Comparison of the Effects of Cabergoline and Bromocriptine on Prolactin Levels in Hyperprolactinemic Patients

Tevfik Sabuncu*, Ender Arikan**, Ertugrul Tasan*** and Hüseyin Hatemi***

Abstract

Objective It is well known that bromocriptine has a suppressive effect on the prolactin release in hyperprolactinemic patients. But it also has some adverse effects. The new, long-acting dopaminergic drug, cabergoline, has been reported to be an effective agent in these patients. However, there are relatively few reports comparing the beneficial and adverse effects of these drugs in the treatment of hyperprolactinemic patients. Therefore, here we studied and compared the efficacy and tolerability of cabergoline with bromocriptine in hyperprolactinemic patients.

Patients Seventeen patients (7 with microprolactinoma, 4 with macroprolactinoma, 6 with idiopathic hyperprolactinemia) were given bromocriptine at a dose of 2.5 mg (or 5 mg for macroprolactinomas) twice daily, and 17 patients (8 with microprolactinoma, 4 with macroprolactinoma, 5 with idiopathic hyperprolactinemia) were given cabergoline at a dose of 0.5 mg twice weekly for 12 weeks.

Results At the end of the study, the prolactin reduction was significantly greater in the cabergoline group than in the bromocriptine group (-93 vs. -87.5%, respectively, p<0.05). Normalization of prolactin levels was achieved in 10 of 17 patients (59%) in the bromocriptine group, and in 14 of 17 patients (82%) in the cabergoline group (p=0.13). Two patients (50%) with macroprolactinoma in the bromocriptine group and three patients (75%) with macroprolactinoma in the cabergoline group demonstrated a normalization of their serum prolactin levels. Adverse events were noted in 53% of bromocriptine patients and in 12% of cabergoline patients (p<0.01).

Conclusion These data indicate that cabergoline is a very effective agent for lowering the prolactin levels in hyperprolactinemic patients and that it appears to offer considerable advantage over bromocriptine in terms of efficacy and tolerability.

Key words: dopamine agonist, hyperprolactinemia, prolactinoma

Introduction

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis. It occurs more frequently in women than in men. Clinical symptoms are amenorrhea, infertility, and galactorrhea in women and decreased libido and impotence in men (1). Most common causes are a prolactin-secreting pituitary adenoma (prolactinoma), idiopathic hyperprolactinemia and medications that alter central bioaminergic activities, usually, a prolactin-inhibitory action of dopamine. Other, less frequent causes are primary hypothyroidism, and non-prolactin-secreting hypothalamic or pituitary tumors that compress the pituitary stalk. Idiopathic hyperprolactinemia can be treated with drugs, and prolactinomas can be treated by drug therapy, surgery, or radiation therapy. Fifteen years ago, transsphenoidal pituitary surgery was the treatment of choice for patients with prolactinomas (2). Although surgical resection of the adenoma offers a potential for cure, in fact cure was later found to be achieved in a minority of patients with large tumors and was associated with a risk of recurrence in all patients. Hyperprolactinemia recurs one to five years after surgery in 10 to 50% of patients with microprolactinomas and in 20 to 91% of patients with macroprolactinomas (3, 4–9). Radiotherapy rarely results in the restoration of normal serum prolactin concentrations and therefore is generally not considered as a primary treatment for prolactinomas. For this reason, it is reserved for patients with tumors that are growing despite medical or surgical treatment (10).

The main therapeutic advance in the management of hyperprolactinemia has been the development of effective drugs. The semisynthetic ergot alkaloid bromocriptine, introduced in 1971, has been the standard drug for hyperprolactinemia. It is an orally active dopamine agonist that not only...
inhibits the synthesis and secretion of prolactin but also reduces cellular DNA synthesis and tumor growth (11). Because of its short half-life, bromocriptine must be given two or three times daily. Some adverse effects, such as headache, dizziness and nausea, can not be tolerated by about 10% of patients. In addition, bromocriptine is not sufficient to normalize hyperprolactinemia in some patients (10, 12). For these reasons, several new dopamine-agonist drugs have been developed, including lisuride, metergoline, terguride and pergolide. Although these drugs are useful for some bromocriptine-intolerant patients, none was superior to the reference compound in overall efficacy and tolerability (13).

Cabergoline is a new, potent ergot derivative that selectively binds to dopamine D2 receptors, and has a long plasma half-life that enables once- or twice-weekly administration (14). In a prospective multicenter study in women with hyperprolactinemic amenorrhea, cabergoline in doses of 0.5 to 1.0 mg twice weekly decreased prolactin secretion, normalizing serum prolactin in 83% of patients (15). Another large-scale retrospective study has found high efficacy and tolerability of cabergoline in the treatment of pathological hyperprolactinemia (16). Because the number of clinical studies with cabergoline is limited, compared with bromocriptine, we carried out this open, prospective, randomized study, which compared the efficacy and tolerability of cabergoline and the standard regimen of bromocriptine. The dopamine agonists were given for 12 weeks in a group of patients with idiopathic hyperprolactinemia, microprolactinoma or macroprolactinoma.

Four women in the cabergoline group and 3 women in the bromocriptine group had galactorrhea. All men in both groups had impotence and loss of libido.

Bromocriptine was started at a dose of 1.25 mg twice daily, and cabergoline at a dose of 0.25 mg twice weekly for the first week. Then bromocriptine was continued at a dose of 2.5 mg twice daily, and cabergoline at a dose of 0.5 mg twice weekly throughout the study. In the patients with macroprolactinomas, the dose of bromocriptine was increased from 2.5 mg twice daily to 5 mg twice daily in the third week, and continued to the end of the study. Women were advised to use barrier contraception during the study to avoid pregnancy.

The patients were monitored before and at 4, 8 and 12 weeks after the start of the treatment for clinical symptoms, laboratory findings and adverse events. Blood samples were also taken for measurement of prolactin, blood count, and hepatic and renal function tests at each visit. Serum prolactin was measured with an Immulite analyzer by using a chemiluminescent assay method (Immulite, Bio-DPC, Los Angeles, CA).

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows, version 7.5). All data are expressed as means±SE. The differences in continuous and categorical variables between the bromocriptine and cabergoline groups were analyzed by unpaired t-test (two-tailed) and $\chi^2$ test, respectively. Difference was considered significant with a $p$ value<0.05.

Results

The patients in each treatment group were similar in terms of number, gender, age, body mass index (kg/m²), menstrual status (for women), potency (for men) and baseline serum prolactin level (Table 1). All patients completed the study. Improvements in amenorrhea and galactorrhea were reported in 8 of the 11 women (73%) with amenorrhea and in 2 of the 3 women (67%) with galactorrhea in the bromocriptine group, and in 10 of the 12 women (83%) with amenorrhea and 3 of the 4 women (75%) with galactorrhea in the cabergoline group, usually during the first eight weeks of the treatments. All men in both groups reported improvements in their libido and potency.

Mean serum prolactin levels were significantly decreased in both groups, especially in the first four weeks of the treatment (Fig. 1). The prolactin reduction was more prominent in the cabergoline group than in the bromocriptine group at the end of the 12 weeks of treatment (13.4±3.3 vs. 23.5±3.5 ng/ml, $p<0.05$). Normalization of prolactin levels was achieved in 10 of 17 patients (59%) in the bromocriptine group, and in 14 of 17 patients (82%) in the cabergoline group ($\chi^2$ test, $p=0.13$). Two patients (50%) with macroprolactinoma and 8 patients (62%) with idiopathic or microprolactinoma in the bromocriptine group and three patients (75%) with macroprolactinoma and 11 patients (85%) with idiopathic or microprolactinoma in the cabergoline group demonstrated a normalization of their

For editorial comment, See p 845.

**Materials and Methods**

Since cabergoline is not normally available in Turkey, it was ordered from Pharmacia & Upjohn Co., Ltd. (Munchen, Germany). Thirty-four patients whose serum prolactin levels were higher than 60 ng/ml (three-fold the normal value) on two occasions were recruited for the present study. All patients were newly diagnosed and none had taken any medication, neurosurgery and/or radiotherapy. They were randomly assigned to receive bromocriptine and cabergoline for 12 weeks. Seventeen patients (15 women, 2 men), who were 19 to 48 years old received bromocriptine and 17 patients (15 women, 2 men), who were 18 to 45 years old received cabergoline. No patients had any other disorders, such as thyroid, adrenal, renal and hepatic diseases, polycystic ovary syndrome, and pregnancy, that affect the serum prolactin level. All patients underwent magnetic resonance imaging (MRI) of the hypothalamic pituitary region. According to MRI, 6 women had no visible adenoma, 7 women had microadenoma, 2 women and 2 men had macroadenoma in the bromocriptine group, while 5 women had no visible adenoma, 8 women had microadenoma, 2 women and 2 men had macroadenoma in the cabergoline group. Twelve women in the cabergoline group and 11 women in the bromocriptine group were amenorrheic for at least three months.
Table 1. Baseline Clinical and Hormonal Characteristics of the Bromocriptine and Cabergoline Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bromocriptine group</th>
<th>Cabergoline group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (women/men)</td>
<td>17 (15/2)</td>
<td>17 (15/2)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>33.4±2.1</td>
<td>32.7±2.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.4±1.3</td>
<td>23.1±1.2</td>
</tr>
<tr>
<td>No. of amenorrheic women</td>
<td>11 (73%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>No. of impotent men</td>
<td>2 (100%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Serum prolactin (ng/ml)</td>
<td>186.8±27.9</td>
<td>189.0±28.6</td>
</tr>
</tbody>
</table>

Data on age, body mass index and prolactin are means±SE.

Figure 1. Changes in prolactin (PRL) levels (mean±SE) in the bromocriptine (BRC) and cabergoline (CAB) groups throughout the study. *p<0.05 for the comparison with the cabergoline group.

Adverse events were less frequent in the cabergoline group than in the bromocriptine group (χ² test, p<0.01). Nine patients (53%) in the bromocriptine group reported drug-related adverse effects, such as headache, dizziness and nausea, whereas only two patients (12%) in the cabergoline group complained of nausea. Adverse events generally occurred in the first month of the treatment, and decreased with time. None of the patients complaining of adverse effects dropped out of the study.

Discussion

Although studies on the new dopamine agonist cabergoline can be found in the literature, they are still limited in number, compared with those on bromocriptine (16). Moreover, many of those studies were retrospective, case-specific (intolerant or resistant to bromocriptine), and/or applied in patients who underwent previous medical or surgical approaches. The present paper describes an open, prospective, randomized study comparing the efficacy and tolerability of cabergoline and bromocriptine in a population of naive hyperprolactinemic patients whose illness was idiopathic or microadenoma- or macroadenoma-related. The shortcomings of this study are the relatively low number of patients and its short duration of treatment. After three months of treatment, we halted the use of cabergoline and switched to bromocriptine, because cabergoline is not ordinarily available in Turkey, and patients had to buy this drug with their own money, which was a costly burden. Bromocriptine, on the other hand, is available free of charge through social security.

In the 12th week of treatment, the rate of normalization of serum prolactin was higher in the cabergoline group than in the bromocriptine group (82 vs. 59%). These success rates are similar to those of other studies (73–90 vs. 59%) evaluating micro- and macroprolactinomas together (15–18). When the patients were analyzed after being divided into two groups (idiopathic + microprolactinoma, and macroprolactinoma), the success rate in the bromocriptine-treated idiopathic + microprolactinoma subgroup was 62%, similar to the 70% rate observed by van der Heijden et al (19), and higher than the 48% rate reported by Pascal-Vigneron et al (20). The 50% success rate we observed for macroprolactinoma treated with bromocriptine is lower than those of several studies (62–67%) which administered higher doses or a long-acting injectable form of bromocriptine in macroprolactinoma patients (21–23).

On the other hand, the 85% normalization rate we found in idiopathic + microprolactinoma patients in the cabergoline group is comparable to the results of Webster et al (15), Cannavo et al (24), Pascal-Vigneron et al (20) and Muratori et al (25).
(83%, 88%, 93% and 96%, respectively), and the 75% normalization rate we found in macroprolactinoma patients is in accordance with the results of Ferrari et al (26), Biller et al (27) and Colao et al (28) (61%, 73% and 81%, respectively), and lower than the 100% rate reported by Cannavo et al (24), who used a higher dose of cabergoline (i.e. 3 mg/week). The results that the prolactin level decreased to a lesser extent and was less frequently normalized in macroprolactinoma patients, though few in number, may be related to the size of the tumor mass and the difference in biological behavior (2). Even in patients whose serum prolactin did not drop to normal levels, there was a considerable decrease with regard to initial levels. Thus, in addition to calculating the prolactin normalization rates of two treatment groups, we also assessed the effects of the drugs on overall prolactin levels. Average serum prolactin levels decreased to a greater extent in the cabergoline group than in the bromocriptine group with respect to basal values (−93 vs. −87.5%, p<0.05). These results clearly indicate that cabergoline is superior to bromocriptine in terms of both the normalization rate and the mean suppressibility of elevated prolactin.

The fact that cabergoline was more efficacious than bromocriptine in patients with idiopathic and micro- and macroprolactinoma-related hyperprolactinemia, suggests that in addition to having a more selective affinity to dopamine D2 than D1 receptors and a longer half-life, it may have another mechanism of action on prolactin as proposed by others (29–31). Thus if cabergoline is tried in patients who have an inadequate response and poor tolerance to bromocriptine, the proportion of patients who undergo additional surgery or radiotherapy, and hence those who will develop pituitary failure, may be reduced.

In some long-term studies (16, 28, 32), tumor shrinkage has been reported. Because our study was relatively short-term, MRI imaging was not repeated at the end of the study. Nonetheless, the clear drop in prolactin levels, particularly in the first month, and the absence of a significant change later on suggest that a three-month study was sufficient for demonstrating the efficacy and tolerability of these drugs.

More side effects were observed in the bromocriptine group than in the cabergoline group (53 vs. 12%), but they were not severe enough to justify ending the study in either group. Webster et al (15) reported side effect rates of 78% in patients receiving bromocriptine and 68% in patients receiving cabergoline, which are much higher than those in our study. This may be because their studies were of longer duration (24 weeks), higher doses of cabergoline were used (1 mg twice weekly), and patients were systematically questioned at every visit about the types and intensities of side effects. We merely asked our patients whether they had any complaint, and, if they did, whether they planned on dropping out of the study because of these complaints. Although we increased the bromocriptine daily dose from 5 to 10 mg in macroprolactinoma patients, we did not increase the 1 mg/week dose of cabergoline, because there are sufficient studies (26, 27) demonstrating that it is efficacious at this dose in macroprolactinoma patients, and also so as not to increase the cost. Colao et al have reported that cabergoline is tolerated remarkably well by 95% of patients (28). Many studies with bromocriptine and a smaller number of studies with cabergoline demonstrated that no harmful effects have occurred during treatment in pregnant women. However, since the use of medicine is generally not recommended during pregnancy (33–35), we advised our patients to use barrier contraception during the 12-week study period.

In patients with idiopathic or microprolactinoma- or macroprolactinoma-related hyperprolactinemia, we have shown that cabergoline is more effective and better tolerated than bromocriptine. Furthermore, its long-lasting effects make it easy to use. For these reasons, cabergoline appears to be a reasonable alternative for patients in whom bromocriptine is not sufficiently efficacious or is not tolerated. For patients of sufficient financial means, it may even be used as an initial treatment.

References


