Differential effects on attention over 24 weeks of a NMDA antagonist versus carbamazepine in paediatric epilepsy patients

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BACKGROUND

- Remacemide hydrochloride, a low-affinity NMDA receptor antagonist with sodium channel-blocking activity, was compared to carbamazepine in a Phase III, double-blind, parallel group, sequential design in newly diagnosed, previously unmedicated, epilepsy patients aged 12 to 17 years.
- The trial planned to have 1000 completed patients and was conducted in 21 countries in Europe, Latin America and Australia.
- This is the first analysis of the attentional effects in the subpopulation aged 12 to 17 years.

METHODS

- 92 first time diagnosis previously unmedicated epilepsy patients aged 12 to 17.
- Randomized to either Carbamazepine or Remacemide.
- Patients were trained on the CDR system twice during the screening period.
- Testing was conducted at baseline prior to dosing, at repeated at 8 and 24 weeks.
- Change from pre-dose data were analysed using mixed model repeated measures, fitting fixed terms for treatment as a between group factor and time as a within group factor.

DISCUSSION

- In this population aged 12 to 17 remacemide generally improved performance over pre-dose levels, whereas carbamazepine worsened it.
- The benefits of remacemide on Power of Attention and the speed scores from the 3 tasks which contribute to this measure all showed large effect sizes.
- The ability to sustain attention as measured by the vigilance signal detection index showed a medium effect size benefit of remacemide.
- At baseline these patients were 121 ms poorer than age-matched controls (effect size 0.629).
- Remacemide reduced this deficit by 67%.
- Carbamazepine increased the deficit by 38%.

REFERENCES


RESULTS

Overall Changes for 24 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Carbamazepine</th>
<th>Remacemide</th>
<th>Delta</th>
<th>p</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigilance %Hits</td>
<td>-0.03*</td>
<td>0.01</td>
<td>0.035</td>
<td>0.53</td>
<td></td>
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<tr>
<td>Vigilance SI</td>
<td>8</td>
<td>28*</td>
<td>0.0017</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Power of Attention</td>
<td>42*</td>
<td>-75*</td>
<td>117*</td>
<td>0.0001</td>
<td>1.03</td>
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</tbody>
</table>

CONCLUSIONS

- In this study a low-affinity NMDA receptor antagonist served to reduce substantially a disease related impairment to focussed attention and information processing in children aged 12 to 17, whereas a widely used and more effective seizure control agent increased the deficit.
- The effects ranged from medium to large effect sizes and were thus clinically relevant.
- Overall, in this young and maturing population, remacemide despite producing less seizure control than carbamazepine, had a protective and restorative effect on the cognitive impairment associated with the disease.
- Thus other novel partial NMDA antagonists, if more effective in seizure control than remacemide and having such a favourable effect on attention and information processing, may be more attractive therapeutic alternatives to compounds such as carbamazepine.