Clinical Endocrinology (2000) **53,** 53–60

The effect of quinagolide and cabergoline, two selective dopamine receptor type 2 agonists, in the treatment of prolactinomas

Antonella Di Sarno, Maria Luisa Landi, Paolo Marzullo, Carolina Di Somma, Rosario Pivonello, Gaetana Cerbone, Gaetano Lombardi and Annamaria Colao

Department of Molecular and Clinical Endocrinology and Oncology, 'Federico II' University of Naples, Italy

(Received 1 March 1999; returned for revision 24 March 1999; finally revised 18 November 1999; accepted 10 March 2000)

Summary

OBJECTIVE To compare effectiveness and tolerability of quinagolide (CV 205–502) and cabergoline (CAB) treatments in 39 patients with prolactinoma.

STUDY DESIGN All 39 patients were treated first with quinagolide for 12 months and then with cabergoline for 12 months. A wash-out period was performed in all patients after 12 months of both treatments in order to evaluate recurrence of hyperprolactinaemia.

PATIENTS Twenty-three patients with microprolactinoma (basal serum PRL levels 1620–18750 mU/l) and 16 patients with macroprolactinoma (basal serum PRL levels 4110–111000 mU/l), previously shown to be intolerant of bromocriptine. All patients had gonadal failure and 11 patients with macroprolactinoma had visual field defects. Five patients with macro- and one with microprolactinoma had previously undergone surgery.

STUDY PROTOCOL The starting doses of quinagolide and CAB were 0·075 mg/day and 0·5 mg/week, respectively, subsequently increased up to 0·6 mg once daily and 1·5 mg twice weekly, respectively. Serum PRL levels were measured monthly for the first 3 months and then quarterly for 12 months. PRL levels were assayed weekly for the first month and then monthly during the wash-out period. Tumour shrinkage was evaluated by serial magnetic resonance imaging (MRI) studies of the hypothalamus–pituitary region at study entry and after 6 and 12 months of both treatments in micro- and macroprolactinomas.

RESULTS After 12 months of quinagolide treatment, serum PRL levels normalized in all 23 patients with microprolactinoma (100%) and in 14 out of 16 with macroprolactinoma (87·5%). A tumour volume reduction of greater than 80% was documented by MRI studies in five of 23 (21·7%) patients with microprolactinoma and in four of 16 (25%) with macroprolactinoma. All patients had recurrence of hyperprolactinaemia after 15–60 days withdrawal of quinagolide treatment. However, before starting CAB treatment basal PRL levels were significantly lower than before quinagolide treatment both in microprolactinomas (4667·4 ± 714·7 *vs.* 2636·1 ± 262·3 mU/l, $P = 0{\cdot}006$) and in macroprolactinomas (24853·1 ± 7566·7 *vs.* 3576·6 ± 413·0 mU/l, $P = 0{\cdot}013$). After 12 months of CAB treatment, serum PRL levels normalized in 22 out of 23 patients with microprolactinoma (95·6%) and in 14 out of 16 with macroprolactinoma (87·5%). No difference in PRL nadir was found after quinagolide and CAB treatments both in micro 174·6 ± 30·6 *vs.* 169·8 ± 37·9 mU/l, $P = 0{\cdot}5$) and in macroprolactinomas (277·5 ± 68·4 *vs.* 341·8 ± 95·2 mU/l, $P = 0{\cdot}6$). A tumour volume reduction of greater than 80% was documented by MRI studies in seven other patients with microprolactinoma (30·4%) and in five other patients with macroprolactinoma (31·2%). After CAB treatment, further tumour shrinkage ranging 4–40% and 2–70% was observed in 12 micro- and seven macroprolactinomas, respectively. The percentage of tumour shrinkage after CAB was significantly higher than that observed after quinagolide in microprolactinomas (48·6 ± 9·5 *vs.* 26·7 ± 4·5%, $P = 0{\cdot}046$) but not in macroprolactinomas (47·0 ± 10·6 *vs.* 26·8 ± 8·4%, $P = 0{\cdot}2$). The withdrawal from CAB treatment, induced an increase in serum PRL levels in all macroprolactinomas between 15 and 30 days, in 15 out of 23 microprolactinoma after 30 days, and in four patients after 2–4 months. In the remaining four patients serum PRL levels remained normal after 12 months of CAB withdrawal.

Both compounds were tolerated satisfactorily by all patients. In the first week of quinagolide treatment, 12

Correspondence: Dr Annamaria Colao, Department of Molecular and Clinical Endocrinology and Oncology, 'Federico II' University of Naples, via S. Pansini 5, 80131 Napoli, Italy. Fax: + 39 81 7463668; E-mail: colao@unina.it

patients reported nausea and postural hypotension, which spontaneously disappeared during the second-third week of treatment. None of the 39 patients reported side-effects during CAB treatment.

CONCLUSIONS Both quinagolide and CAB treatments, induced the normalization of serum PRL levels in the great majority of patients with prolactinoma. Tumour shrinkage was recorded in 22–25% of patients after quinagolide and in 30–31% after CAB treatment. However, CAB induced notable tumour shrinkage even in patients who had partial tumour reduction after quinagolide. CAB treatment was tolerated better than quinagolide treatment in 12 out of 39 patients (30·7%). On this basis, both compounds can be used as first line treatment in prolactinomas, while CAB is preferable in patients poorly tolerant to other dopamine agonists. Finally, the long-lasting hypoprolactinemic effect of CAB allowed an intermittent treatment schedule in eight out of 23 patients with microprolactinomas with a better cost:effectiveness ratio.

Pharmacotherapy with compounds with dopamine-agonist activity is the current first line treatment for both microprolactinomas and macroprolactinomas (Vance *et al*., 1984; Molitch *et al*., 1997; Colao & Lombardi 1998). The objectives of therapy in these tumours are the control of PRL hypersecretion with return to the eugonadal state, tumour shrinkage and reversal of visual field defects, restoration of pituitary function, particularly in patients with macroprolactinoma, and finally, the prevention of disease recurrence (Colao *et al*., 1998). In over two decades, extensive experience has been accumulated by using bromocriptine treatment that suppresses PRL secretion, restores gonadal function and shrinks prolactinomas in approximately 90% of cases (Vance *et al*., 1984). Other compounds provided with similar beneficial effects were mesulergine, pergolide, and lisuride, but the experience with these compounds in the treatment of hyperprolactinemic syndromes is still limited (Grossman *et al*., 1985; Lamberts & Quick, 1991). However, side-effects occur frequently at the beginning of therapy with these drugs. The most important problems are gastrointestinal disturbance (nausea with or without vomiting), postural hypotension, dizziness and headache. Side-effects are generally mild and transient but sometimes they necessitate reduction in drug dosage, thus preventing the attainment of normoprolactinaemia (Grossman *et al*., 1985; Liuzzi *et al*., 1985; Lamberts *et al*., 1991).

In a significant proportion of patients side-effects are so severe as to induce withdrawal from therapy. Side-effects are considered to be due to the elevated drug levels reached in the peripheral circulation after absorption, since most of these compounds have a short half-life so that they have to be administered two or three times daily. Moreover, in some patients normoprolactinaemia is not achieved even after increasing the dose of the drugs (20 mg/day for bromocriptine). These patients are considered partially resistant to dopamine agonists, but usually a poor therapeutic response is due to difficulty achieving a effective dose because of side-effects, rather than to abnormalities at the D_2 receptor level (Pellegrini *et al*., 1989; Bevan *et al*., 1992; Colao *et al*., 1997a).

In recent years, new compounds have been developed with the aim at providing drugs that are selective and long-lasting, so as to allow disease control with better compliance (Brue *et al*., 1992; Vilar & Burke, 1994; Biller *et al*., 1996; Colao *et al*., 1997b). In particular, two compounds characterized by a selectivity for the D_2 receptor have received great attention for their increased efficacy and tolerability: quinagolide (CV 205–502) and cabergoline (CAB). In most patients with prolactinoma both quinagolide, a nonergot, and CAB, an ergot derivative, have been demonstrated to normalize serum PRL levels, restore gonadal function and reduce tumour mass (Webster *et al*., 1994; Colao *et al*., 1998). In the majority of studies the efficacy of quinagolide or CAB treatments was compared to that of bromocriptine (BRC) while a comparison of the effects of these two compounds has been investigated only in one report (Giusti *et al*., 1994) demonstrating that the clinical effects of the two drugs are very similar. No study has, however, investigated the effect of quinagolide and CAB treatment withdrawal on serum PRL levels.

The aim of this study was to compare the effectiveness and tolerability of a 12-month treatment with quinagolide and CAB in 39 patients with prolactinoma. The effect of quinagolide and CAB withdrawal was also investigated.

Patients and methods

Patients

Twenty-three patients with microprolactinoma (21 women and two men; aged 23–54 years) and 16 with macroprolactinoma (10 women and six men; aged 19–76 years) gave their written informed consent to participate in this double treatment single group cross-over study. Five patients with macroprolactinoma and one with microprolactinoma had undergone previous neurosurgery, but hyperprolactinaemia and/or residual tumour mass persisted. At study entry, serum PRL levels ranged from 1620 to 18750 mU/l in microprolactinomas and 4100–111000 mU/l in macroprolactinomas. All men had loss of libido and impotence, whereas all women had menstrual disturbance; 19 women had spontaneous or expressible galactorrhoea. Bitemporal hemianopia was shown by visual

perimetry in 11 patients with macroprolactinoma, in five of these visual disturbances persisted after surgery. All patients were considered to be intolerant of BRC treatment on the basis of the appearance of moderate-to-severe side-effects (nausea, vomiting, headache, postural hypotension or dizziness) after the first administration of 2·5 mg of the drug. The side-effects were considered by the patients to be so severe as to necessitate treatment discontinuation.

Study protocol

Both quinagolide and CAB treatments were given for 12 months. Quinagolide was given orally at the starting dose of 0·075 mg once daily and CAB was given orally at the starting dose of 0·5 mg once weekly; in order to obtain normoprolactinaemia, the dose of the drugs was increased up to 0·6 mg daily and 1·5 mg twice weekly, respectively. Basal PRL levels were measured as average value of a 6 h profile with hourly sampling (0800–1400 h). After 1, 2, 3, 6, 9 and 12 months of quinagolide and CAB treatments, fasting serum PRL levels were assayed in the morning as an average of three samples. The recurrence of hyperprolactinaemia was investigated in all patients after withdrawal from quinagolide and CAB treatment: serum PRL levels were assayed weekly for the first month and then monthly. In the present series hyperprolactinaemia reccurred after 15–60 days of quinagolide withdrawal and after 15 days to 4 months of CAB withdrawal. In four out of 39 patients, recurrence of hyperprolactinaemia after CAB withdrawal could not be investigated since they still had normal PRL levels (see Results section below). Gonadal status was investigated before and quarterly during follow-up. Routine clinical and hormonal evaluations showed no thyroid or adrenal abnormalities in any of the 39 patients.

Magnetic resonance imaging studies

MRI studies were 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 1000 msec repetition time and 40–120 msec echo time. Tumour shrinkage was defined as a reduction to the pretreatment tumour volume of greater than 80%, calculated using the formula:

$$\text{volume} = \text{height} \times \text{length} \times \text{width} \times \pi/6.$$

MRI studies were performed at study entry, after 6 and 12 months of treatment with quinagolide and after 6 and 12 months of CAB treatment both in micro- and macroprolactinomas.

Visual perimetry

At baseline the evaluation of visual field defects, by Goldmann–Friedmann perimetry, and visual acuity was performed in all patients with macroprolactinoma. The ophthalmological examination was repeated every 3–6 months during the follow-up in patients with visual disturbance.

Assay

Serum PRL levels were assessed by IRMA using commercial kits (Radim, Pomezia, Italy). The intra- and interassay coefficients of variation were 5% and 7%, respectively. The normal ranges were below 750 mU/l in women and below 450 mU/l in men.

Statistical analysis

The statistical analysis of the percent PRL suppression after quinagolide and cabergoline treatment was performed using the Student's *t*-test for paired data and are expressed as Mean ± SEM. The 95% CI for all statistical analyses are also reported.

Results

Effect of quinagolide and CAB treatment on serum PRL levels

After 3 months of quinagolide, serum PRL levels normalized in 19 out of 23 patients with microprolactinoma (82·6%) and in six out of 16 with macroprolactinoma (37·5%). In the remaining patients the dose was increased up to 0·3–0·45 mg/daily. After 6 months of treatment, serum PRL levels normalized in all patients with microprolactinoma and in 13 out of 16 with macroprolactinoma (81·2%). In these 3 patients with residual hyperprolactinaemia (nos. 33, 38 and 39, Table 1), the dose of quinagolide was increased up to 0·6 mg/day; serum PRL levels normalized in one of these patients (no. 33) after 12 months of treatment. Gonadal and sexual function recovered in all patients, but five women and one man with macroprolactinoma had persistent gonadal dysfunction (libido and potency failure in the man, oligomenorrhoea in women). Galactorrhoea resolved in all patients. After quinagolide treatment withdrawal, serum PRL levels increased in all patients (see below), without reaching basal values. In fact, before starting CAB treatment basal PRL levels were significantly lower than before quinagolide treatment both in micro- (2636·1 ± 262·3 *vs.* 4667·4 ± 714·7 mU/l $P = 0{\cdot}006$, 95% CI 658·7–3403·9) and macroprolactinomas (3576·6 ± 413·0 *vs.* 24853·1 ± 7566·7 mU/l, $P = 0{\cdot}013$, 95% CI 5082·4–37470·8). After 3 months of CAB treatment, serum PRL levels normalized in 18 out of 23 patients with microprolactinoma (78·2%), and in eight out of 16 with macroprolactinoma (50%). The dose of

Table 1 Effects of a 12-month treatment with quinagolide and cabergoline on serum PRL levels and tumour shrinkage in the 39 patients with prolactinoma included in the study

		Treatment with Quinagolide				Treatment with Cabergoline			
Patient (sex,age)		Serum PRL levels (mU/l) basal	nadir	Maximal dose (mg/day)	Tumour shrinkage (%)	Serum PRL levels (mU/l) basal	nadir	Maximal dose (mg/week)	Tumour shrinkage (%)
Microprolactinomas									
1	f,24	2802	270	0·075	26	1269	48	1	31
2	f,23	2010	27	0·075	93·4	1470	720	3	4
3	f,25	4140	60	0·075	100	1680	45	1	ne
4	f,24	1818	120	0·075	44	4290	48	2	100
5	f,28	4350	354	0·45	10	2145	159	1	30
6	f,29	3690	63	0·075	35	2295	171	1	40
7	f,25	6000	45	0·075	31	6330	3	1	100
8	f,34	4890	30	0·075	100	3000	63	1	ne
9	f,33	4770	420	0·3	9	4500	165	1	15
10	m,33	6900	180	0·075	18	4980	330	1	25
11	f,37	3450	300	0·075	10	2190	600	2	6
12	f,36	3000	21	0·075	100	3090	102	1	ne
13	m,40	18750	108	0·075	100	3750	90	1	ne
14	f,48	3840	207	0·075	15	915	3	1	100
15	f,40	4860	222	0·075	11	4320	195	1	30
16	f,54	7800	30	0·075	37	2880	39	1	100
17	f,41	4110	75	0·075	30	3600	120	1·5	100
18	f,38	2740	90	0·075	40	2460	90	1	14
19	f,32	3480	270	0·075	18	2910	342	2	9
20	f,43	4650	516	0·3	0	1512	246	1	12
21	f,38	1620	114	0·075	25	84	222	1	8
22	f,30	2730	75	0·075	37	1560	51	1	100
23	f,40	4950	420	0·3	18	2100	54	1	100
Macroprolactinomas									
24	f,23	7920	30	0·075	31	5190	45	1	37
25	f,26	10200	342	0·3	0	1740	1140	3	3
26	f,30	7800	42	0·45	100	5700	210	1	ne
27	m,19	4950	9	0·075	100	1290	426	1	ne
28	m,21	5550	330	0·3	0	3900	1260	3	2
29	m,22	111000	66	0·45	83	3510	450	1	0
30	f,23	7650	54	0·075	48	2190	33	3	100
31	f,27	15000	36	0·075	87·7	5400	964	1	0
32	f,26	19500	252	0·45	20	1725	99	1·5	43
33	f,33	37380	600	0·6	6	7110	21	2	100
34	m,29	13890	315	0·3	7	2730	291	1	20
35	f,40	16500	540	0·3	9	3360	30	3	83
36	f,54	69000	189	0·075	19·7	2400	390	1	24
37	m,76	60600	45	0·075	63·8	2700	30	1	70
38	f,24	6600	780	0·6	0	4590	390	1	90
39	f,31	4110	810	0·6	0	3690	90	1·5	86

ne, not evaluable due to tumour disappearance with quinagolide treatment.

CAB was then increased up to 1 mg twice a week; after 6 months serum PRL levels normalized in another eight patients (four micro- and four macroprolactinomas). After 6 months of CAB treatment gonadal and sexual function recovered in all patients with microprolactinoma and also in four out of six patients with macroprolactinoma, who had persistence in gonadal disturbances after 12 months of quinagolide treatment. After 12 months, in the remaining five patients (one micro- and

four macroprolactinomas) the dose of CAB was increased up to 3 mg/week: serum PRL normalization was achieved in three patients (nos. 2, 30 and 35, Table 1). In the remaining two patients with macroprolactinoma (nos. 25 and 28, Table 1) serum PRL levels remained mildly elevated (1140–1260 mU/l). After quinagolide and CAB treatments, no difference was found in PRL nadir in both micro- ($174{\cdot}6 \pm 30{\cdot}6$ *vs.* $169{\cdot}8 \pm 37{\cdot}9$ mU/l, $P = 0{\cdot}5$, 95%CI–89·2–98·8) and in macroprolactinomas ($277{\cdot}5 \pm 68{\cdot}4$ *vs.* $341{\cdot}8 \pm 95{\cdot}2$ mU/l, $P = 0{\cdot}6$, 95%CI–317·8–189·2) as well as in the percent PRL suppression both in micro- ($95{\cdot}5 \pm 0{\cdot}7$ *vs.* $92{\cdot}4 \pm 2{\cdot}3\%$, $P = 0{\cdot}207$, 95%CI–1·78–7·76, respectively) and in macroprolactinomas ($96{\cdot}8 \pm 1{\cdot}3$ *vs.* $88{\cdot}1 \pm 4{\cdot}4\%$, $P = 0{\cdot}078$, 95%CI–1·09–18·57, respectively).

Effect of quinagolide and CAB treatment withdrawal on serum PRL levels

The withdrawal of quinagolide treatment induced an increase in serum PRL levels in all 39 patients after 15–60 days. The withdrawal of CAB treatment, induced an increase in serum PRL levels in all patients with macroprolactinomas after 15–30 days, and in 15 of 23 patients with microprolactinomas after 1 month. In four patients (nos. 1, 6, 8 and 21, Table 1) recurrence of hyperprolactinaemia was observed after 2–4 months. In the remaining four patients (nos. 7, 12, 13 and 23, Table 1) serum PRL levels remained normal after 12 months.

Effects on tumour size

After 6 months of treatment with quinagolide at a dose of 0·075–0·45 mg/day, tumour volume reduction to greater than 80% of the original size was documented by MRI studies in five out of 23 patients with microprolactinoma (21·7%) (nos. 2, 3, 8, 12 and 13, Table 1) and in four out of 16 with macroprolactinoma (25%) (nos. 26, 27, 29 and 31). An example is shown in Fig. 1 (no. 29). On MRI, the tumour mass disappeared completely in four of the five patients with microprolactinoma (nos. 3, 8, 12 and 13) and in two of the four with macroprolactinoma (nos. 26 and 27) after 12 months of treatment. Significant improvement in visual field defects was obtained in one out of six nonoperated patients with macroprolactinoma (no. 27). After 6 months of treatment with CAB at a dose of 0·5–2 mg/week, tumour volume reduction to less than 80% of the original size was documented by MRI in seven other patients with microprolactinoma (30·4%) (nos. 4, 7, 14, 16, 17, 22 and 23, Table 1) and in five other patients with macroprolactinoma (31·2%) (nos. 30, 33, 35, 38 and 39, Table 1). An example is shown in Fig. 2 (patient no. 35). After 12 months of CAB treatment, the tumour mass disappeared completely on MRI in six of the seven patients with microprolactinoma (nos. 14, 16, 17, 22 and 23 Table 1) and in two of the five with macroprolactinoma (nos. 30,33, Table 1). Improvement in visual field defects was obtained in other two out of six nonoperated patients (nos. 30 and 33) with macroprolactinoma. No change in visual field defects was observed with either quinagolide or CAB in the five patients with macroprolactinoma who had previously undergone surgery (nos. 25, 28, 32, 36 and 37 Table 1). After CAB treatment, further tumour shrinkage of 4–40% and 2–70% was observed in 12 microprolactinomas and seven macroprolactinomas, respectively.

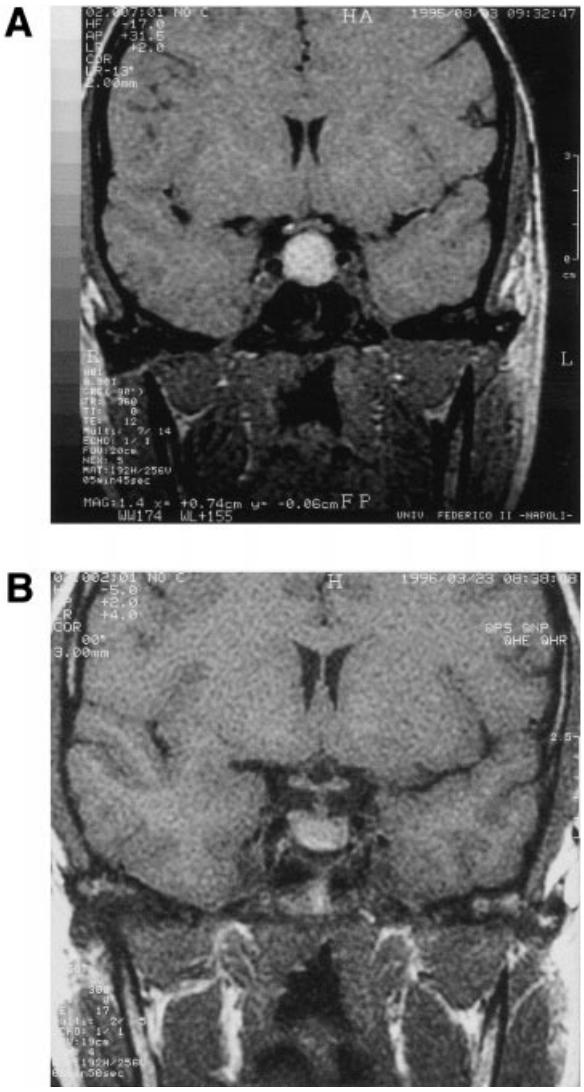

Fig. 1 Magnetic resonance imaging with coronal sections of one example of macroprolactinoma (no. 29, Table 1) (A) before and (B) after six months treatment with quinagolide at a dose of 0·075–0·45 mg/day.

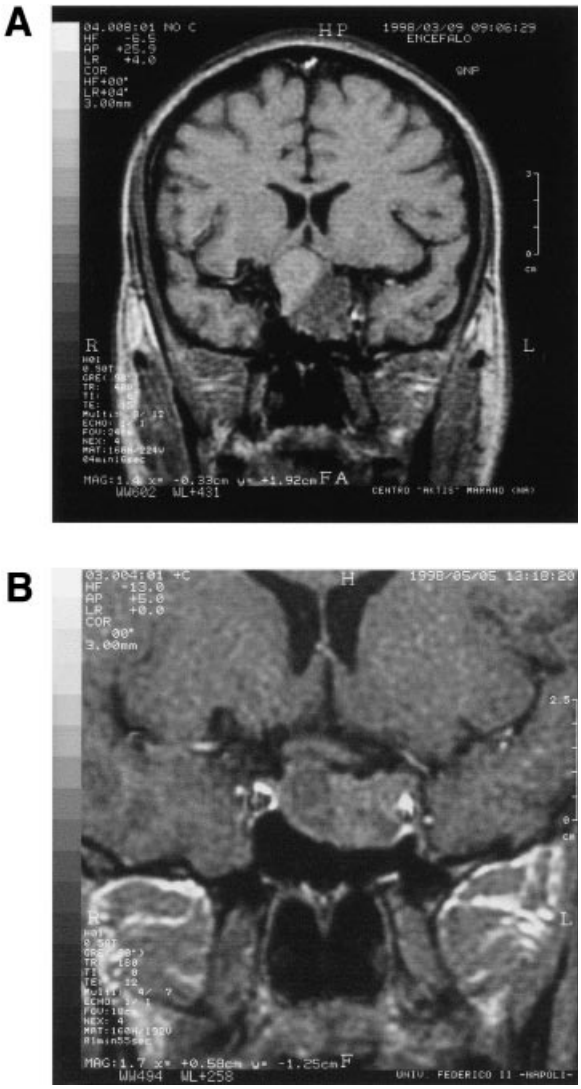

Fig. 2 Magnetic resonance imaging with coronal sections of another example of macroprolactinoma (no. 35, Table 1) (A) before and (B) after six months treatment with cabergoline at a dose of 0·5–3 mg/week.

The percent tumour shrinkage after CAB was significantly higher than that observed after quinagolide in microprolactinomas (48·6 ± 9·5 *vs.* 26·7 ± 4·5%, $P = 0{\cdot}046$, 95%CI–43·4–0·5) but not in macroprolactinomas (47·0 ± 10·6 *vs.* 26·8 ± 8·4%, $P = 0{\cdot}2$, 95%CI–53·1–12·7).

Drug safety and tolerability

At the initiation of quinagolide treatment, seven of 23 patients with microprolactinoma (30·4%) and five of 16 with macroprolactinoma (31·2%) reported mild side-effects, such as nausea and postural hypotension. These symptoms disappeared spontaneously during the second to third weeks of treatment in all 12 patients. The treatment with CAB was optimally tolerated by all patients, no side-effects were reported by any patient including the 12 patients who had tolerance-related problems at the beginning of quinagolide treatment. All patients showed an excellent compliance to both treatments.

Discussion

The results of the present study show that the two selective D_2 agonists, quinagolide and CAB, currently available in most European countries are similarly effective, in terms of normalization of serum PRL levels in the treatment of prolactinomas. In contrast, treatment with CAB induced further tumour shrinkage in 52·1% of micro- and 43·7% of macroprolactinomas, inducing a higher percent tumour reduction in microprolactinomas. As far as tolerability is concerned, both compounds were tolerated well by patients who had reported intolerance of BRC, while CAB was tolerated better than quinagolide by 30·7% of the patients. In addition, our study reported the persistence of normoprolactinaemia in four out of 23 patients with microprolactinoma (17·3%) after 12 months of CAB withdrawal.

Both CAB (Ferrari *et al*., 1986; Ciccarelli *et al*., 1989; Webster *et al*., 1992) and quinagolide (Khalfallah *et al*., 1990; Van Der Lely *et al*., 1991) have been used as long-lasting hypoprolactinemic drugs in recent years and they have been shown as useful alternative to BRC in the treatment of hyperprolactinemic syndromes. The treatment with these dopamine-agonist compounds has been demonstrated to normalize serum PRL levels, reduce tumour mass and restore gonadal function also in patients resistant or intolerant to BRC (Van Der Lely *et al*., 1991; Brue *et al*., 1992; Vilar *et al*., 1994; Colao *et al*., 1995; Colao *et al*., 1997a; present study). However, the efficacy of CAB and quinagolide was generally evaluated in different cohorts of patients and data obtained in the same group of patients treated with both drugs are scant. In the only study reported so far, Giusti *et al*. (1994) demonstrated that CAB and quinagolide have similar efficacy in lowering PRL levels and resolving the clinical symptoms. However, the prevalence of adverse reactions was significantly higher during quinagolide than during CAB treatments (Giusti *et al*., 1994). The effect of a previous administration of a dopamine agonist modifies the response to the subsequent drug with similar pharmacological properties either for PRL level decrease and tumour shrinkage. In fact, in the present cohort of patients serum PRL levels before starting CAB treatment were significantly lower than at study entry while the effect on tumour shrinkage could not be evaluated in six patients achieving total disappearance of their tumours after 12 months of quinagolide treatment. On the other hand, by

calculating the percent tumour reduction obtained with both drugs, it was demonstrated that after CAB treatment further tumour shrinkage was observed in 12 micro- (52·2%) and seven macroprolactinomas (43·7%). This confirms previous data reporting a notable tumour shrinking effect of CAB treatment in prolactinomas even when administered at low doses (Biller *et al*., 1996; Colao *et al*., 1997b; Cannavò *et al*., 1999; Verhelst *et al*., 1999). However, hyperprolactinaemia frequently recurs after drug withdrawal, suggesting that at least some lactotrophs have escaped (Lloyd *et al*., 1975; Landolt *et al*., 1985).

Therefore, although the results of studies aiming at comparing the effect of two dopamine agonists given sequentially should be considered carefully due to the study design itself, the data presented in the current study can be considered informative since they were collected in the same cohort of prolactinoma-bearing patients. The treatment with quinagolide and CAB was completely successful in the 23 patients with microprolactinoma since all achieved normoprolactinaemia, with restoration of gonadal function, and 21 of them (91·3%) also obtained a significant reduction in tumour volume. It should be pointed out that in four out of 23 patients with microprolactinoma, persistence of normoprolactinaemia and normal gonadal function were still present after 12 months CAB withdrawal. Whether this effect is due to the long-lasting hypoprolactinemic effect of CAB or to real cure of the disease, can not be differentiated. Neither compound was able to normalize serum PRL levels in two of 16 patients with macroprolactinoma (12·5%), even when administered at rather high doses (0·6 mg/day and 3 mg/week, respectively). However, it should be considered that in 25 out of 39 patients, normalization of serum PRL was obtained with very low doses of CAB (0·5 mg twice a week) and quinagolide (0·075 mg twice a day). Clearly, the schedule of drug administration for CAB (twice a week) improved compliance during long-term treatment. Patient compliance is a key factor in the evaluation of therapy success in hyperprolactinemic patients since treatment must be maintained for a very long period of time, or even for life (Faglia, 1991). In a previous study (Colao *et al*., 1997a) we demonstrated that CAB treatment was successful in 27 patients shown to be resistant to high dose BRC (20 mg/day) and quinagolide (0·6 mg/day) treatment. CAB treatment at the dose of 0·5–3 mg/week was able to normalize PRL levels in the majority of these patients (78·9% in macroprolactinoma and 100% in microprolactinoma), probably due to the improved tolerability which consented a progressive increase in CAB dosage (Colao *et al*., 1997a). The results of the current study, which was carried out in another cohort of patients, demonstrated that treatment with CAB is undoubtedly better tolerated than that with quinagolide.

In conclusion, our comparison of the effects of long-term quinagolide and cabergoline treatments in patients with prolactinomas, demonstrated that the effects of both these dopamine-agonist compounds on clinical features (gonadal failure, galactorrhoea, visual field defects) and PRL normalization were similar. However, cabergoline induced notable tumour shrinkage even in patients who had partial tumour reduction after quinagolide. Cabergoline was better tolerated in approximately one-third of the patients. Therefore, it could be used as a first-line pharmacological treatment in prolactinomas, particularly in macroprolactinomas, due to its potent effect in reducing tumour mass at low weekly doses. Finally, the long-lasting hypoprolactinemic effect of cabergoline may induce cure of the disease in some patients with microprolactinoma and may permit an intermittent schedule of treatment in others (34·7% in the present series), with a better cost:effectiveness ratio.

Acknowledgements

This study was partially supported by grant 9706151106 from MURST-Rome.

References

Bevan, J.S., Webster, J., Burke, C.W. & Scanlon, M.F. (1992) Dopamine agonists and pituitary tumor shrinkage. *Endocrine Reviews*, **13,** 221–235.

Biller, B.M.K., Molitch, M.E., Vance, M.L., Cannistraro, K.B., Davis, K.R., Simons, J.A., Schoenfelder, J.R. & Klibanski, A. (1996) Treatment of prolactin-secreting macroadenoma with once-a-week dopamine agonist cabergoline. *Journal of Clinical Endocrinology and Metabolism*, **81,** 2338–2343.

Brue, T., Pellegrini, I., Gunz, G., Morange, I., Dewailly, D., Brownell, J., Enjalbert, A. & Jaquet, P. (1992) Effects of the dopamine agonist CV 205–502 in human prolactinomas resistant to bromocriptine. *Journal of Clinical Endocrinology and Metabolism*, **74,** 577–584.

Cannavò, S., Curto, L., Squadrito, S., Almoto, B., Vieni, A. & Trimarchi, F. (1999) Cabergoline: a first-choice treatment in patients with previously untreated prolactin-secreting pituitary adenoma. *Journal of Endocrinological Investigation*, **22,** 354–359.

Ciccarelli, E., Giusti, M., Miola, C., Potenzoni, F., Sghedoni, D., Camanni, F. & Giordano, G. (1989) Effectiveness and tolerability of long-term treatment with cabergoline, a new long-lasting ergoline derivative, in hyperprolactinemic patients. *Journal of Clinical Endocrinology and Metabolism*, **69,** 725–728.

Colao, A., Annunziato, L. & Lombardi, G. (1998) Treatment of prolactinomas. *Annals of Medicine*, **30,** 452–459.

Colao, A., Di Sarno, A., Landi, M.L., Cirillo, S., Sarnacchiaro, F., Facciolli, G., Pivonello, R., Cataldi, M., Merola, B., Annunziato, L. & Lombardi, G. (1997b) Long-term and low-dose treatment with cabergoline induces macroprolactinoma shrinkage. *Journal of Clinical Endocrinology and Metabolism*, **82,** 3574–3579.

Colao, A., Di Sarno, A., Sarnacchiaro, F., Ferone, D., Di Renzo, G., Merola, B., Annunziato, L. & Lombardi, G. (1997a) Prolactinomas resistant to other dopamine agonists respond to chronic cabergoline treatment. *Journal of Clinical Endocrinology and Metabolism*, **83,** 876–883.

Colao, A. & Lombardi, G. (1998) Growth-hormone and prolactin excess. *Lancet*, **352,** 1455–1461.

Colao, A., Merola, B., Sarnacchiaro, F., Di Sarno, A., Landi, M.L., Marzullo, P., Cerbone, G., Ferone, D. & Lombardi, G. (1995) Comparison among different dopamine-agonists of new formulation in the clinical management of macroprolactinoma. *Hormone Research*, **44,** 222–228.

Faglia, G. (1991) Should dopamine agonists treatment for prolactinomas be life-long? *Clinical Endocrinology*, **34,** 173–174.

Ferrari, C., Barbieri, C., Caldara, R., Mucci, M., Codecasa, F., Paracchi, A., Romano, C., Boghen, M. & Dubini, A. (1986) Long-lasting prolactin lowering effect of cabergoline, a new dopamine agonist, in hyperprolactinemic patients. *Journal of Clinical Endocrinology and Metabolism*, **63,** 941–945.

Giusti, M., Porcella, E., Carraro, A., Cuttica, M., Valenti, S. & Giordano, G. (1994) A cross-over study with the two novel dopaminergic drugs cabergoline and quinagolide in hyperprolactinemic patients. *Journal of Endocrinological Investigation*, **17,** 51–57.

Grossman, A., Bouloux, P.M.G., Loneragan, R., Rees, L.H., Wass, J.A.H. & Besser, G.M. (1985) Comparison of the clinical activity of mesulergine and pergolide in the treatment of hyperprolactinaemia. *Clinical Endocrinology*, **22,** 611–616.

Khalfallah, Y., Caustrat, B., Grochowicki, M., Flocard, F., Horlait, S., Serusclat, P. & Sassolas, G. (1990) Effects of a new prolactin inhibitor, CV 205–502, in the treatment of human macroprolactinomas. *Journal of Clinical Endocrinology and Metabolism*, **71,** 354–359.

Lamberts, S.W.J. & Quick, R.F.P. (1991) A comparison of the efficacy and safety of pergolide and bromocriptine in the treatment of hyperprolactinemia. *Journal of Clinical Endocrinology and Metabolism*, **72,** 635–641.

Landolt, A.M., Osterwalder, V., Landolt, T. & A. (1985) Bromocriptine-induced removal of endoplasmic membranes from prolactinoma cells. *Experientia*, **41,** 640–642.

Liuzzi, A., Dallabonzana, D., Oppizzi, G., Verde, G.G., Cozzi, R., Chiodini, P. & Luccarelli, G. (1985) Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. *New England Journal of Medicine*, **313,** 656–659.

Lloyd, H.M., Meares, J.D. & Jacobi, J. (1975) Effect of oestrogen and bromocriptine on in vivo secretion and mitosis in prolactin cells. *Nature*, **255,** 497–498.

Molitch, M.E., Thorner, M.O. & Wilson, C. (1997) Therapeutic Controversy. Management of prolactinomas. *Journal of Clinical Endocrinology and Metabolism*, **84,** 996–1000.

Pellegrini, I., Rasolonjanahary, R., Gunz, G., Bertrand, P., Delivet, S., Jedynak, C.P., Kordon, C., Peillon, F., Jaquet, P. & Enjalbert, A. (1989) Resistance to bromocriptine in prolactinomas. *Journal of Clinical Endocrinology and Metabolism*, **69,** 500–509.

Van Der Lely, A.J., Brownell, J. & Lamberts, S.W.J. (1991) The efficacy and tolerability of CV 205–502 (a nonergot dopaminergic drug) in macroprolactinoma patients and in prolactinoma patients intolerant to bromocriptine. *Journal of Clinical Endocrinology and Metabolism*, **72,** 1136–1141.

Vance, M., Evans, W. & Thorner, M. (1984) Bromocriptine. *Annals of Internal Medicine*, **100,** 78–91.

Verhelst, J., Abs, R., Maiter, D., Van Den Bruel, A., Vanderweghe, M., Velkeniers, B., Mockel, J., Lamberigts, G., Petrossians, P., Coremans, P., Mahler, C., Stevenaert, A., Verlooy, J., Raftopoulos, C. & Beckers, A. (1999) Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. *Journal of Clinical Endocrinology and Metabolism*, **84,** 2518–2522.

Vilar, L. & Burke, C.W. (1994) Quinagolide efficacy and tolerability in hyperprolactinaemic patients who are resistant to or intolerant of bromocriptine. *Clinical Endocrinology*, **41,** 821–826.

Webster, J., Piscitelli, G., Polli, A., D'Alberton, A., Falsetti, L., Ferrari, C., Fioretti, P., Giordano, G., L'Hermite, M., Ciccarelli, E., Crosignani, P.G., DeCecco, L., Fadini, R., Faglia, G., Flamigni, F., Tamburrano, G. & Scanlon, M.F. (1992) Dose-dependent suppression of serum prolactin by cabergoline in hyperprolactinaemia: a placebo controlled, double blind, multicentric study. *Clinical Endocrinology*, **37,** 534–541.

Webster, J., Piscitelli, G., Polli, A., Ferrari, C.I., Ismail, I., Scanlon, M.F. & for the Cabergoline Comparative Study Group. (1994) A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. *New England Journal of Medicine*, **31,** 904–909.