A randomized clinical trial of histamine 2 receptor antagonism in treatment resistant schizophrenia

BACKGROUND

- Histamine has received relatively little attention in clinical studies of psychiatric disorders even though it has important functions as regulator of several other key neurotransmitters.
- The most direct human data on the role of histamine in psychosis shows that patients with schizophrenia have lower histamine H1 receptor levels [1].
- Since a case report in 1990 [2] of an effect of the H2 antagonist famotidine on negative symptoms in schizophrenia, some open-label trials have been performed, but no randomized controlled trial.
- Recently, it was shown that clozapine is a full inverse agonist at the H2 receptor [3].

METHODS

- We performed a researcher-initiated, academically financed, double-blind, placebo controlled, parallel group, randomized trial with the histamine H2 antagonist famotidine in treatment resistant schizophrenia.
- The subjects were all treatment resistant subjects who had a significant level of residual symptoms.
- The subjects (N=30) were randomized to have either high-dose famotidine (100 mg twice daily, N=16) or placebo (N=14) orally, added to their normal treatment regimen for four weeks.
- Before the first assessment there was a one-week placebo run-in. After the trial phase there was a one-week wash out before the last assessment.
- The subjects were followed weekly for the Scale for the Assessment of Negative Symptoms (SANS) as well as Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression-scale (CGI).
- This trial was registered at ClinicalTrials.gov (NCT00564175).

RESULTS

- All of the subjects in the intervention group showed significantly reduced symptomatology while the symptoms of those in the placebo group did not show any significant change.
- In the intervention group the SANS score was reduced by 5.3 points while in the placebo group the SANS score was virtually unchanged (p=0.134).
- PANSS Total score and the General sub-score as well as the CGI showed significantly (p<0.05) greater change in the intervention group than in the placebo group.
- It is noteworthy that the reduction of symptoms started from the baseline measurement and was consistent all the way to the endpoint.

CONCLUSIONS

- This is the first placebo controlled, randomized clinical trial showing a beneficial effect of histamine H2 antagonism on the psychopathology in treatment resistant schizophrenia.
- The effect of famotidine was clinically relevant, with reduction of around 10% in symptomatology in the treatment group during the four-week trial and virtually no change in the placebo group.
- Our results suggest that a H2 receptor antagonist has antipsychotic properties and may provide a new potential pharmacological approach to the treatment of patients with schizophrenia who have not responded well enough to presently available treatments.
- In summary, our study shows that the histamine system in the brain offers a potential drug development target in psychosis.

![Change in the outcome measures from week 2 (baseline) to week 6 (endpoint).](image)

**Change in the PANSS Total scores from baseline (week 2).** Groupwise mean values and SEM error bars.

<table>
<thead>
<tr>
<th></th>
<th>Famotidine group</th>
<th>Placebo group</th>
<th>Difference between groups</th>
<th>p-value</th>
<th>Effect size (Cohen’s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PANSS Total</strong></td>
<td>-9.13 (-11%)</td>
<td>-0.57 (-1%)</td>
<td>-8.56 (-10.8%)</td>
<td>0.041</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>PANSS Positive</strong></td>
<td>-2.69 (-14%)</td>
<td>-0.71 (-3%)</td>
<td>-1.98 (-2.4%)</td>
<td>0.188</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>PANSS Negative</strong></td>
<td>-1.81 (-9%)</td>
<td>-0.29 (-1%)</td>
<td>1.52 (1.9%)</td>
<td>0.238</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>PANSS General</strong></td>
<td>-4.63 (-12%)</td>
<td>0.43 (+1%)</td>
<td>5.06 (+5.9%)</td>
<td>0.022</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>CGI</strong></td>
<td>-0.75 (-7%)</td>
<td>0.36 (+4%)</td>
<td>1.11 (+1.3%)</td>
<td>0.001</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Change in the outcome measures from week 2 (baseline) to week 6 (endpoint).

References:

Disclosures: Author ZH has been in research collaboration with Novo Nordisk, Johnson & Johnson and Ely Lilly; and has been a member of the expert advisory group for Alkab. Author PP has received lecture and consultation compensation from Abbott Laboratories and research grants from Johnson & Johnson. He has had research collaboration with Orion Pharma and he owns stock of Orion Pharma and Delikon Biotechnology. The other authors declare no conflict of interest.