Bromocriptine therapy for prolactin-secreting pituitary adenomas

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An effective systematic approach for the management of prolactin-secreting pituitary adenomas is described. This methodology has stood the test of time and has been modified in accordance with experience. The primary goals are to obtain satisfactory control of the tumor and to avoid undesirable side effects related to dopamine agonist-based therapeutic agents.

Key Words * pituitary adenoma * bromocriptine * prolactin * medical therapy

The fact that the vast majority of prolactin-secreting pituitary adenomas can be effectively controlled by medical therapy using a dopamine agonist such as bromocriptine is almost unique in the treatment of neoplasms.[4,6,7,11,12,15] The phenomenon is related to the fact that normal pituitary lactotrophes are under the tonic inhibitory control of dopamine released by the hypothalamus and transmitted down the pituitary stalk to the adenohypophysis.[5] The activation of dopamine receptors on the cell surface produces marked inhibition of prolactin synthesis and an actual shrinkage of the cytoplasm of the cell along with alterations in the organelles involved in the production of prolactin.

There are two ways in which bromocriptine therapy can control prolactinomas. The first of these is to reduce serum levels of prolactin, thus reducing their physiological effects (for example, amenorrhea, galactorrhea, infertility, and loss of libido). The second is to decrease the size of prolactin-secreting pituitary adenomas. Although most prolactinomas respond to bromocriptine therapy by both reduction in size and decrease in prolactin output, these two aspects of response to therapy are occasionally independent of each other. Lack of response to therapy either because of persistent mass effect or inability to lower the prolactin to normal levels is occasionally viewed as an indication for surgery.[8,13]

Studies have shown that 80% to 90% of prolactinomas do respond to medical management, and the majority of them respond rapidly, at least with regard to lowering prolactin levels. The shrinkage of tumor bulk can occur very quickly; however, in some patients shrinkage may occur gradually and continue over months or years of therapy. The biological basis for this variation in responsiveness has not yet been fully elucidated.

PRINCIPLES OF MANAGEMENT

The clinical presentation of most patients with prolactin-secreting pituitary adenomas is fairly typical. In women it usually consists of amenorrhea, galactorrhea, and infertility. In men, because they lack a biological marker such as the menstrual cycle, tumors generally present when they are larger and the symptoms may include loss of libido and impotence, progressive loss of vision, and headache. Prolactin-secreting pituitary adenomas of all sizes can present with pituitary apoplexy, that is, bleeding into a preexisting tumor, or infarction of a tumor with acute swelling. Although this occurs infrequently, it can represent a medical emergency and the correct diagnosis may not be immediately obvious.

The diagnosis of a prolactin-secreting pituitary adenoma is ascertained by investigating serum prolactin levels and obtaining magnetic resonance imaging of the lesion. Modest elevations in serum prolactin may accompany small prolactin-secreting pituitary adenomas; however, they may also be signs of other structural lesions that inhibit the effect of hypothalamic dopamine on the pituitary.[5,9,10] Therefore, a careful differential diagnosis must be entertained in patients who present with only moderately elevated levels of serum prolactin. Prolactin levels greater than 10 times the normal level almost always indicate the presence of a prolactin-secreting pituitary adenoma related to overproduction of prolactin by the tumor cells. Regardless of the cause of prolactin elevation, bromocriptine can usually reduce the serum prolactin level, and an apparent positive response may be obtained even when the lesion is not actually a prolactin-secreting pituitary tumor.

Medical Management

The accompanying guidelines (Appendix) have been most helpful in initiating and maintaining bromocriptine therapy for our patients with prolactin-secreting pituitary adenomas. Although we have encountered patients in whom drug intolerance has occurred, it is uncommon. By using the guidelines offered herein, a situation in which it initially appeared that a patient was totally intolerant to the drug may be converted to one of acceptable therapeutic management.

If the patient has side effects significant enough to be characterized as intolerance, there are limited options available. One can consider altering the route of administration of bromocriptine. In women it can be given vaginally,[3] in the hope of avoiding symptoms of severe nausea and vomiting. Another formulation of bromocriptine, which is administered intramuscularly, is available outside of the United States, and this can be considered, but clearly represents a hardship for most American patients.[14] Finally, other dopamine agonists may be prescribed even though they are not approved for treatment of pituitary tumors; the most widely used of these is pergolide (Permax).[2] Unfortunately, most patients who are sensitive to bromocriptine have similar side effects from therapeutic doses of pergolide.

In cases in which the prolactinoma is producing significant mass effect, the schedule of medical management may need to be significantly accelerated. In most of these patients this can be accomplished without producing serious clinical problems related to the side effects of bromocriptine therapy. Obviously a prompt effect on headache and visual loss is desirable, and this can usually be produced by administration of normal therapeutic doses of bromocriptine. Studies have shown that there is little to be gained by increasing daily doses of bromocriptine to a level higher than 7.5 mg.

Surgical Management

Surgery will continue to play a role in the management of many patients with prolactin-secreting pituitary adenomas. Patients in whom medical management has failed either because prolactin levels do not normalize or because a large tumor does not shrink will continue to be candidates for surgical

intervention.[1] There will also be patients who are intolerant of the drug because of intractable and disabling side effects, patients who will prefer to have the tumor removed definitively, and patients who cannot be reassured about the lack of adverse effects of bromocriptine on pregnancy.

CONCLUSIONS

We are hopeful that these guidelines will help many patients with prolactin-secreting pituitary adenomas to be effectively treated medically. These methods have been highly effective in our experience, and they represent the results of a great deal of research and clinical evaluation.

APPENDIX

Bromocriptine Therapy Guidelines for Patients

Initiating Treatment With Bromocriptine

Bromocriptine (Parlodel 2.5 mg tablet) is a medication that suppresses prolactin secretion and reduces the size of prolactin-secreting tumors. It is important that you carefully follow our instructions for taking this medication. If you start with too high a dose, you may have side effects such as nausea, vomiting, and low blood pressure when you stand up. If you start with a low dose and gradually build up to the recommended dose, the side effects will not occur, but the beneficial effects of the medication to lower your prolactin levels and shrink the tumor are likely to occur.

The schedule is designed as follows:

- 1) Always take the medication with food. This slows the absorption and helps avoid side effects.
- 2) Increase the dose every three days.
- 3) If you have side effects do not stop the medication, but instead, back off to the previous dose that was free of side effects and then try increasing the dose after a further three days.
- 4) Spreading out the doses during the day helps to maintain suppressive blood levels and mimics normal physiology of prolactin.

Date (insert start date for patient)

1/4 tablet at night on retiring with milk and cookies

Date (plus 3 days)

1/4 tablet at night on retiring with milk and cookies

1/4 tablet with breakfast

Date (plus 3 days)

1/4 tablet at night on retiring with milk and cookies

1/4 tablet with breakfast

1/4 tablet with lunch

Date (plus 3 days)

- 1/2 tablet at night on retiring with milk and cookies
- 1/4 tablet with breakfast
- 1/4 tablet with lunch

Date (plus 3 days)

- 1/2 tablet at night on retiring with milk and cookies
- 1/2 tablet with breakfast
- 1/4 tablet with lunch

Date (plus 3 days)

- 1/2 tablet at night on retiring with milk and cookies
- 1/2 tablet with breakfast
- 1/2 tablet with lunch

Date (plus 3 days)

- 3/4 tablet at night on retiring with milk and cookies
- 1/2 tablet with breakfast
- 1/2 tablet with lunch

Date (plus 3 days)

- 3/4 tablet at night on retiring with milk and cookies
- 3/4 tablet with breakfast
- 1/2 tablet with lunch

Date (plus 3 days)

- 3/4 tablet at night on retiring with milk and cookies
- 3/4 tablet with breakfast
- 3/4 tablet with lunch

Date (plus 3 days)

- 1 tablet at night on retiring with milk and cookies
- 3/4 tablet with breakfast
- 3/4 tablet with lunch

Date (plus 3 days)

- 1 tablet at night on retiring with milk and cookies
- 1 tablet with breakfast
- 3/4 tablet with lunch

Date (plus 3 days)

- 1 tablet at night on retiring with milk and cookies
- 1 tablet with breakfast
- 1 tablet with lunch

It is important to remain on this dose until we see you next. Please do not stop taking the medication as we will need to go through the same escalation process if you do. If you are troubled by side effects please call us so that we can advise you how to minimize them.

Other medications may influence the effect of bromocriptine. Please be certain we know of all medications you are taking and please do not start a new treatment without informing us.

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