Low-dose Almitrine Bimesylate in the Treatment of Hypoxemia due to Chronic Obstructive Pulmonary Disease*

Bernhard R. Winkelmann, M.D.; Thomas H. Kullmer, M.D.; Dieter G. Kneissl, M.D.; Dietmar Trenk, Ph.D.; and Hartmut Kronenberger, M.D.

Study objective: Assessment of acute and chronic effects of low-dose almitrine bimesylate (AB) in stable chronic obstructive pulmonary disease (COPD).

Study design: Oral administration of AB, 25 mg three times a day, for 6 months in all patients. Pulmonary function, blood gases, and peripheral nerve conduction velocity were measured at baseline and after long-term administration of AB. In addition, oral pharmacokinetics and effects on pulmonary circulation at rest were studied in half of the patients. Intravenous pharmacokinetics were measured after a single intravenous dose of 80 mg of AB 3 months before the start of oral AB treatment in the other seven patients.

Setting: Outpatient clinic of a community hospital in a coal mining district in southwest Germany.

Patients: Fourteen patients with clinically stable COPD and hypoxemia.

Results: Acute effects of AB were as follows: a significant increase in arterial oxygen tension (PaO₂) from 61 ± 7 mm Hg to 74 ± 8 mm Hg (p<0.001), a decrease in arterial carbon dioxide tension (PaCO₂) from 41 ± 8 mm Hg to 38 ± 7 mm Hg (p<0.01), a rise in pH from 7.45 ± 0.04 to 7.48 ± 0.04 (p<0.01), and a transient increase in mean pulmonary artery pressure from 28 ± 7 to 29 ± 6 mm Hg (not significant). After long-term treatment, once tissues were saturated with almitrine, improvement in gas exchange persisted with a PaO₂ of 70 ± 10 mm Hg (p<0.001) and a PaCO₂ of 39 ± 6 mm Hg (not significant) without elevation of pH (7.45 ± 0.04) or of pulmonary artery pressure (26 ± 8 mm Hg). The terminal half-life of AB was 56 ± 45 days after a single intravenous administration, and 55 ± 16 days after long-term oral dosing. None of the patients developed clinically manifest peripheral neuropathy. Impaired asymptomatic peripheral motor nerve function was prevalent in 4 (29 percent) of the patients and remained unchanged during long-term AB administration. However, asymptomatic impairment of motor nerve conduction velocity developed in two patients with inadequate high AB plasma levels despite low-dose therapy. Both patients were known to have additional conditions predisposing for neuropathy.

Conclusions: Low-dose AB therapy, 75 mg daily, resulted in sustained elevation of arterial oxygen tension in hypoxemic patients with COPD. Although pulmonary artery pressure increased transiently after the first dose, it remained unchanged with long-term treatment despite persistent improvement of pulmonary gas exchange. Monitoring of AB plasma levels is advisable in select patients during long-term administration to avoid neuropathy, even with such a low daily dose.

(Chest 1994; 105:1383-91)

CI=confidence interval; AB=almitrine bimesylate

Patients with chronic obstructive pulmonary disease (COPD) characteristically have a reduced arterial oxygen tension (PaO₂), often accompanied by an increase in arterial carbon dioxide tension (PaCO₂). The long-term prognosis of patients with COPD is poor, especially after the onset of severe hypoxemia.¹ Long-term domiciliary oxygen therapy is the only treatment that has been shown to improve survival.² Almitrine bimesylate (AB) is a new drug that has been classified as a peripheral chemorecep-

tor agonist of the carotid and aortic bodies.³ The compound induces a significant and persistent increase in arterial oxygen tension of 5 to 10 mm Hg in most hypoxemic patients with COPD at a daily dose of 100 mg.⁴ In contrast to oxygen therapy, the drug also reduces hypercapnia ⁵⁻⁶. However, at doses of 100 to 200 mg/d for 6 to 12 months, side effects such as increased dyspnea and peripheral paresthesia are common, almost certain due to an accumulation of the drug.

Therefore, the purpose of this study was to evaluate whether low-dose AB, 25 mg three times a day, was tolerated better and whether the agent was still effective in the treatment of hypoxemia.

Methods

Subjects

Fourteen patients with hypoxemia due to chronic obstructive lung disease were enrolled in the study after having given written informed consent. The selection criteria for entry into the
study were the same as in the VIMS study\(^5\) and included the following: (1) no previous oxygen treatment; (2) \(\text{PaO}_2 \leq 65 \text{ mm Hg}\) with a variation \(\leq 5 \text{ mm Hg}\) in three measurements during the previous 3 weeks; (3) \(\text{PaCO}_2 > 35 \text{ mm Hg}\); (4) age between 35 and 75 years; (5) FEV\(_1/\text{FVC ratio between 25 and 65 percent and FEV}\(_1\) \leq 70 percent of the predicted value; and (6) less than 2 kg variation in weight within the previous 3 weeks.

Exclusion criteria were as follows: (1) clinically unstable chronic bronchitis and emphysema (CBE), eg, occurrence of three exacerbations of the disease within the past year or one exacerbation within the previous 6 weeks; (2) clinically unstable right or left heart failure; (3) a history of pulmonary embolism; (4) unstable angina or myocardial infarction within the previous 3 months; (5) renal failure (creatinine >180 \(\mu\)mol/L); and (6) abnormal results of liver function tests. Almitrine bismesylate was administered in addition to the usual long-term medication. The concomitant drug regimen was kept constant, as much as possible, throughout the study. The study was performed in the outpatient clinic of the Department of Medicine, St. Elisabeth Clinic, Saarlouis (former affiliation of first author). The 500-bed clinic served as a community hospital for the region, which has been dominated, until now, by the steel and coal mining industry. Thus, six of the patients were coal miners with more than 30 years of active duty; the occupation of the remaining patients was hairdresser (two), locksmith (two), floor tiler (one), white collar worker (two), and housewife (one).

**Study Design**

Figure 1 depicts the study design. Short- and long-term effects of AB on arterial blood gases and pulmonary function (Bodytest plethysmograph, Jäger, Höchberg, Germany) were assessed before, 2 hours after the first dose, and after 6 months treatment in 14 patients. Patients 1 through 7 received a single intravenous infusion of 60 mg of AB 3 months before oral treatment to assess intravenous pharmacokinetics and its short-term effects on pulmonary function and on blood gas values. The other seven patients started directly with oral treatment. In six of the latter, pulmonary hemodynamics were investigated after the first dose and, with the exception of one dropout, again 6 months later after the last dose. One patient was studied without right heart catheterization, because access from the brachial vein was impossible. In those patients, the total daily dose of 75 mg of AB was administered as a single oral dose in the morning of the first and last study day to maximize effects for measurements. Arterial and mixed venous blood samples—the latter were obtained during right heart catheterization—were drawn in duplicate into 2-ml heparinized syringes maintained at room temperature. Measurements were performed within 5 min at 37°C. Blood gases were determined using a blood gas analyzer (CORNING 160, Corning Medical Inc, Medfield, Mass). The samples were obtained by direct puncture of the radial artery.

Multiple venous blood samples were drawn during intravenous administration of the drug in seven of the patients and during oral treatment in all patients for determination of almitrine plasma levels. The drug concentration was measured using high pressure liquid chromatography (detection limit, 5 ng/ml of AB).\(^9\)

The rate of decline was fitted to a multiexponential model by weighted nonlinear regression analysis for determination of the drug’s elimination kinetics after single intravenous administration\(^10\) in seven patients (1 through 7) and after multiple oral dosing in six of the seven other patients (one dropout).

The patients were monitored carefully for side effects throughout the study. On entry, all patients were subjected to a thorough clinical examination, including a neurologic evaluation of the sensory and motor nerve fibers, since relevant side effects of the drug had been reported earlier.\(^11,12\) Electromyography with measurement of the median nerve sensory conduction velocity and the peroneal nerve motor conduction velocity was performed at baseline, before AB administration in all patients, and it was repeated after 6 months of long-term treatment in 11 patients.

**Statistics**

Results are presented as means ± standard deviation. The short- and long-term effects of almitrine were assessed using the Student’s paired t test. Discrete variables were tested with Fisher’s exact test. All p values are reported for a two-tailed test.

**RESULTS**

Baseline clinical characteristics of the patients are summarized in Table 1. There was no difference between the seven patients who were treated only with oral therapy and those who received both intravenous and oral almitrine. In contrast to the “oral only” treatment group, the combined treatment group included two female patients and the group mean for weight was lower (not significant [NS]). There was no difference in exposure to cigarette smoking and concomitant medication.

**Pulmonary Function Testing**

Short-term administration of intravenous almitrine in seven patients did not alter pulmonary function, despite high plasma levels of almitrine (Table 2). Repeated body plethysmography and spirometry after long-term oral treatment in all patients revealed no significant difference in pulmonary volumes with the exception of a slight increase in vital capacity (\(p<0.05\)). However, a significant decrease in airway resistance was seen after long-term AB treatment despite constant continuous bronchodilator therapy throughout the study. Even while under medication, patients were still responsive to an inhaled \(\beta_2\)-mimetic (two metered doses of fenoterol) as shown by a significant and constant decrease of the group means of airways resistance after bronchodilation at any time throughout the study (Table 1).

**Blood Gas Analyses**

After infusion of 60 mg of almitrine over a period
Table 1—Clinical Characteristics of Patients at Study Entry (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intravenous and Oral Treatment Group</th>
<th>Oral Only Treatment Group</th>
<th>Total Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient, No.</td>
<td>7</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Age, yr</td>
<td>62 ± 3</td>
<td>62 ± 8</td>
<td>62 ± 6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64 ± 14</td>
<td>72 ± 8</td>
<td>68 ± 12</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>5/2</td>
<td>7/0</td>
<td>12/2</td>
</tr>
<tr>
<td>History of respiratory complaints, yr</td>
<td>7 ± 5</td>
<td>11 ± 4</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>History of cigarette smoking* No. (%)</td>
<td>6 (86)</td>
<td>7 (100)</td>
<td>13 (93)</td>
</tr>
<tr>
<td>Pack-years of smoking, yr</td>
<td>36 ± 19</td>
<td>44 ± 25</td>
<td>40 ± 22</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline, No. (%)</td>
<td>6 (86)</td>
<td>7 (100)</td>
<td>13 (93)</td>
</tr>
<tr>
<td>β2-adrenergic agonist, No. (%)</td>
<td>4 (57)</td>
<td>4 (57)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Corticosteroid, No. (%)</td>
<td>2 (29)</td>
<td>3 (43)</td>
<td>5 (36)</td>
</tr>
<tr>
<td>(oral + inhaled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis, No. (%)</td>
<td>4 (57)</td>
<td>5 (71)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Diuretics, No. (%)</td>
<td>5 (71)</td>
<td>4 (57)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Vasodilators, No. (%)</td>
<td>3 (43)</td>
<td>4 (57)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>(Ca-antagonists, nitrates, ACE-inhibitors)†</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Four patients were still active smokers despite knowledge and warnings about the adverse effects of smoking (two in each group).
†ACE=angiotensin-converting enzyme.

of 2 h, the mean arterial oxygen tension increased from 64.0 ± 5.9 mm Hg to 76.7 ± 3.7 mm Hg (difference, 12.7 ± 3.5 mm Hg; 95% confidence interval [CI], 9.4 to 15.9; p<0.001). Arterial carbon dioxide tension decreased from 37.1 ± 4.5 mm Hg to 33.4 ± 3.7 mm Hg (difference -3.7 ± 2.5; 95 percent CI, -1.3 to -6.0, p<0.01). The individual changes and mean values are illustrated in Figure 2. Also shown is the response to long-term oral almitrine therapy, 25 mg three times a day, starting 3 months later in the same seven patients. The beneficial effect on blood gas values was maintained with an increase of the PaO₂ from 61.6 ± 6.7 mm Hg by 13.4 ± 5.3 mm Hg (95 percent CI, 8.5 to 18.2) to 75.0 ± 9.9 mm Hg (p<0.001). A 9 percent decrease by -3.3 ± 4.5 mm Hg in arterial carbon dioxide tension from 38.5 ± 6.1 mm Hg to 35.2 ± 4.8 mm Hg was also recorded after 6 months of almitrine treatment, but the difference was not statistically significant (95 percent CI, +0.9 to -7.5; p<0.11).

The mean values of arterial blood gases for all patients before and after almitrine treatment are summarized in Table 3. The mean increase in PaO₂ was 13.2 ± 4.0 mm Hg (95 percent CI, 10.9 to 15.5 mm Hg; p<0.001) after the first dose and 9.3 ± 7.7 mm Hg (95 percent CI, 4.7 to 14.0 mm Hg; p<0.001) after long-term administration. This significant short- and long-term persistent increase in PaO₂ is reflected by a corresponding improvement in hemoglobin oxygen saturation from 90.9 ± 3.9 percent to 95.0 ± 1.6 percent.
### Table 2—Pulmonary Function Data After Short- and Long-term Therapy With Almitrine Bismesylate (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Baseline Short Term†</th>
<th>Baseline Short Term†</th>
<th>Long Term†</th>
<th>p Value vs Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=7)</td>
<td>Intravenous (n=7)</td>
<td>Oral Administration (n=13)</td>
<td></td>
</tr>
<tr>
<td>Almitrine plasma level, ng/ml</td>
<td>BLQ‡</td>
<td>632 ± 295</td>
<td>302 ± 137</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC, L (% pred)</td>
<td>2.9 ± 0.6</td>
<td>2.8 ± 0.6</td>
<td>2.8 ± 0.6</td>
<td>3.2 ± 0.7</td>
</tr>
<tr>
<td>FEVI,L (% FEVI/VC)</td>
<td>1.4 ± 0.5</td>
<td>1.3 ± 0.5</td>
<td>1.3 ± 0.3</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>TLC, L (% pred)</td>
<td>7.4 ± 2.0</td>
<td>7.0 ± 1.9</td>
<td>7.6 ± 2.6</td>
<td>7.8 ± 2.3</td>
</tr>
<tr>
<td>RV, L (% RV/TLC)</td>
<td>4.5 ± 1.5</td>
<td>4.2 ± 1.1</td>
<td>4.8 ± 2.4</td>
<td>4.6 ± 1.9</td>
</tr>
<tr>
<td>FRC, L (% pred)</td>
<td>5.5 ± 1.4</td>
<td>5.0 ± 1.4</td>
<td>5.7 ± 2.6</td>
<td>5.6 ± 2.1</td>
</tr>
<tr>
<td>Raw before bronchodilator, cm H₂O/L/s</td>
<td>11.1 ± 6.4</td>
<td>10.7 ± 6.7</td>
<td>10.7 ± 6.4</td>
<td>6.7 ± 3.1</td>
</tr>
<tr>
<td>Raw after bronchodilator, cm H₂O/L/s</td>
<td>8.1 ± 4.0</td>
<td>8.1 ± 4.3</td>
<td>8.3 ± 4.5</td>
<td>5.0 ± 1.8</td>
</tr>
<tr>
<td>Difference Raw before-after, cm H₂O/L/s</td>
<td>2.9 ± 3.8</td>
<td>2.6 ± 2.7</td>
<td>2.3 ± 2.2</td>
<td>1.7 ± 2.0</td>
</tr>
</tbody>
</table>

*FVC=forced vital capacity; FEVI=forced expiratory volume in 1 s; TLC=total lung capacity; RV=residual volume; FRC=functional residual capacity; Raw=airways resistance. Pulmonary volumes FVC, FEVI, TLC, RV, and FRC are measured after bronchodilation.
†Before and directly after a single intravenous 2-hr infusion of almitrine (60 mg).
‡Long-term effects measured in the morning before almitrine intake after 6 months of almitrine therapy, 25 mg three times a day; the last 25-mg dose was taken in the evening before the measurements.
§BLQ=below limit of quantification (<5 ng/ml).

date short term, and to a slightly lesser, but still highly significant degree of 93.6 ± 2.6 percent long term (p<0.001). However, pH remained unchanged long term, despite the persistent increase in PaO₂ and decrease in PaCO₂. Hemoglobin, hematocrit, and body weight remained unchanged (Table 3).

### Hemodynamics

Short-term oral administration of the first 75-mg dose of almitrine resulted in a transient increase in

### Table 3—Arterial Blood Gases, Hemoglobin, Hematocrit, and Body Weight at Baseline and After Administration of Almitrine Bismesylate (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Baseline Short term†</th>
<th>Long term†</th>
<th>p Value vs Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=14)</td>
<td>(n=14)</td>
<td>(n=13)</td>
</tr>
<tr>
<td>Almitrine plasma level, ng/ml</td>
<td>BLQ‡</td>
<td>405 ± 327</td>
<td>302 ± 137</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>60.8 ± 7.2</td>
<td>74.0 ± 7.3</td>
<td>70.0 ± 9.7</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>41.2 ± 7.5</td>
<td>37.6 ± 6.8</td>
<td>38.9 ± 6.0</td>
</tr>
<tr>
<td>pH, −log[H+]</td>
<td>7.45 ± 0.04</td>
<td>7.48 ± 0.04</td>
<td>7.45 ± 0.04</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>90.9 ± 3.9</td>
<td>95.0 ± 1.6</td>
<td>95.6 ± 2.6</td>
</tr>
<tr>
<td>P(A-a)O₂, mm Hg</td>
<td>40.8 ± 2.1</td>
<td>31.8 ± 6.6</td>
<td>33.8 ± 5.0</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>14.6 ± 1.5</td>
<td>...</td>
<td>14.9 ± 2.0</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>44.7 ± 5.4</td>
<td>...</td>
<td>44.2 ± 5.8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.2 ± 12.5</td>
<td>...</td>
<td>67.2 ± 15.1</td>
</tr>
</tbody>
</table>

*PaO₂=arterial oxygen tension; PaCO₂=arterial carbon dioxide tension; Hb=hemoglobin; P(A-a)O₂=alveolar arterial oxygen tension difference (PaO₂-PaO₂); PaO₂=alveolar oxygen tension.
†Two hours after administration of the first dose of almitrine; either after intravenous administration in seven patients (directly after a 2-h infusion of 60 mg of almitrine) or after oral administration of 75 mg of almitrine in the other seven patients.
‡Long-term effects were measured in the morning before almitrine intake after 6 months of almitrine therapy, 25 mg three times a day in 13 patients; the last dose was taken in the evening before the measurements.
§BLQ=below limit of quantification (<5 mg/ml).
...=not done; —=not applicable.

Low-dose Almitrine Bismesylate for Hypoxemia (Winkelmann et al)

Downloaded From: http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21694/ on 04/06/2017
mean pulmonary artery pressure at rest from 25.6 ± 6.8 mm Hg to 29.4 ± 5.5 mm Hg (difference, 3.8 mm Hg; 95 percent CI, -0.2 to 7.8; p < 0.06) with a concomitant increase of the almitrine plasma level from 0 to 201 ± 177 ng/ml (p < 0.04). No increase of pulmonary artery pressure was seen after long-term almitrine treatment. The long-term baseline mean pulmonary artery pressure (26.2 ± 7.6 mm Hg) was comparable to the pressure before the drug administration (25.6 ± 6.8 mm Hg) and remained so (26.6 ± 7.1 mm Hg) despite renewed administration of 75 mg Hg of almitrine with a concomitant significant increase of the almitrine plasma level from 325 ± 140 to 549 ± 204 ng/ml, which translates into a further mean increase of 224 ± 112 ng/ml (p < 0.02) (Fig 3). Cardiac output, heart rate, stroke volume, systemic arterial pressure, right and left ventricular stroke work, and vascular resistances remained unchanged during short- and long-term almitrine therapy.

**Pharmacokinetics**

Individual and mean increases in almitrine plasma levels after the first and last 75-mg almitrine dose, after 6 months of therapy, are illustrated in Figure 3 in those patients with short- and long-term right heart catheterization. Steady-state trough levels of almitrine after 6 months were 302 ± 137 ng/ml (range, 186 to 544 ng/ml).

A large volume of distribution with 2,264 ± 1,282 and a clearance of 62 ± 54 ml/min were recorded after a single intravenous infusion of 60 mg of AB. The agent's mean terminal half-life was almost 2 months, both after intravenous dosing with 56 ± 45 days (range, 8 to 120 days), and after long-term oral almitrine therapy, 75 mg daily with 55 ± 16 days (range, 33 to 81 days).

**Adverse Effects**

The patients did not report about untoward effects during the regular follow-up visits, which could be attributed to the study drug. Also, the clinical evaluation did not produce any obvious change that was not related to the underlying respiratory disorder. The degree of dyspnea improved in the majority of patients during the study (8/13 patients), remained unchanged in 4 patients, and worsened in 1.

None of the 14 patients spontaneously complained of symptoms suggestive of peripheral motor nerve neuropathy, although four patients had impaired (<43 m/s) peroneal motor nerve conduction velocity before the study, which remained unchanged during almitrine treatment. Peroneal nerve conduction velocity was normal in the other ten patients and remained so after long-term treatment in five out of seven patients with a long-term follow-up neurologic assessment. In two patients, asymptomatic impairment of motor nerve conduction was recorded: in the first one, a drop from 49.5 to 37.0 m/s occurred. He was the second oldest patient and his physical...
condition had worsened rapidly due to progression of his underlying pulmonary disease. The clinical downhill course accelerated once he was not receiving almitrine treatment and he died 1 year later. In the second patient, an asymptomatic drop of the motor nerve conduction velocity from 49.5 to 43.5 m/s was measured. In this patient, who was a gracile 62-year-old woman weighing only 39 kg, the daily 75-mg almitrine dose was obviously a high dose. She had already complained about paresthesias and had shown objective signs of impaired sensory nerve conduction velocity before inclusion into the study. These sensory findings persisted without further deterioration throughout the study. Both patients showed the highest maximal almitrine levels of all subjects after long-term drug administration. A significant correlation between the plasma level and the degree of motor nerve impairment was found (Fig 4). The slope of the regression line between the almitrine plasma level and motor nerve conduction velocity is significantly different from zero (least squares regression, correlation coefficient r=0.7, p<0.02). A similar significant correlation existed between long-term almitrine trough levels or the difference between trough levels and the maximal concentration and the conduction velocity. Concerning the evaluation of the sensory nerve function, no new paraesthesias were reported by the other 13 patients and results of their neurologic examination of the sensory nerve function remained unchanged during low-dose almitrine therapy.

**DISCUSSION**

In the present study, low-dose almitrine was effective in improving arterial blood gas values in patients with COPD and hypoxemia. The mean increase in PaO₂ after the first dose by 13 mm Hg was maintained after long-term treatment with a persistent rise in PaO₂ by 9 mm Hg. A slight reduction of 2 mm Hg in PaCO₂, which had decreased significantly by 4 mm Hg after the first dose, was noted long term. This confirms previous studies that show a persistent rise in PaO₂ in a range of 5 to 11 mm Hg after doses of 100 to 200 mg and a reduction in PaCO₂ of 1 to 4 mm Hg.⁷ The effects were found to be dose related in a study investigating a daily dose of 100 mg and 200 mg concurrently.⁸ Since our study was done in an open, nonplacebo-controlled manner, we cannot rule out that intensified clinical care taken during the period of the trial improved the patients' hypoxemia to some extent. In other long-term, placebo-controlled trials, however, beneficial changes on arterial oxygen tension were not found in the group without active drug⁵,⁷ or were small, and, in contrast to almitrine-treated patients, not significant.⁴,⁶

The mechanisms of improvement with respect to gas exchange are poorly understood. Pharmacologically, almitrine is classified as a respiratory stimulant acting on peripheral chemoreceptors located in the carotid bodies, and to a lesser extend in the aortic bodies. The increase in alveolar ventilation is reflected by the decrease in PaCO₂ and a concomitant rise in pH. A significant rise in pH by 0.04 was seen in our study only after the first dose, together with a slight transient increase in mean pulmonary artery pressure, but not any more after long-term therapy despite persistent elevation of PaO₂. Other authors reported a significant increase in pH after long-term treatment, as well, but only after a high dose of 200 mg.⁶ Several mechanisms are discussed in the literature to explain these discrepancies.

Due to structural defects in lung anatomy, patients with COPD are unable to achieve normal increases in minute volume, tidal volume, or mean inspiratory flow (VT/TI) in response to hypercapnia and hypoxemia. It was suggested that almitrine improves alveolar ventilation by a change in breathing pattern: a slight increase in VT without change in respiratory rate coupled with an increased inspiratory flow rate (VT/TI) and decreased inspiratory duty cycle.¹³ There are conflicting data from several placebo-controlled studies concerning the clinical evidence. No alteration of ventilatory time constants were found in a crossover study investigating the short-term effects of a high oral dose (3 mg/kg) in ten patients,¹⁴ neither did external ventilation change in another placebo-controlled parallel group study with the same dose.¹⁵ In two reports of placebo-controlled 1-year trials of 50 mg of almitrine twice daily, an increase in minute ventilation was described,⁴,¹⁶ but

![Figure 4. Correlation between the almitrine plasma level (maximal level measured 2 to 3 h after drug administration) and the change of peroneal motor nerve conduction velocity after long-term almitrine treatment, 25 mg three times a day. The shaded area represents the normal range of variation (±1 SD) of an age-matched control population with COPD (n=78).³¹](image-url)
only during wakefulness and not during sleep, despite continued increase in PaO₂.16

It was postulated that almitrine improves PaO₂ even without increase in ventilation, especially when smaller doses are administered.17 The most important mechanism seems to be an improvement of ventilation/perfusion ratio (V / Q) by enhancement of hypoxic vasoconstriction. This mechanism would also explain the transient rise in pulmonary pressure. But again this hypothesis does not explain why beneficial effects on gas exchange persist after long-term treatment without a rise in pulmonary artery pressure, as found in this study, as well as by other authors.18,19 Possibly there are other mechanisms such as a direct vasoactive effect via the pulmonary endothelium regulating the vascular tone. Laboratory studies have shown that—depending on a number of pre-existing conditions before almitrine therapy, eg, the pulmonary vascular tone, hypoxia, or normoxia and a low or hight almitrine dosage—the drug has a dual effect and induces either vasodilation or vasoconstriction at the capillary level.20 There is experimental evidence de-emphasizing the role of the carotid bodies in favor of a direct humoral mechanism. The drug seems to induce the release of prostacyclin derivatives or other mediator substances in the lung.21

In general, almitrine does not affect spirometric parameters during short- and long-term administration. Nevertheless, we found, similarly to Bell and colleagues8 and Watanabe and coworkers4 a significant increase in forced inspiratory vital capacity (FVC) after long-term almitrine administration, which was not accompanied by significant changes in FEV₁ and total lung capacity. Interestingly, these authors8 also noted a small but significant improvement in small airways’ function in both the low- and high-dose group in comparison to the placebo group. This finding is supported by the results of this study showing an improvement in airways resistance (Table 2). As stated by those authors,8 we also do not have an explanation for this observation.

Patients with stable COPD usually exhibit mild pulmonary arterial hypertension at rest. It is known that the severity of COPD, as well as the degree of hypoxemia, of hypercapnia, and of the concentration of hydrogen ions are correlated with the increase in pulmonary artery pressure and right ventricular failure in this disease.22,23 Our results imply that treatment with a low daily dose of 75 mg of AB does not induce unfavorable hemodynamic changes with respect to the pulmonary circulation during both short- and long-term administration of almitrine. While Macnee and colleagues24 found a slight, but significant increase in pulmonary artery pressure in five patients after 3 months of oral almitrine therapy, 100 mg three times a day, no significant changes after long-term treatment have been reported in two earlier trials.18,19 An explanation for these contradictory findings could be the fact that in studies with intravenous almitrine, a significant rise in pulmonary artery pressure was seen only in patients with hypercapnia.25

There are also conflicting data concerning complaints of weight loss during long-term almitrine treatment. A significant decrease of body weight was reported in most studies,1,5,26,27 but not in others16 like in our study. No explanation can be given for this phenomenon, but there are several potential mechanisms. Almitrine has been found to have a diuretic effect28,29 and might thus correct the volume overload seen in many patients with COPD.30 Actually, in the VIMS study,5 the significant reduction of episodes of right heart failure was explained as a consequence of the weight loss in the group receiving almitrine. If vice versa weight loss is taken as an indicator for a worsening with respect to prognosis,32 the weight loss seen with almitrine might indicate that the agent could accelerate the downhill course of the disease and thus decrease survival. However, in a 2-year trial with almitrine, 100 to 200 mg daily, survival was unchanged in 43 almitrine-treated patients compared with 49 placebo-treated patients.31 But one might just as well draw the opposite conclusion, such that weight loss in patients with a stable condition is a sign of well being: patients loose weight because they can lead a more active life with almitrine. Thus, clarification of this phenomenon needs further studies.

Almitrine is extensively bound in peripheral lipophilic compartment sites, as demonstrated by a volume of distribution of more than a 1,000 L, which also seems to indicate that there exists an enterohepatic recirculation and the drug is highly protein bound (>99 percent).32–34 In our study, the mean terminal half-life of almitrine was prolonged and identical after both single intravenous administration and after long-term oral treatment with 56 and 55 days, respectively. Steady-state concentrations were reached only after several months of treatment and even with 75 mg daily, the almitrine trough at 6 months, ranging from 186 to 544 ng/ml, was above a recommended upper therapeutic limit of 200 ng/ml35 in all but one patient.

The results of the 2-year multicenter trial31 also show that almitrine doses of 100 and 200 mg are too high according to current knowledge. Mean almitrine plasma levels were double the recommended therapeutic level of 200 to 300 ng/ml in this study. A high incidence of clinical peripheral neuropathy was reported, 14 percent in the almitrine-treated group, 4 percent in the placebo-treated group. It is common consent that almitrine-associated neuropa-
thy is dose related. The disorder is reversible, but it will take several months to resolve because of the drug’s long half-life.\textsuperscript{4,10,20} Since the first reports on almitrine-associated neuropathy,\textsuperscript{11,27} it has been shown that a high prevalence of asymptomatic peripheral neuropathy exists in hypoxemic patients with COPD who never took almitrine.\textsuperscript{36}

Nevertheless, the agent seems to enhance subclinical peripheral neuropathy and in some instances causes overt clinical neuropathy, almost always in association with high plasma levels. Therefore, there exists a considerable clinical interest whether low-dose almitrine therapy could prevent these adverse effects. In our study, none of the patients developed clinical neuropathy. Two patients with the highest plasma levels, however, showed asymptomatic impairment of motor nerve conduction velocity. One of those patients had a very low body weight (39 kg), which remained unchanged; in the other subject, high plasma levels were associated with a weight loss of 10 kg within 6 months due to progression of COPD, thus probably releasing large amounts of previously tissue-bound drug. Our study shows that low-dose almitrine therapy, 75 mg daily, prevents neuropathy unless there are conditions that lead to high plasma levels despite a low daily drug intake.

In conclusion, AB therapy improves pulmonary gas exchange in hypoxemic patients with COPD, not only when administered short term using a single intravenous or oral dose, but also after a long-term 6-month therapy. This persistent beneficial effect on gas exchange, which had already been demonstrated with daily doses of 100 and 200 mg of almitrine, could be confirmed in this study using a reduced daily dose of 75 mg of AB. No clinical overt adverse effect, such as increased dyspnea or paresthesia occurred with this low dose, but asymptomatic impairment of peripheral motor nerve function was documented in two patients with inadequately high plasma levels. Further research studying even lower doses, such as half the current daily dose, 37.5 mg, seems warranted.

ACKNOWLEDGMENTS: The authors would like to thank the patients and the medical staff involved in the patient care. We are also indebted to Prof. Dr. W. Rapp, head of the Department of Internal Medicine of the St. Elisabeth-Klinik, Saarbr drain, Germany, for support and cooperation, and Dr. J. P. Jeanniot (Biologie Servier Orleans, France) for the measurement of the almitrine plasma levels and parts of the pharmacokinetic analysis. Finally, we are very grateful for the many valuable contributions of Dr. J. C. Ansquer, Servier Research, Paris, France, while performing the study and later during analysis of the results.

REFERENCES

10 Heinznel G, Woloszczak B, Thomann P. TopFit 2.0—pharmacokinetic and pharmacodynamic data analysis system for the PC. Stuttgart: Gustav Fischer Verlag, 1983
19 Prefaut CH, Bourguin-Karaouni D, Ramonataxo M, Michel

20 Nakanishi S, Hiramoto T, Ahmed N, Nishimoto Y. Almitrine enhances in low dose the reactivity of pulmonary vessels to hypoxia. Respir Physiol 1988; 74:139-50


