initiated. More training of professionals working in the community is required to improve effectiveness of programmes to identify AD at a stage where treatment with a cholinesterase inhibitor can be optimised. Despite Wilkinson’s concerns (Wilkinson, 2002) extracts showing the older ‘Iris’ could be a valuable educational tool.

REFERENCES

PETER J. CONNELLY
Department of Psychiatry
University of Dundee
Perth, UK
RICHARD ATHAWES
Department of Psychiatry
Grampian Primary Care NHS Trust
Royal Cornhill Hospital
Aberdeen, UK
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/gps.725

Acute akinetic crisis with marked cognitive impairment due to Valproate treatment

Dear Editor

Valproic acid (VPA) is a commonly used mood stabilizer and albeit it is usually well tolerated, there is increasing evidence for CNS side effects especially in the presence of pre-existing brain pathology or co-medication. These risk factors are more frequent in geriatric patients, so that VPA may cause problems especially in this population. Among the published side effects of VPA, extrapyramidal syndrome (EPMS) (Armon et al., 1996; Wils and Goluke-Willemse, 1997; Onofrj et al., 1998) and cognitive decline (Zaret et al., 1986) appear to be more common than expected from literature, yet systematic studies are lacking and little is known about confounding factors. Here, we report on a case in which both EPMS and cognitive impairment acutely developed on VPA dose increase.

Ms P., a 62-year-old lady, was admitted for the first time at the age of 52 due to depressive mood. Lithium was prescribed and well tolerated. In 2000, she developed dysarthria, hypokinesia and ataxia; cranial CT revealed several older vascular lesions. One year later, she was readmitted for treatment of depression; slight cognitive deficits but no motor symptoms were noted. Symptoms improved upon administration of mirtazapine, reboxetine, olanzapine, lithium and VPA (600 mg/d). No side effects were reported.

As Ms P. continuously experienced depressive episodes, she was referred to our department. On admission, she had neither cognitive-mnestic deficits nor motor symptoms apart from a history of occasional falls. Lithium was in the therapeutic range, while VPA was sub-optimal (Table 1), so that it was increased to 1200 mg/d within 10 days. At the fifth day, rigor and hypokinesia were reported. Seven days later, her situation rapidly deteriorated resembling akinetic crisis: Ms P. was stuporous and somnolent, displayed marked rigidity, cog-wheel phenomenon and generalized tremor. Spontaneous movements were sparse and slowed, as was her dysarthric speech. Cognitive deficits were prominent in that she was, for

<table>
<thead>
<tr>
<th>Scene number</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

example, unable to perform simple mathematical tasks and to memorize single words; she was disoriented and perseverated. Her mood was neither depressed nor anxious. Cranial CT as well as MRI showed no acute changes, but older vascular lesions predominantly in the form of lacunary infarctions located in the white matter, basal ganglia and brain stem. Risk factors included mild carotid stenosis, high blood pressure, sporadic atrial fibrillation and homocysteinemia. Additionally, MRI displayed signs of normal pressure hydrocephalus. On lumbar puncture, liquor pressure was normal; tau protein (379 ng/l; normal range < 252 ng/l) and amyloid-β42 (1118 ng/l; normal range > 643 ng/l) argued for a neurodegenerative disorder. Blood analysis revealed ammonemia, therapeutic VPA and slightly elevated lithium levels (Table 1). All psychotropic medication was immediately withdrawn. Thereafter, Ms. P.’s condition steadily improved and ammonium levels normalized (Table 1). From days 4 to 7, she received supportive amantadine treatment (200 mg/d) for her motor symptoms, but no other psychotropic medication. At day 7, Ms P. had no gross cognitive impairments (MMSE, 25 points) and, even after amantadine was tapered, no motor symptoms.

Syndromally, Ms P.’s condition resembled akinetic crisis, accompanied by cognitive deficits with disorientation, similar to transient amential syndrome. In our opinion, the reason was most likely VPA dose increase causing hyperammonemia, a known side effect (Eze et al., 1998). We regard lithium side effects as complicating, but not causal in our case, as proposed similarly by Wils and Golüke-Willemsen, who reported on a patient developing EPMS when VPA was given additionally to lithium (Wils and Golüke-Willemsen, 1997).

There are several reports of cognitive or motor problems caused by VPA (Zaret et al., 1986; Armon et al., 1996; Wils and Golüke-Willemsen, 1997; Onofrj et al., 1998). However, in all reported cases, EPMS and cognitive impairment had slow, insidious onset and resolved within weeks upon VPA discontinuation in striking contrast to our case, in which symptoms both developed and resolved acutely within days. We propose that this was due to the pre-existing brain pathology and psychotropic side medication. The pathophysiology of VPA side effects might include ammonemia, causing both EPMS and cognitive problems, albeit typical symptoms like asterixis were not present. In conclusion, we argue that VPA in elderly, multimorbid patients with organic brain diseases should be used cautiously, and that such patients should be carefully evaluated for VPA side effects.

REFERENCES


ANDREAS REIF, BERNHARD HAMELBECK, AND BRUNO PFUHLMANN

Department of Psychiatry, Julius-Maximilians-University of Würzburg, Würzburg, Germany

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI: 10.1002/gps.729

Table 1. Serum levels of ammonium (normal range 27–102 μg/dl), lithium (therapeutic range 0.6–1.0 mmol/l) and VPA (therapeutic range 50–100 mg/l). Day 0 denotes the day of akinetic crisis as a side effect of VPA medication. VPA, valproic acid; n.d., not determined