Original Article

COMPARATIVE EFFECTS OF BROMOCRIPTINE AND CABERGOLINE ON SERUM PROLACTIN LEVELS, LIVER AND KIDNEY FUNCTION TESTS IN HYPERPROLACTINEMIC WOMEN

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ABSTRACT

Objective: To compare the effects of cabergoline and bromocriptine on serum prolactin levels and liver and renal functions in hyperprolactinemic women.

Methodology: This study involved one hundred women, who had symptoms of hyperprolactinemia and elevated serum prolactin concentration. They were divided into two groups of 50 women. The first group received 0.5 mg of cabergoline weekly and the second group received bromocriptine up to a maximum of 2.5 mg twice daily. Serum prolactin, total bilirubin, serum alkaline phosphatase activity, AST activity, ALT activity, serum creatinine and serum urea concentrations and creatinine clearance were determined at baseline and at 8 week interval (at the end of the trial). The efficacy of treatment was assessed with the regular menstrual cycle, absence of galactorrhea, oligomenorrhea and normalization of serum prolactin levels.

Results: Normalization of serum prolactin level was achieved in 28 of 50 (56%) women taking bromocriptine and in 40 of 50 (80%) women taking cabergoline. Cabergoline group showed a higher percent of improvement of the symptoms of hyperprolactinemia. Figures of 83.33% for amenorrhea, 71.4% for galactorrhea and 95.45% for oligomenorrhea have been noted with cabergoline versus 55.5%, 33.33% and 72%, respectively for bromocriptine. Sixty six percent of the women taking bromocriptine were reported to have adverse effects as compared with 30% of those taking cabergoline therapy. No significant adverse effects on liver and kidney functions have been reported in the study.

Conclusion: The present study demonstrated that both bromocriptine and cabergoline are effective in the treatment of hyperprolactinemia but cabergoline has the advantage over bromocriptine in terms of both efficacy and tolerability. Therefore it is preferred in the treatment of women with hyperprolactinemia. However, both drugs showed no abnormality in liver function as well as kidney function tests.

KEY WORDS: Cabergoline, Bromocriptine, Prolactin, Adverse effects.

How to cite this article:


INTRODUCTION

Hyperprolactinemia is one of 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. Dopamine agonists have become the treatment of choice for the majority of patients with hyperprolactinemic disorders. The goals of treatment are to normalize prolactine levels, restore gonadal function, and reduce the effect of chronic hyperprolactinemia.

Bromocriptine was the first dopamine agonist to be introduced into clinical practice. It is a semisynthetic ergot derivative of ergoline, a D2 receptor agonist with antagonist properties at D1 receptors. Its elimination half-life is relatively short (3.3 hours), and therefore it usually has to be taken 2 or 3 times daily.

Cabergoline is an ergoline derivative with high affinity and selectivity for the D2 receptor. It has an extremely long plasma half-life of about 65 hours allowing once-or twice weekly administration. Unlike bromocriptine, cabergoline has low affinity for D1 receptors.

Drugs are an important causes of liver injury. More than 900 drugs, toxins, and herbs have been reported to cause liver injury, and drugs account for 20-40% of all instances of fulminant hepatic failure. Toxic effects on the kidneys related to medications are both common and expected. Any drugs have nephrotoxic potential and some of them can cause more than one pattern of injury.

Data comparing the effects of cabergoline and bromocriptine on serum prolactin levels and liver and renal functions is limited, thus the present study was undertaken to compare the effects of cabergoline and bromocriptine on serum prolactin levels and liver and renal functions in hyperprolactinemic women.

**METHODOLOGY**

This study involved one hundred women, 19-35 years of age (mean= 28.12 years) who had symptoms of hyperprolactinemia (Amenorrhea, Oligomenorrhea and Galactorrhea) and elevated serum prolactin concentration at least twice the upper limit of normal values (which was considered 19.5 ng/ml) and at least four weeks after the discontinuation of any previous therapy. They were divided into two groups of 50 women. The first group received 0.5mg of cabergoline weekly (Dostinex, 0.5 mg tablets, manufactured by Pharmacia Italia S.P.A. Italy) and the second group received bromocriptine up to a maximum of 2.5 mg twice daily (parlodel, 2.5 mg tablets, manufactured by NOVARTIS PHARMA S.A.E., Cairo, under license from Novartis Pharma AG., Basle, Switzerland).

The patients were enrolled from Al-Batool Teaching Hospital for Gynecology and Obstetric in Mosul city. Excluded from the study were the women who showed the presence of pituitary macroadenoma, any disorder that could prevent normal menstruation, hyperprolactinemia related to polycystic ovary disease, thyroid or adrenal disorder, renal or hepatic disease and history of allergy to ergot derivatives. Women who had used any drug that affect secretion of prolactin from the pituitary such as neuroleptics were also excluded.

Serum prolactin was measured at baseline and at 8 weeks after the initiation of therapy (at the end of the trial) by a Microplate Immunoenzymometric assay using Monobind Inc. (Lake Forest, CA 92630, USA) Kit. Serum total bilirubin concentration, serum alkaline phosphatase (ALP) activity, serum aspartate aminotransferase (AST) activity, serum alanine aminotransferase (ALT) activity, serum creatinine concentration, and serum urea concentration were measured at baseline and at 8 weeks after the initiation of therapy (at the end of the trial) with commercially available kits. Creatinine clearance was determined by using Cockroft and Gault equation.

The women were followed up during the trial period and asked about adverse effects after drug administration and at each visit. The patients were not asked specifically about possible listed side effects but were merely asked whether they had any problems or difficulties with the drug. Any complaint was discussed with the patient, and if it appeared to be drug related, the complaint was reported as drug side effects. The efficacy of treatment was assessed with the occurrence of menses, absence of galactorrhea, oligomenorrhea and normalization of serum prolactin levels.
**Statistical analysis:** Paired student Z-test was used to compare results between before and after drug therapy. Unpaired t-test was used for the comparison of percent variation between the two drugs. Z-test between two proportions was used for the comparison of improvement of amenorrhea, galactorrhea, and oligomenorrhea between the two drugs, in addition to the comparison of the adverse effects between the two drugs. The statistical results were considered significant at P=0.05 or less.

**RESULTS**

Normalization of serum prolactin level was achieved in 28 of 50 (56%) women taking bromocriptine and in 40 of 50 (80%) women taking cabergoline. The differences between baseline measurement and after 8 weeks measurement were statistically significant for both groups (P<0.001) (Table-I and II). Bromocriptine and cabergoline groups were comparable in terms of baseline serum prolactine concentration (P>0.5).

The mean serum prolactin level fell after 8 weeks of treatment from baseline values of 56.02±26.44 ng/ml to 25.81±14.72 ng/ml (total mean reduction, 30.21 ng/ ml) in bromocriptine group and from 56.42±28.45 ng/ml to 17.19±6.21 ng/ml (total mean reduction, 39.23 ng/ ml) in cabergoline group. The percent variation for the two groups were-54.63±10.71 for bromocriptine group and -66.96±8.89 for cabergoline group. The difference between the two treatments is significant (P<0.001). Cabergoline group showed a statistically significant improvement in symptoms of hyperprolactinemia when compared with bromocriptine group (Table-III).

Regarding drug adverse effects, with bromocriptine 66% (33) of the women were reported to have adverse effects as compared with 30% (15) of those taking cabergoline therapy. Among the women treated with cabergoline, headache, palpitation and vomiting were more frequent while in case of bromocriptine GIT adverse effects were more frequent including nausea, vomiting and abdominal pain (Table-IV).

A significant elevations of ALP, AST, and ALT activities and urea and creatinine concentrations were obtained after therapy with bromocriptine and a significant reductions in creatinine clearance (Table-V). The elevations were slight and the parameters still within normal range. In case of cabergoline a slight significant elevations have been obtained only in the activities of ALT and AST (Table-VI).
DISCUSSION

The data obtained from the present study revealed that bromocriptine and cabergoline are both effective in the treatment of hyperprolactinemic women and that cabergoline is more effective and more safer than bromocriptine. They have no significant adverse effects on the liver and the kidneys.

The efficacy of bromocriptine has been evaluated in previous studies which demonstrated the benefit of bromocriptine in lowering serum prolactin level and restoring regular menstrual bleeding and relieving galactorrhea in the majority of patients,8-10 which are in agreement with the results of the current study. Normalization of serum prolactin level obtained in the present study in bromocriptine group (56%) is close to values of 58% obtained by Webster et al.11 and 59% obtained by Sabuncu et al.12

Regarding cabergoline, the present study revealed results which are in agreement with several other studies that also demonstrated the efficacy of cabergoline in the treatment of hyperprolactinemia.13-15 Normalization of prolactin levels obtained in the present study in cabergoline group (80%) is close to values of 81% and 83% obtained by Ciccarelli et al.16 and Webster et al.,11 respectively.

The number of patients suffering from adverse effects in the present study was low in cabergoline group (15 patients, 30%) as compared with bromocriptine (33 patients, 66%). The figures of adverse effects reported in the present study were close or differ from figures reported by other authors in other studies. In case of bromocriptine figures of 53%, 78% and 25% have been reported by Sabuncu et al.,12 Webster et al.11 and Van der Heijden et al.17 Regarding cabergoline, different figures have been reported in other studies including 39.5% by Webster et al.,18 23% by Ferrari et al.13 and 48%, by Ciccarelli et al.16

Table-IV: Adverse effects of cabergoline (noted in 15 women) and bromocriptine (noted in 33 women) reported in the study.

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Bromocriptine N=33 (66%)</th>
<th>Cabergoline N=15 (30%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>23</td>
<td>6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>7</td>
<td>0.016</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16</td>
<td>4</td>
<td>0.0014</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>8</td>
<td>0.301 (NS)</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>6</td>
<td>3</td>
<td>0.149 (NS)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>2</td>
<td>0.023</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>5</td>
<td>3</td>
<td>0.23 (NS)</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>1</td>
<td>0.154 (NS)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>14</td>
<td>12</td>
<td>0.323 (NS)</td>
</tr>
</tbody>
</table>

Table-V: The measured liver and kidney parameters before and after treatment with bromocriptine (Mean±SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP (U/L)</td>
<td>57.26 ± 10.41</td>
<td>68.22 ± 26.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>16.22 ± 4.62</td>
<td>23.26 ± 10.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>16.22 ± 5.03</td>
<td>22.18 ± 9.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Bilirubin (µmol/L)</td>
<td>4.81 ± 2.71</td>
<td>4.83 ± 2.69</td>
<td>0.1 (NS)</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>3.71 ± 1.0</td>
<td>3.87 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine Conc (µmol/L)</td>
<td>76.24 ± 13.72</td>
<td>77.7 ± 13.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CrCl (ml/min)</td>
<td>109.49 ± 19.75</td>
<td>107.05 ± 18.20</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
The present study showed that both bromocriptine and cabergoline have no important effects on the studied biochemical parameters of the liver and the kidneys as is evident by a non important elevations of these parameters although a significant elevations of alkaline phosphatase, ALT and AST activities have been demonstrated in the bromocriptine group. This elevations were mild and still situated within a normal limits of these parameters.

Review of literature revealed the availability of a poor data that deals with the effects of dopamine agonist drugs on the liver and kidneys. The only two studies that deals with this field including those performed by Webster et al. and Gillam et al. showed that small group of patients treated with bromocriptine have a transient asymptomatic increase in serum alkaline phosphatases and/or transaminases activities. Webster et al. assessed liver and renal function in 162 females with hyperprolactinemia treated with cabergoline. No changes in the activities of the liver and renal function parameters have been reported during the study period.

The fact that cabergoline was more efficacious than bromocriptine in patients with 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. Thus, if cabergoline is tried in patients who have an inadequate response and poor tolerance to bromocriptine, the proportion of patients resistant to bromocriptine can respond to cabergoline and the number of patients who undergo additional surgery or radiotherapy, and hence those who will develop pituitary failure, may by reduced.

The better tolerability of cabergoline compared with bromocriptine may be related to the high affinity of cabergoline for D2-type receptors and to the longer half-life, which results in fewer changes in drug concentration in the blood.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP (U/L)</td>
<td>56.62 ± 12.09</td>
<td>57.1 ± 12.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>15.32 ± 4.59</td>
<td>15.66 ± 4.76</td>
<td>0.0012</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>14.9 ± 6.09</td>
<td>14.98 ± 6.25</td>
<td>0.187(NS)</td>
</tr>
<tr>
<td>Total Bilirubin (µmol/L)</td>
<td>4.19 ± 2.07</td>
<td>4.21 ± 2.05</td>
<td>0.468(NS)</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>3.43 ± 0.94</td>
<td>3.46 ± 0.94</td>
<td>0.171(NS)</td>
</tr>
<tr>
<td>Creatinine Conc (µmol/L)</td>
<td>81.82 ± 12.2</td>
<td>82.38 ± 11.96</td>
<td>0.085(NS)</td>
</tr>
<tr>
<td>CrCl (ml/min)</td>
<td>98.49 ± 14.82</td>
<td>98.09 ± 15.27</td>
<td>0.159(NS)</td>
</tr>
</tbody>
</table>

**Table-VI: The measured liver and kidney parameters before and after treatment with cabergoline (Mean±SD)**

CONCLUSION

The present study demonstrated that both bromocriptine and cabergoline are effective in the treatment of hyperprolactinemia. Cabergoline has the advantage over bromocriptine in terms of both efficacy and tolerability, and therefore it is preferred in the treatment of women with hyperprolactinemia. Both drugs have no important adverse effects on liver and kidneys function.

REFERENCES


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