

Comparison of the effects of cabergoline and bromocriptine in women with hyperprolactinemic amenorrhea

Ahmed J Al-Husaynei, M.B.Ch.B, D.O.G., F.I.C.O.G.*

Isam H. Mahmood, Ph.D.†

Zena S. Al-Jubori, M.Sc.†

Al-Batool Teaching Hospital for Obstetrics and Gynecology, and Department of Pharmacology, College of Medicine, University of Mosul, Iraq

ABSTRACT

Objective: There are relatively few reports in the world comparing the beneficial and adverse effects of bromocriptine and cabergoline in the treatment of hyperprolactinemic patients and there is also lack of such studies in Iraq. Therefore, this study sets out to compare the efficacy and safety of cabergoline with those of bromocriptine in women with hyperprolactinemic amenorrhea in Mosul city.

Design: Randomized, 8 - week period comparative trial.

Setting: Al-Batool Teaching Hospital for Obstetric and Gynecology and the department of pharmacology, college of medicine in Mosul city.

Materials and methods: One hundred and thirty women with hyperprolactinemic amenorrhea participated in the study. Women were treated with either cabergoline (0.5 mg weekly) or bromocriptine (2.5 mg twice daily) administered randomly for 8 weeks. Amenorrhea and galactorrhea and serum prolactin levels were assessed at baseline and at the end of the trial.

Main Outcome measures: The efficacy of both treatments was assessed with the occurrence of menses, absence of galactorrhea and normalization of serum prolactin levels.

Results: Amenorrhea persisted in 9 women of the cabergoline-treated women and 20 of the bromocriptine-treated women. Galactorrhea disappeared in the cabergoline group and persisted in 12 of the bromocriptine group. Normoprolactinemia was achieved in 87.7% women treated with cabergoline and in 67.7% of women treated with bromocriptine.

Conclusions: Cabergoline and bromocriptine are effective in the treatment of hyperprolactinemic amenorrhea. Cabergoline has the advantage over bromocriptine in terms of both efficacy and tolerability and therefore it is preferred in the treatment of hyperprolactinemic amenorrhea.

Key words: Hyperprolactinemia, amenorrhea, galactorrhea, bromocriptine, cabergoline.

Elevated prolactin levels can result from physiological causes, such as pregnancy and stress, and pharmacological causes, including the use of neuroleptics, estrogens, opiates, antihypertensive drugs

or calcium channel blockers (1). Once physiological and iatrogenic stimuli have been eliminated as causes of elevated prolactin levels, the presence of a micro- or macroprolactinoma is the most likely cause of persistent pathological hyperprolactinaemia (2). Symptoms of hyperprolactinaemia include signs of gonadal dysfunction, and female patients frequently present with oligomenorrhoea, amenorrhea and galactorrhea (3).

* Al-Batool Teaching Hospital for Obstetrics and Gynecology.

† Pharmacology, Department of Pharmacology, College of Medicine, University of Mosul.

Correspondence and requests for reprints: Isam H. Mahmood, Department of Pharmacology, College of Medicine, Mosul, Iraq, E-mail: isam_mahmood@yahoo.com

Dopamine agonists are the preferred treatment for most patients with hyperprolactinemic disorders (4, 5); these agents are extremely effective in lowering serum prolactin levels, eliminating galactorrhea, restoring regular menses and decreasing tumor size (6, 7). Mimicking the action of dopamine, dopamine agonists, including bromocriptine, quinagolide and cabergoline differ in their efficacy and tolerability (5).

Bromocriptine is a semisynthetic ergot derivative of ergoline, a dopamine D2 receptor agonist with agonist and antagonistic properties on D1 receptors (2, 7). Because of its short half life (3.3 hours), bromocriptine may require multiple dosing throughout the day (6). Approximately 12 percent of patients are unable to tolerate this medication at therapeutic dosages (8). The most common adverse effects are nausea and vomiting, headache, dizziness and decrease in blood pressure (9). Bromocriptine administration via the vaginal route may reduce the incidence of side effects and offer an alternative to oral bromocriptine (10, 11). A range of 5-18% of patients have been reported as resistant to bromocriptine treatment, with only partial lowering of plasma prolactin levels and an absence of tumor shrinkage (12).

Cabergoline is an ergoline derivative with a high affinity and selectivity for D2 receptors (13). It has an extremely long plasma half – life of about 65 hours allowing once- or twice – weekly administration (14). Unlike bromocriptine, cabergoline has low affinity for D1 receptors (8, 15). Cabergoline is more expensive than bromocriptine, and some physicians may reserve the medication for use in patients who are resistant to or intolerant of bromocriptine (16). Cabergoline may be administered at doses ranging between 0.5 and 1.5 mg once or twice per week (17, 18). Because the drug dosing is less frequent and the drug is more tolerable, patient compliance may be better with cabergoline than with bromocriptine (18). Although no detrimental effects on fetal outcomes have been reported in more than 300 pregnant women taking cabergoline, the current recommendation is to discontinue cabergoline one month before conception is attempted (7).

Studies comparing the beneficial and adverse effects of bromocriptine and cabergoline in the treatment of hyperprolactinemic patients were lack

in Iraqi population. Therefore, this study sets out to compare the efficacy and safety of cabergoline with those of bromocriptine in women with hyperprolactinemic amenorrhea in Mosul city.

MATERIALS AND METHODS

The study was randomized, 8 - week period trial comparing cabergoline (Dostinex, 0.5 mg tablets, manufactured by Pharmacia Italia S.P.A., Italy) with bromocriptine (Parlodel, 2.5 mg tablets, manufactured by NOVARTIS PHARMA S.A.E., Cairo, under license from Novartis Pharma AG., Basle, Switzerland) in the treatment of women with hyperprolactinemic amenorrhea, collected from Al-Batool Teaching Hospital for Obstetric and Gynecology in Mosul city. The study protocol was approved by the local research Ethics Committees of the College of Medicine and Mosul Health Administration.

The study tackled one hundred and thirty women, 20 to 39 years of age who had amenorrhea for at least three months and serum prolactin concentration at least twice the upper limit of normal values at least four weeks after the discontinuation of any previous therapy. Excluded from the study were the women who show the presence of a pituitary macroadenoma, any disorder that could prevent normal menstruation, hyperprolactinemia related to polycystic ovary disease, thyroid or adrenal disorders, renal or hepatic disease and a history of allergy to ergot derivatives. Women who had used any drugs that affect secretion of prolactin from the pituitary such as neuroleptics were also excluded.

Each woman was assigned to receive one of the study drugs in a random fashion. Randomization method have performed by placing 130 circular thick colored plastic pieces in a black bag, 65 red in color represent cabergoline and 65 white in color represent bromocriptine. Each woman withdraws a piece of colored plastic from the bag. Red pieces, women have took cabergoline while white pieces, women have took bromocriptine. The women assigned to the cabergoline group received 1 (0.5 mg) tablet of dostinex weekly and those assigned to bromocriptine group received 2 (2.5 mg) tablets of parlodel daily.

Table 1. Number of women with amenorrhea and galactorrhea before and after treatment with cabergoline or bromocriptine.

Drug	Amenorrhea (number of Women)			Galactorrhea (Number of Women)		
	Before	After	Improvement	Before	After	Improvement
Cabergoline	65	9	56 (86%)	52	-	52 (100%)
Bromocriptine	65	20	45 (69.23%)	56	12	44 (78.6%)

P value for amenorrhea <0.05

P value for galactorrhea <0.001

Serum prolactin was measured at baseline and at 8 weeks after the initiation of therapy (at the end of the trial) with commercially available Kit (immunoradiometric assay) (IRMA), Kit, Beckman Coulter Company-Czech Republic. The upper range of normal serum prolactin level was considered 16 µg/L. 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 effect (19). The efficacy of treatment was assessed with the occurrence of menses, absence of galactorrhea and normalization of serum prolactin levels.

All values were quoted as the mean ± SD. Paired t-test was used to compare serum prolactin level at baseline and after treatment. Unpaired t-test was used to compare between the 2 treatments. Z-test was used to compare between the incidence of amenorrhea, galactorrhea and adverse effects of the two groups. Level of significance was considered significance at $P \leq 0.05$.

RESULTS

Normalization of the menstrual cycle was obtained

Table 2. Serum prolactin level before and after treatment with cabergoline (µg/L).

Parameter	Range	Mean±SD	P value
Before Treatment	32.3-140.4	59.13±29.43	$P < 0.001$ □
After Treatment	0.7-43.2	7.18±9.84	

in 56 women (86%) in the cabergoline group and 45 women (69.23%) in the bromocriptine group. Galactorrhea disappeared in all women (100%) having galactorrhea in the cabergoline group while in bromocriptine group galactorrhea disappeared in 44 women (78.6%) having galactorrhea (Table 1).

The women in the cabergoline and bromocriptine groups were comparable in terms of age (Mean 28.96 ± 5.24 year for cabergoline group and 28.2 ± 4.63 years for the bromocriptine group) and baseline serum prolactin concentration ($P > 0.5$).

Normalization of serum prolactin level was achieved in 57 of 65 (87.7%) women taking cabergoline and in 44 of 65 (67.7%) women taking bromocriptine. The mean serum prolactin level fell after 8 weeks treatment from baseline values of 59.13 µg/L to 7.18 µg/L in cabergoline group and from 58.48 µg/L to 18.01 µg/L in the bromocriptine group. The differences between baseline measurement and after 8 weeks measurement were statistically significant for both groups ($P < 0.001$) (Table 2 and 3).

The reduction of prolactin level after 8 week treatment was mean 51.95 µg/L for cabergoline group and mean 40.47 µg/L for bromocriptine group. The difference between the two treatments is significant ($P < 0.001$) (Table 4).

Serum prolactin levels of the 8 women in the cabergoline group, whose serum prolactin levels were not normalized, were felt from 70.15 ± 40.2 µg/L to 30.01 ± 7.5 µg/L, whereas in case of **bromocriptine**,

Table 3. Prolactin level before and after treatment with bromocriptine (µg/L).

Parameter	Range	Mean±SD	P value
Before Treatment	32.5-170.4	58.48±29.75	$P < 0.001$
After Treatment	0.9-63.2	18.01±15.34	

Table 4. Reduction of prolactin level in cabergoline and bromocriptine groups ($\mu\text{g/L}$).

Parameter	Cabergoline	Bromocriptine	P value
Mean $\pm$ SD	51.95 $\pm$ 28.19	40.47 $\pm$ 22.98	P<0.001
Percentage	□87.86	69.2	

serum prolactin level was reduced in the 21 women whose serum prolactin level were not normalized, from 82.05 $\pm$ 36.57 $\mu\text{g/L}$ to 38.25 $\pm$ 9.37 $\mu\text{g/L}$ after treatment.

Regarding drug adverse effects, with cabergoline therapy, 28% (18) of the women were reported to have adverse effects as compared with 55% (36) of those taking bromocriptine. Among the women treated with the cabergoline, headache and nausea are more frequent while in case of bromocriptine GIT adverse effect are more frequent including nausea, vomiting and abdominal pain (Table 5).

DISCUSSION

The data obtained from the present study revealed that cabergoline and bromocriptine are both effective in the treatment of hyperprolactinaemic amenorrhea and that cabergoline is more effective and more safe than bromocriptine.

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, which are in agreement with the results of this study (20-22). The percentage of reduction

of serum prolactin level obtained in the present study in bromocriptine group (69.2%) is close to the value of 70% reported by Verhelst et al. (14) and Van der Heijden et al. (23). Our results are better than the results obtained by Webster et al. (24) where the success rate was only 58% and by Sabuncu et al. (25) and Pascal-Vigneron et al. (26) where the success rate was 59% and 48.2%, respectively.

Regarding cabergoline, the current results are in agreement with several other studies reported in the last 10 years demonstrating the efficacy of cabergoline treatment in hyperprolactinemia (27-29). Our percentage of success in attaining normal level in cabergoline group falls within the margins of 82-93% success of other studies (14, 25-27).

The results in demonstrating that cabergoline is more effective than bromocriptine in both normalizing serum prolactin levels and restoring regular menses, and relief galactorrhea are in agreement with the results obtained by other investigators who reported also the superiority of cabergoline over bromocriptine in treating hyperprolactinemic women with amenorrhea (24-26).

The number of patients suffering from adverse effect in the present study was low in the cabergoline group (28%) compared with the bromocriptine group (55%). There were significant fewer gastro intestinal symptoms in the cabergoline group compared with the bromocriptine group. Our results are similar to those obtained in the previous studies that showed also fewer adverse effects with cabergoline and higher incidence with bromocriptine (24-27).

Table 5. Adverse effects of cabergoline and bromocriptine.

Adverse Effects	Cabergoline (18Women, 28%)	Bromocriptine (36Women, 55%)	P value
Nausea	8 (12%)	30 (46%)	<0.001
Vomiting	4 (6%)	15 (23%)	<0.007
Abdominal Pain	7 (10%)	18 (27%)	<0.016
Headache	8 (12%)	12 (18%)	0.340
Posturalhypotension	6 (9%)	6 (9%)	1.000
Dizziness	4 (6%)	8 (12%)	0.234
Drowsiness	3 (5%)	9 (14%)	0.083

A non-ergot derivative, quinagolide is likely to result in fewer side effects compared with bromocriptine. This difference may be due to the fact that quinagolide possesses high specificity for D2 type dopamine receptors, while bromocriptine also acts on D1 type dopamine receptors (5). Cabergoline has low affinity for D1-type dopamine receptors and demonstrates a high affinity for D2-type receptors (30). Thus the better tolerability of cabergoline compared with bromocriptine may be like quinagolide related to high affinity for D2 type receptors only.

In conclusion, cabergoline and bromocriptine are effective in the treatment of hyperprolactinemic amenorrhea. Cabergoline has the advantage over bromocriptine in terms of both efficacy and tolerability, and therefore it is preferred in the treatment of hyperprolactinemic amenorrhea.

REFERENCES

- Verhelst J, Abs R. Hyperprolactinemia: pathophysiology and management. *Treatments in Endocrinology* 2003; 2: 23-32.
- Mah PM, Webster L. Hyperprolactinemia: etiology, diagnosis, and management. *Semin Reprod Med* 2002; 20: 365-374.
- Luciano AA. Clinical presentation of hyperprolactinemia. *J Reprod Med* 1999; 44: 1085-1090.
- De Luis DA, Becerra A, Lahera M, Botella JJ, Valero MA, Varela C. A randomized cross-over study comparing cabergoline and quinagolide in the treatment of hyperprolactinemic patients. *J Endocrinol Invest* 2000; 23: 428-434.
- Barlier A, Jaquet P. Quinagolide a valuable treatment option for hyperprolactinaemia. *European J Endocrinol* 2006; 154: 187-195.
- Biller BM. Hyperprolactinemia. *Int J Fertil Women's Med* 1999; 44: 74-77.
- Bankowski BJ, Zacur HA. Dopamine agonist therapy for hyperprolactinemia. *Clin Obstet Gynecol* 2003; 46: 349-362.
- Webster J. Dopamine agonist therapy in hyperprolactinemia. *J Reprod Med* 1999; 44(12 suppl): 1105-1110.
- Lamberts SW, Quik RF. A comparison of the efficacy and safety of pergolide and bromocriptine in the treatment of hyperprolactinemia. *J Clin Endocrinol Metab* 1991; 72: 635-641.
- Kletzky OA, Vermesh M. Effectiveness of vaginal bromocriptine in treating women with hyperprolactinemia. *Fertility and Sterility* 1989; 51: 269-272.
- Ginsburg J, Hardiman P, Thomas M. Vaginal bromocriptine – clinical and biochemical effects. *Gynecological Endocrinology* 1992; 6: 119-126.
- Brue T, Pellegrinil I, Priou A, Morang I, Jaquet P. Prolactinomas and resistance to dopamine agonists. *Hormone Research* 1992; 38: 84-89.
- Colao A, Di Sarno A, Sarnacchiaro F, Ferone D, Di Renzo G, Merola B, et al. Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. *J Clin Endocrinol Metab* 1997; 82: 876-883.
- Verhelst J, Abs R, Maiter D, van der Bruel A, Vandeweghe M, Velkeniers B, et al. Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. *J Clin Endocrinol and Metab* 1999; 84: 2518-2522.
- Del Dotto P, Bonuccelli U. Clinical pharmacokinetics of cabergoline. *Clin Pharmacok* 2003; 42: 633-645.
- Leung AKC, Pacand D. Diagnosis and management of galactorrhea. *American Family Physician* 2004; 70: 543-550.
- Serri O, Chik CL, Ehud Ur, Ezzat S. Diagnosis and management of hyperprolactinemia. *Canad Med Ass J* 2003; 169: 575-581.
- Liu JK, Couldwell WT. Contemporary management of prolactinomas. *Neurosurg Focus* 16 (4), 2004. American Association of Neurological Surgeon. Available at internet website related to Medscape. <http://www.Medscape.Com/viewarticle/474899>.
- Huskisson E, Wojtulewski JA. Measurement of side effects of drugs. *Br Med J* 1974; 2: 698-699.
- Buvat J, buvat-Herbaut M. Prolactin, bromocriptine and gonadal function in women: recent advances. 11. Treatment of female hyperprolactinemia and other indications for the use of bromocriptine. *J Gynecol Obstet Biol Reprod (Paris)* 1982; 11: 509-521.
- Al-Suleiman SA, Najashi S, Rahman J MS. Outcome of treatment with bromocriptine in patients with hyperprolactinaemia. *Aust NZJ Obstet Gynaecol* 1989; 176-179.
- Tartagni M, Nicastrì PL, Diaferia A, Di Gesu I, Loizzi P. Long term follow-up of women with amenorrhea-galactorrhea treated with bromocriptine. *Clin Exp Obstet Gynecol* 1995; 22: 301-306.
- Van der Heijden PF, de Wit W, Brownell J, Schoemaker J, Rolland R. CV 205-502, a new dopamine agonist, versus bromocriptine in the treatment of hyperprolactinaemia. *European J Obstet Gynecol Reprod Biology* 1991; 40: 111-118.
- Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemia amenorrhea. *New England J Med* 1994; 331: 904-909.
- Sabuncu T, Arıkan E, Tasan E, Hatemi H. Comparison of the effects of cabergoline and bromocriptine on prolactin levels in hyperprolactinemic patients. *Intern Med* 2001; 40: 857-861.
- Pascal- Vigneron V, Weryha G, Bosc M, Leterre J. Hyperprolactinemic amenorrhea: treatment with cabergoline vs bromocriptine. Results of a national multicenter randomized double blind study. *Press Med* 1995; 24: 753-757.
- Ferrari C, Paracchi A, Mattei AM, de Vincentiis S, D'Alborton A, Crosignani P. Cabergoline in the long term therapy of hyperprolactinemic disorders. *Arch Endocrinol (Copenh)* 1992; 126: 489-494.
- Biller BM, Molitch ME, Vance ML, Cannistraro KB, Davis KR, Simons JA, et al. Treatment of prolactin secreting macroadenomas with the once-weekly dopamine agonist cabergoline. *J Clin Endocrinol Metab* 1996; 81: 2338-2343.

29. Colao A, Di Sarno A, Landi ML, Scavuzzo F, Cappabianca P, Pivonello R, et al. Macroprolactinoma shrinkage during cabergoline treatment is greater in naïve patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. *J Clin Endocrin Metab* 2000; 85: 2247-2252.
30. Rains CP, Bryson HM, Fitton A. Cabergoline. A review of its pharmacological properties and therapeutic potential in

the treatment of hyperprolactinemia and inhibition of lactation. *Drugs* 1995; 49: 255-279.

Received on June 8, 2007; revised and accepted on December 31, 2007