No effect of treatment with sodium valproate on plasma growth hormone in bromocriptine unresponsive acromegaly

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Abstract. Administration of sodium valproate for 6 months at a dose of 300 mg three times daily to 7 bromocriptine unresponsive acromegalic patients who all but one had been treated with pituitary surgery and/or radiotherapy in the past did not result in a significant reduction of the plasma growth hormone (GH) level or in any clinical improvement. It is concluded that sodium valproate is not suitable for the treatment of acromegalic patients who do not show a favourable response to bromocriptine.

The dopamine agonist bromocriptine is a well-known adjunct in the treatment of patients with acromegaly by surgery and/or external pituitary irradiation but the drug is not always effective (Vance et al. 1984).

Evidence has been reported to support both a stimulatory and inhibitory role of gamma amino butyric acid (GABA) in growth hormone (GH) regulation. Administration of baclofen, a GABA derivative, caused acute GH release in man (Koulu et al. 1979). However, these results are at variance with those of another report showing that daily administration of baclofen for 4 days decreased the GH response to hypoglycaemia and to arginine infusions (Cavagnini et al. 1977).

The present study was designed to investigate whether treatment with the GABA transaminase inhibitor sodium valproate affects the plasma GH levels in acromegalic patients who do not respond to bromocriptine.

Patients and Methods

Seven acromegalic patients, 4 males and 3 females, aged 35–68 years (mean: 48 years) were studied. One patient was yet untreated, 2 had been treated with external irradiation, 2 with pituitary surgery and 2 with both surgery and external irradiation. Four patients had partial or complete pituitary insufficiency despite persistent acromegaly; all of them received appropriate hormonal replacement. They all showed clinical activity of acromegaly and plasma GH levels did not fall to 4 mU/l or less after a 75 g glucose load.

All patients had been shown to be bromocriptine unresponsive during treatment with 20–60 mg bromocriptine daily for a period of at least 6 months; in all cases the decrease of plasma GH was <50%. After chronic bromocriptine therapy had been discontinued for at least 2 months treatment with sodium valproate 300 mg three times daily was instituted. This therapy was given for a period of 6 months.

Mean plasma GH levels, obtained by averaging plasma GH levels at 08.30 h (fasting), 11.00 h, 13.00 h, 15.00 h, 17.00 h and 19.00 h were determined before treatment, after 3 and after 6 months during continued administration of sodium valproate.

Plasma GH was measured by radioimmunoassay as reported before (Nortier et al. 1984).

Results

Table 1 summarizes the effect of chronic therapy with sodium valproate on the mean plasma GH
levels during the day. In no patient a significant decrease of plasma GH concentrations was found and there was no subjective clinical improvement in any of the patients. The mean plasma GH levels decreased between 5 and 26% (mean 16%) when the values after 6 months were compared with those before treatment.

Discussion

The present study demonstrates that treatment with sodium valproate at doses of 300 mg three times daily for a period of 6 months did not result in any major reduction of the mean plasma GH level during the day in 7 bromocriptine unresponsive patients with acromegaly, who all but one had been treated with pituitary surgery and/or radiotherapy in the past. The observed changes of the plasma GH levels can probably be considered as spontaneous variations of the plasma GH concentrations. These results suggest that the endogenous GABA-ergic system is unable to alter GH secretion in bromocriptine unresponsive acromegaly. This might be due to a defect of the GABA-ergic system, an alteration of the GABA receptor system at the pituitary level or due to the previous therapy with surgery and/or radiotherapy.

In addition, no improvement of subjective symptoms of acromegaly was noted. In a previous study we demonstrated a good correlation between subjective and objective changes of clinical activity such as glucose tolerance and ring size (Nortier et al. 1985).

It may be that treatment with this neuropharmacological drug requires more time to exert an effect or that the dosage was too low, but in patients with Nelson's syndrome a lower dosage, 200 mg three times daily, caused a significant decrease of ACTH levels after a treatment period of 3–5 weeks (Jones et al. 1981). Nor can it be excluded that untreated acromegalic patients or acromegalics who respond favourably to chronic bromocriptine therapy with decreases of mean plasma GH levels of more than 50%, respond favourably to chronic treatment with sodium valproate. However, no fundamental difference has been found in the neuropharmacological regulation of GH secretion between untreated and unsuccesfully treated patients or between bromocriptine responsive and bromocriptine unresponsive patients with acromegaly. It is concluded that sodium valproate is not a suitable alternative to bromocriptine in acromegalic patients who do not respond to bromocriptine therapy.

Table 1.
Effect of chronic therapy with sodium valproate on mean plasma GH levels during the day.

<table>
<thead>
<tr>
<th>Patient</th>
<th>No.</th>
<th>Previous therapy</th>
<th>B (range)</th>
<th>D* (range)</th>
<th>D** (range)</th>
<th>ΔGH** (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ros</td>
<td>1</td>
<td>TSS, 1971</td>
<td>144 (93–240)</td>
<td>121 (99–130)</td>
<td>122 (95–160)</td>
<td>-15</td>
</tr>
<tr>
<td>Lok</td>
<td>2</td>
<td>TSS, 1971</td>
<td>98 (65–120)</td>
<td>73 (56–90)</td>
<td>73 (50–80)</td>
<td>-26</td>
</tr>
<tr>
<td>Pel</td>
<td>3</td>
<td>TSF, 1966</td>
<td>25 (18–36)</td>
<td>20 (18–23)</td>
<td>19 (17–23)</td>
<td>-24</td>
</tr>
<tr>
<td>Dijk</td>
<td>4</td>
<td>None</td>
<td>19 (14–27)</td>
<td>17 (9–35)</td>
<td>18 (8–40)</td>
<td>-5</td>
</tr>
<tr>
<td>Mas</td>
<td>5</td>
<td>Irr, 1976</td>
<td>13 (10–16)</td>
<td>15 (14–15)</td>
<td>12 (10–13)</td>
<td>-8</td>
</tr>
<tr>
<td>Goe</td>
<td>6</td>
<td>Irr, 1979</td>
<td>5 (4–6)</td>
<td>5 (4–5)</td>
<td>4 (3–4)</td>
<td>-20</td>
</tr>
<tr>
<td>Tan</td>
<td>7</td>
<td>Irr, TSS 1980</td>
<td>6 (5–7)</td>
<td>6 (3–7)</td>
<td>5 (4–5)</td>
<td>-17</td>
</tr>
</tbody>
</table>

Mean change ± SD
-16 ± 8

1 TSS, transphenoidal surgery; TSF, transfrontal surgery; Irr, external irradiation.
B before treatment with sodium valproate.
D during treatment with sodium valproate. * 3 months and ** 6 months after initiation of therapy.

References


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