Chronic treatment with Parlodel LAR® of patients with prolactin-secreting tumours. Different responsiveness of micro- and macroprolactinomas

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Abstract. Forty-one patients with prolactinoma (25 micro-, 16 macroprolactinomas) were treated with a long-acting injectable preparation of bromocriptine (Parlodel LAR®, Sandoz), 25-100 mg (mostly 50 mg) im every 4-8 weeks for as long as 43 months (median 19 months). The first injection caused a prompt fall of plasma PRL which reached its nadir value after 3 days. Thereafter, hormone levels remained well below initial values for 4 weeks or longer, though with the tendency, more pronounced in microprolactinoma patients, to rise again toward baseline. The prevalence of PRL normalization was greater in the macro- than in the microprolactinoma group. By repeated injections plasma PRL could be kept close to or within the normal limits in most of the patients. However, the extent of PRL inhibition was significantly greater in macro- than in microprolactinoma patients (p<0.01). Clinical improvement occurred in the majority of the patients, shrinkage of the tumour in 50% of them. Adverse reactions were generally mild or of moderate severity and subsided spontaneously in 24 h. They were less frequent (NS) and less severe (p<0.05) in macro- than in microprolactinoma patients. In conclusion: a. injectable bromocriptine (Parlodel LAR) is a highly effective preparation particularly suitable for the long-term treatment of tumourous hyperprolactinemia; b. patients with macroprolactinoma exhibit, compared with microprolactinoma patients, better responsiveness and better tolerability to injectable bromocriptine.

The recent development of long-acting formulations of bromocriptine has increased the options available for medical treatment in patients with prolactin-secreting pituitary tumours.

Several studies have documented the ability of Parlodel LA® (Sandoz Ltd, Basel, Switzerland), a long-acting non-repeatable injectable preparation of bromocriptine, to keep plasma PRL steadily suppressed for four or more weeks (1-4). According to Grossman et al. (5) and others (6-8), injection of Parlodel LA should be the first therapeutic approach for patients with huge prolactinomas, because of the rapid tumour shrinkage (5-7) and of the improved tolerability to subsequent administration of oral bromocriptine that it may produce (8).

In contrast, only little information is available on a long-acting preparation of bromocriptine suitable for repeated injections (Parlodel LAR®, Sandoz Ltd, Basel, Switzerland), which has been studied on small series of patients followed for a few months (9-13).

We report here our results obtained in 41 patients with prolactinoma, treated for up to 43 months with repeated injections of Parlodel LAR. This study, besides demonstrating a remarkable effectiveness of this bromocriptine preparation when administered chronically, provides evidence for a better responsiveness of patients with macroadenoma compared with those with microadenoma.
Subjects and Methods

We studied a total of 41 patients, 5 men and 36 women, aged from 18 to 66 years. Twenty-five patients had pituitary microprolactinoma, (tumour size less than 10 mm), 16 had macroprolactinoma (tumour size more than 10 mm). Diagnosis was suggested by clinical findings and established by high resolution CT scan with enhancement and/or by nuclear magnetic resonance (NMR) of the hypothalamic-pituitary region, by visual perimetry according to Goldman, and finally by evaluation of baseline and stimulated plasma PRL levels. Thirty-six patients had previously received oral dopaminergic compounds, which had been discontinued at least three months before the study owing to drug intolerance or on patient's own initiative. Six patients with macroprolactinoma had already undergone unsuccessful pituitary surgery. Fully informed consent to participate in the study was obtained from all patients.

Patients were treated with Parlodel LAR (Sandoz Ltd, Basel, Switzerland), an injectable preparation of 50 mg bromocriptine in which bromocriptine is incorporated into D,L-polylactide co-glycolide microspheres suspended in a liquid vehicle containing carboxy-methylcellulose. Injected deeply intraglutally, this preparation slowly releases its active component, assuring therapeutic plasma levels of bromocriptine for four or more weeks. The complete degradation and absorption of the carrier material in two months permits repetition of the injections at monthly intervals, on alternate sides (9).

Treatment of our patients consisted of injections of Parlodel LAR, which were administered, between 8.30 and 9.00, in the Day Hospital of our institute at 4 to 8-week intervals from 1 to 43 times. To achieve greater PRL inhibition, the dose of the drug was progressively increased to 100 mg per injection in 13 patients; in 5 other patients, whose PRL levels became undetectable, the dose was reduced to 25 mg per injection. A subgroup of 17 patients with microprolactinoma and 13 with macroprolactinoma patients who received monthly injections of 50-100 mg Parlodel LAR for one year was used to evaluate the results of chronic treatment.

Plasma samples for PRL estimation were obtained at 8.00, 10.00, 12.00, 14.00, 16.00 and 20.00 h on the day preceding the first injection, on the day of injection, and on day 3, 7, 14 and 28 after the injection. The mean of the PRL values recorded the day preceding the first injection was taken as baseline PRL level. For the subsequent injections, plasma PRL was measured on three blood samples obtained 10 min apart before and 12 h after each injection, then every two weeks. Clinical evaluation, blood chemistry, laboratory parameters of pituitary, thyroid and gonadal function, and ECG were done at the start of the study and repeated during treatment. CT scan and/or NMR were performed before the start of treatment and repeated within the following twelve months in all macroprolactinoma patients except one who became pregnant and in 13/25 microprolactinoma patients whose tumour diameter exceeded 5 mm. Further evaluations were thereafter performed upon clinical indications.

Plasma PRL was measured by radioimmunoassay, using commercial reagents (Prolactin liso-phase, Slavo, Cinisello Balsamo, Italy). The sensitivity of the method is

![Fig. 1.](image)

Mean PRL profile, expressed in the inset as per cent of baseline, following the first injection of 50 mg Parlodel LAR in 25 patients with microprolactinoma (○—○) and 16 with macroprolactinoma, (●—●). Vertical bars indicate SEM. p<0.01 between the two PRL profiles.
became age both levels microprolactinoma with PRL month lactinoma, in (44.0±5.84% noma, more parable tion and administration the on normalization model in Statistics the differences in the degree of PRL inhibition observed in patients with micro- and macroprolactinoma after Parlodel LAR were evaluated by analysis of variance on repeated measures, performed both on raw numbers and on their logarithms. The differences in the rates of PRL normalization after treatment and in drug tolerability in the two groups of patients were analysed by the Chi-square and the Mann-Whitney test.

Results

PRL levels

First injection of Parlodel LAR. The first im administration of 50 mg Parlodel LAR caused a prompt and sharp PRL fall (baseline values 2555.3±362.94 mU/l in patients with microprolactinoma and 1323.4±4835.98 mU/l in patients with macroprolactinoma), already apparent 12 h after the injection (Fig. 1). Maximal PRL inhibition was of comparable magnitude in the two groups of patients (16.4±2.25% and 14.3±3.57% of baseline patients with microprolactinoma and macroprolactinoma, respectively) and occurred at day 3 (inset in Fig. 1). Thereafter, hormone levels remained steady suppressed in some patients, whereas in others, and more frequently so in patients with microprolactinoma, they tended to rise again toward baseline (44.0±5.84% and 23.3±7.20% of baseline at day 28 in patients with microprolactinoma and macroprolactinoma, respectively).

Thus, considering the PRL pattern during the month following the first injection, the extent of PRL inhibition was significantly greater in patients with macroprolactinoma than in patients with microprolactinoma (p<0.01), though hormone levels remained well below pretreatment values in both groups.

During the month of observation, the percentage of patients with microprolactinoma whose PRL became normal was higher, though not significantly so, than that recorded in patients with macroprolactinoma, whereas the opposite was true at the end of the month, owing to the tendency of PRL to escape early from maximal inhibition in patients with microprolactinoma (Table 1).

Repeated injections of Parlodel LAR. By repeated injections of Parlodel LAR it was possible, in the majority of our patients, to keep plasma PRL close to or within the normal limits for as long as 43 months (Fig. 2). In a homogeneous series of 30 patients, all treated with monthly injections for one year, PRL levels remained suppressed, even if more steadily so in patients with macroprolactinoma than with microprolactinoma, for the whole observation period (Fig. 3). As seen after the first injection, the overall PRL inhibition observed during chronic treatment was significantly more pronounced in patients with macroprolactinoma than with microprolactinoma (p<0.01). PRL normalization was also attained in a higher percentage of patients with macroprolactinoma than with microprolactinoma, though the differences were not statistically significant, (Table 1), in spite of the similar average monthly doses of Parlodel LAR administered (64.7 mg/monthly to patients with microprolactinoma and 59.5 mg/monthly to patients with macroprolactinoma). Further, to achieve the greatest lowering of PRL, the dose of Parlodel LAR had to be increased to 100 mg per injection in 9/21 patients with microprolactinoma but in only 4/16 patients with macroprolactinoma. Conversely, in 3 patients with macroprolactinoma the dose of Parlodel LAR could be reduced to 25 mg per injection.

<table>
<thead>
<tr>
<th>Table 1. PRL normalization after treatment with Parlodel LAR.</th>
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<tr>
<td>First injection - during the 1st month of observation</td>
</tr>
<tr>
<td>20/25 (80.0%)</td>
</tr>
<tr>
<td>9/16 (56.2%) NS</td>
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<tr>
<td>at the end of the 1st month of observation</td>
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<tr>
<td>9/25 (36.0%)</td>
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<tr>
<td>9/16 (56.2%) NS</td>
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<tr>
<td>Chronic treatment a</td>
</tr>
<tr>
<td>10/21 (47.6%)</td>
</tr>
<tr>
<td>13/16 (81.2%) NS</td>
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<tr>
<td>b 7/17 (41.1%)</td>
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<tr>
<td>9/13 (69.2%) NS</td>
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a all patients
b 30 patients followed for 1 year
Altogether, the results obtained after single or repeated administrations of Parlodel LAR seem to indicate that patients with macroprolactinoma are more sensitive to injectable bromocriptine than are patients with microprolactinoma.

**Clinical findings**

The clinical signs and symptoms commonly encountered in hyperprolactinemia greatly improved or disappeared in a high percentage of patients (Table 2). Of note, resumption of menses occurred in 10 patients whose PRL levels, though reduced compared with pretreatment levels, were still above the normal limits (529-7482.2 mU/l). Three of the 4 patients with impotence who did not benefit from treatment had panhypopituitarism and refused androgen replacement therapy. Shrinkage of the pituitary tumour could be documented in 8/15 patients with macroprolactinoma and 6/13 patients with microprolactinoma.

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**Fig. 2.**

Plasma PRL pattern in 41 patients with prolactinoma treated with Parlodel LAR for 1-43 months. Closed and open symbols indicate PRL values before and during treatment. Numbers at the top of the bars indicate, for each patient, the dose of Parlodel LAR administered at each injection; those at the bottom, the number of injections given. The dotted line indicates the upper limit of the normal PRL range.
Fig. 3.
Plasma PRL pattern, expressed in the inset as per cent of baseline, in 17 patients with microprolactinoma (O—O) and 15 with macroprolactinoma (●—●) treated for one year with monthly injections of Parlodel LAR. Arrows indicate the injections given. *p<0.01* between the two PRL profiles.

**Table 2.**
Clinical findings during treatment with Parlodel LAR.

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Disappeared</th>
<th>Improved</th>
<th>Unchanged</th>
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<tr>
<td>Oligo/ame-norrhea</td>
<td>18/27 (66.6%)</td>
<td>4/27 (14.8%)</td>
<td>5/27 (18.4%)</td>
</tr>
<tr>
<td>Galactorrhea</td>
<td>18/22 (81.8%)</td>
<td>2/22 (9.1%)</td>
<td>2/22 (9.1%)</td>
</tr>
<tr>
<td>Impotence</td>
<td>1/4 (25.0%)</td>
<td>–</td>
<td>3/4 (75.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>6/7 (85.7%)</td>
<td>–</td>
<td>1/7 (14.3%)</td>
</tr>
<tr>
<td>Visual field defects</td>
<td>2/6 (33.3%)</td>
<td>1/6 (16.7%)</td>
<td>3/6 (50.0%)</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>5/28 (17.9%)</td>
<td>9/28 (32.1%)</td>
<td>14/28 (50.0%)</td>
</tr>
</tbody>
</table>

**Tolerability**

The typical adverse reactions to bromocriptine (nausea, occasional episodes of vomiting, hypotension, headache, dizziness, drowsiness, nasal congestion) occurred frequently (Table 3). However, except for 4 patients in whom treatment had to be stopped, they were generally mild and short lasting, mostly subsiding spontaneously in 24 h. Moreover, they became less frequent (NS) and milder (*p<0.05*) with continuation of treatment. Of note, 12 patients who were intolerant to oral bromocriptine could tolerate treatment with the injectable preparation of the drug. The overall frequency of adverse reactions was greater, though not significantly so, in patients with microprolactinoma than with macroprolactinoma, after either single or multiple injections. Likewise the severity scores for the
adverse reactions were also greater for patients with microprolactinoma than with macroprolactinoma (p<0.05).

**Discussion**

A non-negligible number of patients with hyperprolactinemia are intolerant to dopaminergic compounds at the doses needed to suppress PRL secretion, or even at very low doses (7,14,15). Grossman et al. reported that administration of Parlodel LA, a depot formulation of bromocriptine developed for single administration, improved the tolerability to subsequent therapy with oral bromocriptine (8). In view of the rapid PRL inhibition and tumour shrinkage that it may induce, they recommended injection of bromocriptine as the first therapeutic approach for patients with microprolactinoma. Only a few studies have been published, so far, on the use of Parlodel LAR, a long-acting injectable preparation of bromocriptine suitable for repeated administrations (10-13). We have treated 41 patients with prolactinoma for as long as 43 months and have been able, by injections of 25-100 mg (generally 50 mg) Parlodel LAR, given every 4-8 weeks, to keep plasma PRL inhibited close to or within the normal limits in the majority of the patients.

PRL lowering was associated with improvement or complete disappearance of the clinical manifestations commonly accompanying hyperprolactinemia. The figure of 50% of the patients displaying tumour shrinkage is somewhat lower than that generally reported of about 70% (16-18). This is probably due to the previous treatment of many of our patients with dopamine receptor agonists and to the presumable reduction of the tumour mass already occurred.

On the whole, treatment was well tolerated and well accepted by the patients. The typical adverse reactions to dopaminergic compounds occurred in more than half of the patients, but were generally mild and subsided spontaneously within 24 h. Also, they became even milder and less frequent with repetition of the injections. Treatment was easily tolerated by 12 patients who had previously been intolerant to oral bromocriptine.

That patients with macroprolactinoma may have spectacular drops in PRL after administration of dopaminergic drugs is a common clinical experience (7,16-18). However, clear evidence for a different behaviour of patients with microprolactinoma and macroprolactinoma as regards their sensitivity to dopaminergic drugs has never been provided. In our series, patients with macroprolactinoma responded better than patients with microprolactinoma to chronic treatment with injectable bromocriptine. In fact, after both single and repeated administrations of Parlodel LAR, the degree of PRL inhibition was significantly greater in patients with macroprolactinoma than with microprolactinoma, in spite of the higher initial PRL levels in the former and of the comparable monthly dose of bromocriptine administered in the two groups. The rate of PRL normalization also tended to be higher in patients with macroprolactinoma than with microprolactinoma. No correlation could be found between previous surgical or pharmacological treatment and the degree of responsiveness to Parlodel LAR. Two of the 6 patients with macroprolactinoma already unsuccessfully operated upon, had a presurgery PRL inhibition after injectable bromocriptine (Parlodel LA, Sandoz) quite similar to that observed in the present study.

The concept of different sensitivity of micro- and macroprolactinomas to dopaminergic agents is
supported by studies in vitro (19), showing that lactotropes of macroprolactinomas are more sensitive than microprolactinoma cells to the PRL suppressive effect of dopamine. This behaviour might be due to lack of endogenous dopamine, because of a smaller number of capillaries within these large tumours (20). In keeping with this view, patients with macroprolactinoma appear to have a blunted PRL response to the antidopaminergic compound domperidone (21) and to be more sensitive to low-dose dopamine infusion (22), as compared with patients with microprolactinoma. Administration of high doses of bromocriptine, by allowing sufficient amounts of the drug to reach dopamine receptors, might thus elicit a dramatic PRL fall. No differences in receptor density between micro- and macroprolactinoma cells have been demonstrated (23,24).

Besides exhibiting greater PRL inhibition, our patients with macroprolactinoma tolerated the injectable bromocriptine better than patients with microprolactinoma. This behaviour is not easy to explain. Hypothetically, it could be related to high concentrations of dopamine, secondary to increased PRL secretion (25), at the suprapituitary level.

Our observations allow the following conclusions: a. the injectable depot preparation of bromocriptine, Parlodel LAR, is a highly effective treatment for patients with prolactinoma, enabling a sustained PRL suppression by monthly administrations. Therefore, it is a valuable alternative to oral dopaminergic agonists, particularly suitable for long-term therapies; b. patients with macroprolactinoma appear to respond better than patients with microprolactinoma to injectable bromocriptine, obtaining a greater and more steady PRL inhibition; they also have a better tolerability to the dopaminergic compound.

References
14. Vermesh M, Fossom GT, Kletzky OA. Vaginal bromocriptine: pharmacology and effect on serum pro-


