^1	P^1	N^1
18	S^2	None	None
19	N^2, S^2	S^3	N^1
20	AP^2	None	None
21	P^2	P^1	None
22	None	/	None
23	None	/	None
24	V^2	AP^1, S^1	None
25	V^3, P^2	P^2	None
26	N^2	N^1, S^2	None
27	N^1	/	None

A, Anorexia; AP, abdominal pain; D, dizziness; N, nausea; P, postural hypotension; S, sleepiness; V, vomiting. Superscript score of side-effects: 1 = mild; 2 = moderate; 3 = severe.

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The National Institute on Aging announces the annual Summer Institute on Aging Research, a week-long workshop for new investigators, focused on current issues, research methodologies, and funding opportunities. The program will also include consultations on the development of research interests. The 1997 Summer Institute will be held July 19–25 in Airlie, VA. Support is available for travel and living expenses.

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