# Clinical efficacy of novel unidirectional buccoadhesive vs. vaginoadhesive bromocriptine mesylate discs for treating pathologic hyperprolactinemia

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**Objective:** To test the clinical effectiveness of new bioadhesive unidirectional buccal and vaginal bromocriptine methylate discs in hyperprolactinemic patients.
**Design:** A preliminary randomized comparative study.
**Setting:** A pharmaceutical phase at the departments of Pharmaceutics, Faculties of Pharmacy, Assiut and El-Minea universities and a clinical phase at the Infertility Out-patient Clinic of Women's Health University Center, Assiut University, Assiut, Egypt.
**Patient(s):** A total of 42 patients with pathologic hyperprolactinemia.
**Intervention(s):** Patients were randomly divided into two groups. Group A comprised 21 patients who used unidirectional buccoadhesive bromocriptine methylate discs once daily for 1 month. Group B included 21 patients who used vaginoadhesive bromocriptine methylate discs once daily for 1 month. Serum prolactin (PRL) was measured before and after therapy in all cases.
**Main Outcome Measure(s):** Decline of serum PRL level after 1 month of therapy.
**Result(s):** Pharmaceutically, tests for swelling, surface pH, in vitro and in vivo bioadhesion and in vitro release expressed satisfactory results. The in vitro release of vaginal bromocriptine from the discs is increased in pH 4.5 media. Both groups showed a highly statistically significant reduction of serum PRL levels after 1 month of therapy without any significant difference between both groups. The decline of serum PRL was not correlated with age, parity, or indication of entering into this study.
**Conclusion(s):** Both buccoadhesive and vaginoadhesive discs containing bromocriptine are of equal efficacy for treating pathologic hyperprolactinemia. Buccoadhesive discs have the advantages of being gender nonspecific (i.e., could be used by men), avoiding manipulating the vagina, which could be inconvenient to some patients, such as virgins; not being dependent on cyclic estrogen (E) levels; and could be easily used during menstruation. (Fertil Steril® 2008;90:1864–8. ©2008 by American Society for Reproductive Medicine.)

**Key Words:** Prolactin, buccal, vaginal, bioadhesive, pluronics

Pathologic hyperprolactinemia is an endocrine disorder caused by an increased secretion of PRL from the pituitary gland, resulting in galactorrhea, irregular menstruation, and possible infertility. The incidence of increased PRL in infertile but ovulatory women ranges from 3.8%–11.5% (1). Despite the expanded introduction of different PRL-normalizing drugs, bromocriptine methylate is the cornerstone in most of the treatment protocols of hyperprolactinemia. If administered orally, it has the advantage of rapid, although incomplete, absorption from the gastrointestinal tract. Its absolute bioavailability is only 4.5%–6% because of extensive presystemic metabolism by the liver, with subsequent prominent side effects (2).

Trials of its vaginal use achieved rapid and effective PRLecline in many studies (3–6). The major disadvantage of the vaginal route is insolubility in water (1:1,250). In a previous study, solubility had been increased by 39 times when the drug was mixed with pluronic F-127 (7). Bioadhesion means the ability of a material (synthetic or biological) to adhere to a biological tissue resulting in focusing a high drug concentration in a localized area. An intimate contact must exist between the bioadhesive and the receptor tissue. Such contact results either from a good wetting of the bioadhesion surface or from the swelling of the bioadhesive. When contact is established, penetration of the bioadhesive into the tissue takes place (8, 9). The major advantages of bioadhesion are

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increased bioavailability and elimination of gastrointestinal tract side effects of some drugs (10–12). The aim of this preliminary study is to evaluate the clinical efficacy of newly developed bioadhesive buccal and vaginal bromocriptine methylate discs in hyperprolactinemic patients.

## MATERIALS AND METHODS

This preliminary study has two phases, a pharmaceutical phase and a clinical stage. The pharmaceutical phase was carried out at the departments of Pharmaceutics, faculties of Pharmacy, El-Minia and Assiut universities, and included formulation and evaluation of bioadhesive buccal and vaginal discs containing 2.5 mg of bromocriptine mesylate as solid dispersion with pluronic F127 under ultra-clean laboratory conditions. Formulation of bromocriptine mesylate/pluronic F-127 solid dispersion passed through the same stages as previously described (7). The raw material of 2.5 mg of bromocriptine mesylate was kindly supplied by Memphis Co. for Pharm. and Chem. industry, Cairo, Egypt.

Unidirectional bilayered buccoadhesive discs were formulated by mixing bromocriptine mesylate/pluronic F-127 solid dispersion (which is equivalent to 2.5 mg of free bromocriptine mesylate) with bioadhesive polymers carbopol 974P, chitosan, and the remainder was lactose as a diluent. The mucoadhesive drug–polymer mixture (100 mg) was directly compressed on a previously obtained backing layer of ethylcellulose (100 mg) using a 13-mm diameter die by a hydraulic press machine. A compression force of two tones for 30 seconds was found to be satisfactory. The disc is called unidirectional because it contains a drug-free backing layer that modifies bromocriptine release toward the mucosa and a drug mucoadhesive layer containing a combination of bioadhesive polymers and bromocriptine mesylate. The prepared discs were of 200 mg total weight, 13 mm in diameter, and 2 mm in average thickness. The swelling index, bioadhesion force, surface pH, in vitro drug release, and residence time of the prepared discs were evaluated. These buccoadhesive discs were evaluated for release pattern, swelling capacity, surface pH, mucoadhesion performance, and in vitro permeation of bromocriptine mesylate through buccal membranes. In vivo testing of mucoadhesion time, strength of adhesion, irritation, bitterness due to drug swallowing, and disc disintegration in the buccal cavity were performed.

The vaginal bioadhesive discs of bromocriptine mesylate (single layered) were formed by mixing bromocriptine mesylate/pluronic F-127 solid dispersion (which is equivalent to 2.5 mg of free bromocriptine mesylate) with bioadhesive polymers including caobopol 974P, chitosan, and the remainder was lactose as a diluent. The mucoadhesive drug–polymer mixture (100 mg) was directly compressed using a 7-mm diameter die by single punch tablet machine. The prepared discs were of 100 mg in total weight, 7 mm in diameter, and 4 mm in average thickness. The produced discs were evaluated for their swelling behavior, bioadhesion force, and in vitro drug release.

The clinical phase was conducted at the outpatient infertility clinic of Women's Health Hospital, Assiut University, from April 2004 to March 2007. Institutional Review Board (IRB) approval was obtained. All patients gave a written consent to participate in this study. In this study we included all patients with pathologic hyperprolactinemia who expressed intolerance or resistance to oral bromocriptine. We excluded patients who received oral PRL-normalizing drugs within at least 2 weeks before the pretreatment blood sample for PRL assay to ensure complete washout of the drug. Search for hyperprolactinemia was carried out by screening for serum PRL among infertile women with evident galactorrhea, amenorrhea, or hypomenorrhea, patients with mastodynea, or infertile patients with sonographic suggestion of hyperprolactinemia. Hyperprolactinemic patients (serum PRL more than 20 ng/mL) were randomly divided into two groups. Randomization was done by means of a computer program using a simple random sample. Neither the subjects nor clinicians involved in the study knew which study treatment was being administered to any given subject.

We recruited 42 hyperprolactinemic female patients who were randomly divided into two groups. Randomization was done by means of sealed envelops. Group A comprised 21 patients who used buccal discs once daily for 1 month. The first disc in all cases was applied elsewhere in the buccal cavity by the clinician who instructed patients to avoid eating or excessive drinking after application. Subsequently, timing of application was at night before sleeping. Patients were instructed to extract the disc in the early morning from the buccal cavity.

Group B included 21 patients who applied vaginal discs once daily for 1 month. Patients were instructed to insert the vaginal discs as high as possible in the vagina while lying on the back, better at bedtime. Serum PRL was measured before and after therapy in all cases. All patients had high pretreatment baseline serum PRL and were advised to take the drug regularly in a fixed time. During the course of the therapy, patients were instructed to take medications regularly, to minimize touching the nipples, and to avoid eating various fowl that contain PRL-releasing factors (2).

After 1 month of therapy, the patient was instructed to come to the clinic 12–24 hours after the last insertion of the drug to be subjected to venipuncture for the estimation of serum PRL using the ELISA method. At the end of the course of treatment, the patient was asked to assess her experience with either approach of therapy.

Data were collected and analyzed with SPSS version 11 (SPSS, Inc., Chicago, IL) and expressed as mean ± SD. Statistical methods were applied including descriptive statistics (frequency, percentage, mean, and SD) and tests of significance (Student's *t*-test was used to determine statistical significance between the two groups, whereas the paired *t*-test was used to determine statistical significance before and after treatment in the same group). The *P* value was considered statistically significant when it was less than .05.