Efficacy of bromocriptine in the treatment of metastatic breast cancer- and prostate cancer-related hyperprolactinemia

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Submitted: August 11, 2000
Accepted: September 3, 2000

Key words: breast cancer; hyperprolactinemia; prolactin; prostate cancer

Abstract OBJECTIVE: Hyperprolactinemia is a frequent evidence occurring in both metastatic breast cancer and prostate cancer, and it has been proven to be associated with poor prognosis and reduced efficacy of the anticancer therapies. Therefore, the pharmacological control of cancer-related hyperprolactinemia could improve the prognosis of advanced breast and prostate carcinomas. Unfortunately, at present it is still controversial which may be the treatment of cancer-related hyperprolactinemia, which could depend at least in part on a direct autocrine production by cancer cells themselves. The present study was performed to evaluate the acute effects of the long-acting dopaminergic agonist bromocriptine on cancer-related hyperprolactinemia.

METHODS: The study included 10 women affected by metastatic breast cancer and 10 men with metastatic prostate cancer, showing persistent hyperprolactinemia. Venous blood samples were collected before bromocriptine, and 2, 4, 10 and 24 hours after bromocriptine administration (2.5 mg orally) serum levels of PRL were measured with the double antibody RIA method.

RESULTS: Bromocriptine induced a normalization of PRL levels in both groups of patients with breast and prostate cancers. Moreover, mean levels of PRL persisted significantly lower than those found before therapy during the whole 24-hour circadian period.

DISCUSSION: This preliminary study shows that low-dose bromocriptine is sufficient to acutely normalize PRL secretion in both metastatic breast cancer and prostate carcinoma patients, irrespectively of the mechanisms involved in inducing cancer-related hyperprolactinemia. Therefore, low-dose bromocriptine could be recommended in association with the classical antitumor therapies in the treatment of metastatic breast cancer and
Introduction

Cancer patients may present several endocrine alterations, whose physiopathological significance is less investigated and it still remains unknown. In particular, hyperprolactinemia would constitute the most frequently detected endocrine alteration, namely in breast cancer and prostate carcinoma [1–4]. In some patients, the evidence of hyperprolactinemia could simply be the endocrine consequence of the effects of drugs commonly used in the palliative therapy of cancer, namely opioids, corticosteroids, antidepressant agents and anti-dopaminergic drugs, whereas in other cases it is the expression of cancer-related endocrine dysfunction, probably depending at least in part on a direct autocrine production of hormones by cancer cells themselves.

According to the knowledge available up to now, cancer-related hyperprolactinemia would not simply represent an epiphenomenon, since PRL may act as a tumor growth factor for some tumor histotypes, mainly breast cancer and prostate carcinoma [5]. In fact, it has been shown that the evidence of abnormally high blood concentrations of PRL is associated with poor prognosis and reduced efficacy of anti-cancer treatments in metastatic breast and prostate cancer patients [6, 7]. This finding could depend on a direct stimulatory effect of PRL on cancer cell proliferation [5], which would impair the destruction of cancer cells by chemotherapy. In contrast, the immunomodulatory effect of PRL on the anticancer immunity still remains controversial. Dopaminergic agents are the most commonly used drugs in the pharmacological therapy of hyperprolactinemia, including that due to PRL-secreting pituitary tumors [8]. Generally, cancer-related hyperprolactinemia is not treated by the oncologists. However, on the basis of the fact that the evidence of hyperprolactinemia has been proven to be associated with reduced efficacy of the various anti-tumor therapies in both metastatic breast and prostate carcinomas [6, 7], it could be clinically important to cure the enhanced PRL secretion occurring in advanced cancer patients. At present, it remains to be established whether cancer-related hyperprolactinemia may respond to the drugs commonly used in the treatment of the hyperprolactinemia due to reasons other than cancer. This clinical question is justified by the fact that cancer-related enhanced PRL secretion may be due at least in part to a direct tumor autocrine production, which could be independent of the dopaminergic control [8], which physiologically inhibits PRL secretion.

Bromocriptine or other long-acting dopaminergic agents are the most commonly used drugs in the treatment of hyperprolactinemia due to reasons other than metastatic cancer. The present study was performed to investigate the acute effects of bromocriptine on PRL blood levels in metastatic breast cancer and prostate cancer patients suffering from cancer-related hyperprolactinemia.

Materials and methods

The study included 10 women with metastatic breast cancer and 10 men with metastatic prostate cancer. The median age of the patients was 58 (range: 42–66). Eligibility criteria were as follows: histologically proven metastatic breast cancer or prostate cancer, evidence of hyperprolactinemia, as assessed at two different controls at weekly intervals, no concomitant therapy with drugs influencing PRL secretion, including opioids, anti-dopaminergic agents, steroids and antidepressant drugs, and no concomitant endocrine or medical illnesses other than cancer.

According to the classical endocrine dynamic tests [9], patients were evaluated after an oral administration of bromocriptine at a dose of 2.5 mg at 8.00 A.M. after an overnight fast. Venous blood samples were drawn at baseline and 2, 4, 10 and 24 hours after bromocriptine administration. Venous blood samples were collected through an indwelling catheter kept patent by a slow saline infusion. On a separate occasion, venous blood samples were drawn during a saline infusion alone as a control.

Serum levels of PRL were measured in duplicate by the double antibody RIA method and commercially available kits (Nichols Institute, S. Juan Capistrano, CA, USA). Intraassay and interassay coefficients of variation were below 3% and 5%, respectively. Normal values of PRL observed in our laboratory (95% confidence limits) were less than 23 ng/ml. Hyperprolactinemia was defined as the evidence of PRL values higher than 25 ng/ml in basal conditions. Data were reported as mean ± SE and statistically analyzed by the Student’s t test and the analysis of variance, as appropriate.

Results

Changes in mean serum levels of PRL observed after bromocriptine administration in breast cancer women and in prostate cancer patients are illustrated in Figs. 1 and 2, respectively.

All patients of both groups showed a normalization of PRL levels in response to bromocriptine
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Fig. 1. Changes in mean serum levels of PRL in response to bromocriptine in metastatic breast cancer patients.

Fig. 2. Changes in mean serum levels of PRL in response to bromocriptine in metastatic prostate cancer patients.
administration, within 2–4 hours from drug administration. Moreover, PRL values remained within the normal range for the whole period of the 24 hours. In addition, PRL behavior in response to bromocriptine was similar in both groups of patients affected by metastatic breast cancer or prostate carcinoma. As illustrated in the Figs., PRL mean levels significantly decreased in response to bromocriptine either in patients with metastatic breast cancer or in those suffering from metastatic prostate carcinoma. Finally, the minimal mean values of PRL were observed after 12–24 hours from bromocriptine administration in both groups of patients. No bromocriptine-related toxicity was seen.

**Discussion**

This study shows that the long-acting dopaminergic agent bromocriptine may be effective in normalizing PRL secretion occurring in metastatic breast cancer and prostate cancer, as well as for hyperprolactinemia due to reasons other than advanced cancer. Therefore, irrespectively of the mechanisms responsible for cancer-related hyperprolactinemia, low-dose bromocriptine is sufficient to obtain a control of PRL secretion for the whole 24-hour circadian period. This evidence is not obvious, since our previous studies had already shown a paradoxical increase in PRL levels in both patients suffering from metastatic breast cancer and prostate carcinoma in response to L-Dopa [10, 11], which is the commonly used inhibitory test for PRL secretion. The previously described paradoxical response of PRL to L-Dopa in the presence of a normal response to bromocriptine is difficult to be explained. It is possible to hypothesize an enzymatic deficiency of the transformation of L-Dopa into dopamine or an eventual direct stimulatory role of L-Dopa per se on PRL secretion by cancer cells. Previous preliminary experimental studies had already shown the existence of subtypes of dopamine receptors at pituitary sites, namely D1 and D5, capable of mediating a paradoxical stimulatory effect on PRL secretion, with respect to the most commonly expressed D2 receptor responsible for the mediation of the inhibitory effect of dopamine on PRL release [12]. According to this evidence, it is possible to hypothesize an overexpression of D1 and DR dopamine receptors mediating a paradoxical stimulatory effect of L-Dopa on PRL release in advanced neoplasms. In contrast, bromocriptine would maintain its capacity of inhibiting PRL secretion also in patients with cancer-related hyperprolactinemia. Finally, we could hypothesize that an eventual paraneoplastic produc-