Eur Respir J
1988, 1, 41–50

A one year double blind follow-up of blood gas tensions and haemodynamics in almitrine bismesylate therapy

Ch. Préfaut*, D. Bourgouin-Karaouni*, M. Ramonatxo*, F.B. Michel**, J. Macabies*

A one year double blind follow-up of blood gas tensions and haemodynamics in almitrine bismesylate therapy. Ch. Préfaut, D. Bourgouin-Karaouni, M. Ramonatxo, F.B. Michel, J. Macabies.

ABSTRACT: Almitrine bismesylate, a chemoreceptor agonist, improves blood gases in chronic obstructive lung disease (COLD). Some authors have observed an increase in pulmonary artery pressure ($\bar{P}pa$) after single doses of almitrine bismesylate (A). This led to the present one year double blind placebo (P) controlled study to assess haemodynamic effects of long-term oral treatment in COLD (1.5 mg/kg/day for one year), together with clinical benefit and blood gas improvement. Twenty moderately severe patients entered the study, fifteen of whom completed it (eight in group (A), seven in group (P)). Blood gas values, minute ventilation ($\dot{V}E$), mean pulmonary artery pressure ($\bar{P}pa$) and cardiac output ($\dot{Q}c$) were periodically measured. $\bar{P}pa$ and $\dot{Q}c$ remained unchanged in both groups throughout the study. We observed relevant clinical improvement without side effects and no significant increase in $\dot{V}E$ in group (A). Arterial oxygen tension (Pa_{O_2}) showed a 1.2 kPa (9 mmHg) mean increase in group (A) and remained unchanged in group (P). These data and those from the literature seem to indicate that almitrine induces a vascular effect, especially after a single dose. However, as long as Pa_{O_2} improves simultaneously no long-term haemodynamic consequence is apparent. The discrepancy between immediate and long-term vascular effects of almitrine might be explained by the improvement in gas exchange which could reduce and/or counter-balance the vasoactive response. In conclusion, after one year of therapy almitrine bismesylate results in considerable clinical and blood gas improvements without significant haemodynamic change.

Eur Respir J. 1988, 1.

* Service d'Exploration de la Fonction Respiratoire.
** Service des Maladies Respiratoires, Hôpital Aiguelongue, 34059 Montpellier Cedex, France.

Correspondence: Dr. Ch. Prefaut, Service d'Exploration de la Fonction Respiratoire, Hôpital Aiguelongue, Avenue du Major Flandre, 34059 Montpellier Cedex, France.

Keywords: Almitrine bismesylate; arterial blood gases; pulmonary hypertension.

Received: February 2, 1987; accepted after revision September 9, 1987.

Almitrine bismesylate, a chemoreceptor agonist [11], is a new drug which improves blood gas values in chronic obstructive lung disease (COLD) when given in single dose [19, 20, 26], short-term ($\leq$1 month) [16, 25], or for 6-months [1]. The beneficial effect may be related to improvement of regional distribution of ventilation/perfusion ratios [20, 26], the mechanism of which remains unclear. Both alveolar ventilation and the pulmonary circulation might be involved.

Several authors have reported modifications of pulmonary artery pressure ($\bar{P}pa$) after almitrine bismesylate administration. NAEIJE *et al.* [15], and WEITZENBLUM *et al.* [31] have reported 1.1–1.3 kPa (8–10 mmHg) $\bar{P}pa$ increases after intravenous perfusion of almitrine bismesylate; on the other hand, CASTAING *et al.* [4] did not observe any $\bar{P}pa$ increase after oral administration of almitrine bismesylate but MELOT *et al.* [14], and SIMONNEAU *et al.* [27] reported a mean $\bar{P}pa$ increase of 0.5 kPa (4 mmHg). These observations raise the question of the persistence of adverse haemodynamic effects after long term oral almitrine bismesylate therapy. In order to assess possible haemodynamic effects, together with therapeutic benefit and acceptability we carried out a randomized double-blind placebo controlled study for 1 yr using continuous oral therapy (daily dose: 1.5 mg/kg) in moderately severe COLD patients.

Patients and methods

Twenty patients aged 45–69 yr (table I) entered the study. They had all been cigarette smokers for at least 30 yr, had COLD with chronic hypoxia (Pa_{O_2}: 7.72 ± 1.09 kPa (58 ± 8.2 mmHg) ($m \pm SD$)), were ambulatory and stable for at least three weeks as shown by repeated blood gas values. No patients showed clinical evidence of right heart failure before onset of the study. Usual therapy was maintained throughout including bronchodilators, mucolytics, diuretics, cardiotonics, domiciliary oxygen-therapy (four patients, two in the almitrine bismesylate group), domiciliary ventilatory assistance (two patients in the almitrine bismesylate group).

Patients were randomized between almitrine bismesylate (1.5 mg/kg/day) and placebo treatment. Almitrine or identical tablets of placebo were given in two

daily doses. Allocation to one or other group was made according to a random number table. Administration was totally double blind and group allocation was disclosed only at the end of the study. All patients were fully informed of the purpose and methods of the study and gave their consent.

Clinical findings and arterial blood gas values in the sitting position were obtained just before the onset of therapy (T0), 1 month after (T1), 2 months after (T2) and every two months thereafter (T4, T6, T8, T10, T12). In addition, minute ventilation, O_2 and CO_2 alveolar-end tidal gradients and haemodynamic parameters were determined in the supine position at T0, T6 and T12 months during the same morning session. The sequence used for supine measurements was as follows: 1) $\bar{P}pa$ measurement; 2) simultaneous measurement of minute ventilation, expired gases, end tidal gas composition and blood gases; 3) Cerretelli's modified rebreathing technique [5]. This supine sequence was repeated twice after pauses to enable the patients to return to a steady state. When in use, oxygen-therapy or ventilation assistance were withdrawn at least 2 h before measurements.

Clinical follow up consisted of patient history along with standard physical examination. Each patient was asked whether he experienced tiredness, shortness of breath, inability to work or sleep disturbances. Breathlessness was evaluated from 1–5 using the Sadoul scale [1]. Clinical signs of right ventricular failure were looked for. Attention was given to possible side effects by measuring blood pressure, heart rate and by checking for nausea, tremor, peripheral paraesthsia and disturbance of gait.

Before the onset of therapy conventional spirographic measurements (Godart) were performed including vital capacity (VC), forced expiratory volume in one second (FEV_1) and residual volume (RV) by the helium dilution method. Total lung capacity was calculated as the sum of VC and RV. Values were expressed as a percentage of predicted [21]. Blood gas values were measured on samples drawn either from a flexible catheter (T0, T6, T12) or from a needle (T1, T2, T4, T8, T10) inserted percutaneously into the brachial artery. Arterial blood was immediately analysed for Pa_{O_2}, Pa_{CO_2} and pH at 37 °C using appropriate electrodes (Corning 168), arterial oxygen saturation (Sa_{O_2}) and plasma bicarbonate (HCO^-_3) were calculated.

Minute ventilation ($\dot{V}E$), tidal volume (VT) and respiratory frequency (f) were determined with a Fleisch No. 2 pneumotachograph connected to a Validyne transducer MP 45 (± 2 cmH_2O) with an electronic integrator.

Haemodynamic parameters were collected with a Grandjean floating catheter [9] (flexo-pulmocath 125×0.1) placed inside the pulmonary artery. Correct placement was checked by recording pressure curves. Pressures were measured with a Statham P 23 DB electromanometer connected together with the electrocardiograph to a Phillips EM 110 recorder. The reference zero pressure level was standardized to a fixed mean mid-chest distance determined from a sample of six patients and used on each test day and for all patients throughout the study in order to compare identical levels of pressure measurements in all patients. Pulmonary artery pressure was measured before each assessment of cardiac output ($\dot{Q}c$). Each pressure value was averaged for five respiratory cycles and the mean of three successive values ($\bar{P}pa$) was retained. $\dot{Q}c$ was indirectly determined according to Fick's principle and the rebreathing technique [5]. Patients were connected to a Douglas bag and expired gases were collected; end-tidal arterial O_2 and CO_2 pressure differences $P(ET\text{-}a)O_2$, $P(a\text{-}ET)CO_2$ were simultaneously measured.

End-tidal gases were measured by a mass spectrometer calibrated for each experiment using the same gas mixture as the blood gas analyser (Centronic MGA 200) and recorded by Gould ES 1000 apparatus; blood samples were simultaneously drawn from the arterial line. At the end of the collection period, CO_2 production ($\dot{V}CO_2$) was calculated. Patients then rebreathed a hypoxic-hypercapnic gas (7% CO_2, 12% O_2, 81% N_2) from a 2-litre bag until CO_2 reached equilibrium between bag, alveoli and capillaries; this was obtained when CO_2 pressure reached a plateau ($P_{plat}CO_2$), usually within 15 s. $P_{plat}O_2$ was measured at same time as $P_{plat}CO_2$. Mixed venous CO_2 and O_2 pressure: ($P\bar{v}CO_2$, $P\bar{v}O_2$) were respectively calculated by subtracting $P(a\text{-}ET)CO_2$ from $P_{plat}CO_2$ and $P(ET\text{-}a)O_2$ from $P_{plat}O_2$ [6]. CO_2 arteriovenous concentration difference was calculated with the Olszowka *et al.* nomogram [17] and $\dot{Q}c$ was then calculated. The complete procedure for $\dot{Q}c$ evaluation was obtained at least 3 times at 15 min intervals and the mean value retained.

Wedge pressure cannot be systematically obtained with a micro-catheter, thus preventing calculation of pulmonary vascular resistance. $\bar{P}pa/\dot{Q}c$ ratio was used instead as an index of pulmonary vascular resistance.

The values are reported as mean $\pm$ SEM. Data collected on entry were compared for homogeneity between the almitrine and placebo groups, using the unpaired Student t-test. T0, T6 and T12 data in patients completing the study were analysed using two-way analysis of variance with repeated measurements to test for between-group differences and using a one-way analysis of variance with repeated measurements [32] to test for within-group changes. If one way analysis of variance was significant the different test day values were further compared two by two using Newman-Keuls' method. Statistical significance was defined at the $p < 0.05$ level.

Results

No significant differences were found between the two groups for clinical, haemodynamic and functional data, except for Pa_{CO_2} which was slightly but significantly higher in the almitrine group (table I). Five patients dropped out of the study: three refused further catheterization (all almitrine bismesylate), one

Table I. - Characteristics of the patients on entry to the study.

	Male/ female	Age yr	FEV_1 *l*	VC *l*	TLC *l*	TLC % predicted	FEV_1/VC %	Pa_{O_2} kPa	Pa_{CO_2} kPa
	F	50	0.77	2.1	4.2	75	37	6.53	6.40
	M	62	0.69	1.8	3.3	67	38	7.73	6.13
	M	69	1.01	3.1	5.4	92	33	5.47	5.93
almitrine	M	45	0.43	1.7	7.1	109	25	8.17	5.47
bismesy-	M	66	0.62	1.7	4.9	84	36	9.33	6.00
late group	M	52	0.70	1.9	6.4	103	37	7.67	5.93
(n=11)	M	68	0.59	1.6	4.8	89	37	8.53	5.73
	M	59	1.23	2.4	5.8	95	51	7.87	5.93
	M*	44	0.59	1.7	4.8	86	35	5.99	5.99
	M*	60	1.51	3.0	4.9	80	50	8.51	5.72
	M*	53	0.49	2.0	5.4	95	25	6.92	6.65
$\bar{x} \pm$ SEM	10M/1F	57.1 ± 2.7	0.78 ± 0.10	2.09 ± 0.1	5.18 ± 0.31	88.7 ± 3.7	36.7 ± 2.5	7.52 ± 0.35	5.99 ± 0.10
	M	69	1.79	3.1	5.7	106	58	8.40	5.20
	M	49	1.78	3.8	6.2	91	47	8.80	4.87
	M	66	1.14	3.1	5.7	90	37	9.33	5.07
Placebo	M	56	2.54	4.3	7.2	126	59	8.33	5.07
group	M	57	2.00	3.6	6.2	93	56	8.00	5.07
(n=9)	M	57	0.65	2.1	4.0	57	31	7.20	5.87
	M	52	0.68	2.8	7.1	116	24	7.87	4.80
	M*	60	1.23	2.4	4.9	82	51	7.85	5.32
	M*	65	1.22	3.4	7.0	119	36	5.85	4.79
$\bar{x} \pm$ SEM	9M	59.0 ± 2.2	1.45 ± 0.21	3.18 ± 0.23	6.00 ± 0.36	97.8 ± 7.2	44.3 ± 4.3	7.96 ± 0.33	5.12 ± 0.11

No significant differences were found between the two groups except for Pa_{CO_2}. TLC: total lung capacity; VC: vital capacity; FEV_1: forced expiratory volume in 1 second; Pa_{O_2}; Pa_{CO_2}: oxygen and carbon dioxide tensions in arterial blood, *:drop-outs.

was lost to follow-up at four months (placebo) and one stopped the tablets (placebo) at one month of his own accord (attributing cor pulmonale to the tablets). Fifteen patients (eight almitrine bismesylate and seven placebo) completed the study.

All patients receiving almitrine bismesylate expressed the sensation of feeling better. Five patients considerably improved their score on the dyspnoea scale, and three others described no change. One patient was able to stop domiciliary oxygen therapy and another was able to stop domiciliary ventilatory assistance, both at their request. Six patients receiving placebo expressed an overall sensation of feeling better. Five of these patients improved their dyspnoea score, one described no change and one described worse dyspnoea. No particular side effects were observed in this study.

Pa_{O_2} and Sa_{O_2} time courses were significantly different between groups. The values improved significantly at T6 and T12 in the almitrine bismesylate group compared to T0 with no change throughout in the placebo group. The Newman-Keuls' test showed significant improvement of Pa_{O_2} and Sa_{O_2} in the almitrine bismesylate group between T0 and T6 and no further increase between T6 and T12 (fig. 1). Compared to T0, Pa_{CO_2} values showed the same slight but significant improvement at both T6 and T12 in the almitrine bismesylate group and no change in the placebo group (fig. 1).

The almitrine bismesylate group showed a slight increase in ventilation (fig. 2) and a slight drop in O_2 and CO_2 arterial-end tidal pressure differences whereas there were no significant differences in any of these data between groups (table II).

Although there were no statistical differences between groups, placebo patients showed slightly decreased $\bar{P}pa$ and $\bar{P}pa/\dot{Q}c$ values (table II, fig. 3). Almitrine bismesylate treated patients showed very stable mean haemodynamic data throughout the study. Considering the previously observed 0.53 kPa (4 mmHg) $\bar{P}pa$ modification after single oral doses of almitrine bismesylate [15, 27], we calculated the power of the statistical test. The power of the test used comparing the two groups of seven and eight patients was very satisfactory; the Beta (type II) error of not detecting a 0.53 kPa (4 mmHg) difference was 8%. This result means that, despite the relatively small number of patients, there was a 92% chance of detecting a difference between the two groups, at the significance level of $p < 0.05$, if any such difference existed.

Considering the importance of detecting haemodynamic variations, individual data were analysed. Again we chose 0.53 kPa (4 mmHg) as the threshold

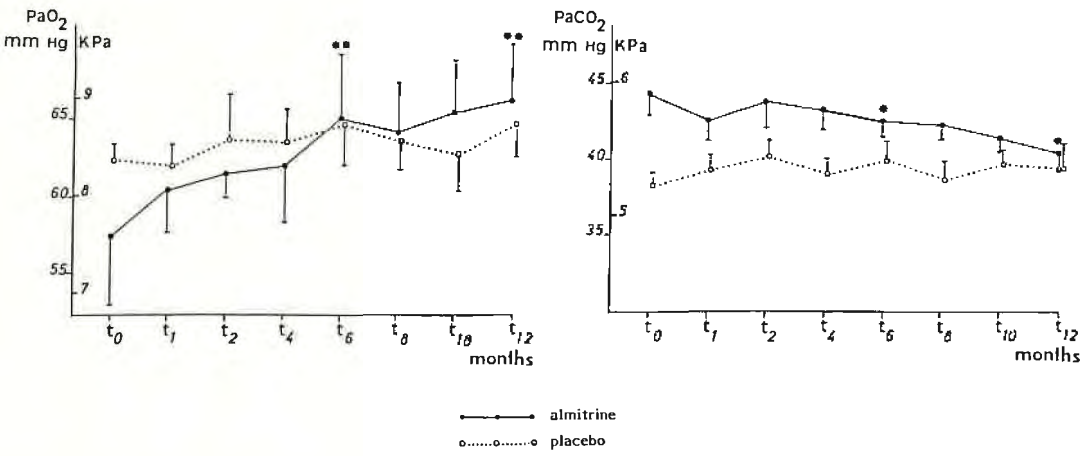

Fig. 1. Time course of Pa_{O_2} and Pa_{CO_2} in almitrine bismesylate (●—●—●) and placebo (○ · · · · ○ · · · · ○) groups. The between group analysis showed a significant difference for Pa_{O_2}, which significantly improved at T6 and T12 ($p<0.01$) within the almitrine group compared to T0 but not in the placebo group. A significant difference was observed on entry for the two groups for Pa_{CO_2}, therefore they were not compared. However the one way analysis of variance showed a significant decrease of Pa_{CO_2} at T6 and T12 ($p<0.05$) compared to T0 in the almitrine group, not in the placebo group.

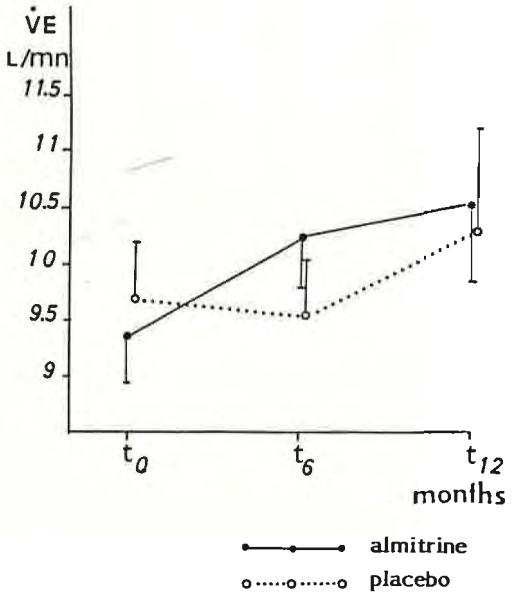

Fig. 2. Time course of ventilation in almitrine bismesylate (●—●—●) and placebo (○ · · · · ○ · · · · ○) groups. No significant changes were observed during the study.

for individual $\bar{P}pa$ variations. In the almitrine bismesylate group, four patients were stable, one showed a decrease in $\bar{P}pa$, and three a single increase at one evaluation time (table III). In the placebo group, five patients were stable and two showed a decrease in $\bar{P}pa$ (table III).

Discussion

This one year study in COLD patients with chronic hypoxia showed that almitrine bismesylate administered orally induced clinical improvement together with a mean increase in Pa_{O_2} of 1.2 kPa (9 mmHg) without deleterious changes in haemodynamic values or in ventilation.

On average, patients had moderate hypoxaemia and low CO_2 retention similar to the majority of patients treated by almitrine bismesylate in our country. The therapeutic aim in such patients is to improve life quality and, if possible, to delay oxygen therapy and lengthen survival.

The need to repeat $\bar{P}pa$ measurements led us to use Grandjean's floating catheter [9] as an easier and less invasive method than the Swan-Ganz catheter. Initial $\bar{P}pa$ values were slightly increased, but were in the range of values reported by WEITZENBLUM *et al.* [30] in similar patients. The use of Grandjean catheters with the smallest internal diameter, necessitated measurement of cardiac output indirectly. We used the CO_2 rebreathing method, which has been validated in healthy subjects [29]. In patients with respiratory diseases the accuracy of such a method is questionable in view of the ventilation/perfusion mismatch. DAVIS *et al.* [7] have reported that the CO_2 rebreathing method for measuring cardiac output was reliable in seriously ill patients (including respiratory distress syndrome). Indeed, using arterial P_{CO_2} instead of end tidal P_{CO_2} they found a very significant correlation ($n=18$; $r=0.935$; $p<0.001$) between rebreathing and direct Fick methods. Similarly, MAHLER *et al.* [13] observed a better correlation ($r=0.84$; $p=0.009$) between the CO_2 rebreathing and direct Fick methods in moderate air flow obstruction than in severe airway disease. However, this good correlation was associated with an underestimation of the indirect values. CHABRILLAT *et al.* [6] improved the Cerretelli CO_2 rebreathing procedure by correcting the plateau pressures with the CO_2 and O_2 end tidal-arterial pressure differences in order to obtain mixed venous pressures. They observed a significant correlation with values obtained by the thermodilution technique ($r=0.897$; $p<0.001$; $n=19$) without underestimation as long as cardiac output was smaller than 8 $l \cdot min^{-1}$. Variability was low, since they

Table II. - Average data on each measurement time and analysis of variance between almitrine and placebo groups.

	Almitrine bismesylate (n=8) $\bar{x} \pm$ SEM			Placebo (n=7) $\bar{x} \pm$ SEM			Between group analysis of variance p value
	T0	T6	T12	T0	T6	T12	time x group interaction
PaO_2 kPa	7.66 ± 0.42	8.75** ± 0.48	8.90** ± 0.38	8.28 ± 0.26	8.65 ± 0.31	8.63 ± 0.24	0.039
$PaCO_2$ kPa	5.94 ± 0.10	5.63 ± 0.11	5.36 ± 0.17	5.13 ± 0.13	5.28 ± 0.10	5.20 ± 0.18	—
pH	7.42 ± 0.01	7.41 ± 0.01	7.40 ± 0.01	7.43 ± 0.01	7.42 ± 0.01	7.41 ± 0.01	0.935
SaO_2 %	89.6 ± 2.0	92.5* ± 1.2	93.1* ± 1.0	92.7 ± 0.8	93.4 ± 0.6	92.9 ± 0.7	0.044
HCO_3^- mmol/*l*	28.1 ± 0.7	25.8 ± 0.5	24.3 ± 0.6	25.1 ± 0.5	25.1 ± 0.6	23.8 ± 0.7	0.060
P (a–ET)CO_2 kPa	0.68 ± 0.09	0.40 ± 0.12	0.41 ± 0.11	0.47 ± 0.11	0.47 ± 0.12	0.52 ± 0.16	0.252
P(ET-a)O_2 kPa	5.36 ± 0.47	4.75 ± 0.57	4.75 ± 0.50	4.55 ± 0.48	4.73 ± 0.40	4.31 ± 0.43	0.147
$\bar{P}pa$ kPa	2.53 ± 0.40	2.47 ± 0.23	2.54 ± 0.28	2.03 ± 0.19	1.77 ± 0.14	1.72 ± 0.18	0.549
Qc *l*·min	4.72 ± 0.31	4.77 ± 0.29	4.72 ± 0.27	5.19 ± 0.37	5.02 ± 0.33	5.01 ± 0.22	0.818
$\bar{P}pa/Qc$ kPa·*l*·min	0.59 ± 0.15	0.52 ± 0.05	0.56 ± 0.08	0.40 ± 0.04	0.36 ± 0.03	0.34 ± 0.04	0.857
VE *l*·min	9.39 ± 0.33	10.27 ± 0.47	10.55 ± 0.74	9.72 ± 0.52	9.58 ± 0.48	10.32 ± 0.87	0.552
VO_2 *l*·min	9.39 ± 0.02	0.32 ± 0.02	0.31 ± 0.02	0.30 ± 0.01	0.30 ± 0.01	0.32 ± 0.01	0.176

When the analysis of variance showed a significant difference between groups, the values significantly improved at T6 and T12 compared to T0 within the almitrine group not in the placebo group (*$p<0.05$, **$p<0.01$) HCO_3: plasma bicarbonate; P(a-ET)CO_2; P(ET-a)O_2: arterial to end tidal CO_2 and O_2 differences; $\bar{P}pa$: pulmonary artery mean pressure; Qc: cardiac output; VE: external ventilation; VO_2: oxygen uptake.

observed a variation factor of 8.9% when three measurements were made within one hour in 18 respiratory patients and 13.2% when three series of three measurements were made within 10–12 days in 17 patients. In the present study we used the correction proposed by CHABRILLAT *et al.* [6] and observed, for three measurements, a mean variability of 9.4±4.3% (m±SD). The initial values observed for cardiac output were in the range of values reported by WEITZENBLUM *et al.* [30] in similar patients. No change was observed after almitrine. Other studies also found no change in $\dot{Q}c$ either after a single dose [14, 23, 31] or after short term therapy [10]. Right ventricular ejection fraction and heart rate were unchanged after three months of therapy [12]. All these findings are consistent with the results of the present study.

It is difficult to obtain wedge pressures with a microcatheter. Pulmonary vascular resistance (PVR) could not be calculated. As an index of PVR, the

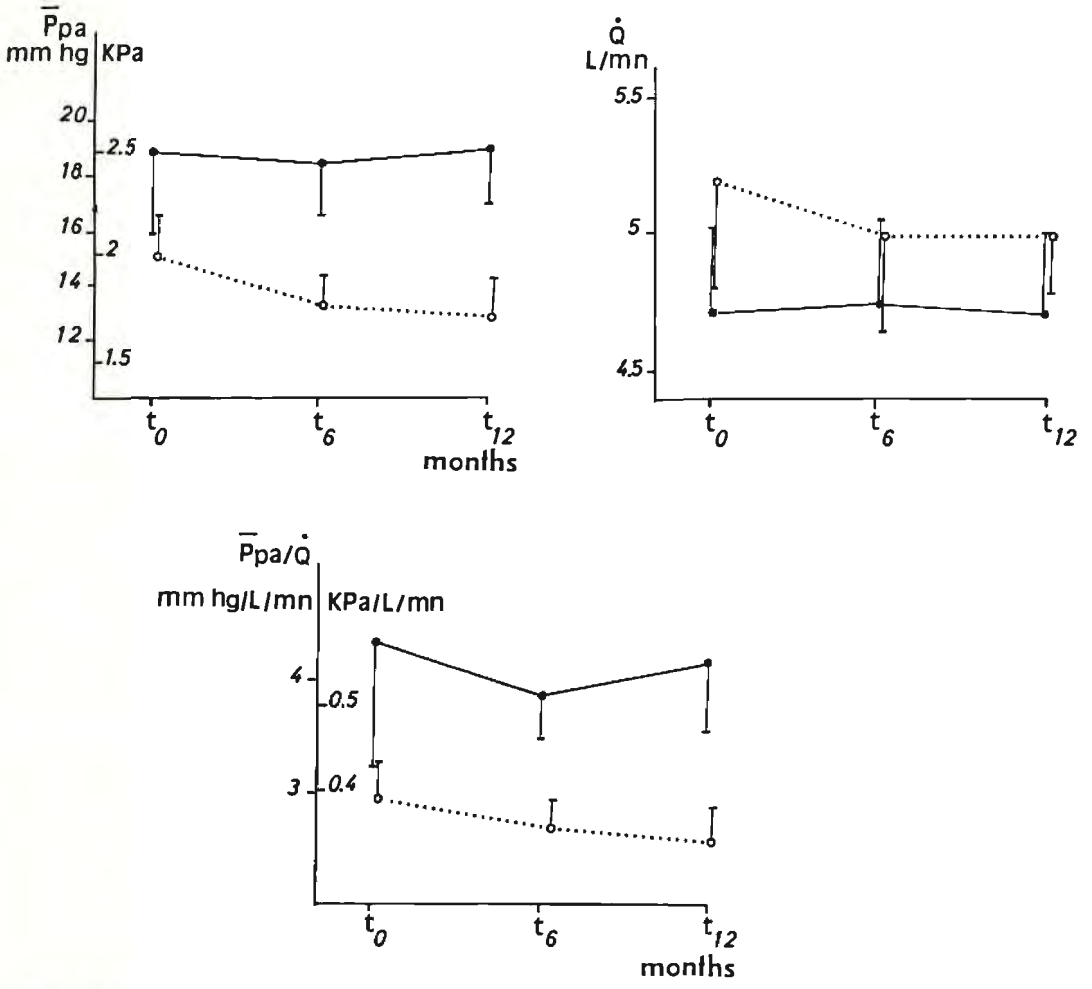

Fig. 3. Time course of mean pulmonary artery pressure, and cardiac output, and an index of pulmonary vascular resistance in almitrine bismesylate (●—●—●) and placebo (○ · · · · ○ · · · · ○) groups. These data were not significantly different on entry (T0) between the two groups and no significant changes were observed during the study.

$\bar{P}pa/\dot{Q}c$ ratio was used. Its reliability has been confirmed by the stability of the wedge pressure after almitrine bismesylate was administered intravenously [8, 23, 31]. Our results, using this ratio, were in the expected range.

Symptoms improved in both groups, all but one patient expressed a sensation of feeling better and the same number of subjects improved their dyspnoea scores. The purely subjective nature of such improvement is obvious but, it is noteworthy that in the almitrine group one patient requested interruption of domiciliary ventilatory assistance and another of domiciliary oxygen therapy.

In our study all but one of the patients were almitrine responders, *i.e.* showed an increase of over 0.67 kPa (5 mmHg) in Pao_2 after almitrine [2]. The mean Pao_2 increase (2.4 kPa, 9.3 mmHg) was similar to that observed in studies where almitrine bismesylate was given intravenously [19, 26]. Similar values were found in a short-term study where almitrine bismesylate was given orally in a larger daily dosage [25]. Finally, the present Pao_2 improvement was superior to that observed after a single dose [20] or after six-month therapy in a large group of COLD patients [1]. The better than average results in this study are possibly due to longer follow-up or more suitable patients who were exclusively pure obstructive and non-asthmatic.

In this study, we observed a slight but insignificant increase in ventilation. As previously emphasized [20, 26], the improvement in blood gas values with almitrine bismesylate cannot be due solely to increased ventilation. Previous studies showing the discrepancy between blood gas improvements and ventilation changes suggest that almitrine bismesylate might improve ventilation-perfusion matching. Indeed, a redistribution of blood flow has been demonstrated [4, 14, 22]. The redistribution of lung perfusion suggests a vascular effect of almitrine bismesylate perhaps a precapillary vasoconstriction. Such an effect might cause a rise in pulmonary arterial pressure.

In animals [23] and normal subjects [8], intravenous almitrine bismesylate causes an increase in pulmonary artery pressure. Haemodynamic studies in COLD

Table III. - Individual $\bar{P}pa$ values

	$\bar{P}pa$ kPa T0	T6	T12
	5.00	3.20	4.04
Almitrine	2.27	2.12	2.29
bismesylate	3.12	2.86	2.76
group	2.23	3.33	2.21
(n=8)	1.96	2.09	2.83
	2.69	2.77	2.83
	1.49	1.87	1.97
	1.49	1.52	1.40
$\bar{x} \pm$ SEM	2.53 ± 0.40	2.47 ± 0.23	2.54 ± 0.28
	2.24	1.87	2.31
Placebo	1.70	2.16	1.36
group	1.47	1.20	1.33
(n=7)	1.72	1.55	1.33
	2.15	1.45	1.41
	1.93	2.00	1.92
	2.99	2.18	2.40
$\bar{x} \pm$ SEM	2.03 ± 0.19	1.77 ± 0.14	1.72 ± 0.18

Individual $\bar{P}pa$ values recorded at each measurement time in almitrine bismesylate and placebo groups.

patients given a single infusion of almitrine bismesylate are contradictory. Some studies reported an increase in $\bar{P}pa$ due to an increase in right ventricular pressure without change in cardiac output [15, 31], other studies observed no change [24, 28]. WEITZENBLUM *et al.* [31] explained these discrepancies by differences in patients and methods but observed with identical methodology, an early and transitory increase in $\bar{P}pa$. After oral almitrine bismesylate administration, a 4 mmHg increase, 2 to 3 h after administration, has been observed [14, 27].

Thus, there is evidence that a single dose of almitrine bismesylate can induce vasoconstriction. Like the ventilatory effect this vascular effect is probably variable from one patient to another.

In the present work, there were no changes in haemodynamic data in patients treated for one year with almitrine bismesylate. The haemodynamic stability confirms previous studies performed on more severe patients after one [10], four [3] and 6 months [18] treatment; in addition stability of right heart function in COLD patients treated with almitrine bismesylate has been observed after more than five yr (personal observations). In contrast to our findings MACNEE *et al.* [12] found in five patients a slight but significant rise in $\bar{P}pa$ after three months of 100 mg of oral almitrine daily. Therefore it is necessary to compare their patients with those in other studies (table IV). Initial hypoxia and CO_2 retention of Macnee's patients were identical to ours but less severe than those of some other middle term haemodynamic almitrine studies [3, 10]. $\bar{P}pa$ values of Macnee's study were smaller than in all other studies, including ours. The most striking discrepancy of Macnee's study is the lack of significant increase of Pa_{O_2} after three months therapy. The study clearly included a large number of non-responders. From results in the literature, out of approximately 200 COLD patients treated with almitrine only 25% were non-responders [2]. Non-responders usually have a mixed restrictive and obstructive functional pattern or pure emphysema, and were not explicitly excluded from the Macnee population. His study essentially shows that almitrine therapy without Pa_{O_2} improvement induces a slight increase in $\bar{P}pa$ in patients with low initial values. From table IV it can be seen that in patients with elevated initial $\bar{P}pa$, no further increase occurs with almitrine. Thus one cannot predict from the initial $\bar{P}pa$ the subsequent effect of almitrine. Therefore the absence of almitrine haemodynamic change in the present study is not explained by the fact that the patients' initial haemodynamic values were not sufficiently severe.

In conclusion, the existence of a possible pulmonary hypertensive effect of almitrine in some patients can be avoided by restricting almitrine therapy to patients who 1) are hypoxic due to pure obstructive COLD and 2) respond to almitrine in less than 2–3 months of therapy. When these conditions are respected no long-term haemodynamic effect is apparent.

A discrepancy between the immediate and long-term vascular effects of almitrine bismesylate seems to exist and should be discussed. The vascular effect might disappear after the transient effect of a single dose. If this were true, $\bar{P}pa$ should return to normal values and then further decrease with improvement in gas exchange. We did not observe such a further decrease either in our study in which $\bar{P}pa$ was slightly increased at T0, or in other studies [3, 10] where $\bar{P}pa$ was even higher at T0. Therefore one can hardly retain this hypothesis.

The observation by MACNEE *et al.* [12], of a modest rise in $\bar{P}pa$ with almitrine when Pa_{O_2} does not improve, suggests that a minimal vascular effect persists in the long-term. Accordingly, one could explain the absence of rise in $\bar{P}pa$ in our study if the initial vasoconstriction was reduced or balanced by other factors, especially an improvement in gas exchange. ROMALDINI *et al.* [23] reported that an increase in the inspired oxygen fraction resulted in a decrease of the pressor response to almitrine in dogs. The slight ventilation increase observed in our study could have improved Pa_{O_2} and induced a similar phenomenon in our patients. The probable vasoconstrictive effect of the drug could also have been neutralized by the direct effect of an improving PO_2, which might reduce hypoxic vasoconstriction in general and perhaps also polycythaemia (ARNAUD *et al.* [1]).

A minimal vasoconstrictor effect of almitrine bismesylate may 1) persist in the long term, 2) be balanced in those patients in whom Pa_{O_2} improves

Table IV. - Effect of almitrine on PaO_2, $PaCO_2$ and $\bar{P}pa$ in chronic studies.

Study	Number of subjects	Length of study	Dose	PaO_2 mmHg			$PaCO_2$ mmHg			$\bar{P}pa$ mmHg		
			mg/kg/24 h	initial	final	p	initial	final	p	initial	final	p
KOFMAN *et al.* 1982 (10)	10	1 month	5	57.0 ± 2.9	65 ± 4.2	0.05	54 ± 2.2	47 ± 2.3	0.05	30.5 ± 2.6	27.8 ± 2.5	NS
PARAMELLE *et al.* 1983 (18)	10	6 months	1.5	56.0 ± 1.5	60 ± 1.1	0.05	39.5 ± 0.7	36.5 ± 1.1	0.05	20.3 ± 2.4	19.1 ± 1.4	NS
BOURGOUIN-KARAOUNI *et al.* 1984 (3)	6	4 months	3	50.8 ± 2.9	63.7 ± 3.6	0.01	51 ± 0.7	43.7 ± 1.2	0.01	24.4 ± 4.7	23.8 ± 3.6	NS
MACNEE *et al.* 1986 (12)	5	103–168 days	1.5	57.0 ± 4	60 ± 3	NS	45 ± 3	40 ± 3	0.01	17 ± 3	23 ± 6	0.05
Present study	8	12 months	1.5	57.4 ± 3.2	66.6 ± 2.9	0.01	44.5 ± 0.7	40.1 ± 1.3	0.05	19.65 ± 3	18.9 ± 2	NS

All the studies except that of Macnee *et al.* were double blind. Only the values of the almitrine groups are shown.

through better pulmonary gas exchange and 3) contribute to persistent improvement of blood gas values without haemodynamic consequences.

In conclusion, important clinical and blood gas improvements without significant haemodynamic modification were observed after one year of almitrine bismesylate therapy in COLD patients. This supports its long term use in COLD patients who respond to the drug.

References

1. Arnaud F, Bertrand A, Charpin J, Chretien J, Decroix G, Guerrin F, Kalb JC, Lissac J, Michel FB, Morere P, Paramelle B, Pariente R, Perrin-Fayolle M, Rochemaure J, Voisin C. – Le bismésilate d'almitrine dans le traitement au long cours (6 mois) de l'insuffisance respiratoire chronique. Etude multicentrique à double insu. *Bull Eur Physiopathol Respir*, 1982, 18(suppl. 4), 373–382.
2. Bourgouin-Karaouni D, Mercier J, Préfaut Ch. – Long term studies on almitrine bismesylate in COPD patients. *Eur J Respir Dis*, 1986, 69(suppl. 146), 695–701.
3. Bourgouin-Karaouni D, Ramonatxo M, Michel FB, Macabies J, Préfaut Ch. – Surveillance hémodynamique pulmonaire d'insuffisants respiratoires chroniques traités à double insu pendant 4 mois par le bismésilate d'almitrine. *Rev Mal Respir*, 1984, 1, 245–250.
4. 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.
5. Cerretelli P, Cruz JC, Fahri LE, Rahn H. – Determination of mixed venous O_2 and CO_2 tensions and cardiac output by a rebreathing method. *Resp Physiol*, 1966, 1, 258–264.
6. Chabrillat Y, Jammes Y, Zwirn P, Gerard R. – Mesure du débit cardiaque par une méthode non agressive. Estimation de la pression artérielle de CO_2 par reinhalation du gaz expiré. Comparaison avec la thermodilution. *Arch Mal Coeur*, 1980, 73, 107–113.
7. Davis CC, Jones ML, Sealey BJ. – Measurements of cardiac output in seriously ill patients using a CO_2 rebreathing method. *Chest*, 1978, 73, 167–172.
8. Gluskowski J, Gorecka D, Hawrylkiewicz I, Zielinski J. – Acute effects of almitrine infusion on pulmonary haemodynamics in normal man. *Bull Eur Physiopathol Respir*, 1984, 20, 313–317.
9. Grandjean T. – Une microtechnique du cathétérisme cardiaque droit applicable au lit du malade sans contrôle radioscopique. *Cardiologia*, 1968, 51, 184–192.
10. Kofman J, Perrin Fayolle M, Groendahl C. – Action hemodynamique du bismésilate d'almitrine sur la circulation pulmonaire chez les brouchitique chronique. *Bull Eur Physiopathol Respir*, 1982, 18(suppl. 4), 353–358.
11. Laubie M, Diot F. – A pharmacological study of the respiratory stimulant action of S 2620. *J Pharmacol*, 1972, 3, 363–374.
12. Macnee W. Connaughton JJ, Rhind GB, Hayhurst MD, Doublas 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.
13. Mahler DA, Matthay RA, Snyder PR, Neff RK, Loke J. – Determination of cardiac output at rest and during exercise by carbon dioxide rebreathing method in obstructive airway disease. *Am Rev Respir Dis*, 1985, 131, 73–78.
14. Melot Ch, Naeije R, Rothchild Th, Mertens Ph, Mols P, Hallemans R. – Improvement in ventilation-perfusion matching by almitrine in COPD. *Chest*, 1983, 83, 528–533.
15. 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.
16. Neukirch F, Castillon Du Perron M, Verdier F, Drutel P, Legrand M, Botto MJ, Lesobre R. – Action d'un stimulant respiratoire (S 2620), administré oralement, dans les bronchopneumopathies obstructives (étude statistique). *Bull Eur Physiopathol Respir*, 1974, 10, 793–800.
17. Olszowka AJ, Rahn M, Fahri LE. – *In*: Blood gases: hemoglobin base excess and maldistribution. Lea and Febiger, Philadelphia, 1973.
18. 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.
19. Powles ACP, Tuxen DV, Mahood CB, Pugsley SO, Campbell EJM. – The effect of intravenously administered almitrine, a peripheral chemoreceptor agonist, on patients with chronic air flow obstruction. *Am Rev Respir Dis*, 1983, 127, 284–289.
20. Préfaut Ch. – Effects of almitrine in oral form on lung exchanges in patients with hypercapnic chronic obstructive lung disease. *Rev Fr Mal Resp*, 1980, 8(suppl), 165–175.
21. Quanjer Ph. – Standardized lung function testiug. *Bull Eur Physiopathol Respir*, 1983, 19(suppl 5), 1–95.
22. Rigaud D, Dubois F, Boutet J, Brambilla C, Verain A, Paramelle B. – The effects of almitrine on the regional distribution of ventilation and perfusion in patients with respiratory failure. *Rev Fr Mal Resp*, 1980, 8(suppl), 183–193.
23. Romaldini H, Rodriguez-Roisin R, Wagner PD, West JB. – Enhancement of hypoxic pulmonary vasoconstriction by almitrine, in the dog. *Am Rev Respir Dis*, 1983, 128, 288–293.
24. Shrijen F, Romero-Colomer P. – Effets hémodynamiques d'un stimulant ventilatoire (almitrine) chez des pulmonaires chroniques. *Bull Eur Physiopathol Respir*, 1978, 74, 775–784.
25. Seignalet Ch, Préfaut Ch, Gonzales Ch, Michel FB. – Oral almitrine in the treatment of chronic obstructive lung disease. *Rev Fr Mal Resp*, 1980, 8(suppl), 217–224.
26. Sergysels R, Etien JL, Schandevyl W, Willeput R, Lenders D, Vachaudez JP, Van Crombeucq JC. – Functional evaluation of new analeptic drug (Vectarion) in patients with chronic hypoxemia and hypercapnia. *Acta Tuberc Pneumol Bel*, 1978, 69, 237–246.
27. Simonueau G, Meignan M, Denjen 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.
28. Tenaillon A, Labrousse J, Longchal J, Chastre J, Lissac J. – The effect of almitrine in acute exarcerbatiou of chronic respiratory failure treated by artificial ventilation. *Rev Fr Mal Resp*, 1980, 8(suppl), 177–182.
29. Van Herwaarden CLA, Binkhorst RA, Fennis JFM, Van't Laar A. – Reliability of cardiac output measurement with the indirect Fick principle for CO_2 during exercise. *Pflügers Arch*, 1980, 385, 21–25.
30. Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Hirth Ch, Roegel E. – Long-term course of pulmonary arterial pressure in chronic obstructive pulmonary disease. *Am Rev Respir Dis*, 1984, 130, 993–998.
31. Weitzenblum E, Ehrhart M, Schweider JC, Hirth C, Roegel E. – Effets hémodynamiques pulmonaires de l'almitrine intraveineeuse chez les bronchiteux chroniques insuffisants respiratoires. *Bull Eur Physiopathol Respir*, 1982, 18, 765–774.
32. Winer BJ. – Statistical principles in experimental design. McGraw-Hill, New York, 1971, pp. 518–538.

RÉSUMÉ: Le bismésylate d'almitrine, un agoniste des chémorécepteurs, améliore les gaz du sang chez les malades atteints de bronchopneumopathie chronique obstructive (BPCO). Certains auteurs ont observé une élévation de la pression artérielle pulmonaire ($\bar{P}pa$) après des doses uniques d'almitrine (A). La présente étude contrôlée réalisée en double insu compare les effets hémodynamiques de l'administration pendant un an de 1,5 mg/kg/jour a'A à celle d'un A placebo (P) à des malades BPCO, sont également comparés le bénéfice clinique et l'amélioration des gaz du sang. Vingt malades sont entrés dans l'étude, et quinze l'ont terminée (8 dans le groupe A, 7 dans le groupe P). Les gaz du sang, la ventilation minute ($\dot{V}E$), la pression artérielle pulmonaire moyenne ($\bar{P}pa$) et le débit cardiaque ($\dot{Q}c$) ont été mesurés périodiquement. $\bar{P}pa$ et $\dot{Q}c$ sont restés inchangés dans les deux groupes. Par contre nous avons noté dans le groupe A une amélioration clinique sans effet secondaire et sans changement de

VE. Pao_2 a augmenté en moyenne 1–2 kPa dans le groupe A et est resté inchangé dans le groupe P. Ces données ainsi que celles de la littérature montrent que l'almitrine exerce des effets vasculaires spécialement après une dose unique. Cependant pour autant que Pao_2 augmente concomittemment, aucune conséquence hémodynamique à long terme ne devient apparente. La discordance entre les effets vasculaires aigüs et chroniques de l'almitrine pourrait s'expliquer par l'amélioration des échanges gazeux qui pourrait réduire et/ou contrebalancer la réponse vasoactive. En conclusion, après un an de traitement le bismésylate d'almitrine entraîne une amélioration clinique et gazométrique notable sans changement hémodynamique significatif.