Prolactin-secreting adenomas: the preoperative response to bromocriptine treatment and surgical outcome

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Controversy exists regarding the effects of bromocriptine on the success of transsphenoidal surgery for patients with prolactinomas. Various studies on this drug have reported adverse effects, improvement, and no effect upon the subsequent surgical outcome. The authors have retrospectively reviewed the case histories of 55 patients with immunocytochemically confirmed prolactin-secreting pituitary adenomas operated on by a transsphenoidal approach between 1981 and 1985. All patients had received bromocriptine in a variety of doses and for variable durations prior to surgery.

Thirty-nine patients were women and 16 were men, with an age range of 8 to 72 years. Basal prolactin levels prior to bromocriptine treatment ranged from 38 to 100 ng/ml in 11 patients, from 101 to 200 ng/ml in 12, and greater than 200 ng/ml in 29. The “cure” rates were 54%, 58%, and 38%, respectively. Thirty-one patients had microadenomas, with a postoperative cure rate of 68%; 12 had diffuse expansive adenomas, with a 17% cure rate; and 12 had grossly invasive tumors, with a 17% cure rate. A response to preoperative bromocriptine therapy was defined as a return of the basal prolactin level to normal: 18 patients were responders and 29 were hyporesponders; in eight the data were not available. The postoperative cure rate was 50% for the responders and 31% for the hyporesponders. Taking into account the distribution of tumor type, there was no actual difference in outcome between the responder and the hyporesponder groups. The total bromocriptine dose received preoperatively was nearly identical for all groups. No significant differences in the frequency or extent of fibrosis, calcification, or prolactin immunoreactivity were observed in the 55 patients when compared with 26 control prolactinomas not treated with bromocriptine. It is concluded that short-term bromocriptine treatment does not adversely affect surgical outcome in any of the prolactin-secreting adenoma groups, nor does response or lack of response to bromocriptine predict surgical outcome.

KEY WORDS: prolactin • bromocriptine • pituitary adenoma • transsphenoidal surgery

Prolactin-secreting adenomas are the most common pituitary tumors, comprising 31% to 41% of pituitary adenomas in several large centers. Hyperprolactinemia is a well-recognized cause of the amenorrhea-galactorrhea syndrome in women and of impotence and sexual dysfunction in men; there is also evidence to suggest that sustained hyperprolactinemia may result in premature osteoporosis. Transsphenoidal microsurgery has been shown to be effective therapy for this condition, especially in treating microadenomas and large diffuse tumors with associated visual loss.

Since its release in the United States in 1978, the dopamine agonist bromocriptine has gained widespread use for the treatment of prolactin-secreting adenomas. In some instances it is used without surgery, such as for cases occurring during pregnancy and for patients with visual field defects. Bromocriptine is often the first line of therapy offered to patients with prolactinomas, and a surgical opinion is sought after failure of this medication to lower the prolactin level or because of intolerance to the drug. Controversy exists in the neurosurgical literature regarding the effect of preoperative treatment of prolactinomas with bromocriptine on surgical outcome, and this has prompted us to review our experience.

Clinical Material and Methods

Clinical Aspects

The case histories of 55 patients with immunocytochemically confirmed prolactin-secreting pituitary adenomas who were operated on by a transsphenoidal approach between 1981 and 1985 were reviewed. The patients comprised 39 women and 16 men, whose ages ranged between 8 and 72 years.
Prolactin-secreting adenomas

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prebromocriptine PRL Levels</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>normalized</td>
<td>≤ 100 ng/ml</td>
<td>0:6</td>
</tr>
<tr>
<td>recurrent</td>
<td>101-200 ng/ml</td>
<td>0:3</td>
</tr>
<tr>
<td>persistent</td>
<td>&gt; 200 ng/ml</td>
<td>1:1</td>
</tr>
<tr>
<td>total cases</td>
<td>Unknown</td>
<td>1:10</td>
</tr>
<tr>
<td>cure rate</td>
<td>54%</td>
<td>58%</td>
</tr>
</tbody>
</table>

*Results are expressed as number of males: females.

their preoperative prebromocriptine prolactin levels. All patients had received bromocriptine at various doses and for variable durations prior to surgery. Those in whom basal prolactin levels returned to normal after bromocriptine administration were termed “responders,” and those whose prolactin levels remained abnormal despite the highest tolerated dose of bromocriptine were considered “non-responders.” (The normal prolactin level for women is < 24 ng/ml, and for men is < 21 ng/ml.) Thirty-eight patients were taking bromocriptine until the day of surgery and 20 had discontinued their medication prior to operation. In the latter group, the average time interval between discontinuation of the drug and surgery was 5.4 months.

Based upon the operative and computerized tomography (CT) findings, the tumors were classified as microadenomas (31 cases), diffuse expansive adenomas (12 cases), or invasive adenomas (12 cases). Outcome was defined at follow-up examination as normalized (normal prolactin levels), recurrent (prolactin level rose after initially normalizing), or persistent (prolactin level always abnormal). The follow-up period averaged 15 months after surgery (range 1 to 49 months). Postoperative thyrotropin-releasing hormone (TRH) provocative responses were measured in 31% of the patients. Baseline determinations of prolactin and thyroid-stimulating hormone were obtained immediately before and 30 and 60 minutes after the administration of TRH. A normal response was considered to be a greater than twofold rise in prolactin level.

Histological Aspects

Histological studies were conducted on 55 bromocriptine-treated and 26 untreated prolactinomas (many with accompanying fragments of adenohypophysis) to examine for the presence of fibrosis, calcification, amyloid deposition, and the degree of prolactin immuno-reactivity. All were graded qualitatively on a four-point scale (0, 1+, 2+, and 3+). Formalin-fixed and paraffin-embedded surgical specimens were consecutively sectioned at 5 μ and were stained by the following routine methods: hematoxylin and eosin, Gomori’s reticulin, and Masson’s trichrome. Sections stained with thioflavin T were examined under ultraviolet light (370 to 410 nm) for the presence of amyloid; reactivity was confirmed by the Congo red technique with polarization microscopy.

The modified peroxidase-antiperoxidase technique described by Sternberger, et al., was used for immunostaining sections for detection of prolactin (dilution 1:400). For positive control material we used normal pituitary gland obtained from a subject at autopsy as well as a known prolactin-producing pituitary adenoma. Negative control studies were performed by substitution of normal non-immune rabbit serum for specific antisera.

Results

Clinical Findings

The following were the presenting symptoms of the 55 patients under study. Headache was noted in 26 and visual field abnormality in eight. Of the 39 women, 38 had amenorrhea and 31 galactorrhea. Of the 16 men, one had galactorrhea and nine were impotent. Precocious puberty was reported in one woman, and delayed puberty in one woman. Side effects of bromocriptine treatment were seen in 21 patients, including nausea, fatigue, dizziness, or headache. Two diabetic patients noted increasing insulin requirements which reversed when bromocriptine was discontinued. Bromocriptine therapy alone resulted in the return of menses in 50% of women in this group and a decrease of galactorrhea in 13 of the 31 women so afflicted. Pregnancy was achieved or impotence relieved in five patients; and improvement in vision occurred in two of the eight patients with visual field abnormality.

Prior to the institution of bromocriptine therapy, prolactin levels ranged from 38 to 100 ng/ml in 11 patients, 101 to 200 ng/ml in 12, and greater than 200 ng/ml in 29. In three patients the exact preoperative levels were unknown. Postoperatively, prolactin levels returned to normal in 54%, 58%, and 38% of these groups, respectively (Table 1).

The surgical “cure” (prolactin normalization) rate was 68% in the 31 patients with microadenomas, 17% in the 12 patients with diffuse expansive adenomas, and 17% in the 12 patients with grossly invasive tumors (Table 2). There was no difference between the out-
comes in microadenomas with prolactin levels of 100 ng/ml or less compared to those with levels over 100 ng/ml. Preoperative prolactin levels after bromocriptine treatment were available in 47 patients. In 18 patients the prolactin level had normalized (responders) and in 29 it had remained abnormal (hyporesponders). The postoperative "cure" (prolactin normalization) rate was 50% for the responders and 31% for the hyporesponders (Table 3). There was no difference in response between the sexes. Large tumors and invasive tumors were less likely to respond favorably to bromocriptine therapy. Following bromocriptine therapy, CT scans revealed cystic cavitation in 14 cases, and three tumors appeared dramatically smaller in response to therapy; however, these changes ultimately had no consistent effect on outcome.

The duration of therapy and the total accumulated bromocriptine dose prior to surgery were analyzed. Thirty-five patients took bromocriptine until the day of surgery (cure rate 31.4%), and 20 patients discontinued the drug at a variable period of time (average 5.4 months) prior to surgery (cure rate 70%). The more favorable results in the latter group are skewed as a result of the higher proportion of patients with microadenomas. More than one-half of these patients had discontinued medication prior to their operation, whereas only two of 24 patients with diffuse macroadenomas or invasive tumors had stopped taking bromocriptine. Evaluating the patients with microadenomas separately, 13 were taking and 18 were not taking bromocriptine at the time of operation. The respective cure rates were 69% and 72% (not significantly different). The mean total accumulated dose of bromocriptine for each outcome group was 1900 ng for patients considered cured, 1035 ng for those with recurrence, and 1338 ng for patients with persistent tumors.

The postoperative prolactin values were examined for a predictive level that might separate long-term cures from those at risk for recurrence. The average postoperative basal prolactin level was 4.9 ng/ml in the 25 patients considered cured at follow-up examination; only two of these had postoperative levels greater than 10 ng/ml. The 10 patients who had a subsequent recurrence had an average postoperative prolactin level of 15.3 ng/ml; only three of these had levels less than 10 ng/ml. The average time to recurrence was 4.0 months (range 1 to 9 months). Postoperative TRH responses were determined at 3 months in nine patients who were apparently cured. Three patients had blunted responses: two of these have subsequently suffered a recurrence,11,20,26,28 the third had a microadenoma and is apparently cured with an immediate postoperative prolactin level of 2.1 ng/ml and a value of 5.2 ng/ml 28 months later. Six patients had normal TRH responses and are still considered cured at follow-up review. Five women became pregnant following surgery.16

### Table 3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Responder</th>
<th>Hyporesponder</th>
<th>Unknown:</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total M:F</td>
<td>Total M:F</td>
<td>Total M:F</td>
</tr>
<tr>
<td>normalized</td>
<td>9 2:7</td>
<td>9 0:9</td>
<td>7</td>
</tr>
<tr>
<td>recurrent</td>
<td>5 1:4</td>
<td>5 1:4</td>
<td>0</td>
</tr>
<tr>
<td>persistent</td>
<td>4 3:1</td>
<td>15 9:6</td>
<td>1</td>
</tr>
<tr>
<td>total cases</td>
<td>18 6:12</td>
<td>29 10:19</td>
<td>8</td>
</tr>
<tr>
<td>cure rate</td>
<td>50%</td>
<td>31%</td>
<td>87%</td>
</tr>
</tbody>
</table>

*See text for definitions.
†All patients in whom the postbromocriptine prolactin levels were unknown were female.

### Table 4

<table>
<thead>
<tr>
<th>Feature</th>
<th>Bromocriptine-Treated Group (55 cases)</th>
<th>Untreated Group (26 cases)</th>
<th>Mean Score*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Grade 0</td>
<td>Grade 1+</td>
<td>Grade 2+</td>
</tr>
<tr>
<td>fibrosis</td>
<td>22</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>calcification</td>
<td>31</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>amyloid deposition†</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>prolactin reactivity</td>
<td>0</td>
<td>8</td>
<td>17</td>
</tr>
</tbody>
</table>

*Score calculated by assigning numerical equivalents to qualitative grades.
†Interstitial or intracellular amyloid deposits.

### Histological Findings

No significant difference in the frequency or extent of fibrosis, calcification, amyloid deposition, or prolactin immunoreactivity was noted in the 55 bromocriptine-treated patients when compared to the 26 untreated control patients (Table 4). In the treated group, when those patients who had discontinued bromocriptine prior to surgery are compared with those receiving bromocriptine until the day of operation, there is a trend favoring slightly less prolactin staining intensity and more fibrosis in the latter group. A similar trend was noted when fibrosis was correlated with duration of bromocriptine therapy (Fig. 1). When examining the histological slides at random, we could not determine...
which patients were receiving the drug at the time of surgery, nor could we detect consistent bromocriptine-related histological changes.

Discussion

In 1982, Landolt and colleagues suggested that preoperative treatment with bromocriptine may adversely affect the surgical success of patients with prolactinomas. They reported that 81% of untreated patients with microadenomas were cured by transsphenoidal microsurgery compared with 33% of those treated with bromocriptine prior to operation, and those treated for longer than 1 year fared the worst. No similar adverse effect was found among a group of patients with macroadenomas who were not treated with bromocriptine.

Faglia, et al., reported 49 women with microadenomas, 20 of whom received bromocriptine preoperatively. They found no difference in the postoperative cure rate (69% vs. 65%) although the drug was discontinued 2 to 24 months prior to surgery in 19 of the 20 treated patients. The duration of bromocriptine therapy was not found to have an effect on outcome. Fahlbusch, et al., reported their experience with 75 women with microadenomas; they found no bromocriptine effect if the pretreatment prolactin levels were less than 200 ng/ml, but prior bromocriptine treatment in those whose prolactin levels exceeded 200 ng/ml was associated with worse results following surgery (33% treated vs. 58% untreated). As in Faglia’s report, they discontinued bromocriptine treatment weeks to months prior to surgery. On the other hand, Marcovitz and Hardy found no difference in the cure rate following surgery comparing bromocriptine-treated and untreated microprolactinomas in a series of men and women.

Comparing our results with those of a historical control series from our institution (99 pituitary adenoma patients not treated with bromocriptine), no appreciable difference is noted between the treated and untreated surgical groups. In our bromocriptine-treated patients, the cure rates for microadenomas, diffuse expansive adenomas, and invasive tumors were 68%, 17%, and 17%, respectively, compared with 72%, 47%, and 17% in the corresponding groups of untreated patients in the previous report. The cure rate for diffuse expansive adenomas in other series varies from 21% to 62%, and the small number (12) of this type of adenoma in this study makes the comparison speculative at best.

A spectrum of response of the prolactin level to bromocriptine in hyperprolactinemic patients has been noted. This is thought to be due to a differential sensitivity of lactotrophs to the drug. Weiss and colleagues found that radiographic reduction in the size of a macroadenoma with bromocriptine treatment improved surgical outcome (70% cure rate in responders vs. 22% in nonresponders). In our study, 17 patients with macroadenomas developed either cystic cavitation or a dramatic reduction in tumor size after bromocriptine administration as determined by serial CT scans, with a 47% cure rate in this subgroup. Those patients with prolactinomas whose prolactin level normalized after bromocriptine treatment fared no better than those with persistent prolactin elevation.

Landolt and Osterwalder noted an increase in perivascular fibrosis in prolactinomas pretreated with bromocriptine. They found no correlation between the degree of fibrosis and the preoperative prolactin level, nor with the duration or total dose of bromocriptine used. The amount of fibrosis appeared to persist despite discontinuation of bromocriptine, while the morphological changes of prolactinoma cell shrinkage reversed within 1 week. Clinically, this fibrosis has been thought to increase the difficulty of surgical dissection and to result in a lower cure rate. Other investigators have noted that preoperative bromocriptine treatment may facilitate the removal of macroadenomas.

Our data suggest that interstitial fibrosis tends to occur more frequently in those patients receiving bromocriptine until the day of surgery. However, when the drug is discontinued for an average of 5.4 months preoperatively, there is no difference between treated and untreated patients. In addition, we did not find that bromocriptine treatment contributed to the difficulty of surgical removal, nor was the outcome appreciably affected. On this basis, we do not recommend discontinuing bromocriptine prior to surgery. There was no histological evidence of cellular necrosis in our bromocriptine-treated patients, who had as much as 42 months of therapy prior to surgery.

The greatest concern in reporting the short-term success of surgical treatment of prolactinomas is the possibility of late recurrences. Other clinicians have reported the prognostic significance of postoperative prolactin levels and of postoperative prolactin secretory dynamics in predicting long-term cure. In nonbromocriptine-treated patients, postoperative prolactin levels up to 6.4 ± 1.1 ng/ml have been reported to
portend a long-term cure, while levels above 11.7 ± 1.5 ng/ml are associated with recurrence. Our results in bromocriptine-treated patients are similar, with an average postoperative prolactin level of 4.6 ± 4.8 ng/ml in those cured and 15.3 ± 5.9 ng/ml in those who suffered a recurrence. The role of postoperative secretory dynamics tested with TRH stimulation is more controversial; these factors have been reported as abnormal in all patients in whom hyperprolactinemia subsequently recurred, but they may also be abnormal in those without evidence of recurrence. A normal TRH stimulation response is generally associated with a long-term cure; this is supported in our group of patients, with six such patients still considered cured.

In summary, bromocriptine treatment of prolactinomas does not appear to affect surgical outcome adversely, and it is not necessarily desirable to discontinue medication before transphenoidal surgery. Although the data indicate that bromocriptine therapy may result in an increase in interstitial fibrosis, this is generally not clinically significant, at least after short-term medical therapy. Postoperative determinants of long-term cure based upon prolactin levels and TRH secretory dynamics remain reliable, even if bromocriptine has been continued until the day of operation. These conclusions may not be valid for patients with long-term bromocriptine therapy who subsequently become candidates for surgical intervention.

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References


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