A COMPARISON OF CABERGOLINE AND BROMOCRIPTINE IN THE TREATMENT OF HYPERPROLACTINEMIC AMENORRHEA

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Abstract Background. Cabergoline is a long-acting dopamine-agonist drug that suppresses prolactin secretion and restores gonadal function in women with hyperprolactinemic amenorrhea. We designed a study to compare its safety and efficacy with those of bromocriptine, which has been the standard therapy.

Methods. A total of 459 women with hyperprolactinemic amenorrhea were treated with either cabergoline (0.5 to 1.0 mg twice weekly) or bromocriptine (2.5 to 5.0 mg twice daily), administered in a double-blind fashion for 8 weeks and subsequently in an open fashion for 16 weeks, during which adjustments in the dose were made according to the response. Of the 459 women, 279 had microprolactinomas, 3 had macroprolactinomas, 1 had a craniopharyngioma, 167 had idiopathic hyperprolactinemia, and the remainder had an empty sella. Clinical and biochemical status was assessed at 2-week intervals for 8 weeks and monthly thereafter for a total of 6 months, with an additional assessment at 14 weeks.

DOPAMINE-AGONIST drugs are the treatment of choice for most patients with hyperprolactinemia.1-2 Bromocriptine has been the reference compound and effectively suppresses prolactin secretion, restores gonadal function, and shrinks prolactinomas.3 It has a number of side effects, however, including nausea, dizziness, and headache, that limit the dose and may even necessitate the withdrawal of treatment.4,6 Furthermore, its half-life is short so that it must be given two or three times daily.

Cabergoline is a new, selective, potent, and long-lasting dopamine agonist that inhibits prolactin secretion in both normal subjects and those with hyperprolactinemia, with a duration of action of up to 21 days after single oral doses of 0.3 to 1.0 mg.7-9 It has a number of side effects, however, including nausea, dizziness, and headache, that limit the dose and may even necessitate the withdrawal of treatment. Furthermore, its half-life is short so that it must be given two or three times daily.

Cabergoline is more effective and better tolerated than bromocriptine in women with hyperprolactinemic amenorrhea. (N Engl J Med 1994;331:904-9.)

Results. Stable normoprolactinemia was achieved in 186 of the 223 women treated with cabergoline (83 percent) and 138 of the 236 women treated with bromocriptine (59 percent, P<0.001). Seventy-two percent of the women treated with cabergoline and 52 percent of those treated with bromocriptine had ovulatory cycles or became pregnant during treatment (P<0.001). Amenorrhea persisted in 7 percent of the cabergoline-treated women and 16 percent of the bromocriptine-treated women. Adverse effects were recorded in 68 percent of the women taking cabergoline and 78 percent of those taking bromocriptine (P = 0.03); 3 percent discontinued taking cabergoline, and 12 percent stopped taking bromocriptine (P<0.001) because of drug intolerance. Gastrointestinal symptoms were significantly less frequent, less severe, and shorter-lived in the women treated with cabergoline.

Conclusions. Cabergoline is more effective and better tolerated than bromocriptine in women with hyperprolactinemic amenorrhea. (N Engl J Med 1994;331:904-9.)

METHODS

Study Design

The study was a randomized, multicenter 24-week trial comparing cabergoline (0.5 to 1.0 mg twice weekly) with bromocriptine (2.5 to 3.0 mg twice daily) in the treatment of women with hyperprolactinemic amenorrhea. The women were recruited from 67 gynecological and endocrinologic centers in Europe and Argentina. The study was approved by the institutional review board at each center, and the women gave their informed consent, either written or oral and witnessed. Treatment was given under double-blind conditions for the first eight weeks and subsequently continued on an open-label basis. The reasons for this combined design included the different dose schedules for the two drugs, which, if double-blind conditions were continued throughout the study, would have imposed a twice-daily administration schedule on the women assigned to receive cabergoline. In addition, side effects from ergot derivatives occur during the first few weeks of treatment and decline progressively thereafter. Hence, double-blind administration during the first part of the study would ensure unbiased assessment of side effects when most would be anticipated to occur. Adequate comparison of the effectiveness of the two drugs under open conditions was ensured by the objective criteria used for this purpose.

Selection of Patients

We studied 459 women 16 to 45 years of age who had had amenorrhea for at least three months and serum prolactin concentrations at least twice the upper limit of normal values for each center (Table 1) on two occasions at least four weeks after the discontinuation of any previous therapy; serum prolactin concentrations of this magnitude were obtained in all but 9 of the 313 women who had been previously treated. Women who had been treated previously with either drug were not excluded unless they had had to discontinue treatment because of adverse events or had not had a 50 percent reduction in serum prolactin concentrations. Additional criteria for exclusion were the presence of a pituitary macroadenoma, any disorder that could prevent normal menstruation after the restoration of normoprolactinemia, hyperprolactinemia related to polycystic ovary disease, thyroid or adrenal disorders, renal or hepatic disease,
Table 1. Characteristics of the Women with Hyperprolactinemic Amenorrhea Treated with Bromocriptine or Cabergoline.*

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PREVIOUSLY TREATED</th>
<th>PREVIOUSLY UNTREATED</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRC (n = 163)</td>
<td>CAB (n = 153)</td>
<td>BRC (n = 74)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>32±7</td>
<td>32±6</td>
<td>30±7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163±6</td>
<td>162±7</td>
<td>163±7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63±13</td>
<td>63±12</td>
<td>63±15</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Microprolactinoma</td>
<td>101</td>
<td>102</td>
<td>38</td>
</tr>
<tr>
<td>Idiopathic hyperprolactinemia?</td>
<td>54</td>
<td>47</td>
<td>34</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Base-line serum prolactin (μg/liter)</td>
<td>124±132</td>
<td>122±102</td>
<td>103±106</td>
</tr>
<tr>
<td>Duration of amenorrhea (mos)</td>
<td>17±29</td>
<td>15±25</td>
<td>20±32</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ±SD. BRC denotes bromocriptine, and CAB cabergoline.
+No detectable adenoma on computed tomography or magnetic resonance imaging.
+One woman dropped out before starting treatment, but she had a history of a macroadenoma that had shrunk to 6 mm in diameter after dopamine-agonist therapy.
+Macroadenoma was treated surgically, with no residual tumor tissue visible on computed tomography.
+One woman underwent computed tomography or magnetic resonance imaging of the pituitary region (unlike those tests had been performed within the preceding 12 months).

Treatment

Each woman was centrally assigned to receive one of the study drugs in a double-blind fashion, according to computer-generated randomization lists that were stratified on the basis of country and previous therapy with either drug. During the first eight weeks the women took one tablet and one capsule (containing active drug or placebo) twice daily, with their morning and evening meals. The women assigned to the cabergoline group initially received 0.25 mg in the evening and then 0.5 mg three times weekly (days 1, 8, and then to 1 mg twice weekly).

Monitoring

Serum prolactin was measured at base line and 2, 4, 6, 8, 12, 14, 16, 20, and 24 weeks after the initiation of therapy. The duration of each episode of vaginal bleeding was recorded, but only episodes lasting at least two days were considered to be menses. When menses were restored, plasma progesterone was measured during the presumed luteal phase as an indicator of ovulation. If necessary, extra visits were arranged (on day 21 of the cycle) for this purpose. Serum prolactin and plasma progesterone were measured at each center soon after the samples were obtained by different immunologic methods with the use of international standards.

At each visit the women were asked about side effects, which were classified as mild (awareness of symptoms, but easily tolerated), moderate (enough discomfort to interfere with usual activities), or severe (incapacitating with inability to work or perform usual activities). Blood samples were collected after 4, 8, 16, and 24 weeks for blood counts and renal- and hepatic-function tests (as described above). During the double-blind period, women at risk of becoming pregnant were advised to use barrier contraception, but in the open-label period only those taking cabergoline were advised to continue such measures. A pregnancy test was performed the week before treatment was begun, at week 4, at each subsequent visit, and in any woman in whom menses had resumed but in whom a delay in menstruation was noted (beyond 32 days). Treatment was stopped if pregnancy was confirmed.

Criteria of Efficacy

The efficacy of treatment was assessed with clinical criteria (the occurrence of menses and ovulation) and biochemical measurements (serum prolactin concentrations). Complete clinical success was defined as the occurrence of at least two consecutive menses with biochemical evidence of ovulation and at least one occurrence (plasma progesterone one concentration above 7.9 ng per milliliter [25 nmol per liter] in samples obtained during the mideutal phase or above 3.2 ng per milliliter [10 nmol per liter] in samples not taken during the mideulal phase) or pregnancy. Partial clinical success was defined as the occurrence of two menstrual cycles without evidence of ovulation or a single ovulatory cycle. For women who did not require an adjustment of dose, complete biochemical success (defined as a serum prolactin value within the normal range after week 6) for those whose dose was changed at week 8 or 16, biochemical success was defined as a normal serum prolactin value from week 12 or 20, respectively. Partial success was defined as a serum prolactin value above the normal range at these times, but less than 50 percent of the base-line value. Biochemical failure was defined as serum prolactin concentrations remaining above 50 percent of the base-line values.

Statistical Analysis

The null hypothesis of the superiority by 10 percent or more of bromocriptine was tested against an alternative hypothesis of a difference of less than 10 percent in favor of bromocriptine, which was considered to be clinically irrelevant. The clinical and biochemical success rates in the two groups were compared with Blackwelder's modified z statistics. A complementary analysis of success rates used a logistic model including stratum (previous treatment with test drugs), treatment, and their interaction as explanatory variables. The intention-to-treat approach was used in evaluating the results. The results of analysis based only on women who could be fully evaluated (i.e., those fulfilling the eligibility criteria and completing the entire treatment period with correct dose adjustments) were similar to those of the intention-to-treat analysis.

Results

The women in each treatment group were comparable in terms of age, height, weight, base-line serum prolactin concentration, duration of amenorrhea, and diagnosis (Table I). The median periods without...
treatment were five months in the bromocriptine group and six months in the cabergoline group. At base line 434 of the 459 women had amenorrhea; 14 women in the bromocriptine group and 11 in the cabergoline group reported vaginal bleeding in the preceding three months.

In the bromocriptine group, 214 of the 236 women (91 percent) completed eight weeks of treatment and 169 (72 percent) completed the entire treatment period. The corresponding figures for the 223 women in the cabergoline group were 211 (95 percent) and 186 (83 percent). Seven women did not start treatment (five in the bromocriptine group and two in the cabergoline group). The final drug doses are shown in Figure 1. Therapy was discontinued before the end of the study in 67 women in the bromocriptine group and 37 women in the cabergoline group for the following reasons: pregnancy (12 in the bromocriptine group and 18 in the cabergoline group), drug intolerance (27 and 7, respectively), loss to follow-up (4 in each group), poor compliance with the visit schedule (6 in the bromocriptine group), and miscellaneous causes (18 in the bromocriptine group and 8 in the cabergoline group). Compliance was good in both treatment groups: none of the women in the cabergoline group and only six women in the bromocriptine group took less than 80 percent of the prescribed dose. During the open-label period, compliance with the twice-weekly schedule adopted for cabergoline was better than that with the twice-daily bromocriptine regimen (18 percent of women missed at least one dose of cabergoline, and 44 percent of women missed a dose of bromocriptine).

Clinical Efficacy

Menses resumed in 191 of the 231 women (83 percent) treated with bromocriptine and in 201 of the 221 (91 percent) treated with cabergoline, usually during the first eight weeks of therapy. Regular menstrual periods (intermenstrual intervals of 21 to 35 days) were recorded in 157 women taking bromocriptine (68 percent) and 181 (82 percent) taking cabergoline. Among the women who completed the study, menses resumed in 87 percent of those taking bromocriptine and 96 percent of those taking cabergoline. When we excluded the women who became pregnant without resuming menses (3 women treated with bromocriptine and 4 treated with cabergoline) and those who were randomized but never started treatment (5 treated with bromocriptine and 2 with cabergoline), amenorrhea persisted in 37 of those taking bromocriptine (16 percent) and in 16 of the women treated with cabergoline (7 percent).

Among women whose menses resumed, plasma progesterone was measured at least once in 187 of those in the bromocriptine group (98 percent) and 191 of those in the cabergoline group (95 percent). Of these, 123 in the bromocriptine group (66 percent) and 156 in the cabergoline group (82 percent) had at least one ovulatory cycle. The proportions of women with complete or partial clinical success or failure are shown in Table 2. The difference in the rates of complete success was 20 percent (95 percent confidence interval, 11 to 28 percent) and clearly indicated the superiority of cabergoline over bromocriptine. Of the 90 women in whom a clinical response could not be determined,
most (the "not applicable" category in Table 2) dropped out of the study with no proved ovulation, and the remainder did not have plasma progesterone measurements. The effects of cabergoline were superior to those of bromocriptine when the rate of clinical success was analyzed according to base-line serum prolactin values (77 percent vs. 59 percent in women with pretreatment serum prolactin concentrations below 100 μg per liter and 62 percent vs. 39 percent in those with pretreatment serum prolactin concentrations of at least 100 μg per liter). Before therapy, 48 women in the cabergoline group and 45 women in the bromocriptine group had galactorrhea, which disappeared in 90 percent and 78 percent, respectively, usually within eight weeks after the start of treatment.

Sixteen women treated with bromocriptine and 25 treated with cabergoline conceived, but only pregnancies in the latter group were actively monitored. There were 4 elective terminations because of unintended pregnancy, 2 early spontaneous abortions, 16 deliveries (1 cesarean and 15 vaginal), and 1 therapeutic abortion in a woman carrying an abnormal fetus (the fetus had anomalies of the legs probably related to amniotic bands); two women were lost to follow-up. All infants delivered were normal.

Biochemical Efficacy

The base-line serum prolactin concentrations were similar in the two groups (Table 1). The mean serum prolactin concentrations during the study are shown in Figure 2. The mean serum prolactin concentration fell rapidly during the first two weeks of treatment in both groups. From week 4 onward, it was well within the normal range in the cabergoline group but remained slightly above normal in the bromocriptine group. The rates of complete and partial biochemical success and biochemical failure are shown in Table 2. The difference in the rate of complete success was 25 percent (95 percent confidence interval, 17 to 33 percent) in favor of cabergoline. The serum prolactin response was not adequately assessed in 67 women (the "not applicable" category in Table 2) because they dropped out of the study or because only a single prolactin measurement was made at the final dose. In the bromocriptine group, the effective daily dose was 2.5 mg in 1 woman, 5 mg in 124, 7.5 mg in 10, and 10 mg in 3. The effective weekly cabergoline doses were 0.5 mg in 3 women, 1 mg in 167, 1.5 mg in 14, and 2 mg in 2.

The differences were more pronounced in favor of cabergoline in women who had not received any previous treatment (Table 2). Cabergoline also was more effective in women with base-line serum prolactin values of either less than 100 μg per liter or 100 μg per liter or higher and in women with either microprolactinomas or idiopathic hyperprolactinemia. However, in both treatment groups the rate of complete success was higher in women with pretreatment serum prolactin concentrations below 100 μg per liter (66 percent in the bromocriptine group and 89 percent in the cabergoline group) than in those with pretreatment concentrations of 100 μg per liter or higher (43 percent in the bromocriptine group and 73 percent in the cabergoline group).

Drug Safety

With cabergoline therapy, 68 percent of the women reported adverse events, as compared with 78 percent of those taking bromocriptine (P = 0.03); during the double-blind period, the corresponding values were 63 and 71 percent, respectively (P = 0.07). The cumulative risk of adverse events during cabergoline treatment was significantly lower than during bromocriptine treatment (odds ratio, 0.6; 95 percent confidence interval, 0.4 to 1.0). In two thirds of the women who had adverse events, the events occurred within two weeks after therapy was begun; however, 15 to 20 percent of the women in each group had persistent or recurrent early symptoms or had new symptoms in subsequent weeks (Fig. 3). Overall, adverse events (Table 3) were less frequent and less severe with cabergoline (14 percent vs. 20 percent, P = 0.06), and only 7 women (3 percent) had to discontinue treatment because of intolerance, as compared with 27 women (12 percent) in the bromocriptine group (P<0.001). Among the women treated with bromocriptine, nausea was significantly more frequent (P<0.001), more severe (occurring in 9 percent, as compared with 1 percent of the women treated with cabergoline; P<0.001), and of longer duration. Also, vomiting was more frequent and severe with bromocriptine than with cabergoline. Severe vomiting was reported by 5 percent of the bromocriptine-treated women but by none of the women receiving cabergoline.

Test Results

Five women (two in the bromocriptine group and three in the cabergoline group) had transient increases in serum alkaline phosphatase or aminotransferase values (>100 percent above the upper limit of nor-
There were no electrocardiographic changes.

of women than did bromocriptine. The effective doses were 2.5 mg twice daily for bromocriptine and 0.5 mg cent of the women in whom serum prolactin

mal), four of whom had slightly abnormal results at base line. In two women (one in each group), the abnormality resolved only after treatment was discontinued. Approximately 50 percent of the women in each group had a drop in blood pressure (median decrease, 10 mm Hg), particularly diastolic pressure, which was symptomatic in only three women in the cabergoline group and four in the bromocriptine group. There were no electrocardiographic changes.

DISCUSSION

These results provide clear evidence that cabergoline is more effective than bromocriptine in both normalizing serum prolactin and restoring gonadal function in women with hyperprolactinemic amenorrhea. In the doses used, cabergoline resulted in stable normoprolactinemia in a significantly higher proportion of women than did bromocriptine. The effective doses were 2.5 mg twice daily for bromocriptine and 0.5 mg twice weekly for cabergoline in approximately 90 percent of the women in whom serum prolactin concentrations became normal. The effect of cabergoline was also more rapid. As anticipated, the prolactin response was dependent on the pretreatment serum prolactin concentration; women with values below 100 μg per liter more often had normal values during treatment.

Cabergoline was also significantly more effective than bromocriptine in restoring gonadal function. The pregnancy rate cannot be interpreted as an indicator of clinical efficacy, since all women were advised to avoid conception during the double-blind period, as were those treated with cabergoline during the open-label period. The observation of only two spontaneous abortions in each group is consistent with the known rate of miscarriage in normal women.

The incidence of adverse symptoms and the number of women discontinuing treatment because of side effects were lower in the cabergoline group. The higher incidence of symptoms in previously treated women may be explained by their earlier experiences of side effects. The most frequent symptoms, typical of dopamine-agonist drugs, included nausea, headache, dizziness or vertigo, abdominal pain, weakness or fatigue, and constipation. The incidence of these symptoms was similar, except that gastrointestinal problems were less common, less severe, and shorter-lived in women treated with cabergoline. Our results are similar to those of a previous short-term, placebo-controlled trial using the same doses of cabergoline in 188 women10 and of open, uncontrolled studies of long-term therapy.11-13

The data concerning the efficacy and tolerability of bromocriptine differ from those of earlier open, uncontrolled studies that showed fewer adverse symptoms and better efficacy, but are in agreement with those of three recent double-blind, randomized trials comparing bromocriptine with quinagolide.4,6 In two of these studies,4,6 the doses of bromocriptine and the duration of treatment were the same as in our study, whereas in the third,5 higher doses of bromocriptine (up to 20 mg daily) were allowed and a once-daily dose was used. In all, 81 women with hyperprolactinemia were studied, of whom 40 were treated with bromocriptine. Normoprolactinemia was achieved in 22 of the 40 (55 percent), and menses resumed in 22 of 28 women (78 percent) with oligomenorrhea or amenorrhea.

In conclusion, cabergoline is highly effective and well tolerated in the majority of women with hyperprolactinemic amenorrhea. It has advantages over bromocriptine in terms of both efficacy and tolerability and therefore is an important advance in the treatment of hyperprolactinemia.

APPENDIX

The members of the Cabergoline Comparative Study Group are as follows: A. Chervin, H. Fideleff, C. Gurucharri, and I. Sinay, Buenos Aires, Argentina; J. Huber and S. Leodolter, Vienna, Austria; G. Tsherne, Graz, Austria; R. Abs, Antwerp, Belgium; A. Beckers and A. Stevengaert, Liege, Belgium; P.R. Koninckx, Leuven, Belgium; M. L’Hermite, Brussels, Belgium; Y. Lorcy, Rennes,
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