Oral almitrine in treatment of acute respiratory failure and cor pulmonale in patients with an exacerbation of chronic obstructive airways disease

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Abstract

The effects of oral almitrine bismesylate, a respiratory stimulant that acts on peripheral arterial chemoreceptors, was studied in patients with chronic obstructive airways disease and hypoxaemic cor pulmonale. Twenty three patients admitted to hospital with an acute exacerbation of ventilatory failure were randomised to receive either almitrine 100 mg twice a day reducing to 50 mg twice a day over 48 hours or placebo in addition to conventional treatment. On admission the mean (SE) values for blood gas tensions were Pa_{O_2} 4·8 (0·3) and Pa_{CO_2} 7·7 (0·3) kPa in the 12 patients who received almitrine and Pa_{O_2} 4·9 (0·1) and Pa_{CO_2} 7·6 (0·3) kPa in the 11 who received placebo. After three hours of oxygen therapy at 1 l/min there was a similar rise in Pa_{O_2} in both groups, 6·4 (0·2) kPa in those receiving almitrine and 6·6 (0·4) kPa in those receiving placebo. After 24 hours of oxygen therapy values of Pa_{O_2} were again similar at 6·3 (0·8) kPa and 6·7 (2·2) kPa respectively. Arterial blood gas tensions improved during the study in those who survived but no significant differences were apparent between the two groups. There were six deaths, five in the almitrine group and one in the placebo group. There were no differences between the groups in respiratory rate, results of spirometry, oxygen requirement, or degree of dyspnoea (on visual analogue scale). The results did not show any benefit from oral almitrine in patients with acute respiratory failure secondary to chronic obstructive airways disease. Plasma almitrine concentrations, however, were often below the optimum therapeutic range, suggesting impaired drug absorption.

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Almitrine bismesylate is a recently developed respiratory stimulant that acts on peripheral chemoreceptors, principally of the carotid body, to increase tidal volume.[1] It also causes pulmonary vasoconstriction and may have beneficial effects on ventilation or perfusion matching within the lung.[2] Oral almitrine 100–200 mg daily when taken for up to a year improves arterial blood gas tensions in patients with stable hypoxaemic chronic obstructive airways disease.[3] Little information is available on the effect of the drug in patients with an acute exacerbation of chronic bronchitis and emphysema associated with acute ventilatory failure.

In theory almitrine, like other respiratory stimulants, would be an attractive means of reducing the requirement for oxygen and of limiting excessive hypercapnia during low flow oxygen therapy. It has the advantage that it can be taken orally. There is some evidence that intravenous almitrine can improve arterial oxygen tensions in patients with chronic obstructive airways disease and acute ventilatory failure,[4–6] but concern was expressed in one study because pulmonary artery pressure rose in all 12 patients, four of whom complained of malaise and increased dyspnoea.[4] There are few studies of oral almitrine in patients with this condition and none has looked specifically at patients with hypoxaemic cor pulmonale. Patients with acute on chronic ventilatory failure given oral almitrine in a double blind study over two weeks did not show any improvement in blood gas tensions until day 10,[7] and in another study oral almitrine did not reduce the requirement for assisted ventilation.[8]

Whether almitrine has a useful role in the treatment of acute ventilatory failure secondary to chronic obstructive airways disease has not been established clearly, and whether the drug is associated with a more rapid recovery or, more importantly, a reduction in the appreciable mortality associated with this condition is not known. We examined the effect of oral almitrine on arterial blood gas tensions, inspired oxygen requirement, symptoms, and survival in patients with acute respiratory failure and hypoxaemic cor pulmonale secondary to an exacerbation of chronic obstructive airways disease.

Methods

PATIENTS

We studied 23 patients with chronic obstructive airways disease and hypoxaemic cor pulmonale admitted to hospital with an acute exacerbation of ventilatory failure. Patients were randomly allocated to receive oral almitrine or placebo in a double blind manner in addition to conventional treatment. The criteria for entry into the study were respiratory failure with arterial oxygen tension (Pa_{O_2}) less than 8·0 kPa on admission to hospital and arterial carbon dioxide tension (Pa_{CO_2})

greater than 6·0 kPa while breathing room air; peripheral oedema on clinical examination; a forced expiratory volume in one second (FEV_1) less than 1·5 l (recorded either in the past or when clinically stable); and a forced expiratory ratio (FEV_1/forced vital capacity (FVC)) of less than 70%. Patients with asthma, reversible airflow obstruction, interstitial pulmonary fibrosis, chest wall disorders, or neuromuscular disorders were excluded, as were those with clinically relevant cardiac, renal, or hepatic disease. No patients had received almitrine or any other respiratory analeptic within the previous two months.

ASSESSMENT AND STANDARD TREATMENT

On admission a clinical assessment was made and an arterial blood sample taken. If the patient had received oxygen the arterial sample was taken after this had been stopped for at least 30 minutes. If the entry criteria were fulfilled informed consent was obtained and the patient entered into the study. A venous blood sample was taken for standard haematological and biochemical testing, chest radiography and electrocardiography were performed, and sputum was sent for microbiological analysis. All patients were then scored on a visual analogue scale (0–100 mm) for sense of wellbeing and degree of breathlessness (for wellbeing 0 = feeling ill, 100 = feeling well; for breathlessness 0 = not breathless, 100 = extremely short of breath).

Oxygen was given initially at a flow rate of 1 l/min through nasal cannulas, and oral almitrine 100 mg or placebo was then given. All patients were treated in the standard way with chest physiotherapy, an antibiotic (usually amoxycillin 500 mg three times a day or trimethoprim or erythromycin if the patient was allergic to penicillin), intravenous salbutamol (10 mg in 50 ml of physiological saline infused over 24 hours), and diuretics (oral frusemide 80 mg and spironolactone 100 mg daily). After three hours a venous blood sample was taken to determine the plasma almitrine concentration and a further arterial sample taken. If the $Paco_2$ had decreased or remained constant the inspired oxygen flow rate was increased to 1·5 l/min, if it had increased by less than 1 kPa the oxygen flow rate was left at 1·0 l/min, and if it had increased by more than 1 kPa the flow rate was reduced to 0·5 l/min. Blood was taken for estimation of the plasma almitrine concentration at five, eight, and 12 hours. Arterial blood gas tensions were rechecked again after 24 hours of treatment and as indicated clinically.

Table 1 Characteristics of patients randomly allocated to receive almitrine or placebo (mean (SE) values)

Characteristic	Patients receiving almitrine (n = 12)	Patients receiving placebo (n = 11)
Age (y)	65·0 (2·0)	72·0 (2·0)*
Sex (M/F)	6/6	8/3
Weight (kg)	58·0 (6·0)	59·0 (5·0)
Pao_2 (kPa):		
Initial	4·8 (0·3)	4·9 (0·3)
After three hours	6·4 (0·2)	6·6 (0·4)
$Paco_2$ (kPa):		
Initial	7·7 (0·3)	7·6 (0·3)
After three hours	8·1 (0·3)	8·8 (0·5)
H^+ concentration (nmol/l):		
Initial	44·0 (1·0)	43·0 (1·0)
After three hours	43·0 (1·0)	46·0 (2·0)
FEV_1 (l)	0·43 (0·1)	0·40 (0·1)
FVC (l)	1·08 (0·23)	0·97 (0·29)
Respiratory rate (breaths/min)	27·0 (3·0)	28·0 (3·0)
Visual analogue score for dyspnoea (mm)	56·0 (11·0)	43·0 (8·0)
Visual analogue score for wellbeing (mm)	33·0 (9·0)	44·0 (7·0)
Packed cell volume	49·0 (2·0)	43·0 (2·0)

*$p < 0·05$.
Pao_2—arterial oxygen tension; $Paco_2$—arterial carbon dioxide tension; FEV_1—forced expiratory volume in one second; FVC—forced vital capacity.

DRUG TREATMENT

Almitrine was given 100 mg twice daily with food for 24 hours followed by 100 mg in the morning and 50 mg in the evening for a further 24 hours and 50 mg twice daily with food for the next 18 days. Patients received chest physiotherapy twice daily and were not allowed to smoke. Fluid intake was initially restricted to 1 litre per day; the diuretics were continued for the duration of the trial. When the Pao_2 had risen above 8 kPa for 24 hours the intravenous infusion of salbutamol was stopped and this drug was given by nebuliser (5 mg/5 ml four times a day). Antibiotic treatment was continued for 10 days. Other drug treatment on admission, including any corticosteroids, was continued unchanged.

MONITORING OF PATIENTS

The study was continued for three weeks. Patients were assessed each morning and arterial blood gas tensions checked before almitrine was given. Inspired oxygen concentration was adjusted to try to maintain Pao_2 at around 8 kPa. Respiratory rate, results of spirometry, and visual analogue scores were recorded daily during the first week and then on alternate days. On these days the oxygen flow rate was also checked with a rotameter. On days 2, 4, 7, 14, and 21 venous blood samples were taken for estimation of the blood count and electrolyte and plasma almitrine concentrations. Blood samples were taken two to three hours after administration of almitrine, when peak plasma concentrations would be expected.[9] At the end of the study arterial blood gas tensions were recorded with the patient breathing air after having stopped receiving oxygen for at least four hours.

All arterial blood samples were analysed immediately with a Corning 170 machine and spirometry was performed with a portable spirometer (Micro Medical Instruments). Plasma almitrine concentrations were measured by gas-liquid chromatography to a sensitivity of 5 ng/ml.[10] The study was approved by the hospital ethics committee.

STATISTICAL ANALYSIS

Patients withdrawn from the study were included in the analysis. Mean values and standard errors (SE) of measurements are given. Measurements on entry into and during the study were compared between and within groups with a paired or unpaired Student's t test as appropriate. Survival be-

Table 2 Details of six patients who died during study

Age (y)	Sex (M/F)	Receiving almitrine or placebo	Blood gas tensions on admission (kPa)		Blood gas tensions within 24 hours after death (kPa)		Oxygen flow rate (l/min)	Day of death	Further details
			Pa_{O_2}	Pa_{CO_2}	Pa_{O_2}	Pa_{CO_2}			
68	M	Almitrine	4·3	7·3	4·6	8·3	1·0	5	*Haemophilus influenzae* infection Severe emphysema at postmortem examination
74	F	Almitrine	4·9	8·8	5·2	9·2	1·5	2	Died in respiratory failure No postmortem examination
68	M	Almitrine	5·9	7·2	5·5	8·0	2·0	3	Died in ambulance during transfer to intensive therapy unit *H influenzae* infection Severe emphysema at postmortem examination
68	F	Almitrine	3·6	8·1	7·2	10·4	1·0	7	Grand mal convulsion Subsequent respiratory arrest No postmortem examination
71	M	Almitrine	4·0	6·2	7·1	8·2	1·0	3	Sudden cardiorespiratory arrest Severe emphysema at postmortem examination
77	M	Placebo	5·8	6·8	4·2	10·2	0·5	2	Treated with doxapram Subsequent respiratory arrest Severe emphysema and widespread coronary artery disease at postmortem examination

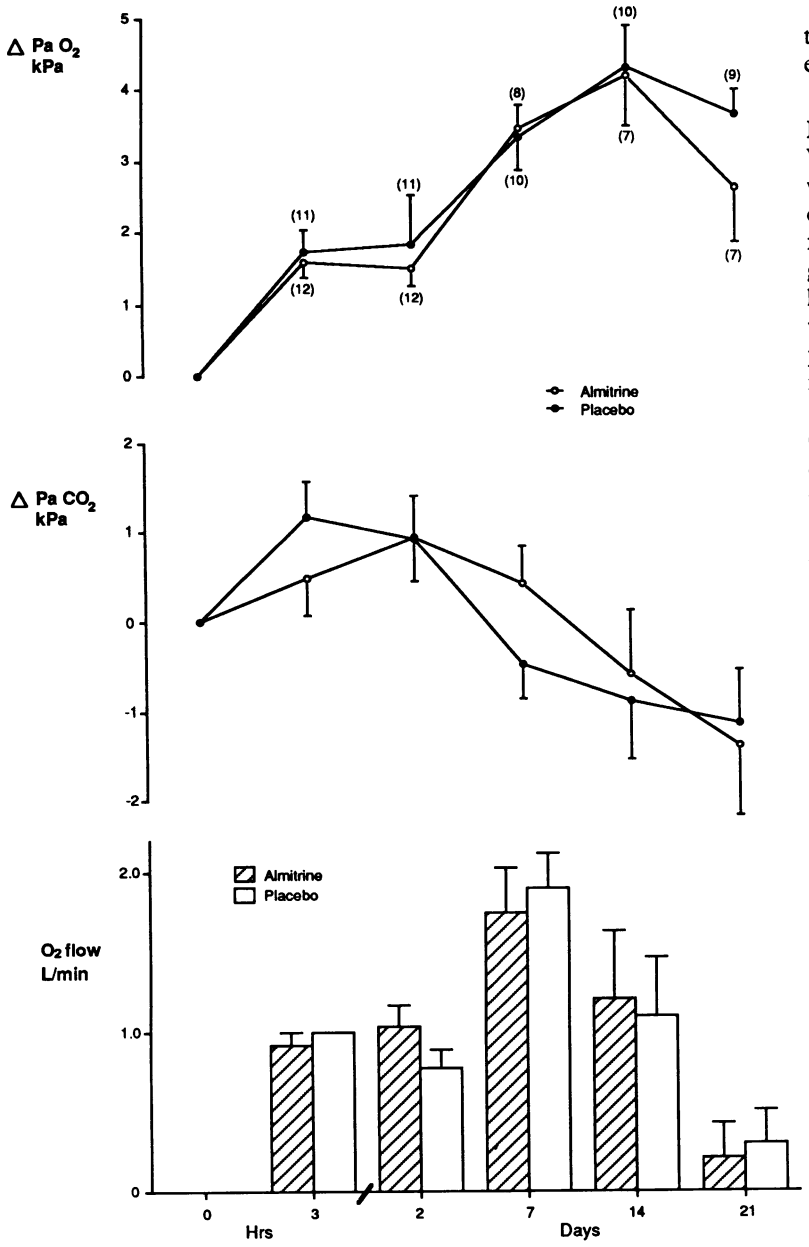

Figure 1 Mean changes in Pa_{O_2} and Pa_{CO_2} at 3 hours and on days 2, 7, 14, and 21 for patients treated with almitrine or placebo. The numbers of patients are in parentheses. All values were obtained with the patient breathing oxygen; the mean inspired oxygen flow rates are given (bottom). Bars indicate standard errors.

tween the groups was compared by Fisher's exact probability test.

Results

We studied 23 patients (14 men and nine women; age 51–82 years) with severe airflow obstruction (FEV_1 0·21–1·11 l) and ventilatory failure (on admission to hospital arterial blood gas tensions breathing air were Pa_{O_2} 3·2–6·7 kPa and Pa_{CO_2} 6·2–10·0 kPa). Twelve patients were treated with almitrine and 11 with placebo. Table 1 shows the patients' characteristics on entry to the study.

Treatment was well tolerated and no patient complained of any symptom that could be attributed to the drug. Seventeen patients completed the study. No patient was withdrawn owing to side effects of the drug. Six patients died, five of those receiving almitrine and one receiving placebo. Details of the deaths are given in table 2. The difference in death rate between the two groups was not significant ($p = 0·09$).

There were no significant differences in arterial blood gas tensions or oxygen flow rates. After three hours of oxygen at 1 l/min the mean Pa_{O_2} had risen from 4·8 (0·3) to 6·4 (0·2) kPa in those receiving almitrine and from 4·9 (0·1) to 6·6 (0·4) kPa in those receiving placebo. After 24 hours of oxygen therapy mean values were 6·3 (0·8) kPa and 6·7 (2·2) kPa respectively. Figure 1 shows the mean changes in both Pa_{O_2} and Pa_{CO_2} from baseline over time.

Arterial blood gas tensions improved during the study and after three weeks mean arterial blood gas tensions when patients were breathing air were Pa_{O_2} 7·1 (0·83) kPa, Pa_{CO_2} 6·0 (0·5) kPa ($n = 7$) in those receiving almitrine and Pa_{O_2} 8·1 (0·5) kPa, Pa_{CO_2} 6·5 (0·5) kPa ($n = 10$) in those receiving placebo. Figure 2 gives the mean FEV_1, FVC, and respiratory rate and figure 3 gives the mean visual analogue scores for breathlessness and wellbeing. There were no significant differences between the two groups for any of these measurements. Table 3 gives the mean plasma almitrine concentrations in those receiving the drug.

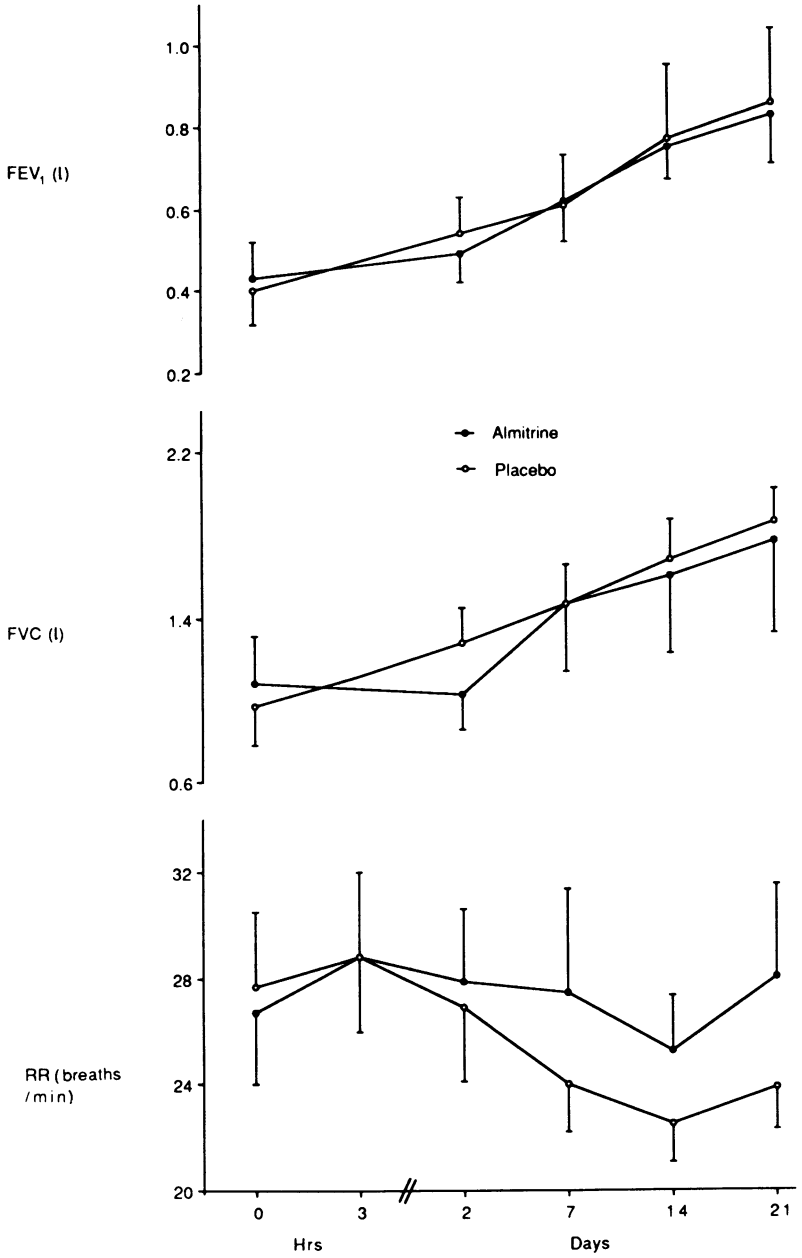

Figure 2 Mean values for forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and respiratory rate (RR) for patients treated with almitrine or placebo. Bars indicate standard errors.

Discussion

Patients with acute ventilatory failure secondary to an exacerbation of chronic obstructive airways disease are treated initially with controlled oxygen. If an acceptable Pao_2 cannot be achieved without incurring excessive hypercapnia with worsening respiratory acidosis assisted ventilation must be considered. The difficulties of weaning such patients from assisted ventilation are widely recognised and so many patients are treated with the respiratory stimulant doxapram by intravenous infusion while other treatment starts to take effect. The non-specific arousal produced by doxapram often limits its use. Almitrine offers a different therapeutic approach and has the advantages of being active when taken orally and having no central side effects. However, the use of respiratory stimulants in patients with acute ventilatory failure is controversial. They are often prescribed on the assumption that central respiratory drive is insufficient, yet it is often increased in patients with acute ventilatory failure.[11] Concern has also been expressed about respiratory analeptics worsening dyspnoea and exacerbating respiratory muscle fatigue. Nasal intermittent positive pressure ventilation may be helpful for these patients in the future.[12]

We assessed the effect of oral almitrine in patients with acute on chronic ventilatory failure and cor pulmonale secondary to chronic bronchitis and emphysema. All patients had severe, irreversible airflow obstruction. Patients treated with almitrine were well matched with those given placebo and all patients were treated in a standard manner with controlled oxygen, bronchodilators, chest physiotherapy, diuretics, and antibiotics.

Our regimen for giving controlled oxygen therapy was designed to try to standardise patient management as far as possible. The inspired oxygen was titrated to try to achieve a Pao_2 above 8 kPa. However, a lower Pao_2 was accepted if hypercapnia or respiratory acidosis worsened. In the first 24 hours seven patients treated with almitrine (three of whom subsequently died) and four treated with placebo had a Pao_2 while breathing oxygen of less than 6·7 kPa, mainly because of worsening hypercapnia. A Pao_2 greater than 8 kPa was often not achieved until days five to seven. Monitoring the degree of acidosis rather than the absolute $Paco_2$ might have been a better guide to oxygen requirement.[13] Six patients, three in each group, became acidotic during oxygen therapy with a hydrogen ion concentration greater than 55 nmol/l (two of these patients died). There was no evidence that almitrine allowed a higher inspired oxygen concentration to be tolerated. No differences in oxygen flow rates between the groups were apparent at any stage. FEV_1 and FVC were virtually the same in the two groups and improved in both over time. The Pao_2 rose and $Paco_2$ fell progressively apart from during the initial worsening of hypercapnia. The respiratory rate was higher in the patients treated with almitrine. Breathlessness was more difficult to assess, but those given almitrine had a higher symptomatic score throughout the study. There was no correlation between the degree of dyspnoea and plasma almitrine concentration. Overall, wellbeing did not differ between the two groups.

Acute ventilatory failure in patients with chronic bronchitis and emphysema is associated with a high mortality. Six of the 23 patients (26%) entered into the study died: five of those given almitrine and one of those given

Table 3 Mean (SE) plasma almitrine concentrations for the 12 patients treated with the drug at entry (T_0) and at intervals thereafter

	T_0	3 h	5 h	8 h	12 h	Day 2	Day 4	Day 7	Day 14	Day 21
Mean (SE) almitrine concentration (μg/l)	0 (0)	150 (35)	113 (22)	153 (82)	209 (88)	90 (38)	127 (44)	95 (30)	156 (38)	213 (48)

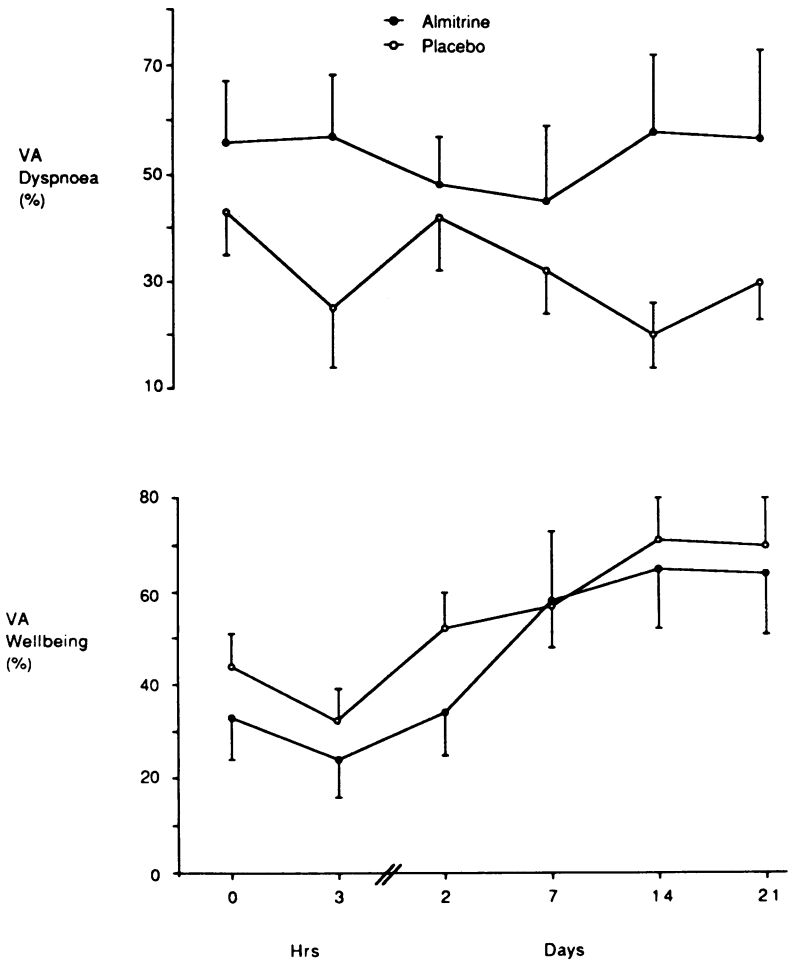

Figure 3 Visual analogue (VA) scores for breathlessness and wellbeing on a 0–100 mm scale (0 = not breathless and 100 = extremely short of breath) and for wellbeing (0 = feeling ill and 100 = feeling well). Values are means with standard errors.

placebo. The deaths occurred in elderly patients with severe disease and poor quality of life, and in most of these cases a decision not to proceed with assisted ventilation had already been made. Two patients were withdrawn from the study just before death. One patient receiving placebo was treated unsuccessfully with intravenous doxapram and one receiving almitrine died during transfer to another hospital for assisted ventilation. Of the patients who died, three had achieved a Pao_2 greater than 6·7 kPa on treatment before terminal deterioration in arterial blood gas tensions. In the other three patients adequate oxygenation was limited by worsening hypercapnia (peak $Paco_2$ 9·1–11·0 kPa), although none had a hydrogen ion concentration above 55 nmol/l litre.

Although numbers in this study were small, there was no suggestion that almitrine improves survival, and it may have had an adverse effect. This adverse effect might be caused by an acute rise in pulmonary arterial pressure. Previous studies of acute administration of both oral and intravenous almitrine have shown a correlation between the rise in pulmonary artery pressure and the degree of hypoxaemia, pre-existing pulmonary hypertension, and change in $Paco_2$.[14 15] Although we did not measure pulmonary artery pressure, cor pulmonale was not more difficult to control in the surviving patients receiving almitrine. Further studies are needed to address this question.

The disappointing effect of almitrine on arterial blood gas tensions may be owing to low therapeutic drug concentrations. Despite a large initial dose, plasma almitrine concentrations were still below the optimum therapeutic range of 200–300 μg/l in most patients until day 14. A therapeutic plasma almitrine concentration was reached at 12 hours in seven patients but was not sustained. Only one patient had acceptable concentrations throughout the study. Almitrine is usually well absorbed; the slow rise in blood concentrations suggests impaired absorption, probably due to severe hypoxaemia and oedema of the bowel wall affecting gastrointestinal function. The bioavailability of oral almitrine is about 70% of that of an intravenous dose, and the pharmacokinetics in patients with chronic obstructive airways disease do not differ appreciably from those in healthy subjects.[16] Higher oral doses could be tried, but in stable patients doses above 100 mg a day tend to be associated with a high incidence of side effects such as nausea, abdominal discomfort, headache, and flushing.[17] We did not find any significant correlation between arterial blood gas tensions and plasma almitrine concentrations.

Our results do not show any beneficial effects of oral almitrine in the treatment of acute ventilatory failure and cor pulmonale secondary to chronic obstructive airways disease. For the present this drug is better suited to the treatment of chronic than of acute respiratory failure.

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