Effects of longterm treatment with acetazolamide in central sleep apnea

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Aim of the study
Aim of the present study was to evaluate the usefulness of a prolonged treatment with low dose acetazolamide in a group of highly selected patients with idiopathic central apnea syndrome. Previous reports have indicated that high dose acetazolamide reduces the number of central apneas (1), but was accompanied by rather severe acidosis and patients were followed only for one week.

Patients and methods
Patients were included if their central apnea index (CAI) ≥ 5 or their apnea-hypopnea index (AHI) ≥ 10 and their obstructive apnea index (OAI) < 5. Patients (n=14) were middle aged (48 ± 3 y), obese (BMI 32±2 kg/m²) and all had normal dynamic and static lung volumes (FEV₁=88±6 %Pred; TLC=99±4 %Pred). Selected patients then were included into the study protocol. At study day one (Night 2), patients underwent arterial blood gas analysis and the measurement of the hypercapnic ventilatory response (HCVR) according to the Read method (2). In the evening they received 250 mg acetazolamide 1 hour before sleep. In the morning blood gases and the measurement of the HCVR were repeated. Patients then were treated continuously for one month with acetazolamide (ACET) at night in the same dose (250 mg 1 hour before sleep). After one month they were once again studied during one night (Night 3). In the morning after night 3 blood gases and HCVR were also determined.
The breathing pattern is shown in Table 1.

Results

The breathing pattern is shown in Table 1.

Mean CAI during the selection night was 25.5 ± 6.8. After one month of chronic treatment with ACET CAI decreased significantly to 6.6 ± 2.9 (p<0.01). There were no significant changes in the number of obstructive apneas nor in the hypopnea index, but the AHI also decreased significantly after one month therapy. The mean apnea duration was not influenced (19.0 ± 1.1 s. to 17.2 ± 1.6 s) (p=0.38). Central apneas were often accompanied by changes in sleep stage and/or (micro) arousals. The number of arousals decreased from 62 ± 11 at night 1 to 40 ± 5 at night 3 (p=0.02). pH dropped already significantly after one night ACET therapy (from 7.41 to 7.37) and remained also significantly below control level after one month ACET therapy (7.39). Nevertheless the observed changes in pH only accounted for maximally 0.04. PaO2 increased very significantly from 77.0 ± 2.7 (Night 1) to 91.0 ± 2.4 (Night 3), whereas PaCO2 dropped significantly from 39.3 ± 0.4 (Night 1) to 36.4 ± 0.6 (Night 3). Bicarbonate decreased from 25.2 ± 1.1 (mean/SD) at N1 to

<table>
<thead>
<tr>
<th></th>
<th>CAI ± SEM</th>
<th>OAI ± SEM</th>
<th>HI ± SEM</th>
<th>AHI ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night 1</td>
<td>25.5 ± 6.8</td>
<td>3.5 ± 1.5</td>
<td>8.2 ± 2.2</td>
<td>37.2 ± 6.2</td>
</tr>
<tr>
<td>Night 2</td>
<td>13.8 ± 5.2</td>
<td>3.7 ± 1.8</td>
<td>9.4 ± 2.5</td>
<td>27.1 ± 5.6</td>
</tr>
<tr>
<td>Night 3</td>
<td>6.6 ± 2.9 *</td>
<td>0.3 ± 0.1</td>
<td>6.3 ± 1.6</td>
<td>12.8 ± 2.9 *</td>
</tr>
</tbody>
</table>

The number per hour of central apneas (CAI), obstructive apneas (OAI), hypopneas (HI) and apneas/hypopneas (AHI) for all study nights.

Night 1 = Selection Night; Night 2 = First study night after administration of 250 mg acetazolamide; Night 3 = Second study night after chronic treatment with acetazolamide for one month and without additional treatment with ACET the evening before the study night. Values are expressed as mean ± SEM. * p<0.01 compared to values during selection night

Table 1: Breathing pattern at inclusion and during all study nights.

Table 2: Hypercapnic ventilatory response during wakefulness before and during treatment with acetazolamide

<table>
<thead>
<tr>
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<th>SHCVR (l/min/mmHg)</th>
<th>IIHCVR (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night 1</td>
<td>2.32±0.28</td>
<td>41.0±0.9</td>
</tr>
<tr>
<td>Night 2</td>
<td>2.65±0.36</td>
<td>39.8±2.1</td>
</tr>
<tr>
<td>Night 3</td>
<td>2.66±0.41</td>
<td>32.7±3.8</td>
</tr>
</tbody>
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SHCVR = slope of the hypercapnic ventilatory response (l/min/mmHg); IIHCVR = intercept of the hypercapnic ventilatory response (mmHg). See further legend Table 2

Table 2: Hypercapnic ventilatory response during wakefulness before and during treatment with acetazolamide
21.8 ± 1.5 at N3. SaO₂ above 90% was observed during 87.3 ± 6.3 % (mean/SE) of TIB at N1 and during 91.0 ± 7.6 % of TIB at N3 (NS). Changes in HCVR are given in Table 2. There was no significant changes in the slope of the HCVR (ANOVA p=0.89). In all patients CO₂ drive was preserved.
The treatment with ACET was generally well accepted and tolerated. Some patients complained of mild paresthesias.

**Conclusion**

Patients with predominantly central sleep apnea syndrome benefit from a prolonged low dose treatment with acetazolamide. There is a significant reduction in the CAI without increase in OAI, whereas also pulmonary gas exchange during the daytime improves substantially. CO₂ drive during wakefulness in the patients recruited for this study was normal. The unmasking of a very sensitive CO₂ threshold during sleep (3) combined with an overall plant gain and decreased chemical drive during sleep probable represent the most important pathogenetic mechanism.

The interference of ACET with these mechanisms remains very controversial. Local changes at the level of the central chemoreceptors due to tissue brain acid-base changes are important (4). Different effects of carbonic anhydrase inhibition on the hypercapnic and hypoxic ventilatory responses between acute administration of ACET (only associated with local tissue changes in pH) and chronic ACET administration (associated also with changes in systemic pH) indicate that ACET can act not only by changes in systemic acid-base balance, but also by direct effects on chemoreceptors (4). ACET has also a depressant effect at the level of the peripheral chemoreceptors (4). ACET should be (re)considered as a valuable treatment for these patients whether or not in combination with other (less effective or more invasive) therapies.

**References**