Cluster headache: trial of a combined histamine H1 and H2 antagonist treatment

DAVID RUSSELL

From the Department of Neurology, Rikshospitalet, Oslo University Hospitals, Oslo, Norway

SUMMARY Fifteen patients with symptomatic cluster headache participated in a double-blind crossover trial of a combined histamine H1 and H2 antagonist treatment. The trial lasted six weeks. There was no significant improvement on active treatment as regards mean number of headache attacks per week, intensity, or duration of attacks. These results suggest that histamine does not play a significant role in the pathogenesis of cluster headache.

There is evidence that histamine is implicated in the pathogenesis of cluster headache. Spontaneous attacks in some patients are associated with increased urinary excretion of histamine (Sjaastad and Sjaastad, 1970), and an increase in whole blood histamine (Anthony and Lance, 1971). Studies with histamine H1 and H2 antagonists in the monkey have shown that the vasodilator effect of histamine on the external carotid artery is mediated predominantly by H2 receptors, whereas in the internal carotid artery both H1 and H2 receptors are involved (Lord et al., 1976). The probability of a similar distribution of histamine receptor sites in man suggested, therefore, that if histamine is involved in the pathogenesis of cluster headache, a therapeutic effect was most likely with a combined histamine H1 and H2 antagonist treatment.

Patients and methods

Fifteen symptomatic adult patients, aged 33–69 years (mean 49 years), suffering from cluster headache as defined by the “ad hoc” committee on the classification of headache (1962), were included in a double-blind trial. Patients were allocated to one of four treatment schedules. In two of the schedules, active treatment and placebo were crossed over at weekly intervals, whereas in the other two, each treatment was continued for two weeks at a time. Active treatment consisted of cimetidine 400 mg three times a day after meals, and 800 mg at bedtime, together with chlorpheniramine 4 mg three times a day and 8 mg at bedtime. The duration of the study was six weeks. Patients were asked to record the incidence, duration, and severity of their headache attacks on a diary card. They were also asked to restrict all other medication to a simple analgesic and to note their intake of this medication on the diary card. Patients were seen at weekly intervals for assessment.

Results

Twelve of the 15 patients entering the trial completed the six weeks treatment schedule. Two patients were withdrawn because of drowsiness; one was receiving placebo and one active treatment at the time of withdrawal. A third patient developed a transient erythematous skin rash during treatment with cimetidine and chlorpheniramine, and was withdrawn. Otherwise no significant side effects were recorded.

As regards mean number of headache attacks per week, seven of the 12 patients completing the

<table>
<thead>
<tr>
<th>Patient</th>
<th>Placebo</th>
<th>Cimetidine and Chlorpheniramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.7</td>
<td>9.5</td>
</tr>
<tr>
<td>2</td>
<td>2.3</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>4.7</td>
<td>8.7</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>3.5</td>
</tr>
<tr>
<td>5</td>
<td>8.5</td>
<td>5.5</td>
</tr>
<tr>
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<td>3.0</td>
<td>2.5</td>
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<tr>
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<tr>
<td>12</td>
<td>10.7</td>
<td>8.7</td>
</tr>
</tbody>
</table>
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trial improved on cimetidine and chlorpheniramine whereas five deteriorated (see Table). This difference was not statistically significant (P = 0.3, Student’s t test and null hypothesis). There was also no significant difference as regards mean number of analgesics used per week, intensity, or duration of headache attacks. In three patients (cases 2, 4, 8), the number of headache attacks per week decreased, irrespective of treatment, suggesting that they had a spontaneous remission, during the trial period.

Discussion

In this trial, a combination of histamine H1 and H2 antagonists was found to be unsuccessful as a treatment for cluster headache. These results suggest that histamine does not play a significant role in the pathogenesis of this condition. They cannot, however, exclude such a role as it is possible that the receptors involved differ in their affinity for the two antagonists so that the doses studied were insufficient to produce a clinical effect. Alternatively, the histamine antagonists studied may be ineffective against so-called induced histamine (Kahlson and Rosengren, 1971) formed and active at the cellular level, or undiscovered histamine receptor sites may exist which are not blocked by either H1 or H2 receptor antagonists.

References


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D Russell

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