Clinical and pathological effects of bromocriptine on prolactin-secreting and other pituitary tumors

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Bromocriptine inhibits prolactin secretion and causes size reduction of prolactin-secreting adenomas. The effect of the drug upon pituitary tumors other than prolactinomas is uncertain. The authors report a prospective series of 12 patients with pituitary macroadenomas in whom bromocriptine was administered for 6 weeks prior to transsphenoidal surgery. Five of the patients had computerized tomographic documentation of significant reductions in tumor size (Group A) and six had no change (Group B) during 3 and 6 weeks of bromocriptine administration. One patient who demonstrated size reduction in his tumor was not assigned to either group as he was treated with high-dose dexamethasone concurrently with the bromocriptine. Pathological examination (light and electron microscopy and immunocytochemistry) indicated that all Group A patients harbored tumors with prolactin granules whereas all Group B tumors lacked such granules. Adenoma cells in the responsive tumors were involuted with reduced cytoplasmic, nuclear, and nucleolar areas. Neither widespread cell necrosis, infarction, nor vascular injury was observed. Two of the five Group A patients discontinued bromocriptine prior to completion of the 6-week protocol and had a rapid return of their tumors to pre-treatment size.

Although bromocriptine has been reported to cause shrinkage of nonfunctional tumors, there was no radiological evidence of size reduction or pathological changes in the nonfunctional tumors of this series. Interestingly, serum levels of prolactin were modestly elevated (84 and 113 ng/ml) in two of the six Group B patients, an elevation due to stalk compression rather than secretion by adenoma cells. This finding underscores the fact that failure of bromocriptine to reduce pituitary tumor size in the presence of hyperprolactinemia may occur because the tumor is other than a prolactinoma.

This is the first moderate-sized group of patients in whom pathological changes in responsive prolactinomas during bromocriptine therapy have been demonstrated. As bromocriptine is not tumoricidal, and thus not curative, there is insufficient evidence to recommend this drug as primary therapy for either prolactin-secreting or nonfunctional macroadenomas, but the drug may have potential as a preoperative adjunct to effect shrinkage of prolactinomas and theoretically, at least, make excision easier and possibly more complete.

KEY WORDS: pituitary tumor · prolactinoma · bromocriptine · prolactin · transsphenoidal surgery · immunocytochemistry · electron microscopy

Bromocriptine (2-bromo-alpha-ergocryptine), an ergot derivative with dopamine receptor agonist properties, has been shown to produce significant shrinkage of prolactin-secreting pituitary tumors (prolactinomas). This results from the involution of adenomatous prolactin cells with reduction in cytoplasmic, nuclear, and nucleolar areas. However, the drug does not have a cytotoxic effect and thus does not eradicate the tumor. The effect of bromocriptine upon pituitary adenomas other than prolactinomas is uncertain. Isolated reports have suggested that some nonfunctional pituitary adenomas as well as those secreting growth hormone may show reduction in size following use of the drug. In order to evaluate this further, we designed a prospective study in which bromocriptine was administered to a total of 12 patients with pituitary macroadenomas (greater than 10 mm in diameter) for a period of 6 weeks, following which transsphenoidal surgery was performed. We report here the effects of the drug on the size of the tumor as determined radiologically and grossly at surgery, and also the histological findings. Based on the clinical and histological appearances, we now report the specificity of bromocriptine on prolac-
Clinical Material and Methods

Over the period from November, 1980, until June, 1982, a total of 12 patients with verified pituitary macroadenomas were treated preoperatively with bromocriptine. After the diagnosis was established by computerized tomography (CT) and endocrine testing, the patients were started on gradually increasing doses of bromocriptine, beginning with 2.5 mg daily and increasing to a total of 2.5 mg three times daily at the beginning of the 3rd week of therapy. Immediately prior to starting the drug, a high-resolution coronal CT scan of the sella was obtained with and without contrast enhancement. Bromocriptine was administered for a period of 6 weeks up to the morning of surgery (although in two patients the drug was stopped several days prior to surgery), and transsphenoidal microsurgical removal of the tumor was performed. In order to determine whether the bromocriptine affected the size of the tumor, a CT scan was obtained after 3 weeks of drug therapy. Also, immediately prior to surgery, metrizamide cisternography with CT (as previously described) was performed on some patients early in the series to avoid a false impression of a size reduction in the tumor if the bromocriptine interfered with tumor enhancement on the CT. By outlining the surface of the tumor the metrizamide cisternogram provided an accurate picture of the tumor size, allowing comparison with the original pre-bromocriptine CT scan. This test was discontinued when it became apparent that there was no difference between the metrizamide cisternogram and the CT scan performed at the same time. A serum prolactin level was obtained before starting bromocriptine, immediately before surgery, and 7 to 10 days following operation.

Transsphenoidal surgery and routine postoperative care was performed as described in previous publications. Serum prolactin was measured by radioimmunoassay (RIA) using homologous human prolactin with an inter-assay variation of 10% at 5 ng/ml. At our institution the normal range for serum prolactin is 2 to 12 ng/ml for males and 2 to 20 ng/ml for pre-menopausal females.

Pathological specimens were examined by light microscopy, immunocytochemistry, and electron microscopy. For light microscopy, the tissue was fixed in 10% buffered formalin and embedded in paraffin. Staining of sections 4 to 6 μm was performed with hematoxylin and eosin and by the periodic acid-Schiff (PAS) method. The immunoperoxidase technique as described elsewhere was used to demonstrate prolactin.

For electron microscopy, tissue was fixed in 2.5% glutaraldehyde, osmicated, dehydrated in graded ethanol, processed through propylene oxide, and embedded in an Epon-araldite mixture. Toluidine blue was used to stain semi-thin sections, and areas were selected for fine structural study. Ultra-thin sections were stained with uranyl acetate and lead citrate and were studied with a Philips 300 electron microscope.

The pathological findings in four of these patients have been reported in part elsewhere.

Results

Clinical and Radiological Findings

Pertinent data for the patients are summarized in Table 1. The patients were divided into Groups A and B.
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Based on their response to bromocriptine. One patient was not assigned to either group since he was treated with high-dose dexamethasone concurrently with bromocriptine. This patient demonstrated reduction in the size of his tumor. He had a "null cell" adenoma. It is not clear whether bromocriptine or dexamethasone affected the radiographic reduction in mass and caused his clinical improvement.

In the five Group A patients, tumors were reduced significantly in size during bromocriptine therapy (Fig. 1). In each case the decrease in tumor size occurred after the patient had been receiving bromocriptine for only 3 weeks. All of the Group A patients had lower prolactin levels and some had relief of symptoms while taking bromocriptine. Patients with galactorrhea had resolution or diminution of their discharge. The average pretreatment serum prolactin level in the entire group was 3065 ng/ml (range 156 to 9880 ng/ml), while the average level during treatment was 501.6 ng/ml (range 6 to 1600 ng/ml). Four of the five Group A patients were proved pathologically to have prolactinomas. One patient had an acidophil stem-cell adenoma that contained prolactin granules as determined by immunocytochemistry.

There were no radiographically demonstrable changes in tumor size in any of the six Group B patients. All but one patient had a reduction in serum prolactin level while receiving bromocriptine. The average pretreatment prolactin level was 41 ng/ml (range 9 to 113 ng/ml), and during bromocriptine therapy the prolactin level was 18 ng/ml (range 2 to 47 ng/ml). All six patients in Group B had pathologically verified pituitary tumors other than prolactinomas.

Two of the five Group A patients developed side effects, and bromocriptine was discontinued prior to completion of the 6-week protocol. One patient stopped the drug 2 weeks and another 1 week before surgery. In both cases the 6-week metrizamide cisternogram showed that the tumor had returned to its original pre-bromocriptine treatment size, after the 3-week radiographic study had revealed significant tumor reduction (Fig. 2).

Surgical Observations

Particular note was made of the appearance and texture of the tumor and the ease and completeness of removal at surgery. Although the impressions are purely subjective, it was noteworthy that the tumors that were responsive to bromocriptine appeared to be softer and more fluid than usual. This consistency facilitated removal by suction.

Pathological Observations

The five Group A tumors represented partly chromophobic, partly slightly acidophilic, pituitary adenomas. The immunoperoxidase technique demonstrated the presence of prolactin in the cytoplasm of adenoma cells. By electron microscopy, four tumors represented sparsely granulated prolactin cell adenomas, and one an acidophil stem-cell adenoma. Compared to prolactin-producing adenomas removed from untreated patients, the tumors of patients treated with bromocriptine up to the time of surgery appeared to consist of smaller cells with a decrease in prolactin content as assessed by the immunoperoxidase technique. Electron microscopy revealed that, in the bromocriptine-treated Group A patients, the adenoma cells were reduced in size, especially the cytoplasmic area. Involution of rough endoplasmic reticulum membranes and Golgi complexes was a prominent finding. The secretory granules seemed to be slightly increased in size and number. There was no evidence of lysosomal accumulation, widespread necrosis, vascular injury, endothelial cell damage, plate-

FIG. 1. Sequential high-resolution coronal computerized tomography (CT) scans from a Group A patient. Upper: Pretreatment scan showing a large sellar mass with suprasellar extension. Center: Scan performed after 3 weeks of treatment with bromocriptine showing dramatic reduction in the extrasellar component of the tumor. Lower: Metrizamide CT cisternogram obtained after 6 weeks of bromocriptine treatment. Contrast material in the suprasellar cistern outlines the tumor and confirms maintenance of the size reduction seen at 3 weeks of therapy.
let aggregation, or thrombosis. The tumors removed from the two Group A patients after withdrawal of bromocriptine resembled those of untreated patients, indicating the reversibility of the bromocriptine effect. The tumor of Case 6 (not assigned to either group) and the tumors of Group B were found to be chromophobes adenomas on light microscopy, and contained no prolactin as assessed by the immunoperoxidase technique. Based on the ultrastructural investigation, four tumors were diagnosed as “null cell” adenomas and two tumors as pituitary oncocytomas. One additional tumor seemed to arise from gonadotroph cells. The gonadotroph cell derivation of this tumor was also confirmed by the immunoperoxidase technique. The light and electron microscopic features of these tumors were compared with adenomas of similar diagnoses removed from patients with no bromocriptine treatment. These studies showed conclusively that bromocriptine induced no structural changes in the pituitary adenomas not composed of prolactin cells. The morphological findings are illustrated in Figs. 3 and 4.

**Discussion**

Bromocriptine, a dopamine agonist, is a potent inhibitor of the synthesis and release of prolactin. It has a direct action on the dopamine receptors in the pituitary gland, causing inhibition of both spontaneous and thyrotropin-releasing hormone (TRH)-stimulated prolactin release. Experimental animal studies indicate that bromocriptine affects the process of exocytosis and reduces prolactin granule release from the cell. This process is associated with a lowering of intracellular cyclic adenosine monophosphate concentrations. Subsequently, the serum level of prolactin falls and intracellular concentrations rise. Deoxyribonucleic acid (DNA) synthesis is inhibited, and decrease in mitotic activity is observed. Human tumor cells treated with bromocriptine demonstrate volume reduction.

Evidence for a tumor inhibitory effect of dopamine agonists has come from clinical as well as experimental observations. There have been several reports of improvement in visual fields and in extraocular movements during dopamine agonist therapy of patients with prolactinomas. Restoration of normal endocrine function by bromocriptine with maintenance of normal function after drug discontinuation has been cited as evidence for an antitumor effect. Radiographic evidence of significant tumor shrinkage, as shown by pneumoencephalography and CT, has been reported by numerous investigators.

Experimental data have further supported the proposed tumor-inhibitory action of dopamine agonist drugs. Inhibition of prolactin secretion and tumor regression has been observed in rodents during dopamine agonist therapy of patients with prolactinomas. Restoration of normal endocrine function by bromocriptine with maintenance of normal function after drug discontinuation has been cited as evidence for an antitumor effect. Radiographic evidence of significant tumor shrinkage, as shown by pneumoencephalography and CT, has been reported by numerous investigators.

Microscopic studies have demonstrated the cellular effects of bromocriptine on pituitary tumor cells. In prolactinomas removed surgically from patients treated with bromocriptine, Rengachary, et al., and we have observed pathological changes consisting of a reduction of cytoplasmic volume due to reduction of ribosomes, rough endoplasmic reticulum, and Golgi complexes. This was interpreted as a reversible inhibition of the protein-synthetic machinery of the neoplastic cell. These changes were not identified by Rengachary and his group in a growth hormone-secreting tumor treated with bromocriptine for 6 weeks.

The mechanism of action of bromocriptine in effect-
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![Image of histology and electron micrograph](attachment:image.png)

**Fig. 3.** Histology of a prolactin-secreting adenoma from an untreated (left) and a bromocriptine-treated (right) patient. The cells of the typical Group A patient (right) are smaller and contained smaller and darker nuclei. The cellularity is increased due to a reduction in cytoplasmic volume. H & E, × 250.

A surprising reduction in size of responsive prolactinomas is as yet unknown, but the observations do permit some reasonable hypotheses. It has been suggested that bromocriptine produces its effect by decreasing tumor vascularity and blood flow with resultant infarction of the tumor. Our observation of absence of widespread cellular necrosis, infarction, or vascular damage in the presence of significant changes in cell size indicates that bromocriptine may selectively inhibit protein and hormone synthesis in prolactinoma cells rather than have a direct vascular or cytotoxic effect. The rapid reexpansion of the tumor and lack of bromocriptine-induced

**Fig. 4.** Electron micrograph of a prolactin-secreting adenoma from an untreated (left) and a bromocriptine-treated (right) patient. Arrows illustrate exocytoses, × 4850. **Left:** There is light chromatin substance and a prominent nucleolus in the nuclei. Within the cytoplasm, there are extensively developed rough endoplasmic reticulum and Golgi complexes. **Right:** Nuclei are irregular and cleaved, with dark clumped chromatin and smaller nucleoli. The cell size is decreased, with a reduction of rough endoplasmic reticulum and involution of the Golgi complex.
pathological changes seen in the two patients in whom therapy was discontinued is further evidence that the drug is not tumoricidal.

In our relatively small series, all patients in whom tumors were unresponsive to bromocriptine (Group B) had a pathological diagnosis other than prolactinoma. On the other hand, Group A patients all had tumors with cells positive for prolactin as evidenced by immunocytochemistry. One patient (Case 6) with a null cell adenoma was treated concurrently with high-dose dexamethasone and bromocriptine because of significant mass effect from the large tumor. It is not possible to determine which drug caused the apparent radiographic reduction in size and the clinical improvement.

Cases 7, 8, and 9 illustrate an important point, in that elevated serum prolactin levels before treatment (113, 84, and 22 ng/ml, respectively) were apparently due to stalk compression, and impaired delivery of prolactin-inhibiting factor, resulting in an unrestrained release of prolactin from the normal gland and were not a result of autonomous tumor secretion. The pathological tumor type was a null cell adenoma in Cases 7 and 8, and an oncocytoma in Case 9. Neither of these cell types store or secrete prolactin. Without pathological verification, one might have concluded that the tumor was a prolactinoma that had failed to respond to bromocriptine therapy. However, the size of the tumor with the modest prolactin elevation made this diagnosis unlikely preoperatively.

The enthusiasm among some clinicians over the initial results with bromocriptine in prolactinomas has led to the suggestion that the drug can be used as primary treatment for these lesions, reserving surgery for those cases in which actual tumor regression fails to occur. While this may appear to be a reasonable option, it should be stressed that there are currently no data available to indicate that this therapy will result in tumor cure. In fact, Landolt, et al., recently reported that the use of bromocriptine may actually reduce the chance of a surgical cure should one choose the latter option after treatment with bromocriptine. However, because of the structural changes that occur in these lesions, it did seem appropriate to use bromocriptine as preoperative treatment in an effort to achieve shrinkage of the tumor, a favorable change that we reasoned would make excision of the tumor not only easier but probably more certain. The results of this study, which can only be considered preliminary, indicate that the tumors are not only smaller, but softer and easier to remove with suction. The pathological changes, which reveal suppressive or regressive effects of the drug, substantiate the gross observations. At least on the basis of this study in the five Group A patients, it would appear that the drug may be a useful adjunct in patients with large prolactinomas in whom surgery is planned. There will still be patients in whom a surgical cure will prove impossible, especially those with tumor involvement of the cavernous sinus. It appears reasonable to attempt a surgical excision after maximal shrinkage with bromocriptine in responsive tumors. Patients with responsive tumors in whom total surgical excision is impossible may be maintained on bromocriptine as an alternative to radiation therapy.

While difficult to document quantitatively, it did appear that following bromocriptine therapy the tumors were softer and easier to remove than in cases in which no bromocriptine had been administered. This preliminary observation will require documentation in many cases because of the relatively variable gross state of prolactinomas in patients who have received no bromocriptine treatment. For instance, experience in large series of prolactinoma cases has shown that, under normal circumstances with no previous therapy, the consistency and nature of the tumor may vary from tough and fibrous in some cases to soft and partially necrotic in others. A large series in which most, if not all, prolactinomas treated with bromocriptine are soft and easily removed by suction will be required before one can conclude that the changes in the tumor following the use of the drug facilitate surgical removal.

The duration of bromocriptine therapy prior to surgery is important. Ideally, surgery should be performed when maximal shrinkage of the tumor has occurred. All of our patients with responsive tumors obtained no further shrinkage after 6 weeks of therapy beyond that observed at 3 weeks, suggesting that maximal acute shrinkage in a responsive prolactinoma is obtained around the 3rd week of therapy; however, during longer-term treatment there may be further reduction in tumor size. It is theoretically possible that bromocriptine continued for too long a period may actually interfere with the surgery. For instance, long-term treatment may ultimately cause fibrosis, a change that could make surgical excision difficult, thus making it impossible to achieve a cure. Also to be considered is the relatively fast return to pretreatment tumor size following bromocriptine withdrawal, as illustrated by two cases in our series in which the tumor returned to its original size within 7 to 14 days following discontinuation of the drug. It is therefore essential to maintain the patient on bromocriptine right up to the time of actual operation.

References
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