Long-term treatment of acromegalic patients with repeatable parenteral depot-bromocriptine

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Summary. We studied the efficacy and tolerability of a repeatable long-acting parenteral depot-bromocriptine preparation (Parlodel LAR) in 14 acromegalic patients, 10 of whom had received oral bromocriptine therapy previously, 2 of them showing intolerance to oral bromocriptine. Patients received i.m. injections of 50-100 mg depot-bromocriptine at 4-week intervals for 3-24 months (median 6). Growth hormone profiles were assessed by four daily samples at 4-week intervals. Main daily growth hormone levels decreased from 52.1±12.3 μg/l (mean±SEM) to 19.4±4.7 μg/l on the day of injection. In 6 patients, growth hormone values were lowered by more than 50%, whereas IGF-I levels decreased only slightly and growth hormone values during the oral glucose tolerance test remained non-suppressible. Tumour sizes were not affected. Two women became pregnant and were delivered of healthy babies. Side-effects typical of bromocriptine occurred frequently on the days of injection and diminished in most patients after 2 months of therapy despite increasing dosage. Compared with previous oral bromocriptine therapy, 9 of 10 patients preferred the depot preparation, whereas the reduction of growth hormone levels was similar during both treatments. In conclusion, depot-bromocriptine should be considered for acromegalic patients intolerant to oral bromocriptine.

Key words: Depot-bromocriptine – Acromegaly – Pregnancy

Pituitary surgery and irradiation are the main therapeutic options for the treatment of acromegaly. However, an appreciable number of patients do not achieve cure with either or both of these therapies [5, 15]. Therefore, drug treatment has remained a cornerstone in the therapy of hypersonomatropism. Oral therapy with the dopaminergic agent bromocriptine (br.) has been widely used since 1974, although normalization of growth hormone (GH) and shrinkage of the pituitary adenoma are rare [10, 17]. Limitations of oral bromocriptine (oral br.) therapy are poor bioavailability, the need for intake several times daily and such side-effects as nausea, dizziness and orthostatic hypotension in an appreciable number of patients, especially at higher dosages [16].

A parenteral br. form for non-repeatable i.m. application has been used in 7 acromegalic patients and shown to lower GH levels [4, 6]. Recently, a repeatable long-acting parenteral br. preparation became available (Parlodel LAR, Sandoz, Basel, Switzerland). This depot formulation consists of 50 or 100 mg br. bound to microspheres of a polymer, DL-polyactid-co-glycolid glucose, suspended in a liquid vehicle. We studied the efficacy and tolerance of 4-weekly i.m. injections of depot-bromocriptine (depot-br.) in 14 acromegalic patients for 3-24 months (mean 10.4 months, median 6 months).

Subjects and methods

Nine women and five men with active acromegaly (aged 24–68 years, mean 46) gave their informed consent to participate in this study. The trial was approved by the local Ethical Committee. All patients presented with clinical symptoms (i.e. increased perspiration, soft tissue swelling, headache or joint pain) as well as elevated IGF-I levels and lack of suppression of serum GH below 2 μg/l during a 100 g oral glucose tolerance test (oGTT). Exclusion criteria were optic nerve involvement and severe cardiovascular, renal or hepatic disease. High-resolution computer tomographic (CT) and/or nuclear magnetic resonance (NMR) scans documented pituitary microadenomas (tumour size less than 10 mm) in 4 subjects and macroadenomas in
Table 1. Patient data and mean serum GH levels during previous oral br. therapy, before (I.0), on days 1 and 28 of months I and VI and on day 1 of the last month of treatment with depot-br.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>Tumour size</th>
<th>Oral br.</th>
<th>Serum GH (µg/l)</th>
<th>Last month (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I.0</td>
<td>I. 1</td>
<td>I. 28</td>
</tr>
<tr>
<td>1</td>
<td>25/F</td>
<td>MA</td>
<td>121</td>
<td>46</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>68/M</td>
<td>MA</td>
<td>48</td>
<td>115</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>51/M</td>
<td>MI</td>
<td>n.t.</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>58/M</td>
<td>MA</td>
<td>21</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>55/F</td>
<td>MA</td>
<td>26</td>
<td>73</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>39/F</td>
<td>MA</td>
<td>27</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>26/M</td>
<td>MA</td>
<td>72</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>50/F</td>
<td>MI</td>
<td>41</td>
<td>41</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>26/F</td>
<td>MA</td>
<td>13</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>60/F</td>
<td>MI</td>
<td>27</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>62/F</td>
<td>MA</td>
<td>170</td>
<td>38</td>
<td>26</td>
</tr>
<tr>
<td>12</td>
<td>29/F</td>
<td>MA</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>49/F</td>
<td>MI</td>
<td>170</td>
<td>38</td>
<td>26</td>
</tr>
</tbody>
</table>

a MA, macroadenoma; MI, microadenoma
b n.t., not tolerated

10 subjects (Table 1). One patient (no. 6) had a complete loss of gonadotrophin and a partial loss of corticotrophin function. In all other patients, normal pituitary function had been established by extensive endocrine evaluation.

The mean duration of acromegaly from diagnosis was 7 years (range 0–10 years). In one patient (no. 11), transphenoidal surgery had been performed 11 years before. Pituitary irradiation had not been performed in any of the patients. Previous oral br. therapy had been given to 8 patients, for 5 to 72 months (mean 22.1). In 2 patients (nos. 8, 11) intolerance to oral br. had been observed. Normalization of GH secretion had been achieved in none of the patients at the highest tolerated dose of oral br. (mean 10.3 mg per day; range 5–20 mg). Oral br. had been discontinued at least 2 weeks before study in all patients but 1 (no. 14). This patient stopped oral br. therapy only 2 days before the first injection. For him, average levels of a GH profile after a therapy-free interval of 1 week 1 month before were used as baseline values.

Patients received deep i.m. injections of 50 mg depot-br. at 08:00 h at 4-week intervals. The dosage of depot-br. was increased up to 100 mg in patients with a suppression of GH levels by less than 50% after 2 months of treatment. Subjects were observed as in-patients for 24 h following the first and for 12 h following subsequent injections. GH and PRL profiles (08:00, 12:00, 16:00, 20:00 h) and plasma IGF-I measurements (08:00 h), were performed on the day before the first injection and on days 1, 3, 7, 14 and 28 of the first month. GH and PRL profiles, IGF-I determinations, clinical evaluation for signs of acromegaly and routine blood chemistry were repeated on day 1 of subsequent months and on day 28 of the sixth month. Endocrine assessments, including an oGTT, a thyrotropin-releasing hormone (TRH) test (200 µg i.v.), a gonadotropin-releasing hormone (GnRH) test and high-resolution CT or NMR scan of the pituitary fossa, were performed a few days before treatment and on days 27 and 28, respectively, of the first and sixth months.

Subjects with suppression of GH by more than 50% following each injection were defined as responders, those with suppression by 25–50% as partial responders. Normalization of GH secretion was defined as suppression of GH levels below 2 µg/l at 120 min during oGTT accompanied by normal IGF-I values (2, 10, 13). A paradoxical response to TRH application was defined as an increase of GH values by more than 50% at 30 min after injection of 200 µg TRH. Serum GH (Pharmacia, Uppsala, Sweden; normal adult range: 0–5 µg/l; 1 µg/l = 2.56 mU/l) and plasma IGF-I (Nichols Institute, San Juan Capistrano, USA; normal adult range: 0–2.2 U·10^3/l; standard reference preparation: IGF-I 87/518) were determined by radioimmunoassay. Serum PRL was measured by immunoenzymetric assay (Serono, Coisins, Switzerland; normal ranges: <26 µg/l for women; <15 µg/l for men; 1 µg/l = 20 mU/l). Results are presented as mean ± SEM. GH levels were calculated as the mean of the concentrations at 08:00, 12:00, 16:00 and 20:00 h. GH levels on the day