Evaluation of a novel vaginal bromocriptine mesylate formulation: a pilot study

Because of the frequent side effects found with oral bromocriptine, we created two formulas of vaginal bromocriptine suppositories to compare with vaginal application of bromocriptine tablets. The formula containing bromocriptine and a releasing agent (Pluronic F127) showed an increased dissolution rate, 39-fold greater than that of the pure drug alone, and subsequently was effective in lowering serum prolactin. (Fertil Steril® 2005;83:1053–5. ©2005 by American Society for Reproductive Medicine.)

Oral bromocriptine has long been considered the gold standard of therapy for hyperprolactinemia. However, adverse effects occur in over 50% of women taking oral bromocriptine, resulting in a discontinuation rate of at least 10% (1). The adverse effects include gastrointestinal (GIT) troubles, minimal absorption, extensive liver metabolism, and hypotension. Alternatively, parenteral bromocriptine has been used in selected cases; however, owing to the intensive and prolonged side effects, use of the parenteral approach has been very limited (2). Increasingly, prolactin-normalizing drugs are being manufactured for use in intolerant patients, but they are expensive and, again, are not tolerated by many patients (3).

In the recent years, research has focused on the vaginal placement of commercial tablets as a logic alternative for patients who cannot tolerate oral treatment. Many studies have demonstrated the superiority of the vaginal over the oral route in terms of dramatic minimization of general and gastrointestinal side effects (1, 4). In practice, however, patients find placing orally designed tablets inside the vagina to be inconvenient, a source of local irritation, and a potential hindrance to sexual intercourse. The aims of this study were to create new formulations of bromocriptine vaginal suppositories that have improved pharmaceutical features and to test their clinical effectiveness and tolerability among hyperprolactinemic patients in comparison with vaginally inserted, commercial bromocriptine tablets.

This study has two phases. The pharmaceutical phase was carried out at the Department of Pharmaceutics, Faculty of Pharmacy, Assiut University between May 2001 and August 2002. First, the preparation of vaginal suppositories incorporated 2.5 mg of bromocriptine mesylate (raw material supplied by Novartis Pharma Co., Cairo, Egypt) using a fusion method under ultraclean laboratory conditions. The suppositories were cone shaped, and weighed 1 gram; they were 20 mm in length and 424 mm³ in size. Second, the physical characteristics the suppositories were tested: weight variation, content uniformity, hardness, melting point, liquification time, and disintegration time.

Third, in vitro release studies were performed to examine the type of base, partition coefficient of the drug, melting point of the base, hydroxyl number of the base, presence of additives, and concentration of additives. Last, we explored the interaction between the drug and suppository base using differential scanning calorimetry (DSC), and x-ray diffractometer infrared spectroscopy (IR). Formulation A included the drug and a base (80% propylene glycol plus 20% polyethylene glycol 20000). Formulation B included Formulation A with solid dispersion with Pluronic F127, prepared by solvent evaporation method.

The clinical phase was conducted at the outpatient infertility clinic of Assiut University hospital from September 2002 to August 2003. Fifty-four hyperprolactinemic patients were randomly divided into three groups using 2.5 mg of bromocriptine once daily for 1 month. Formulation A was used by 15 patients (group A), and formulation B was used by 20 patients (group B); commercial vaginal bromocriptine tablets (2.5 mg, Parlodel; Novartis Pharm Co., Cairo, Egypt) were used by 19 patients (group C). This study was approved by the institutional review board of the faculty of medicine. All patients provided written consent for participation.

On gynecologic examination, patients with local lesions (e.g., ectopy or polyp) were excluded until properly treated. All study patients had pretreatment high serum prolactin (SP). After 1 month of therapy, patients were instructed to come in 3 to 4 hours after the last insertion of the drug for a venipuncture to be used for the estimation of SP using the enzyme-linked immunoabsorbent assay (ELISA) method. At the end of the course of treatment, the patient was asked to assess her experience with this approach of therapy. Moreover, thorough inspection of the cervix and vaginal mucosal integrity was done using Schiller’s iodine solution. Local ulceration expressed an iodine-negative appearance due to epithelial denudation. Data were collected and analyzed with SPSS version 11 (SPSS, Inc., Chicago, IL).
and expressed as median and mean ± standard deviation (SD). Student’s t-test was used to determine statistical significance between two groups; analysis of variance (ANOVA) test was used for all groups.

The pharmaceutical phase of the study showed an increased dissolution rate of bromocriptine/Pluronic F127 that was 39-fold greater than that of the pure drug alone. First-order release kinetic mechanisms were assessed for formulations A and B. Formula B exhibited a higher release rate constant (k = 0.51 min⁻¹) than formula A (k = 0.048 min⁻¹). The occurrence of in vitro and in vivo agreement can be explained by the presence of non-ion surfactant Pluronic F127.

Clinically, most patients entered this study because of intolerance to the oral route (A: 11, 73.4%; B: 17, 85%; and C: 15, 79%, respectively). All groups were nearly similar as regards age, parity, and gravidity. There was a statistically significant drop in SP levels after 1 month of therapy in groups A and B, and group C showed a definite but insignificant drop in SP after treatment, as shown in Table 1. Four patients in group A unexpectedly showed elevated SP levels after treatment. Those women were switched into group B for another month, and showed a statistically significant drop in their SP levels after 1 month of treatment. Three patients in group B became pregnant at the end of therapy, one of whom had experienced a 5-year period of infertility.

Group C showed a statistically significant increase in the percentage of excessive vaginal discharge (13 women, 68.4%), dyspareunia (11, 57.9%), vaginitis (12, 63%), and inconvenience (16, 84%) when compared with group A (3, 20%; 0, 4, 26.2%; and 3, 20%, respectively) and group B (5, 25%; 3, 15%; 3, 15%; and 3, 15%, respectively). However, nausea (0 cases), dizziness (3, 15%), and fainting 5, 26.3%) showed insignificant variation among the three groups.

For females, the vaginal approach seems to be a suitable alternative as it avoids direct contact of the drug with the gastrointestinal tract and the first pass through the liver. Pharmaceutically, tablets are not designed for vaginal use as they rapidly disintegrate with fast drug release. Moreover, the base of tablets is not absorbed through the vagina, with subsequent vaginal burning (5). This observation may explain, in this study, the significantly high percentage of local vaginal irritation, excessive vaginal discharge, and subsequent dyspareunea in group C. Estimation of bromocriptine in serum was omitted, as the testing is costly and has been previously performed (6). Formula B is superior to the other formulations in terms of significant reduction of SP, and its efficacy in treating the four women of group A who had persistent, high SP even after 1 month of proper treatment shows promise.

The duration of therapy in this study was only 1 month because it had been noted that SP levels attained the normal range after approximately 20 days of use of the drug (7). The dissolution rate of bromocriptine mesylate, which is a poorly water-soluble drug, was improved 39-fold after mixture with Pluronic F127 due to improved wettability and dispensability (8).

In conclusion, the bromocriptine vaginal suppositories containing Pluronic F127 proved to be effective in lowering SP, were well tolerated by most of the patients, had minimal local irritative vaginal effects, and were more convenient for vaginal use than the tablet form.

<table>
<thead>
<tr>
<th>Group A (15 patients)</th>
<th>Group B (20 patients)</th>
<th>Group C (19 patients)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pretreatment SP</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>42.92 ± 16.68</td>
<td>59.6 ± 64.65</td>
<td>35.77 ± 7.65</td>
</tr>
<tr>
<td>Median (range)</td>
<td>39 (19–87.2)</td>
<td>40 (21.4–120)</td>
<td>34.2 (25.1–50.1)</td>
</tr>
<tr>
<td><strong>Posttreatment SP</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>30.86 ± 23.07</td>
<td>22.05 ± 23.47^a</td>
<td>25.37 ± 4.28</td>
</tr>
<tr>
<td>Median (range)</td>
<td>23.4 (2.9–81)</td>
<td>15 (1.5–91.3)</td>
<td>24.2 (20–34.6)</td>
</tr>
<tr>
<td>P value</td>
<td>.011</td>
<td>.014</td>
<td>.792</td>
</tr>
</tbody>
</table>

^a Only 17 patients as three cases got pregnant.

TABLE 1
Serum prolactin (SP) before and after 1 month of treatment in different groups.

REFERENCES