Safety of expanded therapeutic range of valproic acid

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BACKGROUND:

- Therapeutic drug monitoring (TDM) of total valproic acid (TVPA) concentrations is challenging for its variable pharmacokinetics.
- In our service the TVPA is normalized according to serum albumin (NTVPA).
- The accepted serum concentration range is 50-150 mg/L. Higher concentrations could be useful in complicated seizures such as status epilepticus (SE).
- The aim of this study was to evaluate the security of high NTVPA levels.

MATERIAL AND METHODS:

- Retrospective observational study in patients treated with VPA included in TDM program with a minimum of two NTVPA levels over 150 mg/L separated by at least 7 days.
- NTVPA was calculated from TVPA according to serum albumin*:

\[
\text{NTVPA} = \frac{(\text{TVPA} \times \text{unbound fraction})}{6.5}
\]

RESULTS:

- Demographics
  - 24 patients were included (13 men), followed for a mean of 32 days [7-156].
  - Mean age was 62 years [29-86].
  - 16 (67%) patients were admitted to intensive care units.

- Pharmacological treatment
  - 140 TVPA analyses (6 analyses/patient [2-13]).
  - 14 (58%) were treated for status epilepticus.
  - The results of the TVPA and NTVPA, albumin serum concentrations are shown in Table 1 and Graph 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Max</th>
<th>Min</th>
<th>P25</th>
<th>P75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/L)</td>
<td>25</td>
<td>38</td>
<td>18</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>TVPA (mg/L)</td>
<td>64</td>
<td>140</td>
<td>32</td>
<td>53</td>
<td>77</td>
</tr>
<tr>
<td>NTVPA (mg/L)</td>
<td>203</td>
<td>377</td>
<td>151</td>
<td>174</td>
<td>245</td>
</tr>
</tbody>
</table>

- Most of the patients (n=17) received a combined therapy with one or more of the following antiepileptic drugs: phenytoin, levetiracetam, oxcarbazepine, carbamazepine, clonazepam, phenobarbital and lacosamide.

- Efficacy variables
  - 2 patients had clinical seizures despite high levels of NTVPA, both confirmed by EEG.

CONCLUSIONS:

1. Expanded therapeutic range NTVPA levels may be a safe option to treat complicated seizures such as status epilepticus
2. According to our results, we could propose 245 mg/L as an upper level of therapeutic range of NTVPA with a close monitoring of platelet count and liver enzymes.

Bibliography: