Treatment of hyperprolactinaemic patients with pergolide

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Abstract. Eighteen hyperprolactinaemic patients were orally treated for up to 16 months with pergolide mesylate, a new potent long-lasting dopaminergic ergot derivative. In all cases, Prl normalization (< 25 ng/ml) was achieved at a once-a-day dose of 50–300 µg. All women recovered and/or exhibited normal menstrual function. Among the 6 women wishing to become pregnant, 4 of them conceived within 4 months; there were other causes for infertility than hyperprolactinaemia in the 2 other couples.

A macroprolactinoma man experienced important improvement in well-being as well as objective regression of his visual fields defect. This suggests a shrinkage effect of pergolide on the tumoural process. Another man regained normal potency and normal testosterone within 2 weeks.

While 10 patients were completely free of any side effect, 7 experienced transiently mild gastro-intestinal side effects or postural hypotension. Only one patient discontinued her treatment because of dizziness.

The present study demonstrates the high potency, the good tolerance and the excellent efficacy of pergolide in the treatment of hyperprolactinaemia.

We have previously reported (L'Hermite & Debusschere 1982) the sustained acute inhibition of prolactin (Prl) by pergolide, a new synthetic dopaminergic ergot alkaloid: a single 50 µg oral dose suppressed and normalized Prl levels for up to 48 h in 4 of the 5 hyperprolactinaemic women tested.

From these and other preliminary data (Callaghan et al. 1981; Franks et al. 1981) it was suggested that the advantages of a single daily administration and of rather low effective doses would improve the efficiency and the acceptability of the long-term medical treatment of hyperprolactinaemia.

Presently, we report the results of such a treatment with pergolide, for up to 16 months, in 17 out of 18 hyperprolactinaemic patients.

Patients and Methods

Eighteen hyperprolactinaemic patients (16 women aged 18 to 47 years and 2 men, aged 39 and 66 years) were treated orally with pergolide mesylate – (8ß)-8 [(methylthio)methyl]-6-propylergoline (Eli Lilly, Benelux).

Prominent clinical data are given in Table 1 for each patient. Twelve patients had been previously treated with bromocriptine; among them, two had undergone prior transsphenoidal selective adenomectomy. All the patients previously treated with bromocriptine were told to stop it at least 30 days before pergolide was started. No patient used any other drug known to influence Prl secretion. At the onset of pergolide, three women (Nos. 1, 3 and 12) were amenorrhoeic. Pregnancy was desired by 6 women. Both men were impotent at the onset of therapy and had low and even very low (No. 16) testosterone serum levels.

Prl levels were measured by radioimmunoassay using, as previously described (L'Hermite & Debusschere 1982) commercial Serono kits. Mean basal Prl ranged between 32 and 284 ng/ml (mean of 3 to 13 separate determinations).

High resolution computerized tomography (CT) scanning of the pituitary was performed in 17 patients (Table 1) on a Somaton II, with contrast and adjacent 2 mm thick slices. Accordingly, there were one macroprolactinoma with bulging of theellar diaphragma, 10
Table 1.
Prominent characteristics of the hyperprolactinaemic patients before pergolide therapy.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Initial clinical pattern</th>
<th>CT scan</th>
<th>Previous therapy</th>
<th>At onset of pergolide</th>
<th>Clinical status</th>
<th>Mean Prl ng/ml (n)</th>
<th>LH mIU/ml</th>
<th>FSH mIU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>F</td>
<td>Primary amenorrhoea</td>
<td>Normal</td>
<td>None</td>
<td>Primary amenorrhoea</td>
<td>50 (13)</td>
<td>5.6</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>F</td>
<td>Amenorrhea</td>
<td>EST</td>
<td>CB 154</td>
<td>Irregular cycles</td>
<td>47 (13)</td>
<td>7.2</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>F</td>
<td>Amenorrhoea</td>
<td>EST + micro?</td>
<td>None</td>
<td>Amenorrhoea</td>
<td>78 (13)</td>
<td>4.8</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>F</td>
<td>Amenorr-hoea</td>
<td>Micro</td>
<td>CB 154</td>
<td>Regular cycles</td>
<td>55 (13)</td>
<td>12.4</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>F</td>
<td>Amenorrhoea</td>
<td>Micro</td>
<td>Tx + CB 154*</td>
<td>Irregular cycles</td>
<td>106 (13)</td>
<td>5.2</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>F</td>
<td>Regular cycles</td>
<td>Micro</td>
<td>CB 154</td>
<td>Persistent infertility</td>
<td>36 (13)</td>
<td>11.0</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>F</td>
<td>Amenorr-hoea</td>
<td>Normal*</td>
<td>CB 154</td>
<td>Irregular cycles</td>
<td>50 (13)</td>
<td>6.1</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>F</td>
<td>Amenorr-hoea</td>
<td>Micro</td>
<td>CB 154</td>
<td>Oligomenorrhoea</td>
<td>41 (3)</td>
<td>13.3</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>F</td>
<td>Regular cycles</td>
<td>Micro</td>
<td>None</td>
<td>Regular cycles</td>
<td>32 (13)</td>
<td>11.3</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>26</td>
<td>F</td>
<td>Regular cycles</td>
<td>EST*</td>
<td>CB 154</td>
<td>Persistent infertility</td>
<td>39 (13)</td>
<td>12.9</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>32</td>
<td>F</td>
<td>Regular cycles</td>
<td>None</td>
<td>CB 154</td>
<td>Regular cycles</td>
<td>39 (13)</td>
<td>8.3</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>F</td>
<td>Amenorr-hoea</td>
<td>Micro</td>
<td>Tx + CB 154*</td>
<td>Post-partum amenorrhoea</td>
<td>182 (5)</td>
<td>6.1</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>35</td>
<td>F</td>
<td>Amenorr-hoea</td>
<td>Micro</td>
<td>CB 154</td>
<td>Irregular cycles</td>
<td>47 (3)</td>
<td>8.8</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>39</td>
<td>F</td>
<td>Amenorr-hoea</td>
<td>Micro</td>
<td>CB 154*</td>
<td>Breast-feeding</td>
<td>99 (3)</td>
<td>9.3</td>
<td>20.3</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>26</td>
<td>F</td>
<td>Amenorr-hoea</td>
<td>Normal</td>
<td>CB 154; DXM</td>
<td>Irregular cycles</td>
<td>95 (13)</td>
<td>7.0</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>66</td>
<td>M</td>
<td>Pituit. insuffic. VF defect</td>
<td>Macro</td>
<td>None</td>
<td>Pituit. insuffic. VF defect</td>
<td>284 (13)</td>
<td>1.7</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>46</td>
<td>F</td>
<td>Irregular cycles</td>
<td>Micro</td>
<td>None</td>
<td>Irregular cycles</td>
<td>53 (13)</td>
<td>3.8</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>39</td>
<td>M</td>
<td>Impotence</td>
<td>Micro</td>
<td>CB 154</td>
<td>Impotence²</td>
<td>200 (3)</td>
<td>4.4</td>
<td>9.3</td>
<td></td>
</tr>
</tbody>
</table>


1 One or several pregnancies occurred during treatment.

2 Not using high resolution scan.


1 Not using high resolution scan. 2 Impotence reappeared, together with hyperprolactinaemia, after CB 154 withdrawal.
microprolactinomas and 3 empty sella turcica (one with possible microprolactinoma); in the 2 previously operated patients, there was no evidence of tumour recurrence.

In the 4 other patients, hyperprolactinaemia had to be considered idiopathic.

Visual fields were normal in all patients except No. 16, who had a unilateral temporal superior defect, probably related to the bulging of the sellar diaphragma documented by the CT scan. This patient was the macroprolactinoma man that had suffered from complete pituitary insufficiency for 45 years; recently, he exhibited signs of tumoural expansion.

LH and FSH were measured by radioimmunoassay using IRE kits and expressed as mIU/ml in terms of the 2nd IRP of hMG. Basal levels are given in Table 1 and were normal, as well as the responses to 100 µg LRH iv, in all patients except case no 16. In this patient, gonadotrophins were very low and there was no response to LRH.

In 12 patients, blood samples were collected every 2–3 h for up to 48 h after the initial 50 µg pergolide dose. Thereafter the patients were told to take pergolide during the evening meal or, in case of side effects, immediately before retiring, with some food. Prl, determined 12 to 20 h after the previous pergolide intake, was then monitored every 5–15 days; the daily pergolide dose was eventually increased according to these results in order to reach normalization of Prl.

The protocol has been approved by the Ethical Committee of the University School of Medicine.

Results

Prolactin levels

In all cases, normalization (< 25 ng/ml) of Prl secretion was achieved (Fig. 1); in 9 patients, it was already achieved after the initial 50 µg dose. The 9 other patients required a proper dosage increase to 100 (n = 5), 150 (n = 1), 200 (n = 2) or even 300 µg (n = 1) daily; the time required for Prl normalization in these patients was 10 days to 18 weeks (Table 2). Prl levels remained thereafter suppressed during continued therapy, up to 16 months. However, one patient (No. 9) decided for personal convenience to undergo surgery after 3 months and thus discontinued therapy at that time.

Clinical results

The 3 women with secondary amenorrhea (Nos. 3 and 12) or oligomenorrhea (No. 8) at the onset of pergolide administration, regained menses within 3 to 6 weeks. The woman with primary amenorrhea (No. 1) experienced her first menstruation after 11 months of treatment, although her Prl had been suppressed since the first drug intake. During chronic pergolide use, all the other women exhibited ovulatory cycles, as documented by elevated progesterone levels.

Out of the 6 women wishing a pregnancy, 4 of them conceived. One and 3 months, respectively, after Prl normalization were required in cases Nos. 7 and 15. It should be mentioned that patient No. 7 received, in addition to pergolide, clomiphene plus hCG right at the time at which Prl had finally become normal. Patient No 4 became pregnant 4 months after withdrawal of her intrauterine device. Because of absent sperms at repeated post-coital tests, Case No. 10 required donor artificial insemination and became pregnant in the first cycle.

As to the men, case No. 18 regained normal potency and normal testosterone within 2 weeks. Patient No. 16 experienced a marked improvement
in general well-being as well as disappearance of his visual field defect within 3 months of treatment. However, there was no increase of his testosterone level despite a slight improvement of his basal gonadotrophin levels.

Side effects (Table 2)

Ten patients were completely free of any side effect. Five patients experienced transiently (1–20 days) slight gastro-intestinal side effects (nausea or vomiting). Three other patients experienced dizziness and one of them decided that she could not tolerate it and discontinued the treatment after 2 weeks; the latter patient has also been the only one to complain of nasal stuffiness.

Discussion

Our data confirm and extend the preliminary evaluations of pergolide treatment that were reported by Callaghan et al. (1981) and Franks et al. (1981) in, respectively, 3 hyperprolactinaemic women treated for 90 days and 10 hyperprolactinaemic patients treated for 3 to 6 months.

Pergolide, on a once-a-day administration basis for up to 16 months, proved to be an effective treatment of hyperprolactinaemia and of related clinical symptoms in all patients. Thus, all chronically treated women recovered or exhibited normal menstrual function. Four of the 6 women wishing a child conceived; in the 2 other cases, there were
obvious additional causes for couple infertility: the age of the woman (41 years old) or severe oligo-asthenospermia.

Both men, exhibiting incidentally the highest basal Prl levels, required a high pergolide dose (100–200 µg daily) and up to 7 weeks before restoration of normal Prl levels. On the contrary, there was, in women, no clearcut relationship between initial Prl values and neither the dose nor the delay required. The male patient with normal pituitary gonadotrophin reserve regained normal potency while the macroprolactinoma patient with long-lasting pituitary insufficiency experienced a marked subjective improvement as well as objective regression of his visual field defect. This suggests a shrinkage effect of pergolide on the tumoural process. Such an effect of dopaminergic drugs has indeed been repeatedly observed with bromocriptine (Thornor et al. 1980) and recently documented, using metrizamide cisternography, in 2 men with large prolactinoma on pergolide treatment (Kendall-Taylor et al. 1982).

It is noticeable that more than half of the patients did not experience any side effects; with the exception of one drop-out for intolerable dizziness, side effects were mild and quite transient. This compares favourably to bromocriptine use. The present study demonstrates the high potency, the good tolerance and the excellent efficacy of pergolide in the treatment of hyperprolactinaemia. Furthermore, the once-a-day schedule of administration did indeed improve considerably over bromocriptine the patient's acceptability of chronic long-term therapy.

**Acknowledgments**

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**References**


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