Comparison of Acetazolamide and Medroxyprogesterone as Respiratory Stimulants in Hypercapnic Patients With COPD*

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Background: Acetazolamide and medroxyprogesterone acetate (MPA) are two respiratory stimulants that can be used in patients with stable hypercapnic COPD.

Design and methods: The effects of acetazolamide, 250 mg bid, and MPA, 30 mg bid, on daytime and nighttime blood gas values and the influences on the hypercapnic and hypoxic ventilatory and mouth occlusion pressure (P0.1) at 100 ms response were studied in a crossover design in 12 hypercapnic patients with stable COPD (FEV1, 33 ± 4% predicted [mean ± SEM]).

Results: Daytime PaCO2 decreased from 47.3 ± 0.8 mm Hg (placebo) to 42.0 ± 1.5 mm Hg during acetazolamide treatment (p < 0.05) and to 42.8 ± 1.5 mm Hg during MPA treatment (p < 0.05). Daytime PaO2 improved with acetazolamide from 65.2 ± 2.3 to 75.0 ± 3.0 mm Hg (p < 0.05), whereas no significant changes were seen with MPA. Mean nocturnal end-tidal carbon dioxide tension decreased with both treatments, from 42.0 ± 2.3 to 35.3 ± 2.3 mm Hg with acetazolamide (p < 0.05) and to 34.5 ± 0.8 mm Hg with MPA (p < 0.05). The percentage of time that the nocturnal arterial oxygen saturation was < 90% was reduced significantly with acetazolamide, from 34.9 ± 10.7% to 16.3 ± 7.5% (p < 0.05). Mean nocturnal saturation did not change with MPA. Resting minute ventilation increased significantly only with MPA from 9.6 ± 0.7 to 10.8 ± 0.8 L/min (p < 0.05). The slope of the hypercapnic ventilatory response did not change during acetazolamide and MPA therapy. The hypoxic ventilatory response increased from −0.2 ± 0.05 to −0.4 ± 0.1 L/min/% during acetazolamide (p < 0.05) and to −0.3 ± 0.1 L/min/% during MPA (p < 0.05). The hypoxic P0.1 response improved with acetazolamide treatment from −0.05 ± 0.008 to −0.15 ± 0.02 mm Hg/% (p < 0.05).

Conclusions: This study shows that acetazolamide and MPA both have favorable effects on daytime and nighttime blood gas parameters in ventilatory-limited patients with stable COPD. However, the use of acetazolamide is preferred because of its extra effect on nocturnal saturation.

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Key words: acetazolamide; COPD; hypercapnia; medroxyprogesterone acetate

Abbreviations: HCVR = hypercapnic ventilatory response; HVR = hypoxic ventilatory response; MPA = medroxyprogesterone acetate; PETCO2 = end-tidal carbon dioxide tension; P0.1 = mouth occlusion pressure; SaO2 = arterial oxygen saturation; T1 = start of the study; T2 = end of placebo treatment; T3A = after 2 weeks of treatment with acetazolamide plus placebo; T3M = after 2 weeks of treatment with medroxyprogesterone acetate plus placebo; T4A = again after 2 weeks of treatment with acetazolamide plus placebo; T4M = again after 2 weeks of treatment with medroxyprogesterone acetate plus placebo; V̇e = minute ventilation

Some patients with severe COPD become chronically hypoxic and/or hypercapnic as the disease progresses. In general, their prognosis is poor, as shown by Cooper and Howard,1 who analyzed patients with COPD retrospectively from the moment of death, and concluded that hypoxia as well as hypercapnia were signs of imminent death within 3 years. Moreover, Foucher et al2 found that the rate of death in patients with COPD receiving long-term...
oxygen therapy was higher in the hypercapnic group ($\text{PaCO}_2 > 43 \text{ mm Hg}$) as compared to the normocapnic group ($\text{PaCO}_2 < 43 \text{ mm Hg}$). Hence, hypercapnia itself is probably an independent poor prognostic factor, although this is not supported by all investigators. Treatment of hypoxia with supplemental oxygen improves survival, however, the degree of hypercapnia worsens in many patients during oxygen therapy, which may influence the prognosis. This hypercapnia is probably due to a combination of a slightly worsened ventilation/perfusion mismatch, initial carbon dioxide retention with oxygen-mediated blunting of the peripheral chemoreceptor drive, Haldane effect-related changes in carbon dioxide, and $\text{H}^+$ buffering by hemoglobin. During sleep, hypoxia and hypercapnia increase due to hypoventilation. This is caused by a diminished intercostal and accessory muscle function during rapid eye movement sleep stage, superimposed on a dysfunctional diaphragm. Also, low hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR) contribute to the nocturnal hypoventilation.

The respiratory stimulants medroxyprogesterone acetate (MPA) and acetazolamide may improve daytime and nighttime blood gas values in patients with COPD, although not all studies are consistent. Acetazolamide stimulates ventilation by inducing a metabolic acidosis. In a previous study, we found an increase in the slope of the HCVR in hypercapnic patients with COPD, in contrast to other studies in which only changes in intercept are shown. The effect of acetazolamide on the HVR is equivocal in various studies ranging from no change to an improvement.

Progesterone increases ventilation via progesterone receptors in the hypothalamus. Most human studies show an increase in HCVR during (synthetic) progestagens; however, the results on HVR are conflicting. The aim of the present study was to compare the effects of acetazolamide and of MPA on daytime and nighttime blood gas values as well as HCVR and HVR in chronic hypercapnic patients with COPD.

**Materials and Methods**

**Patients**

Nineteen hypercapnic patients with severe COPD (mean ± SEM age, 68 ± 2 years), as defined by the American Thoracic Society, were enrolled in this study. Patient characteristics are shown in Table 1. Inclusion criteria were as follows: optimal bronchodilator treatment, daytime $\text{PaCO}_2 \geq 45.0 \text{ mm Hg}$, no long-term oxygen treatment, and ability to lower the end-tidal carbon dioxide tension ($\text{PETCO}_2$) at least 7.5 mm Hg in a voluntary hyperventilation test, to establish the ventilatory pump reserve. Exclusion criteria were as follows: exacerbation of COPD within the last 3 months, abnormal renal and liver functions, use of respiratory stimulating drugs, and obstructive sleep apnea/hypopnea syndrome. Seven patients dropped out of the study after inclusion, because of an exacerbation, evenly distributed over both treatment modalities.

**Study Design**

In a double-blind, randomized, crossover study, the effects of acetazolamide and MPA treatment on daytime and nocturnal blood gas and ventilatory parameters were investigated. The design is shown in Figure 1. The patients were studied four times in 6 weeks, at the start of the study (T1), at the end of placebo treatment (T2), after 2 weeks of treatment with acetazolamide plus placebo (T3A [250 mg bid]) or MPA plus placebo (T3M [30 mg bid]), and again after 2 weeks of treatment with acetazolamide plus placebo (T4A) or MPA plus placebo (T4M) [Fig 1]. All patients received placebo from T1 to T2 to assess the intraindividual variability. Acetazolamide and MPA treatments were administered in identical capsules. Written informed consent was obtained from all patients, and the study was approved by the Hospital Ethics Committee.

**Daytime Measurements**

After each study night (at 9 AM), an arterial blood sample was obtained after 15 min of rest (Ciba-Corning 278 blood gas analyzer; Ciba-Corning, Houten, the Netherlands). Liver and renal functions were tested.

**Pulmonary Function Tests**

HCVR and HVR. HCVR was assessed by the steady-state method. The patient was connected to a closed spirometric circuit (Pulmotest; Godart; Bilthoven, the Netherlands) via a mouthpiece. A valve (model 2700; Hans Rudolph; Kansas City, MO) was placed in the system to maintain a one-way circuit. The $\text{PETCO}_2$ level was measured by a side-stream capnograph.

**Table 1—Characteristics at Start of Study**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Male/female sex, No.</td>
<td>8/4</td>
</tr>
<tr>
<td>Age, yr</td>
<td>68 ± 2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68 ± 3</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170 ± 3</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23 ± 1</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
<tr>
<td>Total lung capacity, % predicted</td>
<td>105 ± 5</td>
</tr>
<tr>
<td>Residual volume, % predicted</td>
<td>168 ± 14</td>
</tr>
<tr>
<td>FEV$_1$, L</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>% predicted</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>FEV$_1$/inspiratory vital capacity, % predicted</td>
<td>46 ± 3</td>
</tr>
<tr>
<td>Arterial blood gas analysis</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.01</td>
</tr>
<tr>
<td>$\text{PaO}_2$, mm Hg</td>
<td>66.0 ± 2.3</td>
</tr>
<tr>
<td>$\text{PaCO}_2$, mm Hg</td>
<td>47.3 ± 1.5</td>
</tr>
<tr>
<td>Base excess, mmol/L</td>
<td>3.9 ± 0.5</td>
</tr>
<tr>
<td>$\text{SaO}_2$, %</td>
<td>92.4 ± 0.8</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM unless otherwise indicated.
Inspiratory PCO₂ could be gradually raised by adjusting a three-way valve, partly short-circuiting the carbon dioxide absorber in the inspiratory limb of the circuit. Two different levels of PETCO₂ were studied: PETCO₂ at zero inspiratory PCO₂, and PETCO₂ at 7.5 to 11.3 mm Hg above the resting value. Both levels of PETCO₂ were maintained for at least 7 min. Oxygen was added to the system to keep the arterial oxygen saturation (SaO₂) level ≥ 90%. SaO₂ was measured with a pulse oximeter (Oxyshuttle; Sensor Medics; Anaheim, CA). At the end of each steady-state period of the HCVR ("high" PCO₂ level), an arterialized capillary blood sample was obtained. The steady-state relation of minute ventilation (VE) to PETCO₂ at constant end-tidal oxygen tension was considered to be linear down to the PETCO₂ axis:

\[ VE = S(PETCO₂ - B), \]
in which the parameter S is the carbon dioxide sensitivity of the peripheral and central chemoreflex loops, and the offset B is the apneic threshold or extrapolated PETCO₂ at zero ventilation. The mouth occlusion pressure (P₀) was measured during the final 2 min of each steady-state period at the two different levels of PETCO₂ using a solenoid valve, in the inspiratory part of the circuit.

The HVR was performed by inducing progressive hypoxia. PETCO₂ was maintained at the initial predrug level (placebo, T2) during all HVR tests, by adding carbon dioxide to the inspirate, when necessary. All patients started the test at an SaO₂ level of 98% by adding supplemental oxygen. Then, the oxygen supplementation was stopped and the HVR test was performed until the SaO₂ reached 80%, which took < 7 min.

**Spirometry:** FEV₁, inspiratory vital capacity, total lung capacity, and residual volume were measured with a wet spirometer and helium dilution technique (Pulmonet III; Sensor Medics), respectively. Reference spirometric values were derived from European Respiratory Society standards.²⁵

**Subjective Parameters:** After each study period, the dyspnea sensation was scored with the modified Medical Research Council scale.²⁶ Side effects of the drugs were noted.

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**Nocturnal Measurements**

Nocturnal SaO₂ was measured with a pulse oximeter. The baseline SaO₂ "awake" was defined as the mean SaO₂ during the first 15 min, when the patient was awake and in a supine position.²⁷ The PETCO₂ was measured by sampling air through a nasopharyngeal cannula (Mijnhart Capnolyser; Mijnhart; Bilthoven; the Netherlands).⁹ The mean PETCO₂ and SaO₂ were defined as the mean PETCO₂ and SaO₂ of the total recording time. SaO₂ and PETCO₂ signals during the night were stored on a computer (Compaq 4/66; Compaq; Houston, TX).

**Statistical Analysis**

Data are presented as mean values ± SEM. Carryover effects were analyzed according to Pocock²⁸ by comparing the treatment with acetazolamide as well as MPA in the different study arms (Mann-Whitney U test) [ie, for acetazolamide, T4A – T2 and T3A – T2; for MPA, T4M – T2 and T3M – T2; Fig 1]. After determining that there were no significant differences in mean values of the group between control (T1) and placebo (T2), and that carryover effects could not be measured 2 weeks after stopping the previous medication, the data obtained in the "baseline situation" (mean of T1 and T2) were compared with those after acetazolamide and MPA treatment (Wilcoxon signed rank tests). Statistical significance was defined at p < 0.05. For all analysis, SPSS (version 6.1.3; SPSS; Chicago, IL) was used.

**Results**

No significant differences were observed in ventilatory or in blood gas variables after placebo treatment compared to control. Hence, the mean data of the control and placebo measurements were used as baseline values in the analysis of the effects of acetazolamide and MPA treatment. Baseline charac-
**Table 2—Carryover Effects***

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Acetazolamide</th>
<th>MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T4A – T2</td>
<td>T3A – T2</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>3.8 ± 0.8</td>
<td>6.8 ± 1.5</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>3.8 ± 2.3</td>
<td>4.5 ± 3.8</td>
</tr>
<tr>
<td>Ve, L/min</td>
<td>0.7 ± 0.9</td>
<td>1.6 ± 0.7</td>
</tr>
<tr>
<td>Pco₂, mm Hg</td>
<td>0.8 ± 1.5</td>
<td>0.8 ± 0.0</td>
</tr>
<tr>
<td>SHVR, L/min/mm Hg</td>
<td>0.6 ± 0.2</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td>ShVR, L/min/%</td>
<td>−0.1 ± 0.1</td>
<td>−0.2 ± 0.1</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM. Differences in ventilatory and blood gas parameters between the various stages in the study, indicating that at T4 no carryover effects from the previous medication could be observed. SHVR (ΔVe/ΔPaCO₂) = the slope of the ventilatory carbon dioxide response curve; ShVR (ΔVe/ΔSaO₂) = slope of the HVR.

### Daytime Laboratory Measurements

The effects of acetazolamide and MPA on daytime blood gas parameters are shown in Table 3. The mean PaO₂ improved significantly during acetazolamide treatment by 9.8 ± 3.0 mm Hg (p < 0.05), whereas the mean PaO₂ did not significantly increase with MPA. The mean PaCO₂ decreased significantly after treatment with acetazolamide (5.3 ± 0.8 mm Hg) and MPA (4.5 ± 0.8 mm Hg) [both p < 0.05]. The mean decrease of PaCO₂ with acetazolamide was significantly larger than that obtained with MPA treatment (p < 0.05; Table 3, Fig 2). The base excess decreased significantly after acetazolamide treatment (approximately 6.0 mmol/L) and after MPA treatment (approximately 2 mmol/L).

### Ventilation and Hypercapnic/Hypoxic Responses

Ve did not change significantly with acetazolamide treatment but increased significantly with MPA treatment (1.2 L/min) [Table 4]. The slope of the HCVR curve did not differ significantly during acetazolamide nor during MPA, as compared to baseline (Fig 3). The ventilatory carbon dioxide response curve showed a nonsignificant shift to the left, as indicated by a small decrease in the apneic threshold (x-intercept) both with acetazolamide (from 24.0 to 15.8 mm Hg) and with MPA (from 24.0 to 19.5 mm Hg).

P₀.₁ increased significantly with MPA; however, the slope and x-intercept of the response of P₀.₁ to PaCO₂ did not change significantly with acetazolamide nor with MPA treatment. The slope of the HVR significantly increased during acetazolamide as well as during MPA treatment (Fig 4). Only during acetazolamide, the slope of the relationship between ΔP₀.₁ and ΔSaO₂ was significantly increased (Fig 5).

### Subjective Parameters

In the acetazolamide group, three patients complained of paresthesias and three patients noted GI discomfort. Seven patients reported side effects during MPA therapy: GI discomfort (n = 5) and fatigue (n = 2). Dyspnea sensation (Medical Research Council scale) did not change significantly after introduction of the drugs: 1.83 ± 0.17 at baseline to

**Table 3—Effect of Acetazolamide and MPA on Daytime Blood Gas Parameters***

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline (T1 and T2)</th>
<th>Acetazolamide (T3A and T4A)</th>
<th>MPA (T3M and T4M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.40 ± 0.01</td>
<td>7.35 ± 0.01†</td>
<td>7.41 ± 0.01</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>65.2 ± 2.3</td>
<td>75.0 ± 3.0†</td>
<td>69.8 ± 3.0</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>47.3 ± 0.8</td>
<td>42.0 ± 1.5†</td>
<td>42.8 ± 1.5</td>
</tr>
<tr>
<td>ΔPaCO₂, mm Hg</td>
<td>−5.4 ± 1.0</td>
<td>−8.4 ± 1.0†</td>
<td>−4.6 ± 0.8</td>
</tr>
<tr>
<td>Base excess, mmol/L</td>
<td>3.9 ± 0.5</td>
<td>−2.0 ± 0.7†</td>
<td>2.1 ± 0.4†</td>
</tr>
<tr>
<td>P(a-ET)CO₂, mm Hg</td>
<td>6.0 ± 1.5</td>
<td>5.3 ± 1.5</td>
<td>4.5 ± 1.5</td>
</tr>
<tr>
<td>SaO₂%</td>
<td>92.4 ± 0.8</td>
<td>93.8 ± 0.7</td>
<td>93.4 ± 0.8</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM. P(a-ET)CO₂ = arterial-to-end-tidal PCO₂ gradient. ΔPaCO₂ = mean change in PaCO₂ (drug vs baseline).

†p < 0.05 between treatment and baseline.

*p < 0.05 between acetazolamide and MPA treatment.
1.83 ± 0.24 (not significant) during acetazolamide therapy and to 2.33 ± 0.31 (not significant) during MPA therapy.

Nocturnal Parameters

Mean \( \text{PETCO}_2 \) decreased significantly by both acetazolamide and MPA, with 6.8 mm Hg and 7.5 mm Hg, respectively (Table 5). The mean \( \text{SaO}_2 \) did not improve significantly with acetazolamide. However, the percentage of nocturnal recording time with saturation < 90% did improve significantly with acetazolamide therapy from 34.9 ± 10.7% to 16.3 ± 7.5%. MPA did not significantly change nocturnal saturation.

**Figure 2.** The effect of \( \Delta \text{PaCO}_2 \) (acetazolamide) vs \( \Delta \text{PaCO}_2 \) (MPA) in 12 patients with severe COPD. All data points are the individual data of each patient. Dotted line indicates identity. See Figure 1 legend for expansion of abbreviation not used in text.

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### Table 4—Effect of Acetazolamide and MPA on Ventilatory Variables*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline (T1 and T2)</th>
<th>Acetazolamide (T3A and T4A)</th>
<th>MPA (T3M and T4M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Ve} ), L/min</td>
<td>9.0 ± 0.8</td>
<td>10.0 ± 0.6</td>
<td>10.8 ± 0.8†</td>
</tr>
<tr>
<td>( P_{1.1} ) at rest, mm Hg</td>
<td>3.0 ± 0.3</td>
<td>3.0 ± 0.2</td>
<td>3.8 ± 0.3†</td>
</tr>
<tr>
<td>( \text{BHCRV} ), L/min/mm Hg</td>
<td>0.7 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>( \text{BHCRV} ), mm Hg</td>
<td>24.0 ± 4.5</td>
<td>15.8 ± 5.3</td>
<td>19.5 ± 5.3</td>
</tr>
<tr>
<td>( \text{SHCR}_{0.1} ), mm Hg/mm Hg</td>
<td>0.20 ± 0.02</td>
<td>0.3 ± 0.05</td>
<td>0.3 ± 0.04</td>
</tr>
<tr>
<td>( \text{BHCR}_{0.1} ), mm Hg</td>
<td>30.0 ± 2.3</td>
<td>27.0 ± 2.3</td>
<td>25.5 ± 3.0</td>
</tr>
<tr>
<td>( \text{SHVR} ), L/min</td>
<td>−0.02 ± 0.05</td>
<td>−0.4 ± 0.11</td>
<td>−0.3 ± 0.11</td>
</tr>
<tr>
<td>( \text{SHVR} ), mm Hg/%</td>
<td>−0.05 ± 0.008</td>
<td>−0.15 ± 0.02†</td>
<td>−0.08 ± 0.02†</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM. \( \text{BHCRV} \) (x-intercept) = apneic threshold or extrapolated \( \text{PETCO}_2 \) at zero ventilation; \( \text{SHCR}_{0.1} \) = slope of the \( P_{0.1} \) response to carbon dioxide; \( \text{BHCR}_{0.1} \) = x-intercept of the \( P_{0.1} \) response to carbon dioxide; \( \text{SHVR} \) = slope of the HVR; \( \text{SHR}_{0.1} \) = \( \Delta P_{0.1}/\Delta \text{SaO}_2 \) = slope of the \( P_{0.1} \) response to oxygen.

\( p < 0.05 \) between baseline and treatment.

### Discussion

The present study showed that in hypercapnic patients with COPD, acetazolamide and MPA treatment both have favorable effects on several daytime and nighttime blood gas parameters as well as on ventilatory responses; acetazolamide showed more and larger effects than MPA.

**Daytime Laboratory Tests**

The present study showed that acetazolamide treatment improved daytime \( \text{PaCO}_2 \) and \( \text{PaO}_2 \). This is in agreement with the literature. The mechanism by which acetazolamide improves daytime blood gas values is not yet clear; however, it is generally believed that the metabolic acidosis induced by acetazolamide is responsible for the improvements. We observed an increase in daytime \( \text{PaO}_2 \) of 9.8 mm Hg only with acetazolamide. If one calculates alveolar-arterial oxygen pressure differences, it appears that (assuming a respiratory exchange ratio of 0.8) acetazolamide has reduced the alveolar-arterial oxygen pressure difference by 3.8 mm Hg. Therefore, the improvement in \( \text{PaO}_2 \) cannot be caused by an increase in alveolar ventilation alone, but it may also be due to a slight improvement of alveolar ventilation/perfusion matching and/or a small diuretic effect resulting in a decrease in interstitial lung water. In our previous animal studies, we determined that the effect of acetazolamide on the HCRV may be caused by a direct effect on the carotid bodies as well as on the cerebral vessels, which may be responsible for the decrease in \( \text{PaCO}_2 \) and increase in \( \text{PaO}_2 \).

MPA improved daytime \( \text{PaCO}_2 \) as was shown by others. Skatrud et al. classified their COPD patients in “correctors” (10 of 15 patients), in whom tidal volume increased and \( \text{PaCO}_2 \) decreased (≥ 5.0 mm Hg) during both MPA and acetazolamide.
administration, vs “non-correctors” (5 of 15 patients), showing no fall in PaCO₂ (≤ 5.0 mm Hg). This is in agreement with our study, where VE increased with MPA treatment. In 7 of 12 patients, PaCO₂ decreased > 5.0 mm Hg, and they should thus be considered correctors. Our Figure 2 suggests that there is a wide interindividual range of responses, but we found no suggestion of two distinct groups of responders and nonresponders.

Ventilation and Hypercapnic/Hypoxic Responses

The present data showed that neither acetazolamide nor MPA therapy changed the slope and x-intercept of the HCVR. This is in contrast with animal studies. In anesthetized cats, it was shown that the slope of the HCVR was decreased by an acute low IV dose of acetazolamide, which was attributed to a direct effect of acetazolamide on the peripheral chemoreflex loop as well as an effect on cerebral blood flow regulation. In humans, several authors studied the effect of acetazolamide on the ventilatory carbon dioxide response using the Read rebreathing technique. It has been shown, however, that during metabolic acidosis the Read rebreathing technique results in a considerable overestimation of the response slope.

Swenson and Hughes showed that in healthy volunteers, acute IV infusion of the drug (one IV dose of acetazolamide, 500 mg) resulted in a parallel shift of the HCVR to the left, whereas longer-term administration (three oral doses of acetazolamide, 500 mg, over 24 h) resulted in an increase in the slope of the HCVR. An explanation for the contradiction with our study could be the large, longer-term dose of acetazolamide used by Swenson and Hughes, the time sequence the drug was administered (two vs three oral doses), as well as the different study group (hypercapnic patients vs healthy volunteers). We found that MPA did not significantly influence the slope and x-intercept of the HCVR. This was also found by Morikawa et al.

P₀.₁ is considered to be useful in the assessment of central inspiratory neuromuscular drive, especially in patients with COPD, since P₀.₁ is less affected by airway resistance. Therefore, P₀.₁ was measured at rest, and the P₀.₁ response to carbon dioxide was

![Graph of ventilatory carbon dioxide (VCO₂) response curve](http://www.chestjournal.org)
calculated. However, $P_{0.1}$ may underestimate the respiratory drive in patients with COPD because it reflects the force output of respiratory muscles, which are sometimes weak and reflects the neuro-mechanical coupling that is changed.36 In our patients, the $P_{0.1}$ values prior to drug administration were higher and the relation between $P_{0.1}$ and $Pa_{co2}$ were lower than in healthy subjects, which is in agreement with literature. 8,37 During acetazolamide treatment, no significant changes in $P_{0.1}$ and in the relationship between $P_{0.1}$ and $Pa_{co2}$ were observed, whereas $P_{0.1}$ increased significantly by MPA treatment. This is consistent with the observed increase in ventilation with MPA therapy. The relationship between $\Delta P_{0.1}$ and $\Delta Pa_{co2}$ did not change with MPA treatment. These findings are in agreement with Skatrud and Dempsey8 and Morikawa et al,21 who also did not find any change in this relationship. When considering the carbon dioxide response curves in COPD, the ventilation of the patients will increase during hypercapnia. This will lead to increased hyperinflation, taking the lungs and thoracic wall to a stiffer part of their pressure-volume curve. Furthermore, the process of shortening of the diaphragm due to hyperinflation will bring it on a disadvantageous part of the length-tension curve. This might explain the lack of response in $P_{0.1}$ in the carbon dioxide response curves.37

The ventilatory control system can be subdivided into a controller or controlling system, and a controlled system. The controller has an input ($Pa_{co2}$) and an output ($Ve$). The characteristic of the controller is the ventilatory response to carbon dioxide. The controlled system is the gas exchanging process in the lungs; its input is $Ve$ and its output is the $Pa_{co2}$. The characteristic of the controlled system depends on the metabolic carbon dioxide production, and is called the metabolic hyperbola. In our model, due to a higher metabolic rate in patients with COPD,38 we calculated a resting carbon dioxide production of 400 mL/min by using the steady-state resting $Pa_{co2}$ and $Ve$ values as points of the hyperbola. Metabolism will even be a little higher during MPA treatment. Therefore, carbon dioxide production was calculated at 450 mL/min (steady-state resting $Pa_{co2}$ and $Ve$ values during MPA therapy).19,32 During spontaneous breathing, the output of the controlled system ($Pa_{co2}$) is at the same time input of the controller. Alternatively, the output of the controller ($Ve$) is the input of the controlled system. Thus, the system settles at the point where the carbon dioxide response curve crosses the metabolic hyperbola. This is called the closed-loop situation.

As shown in Figure 3, for both acetazolamide and

**Figure 4.** The effect of treatment with 250 mg of acetazolamide bid and 30 mg of MPA bid on the ventilatory response to oxygen (HVR) is calculated from the mean data in 12 patients with severe COPD. The continuous line represents the baseline situation, and the dashed lines represent the situations during acetazolamide and MPA therapy. See Figure 1 legend for expansion of abbreviation not used in text.

**Figure 5.** The effect of treatment with 250 mg of acetazolamide bid and 30 mg of MPA bid on the relationship between $Delta P_{0.1}$ and $Delta Sa_{o2}$ is calculated from the mean data in 12 patients with severe COPD. The continuous line represents the baseline situation, and the dashed lines represent the situations after 250 mg of acetazolamide bid and after 30 mg of MPA bid, respectively. See Figure 1 legend for expansion of abbreviation not used in text.
MPA, this model will predict a decrease in PaCO₂ of 6.0 mm Hg and 3.8 mm Hg, respectively. This is in close agreement with the actual decrease of 5.3 mm Hg and 4.5 mm Hg that we found in our patients. Since the point of intersection of the ventilatory carbon dioxide response curve with the metabolic hyperbola is in the relatively flat part of the hyperbola, it is not surprising that with acetazolamide treatment a decrease in PaCO₂ was observed without a significant increase in ventilation. This also means that acetazolamide seems to be able to improve blood gas values without adding a substantial load to the ventilatory muscles. As shown in Figure 3, the (nonsignificant) ventilatory increase of 0.4 L/min (ΔVe) would result in a decrease in PaCO₂ of only ±2.3 mm Hg as indicated by the metabolic hyperbola. Since we observed a larger decrease in PaCO₂ (5.3 mm Hg), other factors in the gas exchange must be responsible for this “extra” decrease in PaCO₂. A decrease in carbon dioxide output (VCO₂), as observed by Hirahara et al.39 could possibly explain this extra decrease. This is due to the fact that the point of intersection of the ventilatory carbon dioxide response curve with the metabolic hyperbola is in the relatively flat part of the hyperbola. Another explanation could be the appearance of tissue carbon dioxide retention, since the carbonic anhydrase is inhibited, leading to a relative tissue hypercapnia, with either no change or a relative arterial hypocapnia.15

Taken all together, the concern of Swenson10 about prescribing acetazolamide to patients with severe COPD with ventilatory pump failure seem to be of great clinical importance, as can also be concluded from the present study. Acetazolamide should not be administered to patients with very severe obstruction and hypercapnia (FEV₁ < 25% and PaCO₂ > 60 mm Hg), or in those who have not the mechanical ability to lower their PaCO₂ by voluntary hyperventilation.

In the current study as well as in others, the HVR was augmented by acetazolamide and MPA treatment, which indicates that both respiratory stimulants have an effect on the peripheral chemoreflex loop.19,20 The HVR was not increased in all acetazolamide and MPA studies.9,12,17 A possible explanation could be a different technique: measurement of the HVR at predrug PCO₂ level resulted in an increased HVR12,15,19 instead of a decrease under lower postdrug PCO₂ levels.9,12,17 The slope of ΔP0.1 vs ΔSaO₂ was significantly increased by acetazolamide (Fig 5), but did not reach any significance with MPA. For MPA, this is in agreement of the observations of Schoene et al.40 although this is inconsistent with the observed increase in HVR. This might be due to the large interindividual and intraindividual variability as mentioned by Whitelaw et al.24

**Nocturnal Parameters**

Acetazolamide treatment significantly decreased nocturnal desaturation time (the percentage of time with SaO₂ <90%). It is known that the respiratory stimulant may contribute to improvement of desaturation time by diminishing central sleep apnea and periodic breathing.41 This supports the opinion that acetazolamide augments the chemical drive, as was shown in those patients. This may also explain the decrease in PETCO₂, although occasional nocturnal hypoventilation may still be present. MPA has a beneficial effect on PETCO₂ as shown in Table 5. This is in agreement with others.42

**Clinical Implications**

The current study showed that short-term acetazolamide treatment is more beneficial compared to short-term MPA treatment, as can be seen from a larger change in daytime PaCO₂ in hypercapnic patients with COPD. However, the long-term clinical benefit of acetazolamide and MPA treatment on patients with severe COPD remains to be investigated. The possible effect on survival of a modest increase in PaO₂ and a decrease in PaCO₂ is not yet clear. Hypoxia and hypercapnia are both considered to be independent poor prognostic factors for survival.2,4,43 yet others question the prognostic role of hypercapnia.3 If the role of PaCO₂ as an independent predictor for a prognostic poor prognosis will be

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### Table 5—Nocturnal Parameters*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline (T1 and T2)</th>
<th>Acetazolamide (T3A and T4A)</th>
<th>MPA (T3M and T4M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PETCO₂ mm Hg</td>
<td>42.0 ± 2.3</td>
<td>35.3 ± 2.3</td>
<td>34.5 ± 0.8†</td>
</tr>
<tr>
<td>Mean SaO₂ %</td>
<td>90.6 ± 1.0</td>
<td>92.0 ± 0.9</td>
<td>91.6 ± 1.0</td>
</tr>
<tr>
<td>Lowest SaO₂ %</td>
<td>84.0 ± 1.8</td>
<td>83.7 ± 2.7</td>
<td>83.8 ± 2.1</td>
</tr>
<tr>
<td>% time SaO₂ &lt; 90%</td>
<td>34.9 ± 10.5</td>
<td>16.3 ± 7.5†</td>
<td>23.8 ± 11.5</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM.
†p < 0.05, treatment and baseline.
further established, the use of acetazolamide might be preferred because of its extra effect on nocturnal saturation.

REFERENCES


11 Dolly FR, Block AJ. Medroxyprogesterone acetate and COPD: effect on breathing and oxygenation in sleeping and awake patients Chest 1983; 84:394–398


