

Bromocriptine Response in Pathological Hyperprolactinemia: A 34 Year Follow-Up of a Homogeneous Population of 827 Patients

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Abstract: 827 patients with symptomatic pathological hyperprolactinemia were treated with bromocriptine. The evaluation, treatment, and follow-up was by a single individual, making this a large and unique homogeneous group for purposes of treatment evaluation.

INTRODUCTION

Bromocriptine was introduced into large clinical trials in the mid-1970s. The author was fortunate to take part in the large Canadian multicenter study [1]. Since then, patients with symptomatic hyperprolactinemia resulting from pituitary microprolactinoma, pituitary macroprolactinoma, or normal visualized pituitaries (idiopathic) were diagnosed, investigated, and treated by the same person. Therapy was initiated, followed and modified by the same person. From 20 to 30 patients a year were added to the series. Unlike most large series in number or duration which are usually multicenter and/or involving several different investigators, this series is unique by the nature of its long duration, high number of patients, and only a single person involved, rendering it relatively homogeneous in nature. This is a report of the observed response.

PATIENT SELECTION

Patients were selected if symptomatic of hyperprolactinemia (presence of oligo-amenorrhea, galactorrhea, or decreased libido in women) and/or of the underlying pituitary tumor (pituitary tumor and appropriate hyperprolactinemia for tumor size), and other causes of hyperprolactinemia were excluded. Men may have had few symptoms but had the presence of pituitary tumor and appropriate hyperprolactinemia for tumor size. Asymptomatic hyperprolactinemia was not otherwise treated, and thus macroprolactinemia [2] was not inappropriately included and treated. For the last decade, macroprolactinemia was routinely screened in all hyperprolactinemic samples. Patients with pituitary tumors greater than 1 cm but serum prolactin less than 100 nmol/L were not diagnosed as prolactinomas but rather thought to have disconnection hyperprolactinemia [3], and not entered into this series. All patients agreed to treatment, with the treatment goals outlined: loss of hypogonadism/return of menses and estrogenization, treatment of infertility, loss of bothersome galactorrhea, improvement of bothersome low libido, and/or tumor shrinkage if macroprolactinoma was present (especially with headache, visual field defect, or diplopia).

BROMOCRIPTINE TREATMENT

To minimize side effects, 1.25 mg was initiated with meals once a day for a week, then twice a day with meals for a week, then 3 times a day for a week, then 2.5 mg with meals twice a day. If clinical goals were not met, up to 7.5 mg a day was used. Many patients were able to decrease the drug to 2.5 mg once a day without recurrence of symptoms. The drug was discontinued with a diagnosis of pregnancy, and only restarted postpartum if symptomatic hyperprolactinemia returned. The drug was discontinued after menopause, almost always without return of symptoms. After 2-5 years of therapy in most patients, the drug was tapered and stopped, and reintroduced if there was return of symptomatic hyperprolactinemia. This was done on an ad hoc basis, in an inconsistent manner. The exact numbers remaining in remission or relapsing are thus not readily available, but the impression is similar to that of other studies [4].

Drug intolerance that resulted in its discontinuation within 3 months of onset of therapy, despite attempts to use it in lower doses, or through alternative routes such as intravaginal administration, dictated the use of other dopamine agonists [5], or other therapies such as estrogen administration or ovulation induction. Ovulation induction was highly successful with pulsatile GnRH [6]. The patients treated for less than 3 months (other than for onset of pregnancy) are not included in this series. 32 patients unable to tolerate bromocriptine were tried with cabergoline. 25 (78%) were able to tolerate cabergoline and successfully treated. Alternate therapies were also offered to patients resistant to bromocriptine, after an adequate trial.

RESULTS

827 patients were treated for at least 3 months. These included 207 with normal pituitary CT or MRI (idiopathic), 539 with microadenoma, and 81 with macroadenoma (Fig. 1). Over the duration on this report, radiological separation of idiopathic from microadenoma was done by early generation CT scan, late generation CT scan, and then MRI. Thus, relatively more microadenomas and fewer normal pituitaries were visualized over time. 784 were reproductive age females, and 43 were postpubertal males. Serum prolactin normalized in 705 (85%), with loss of

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hyperprolactinemic symptoms in 771 (93%). Thus, the clinical objectives were met without normalization of prolactin in 66 patients. In this situation the drug dosage was not increased. Of 784 women with menstrual irregularity or complete amenorrhea, 739 (94%) had return of regular menses.

189 women were desirous of pregnancy, and with no other cause of subfertility present in the couple, treatment was with bromocriptine. Bromocriptine is thought to be safe in early pregnancy [7]. Bromocriptine was discontinued with the diagnosis of pregnancy, and only restarted if there was symptomatic expansion of the sellar contents.

162 (86%) delivered at least one child, 294 deliveries in total (Fig. 2). Two women had onset of headaches and visual field disturbances after the first trimester, with resolution of these symptoms within 24 hours after reintroduction of bromocriptine. This occurred in 1% of the women, and 1% of the pregnancies. Both women had macroprolactinomas prior to bromocriptine therapy. In the 21 women with macroprolactinomas, symptomatic tumor growth thus occurred in 10% of these 21 women, or 11% of the 28 pregnancies in these women with macroprolactinomas.

43 men were treated. 31 had macroprolactinomas, 12 had microadenomas. Despite normalization or marked improvement of the hyperprolactinemia, 14 required added testosterone administration because of the serum testosterone continuing to be below normal.

81 patients had macroadenomas (Fig. 3). Follow-up CT or MRI demonstrated decrease in tumor size greater than 25% in 76 (94%). Of 37 with abnormal visual fields documented by Goldmann perimetry, 35 (95%) became normal or improved. The 2 failures both had cystic

macroprolactinomas with little observed shrinkage on follow-up CT scanning.

No patient treated with bromocriptine demonstrated clinical or radiological tumor growth during treatment.

DISCUSSION

Bromocriptine is an effective and safe medication for the treatment of pathological hyperprolactinemia. Because it is an agonist for both D1 and D2 receptors, the side effect profile is wider than that of D2 agonists such as cabergoline or quinagolide. The problems of drug intolerance may be minimized by slow introduction and gradual increase of the drug, with meals. Despite this, at least 5% are intolerant to its use. Another 5% are resistant to its action, with the clinical objectives not being met. Changing to cabergoline renders these patients both tolerant and sensitive in the majority of cases [5]. Tumor shrinkage is usually expected, since its first report [8]. Tumor shrinkage may even be greater with cabergoline, a more potent D2 agonist with a long half life [5]. Bromocriptine has the most data regarding safety in pregnancy and subsequent child development [7]. Recent finding of cardiac valve dysfunction associated with high dose cabergoline [9] has not been demonstrated with the doses used for pathological hyperprolactinemia, but may be of concern in resistant patients requiring higher doses of cabergoline. Compared to cabergoline, bromocriptine has much less agonist activity with the serotonin 2b receptor which is thought to mediate the cardiac valve response.

This report of the long-term use of bromocriptine is not to indicate the advantage of this dopamine agonist for the treatment of pathological hyperprolactinemia, but rather to show that any dopamine agonist used in the correctly

Bromocriptine treatment for at least 3 months

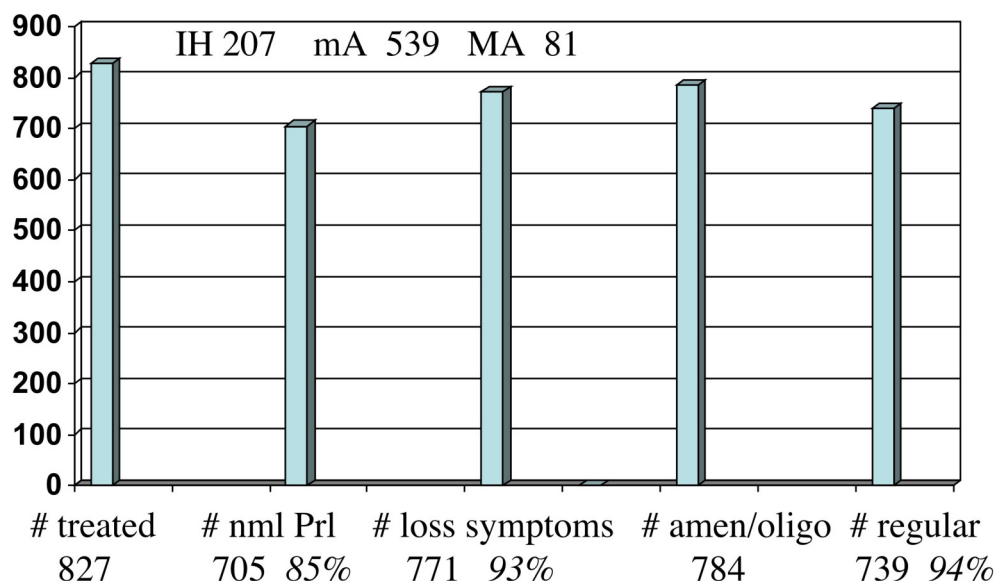


Fig. (1). Response of 827 patients to bromocriptine. 93% had loss of pre-treatment symptoms (menstrual change, galactorrhea, decreased libido, mass symptoms, and/or infertility). 85% normalized the serum prolactin, indicating that reversal of symptoms may occur without normalizing the serum prolactin. Of the 784 reproductive aged women with menstrual dysfunction, 94% normalized their menses and/or conceived.

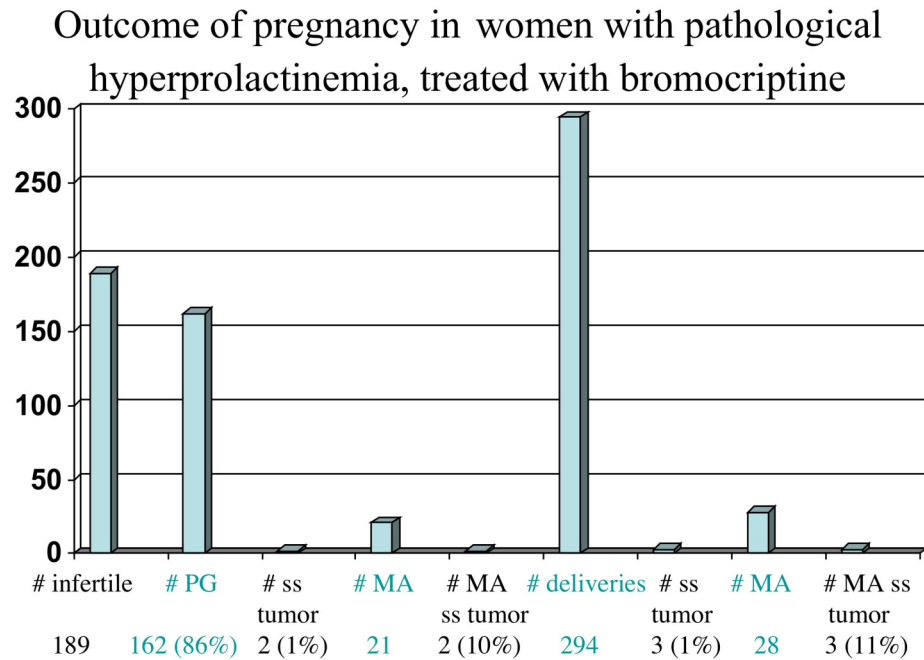


Fig. (2). Response of women with infertility and pathological hyperprolactinemia to bromocriptine therapy. In 189 women with infertility, 86% delivered at least one child. In the 189 women, 2 (1%) during pregnancy had symptomatic expansion of sellar contents (headache and visual field changes), both cases amongst the 21 women with macroprolactinomas (10% of macroprolactinomas). Of the 294 term pregnancies, 3 (1%) had symptomatic sellar enlargement, all in the 28 pregnancies in women with macroprolactinomas (11%).

Bromocriptine and macroprolactinoma response

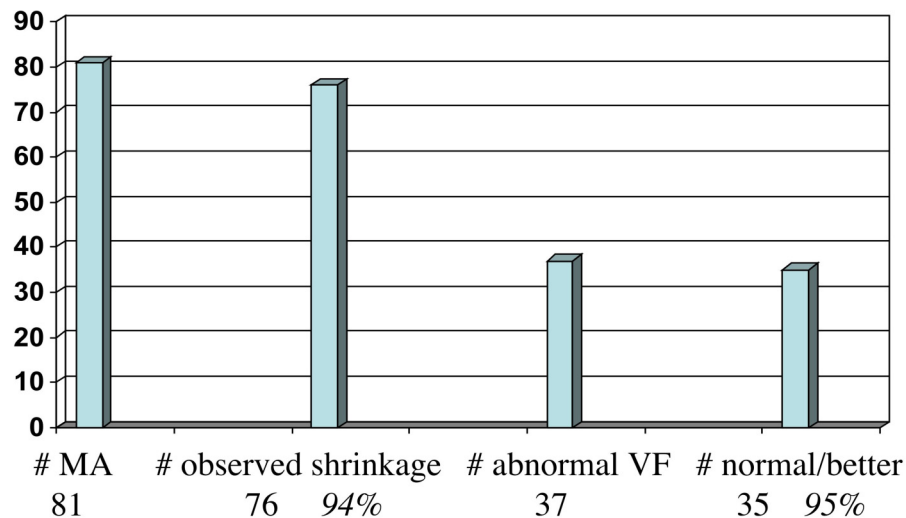


Fig. (3). Response of macroprolactinoma tumor size to bromocriptine. Decrease in size of at least 25% was visualized in 94% of 81 patients with macroprolactinomas. Of the 37 with documented visual field defects, 95% normalized or markedly improved.

diagnosed and evaluated patient population would be expected to demonstrate generally a good clinical response. Unlike most series that may have included nonsecreting pituitary tumors, macroprolactinemia (hyperprolactinemia without symptoms), this is a large and relatively homogeneous population evaluated and treated by a single individual over 34 years, and thus unique by its nature.

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