Clinical response and prolactin concentration in hyperprolactinemic women during and after treatment for 24 months with the new dopamine agonist, CV 205-502

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Abstract. Twenty-four hyperprolactinemic women of whom 23 previously had been given bromocriptine, were treated between 6 and 24 months with a new non-ergot dopamine agonist, CV 205-502 (quinagolide; Norprolac®, Sandoz Ltd, Basle Switzerland). Twenty-four weeks of treatment resulted in normalization of prolactin secretion in 16 of the 24 women. All of these women as well as 4 of those who remained hyperprolactinemic had regular menstrual bleedings. Fifteen of the 24 women were treated for 24 months and all had normalized prolactin levels in serum at the end of this period. Regular menstrual bleedings were observed in 13 women. Mild to moderate galactorrhea was recorded at baseline in 14 of the 15 women. After 24 months of treatment, mild galactorrhea was still present in 5 women. All 15 women had been treated with bromocriptine or other dopamine agonists before they entered the study. In 9 of the women the tolerability had been judged to be fair (N=4) or poor (N=5). Five of the 15 women had previously discontinued bromocriptine treatment because of adverse effects but had few problems tolerating CV 205-502. Prolactin in serum increased in all the patients after discontinuation of the medication. The results confirm that CV 205-502 seems to be a valuable compound in the management of patients with hyperprolactinemia.

It is well established that prolactin secretion is under tonic inhibitory control by dopamine. This inhibitory effect of dopamine has been clinically exploited by the development of dopaminergic drugs. CV 205-502 (quinagolide; Norprolac®, Sandoz Ltd, Basle, Switzerland), an octahydrobenzo[g]quinoline, is a new long-acting dopamine agonist. This compound is the first dopaminomimetic substance which does not possess an ergot structure. Receptor binding studies have shown that quinagolide possesses clear-cut dopamine receptor interactions as a potent and selective D₂ agonist with high affinity (1). It should therefore have a profile with fewer adverse reactions, such as nausea, peripheral vasospasm and orthostatic hypotension, compared with other dopamine agonists, for instance bromocriptine. Short-term pharmacology and dose-ranging studies, both in animals (2) normoprolactinemic volunteers (3) and hyperprolactinemic patients (4,5) have confirmed that quinagolide has a strong prolactin-lowering effect given once daily. Despite the potent and sustained suppression of prolactin secretion, it was well tolerated and produced only few and moderate adverse reactions.

Owing to these results it was decided to evaluate the prolactin-lowering capacity and tolerability in hyperprolactinemic women during long-term treatment. Here we present the results of treatment for 24 months with quinagolide and the effect of the treatment on prolactin secretion after discontinuation of medication in a group of women with hyperprolactinemia.
Patients and Methods

Twenty-four women, 22 to 48 years of age (median 39) with persistent hyperprolactinemia volunteered to participate in the study. Eighteen of the 24 women had presented originally with secondary amenorrhea of 3-240 months duration (median 84). Two women had primary amenorrhea and 4 women had oligomenorrhea with menstrual intervals of 2-4 months. One woman had not been treated with any dopamine agonist before she entered the study, whereas the other 23 women had received bromocriptine treatment for 1-108 months (median 43) at daily doses of between 2.5 and 50 mg (median 5). Five patients (patients No. 14, 15, 16, 17, 22, Table 1) had discontinued the bromocriptine therapy because of undesirable adverse reactions such as nausea, emesis or hypotension. Six patients had continued treatment despite poor tolerance. All the patients had been instructed to take bromocriptine during a meal. If they experienced intolerable adverse reactions, the dose was reduced to 1.25 or 0.625 mg once or twice daily before therapy was given up. None of the patients had received bromocriptine or any other drug that could interfere with prolactin secretion within one month before the start of the study. All the women had serum prolactin concentrations of 30 μg/l or more, measured on at least two occasions during the month preceding the study. Mild to moderate galactorrhea was found at the baseline examination in 19 of the 24 women. Routine clinical endocrinological examination showed no evidence of any thyroid or adrenal abnormalities. All the patients were screened during the baseline period with physical examinations, laboratory examination including hematological tests and electrocardiographical examination (ECG).

Radiological examination, including polytomography and coned view of the sella turcica showed asymmetrical pituitary fossae in 18 of the 24 women. The asymmetry was pronounced in 5 of the women with sellar classification of B4-B5 according to Thorner et al. (6), whereas 13 had minor radiological changes (B1-B3). Computed tomography (CT-scan) had been performed in 14 of the 24 women without any signs of extrasellar extension of a pituitary tumour. One woman had a partially empty sella (patient No. 2). In 10 women with only moderate hyperprolactinemia CT-scan examination had not been performed.

Prolactin in serum was measured radioimmunologically by the use of rabbit antihuman prolactin antibodies coupled to cyanogen-bromide-activated ultrafine Sephadex particles (7). A purified preparation of human pituitary prolactin was labelled with 125I and also used as a reference standard (8). Serum prolactin concentration before treatment with quinagolide ranged between 31 and 1100 μg/l (mean 84). The normal upper limit for women of reproductive age in our laboratory is 20 μg/l. One microgram is comparable to 50 mU of first I.R.P. of h prolactin 75/504.

A double-blind, placebo-controlled design was used. All the patients were randomly assigned to receive capsules with either placebo or 0.050 mg quinagolide once daily for the first 4 weeks of the study. The capsules were administered at bedtime together with a snack. All the blood samples were drawn between 12.00 and 14.00 h. After 4 weeks of treatment the code was broken and showed that 11 patients had received placebo. The patients who had had placebo during the first 4 weeks of treatment started to take 0.05 mg of quinagolide once daily at the end of week 4. All the patients, including the patients who started with placebo received 6 months treatment with quinagolide. In the quinagolide-treated patients who had not become normoprolactinemic, the daily dose was increased by 0.025 mg every 4 weeks during the first 6 months, by 0.050 mg from month 6 to month 12, and by 0.1 mg (one patient) until month 21, with a maximum dose of 1.3 mg daily. Twenty-four patients had 6 months of treatment, 21 were treated for 12 months, 18 for 18 months, and 15 for 24 months. The treatment doses are shown in Table 1. The treatment was stopped after 24 months in all the 15 women who were still participating in the study. The prolactin levels in serum were measured 2, 4 and 6 weeks after discontinuation of the treatment.

All the patients were evaluated at regular clinic visits with extensive safety laboratory tests (liver and kidney function and hematological tests), ECG and recording of vital signs, including blood pressure and pulse rate in both the supine and standing position. The women were interviewed for the occurrence of adverse effects at each clinic visit. Ovulation was assessed during the first 6 months by measurement of the serum progesterone concentration in the mid-luteal phase of the menstrual cycle in the women with regular menstrual bleedings. Ovulation and luteal function were regarded to be normal when the progesterone level in serum was more than 30 nmol/l.

All the women were fully informed and gave their consent to participate according to the Tokyo Amendment of the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Medical Faculty, Uppsala University. In the statistical calculations, the hormone values were converted into logarithms. All the mean values given in the text are geometrical means. Student's t-test was used for calculation of differences between mean values.

Results

An overview of the changes in serum prolactin levels in all the women, both during the period with active treatment and during the period after treatment are given in Table 1 and Fig. 1.
Table 1.
Prolactin levels in serum (µg/l) before, during and after 24 months of treatment with quinagolide. The given dose (mg) was the dose at which the prolactin level was normalized or the last dose before discontinuation of the study.

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Treatment for 24 weeks
The prolactin levels in serum decreased in all the patients during treatment with quinagolide as reported previously (9). Mean prolactin concentration decreased from baseline by an average of 75% (P<0.001) after 2 weeks of treatment and by 90% at week 24. Sixteen of the 24 women were normoprolactinemic at the end of 24 weeks treatment. Nine patients became normoprolactinemic at a daily dose of 0.050 mg quinagolide. The mean treatment dose in the group of patients who had become normoprolactinemic was 0.075 mg daily (range 0.050-0.175). Regular menstrual bleedings occurred in all but one of the 16 women with normal prolactin levels. Ovulation was confirmed by progesterone determinations in 15 of the 16 women. Eight women were still hyperprolactinemic after 24 weeks of treatment. In six of the women (patients No. 2, 3, 6, 21, 23, 24) a marked decrease in prolactin concentration occurred, whereas two patients (No. 5, 9) responded to quinagolide with only a minor decrease. Regular menstrual bleedings occurred in 4 of the 8 women (patient No. 5, 21, 23, 24). Ovulation was confirmed in all 4 women. There was no difference in the mean prolactin level before therapy in the group which became normoprolactinemic compared with the group that was still hyperprolactinemic at the end of 24 weeks of treatment. At this time 3 women discontinued the treatment, one because of pregnancy and 2 for personal reasons (travel distance). One woman (No. 2) was still hyperprolactinemic, but the prolactin level in serum had decreased by more than 50%.

A further 6 women discontinued the treatment after 12 (N=3), 18 (N=2) and 21 (N=1) months. The reason for discontinuation was in one case social (patient No. 4, preferred to be without medication), in one therapy resistance (patient No. 9), and in 4 pregnancy. One of the patients who
became pregnant (No. 6) was still hyperprolactinemic (87 µg/l) and amenorrheic after 12 months of treatment despite increasing dosage of quinagolide (maximum dose 0.5 mg daily), but conceived after addition of clomiphene citrate (50 mg daily for 5 days) to the treatment.

The course in a 35-year-old woman (patient No. 9) (Fig. 2) deserves special mentioning. She was admitted to our department because of three years of secondary amenorrhea and therapy resistant hyperprolactinemia. She had been treated with increasing doses of bromocriptine to a maximum of 25 mg daily with only a minor decrease in the serum prolactin levels. CT-scan showed only minor asymmetry of the pituitary fossa. When she entered the study her dose was titrated in the usual way to month 12. After that the dose was increased by 0.1 mg every month to 1.3 mg daily without any major effect on the serum prolactin levels. No adverse reactions were recorded. The treatment was discontinued after 21 months. At that time the patient developed a postmenopausal syndrome with flushing and sweating. The serum levels of FSH and LH were normal, whereas she had a low estradiol level in serum. After 3 months without treatment she received one injection of 50 mg Parlodel LA® (long-acting injectable bromocriptine) without any effect on the symptoms or the prolactin values.

After a further 3 months quinagolide treatment was re-instituted, mainly because of the postmenopausal problems. During the first months she was treated with 0.075 mg quinagolide daily, resulting in a marked decrease in the prolactin concentration. During the second month the dose was increased to 0.300 mg daily, resulting in normalization of the prolactin concentration in serum and return of menstrual bleedings.

Treatment for 24 months
Fifteen of the 24 women were treated for 24 months. The prolactin level in serum before treatment ranged between 31 and 390 µg/l (mean 60) and decreased in all the patients. At the end of the study, the mean concentration had decreased from baseline by an average of 89% (mean 7 µg/l, range 3-41).

The serum prolactin levels were normal in all the patients at the end of 24 months of treatment. Two women (patients No. 22 and 23) were slightly hyperprolactinemic at the last clinic visit, but had been normoprolactinemic previously during the study. Both had discontinued the treatment a few days before the last visit. The mean dose of quinagolide was 0.135 mg (range 0.050-0.500). In 8 patients a dose of 0.050 mg of quinagolide was adequate to normalize the prolactin levels in serum.

Regular menstrual bleedings occurred in all the patients except two (No. 13 and 14). Ovulation was
confirmed by progesterone determinations in 13 of the women. Low progesterone values, indicating anovulation, were found in 2 women. One of these women, however, was 50 years of age and had postmenopausal FSH values.

Mild to moderate galactorrhea was found at the baseline examination in 14 of the 15 women. After 24 months of treatment only 3 women still reported mild galactorrhea.

Quinagolide was well tolerated, also by the 9 women who had experienced fair (N=4) or poor (N=5) tolerability to earlier dopamine agonist treatment. Eight women reported no adverse reactions at all during the 24 months of treatment with quinagolide, whereas 7 women complained of minor adverse reactions such as nausea (5), tiredness (3), vomiting (2), depression (1), and obstipation (1). Most of the adverse reactions were reported during the beginning of the study. They were mild or occasionally moderate in intensity, and in none of the women led to discontinuation of the treatment.

Safety laboratory tests were normal in all the women at baseline and when repeated during the treatment period. Also, no change in ECG, blood pressure or pulse rate was recorded during the study.

Post treatment
Quinagolide treatment was discontinued in all 15 women after two years of medication. The mean concentration of prolactin in serum before discontinuation of quinagolide treatment was 7 μg/l (range 3-41) and had increased to 45 μg/l (range 19-220) (p<0.001) after two weeks, 47 μg/l (range 17-240) after 4 weeks, and 49 μg/l (range 18-230) after 6 weeks without treatment. The prolactin concentration in serum increased in all the patients except 2. Two women were still normoprolactinemic after 6 weeks of follow-up. Higher prolactin levels in serum after withdrawal of the treatment than had been present before treatment were found in 3 women (No. 12, 20, 24). Menstrual bleedings disappeared in 4 women during the first 6 weeks after discontinuation of treatment.

At 6 months follow-up, treatment had been reinstalled in 8 women, mainly because of increasing prolactin levels and amenorrhea. Six women were still without treatment at month 6, but all were hyperprolactinemic. Four of these patients still had regular menstrual bleedings. One woman conceived after 2 months without treatment. In this patient, quinagolide treatment had restored ovulatory menstrual cycles following failure of bromocriptine therapy.

Discussion
The results of this extended study confirm the value of once-daily quinagolide therapy in the treatment of hyperprolactinemic women. The gradual dose titration scheme allowed each patient to reach the dose required to achieve and sustain clinical efficacy. Consequently doses varied between 0.050 and 0.500 mg in those who responded. However, it should be mentioned that 8 of the 24 women were normoprolactinemic after one month with a minimum dose of 0.050 mg quinagolide, which suggest that quinagolide is at least as effective in its prolactin-lowering capacity as bromocriptine (10). Optimal individual doses were not predictable from baseline serum prolactin levels, an observation also reported earlier from quinagolide studies (9,10), as well as from experience with bromocriptine (11). These latter investigators postulated a differential sensitivity of the pituitary lactorropes, pharmacokinetic variations between individuals or differences in prolactin metabolism as factors responsible for the lack of predictability, any of which may also apply to quinagolide. Which patients would respond to or tolerate quinagolide was also not predictable from the history under other dopamine-agonist drugs.

The results of the initial 4-week double-blind, placebo-controlled portion of the study provided objective assessment of tolerability of quinagolide at a clinically relevant dose of 0.050 mg. The adverse events reported by the quinagolide group were mostly trivial and short-lasting (4,9). Later dose titration steps did not lead to seriously intensified complaints or to any study discontinuations.

This good tolerability is in agreement with other recent quinagolide studies (10,12-14). Each of the groups in the afore-mentioned trials included a number of patients with varying degrees of intolerance to earlier dopamine agonist treatment but who tolerated quinagolide without severe complaints. The study by Homburg et al. (10) was double-blind against bromocriptine control with 11 patients randomized to each treatment. The quinagolide-treated patients reported better tolerability than that reported by the bromocriptine-treated patients. Three patients in the bromocriptine

174
group, but none in the quinagolide group, dropped out owing to adverse effects and the three discontinuants were then treated with quinagolide without further problems. The fact that quinagolide is a specific dopamine D2-receptor agonist and also is a non-ergot compound may play a role in its improved tolerability and efficacy against the ergot-related prolactin-lowering compounds (1).

Our long-term data also indicate that persistence in dose increase over time as long as tolerability allows seems to be necessary to achieve full response in some patients. Specifically, 4 patients required more than 24 weeks of treatment and daily doses of 0.400, 0.250, 0.500 and 0.500 mg of quinagolide, respectively, to reach normal serum prolactin levels. In 3 women the serum prolactin level had not normalized by the end of their study participation at 6, 12 and 18 months, respectively. In the case of patient No. 2 in whom the serum prolactin level at week 24 which was 65% lower than at baseline, it is possible that continuing dose increases would have resulted in successful prolactin suppression. However, the other 2 women had shown partial or complete resistance to quinagolide up to doses of 0.500 mg and 1.3 mg, respectively. Patient No. 9 who was initially resistant to high doses of quinagolide, experienced the remarkable outcome of full response to 0.300 mg quinagolide following an interval of washout and further resistance to a 50 mg injection of long-acting bromocriptine. It is difficult to speculate what caused this delayed sensitivity to quinagolide. The normal gonadotropin and low estradiol levels found when the patient complained of menopausal symptoms would rule out any possibility of a priming effect of these hormones on the pituitary lactotropes, as has been reported to have occurred in similar situations (15,16). This finding remains, therefore unexplained.

Bromocriptine and other dopamine agonists are successfully used in the normalization of serum prolactin concentrations in women with hyperprolactinemia. Unfortunately, so far the results of bromocriptine withdrawal have been disappointing as prolactin levels have invariably risen above the normal range indicating persistence of prolactin hypersecretion. However, in many patients the increase in serum prolactin secretion after bromocriptine withdrawal did not reach pretreatment values (17-19) and even some patients remained normoprolactinemic at follow-up. It was also found that the degree of suppression after drug withdrawal correlates with the duration of treatment. In this study quinagolide treatment was discontinued in all the 15 women after 24 months of medication. The prolactin levels increased in all the patients except 2 during the 6 weeks of follow-up. At 6 months, treatment was re-instituted in 8 women, mainly because of increasing prolactin levels. Six women were still without treatment, but all were hyperprolactinemic. The ongoing study will show whether prolonged treatment with quinagolide will have the same positive effect on the prolactin hypersecretion as has been reported with bromocriptine under similar conditions.

To conclude, this study shows that quinagolide was a safe compound. The drug was effective in a once daily dose and adverse reactions were mild and transient also in patients with tolerance-related problems during earlier bromocriptine treatment. Quinagolide seems to be a valuable alternative to the dopamine agonists which are used today in the treatment of patients with prolactin disorders.

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