Eur Respir J
1991, 4, 1215–1222

One year treatment with almitrine improves hypoxaemia but does not increase pulmonary artery pressure in COPD patients

E. Weitzenblum*, F. Schrijen**, M. Apprill*, C. Prefaut***, J.C. Yernault†

One year treatment with almitrine improves hypoxaemia but does not increase pulmonary artery pressure in COPD patients. E. Weitzenblum, F. Schrijen, M. Apprill, C. Prefaut, J.C. Yernault.

ABSTRACT: Almitrine bismesylate, a chemoreceptor agonist, improves hypoxaemia in a high percentage of chronic obstructive pulmonary disease (COPD) patients and its long-term use may thus be of interest in these patients.

The course of pulmonary haemodynamics during a one year treatment was investigated in severe COPD patients (forced expiratory volume in one second FEV_1 = 1,040±80 SEM ml) with persistent hypoxaemia (initial arterial oxygen tension (Pao_2) in the range 6.6–8.6 kPa (50–65 mmHg)). Patients were given either almitrine (A, n=27), 100 mg·day^{-1}, during two consecutive months per quarter followed by a one month wash-out period (intermittent "schedule"), or placebo (P, n=18) with the same schedule. Eleven patients in group A and 8 in group P could not complete the one year study because of lack of compliance, worsening of respiratory insufficiency, or for other reasons. In the remaining patients, Pao_2 significantly increased in group A (n=16) from 7.6±0.1 to 8.3±0.2 kPa (56.9±1.0 to 62.7±1.7 mmHg) ($p<0.001$) but not in group P (n=10) from 7.5±0.3 to 7.9±0.3 kPa (56.1±2.3 to 59.1±2.1 mmHg). $Paco_2$ did not significantly change in either group. Pulmonary artery mean pressure (PAP) was stable in both groups: from 26.8±2.1 to 25.4±1.9 mmHg in group A, and from 20.6±1.1 to 20.9±1.5 mmHg in group P. Exercising PAP, right heart filling pressures, wedge pressure, cardiac ouput, pulmonary vascular resistance did not change significantly after one year in either group.

It is concluded that in patients with advanced COPD a one year treatment with almitrine improves hypoxaemia without worsening pulmonary hypertension at rest and during exercise.

Eur Respir J., 1991, 4, 1215–1222.

* Hôpital Universitaire, Strasbourg, France.

** INSERM, U14, Vandoeuvre-les-Nancy, France.

*** Laboratoire d'Explorations Fonctionnelles, Hôpital Universitaire, Montpellier, France.

† Service de Pneumologie, Hôpital Universitaire Erasme, Bruxelles, Belgique.

Correspondence: E. Weitzenblum, C.H.R.U. Hôpital de Hautepierre, Avenue Molière, 67098 Strasbourg Cedex, France.

Keywords: Almitrine bismesylate; chronic hypoxaemia; chronic obstructive pulmonary disease; long-term treatment; pulmonary arterial hypertension.

Received: October 1990; accepted after revision August 8, 1991.

Recent studies have demonstrated that almitrine bismesylate, a peripheral chemoreceptor agonist [1], improved hypoxaemia in a high percentage (about 80%) of patients with severe chronic obstructive pulmonary disease (COPD) [2] and that its long-term use could be of interest in these patients [2–4]. However, there is still some uncertainty about the pulmonary haemodynamic effects of almitrine, since an acute increase of pulmonary artery mean pressure (PAP) has been observed in short-term studies after either intravenous infusion of almitrine [5–7] or oral intake of the drug [8, 9], but these results were not confirmed by other studies [10, 11]. One to six month's treatment with oral almitrine has been shown to increase PAP [9] or was not associated with any change in pulmonary haemodynamics [12–14]. These results were generally obtained from limited series of patients and in the only one year study, that of PREFAUT *et al.* [15], cardiac output was obtained by an indirect (rebreathing) method and results of pulmonary vascular resistance and exercising data were lacking.

PREFAUT *et al.* [15] did not detect any rise in PAP in the almitrine treated group. This point is so important, if almitrine is to find its place in COPD therapy, that we have undertaken a further trial in four centres. Several advances were possible, compared with PREFAUT *et al.* [15]. We used intermittent schedule since it is now realized that almitrine can build up in the blood when given over a long period [2]. We used Swan-Ganz catheters, measured wedge pressure, exercised our patients and were able to measure cardiac output by a better method. We also monitored blood almitrine levels which is extremely important if we are to relate therapeutic results to dosage.

In this double-blind, controlled study 45 COPD patients with moderate to severe hypoxaemia were included and 26 could complete the one year follow-up period.

Methods

Patients

Patients were selected on the following criteria: they had COPD assessed on past history and clinical grounds and their forced expiratory volume in one second/vital capacity (FEV_1/VC) ratio was between 25 and 65%, FEV_1 being ≤70% and total lung capacity (TLC) ≥80% of the respective predicted values. FEV_1 had not to increase by ≥20% of its baseline value after inhalation of two puffs (200μg) of salbutamol. The age had to range between 35–75 yrs and the weight between 50–95 kg. Arterial oxygen tension (Pao_2) in room air, during a stable state of the disease, was in the range 6.6–8.6 kPa (50–65 mmHg) and arterial carbon dioxide tension ($Paco_2$) in the range 4.6–8.6 kPa (35–65 mmHg).

Exclusion criteria were: a previous history of asthma, the presence of left heart disease, including unstable angina pectoris and recent myocardial infarction, of an associated chronic lung disease (other than COPD), of a significant renal or hepatic disease, of central nervous system diseases, of a peripheral neuropathy (since peripheral paraesthesiae have been observed in patients undergoing continuous long-term treatment with almitrine [2]), and of any other severe disease. Patients could not receive pulmonary vasodilators (such as calcium channel blockers, hydralazine, beta-agonists given orally *etc.*), respiratory analeptics (acetazolamide, doxapram, medroxyprogesterone), and long-term oxygen therapy (LTO) since LTO has been shown to improve pulmonary haemodynamics in hypoxaemic patients [16, 17]. Pre-menopausal women were excluded.

Patients were informed about the aim of the study, the modalities of the follow-up and the investigations to be performed and a written consent was required. The study protocol was approved by the Ethical Committees of the University Hospitals of each of the four centres involved in the study.

Schedule of the study

The plan of the study appears on figure 1. Prior to the inclusion of the patients in the study, the stable state of their disease was assessed during a three week period (from T_{-21} days to T_0). The criteria of stability were: the absence of any significant change in the clinical condition, a change in weight <2 kg, a change in FEV_1 <300 ml, changes in Pao_2 and $Paco_2$ <0.8 kPa (6 mmHg). Patients could only be included if they fulfilled the criteria of stability. At T_0 the patients were randomly allocated either to almitrine treatment (two tablets of 50 mg per day) or to placebo (two tablets per day) in a double-blind manner. The randomization code has been balanced according to the ratio of three patients receiving almitrine bismesylate for two receiving placebo. Almitrine was given according to an intermittent schedule, in agreement with the Vectarion International Multicentre Study (VIMS) [2] which has clearly indicated that a continuous schedule (100–200 mg almitrine·day^{-1}) resulted in a progressive increase of almitrine plasma concentrations and that paraesthesiae were frequently observed in the presence of a high almitrine plasma level (>500 ng·ml^{-1}). The treatment (or the placebo) was withheld during one month after the first three months (from T_3 to T_4); the treatment resumed from T_4 to T_6, was withheld from T_6 to T_7, and so on up to T_{12} (fig. 1). The aim of the intermittent schedule was to stabilize the blood level of almitrine.

Right heart catheterization was performed at T_0 and again after one year (T_{12}). Clinical examination, a six minute walking test, laboratory tests (complete blood count, platelet count, prothrombin time, assessment of renal and hepatic function), measurement of plasma almitrine concentration, measurement of pulmonary volumes and of arterial blood gases in room air, were performed at T_{-21} days, T_0 and repeated at T_3, T_6, T_9, and T_{12}. At T_4, T_7, T_{10} (end of the one month interruption of treatment) the evaluation was limited to clinical examination, arterial blood gases and measurement of plasma almitrine concentration.

The compliance to treatment was assessed every three months from the interview with the patient, from the ratio of the number of tablets actually used to the number of tablets given to the patient, and from the level of plasma almitrine concentration.

Methods of investigation

Pulmonary volumes were measured with a closed-circuit spirograph or with a body plethysmograph according to the use of each centre. Reference values were those of the European Community [18]. The obligatory measurements were those of vital capacity and FEV_1, but total lung capacity had to be measured at least once, at T_{-21} days.

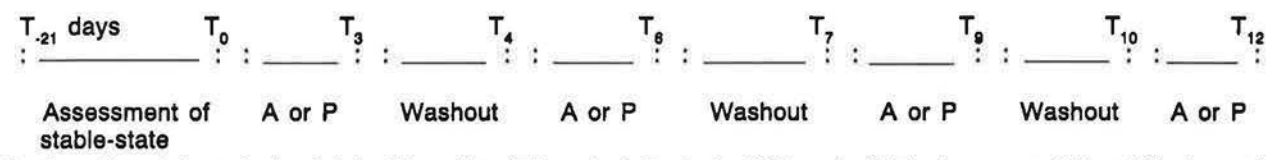

Fig. 1. – Plan of the study. A: almitrine bismesylate (100 mg·day^{-1}; P: placebo (100 mg·day^{-1}); T_{-21} days: onset of the stabilization period, *i.e.* 21 days before T_0; T_0: onset of the study; T_3: after three months; T_4: after four months *etc.*

Arterial blood samples were withdrawn in the supine position after a resting period of at least fifteen min. Pao_2, $Paco_2$ and pH were measured by conventional electrodes.

Right heart catheterization was performed in the supine position, in the morning, without premedication. The method has been described elsewhere [19] and we will only record that F_7 triple lumen Swan Ganz catheters were used. The zero reference point was at mid-thoracic level. Cardiac output was measured by the thermal dilution method and each result was the mean of a triplicate measurement. Right atrial pressure, right ventricular end-diastolic pressure, pulmonary systolic, diastolic and mean pressure, and wedge pressure, were averaged over five respiratory cycles. A catheter was inserted into a brachial or radial artery and this allowed sampling of arterial blood and measurement of the systemic pressure. Measurements of intravascular pressures, cardiac output, and arterial blood gases were obtained after 15 min of rest and at the end of a 7–10 min steady exercise in the supine position, with a bicycle ergometer, the load being of 40 W or less according to the degree of dyspnoea. The haemodynamic investigation was performed in the same way at T_0 and T_{12}.

Plasma levels of unchanged almitrine bismesylate were measured by specific gas liquid chromatography method [20, 21].

Statistical analysis

The stability before treatment (T_{-21} days, T_0) was assessed with a two-way analysis of variance: group (almitrine, placebo) × time with repeated measures on one factor.

The homogeneity of groups (almitrine, placebo) at T_0 was analysed with the Student's t-test for unpaired data.

A two-way analysis of variance (group × time) with repeated measures on time factor was used to compare the evolution between groups. A two-way analysis of variance (time × subject) was used to test the evolution of each group. The level of statistical significance was $p<0.05$.

Results

Forty five subjects were included in the study after the stabilization period. There were only two women. Twenty seven patients were given almitrine (group A) and 18 placebo (group P). The average values (±SEM) of pulmonary volumes, arterial blood gases, and pulmonary artery mean pressure (PAP), at T_0 appear in table 1. It can be observed that there were no significant differences between groups A and P. Bronchial obstruction was severe in both groups. A moderate hypoxaemia, in both groups, could be expected from the inclusion criteria (Pao_2 ranging between 6.6–8.6 kPa (50–65 mmHg)). Most patients in either group (n=18 in group A and n=13 in group P) were not hypercapnic ($Paco_2$ <6 kPa (45 mmHg)).

Pulmonary hypertension, defined by a resting PAP ≥20 mmHg was observed in 19 patients of group A and 14 patients of group P. The difference between the groups was not significant. PAP markedly increased during steady state exercise (table 1), as generally observed in patients with advanced COPD.

Nineteen of forty five patients (11 of 27 in group A and 8 of 18 in group P) could not complete the one year study for various reasons which are given in detail in table 2. Non-compliance to treatment and follow-up and worsening of respiratory insufficiency were the main reasons and were observed with the same frequency in the two groups. Side-effects, which occurred in two patients of group A, did not include peripheral neuropathy: depressive disorder in one patient, anxiety and anorexia in another patient.

The patients who could not complete the study did not differ from the remainder except for resting and exercising pulmonary vascular resistance which were found to be higher in the former, but only in the placebo group. The final almitrine group comprised 16 patients (including one woman) and the final placebo group, 10 patients (no women). Arterial blood gases and pulmonary volumes at T_0 were identical in the final A and P groups (table 3) but resting PAP and pulmonary vascular resistance (PVR) were significantly higher in group A (table 4) due to

Table 1. – Comparison of groups Almitrine and Placebo at T_0

	Almitrine n=27	Placebo n=18	Difference
Age yrs	60±2	63±2	NS
Walking distance in 6 min m	445±11	437±23	NS
Vital capacity *l*	2.68±0.14	2.52±0.13	NS
FEV_1 *l*	1.04±0.7	1.04±0.9	NS
FEV_1/VC %	39±2	40±2	NS
Pao_2 kPa	7.6±0.1	7.6±0.1	NS
$Paco_2$ kPa	5.8±0.2	5.7±0.2	NS
Haematocrit %	48.2±1.3	45.9±0.7	NS
PAP rest mmHg	24.6±1.5	22.8±1.9	NS
PAP exercise mmHg	43.9±2.3	37.7±2.9	NS

FEV_1: forced expiratory volume in one second; FEV_1/VC: FEV_1/vital capacity ratio; Pao_2 and $Paco_2$: arterial oxygen and carbon dioxide tension, respectively; PAP: mean pulmonary artery pressure; NS: statistically nonsignificant, (Mean±SEM).

Table 2. – Causes for failure to complete the study by 19 out of 45 patients

Causes	Group A 11 out of 27	Group P 8 out of 18
Non-compliance to treatment and follow-up	4	2
Worsening of respiratory insufficiency	3	4*
Deaths from non-respiratory causes	1	2
Side-effects	2	-
Other causes	1	-

A: almitrine; P: placebo; *: including two deaths.

Table 3. – Results of a one year treatment: arterial blood gases, pulmonary volumes and minute ventilation

	Almitrine n=16			Placebo n=10		
	T_0	T_{12}	Difference	T_0	T_{12}	Difference
Pao_2 kPa	7.6±0.1	8.3±0.2	p<0.001	7.5±0.3	7.9±0.3	NS
Sao_2 %	88.9±0.9	91.3±0.5	p<0.05	89.3±0.9	90.1±1.0	NS
$Paco_2$ kPa	5.9±0.2	5.5±0.2	NS	5.7±0.2	5.7±0.2	NS
Vital capacity *l*	2.56±0.18	2.76±0.20	NS	2.56±0.18	2.57±0.18	NS
FEV_1 *l*	1.03±0.12	1.04±0.10	NS	1.04±0.10	1.05±0.12	NS
FEV_1/VC %	39±2	38±2	NS	40±2	40±3	NS
$\dot{V}E$ $l \cdot min^{-1}$	9.7±1.0	10.0±0.6	NS	10.6±1.4	9.7±0.8	NS

Sao_2: arterial oxygen saturation; $\dot{V}E$: minute ventilation. For further definitions see legend to table 1. (Mean±SEM).

Table 4. – Results of one year treatment: haemodynamic data at rest

	Almitrine n=16			Placebo n=10		
	T_0	T_{12}	Difference	T_0	T_{12}	Difference
PAP mmHg	26.8±2.1*	25.4±1.9	NS	20.6±1.1*	20.9±1.5	NS
PAPsyst mmHg	40.8±3.3**	39.6±3.2	NS	30.3±1.4**	30.9±1.5	NS
PAPdiast mmHg	18.5±1.5	18.3±1.4	NS	15.2±1.2	15.0±1.4	NS
PWP mmHg	7.9±0.9	6.3±0.9	NS	6.9±0.8	8.0±0.7	NS
RAP mmHg	4.8±0.8	4.0±1.1	NS	2.9±0.8	4.1±0.9	NS
Q $l \cdot min^{-1}$	5.4±0.4	5.2±0.2	NS	6.6±0.7	5.8±0.4	NS
PVR mmHg$\cdot l^{-1} \cdot$min	3.6±0.4*	3.2±0.4	NS	2.2±0.2*	2.3±0.3	NS

PAP: mean pulmonary artery pressure; PAPsyst: pulmonary artery systolic pressure; PAPdiast: pulmonary artery diastolic pressure; PWP: pulmonary wedge pressure; RAP: right arterial pressure; Q: cardiac output; PVR: pulmonary vascular resistance. *:difference between groups almitrine and placebo at T_0 significant with p<0.05; **: difference between groups almitrine and placebo at T_0 significant with p<0.01. (Mean±SEM).

the fact that patients lost to follow-up had higher PAP than the remainder in group P, and lower PAP than the remainder in group A. The same differences were observed for exercising haemodynamic variables (table 5).

The evolution of almitrine plasma levels from T_3 to T_{12} in group A is shown on table 6. It appears that the mean almitrine plasma level was nearly identical at T_6, T_9 and T_{12}, and that one month interruptions of treatment resulted in a decrease of plasma almitrine concentration, at T_7 and T_{10}, by not more than 50% of its initial value at T_6 and T_9, respectively.

After one year, Pao_2 significantly (p<0.001) increased in group A from 7.6±0.1. to 8.3±0.2. kPa (56.9±1.0 to 62.7±1.7 mmHg), but not in group P (table 3). $Paco_2$ tended to decrease in group A but the difference did not reach the level of statistical significance. Improvement of hypoxaemia in the group treated with almitrine was not related to bronchodilation or to an analeptic effect since FEV_1 and minute ventilation ($\dot{V}E$) were unchanged from T_0 to T_{12} (table 3).

The changes in haemodynamic data from T_0 to T_{12} are shown in table 4 (resting data) and table 5

Table 5. – Results of one year treatment: haemodynamic data during exercise

	Almitrine n=16			Placebo n=10		
	T_0	T_{12}	Difference	T_0	T_{12}	Difference
PAP mmHg	45.4±1.7*	49.0±2.6	NS	34.1±2.6*	35.6±2.2	NS
PAPsyst mmHg	67.4±2.0**	76.7±4.6	NS	49.3±3.9**	52.9±2.2	NS
PAPdiast mmHg	33.0±1.7*	34.6±1.7	NS	25.6±2.1*	25.0±1.2	NS
PWP mmHg	15.7±1.8	17.5±1.9	NS	12.3±1.6	13.6±0.8	NS
RAP mmHg	11.3±2.0	9.0±2.0	NS	6.5±0.8	7.8±0.7	NS
Q $l \cdot min^{-1}$	8.8±0.7	8.5±0.7	NS	9.8±0.6	8.7±0.7	NS
PVR $mmHg \cdot l^{-1} \cdot min$	3.9±0.5*	3.9±0.6	NS	2.3±0.2*	2.8±0.3	NS

*: difference between groups almitrine and placebo at T_0 significant with $p<0.05$; **: difference between groups almitrine and placebo at T_0 significant with $p<0.01$. For definitions see legend to table 4. (Mean±SEM).

Table 6. – Almitrine plasma levels ($ng \cdot ml^{-1}$) in the group treated with Almitrine

	T_3	T_4	T_6	T_7	T_9	T_{10}	T_{12}
Mean	248	121	317	194	322	173	285
SEM	35	24	41	35	48	31	38

T_3: after 3 months; T_4: after 4 months *etc.*

(exercising data). Resting PAP did not change in either group: from 26.8±2.1 to 25.4±1.9 mmHg in group A, and from 20.6±1.1 to 20.9±1.5 mmHg in group P. In group A, PAP increased by ≥3 mmHg in three patients, decreased by ≥3 mmHg in six patients and did not change by more than 3 mmHg in seven patients (table 7). In group P, PAP increased by ≥3 mmHg in three patients, decreased by ≥3 mmHg in three patients and did not change by more than ≥3 mmHg in four patients. Resting right atrial pressure, wedge pressure, cardiac output and pulmonary vascular resistance were also unchanged after one year in both groups. Exercising PAP did not change significantly in either group nor did the other exercising haemodynamic variables.

The individual results of Pao_2 and PAP at T_0 and T_{12} and of almitrine plasma level at T_{12}, in group A, appear in table 7. It can be observed that there was no link between changes in Pao_2 and PAP on the one hand and almitrine plasma concentration on the other. Linear regressions between almitrine plasma concentration and changes in Pao_2 and PAP did not show any significant correlation. There was no correlation between initial Pao_2 and the change of PAP in the almitrine group.

Table 7. – Individual results of Pao_2 and PAP at T_0 and T_{12}, and almitrine plasma level at T_{12} in the group treated with almitrine

Patient no.	Pao_2 kPa		PAP mmHg		Almitrine plasma level $ng \cdot ml^{-1}$
	T_0	T_{12}	T_0	T_{12}	T_{12}
1	7.5	8.2	30	30	501
2	7.3	8.6	24	15	420
3	6.8	8.2	30	25	220
4	7.0	8.1	16	17	452
5	6.6	7.5	35	33	263
6	8.2	8.8	23	28	307
7	7.6	9.0	26	22	196
8	7.7	8.1	25	24	58
9	6.9	7.7	50	38	46
10	7.5	7.6	27	29	150
11	8.0	8.1	16	11	-
12	8.0	8.1	23	28	376
13	8.4	8.1	24	36	391
14	7.7	9.0	29	22	-
15	6.8	7.0	33	31	245
16	8.5	11.0	18	17	368
Mean±SEM	7.6±0.1	8.3±0.2	26.8±2.1	25.4±1.9	285±38

For definitions see legend to table 1.

Discussion

The present results clearly show that a one year treatment with oral almitrine, at the dose of 100 mg·day^{-1}, according to the so-called intermittent schedule, results in a significant improvement of Pao_2, which increased by nearly 0.8 kPa (6 mmHg) as a mean, without noticeable changes of pulmonary haemodynamics at rest and during exercise. The increase in Pao_2 was not associated with any significant change of FEV_1 or minute ventilation and could not, thus, be accounted for by a bronchodilating or a respiratory analeptic effect, in agreement with the results of previous studies [2, 3]. The changes in $Paco_2$ were modest and not statistically significant, a result which was not unexpected since oral almitrine is known to improve ventilation-perfusion mismatching rather than to increase alveolar ventilation in COPD patients [11, 22, 23].

Indeed, 19 of 45 patients (42%) could not complete the study but comparable percentages of patients lost to follow-up have been observed in one year trials including haemodynamic investigations [15]. Even in the VIMS study [2], which was only devoted to the clinical and arterial blood gases evolution under almitrine (or placebo), the rate of patients lost to follow-up after one year, was 25% in the placebo group and 40% in the almitrine group.

An acute rise of PAP and pulmonary vascular resistance has been observed after intravenous infusion of almitrine [5–7] and was generally attributed to an enhancement of hypoxic vasoconstriction by the drug. When almitrine was given orally the short-term results were contradictory and varied from no increase in PAP [11] to a slight but significant increase [8] and to a marked increase [9]. The pulmonary haemodynamic effects of long-term treatment with oral almitrine have been investigated in few studies [9, 12–15] and no significant changes of PAP or any other haemodynamic variable were observed after one month [12], four months [14], six months [13] or one year [15]. However, MACNEE *et al.* [9] have reported a persistent increase of PAP after a 3–6 month treatment, in patients receiving 100 mg almitrine·day^{-1}, but their study was limited to five patients and there was no control group. The individual results were not given but it appears from their figure 6 that a marked increase in PAP was only present in one patient.

In all these previous studies [9, 12–15] several haemodynamic data were lacking: pulmonary wedge pressure, allowing the calculation of pulmonary vascular resistance, was not measured. Cardiac output was lacking in two studies [9, 13] and was obtained by an indirect (rebreathing) method in two others [14, 15]. Exercising data were absent in all of these studies. Furthermore, almitrine plasma concentrations were only available in the study of MACNEE *et al.* [9]. The present study was the first to include all of the usual pulmonary haemodynamic variables both at rest and during steady-state exercise.

Our results obtained in 16 patients (group A) are in good agreement with those of KOFMAN *et al.* [12], BOURGOUIN-KAROUANI *et al.* [14], PARAMELLE *et al.* [13] and PREFAUT *et al.* [15], which all together concern 34 patients given oral almitrine. An additional difference between the data of MACNEE *et al.* [9] and those of other groups, including the present study, is that Pao_2 did not increase significantly in their five patients after 3–6 month's treatment with oral almitrine. Most of their patients were probably non-responders to long-term treatment, whereas the percentage of such non-responders has been estimated to be 20–25% in the study which has included the largest number of patients [2].

It must be emphasized that in our study pulmonary haemodynamic variables, both at rest and during exercise, were found to be stable after a one year treatment. In particular there was no significant change in exercising PAP and this is indeed an important finding since resting pulmonary hypertension is generally mild to moderate in these patients (average initial PAP in group A = 26.8±2.1 mmHg) whereas PAP markedly increases during steady-state exercise in most patients with advanced COPD (average initial exercising PAP in group A = 45.4±1.7 mmHg) and a further increase due to treatment could have deleterious effects on the right ventricular function.

How can one explain that acute administration of almitrine often elicits a rise of PAP, probably due to an enhanced hypoxic pulmonary vasoconstriction, whereas long-term treatment is not accompanied by any significant change in pulmonary haemodynamics? There are at least three possible explanations:

Firstly, the plasma levels of almitrine may not be comparable after an acute administration and after long-term oral intake. An acute administration, particularly when almitrine is given intravenously, rapidly results in high plasma levels and the improvement of arterial blood gases is pronounced in most cases, averaging near 1.3 kPa (10 mmHg) for Pao_2 and 0.7 kPa (5 mmHg) for $Paco_2$ [6, 8]. In long-term trials the rise in Pao_2 may be modest, even if significant, as in the study of PARAMELLE *et al.* [13] and the present one, or may even not be found [9], which could be accounted for by lower levels of plasma almitrine. In fact blood levels of almitrine have been measured in few long-term studies [2, 4] and in none of those devoted to the long-term evolution of pulmonary haemodynamics, except our own. In acute investigations no relationship between the level of plasma almitrine and the change in Pao_2 could be demonstrated [9, 24] but a correlation between almitrine concentration and the rise of PAP was observed [9]. In the present study, there was no link between long-term changes in Pao_2 and PAP on the one hand and almitrine plasma levels on the other (table 7), but it can be argued that blood almitrine concentration at T_{12} was rarely high, always ≤500 ng·ml^{-1} whereas in the acute investigation of MACNEE *et al.* [9] two out of ten patients had plasma levels ≥500 ng·ml^{-1} and four, 400 ng·ml^{-1}.

Thus, a pulmonary vasoactive effect of almitrine could be accounted for by high plasma levels which are unlikely to occur during long-term administration, when the "intermittent" schedule is used.

Secondly, several studies have indicated that the pulmonary haemodynamic effects of almitrine are of short duration and disappear soon after the end of an intravenous infusion, whereas improvement of arterial blood gases is still present [5, 6]. There is, at present, no explanation for this dissociation between gasometric and haemodynamic effects of almitrine.

Thirdly, the potential vasoconstrictive effects of almitrine could be counterbalanced by the improvement of hypoxaemia which is known to induce a slight but significant decrease of PAP in COPD patients given long-term oxygen therapy [16, 17]. This hypothesis has been recently raised by PREFAUT *et al.* [15] to explain the observed stability of PAP after a one year treatment with almitrine.

Whatever the mechanism involved, it is clear that long-term treatment with oral almitrine has no adverse effect on pulmonary haemodynamics at rest or during exercise, and it follows that there is no risk of overloading the right ventricle. Finally it must be underlined that side-effects were rare and did not include peripheral neuropathy, or weight loss which has been observed in a recent study [4]. This is probably due to the intermittent schedule which allowed a rather good stabilization of almitrine plasma concentration with average values in the range 300–350 $ng \cdot ml^{-1}$, *i.e.* significantly lower than values observed with the continuous treatment [2, 4]. These results are of interest since it has been demonstrated that there is a close relationship between the almitrine plasma level and the occurrence of side-effects such as peripheral neuropathies [2].

It can be concluded that long-term treatment with oral almitrine bismesylate, 100 $mg \cdot day^{-1}$, according to the intermittent schedule, is safe, ameliorates arterial blood gases and does not worsen pulmonary haemodynamics in patients with advanced COPD.

Acknowledgements: The authors are indebted to the Institut de Recherches Servier (Courbevoie-sur-Seine, France) for help and assistance during this study.

References

1. Laubie M, Diot F. – A pharmacological study of the respiratory stimulant action of S2620. *J Pharmacol*, 1972, 3, 363–374.
2. Voisin C, Howard P, Ansquer JC. – Almitrine bismesylate: a long-term, placebo-controlled, double-blind study in COAD. Vectarion international multicentre study group. *Bull Eur Physiopathol Respir*, 1987, 23, (Suppl. 11), 169–182.
3. Arnaud F, Bertrand A, Charpin J, Chrétien J, Decroix F, Guerrin F, Kalb JC, Lissac J, Michel B, Morère P, Paramelle B, Pariente R, Perrin-Fayolle M, Rochemaure J, Voisin C. – Almitrine bismesylate in long-term treatment of patients with chronic bronchitis at the stage of chronic respiratory insufficiency: a multicentre double-blind, placebo-controlled study. *Bull Eur Physiopathol Respir*, 1982, 18, (Suppl. 4), 373–382.
4. Watanabe S, Kanner RE, Cutillo AG, Menlove RL, Bachand RT Jr, Szalkowski MB, Renzetti AD Jr. – Long-term effect of almitrine bismesylate in patients with hypoxaemic chronic obstructive pulmonary disease. *Am Rev Respir Dis*, 1989, 140, 1269–1273.
5. Naeije R, Melot C, Mols P, Hallemans R, Naeije N, Cornil A, Sergysels R. – Effects of almitrine in decompensated chronic respiratory insufficiency. *Bull Eur Physiopathol Respir*, 1981, 17, 153–161.
6. Weitzenblum E, Ehrhart M, Schneider JC, Hirth C, Roegel E. – Effets hémodynamiques pulmonaires de l'almitrine intraveineuse chez des bronchiteux chroniques insuffisants respiratoires. *Bull Eur Physiopathol Respir*, 1982, 18, 765–774.
7. Dull WL, Polu JM, Sadoul P. – The pulmonary heamodynamic effects of almitrine infusion in men with chronic hypercapnia. *Clin Sci*, 1983, 64, 25–31.
8. Simonneau G, Meignan M, Denjean A, Raffestin B, Harf A, Prost JF. – Cardiopulmonary effects of a single oral dose of almitrine at rest and on exercise in patients with hypoxic chronic airflow obstruction. *Chest*, 1986, 89, 174–179.
9. Macnee W, Connaughton JJ, Rhind GB, Hayhurst MD, Douglas NJ, Muir AL, Flenley DC. – A comparison of the effects of almitrine or oxygen breathing on pulmonary arterial pressure and right ventricular ejection fraction in hypoxic chronic bronchitis and emphysema. *Am Rev Respir Dis*, 1986, 134, 559–565.
10. Schrijen F, Romero Colomer P. – Effets hémodynamiques d'un stimulant ventilatoire (almitrine) chez des pulmonaires chroniques. *Bull Eur Physiopathol Respir*, 1978, 14, 775–784.
11. Melot C, Naeije R, Rothschild T, Mertens P, Mols P, Hallemans R. – Improvement in ventilation perfusion matching by almitrine in COPD. *Chest*, 1983, 83, 528–533.
12. Kofman J, Perrin-Fayolle M, Groendahl C. – Etude de l'action hémodynamique du bismesylate d'almitrine sur la circulation pulmonaire chez le bronchitique chronique. *Bull Eur Physiopathol Respir*, 1982, 18, (Suppl. 4), 353–358.
13. Paramelle B, Levy P, Pirotte C. – Long term follow-up of pulmonary arterial pressure evolution in COPD patients treated by almitrine bismesylate. *Eur J Respir Dis*, 1983, 64, (Suppl. 126), 333–336.
14. Bourgouin-Karouani D, Ramonatxo M, Michel FB, Macabies J, Prefaut C. – Surveillance hémodynamique pulmonaire d'insuffisants respiratoires chroniques traités à double insu pendant 4 mois par le bismesylate d'almitrine. *Rev Fr Mal Respir*, 1984, 1, 245–250.
15. Prefaut C, Bourgouin-Karouani D, Ramonatxo M, Michel FB, Macabies J. – A one year double-blind follow-up of blood gas tensions and haemodynamics in almitrine bismesylate therapy. *Eur Respir J*, 1988, 1, 41–50.
16. Timms RM, Khaja FU, Williams GW and the Nocturnal Oxygen Therapy Trial Group. – Haemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. *Ann Intern Med*, 1985, 102, 29–36.
17. Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Pelletier A. – Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*, 1985, 131, 493–498.

18. Commission des communautés européennes - CECA. Aide-mémoire pour la pratique de l'examen de la fonction ventilatoire par la spirographie. Collection d'hygiène et de Médecine du Travail, n° 11, 2° ed, Luxembourg, 1971.
19. Weitzenblum E, Schrijen F, Mohan-Kumar T, Colas des Francs V, Lockhart A. – Variability of the pulmonary vascular response to acute hypoxia in chronic bronchitis. *Chest*, 1988, 94, 772–778.
20. Baune A, Bomet N, Courte S, Voisin C. – Trace determination of almitrine in plasma by gas-liquid chromatography using a nitrogen-phosphorus detector. *J Chromato Biomed Applic*, 1981, 223, 219–224.
21. Bromet N, Courte S, Aubert Y, Baune A, Balem MP, Duvignaud P. – Pharmacokinetics of almitrine bismesylate studies in patients. *Eur J Respir Dis*, 1983, 64 (Suppl. 126), 363–375.
22. Sergysels R, Naeije R, Mols P, Hallemans P, Melot C. – Ventilation and blood gases dissociation during almitrine infusion in chronic and acute stages of chronic obstructive lung disease. *Rev Fr Mal Respir*, 1980, 8, 577–585.
23. Castaing Y, Manier G, Varene N, Guenard H. – Almitrine orale et distribution des rapports VA/Q dans les bronchopneumopathies chroniques obstructives. *Bull Eur Physiopathol Respir*, 1981, 17, 917–932.
24. Stradling JR, Nicholl CG, Cover D, Davies EE, Hughes JMB, Pride NB. – The effects of oral almitrine on pattern of breathing and gas exchange in patients with chronic obstructive pulmonary disease. *Clin Sci*, 1984, 66, 435–442.

Un traitement d'un an par almitrine améliore l'hypoxémie mais n'augmente pas la pression artérielle pulmonaire chez les patients BPCO. E. Weitzenblum, F. Schrijen, M. Apprill, C. Prefaut, J.C. Yernault.

RÉSUMÉ: Le bismesylate d'almitrine, un agoniste des chémorécepteurs, améliore l'hypoxémie chez un pourcentage élevé de patients atteints de BPCO, et son utilisation au long cours pourrait dès lors être intéressante chez ces patients.

L'évolution de l'hémodynamique pulmonaire au cours d'un traitement d'un an a été investiguée chez des patients atteints de BPCO sévère (VEMS = 1040±80 SEM ml) avec hypoxémie persistante (Pao_2 initiale située entre 6.6 et 8.6 kPa (50–65 mmHg). Les patients ont reçu, soit de l'almitrine (A, n = 27) à raison de 100 mg par jour pendant deux mois consécutifs par trimestre suivis d'un mois de période de wash-out ("schéma intermittent"), soit un placebo (P, n=18) avec le même schéma. L'année d'observation n'a pas pu être complétée chez 11 patients du groupe A et 8 du groupe P, en raison de leur manque d'observance, d'une aggravation de l'insuffisance respiratoire, ou pour d'autres raisons. Chez les patients restants, la Pao_2 a augmenté de façon significative dans le groupe A (n = 16); elle est passée de 7.6±0.1 à 8.3±0.2 kPa (56.9±1.0 à 62.7±1.7 mmHg) ($p<0.001$). Par contre, dans le groupe P (n=10), l'augmentation de 7.5±0.3 à 7.9±0.3 kPa (56.1±2.3 à 59.1±2.1 mmHg) n'est pas significative. La $Paco_2$ ne s'est modifiée significativement dans aucun des groupes. La PAP est stable dans les deux groupes; elle varie de 26.8±2.1 à 25.4±1.9 mmHg dans le groupe A, et de 20.6±1.1 à 20.9±1.5 mmHg dans le groupe P. La pression artérielle pulmonaire d'effort, les pressions de remplissage du ventricule droit, la pression bloquée, le débit cardiaque, et la résistance vasculaire pulmonaire, n'ont pas changé de façon significative après un an dans aucun des groupes.

L'on conclut que chez les patients atteints de BPCO avancée, un traitement d'un an par almitrine est efficace sur l'hypoxémie, sans aggravation de l'hypertension pulmonaire au repos et à l'effort.

Eur Respir J., 1991, 4, 1215–1222.