The efficacy and tolerability of long-term cabergoline therapy in hyperprolactinaemic disorders: an open, uncontrolled, multicentre study

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(Received 19 October 1992; returned for revision 27 January 1993; finally revised 3 March 1993; accepted 26 March 1993)

Summary

OBJECTIVE We assessed the efficacy and safety of the new, long-acting dopamine agonist drug cabergoline during long-term therapy of hyperprolactinaemia.

DESIGN Open, prospective, multicentre study.

PATIENTS One hundred and sixty-two females with either a microprolactinoma (n = 100), idiopathic hyperprolactinaemia (n = 54), empty sella syndrome (n = 7) or residual hyperprolactinaemia after surgery for a macroprolactinoma (n = 1). All had previously been treated with cabergoline or placebo for 4 weeks as part of a dose-finding study.

MEASUREMENTS Menstrual pattern, adverse symptoms, blood pressure and pulse, serum PRL, blood count, liver and renal function were assessed after one month and subsequently at two-monthly intervals.

RESULTS Treatment was started at doses of 0.25 mg (n = 3), 0.5 mg (n = 8), 1 mg (n = 150) or 2 mg (n = 1) per week, given either as a single weekly dose (n = 8) or divided into twice-weekly doses (n = 154), and was continued for at least 49 weeks in 123 patients. Final treatment doses ranged from 0.25 mg fortnightly to 2 mg twice weekly: most patients finished the study taking 0.5 mg once (n = 31) or twice (n = 77) weekly.

Stable normalization of PRL levels was achieved in 138 subjects (85%), in 129 of whom the effective dose was < 1 mg per week. In the subset of 114 patients completing 49 weeks of therapy and having dose adjustments according to the protocol, the biochemical success rate was 92%. Fifty-nine of the 65 previously amenorrhoeic women (91%) and 44 of the 49 (90%) who were previously oligomenorrhoic resumed regular menses and/or became pregnant during the study.

Adverse events were reported in 64 patients (39.5%). In 84% of cases with adverse events, the symptoms were of mild or moderate severity and most occurred during the first few weeks of therapy; five patients (3%) discontinued treatment because of poor tolerance. The most frequent symptoms were dizziness (13% of patients), headache (13%), nausea (10%) and weakness and/or fatigue (10%). Of 27 patients who had previously been poorly tolerant of other dopamine agonists, 17 (63%) did not experience any side-effects and only one was intolerant of cabergoline.

No adverse haematological or biochemical effects were detected except for a slight downward trend in haemoglobin which may have been related to the resumption of regular menses in previously amenorrhoeic or oligomenorrhoeic women. A mild hypotensive effect was observed, mean systolic and diastolic blood pressures falling by 5 and 4 mmHg respectively during treatment.

CONCLUSIONS The results provide evidence for the long-term effectiveness and safety of cabergoline in the treat-
ment of hyperprolactinaemia. Its ability to normalize PRL and restore gonadal function compares favourably with reported data on reference compounds while its tolerability profile and simple administration schedule offer potential advantages in terms of patient acceptability.

During the last two decades, dopamine agonists have been used increasingly as first line therapy in patients with prolactinomas (Molitch, 1989). Bromocriptine, the most widely used of these drugs, is highly effective in normalizing PRL levels, reducing tumour size and restoring gonadal function but its use is associated with side-effects in a significant proportion of patients (Vance et al., 1984; Van't Verlaat et al., 1988; Ciccarelli et al., 1989a; Kocejnic et al., 1990; Schettini et al., 1990).

Cabergoline (1-[6-allylergolin-8-fl-yl] carbonyl]-1,43-(dimethylamino) propyl]-3-ethylurea), is a novel ergoline derivative with selective, potent and very long lasting dopamine agonist properties. It is highly effective and well tolerated in suppressing PRL levels in both normal and hyperprolactinaemic subjects and has a duration of action of up to 21 days after single oral doses of 0.3-1.0 mg (Ferrari et al., 1986; Pontroli et al., 1987; Mattei et al., 1988). In a recent double-blind, placebo controlled, multicentre study in hyperprolactinaemic women, we have shown that cabergoline, at doses of 0.125-1.0 mg twice weekly for 4 weeks, suppresses PRL levels in dose-dependent fashion, with 95% of those receiving 1.0 mg twice weekly achieving a normal serum PRL (Webster et al., 1992). In short-term studies and in the first published reports of long-term treatment (Mattei et al., 1988; Ferrari et al., 1989; Ciccarelli et al., 1989b; Webster et al., 1992), the drug was well tolerated. Side-effects were similar to those reported with bromocriptine, comprising mainly nausea, dizziness and headache, and tended to resolve with continued therapy.

Here we report on the tolerability and efficacy of cabergoline in inducing stable normoprolactinaemia and restoring menses during long-term follow-up of a large number of hyperprolactinaemic women who had previously participated in the short-term, dose-finding study on cabergoline (Webster et al., 1992). In contrast to the latter study, the present investigation was carried out under open conditions, allowing dose changes as necessary, and was not placebo controlled.

Patients and methods

This was an open, uncontrolled, multicentre study involving 162 patients in 14 European centres between December 1988 and January 1991. All patients gave informed consent and the study protocol was approved by the Ethics Committee in each institution.

Patients

All patients had already completed 4 weeks cabergoline (or placebo) therapy at doses of 0, 0.125, 0.5, 0.75 or 1.0 mg twice weekly, as part of a double-blind dose-finding study and wished to continue (or start) treatment. All were female, aged 16-46 (mean ± SD 32.1 ± 7.1) years, with hyperprolactinaemia (PRL > 30 μg l or 700 mU l, mean ± SEM pretreatment PRL 95.8 (±7.2) μg l) at entry to the dose-finding study. In each case thyroid disease and drug therapy had been excluded as a cause of hyperprolactinaemia, and a pituitary CT or MRI scan performed during the 12 months prior to study entry. Diagnoses included microprolactinoma (n = 100, 62%), idiopathic hyperprolactinaemia (patients in whom CT or MRI scan failed to identify an adenoma, n = 54, 33%), empty sella syndrome (n = 7, 4%) or failed surgery for a macroadenoma (n = 1). Exclusion criteria included the presence of a macroadenoma, hyper or hypo-thyroidism, pregnancy, weight loss-related or exercise-related amenorrhoea and hypogonadotropic hypogonadism. Patients receiving drugs known to modify PRL secretion and those with renal or hepatic impairment were excluded.

Methods

Cabergoline was started after a washout period of 1-35 weeks following the previous short-term administration (Webster et al., 1992) and the planned duration of therapy was 12 months. A starting dose of 0.5 mg twice weekly was chosen as this had been shown to normalize PRL levels in about 70% of cases in previous pilot studies. However, in 12 patients, different starting doses were used. Subsequent dose adjustments were to be made during treatment on the basis of PRL levels and drug tolerability, in those with supranormal PRL levels, progressive dose increases were allowed, while in those with undetectable PRL or troublesome adverse symptoms, a reduced dose was recommended.

Patients were assessed one and two months after starting therapy, and at two-monthly intervals thereafter. At each visit, patients were questioned regarding their menstrual pattern and adverse events; in those responding positively to a general question about symptoms, the physician enquired specifically about each of the common adverse effects known to occur with dopamine agonists. A symptom was recorded as mild if the patient could easily cope with it, moderate if it worried the patient but not the physician, and severe if both
the physician and patient felt that the patient's quality of life was threatened. Erect and supine blood pressure were recorded at each visit and blood was drawn for serum PRL estimation. Haematological (full blood count) and biochemical (urea, creatinine, electrolytes, alanine and or aspartate transaminase, bilirubin and alkaline phosphatase) analysis. ECGs were performed at 6-monthly intervals.

If pregnancy occurred, therapy was discontinued immediately after its confirmation. Women becoming pregnant during the study were followed up until delivery.

Efficacy criteria. Mean PRL levels were calculated starting from the first value obtained at the final dose regimen for each patient. A mean PRL within the normal range for the institution was considered as 'biochemical success'. The occurrence of cyclical menses (within menstrual intervals of 21-35 days) and/or the occurrence of pregnancy were considered as evidence of clinical efficacy in women with a history of amenorrhoea or oligomenorrhoea. In those completing 49 weeks uninterrupted therapy, success was defined as the occurrence of at least 7 cyclical menses in the case of no dose adjustment, or at least 3 cycles in the case of dose titration. These criteria were based on the observation that menses may take as long as 12 weeks to resume after institution of PRL-lowering therapy, and on the median time (139 days) required to achieve the final drug dose in those patients in whom dose adjustment was necessary.

All patients entered into the study were evaluated for treatment effectiveness and drug safety, on an 'intention to treat' basis. In addition, a separate analysis was carried out including only patients considered fully evaluable for clinical or biochemical efficacy, that is, those completing at least 49 weeks treatment with appropriate dose adjustments, if required (except patients stopping treatment because of pregnancy). Hysterectomized patients \( (n = 2) \) were considered not to be evaluable for clinical efficacy; patients receiving long-term treatment with drugs known to modify PRL secretion were excluded from both clinical and biochemical analyses.

Results

Patients entered

Of the 162 patients who entered the study, 123 \( (76\%) \) completed at least 49 weeks of cabergoline therapy (maximum duration 73 weeks). Among the 39 \( (24\%) \) patients who discontinued treatment before 49 weeks, 18 \( (11\%) \) stopped because of pregnancy, 5 \( (3\%) \) were intolerant of the drug, and 8 \( (5\%) \) were lost to follow-up. Other reasons for early discontinuation of therapy included poor compliance \( (n = 1) \), meningioma \( (n = 1) \) and pituitary surgery \( (n = 1) \). Patients were allowed to continue cabergoline therapy on a compassionate basis after completion of the study if they so wished.

One hundred and fifty patients started cabergoline at a dose of 0.5 mg twice weekly, and of these, 74 remained on this dose throughout the treatment period. 19 had their dose increased (up to a maximum of 2 mg twice weekly) and in 57 it was reduced (to a minimum of 0.25 mg fortnightly). Twelve patients started on doses other than 0.5 mg twice weekly: 11 on lower doses (0.25 or 0.5 mg once weekly) because of side-effects during previous treatment \( (n = 8) \) or PRL oversuppression \( (n = 3) \); one patient started on a higher dose (1 mg twice weekly) because of persistent elevation of serum PRL. Overall, the final treatment dose was between 0.125 and 0.35 mg per week (administered as 0.25 or 0.5 mg at 7, 10 or 14 day intervals) in 26 patients \( (16\%) \), 0.5 mg per week (as a single weekly dose or 0.25 mg twice weekly) in 38 \( (23\%) \), 0.5mg twice weekly in 77 \( (48\%) \), and between 1.5 and 4 mg per week, in divided doses, in 21 patients \( (13\%) \).

A total of 48 patients were considered not fully evaluable for biochemical efficacy (reasons including failure to take the full 49 weeks uninterrupted therapy \( (n = 45) \), incorrect dose escalation \( (n = 2) \); and no blood sample taken on the final dose \( (n = 1) \) and 34 for clinical efficacy (less than 49 weeks uninterrupted treatment \( (n = 24) \), inadequate documentation of menstrual pattern \( (n = 4) \), incorrect dose escalation \( (n = 2) \), intermittent hysterectomy \( (n = 3) \) or menopause \( (n = 1) \).

Efficacy

Biochemical efficacy. All patients had been hyperprolactinaemic before entering the previous cabergoline dose-finding study (mean \( \pm \) SEM serum PRL 958 \( \pm \) 72 \( \mu \)g/l, range 24.2-593 \( \mu \)g/l; PRL \( \mu \)g/l \( \times \) 1.2 = mU/l), but only 54% had developed recurrent hyperprolactinaemia at entry to the present study. In 22\%, PRL was above the normal range but
still partially suppressed compared with pretreatment and in 32% the PRL level was comparable to pretreatment. Among the 87 subjects with elevated PRL levels at study entry the PRL values were < 50 μg/l in 33, between 51 and 100 μg/l in 38, and >100 μg/l in 16.

Cабергонин was effective in achieving or maintaining stable normalization of PRL levels in 138 of the 162 patients (85%), including 66 of the 87 (76%) who were hyperprolactinamie at study entry (Table 1). In 10 of the 20 patients not achieving complete normalization of serum PRL concentration, mean PRL values were only slightly elevated (i.e. <10 μg/l); in only six cases was PRL > 50 μg/l. Overall, normalization of PRL was achieved or maintained with weekly doses of cabergoline (in single or divided doses) of < 0.5 mg in 25 cases (15%), 0.5 mg in 36 (22%) and 1 mg in 68 (42%) cases (Table 2).

In the subset of 114 patients considered fully evaluable, PRL normalization was achieved in 105 (92%) (Table 3). Effective treatment doses in this subgroup are shown in Table 4. Of the 27 patients in whom PRL was not normalized during the earlier short-term dose-finding study (Webster et al., 1992), 21 achieved normoprolactinemia during longer-term administration, although 13 required higher doses than previously.

**Clinical efficacy.** In the absence of any treatment affecting the menstrual cycle, 65 (40%) patients were amenorrhoeic (> 6 months), 50 (31%) oligomenorrhoeic, 42 (26%) normo- menorrhoeic, and four were polymenorrhoeic (in one case the menstrual history prior to therapy was not recorded). Excluding the two patients who had previously undergone a hysterectomy, 156 out of 160 patients (97%) had at least one menstrual period during the study. The remaining four had all dropped out of the study before 12 weeks because of drug intolerance, poor compliance, pregnancy or loss to follow-up. Cabergoline was effective in restoring regular menses and allowing the patient to become pregnant in 59 out of 65 previously amenorrhoeic women (91%) and 44 out of 49 oligomenorrhoeic subjects (90%). In the subset of 103 fully evaluable patients who did not become pregnant during the study, regular periods were recorded in all but three cases; the clinical success rate in the previously amenorrhoeic or oligomenorrhoeic women was 88.9%.

During the study, 26 pregnancies occurred in 25 women after 5-50 weeks of cabergoline therapy. The duration of fetal exposure (assuming conception was 13 days after the first day of the last menstrual period) was 13-87 days. Three women underwent elective abortions as conception had not been intended and one 42-year-old woman, who was found to be carrying a fetus with Down's syndrome, underwent a therapeutic abortion; a subsequent cabergoline induced pregnancy in this woman was unremarkable and she delivered a healthy baby. The remaining 21 women had uneventful pregnancies. There were no multiple births or congenital abnormalities. Birth weights and Apgar scores were within the normal range and the infants' physical and mental development have been normal to date.

**Safety.**

**Adverse events.** Adverse events were reported in 64 patients (39.5%). Symptoms were almost typical of ergoline derivatives and included dizziness (13%), headache (13%), nausea (10%), asthenia fatigue (10%) and constipation (4%). However, 15 patients complained of symptoms which were either unexpected or which have been observed only rarely during cabergoline treatment, including hot flushes (four cases), alopecia and or hypertrichosis (two cases), a
sensation of suffocation (two cases), pruritus, paraesthesia of the lower limbs, scalp irritation, clouding of vision, dry eyes and loss of appetite, dry mouth and dyspnœa (one case each).

The reported severity of symptoms was mild in 34 patients (53% of those with symptoms) and moderate in 20 (31%). There was no clear relationship between cabergoline dose and the incidence of adverse events.

**Severe adverse events and patients discontinuing therapy.** Ten patients (6.7%) reported symptoms which were considered to be severe. These comprised weakness, fatigue, dizziness, headache, a sensation of suffocation after meals, paraesthesia of the lower limbs, breathlessness and vertigo, alopecia, scalp irritation, and nausea and constipation. Cabergoline therapy was discontinued in five patients (3%); four of these had severe symptoms, one had repeated symptoms of moderate severity (Table 5).

*Tolerability in patients with history of poor tolerance of other dopamine agonists.* Twenty-seven patients entering the study had previously been reported as intolerant of other dopamine agonist drugs, including bromocriptine (18), lisuride (5), metergoline (1), dihydroergocryptine (2) or terguride (1). Seventeen of these (63%) had no side-effects while on cabergoline and only one of the 10 who experienced adverse symptoms had to discontinue therapy, because of severe nausea.

**Blood pressure.** During cabergoline therapy the mean values of both systolic and diastolic blood pressure (BP) decreased slightly (by up to 50 and 40 mmHg respectively), reaching a nadir at 22–30 weeks. Decreases, compared with basal, in both systolic and diastolic BP of >20 and >10 mmHg respectively were recorded in 29 patients (19%) in the lying position and 34 cases (22%) standing.

**Electrocardiogram.** Two patients were found to have minor conduction abnormalities on ECG during the course of cabergoline therapy; in one case this was associated with known mitral valve prolapse.

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**Table 4** Biochemical efficacy in fully evaluable patients: distribution according to final dose of cabergoline

<table>
<thead>
<tr>
<th>Final cabergoline dose (mg week)</th>
<th>0.175</th>
<th>0.25</th>
<th>0.35</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>1.75</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PRL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>3</td>
<td>17</td>
<td>1</td>
<td>27</td>
<td>49</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>18</td>
<td>1</td>
<td>27</td>
<td>51</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>114</td>
</tr>
</tbody>
</table>

**Table 5** Adverse events requiring treatment withdrawal

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg)</th>
<th>Onset (time after starting therapy)</th>
<th>Symptom</th>
<th>Duration</th>
<th>Outcome comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 twice weekly</td>
<td>4 weeks</td>
<td>Dizziness</td>
<td>14 days</td>
<td>Full recovery</td>
</tr>
<tr>
<td>2</td>
<td>0.5 twice weekly</td>
<td>1 day</td>
<td>Sensation of suffocation after meals</td>
<td>10 minute episodes</td>
<td>Full recovery within 2 days of treatment discontinuation</td>
</tr>
<tr>
<td>3</td>
<td>0.5 weekly</td>
<td>8 weeks</td>
<td>Asthenia, dyspnœa, vertigo</td>
<td>3 days</td>
<td>Full recovery</td>
</tr>
<tr>
<td>4</td>
<td>0.5 twice weekly</td>
<td>9 weeks</td>
<td>Scalp irritation, Facial oedema</td>
<td>10 days</td>
<td>Full recovery of oedema within 1 day and irritation within 8 days</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>4 days</td>
<td>Nausea</td>
<td>2 days after each dose</td>
<td>Full recovery</td>
</tr>
</tbody>
</table>

* Symptom recorded as 'moderate' severity.
**Discussion**

This is the first major trial of the long-term efficacy and safety of cabergoline in treating hyperprolactinaemic disorders. Although patients entering the study had participated in a previous, short-term (4-week), placebo controlled, dose-finding study of cabergoline (Webster et al., 1992), they were not selected according to their responsiveness or tolerability during this treatment period as the earlier study was conducted under double-blind conditions and the code was not available to the investigators at the time of patient inclusion. The patients evaluated in the present study therefore form a representative sample of out-patient hyperprolactinaemic women subject to relatively minor exclusion criteria, the most important being the presence of a macroprolactinoma.

Stable normalization of serum PRL levels was attained in 138 (85%) of the 162 patients included in the study and in 92% of the 114 patients considered fully evaluable (that is, completing at least 49 weeks of uninterrupted therapy with appropriate dose adjustments if necessary). The effective cabergoline dose was ≤ 1 mg per week (in one or two doses) in 129 cases (80%) and 1.5–4.0 mg per week in a further nine patients (5%). A marked PRL decrease was also obtained in most of the patients not achieving complete PRL normalization. PRL levels > 50 μg/l persisting in only five out of 24.

A clear dose-response relationship for the PRL-lowering effect of cabergoline in hyperprolactinaemia was demonstrated in the previous 4-week dose-finding study (Webster et al., 1992). The PRL response in those patients whose PRL level was not normalized during the previous 4-week study confirms that patients not responding to lower doses may benefit from an increase in dose level (as was implicit in the dose-finding study) and, furthermore, that prolonged therapy at the same dose-level may succeed in normalizing PRL in patients partially resistant during short-term treatment.

The clinical efficacy of cabergoline in restoring gonadal function was demonstrated in 59 out of 65 (91%) previously amenorrhoeic, and 44 out of 49 (90%) oligomenorrhoeic women, who resumed regular menstrual cycles and became pregnant during the course of the study. The pregnancy rate during the study cannot be used as an efficacy criterion as information on the desire or otherwise of the patients to become pregnant was not collected. However, data obtained in the 22 women who became pregnant and continued to term did not suggest any adverse effect of cabergoline on the course of the pregnancy or on fetal development.

The results therefore confirm that cabergoline is highly effective in treating hyperprolactinaemic disorders, and compares favourably with data published for bromocriptine which is reported to normalize serum PRL in approximately 80% of patients with microprolactinomas or idiopathic disease and to restore gonadal function in about 85% of cases (Thorner et al., 1980; Molitch, 1989).

The present study, in which 39.5% of patients reported adverse symptoms on direct questioning, indicates a similar tolerability profile for cabergoline compared with other dopamine agonist drugs currently available. However, the observed incidence of side-effects in this and other studies may be a considerable overestimate, principally because patients were asked directly about symptoms and were fully aware of the possible side-effects they may encounter by virtue of their informed consent. In the earlier placebo controlled double-blind study on cabergoline (Webster et al., 1992), 45% of patients taking placebo reported side-effects typical of dopamine agonists. Bromocriptine, either in oral or long-acting repeatable form, has been reported to be associated with adverse symptoms in up to 69 and 71% of patients respectively (Van’t Verlaat et al., 1988; Cicerelli et al., 1989a; Koetjancic et al., 1990; Schettini et al., 1990), while at least 44% of those taking the non-ergot derivative quinagolide (CV 205 502), which is currently under investigation, report adverse symptoms (Rasmussen et al., 1988; Newman et al., 1989; Vincze et al., 1989, 1990; Van der Heijden et al., 1989, 1990; Barnett et al., 1990; Homburg et al., 1990; Serri et al., 1990; Van’t Verlaat et al., 1990). Almost all the adverse events reported during the present study were of mild or moderate severity; most occurred during the first few weeks of therapy and settled with continued treatment. Five patients out of 162 (3%) discontinued cabergoline because of poor tolerance which compares with a reported 5% with oral bromocriptine. A finding of particular clinical importance is...
that only one of the 27 patients who had previously been intolerant of other dopamine agonists (18 taking bromocriptine), was unable to tolerate cabergoline at effective doses. Furthermore, 63% of this subgroup had no reported side-effects during cabergoline therapy.

In conclusion, the efficacy of cabergoline in suppressing PRL secretion and restoring gonadal function compares favourably with published data on the reference compound, bromocriptine. It also possesses possible advantages over other dopamine agonists currently available in terms of the incidence and severity of side-effects and its simple administration schedule which may improve patient compliance.

Acknowledgements
The authors gratefully acknowledge the assistance of Drs A. Boneschi, A. Caufric, C. Crescenti, S. De Vincentis, E. Galibignani, M. Giusti, E. De Marchi, A. Mattei, G. B. Melis, J. Mockel, M. Muratori, A. Paracchi, and P. L. Venturini in gathering data during the course of this study. J. Webster is an MRC Training Fellow.

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Long-term cabergoline in hyperprolactinaemia

Clinical Endocrinology, 33, 161 169.


