# THE EFFICACY OF ALMITRINE BISMESYLATE ON HYPOXEMIA, EXERCISE PERFORMANCE AND SLEEP DESATURATION OF PATIENTS WITH SEVERE COPD

(Received 18 January, 1993)

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## SUMMARY

Almitrine bismesylate (AB), a peripheral chemoreceptor agonist, has been shown to improve arterial blood gases in patients with chronic obstructive pulmonary disease (COPD). This study was designed to test the efficacy of almitrine bismesylate in patients with COPD. AB was administered 3 mg/kg po bid to 17 patients (12 men, 5 women, mean predicted FEV1%:33%(21-51). Arterial blood gas analysis revealed incline of $PaO_2$ from 55.2±11.7 mmHg to 62.7±10.4 mmHg and incline of oxygen saturation ($SaO_2$) from 84.3±9.7% to 89.7±6.1% ($p<0.003$, $p<0.002$) 3 hours after intake of a single dose, 7 patients dropped out of the study. Mean $PaO_2$ increased 10.2 mmHg ($p<0.003$), mean $PaCO_2$ decreased 8.5 mmHg ($p<0.003$) and oxygen saturation increased 5.9%($p<0.009$) 3 months after in 10 patients.

In sleep studies, the oxygen saturation duration under 85% showed a decline from 259±219 min to 119±195 min. ($p<0.02$), the radio of duration under 85% to the total sleep time decreased from 53±41% to 24±36% ($p<0.01$) after 3 months of therapy.

Tread-mill exercise test was performed in 6 patients at the beginning and three months after AB therapy. Exercise time and the lowest oygen saturation during exercise showed incline insignificantly.

Finally, the current study shows, AB as a single dose and long-term therapy, can improve arterial blood gases of COPD patients, awake and during sleep.

**Key Words :** Almitrine bismesylate, chronic obstructive pulmonary disease.

## INTRODUCTION

Almitrine bismesylate (AB) is a triazine derivative that stimulates peripheral chemoreceptors, thus increasing ventilatory response to hypoxia in humans. Almitrine given in a single dose and chronic oral dosage has been shown to increase $PaO_2$and reduce $PaCO_2$ with improving ventilation-perfusion matching in COPD patients (1,2).

Patients with chronic bronchitis and emphysema who are hypoxic when awake become transiently more hypoxemic during rapid eye movement (REM) sleep (3). Orally administered AB has been reported to reduce hypoxemia during sleep (4,5). Also, beneficial effect in exercise-induced hypoxemia is observed with AB (6).

We investigated the acute and chronic effects of AB in patients with COPD during wakefullness, sleep and exercise.

## PATIENTS AND METHODS

Seventeen patients (5 female, 12 male) with COPD were included in this study. They were between 41-80 (mean: 64) years of age. All were clinically stable for at least 3 months prior to the study. Criteria for admission in the study included $PaO_2<70$ mmHg and $PaCO_2>35$ mmHg during ambient air breathing. Existing medication, which was continued unaltered throughout the study, included digoxin, theophylline, inhaled $B_2$-stimulants. 11 were receiving continuous domiciliary oxygen therapy, but this was withheld during the study. Each patient received 3 mg/kg po bid AB. Arterial blood gases was sampled before the start of the study and 3 hours later. At 1-month

intervals during 3 months, samples were obtained. Oxygen saturation ($SaO_2$) during sleep and exercise was measured with a pulse oximeter (Minolta Pulsox 7). The exercise was performed on a tread-mill using modified Naughton protocol. Heart rate and blood pressure were measured during exercise. Exercise and sleep study were repeated at the end of 3-month therapy of AB.

Statistical significance was analyzed using the paired t-test.

## RESULTS

Patient characteristics are summarized in table I.

Mean $PaO_2$ significantly increased from 55.2±11.7 mmHg to 62.7±10.4 ($p<0.003$), $SaO_2$ significantly increased from 84.3±9.7% to 89.7±6.1% ($p<0.002$) 3 hours after a single dose intake. The changes in $PaCO_2$ and pH were modest and not statistically significant (Fig. 1). The long-term study was completed with 10 patients. 7 patients dropped out of the study, one died with acute myocardial infarction, one discontinued drug intake because of peripheral neuropathy in the first week therapy, 5 patients suffered from acute exacerbation attacks during the study. Mean $PaO_2$ increased from 53.1±11.6 to

**Table I.** Patient Characteristics

| | |
|---|---|
| Number of patients | 17 |
| Female | 5 |
| Male | 12 |
| Age | 64±10 (41-80) |
| FEV1 % predicted | 33±11 (21-51) |
| FEV1/FVC% | 52±10 (40-61) |
| Bronchodilator response% | 7.5±5 (0-14) |
| Arterial blood gases (room air) : | |
| $PaO_2$ | 55.2 ±11.7 mmHg |
| $PaCO_2$ | 48.4 ± 9.3 mmHg |
| pH | 7.40± 0.06 |
| $SaO_2$ | 84.3 ± 9.7% |

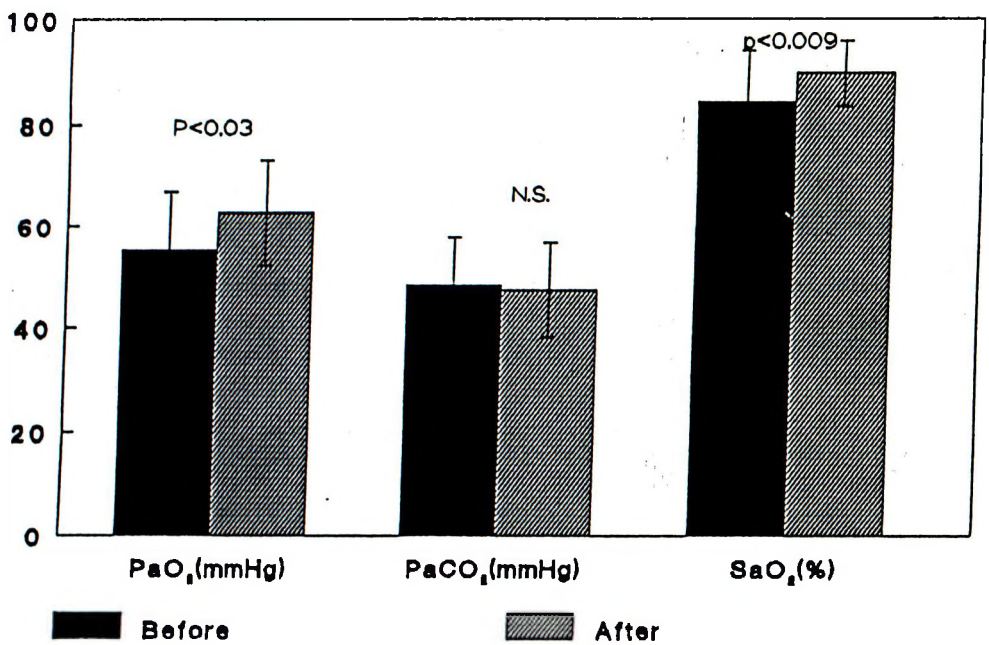


Fig. 1. Short term effects of almitrine

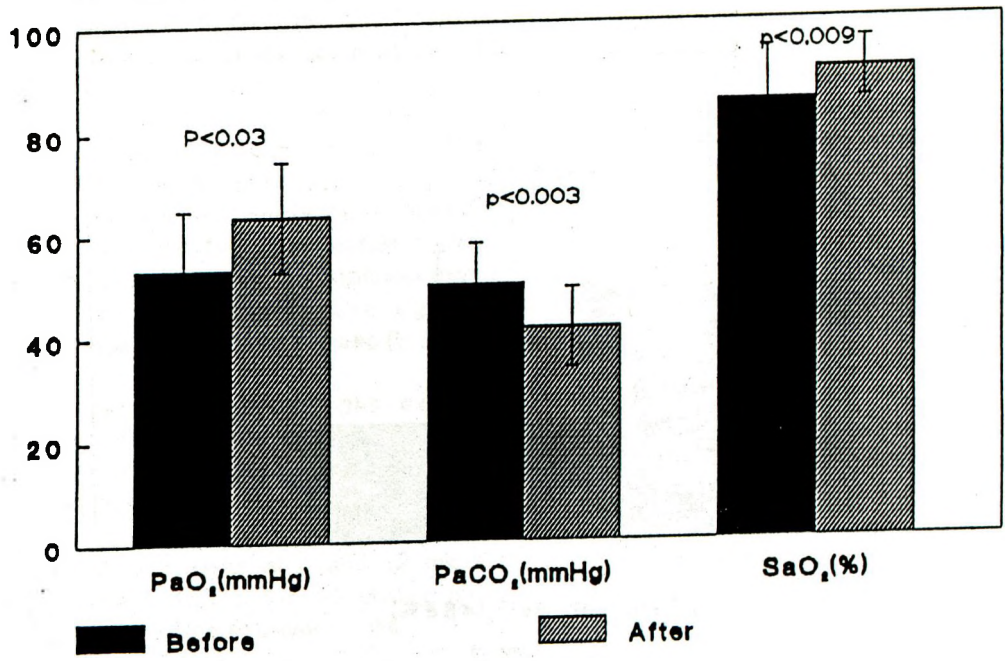


Fig. 2. Long-term effects of almitrine

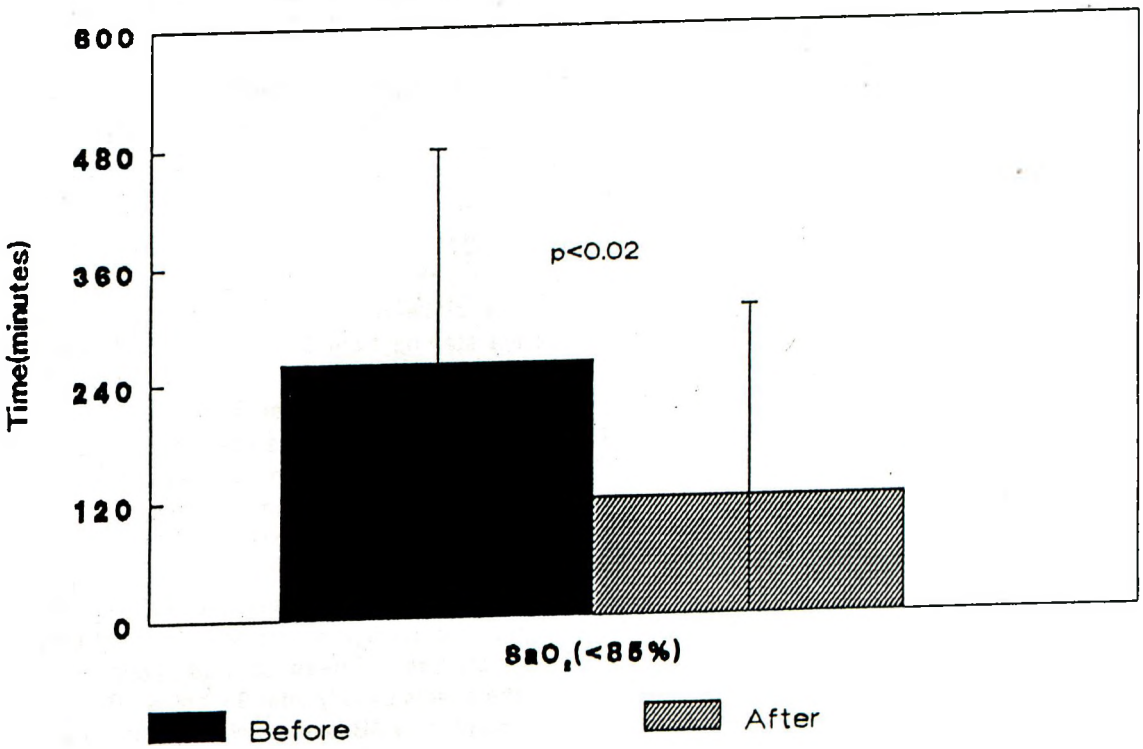


Fig. 3. Desaturation time below 85% $SaO_2$

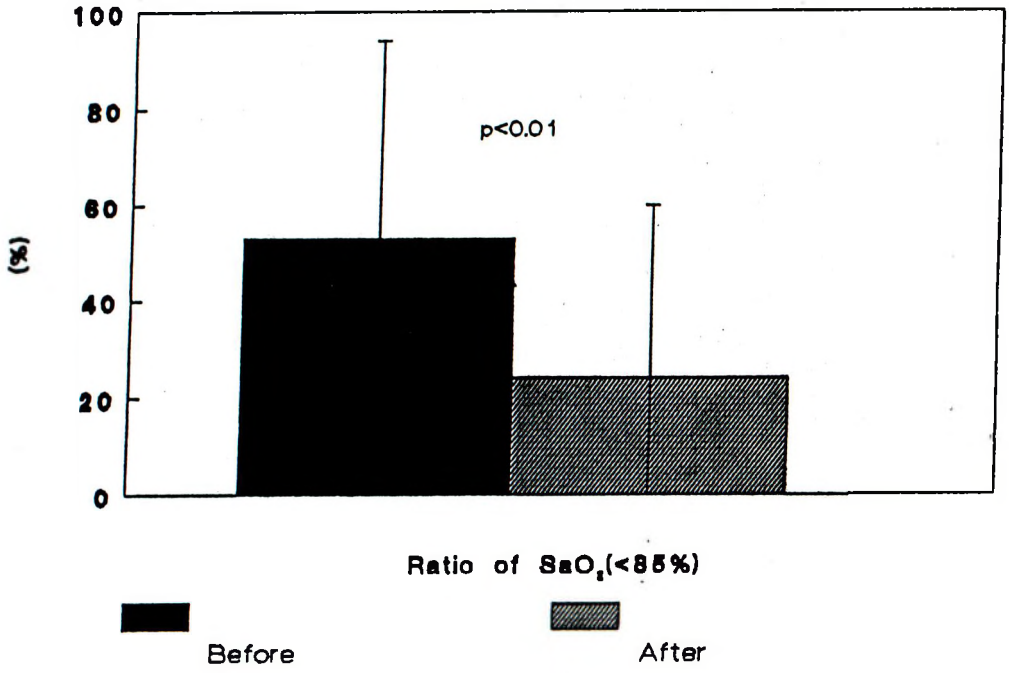


Fig. 4. Ratio of desaturation time to total sleep time

63.3±10.7 ($p<0.003$), mean $PaCO_2$ decreased from 49.8±7.9 mmHg to 41.3±7.7 mmHg ($p<0.003$), oxygen saturation increased from 84.9±10% to 90.8±5.6% ($p<0.009$), pH did not change significantly after 3 month therapy (Fig. 2).

Nocturnal oxygenation improved after almitrine therapy. The lowest $SaO_2$ recorded during sleep did not change significantly after almitrine (before 62±10% to after 65±9%), (NS). The duration of $SaO_2$ recorded below 85% showed a decline from 259±219 min to 119±195 min ($p<0.02$). The ratio of desaturation time to the total sleep time decreased from 53±41% to 24±36% ($p<0.01$) after 3 months of therapy (Fig. 3,4).

Exercise test was performed in 6 patients at the beginning and 3 months after therapy. The other 4 patients did not carry out the work load. Exercise time increased from 300±185 s to 390±239 s insignificantly. The lowest $SaO_2$ recorded during exercise improved insignificantly from 76±14% to 86±6%.

No consistent changes were noted during the course of the study in either the biochemical profiles or urinalysis. Respiratory function tests remained stable.

One patient with diabetes mellitus reported severe peripheral paresthesia. There was no significant change in body weight, none reported increased dyspnea.

## DISCUSSION

This study showed that almitrine can improve hypoxemia starting from 3 hours. This time was similar to that observed in earlier studies in which the same oral dose was administered (6). Furthermore, this beneficial effect of AB was seen in patients with chronic obstructive pulmonary disease during mechanical ventilation without changing ventilator parameters (7). In the present study, 3-month treatment with oral AB, at the dose of 3 mg/kg, resulted in a significant improvement of $PaO_2$. Our results are in good agreement with those of other long-term studies. These studies designed to observe the effects usually after 3 months. Because the maximal plasma AB level reaches a plateau after 3 months (8). Many of the previous trials in patients with COPD and hypoxemia have shown that AB

improves blood gases and decreases the hospital care. However, the long-term placebo controlled studies have not showed a decrease in mortality rates with AB (9,10).

Improvements in nocturnal oxygenation similar to our present study have been described. The lowest $SaO_2$ during sleep rose on average from 65±6% to 77±3% ($p<0.002$) and the desaturation duration below 80% also improved (4). AB improved oxygen saturation during sleep without any significant changes in the quantity or quality of sleep (5, 11, 12).

The improvement of pulmonary gas exchange obtained at rest with almitrine was well maintained during exercise, a single orally administered dose of AB improved pulmonary gas exchange during exercise in patients with chronic airflow obstruction (6). The distance covered at 6 and 12 minutes increased significantly (6,13). But, our study group is very small to confirm these exercise results.

The number of patients studied was limited by the fact that majority of COPD patients lack effort tolerance and frequently have attacks of acute exacerbation. Reviewing the literature, most of the studies used the walking test at 6 and 12 minutes to assess the exercise capacity of COPD patients. This is because tread-mill exercise test may not be well tolerated by severely hypoxemic patients.

Side effects such as increased dyspnea, peripheral neuropathy, weight loss were reported in previous studies (8,9). Peripheral neuropathy can be seen in 24% of COPD patients without any drug intake (14). One patient with diabetes mellitus dropped out of the present study because of the peripheral neuropathy, the other side effects were not reported.

This present study confirms that AB is effective in hypoxemia as a single dose and long-term therapy. These changes were accompanied by improvements in desaturation during sleep but not in exercise tolerance. However, long-term trials in large numbers of subjects are necessary to assess the efficacy on exercise performance.

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