Primary treatment of macroprolactinomas with Parlodel LAR®

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Abstract. Five patients, 3 women and 2 men, with macroprolactinomas characterized by extrasellar extension and basal plasma prolactin levels ranging from 4.6 to 102 U/l received six monthly injections of 50–100 mg Parlodel LAR®, an injectable long-acting repeatable form of bromocriptine. The following observations were made: 1. Plasma prolactin levels fell dramatically in all patients and values in the normal range were obtained in 3 patients. 2. In all patients, the onset of tumour reduction was visible on CT scans made one week after the first Parlodel LAR injection. After six Parlodel LAR injections, tumour size was reduced by more than 75% in 3 patients and by 50–75% in two patients. 3. Diminished visual acuity (one patient), bitemporal hemianopia (2 patients), and oculomotor and trochlear nerve dysfunction (one patient) were restored to normal after the first Parlodel LAR injection. 4. Hypogonadism normalized in 2 patients and improved in one patient, whereas plasma gonadotropins remained low in the 2 postmenopausal women. In one patient with hypothyroidism and hypocorticism, thyroid and adrenal functions normalized. It is concluded that bromocriptine retard (50–100 mg monthly) is a useful alternative for oral treatment of patients with prolactinomas, especially in those patients with compliance problems on oral bromocriptine therapy.

The treatment of choice for macroprolactinomas still is a subject of controversy. Neurosurgeons tend to postulate that medical treatment of prolactinomas has to be continued indefinitely. However, after several years of dopaminergic treatment, macroprolactinomas will not re-expand with a greatly reduced dose (Liuzzi et al. 1985). Studies on withdrawal of the drug after a long period of treatment (5 to 10 years) are not yet available. Transsphenoidal surgical therapy for macroprolactinomas will only seldom be curative. These patients will require dopaminergic drugs after surgery (Fahlbusch et al. 1987). In our hospital, macroprolactinomas are primarily treated with oral bromocriptine, 10 mg daily in four divided doses (van 't Verlaat et al. 1986). In 5 patients with macroprolactinomas we used the long-acting repeatable form of bromocriptine (Parlodel LAR®), during 6 months to collect data about the tolerability, the safety and the effectiveness of this drug.

Patients and Methods

Patients and experimental protocol

The study was carried out in 5 patients with untreated macroprolactinomas, who gave informed consent to participation in the study. The investigation was approved by the Medical Ethical Committee of the University Hospital Utrecht. At 8.00 h the patients were given a deep intragluteal injection with 50 mg Parlodel LAR® (Sandoz, Switzerland) which contains bromocriptine in microspheres, employing glucose D,L-poly-lactide-coglycolide as carrier material. In case of good tolerability of the first injection and a decrease of plasma prolactin concentrations to below 70% of the basal level after the first injection of Parlodel LAR, the...
injections were repeated at monthly intervals during 6 months. If plasma prolactin concentrations did not decrease to below 30% of the basal level, 100 mg Parlodel LAR was used.

**Hormonal studies**

Before treatment, the basal plasma prolactin level was determined by averaging 8 measurements in blood samples obtained during the day (08.00, 09.00, 10.00, 11.00, 12.00, 14.00, 16.00 and 20.00 h). On the day of the first injection of Parlodel LAR and 7, 14 and 28 days afterwards day-profiles of plasma prolactin levels were made, as well as 28 days after the sixth injection. Two, 3 and 4 weeks after the second, third, fourth and fifth injection of Parlodel LAR basal plasma prolactin levels were measured at 08.00 h. Prolactin values are expressed as U/l (1 IU MRC 81/541 = 25 µg). Normal plasma prolactin values: for men < 0.48 U/l, for women < 0.60 U/l.

Anterior pituitary function was assessed before treatment and 28 days after the first and last injection of Parlodel LAR. Gonadal function was assessed by measuring LH and FSH, estradiol in women and testosterone in men. Thyroid function was assessed by the basal plasma TSH level, total T₄ and T₃-resin uptake. A free T₄ index was calculated from the product of total T₄ and T₃-resin uptake. Adrenocortical function was evaluated by the basal plasma cortisol level at 08.00 h.

**Radiology**

High-resolution CT scans (Philips Tomoscan 350) were made before and 7 and 28 days after the first Parlodel LAR injection and 28 days after the sixth injection. Routine 3-mm coronal and axial sections were obtained with 9.6 sec scan time and 720 mAs. Just before each slide (10–20 sec), a 25-ml contrast bolus of a 44% iodinated contrast medium (diatrizoate) was given at a maximum dose up to 150 ml. Tumour reduction was expressed semiquantitatively as follows: no reduction in tumour size (0), up to 50% reduction (+), 50–75% reduction (++) and more than 75% (+++).

**Ophthalmology**

Ophthalmological examination (measurement of visual acuity, fundoscopy and perimetry according to Goldmann) was performed before treatment. In case of abnormalities, it was repeated 3, 7, 14 and 28 days after the first injection of Parlodel LAR and thereafter if appropriate.

**Results**

**Prolactin levels**

Before treatment, plasma prolactin levels ranged from 4.6 to 102 U/l (Table 1). In all patients plasma prolactin decreased gradually on the day of the first Parlodel LAR injection to value ranging from 10 to 48% of the basal values at 20.00 h (Fig. 1). A further decrease to values ranging from 1 to 4% of the basal value was obtained in 3 patients (No. 2, 4 and 5) after 4 weeks and in one of them (No. 2) this value was within the normal range (Table 1). Four weeks after the first Parlodel LAR injection in patients No. 1 and 3, plasma prolactin levels were decreased to 44% and 58% of the basal values, respectively (Fig. 1). Therefore, in these two patients treatment was continued with monthly injections containing 100 mg Parlodel LAR. Following this regimen, plasma prolactin levels decreased gradually in all patients after the following injections. At the end of the observation period, normal plasma prolactin values were obtained in patients No. 2, 4 and 5 (Table 1).

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex (F/M)</th>
<th>Age (years)</th>
<th>Plasma prolactin levels (U/l)</th>
<th>Tumour reduction at end of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before treatment</td>
<td>28 days after first injection</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>17</td>
<td>4.6</td>
<td>2.0</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>21</td>
<td>8.9</td>
<td>0.09</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>34</td>
<td>35.0</td>
<td>20.0</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>61</td>
<td>39.0</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>69</td>
<td>102.0</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Normal plasma prolactin values: for men < 0.48 U/l, for women < 0.60 U/l.
Patients No. 1 and 2 had hypodense macroadenomas with suprasellar extension on CT scan. On coronal CT scan sections, the maximal height of their tumours amounted to 23 and 14 mm, respectively. Patients No. 3, 4 and 5 had hyperdense macroadenomas with suprasellar and unilateral laterosellar extension. One week after the first injection of bromocriptine, the tumours of all patients were reduced in size. The CT scans made 28 days after the first injection and 28 days after the sixth injection of Parlodel showed progressive tumour reduction in all patients (Table 1).

Fig. 2 shows the pretreatment scan of patient No. 5, as well as three scans made after treatment with injectable bromocriptine.

Ophthalmology
Patient No. 3 had bilateral superotemporal visual field defects which disappeared two weeks after the first Parlodel injection. Patient No. 5 had diminished visual acuity (VOD 5/15, VOS 5/50), bitemporal hemianopia, and loss of function of oculomotor and trochlear nerves on the left side. Improvement of visual fields was noticed by the patient within 12 h after the first injection. On the third day objective improvement of visual acuity, visual fields and cranial nerve functions was documented. One month later no abnormalities were found.

Clinical symptoms and hormonal studies
All patients complained of headache and showed clinical and biochemical evidence of hypogonadism. In the two postmenopausal women, menses had stopped at the age of 30 and 42 years, respectively; the third woman had secondary amenorrhea since 2.5 years. Hypothyroidism and hypocorticism were present in patient No. 2. No patient had galactorrhea.

During treatment with Parlodel LAR, headache disappeared in all patients. Menses re-appeared in the premenopausal woman after the third injection; plasma gonadotropins remained low in the postmenopausal women. Libido and sexual potency improved in both men, whereas plasma testosterone levels increased from 5.8 to 16.8 and from 2.0 to 7.7 nmol/l (normal range 10–35 nmol/l). In patient No. 2, a significant clinical improvement was associated with a rise of the free T4 index from 22 to 40 (normal range 30–69) and of the basal plasma cortisol level at 8.00 h from 0.11 to 0.63 µmol/l (normal range 0.20–0.60) 4 weeks after the first injection of Parlodel LAR and remained normal thereafter.

Adverse reactions
Adverse reactions included mild nausea in 2 patients during 2–3 days after the first injection of Parlodel. Subsequent injections were well tolerated. A third patient suffered from severe nausea and vomiting for several days after the first and second injection, but again subsequent injections were well tolerated. Previously a variety of oral drugs administered for other diseases had also induced vomiting. Patient No. 2 developed severe symptomatic postural hypotension lasting 2 days after the first injection. The symptoms disappeared spontaneously. This patient had clinical and biochemical evidence of hypothyroidism and hypocorticism. No serious reactions were seen at the injection site in any patient.
Fig. 2.
CT scans of patient No. 5.

a: Pretreatment scan showing a pituitary adenoma with suprasellar extension as well as extension in the left carotid sinus and the sphenoid sinus.
b: Tumour reduction 1 week after a 50-mg Parlodel LAR injection. The optic chiasm is decompressed.
c: Tumour reduction 3 weeks later. Decreased tumour volume in the left cavernous sinus and the sphenoid sinus.
d: Hypodense tumour rest in the left part of the sella after six 50-mg Parlodel LAR injections. The pituitary connected with the stalk is visible in the right part of the sella.

Discussion

Parlodel LA (bromocriptine retard), the first long-acting injectable form of bromocriptine has been used in the short term treatment of hyperprolactinemia for several purposes. Parlodel LA was successfully used in suppression of postpartum lactation (Peters et al., 1986). One injection of bromocriptine retard was used as an alternative to emergency surgical decompression in a patient with acute, estrogen-induced swelling of an invasive prolactinoma (Landolt et al., 1984). Grossman et al. (1985, 1987) used one 50 mg bromocriptine
Retard injection in patients with prolactinomas and growth hormone producing adenomas and in patients with hyperprolactinemia as a predictor of unresponsiveness to dopamine agonist therapy. Furthermore, these authors suggest that bromocriptine retard may well be the treatment of choice for rapid shrinkage of large pituitary tumours sensitive to dopamine agonist therapy. Fahlbusch et al. (1987) prefer injectable bromocriptine some weeks before transsphenoidal surgery for macroprolactinomas to improve the surgical results. One injection of long-acting bromocriptine has been used with success in patients with macroprolactinomas (Benker et al. 1986; Bronstein et al. 1987; Montini et al. 1986).

The present study describes the medium-term effects of a new injectable form of Parlodel which can be administered repeatedly. Studies in normal subjects have shown that plasma prolactin levels are depressed until the 28th day after the injection of 50 mg Parlodel LAR; thereafter they gradually increase to normal levels by day 42 (Lancranjan et al. 1987). We therefore treated 5 patients with macroprolactinomas with monthly injections of 50–100 mg Parlodel LAR for a period of six months. The results demonstrate that Parlodel LAR is a very effective therapeutic agent inducing rapid tumour shrinkage and reduction of plasma prolactin associated with restoration of anterior pituitary function and cranial nerve function. The overall results in this small series are comparable to the best results obtained with oral bromocriptine treatment (van't Verlaat et al. 1986). Although other authors report a very good tolerability for Parlodel LAR, the initial adverse reactions to Parlodel LAR in 2 out of 5 patients in our study are relatively severe when compared with the results of oral bromocriptine treatment (van't Verlaat et al. 1986). This might be explained by the rapid rise of plasma bromocriptine levels to high values, reaching a maximum 3 hours after the im injection of Parlodel LAR (Lancranjan et al. 1987). It is concluded that long-acting repeatable bromocriptine is a useful alternative to oral treatment of patients with prolactinomas, especially in those patients with compliance problems on oral bromocriptine therapy. Treatment of patients with macroprolactinomas using Parlodel LAR may be continued indefinitely; alternatively, progressive tumour shrinkage may make these tumours amenable to radiotherapy or transsphenoidal surgery.

References


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