Shrinkage of pituitary PRL-secernent adenoma after short-term treatment with bromocriptine long-acting repeatable injections

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Summary: The efficacy, safety and tolerability of a single bromocriptine-LAR injection (50 mg) and of a 6 injection course at 28-day intervals, were evaluated respectively in 13 and in 9 hyperprolactinemic women with radiological signs of PRL-secreting pituitary adenoma. The long-lasting repeatable formulation of bromcryptine induced a rapid and prolonged hypoprolactinemic effect. Side effects related to central activity of the compound were observed only on the first day of compound administration in all subjects except one, whereas no modifications of cardiologic and haematologic parameters were observed. In one subject the occurrence of side effects was observed also during the 6 injection course of treatment. A significant shrinkage of pituitary adenoma was observed at the second CT scan performed in 7 of the 9 subjects treated for 6 months with bromocriptine-LAR. CT scan was not performed in one subject who achieved pregnancy after second bromocriptine-LAR injection, whereas unmodified size of pituitary microadenoma was found in one subject whose PRL secretion did not decrease during the treatment and who referred severe side effects.

Key words: Pituitary PRL-secernent adenoma treatment.

INTRODUCTION

The incidence of pituitary adenomas as etiologic factors of pathological hyperprolactinemic states has been calculated within a range of 16-48% ([1]). Among these pituitary adenomas only 70% secrete prolactin (PRL) and are referred to as PRL-producing adenomas ([2]). This type of adenoma develops in the lateral portion of the pituitary gland, and accounts for the early appearance of the asymmetric distortion of the sella ([3]). Microadenomas refer to tumors 10 mm or smaller in diameter; macroadenomas are greater than 10 mm of diameter ([4]). The use of CT scans or Nuclear Magnetic Resonance (NMR), together with circulating PRL levels and response to stimuli with antidopaminergic agents and TRH ([5]), permit the diagnosis of PRL-producing adenoma with high degree of accuracy. The clinical adenoma-

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induced features of hyperprolactinemia is commonly represented by galactorrhea and chronic anovulation. This latter is probably consequent to a PRL-induced increase in the activity of tuberoinfundibolar dopaminergic neurons, which, in turn, inhibits GnRH pulsatile release, via the activation of β-endorphin neuronal system ([6–8]). The presence in adenomatous cells of functionally intact dopamine receptors of D2 subtypes permits the performance of a medical management of these hyperprolactinemic states by specific D2 dopamine agonist administration ([3]). Among these, bromocriptine, an ergot-derivative ([4]), has represented and represents the gold standard and it is used as the first therapeutical approach ([5, 9–11]). A new generation of dopamine agonists with a high degree of potency, longer duration of action and less side effects have recently been used. Bromocryptine Long Acting (bromocriptine-LA), a new bromocriptine formulation with bromocriptine microspheres linked to a carrier of polylactic acid, which are suspended in dextran, before their intramuscular (im) injection, showed a release of the drug characterized by a first rapid release (T/2=0.9 hour) followed by a slow one (T/2=22 days) ([12]) and a good efficacy both in the inhibition of puerperal lactation ([13]) and in the reduction of PRL and Growth Hormone (GH)- secreting tumors ([14–16]).

More recently, a new depot formulation of bromocriptine long-active, bromocriptine LA repeatable (bromocriptine-LAR), characterized by DL polylactic co-glucoside as carrier for bromocriptine, has been produced. This compound is completely degraded within 3 months, and therefore repeatable injections are possible ([17]).

The aim of the study was to evaluate the efficacy of bromocriptine-LAR in the treatment of pathological hyperprolactinemic states related to PRL-secreting adenomas.

MATERIALS AND METHODS

The patients participating to the study were 13 hyperprolactinemic women (range of age 18-40 years) with radiological signs (CT scan) of pituitary adenoma (6 with microadenoma and 7 with macroadenoma). All subjects were affected by amenorrhea, while only 10 suffered from galactorrhea.

After haematological and cardiologic examinations, the subjects were submitted to a single im injetion of bromocriptine-LAR (50 mg) at 08.00 am.

PRL levels were evaluated in blood samples collected at 08.00, 10.00, 12.00, 16.00 and 20.00 on the day preceding and 3, 7, 14. 21 and 28 days following bromocriptine-LAR injection. After 28 days of observation, 9 women (5 with microadenoma and 4 with macroadenoma) continued the every 28 day injection of bromocriptine-LAR for at least other 6 administrasions whereas, for personal reasons, 4 subjects did not accept the chronic treatment. During each 28 day cycle, PRL levels were evaluated on the injection day and on days 14, 21 and 28 in plasma samples collected at 08.00, 10.00, 12.00, 14.00, 16.00 and 20.00 hours. PRL assay was performed by RIA method with commercial kits (Areas Serono, Milano, Italy).

A second CT scan was performed 28-60 days after the last bromocriptine injection in 8 patients, whereas in the other one CT scan was not repeated because of the occurrence of a pregnancy. At each visit treatment tolerability was evaluated by asking about side effects occurrence. Moreover, in each patient haematological and cardiologic examinations were repeated 28 days after the first injection of bromocriptine-LAR and at the end of treatment.

RESULTS

Variations of plasma PRL levels on the first day of treatment and in the following days of observation with a single im 50 mg bromocriptine-LAR injection are reported in Fig. 1 and Fig. 2. A rapid, significant and prolonged hypoprolactinemic effect was observed immediately after the drug administration. Only after 28 days, PRL levels started to increase, but the values were still significantly lower than before treatment.

In bromocriptine-LAR chronic treatment, the evaluation of PRL levels was performed in all subjects except one (microadenoma), who became pregnant after

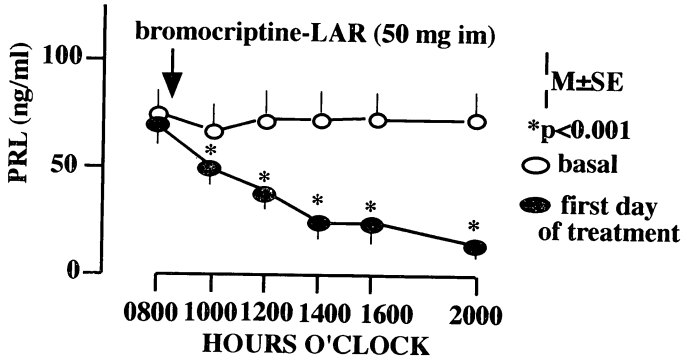

Fig. 1. — Plasma PRL levels measured in 13 hyperprolactinemic women with radiological signs of PRL-secreting pituitary adenoma on day preceding and following bromocriptine-LAR (50 mg im) administration. A significant decrease ($p < 0.001$) of PRL levels was observed after a single administration of the compound.

the second drug injection. In all subjects, except one, plasma PRL levels were significantly inhibited during the time of observation (Fig. 3). In the 13 subjects treated with a single bromocriptine-LAR injection, side effects (nausea, vomiting, vertigo) were reported on the day of bromocriptine-LAR injection, whereas they were described as slight or absent from the 2nd to the 28th day of treatment.

In the 9 subjects treated with 6 injections of bromocriptine-LAR, no side effects were reported by 8 patients, but the patient whose PRL secretion was not moderated during the treatment, referred the appearance of invalidating side effects, such as vertigo, nausea and vomiting. However, the patient chose to continue the treatment.

No modifications of haemotological and cardiologic parameters were observed before and after one single or six bromocriptine-LAR administrations. In all women spontaneous menses appeared within

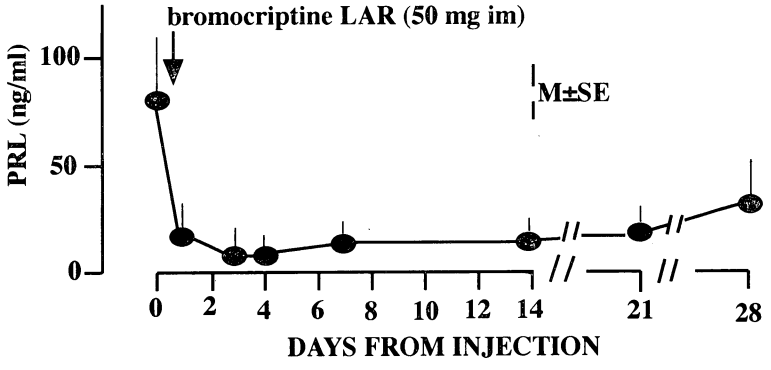

Fig. 2. — Plasma PRL levels measured in 13 hyperprolactinemic women with radiological signs of PRL-secreting pituitary adenoma before and during 28 days of observation from a single in injection of bromocriptine-LAR (50 mg). A significant decreare ($p < 0.001$) was observed from the first day of treatment until the end of observation.

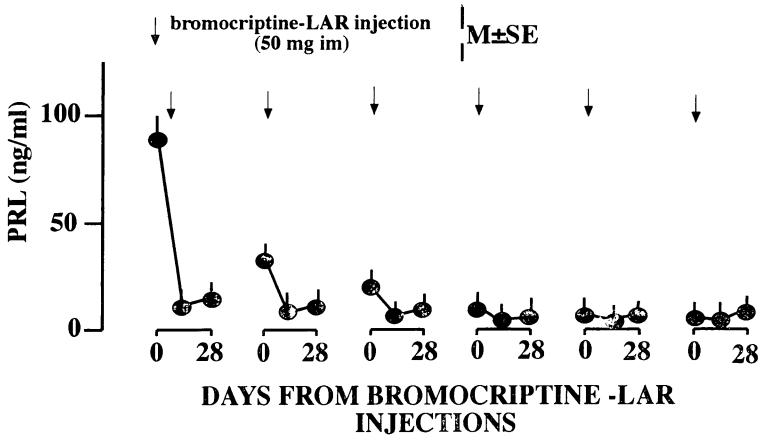

Fig. 3. — Plasma PRL levels during a course of 6 cycles of bromocriptine-LAR treatment. PRL secretion shows a significant decrease after the first and second injections of bromocriptine-LAR. Thereafter the values always remained within the normal range.

28 days from the single injection of bromocriptine-LAR. In the women submitted to chronic treatment, normal menstrual cycles were reported by all subjects, and one patient became pregnant after the second bromocriptine-LAR injection.

The second CT scan showed that the size of pituitary adenoma was unmodified in the PRL non-responder patient (microodenoma). In one subject with macroadenoma and in 3 subjects with microadenoma, the pituitary adenomas radiologically disappeared, whereas, on three other subjects with macroadenoma a shrinkage of the adenoma was observed.

DISCUSSION

The depot formulation of bromocriptine-LAR exerts a prolonged dopaminergic effect, that is able to moderate prolactin levels and the size of PRL secreting adenomas, permitting the restoration of a normal cyclic secretion of gonadotropins. These effects are more pronounced than with the oral formulation of bromocriptine that induced a decrease of adenoma size only after 1-2 years of administration. Since bromocriptine depot formulation is able to release constant doses of the dopaminergic compound, it can be hypothesized that a prolonged and stable stimulation at D2 receptors on adenomatous cells is required to obtain a maximal inhibitory effect. This greater therapeutical efficacy is also associated with the advantage of performing a therapeutic management with only one monthly administration of the drug, instead of the daily assumption of multiple tablets of bromocriptine or other dopaminergic compounds. In our study only one subject experienced a pronounced intolerance to bromocriptine-LAR treatment. In the other subjects side effects occurred only on the first day of drug administration. The subjects experiencing severe side effects was the same, showing no inhibitory PRL response to bromocriptine-LAR administration. Although the association between these two phenomena is hard to explain, it is possible that a reduction of D2 receptors in microadenoma may have favoured a greater concentration of the dopaminergic compound at central level. Since no haematological or cardiologic impact was observed with bromocriptine-LAR treatment, this compound

seems to represent an effective, safe and well tolerated drug for the management of PRL-secretin pituitary adenoma.

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