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Dose-response and pharmacokinetic study with almitrine bismesylate after single oral administrations in COPD patients

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Dose-response and pharmacokinetic study with almitrine bismesylate after single oral administrations in COPD patients. Th. Bury, J.P. Jeannot, J.C. Ansquer, M. Radermecker.

ABSTRACT: To better define the dose-effect relationship and the pharmacokinetics of almitrine, sixteen stable hypoxaemic COPD patients received random single oral administrations of almitrine bismesylate 50, 100 and 150 mg or placebo at two-week intervals in a double-blind manner. Resting ventilation, arterial blood gases and plasma almitrine levels were measured. No significant changes were seen after placebo administration. Almitrine 50 and 100 mg caused a significant dose-related improvement in arterial oxygen tension (Pao_2) in thirteen of the sixteen patients. Almitrine 150 mg caused little if any additional Pao_2 increment. Pao_2 returned to near basal values after 24 h. Two patients responded to almitrine 100 and 150 mg only, whereas one patient did not respond at all. Mean Pao_2 increases in the sixteen patients were 0.9 kPa (7 mmHg), 1.5 kPa (11 mmHg) and 1.6 kPa (12 mmHg) 3 h after 50, 100 and 150 mg, respectively. A significant mean 0.9 kPa (7 mmHg) decrease in arterial carbon dioxide tension ($Paco_2$) and a $l \cdot min^{-1}$ increase in ventilation were observed after almitrine 150 mg. Mean maximum almitrine plasma concentration and area under the curve correlated linearly with dose. The relationship between mean Pao_2 improvement and mean almitrine plasma level was curvilinear with a flattening of the curve over plasma levels of 150 $ng \cdot ml^{-1}$. Almitrine plasma half-life was found to be 116–140 h.

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Almitrine†, a peripheral chemoreceptor agonist, has been shown to improve blood gases in patients with chronic obstructive pulmonary disease (COPD) in both acute and chronic administration [1–3]. This effect is thought to be due to an improvement in alveolar ventilation/perfusion matching as it can be obtained in most COPD patients with low doses of almitrine, *i.e.* ≤1.5 $mg \cdot kg^{-1}$, without any increase in external ventilation, or when ventilation is kept constant [4, 5]. A relationship between almitrine dose, blood gas changes and plasma almitrine levels has never clearly been established in COPD patients [6]. Several studies [7–9] were carried out in healthy subjects to determine the basic pharmacokinetic profile of the drug and a half-life of between 30 and 45 h has been reported. In COPD patients, only one study, CONNAUGHTON *et al.* [10], examined plasma almitrine levels after a single oral dose of 100 mg almitrine bismesylate: plasma almitrine peaked at 2.5 h after administration and the mean plasma level was 265 $ng \cdot ml^{-1}$. We therefore studied kinetic parameters and dose-response curves of almitrine in relation to arterial blood gases and ventilation measurements 2, 3 and 24 h after single oral administrations, with two-week intervals, in COPD patients.

† Almitrine is used as a bismesylate salt. All doses are given in mg almitrine bismesylate.

Patients and methods

The criteria for inclusion in the study were as follows: 1) ambulatory male patients suffering from COPD as defined by the American Thoracic Society [11] with clinically stable disease; 2) age 45–75 yrs; 3) body weight 50–90 kg and not exceeding 120% of the theoretical weight according to the tables of the Metropolitan Life Insurance Company [12]; 4) arterial blood gases measured at rest, when breathing ambient air 6 kPa (45 mmHg) ≤Pao_2 ≤8.7 kPa (65 mmHg) and 4.7 kPa (35 mmHg) ≤$Paco_2$ ≤7.3 kPa (55 mmHg); 5) forced expiratory volume in one second (FEV_1) ≤70% of the predicted value [13]; 6) 30% ≤FEV_1/VC ≤65%.

The protocol of the study was approved by the Ethical Committee of the University of Liege. Sixteen patients volunteered for this double-blind, randomized, cross-over, placebo-controlled study and gave their

informed written consent. The characteristics of the patients are given in table 1. All patients had been cigarette smokers for at least 20 yrs (>20 packs per year). Ten had stopped smoking for at least six months before the start of the study and the others had continued smoking 4–10 cigarettes per day. All patients had chronic cough and/or sputum production for at least three months a year, with an average duration of 10 yrs. All patients were on bronchodilators: theophylline (mean plasma level 10 $\mu g \cdot ml^{-1}$) and/or β_2 agonists and mucolytics (bromhexine or acetylcysteine). Two patients received low-flow oxygen intermittently (1–2.5 $l \cdot min^{-1}$) for 3 or 4 h per day.

Table 1. – Characteristics of the sixteen subjects studied (mean ±SD)

	Units	Actual value	Predicted values %
Age	yr	61.7±7.8	
Height	m	1.68±0.07	
Weight	kg	63.1±11.7	
FEV_1	l	1.14±0.49	39±18
VC	l	2.55±0.69	66±18
FEV_1/VC	%	44±12	58±17
RV	l	3.20±0.84	138±39
TLC	l	5.75±1.18	90±18
Pao_2	mmHg	60.1±7.4	
Pao_2	kPa	8.0±0.9	
$Paco_2$	mmHg	43.6±5.6	
$Paco_2$	kPa	5.8±0.7	
Hb	$g \cdot 100\ ml^{-1}$	15.6±1.3	
RBC	$10^{12} \cdot l^{-1}$	5.14±0.52	
Hct	%	47±4	

FEV_1: forced expiratory volume in one second; VC: vital capacity: RV: residual volume; TLC: total lung capacity; Pao_2: arterial oxygen tension; $Paco_2$: arterial carbon dioxide tension; Hb: haemoglobin; RBC: red blood cells; Hct: haematocrit.

With the exception of β_2 agonists and oxygen therapy, which were withheld one week prior to entry into the study, basic treatment was maintained throughout the clinical trial. None of the patients had right heart failure, liver or renal disease.

Each patient was randomly allocated to almitrine bismesylate 50, 100 or 150 mg or placebo, and the other dosages were subsequently given in random order according to a latin square design. An interval of approximately fourteen days was maintained between each administration. Drug or placebo was administered orally at 8 a.m., in the fasting state, in a double-blind manner, as 50 mg tablets of almitrine bismesylate or identical placebo. On each test day, the patients received a total of three tablets (active product + balanced placebo) with 100 ml of water. Resting minute ventilation, respiratory frequency and tidal volume were all measured during a 3 min period. The patient, in a sitting position, breathed into a Godart spirometer through a mouthpiece with a noseclip. Ventilatory parameters were measured before as well as 3 and 24 h after drug intake. Arterial blood obtained by percutaneous sampling from the femoral artery was immediately analysed for arterial oxygen and carbon dioxide tensions (Pao_2, $Paco_2$), pH and arterial oxygen saturation (Sao_2), using a blood gas analyser (Radiometer ABL4, Copenhagen). Plasma bicarbonate concentration (HCO_3^-) was calculated by the Henderson Hasselbach equation. Blood gas analyses were carried out before and 2, 3 and 24 h after each administration. Accuracy of the blood gas measurements was regularly checked against internal standards. Taking into account the reproducibility of Pao_2 measurements, the standard deviation of which on repeated measurements was 0.3 kPa (2.5 mmHg), we considered increases in Pao_2 of 0.7 kPa (5 mmHg) or more to be significant.

Twenty-four hours after almitrine or placebo administration, the patients were questioned about possible side effects. Venous blood samples were taken for the determination of almitrine plasma level and for monitoring various biological parameters (haemoglobin, red cell count, haematocrit, serum proteins, albumin, triglycerides) before each administration. For almitrine determination, blood was also taken at different times over a 72 h period following administration of the drug. Blood was immediately centrifuged (at 1000 g for 10 min) and the plasma stored at -20°C until analysis. Plasma almitrine level was measured by gas-liquid chromatography using a nitrogen specific detector, the detection limit of which is at the $ng \cdot ml^{-1}$ level [14]. Each individual plasma concentration-time curve was fitted to a polyexponential equation by non-linear regression analysis, using the extended least squares modelling system ELSMOS [15] run on a VAX 750 computer (digital). Pharmacokinetic parameters were chosen or calculated as follows:

- the maximal plasma concentration (C_{max}) and the time to the peak plasma level (t_{max}) used were the experimental values;
- the area under the plasma concentration *vs* time curve (AUC) was extrapolated to infinite time according to the equation:

$$AUC = AUC_{obs} + \frac{C_t}{\lambda_z}$$

where AUC observed was calculated by the trapezoidal rule between zero and the last sampling time. C_t was the concentration of almitrine at the last sampling time. λ_z was the slope of the terminal phase. The last sampling time for almitrine determination was just before the subsequent 2nd, 3rd, or 4th administration;

- the total plasma clearance CL was calculated as the ratio:

$$CL = \frac{F \cdot dose}{AUC}$$

F, the bioavailability factor, unknown in this study, was assumed to be equal to 1;

- the apparent volume of distribution, V, during the

terminal phase was the ratio:

$$V = \frac{CL}{\lambda_z}$$

- the plasma half-lives associated with each phase were calculated as:

$$t_{\frac{1}{2}}, i = \frac{Ln\,2}{\lambda_i} \quad (i = 1 \text{ to } z).$$

Statistical analysis

Results are presented as means ±1 standard deviation. The administration of placebo or almitrine bismesylate, 50, 100 or 150 mg was balanced using a repeated 4×4 latin square design, *i.e.*, on each of the four test days, each dose was given to four patients. This enabled separate testing of both the drug effect and possible changes between visits. Such visit effects were ruled out by the analysis of baseline values of arterial blood gases, ventilatory parameters and residual almitrine plasma levels. Statistical analysis of the drug effect was then carried out using a two-way analysis of variance in order to test the difference between doses and the time-course effects. When a significant dose or time-course effects were found, pairwise comparisons between doses or hours were made using the Newman-Keuls method.When a significant dose-effect was shown for any pharmacokinetic parameter, linear relationships were tested using the least squares method to fit the model $y=ax^b$ with the hypothesis that b=1. For each statistical analysis, $p \leq 0.05$ was considered significant.

Results

Arterial blood gases

Mean Pao_2 values of our sixteen patients as a function of almitrine dose and time after oral intake are shown in figure 1. Placebo did not produce any significant effect on Pao_2. In contrast, almitrine 50 and 100 mg caused a dose-related Pao_2 improvement 2 and 3 h after oral intake. The improvement of Pao_2 over baseline was 1.2 kPa (9 mmHg) and 0.9 kPa (7 mmHg), respectively, 2 and 3 h after almitrine 50 mg and 1.6 kPa (12 mmHg) and 1.5 kPa (11 mmHg), respectively, 2 and 3 h after almitrine 100 mg. Only a slight 0.1 kPa (1 mmHg) additional effect was noted following administration of almitrine 150 mg. Twenty-four hours later, Pao_2 was not significantly different from baseline but on average 0.4 kPa (3 mmHg) higher following 100 and 150 mg almitrine bismesylate.

Three of our sixteen patients did not respond to almitrine 50 mg in spite of appreciable plasma almitrine levels (66, 63 and 92 ng·ml^{-1}, respectively, 3 h after intake). Two of these patients responded to almitrine 100 and 150 mg in a dose-related fashion. The third patient did not respond at all, even after almitrine

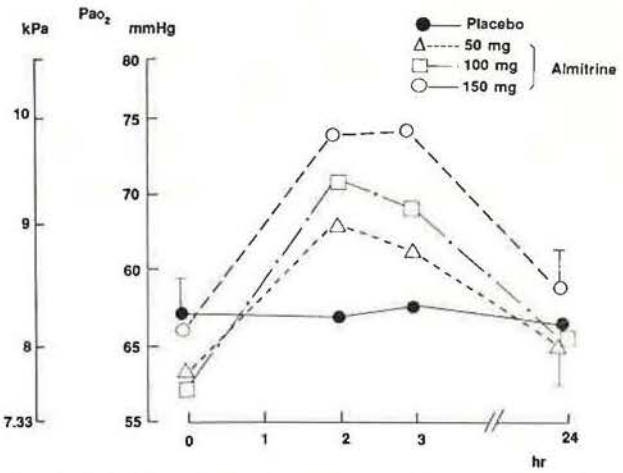

Fig. 1. – Mean Pao_2 in sixteen COPD patients before and after single oral intake of almitrine bismesylate 50 (Δ), 100 (□) or 150 mg (○) versus placebo (●).

150 mg, although plasma almitrine levels of 392 and 288 ng·ml^{-1}, respectively, 2 and 3 h after intake were observed.

For a given dose and time after drug intake, no correlation was found between individual Pao_2 changes and plasma almitrine concentration.

In the responsive patients, Sao_2 changed in parallel to Pao_2. Mean Pao_2 changes (ΔPao_2) as a function of mean plasma almitrine level 2 and 3 h after drug intake are shown in figure 2. The relationship is curvilinear with a maximal Pao_2 increase of about 1.5 kPa (11 mmHg), 2 or 3 h following almitrine 100 mg, which corresponds to a mean plasma almitrine concentration of 150 ng·ml^{-1}. Figure 3 illustrates the variations of mean $Paco_2$ following oral administration of almitrine or placebo. In contrast to placebo, $Paco_2$ decreased 2 and 3 h after administration of the drug, but only almitrine 150 mg caused a statistically significant 0.9 kPa (7 mmHg) $Paco_2$ decrease ($p<0.01$). Three hours after drug intake, there was a trend towards an increase in pH and a decrease in HCO_3^-. These changes were statistically significant ($p<0.01$) only after almitrine 100 and 150 mg.

Ventilation

The effects of almitrine or placebo on mean minute ventilation 3 h after oral intake of the drug are shown in figure 4. Neither almitrine nor placebo caused notable variations in minute ventilation except for a significant 1 *l*·min^{-1} increase observed 3 h after intake of almitrine 150 mg ($p<0.01$). Increase in ventilation, when present, was due to a significant increase in respiratory rate while tidal volume did not change significantly.

Clinical tolerance

No significant variations in the monitored biological parameters were shown between the test days and no side effects were observed after administration of almitrine or placebo.

Dose	2 h		3 h		2 h	3 h
	mmHg	kPa	mmHg	kPa	ng·ml	ng·ml
50 mg	9	1.2	7	0.93	65	71
100 mg	12	1.6	11	1.46	147	151
150 mg	12	1.6	12	1.6	234	275
	mean Pao_2 change				mean plasma level	

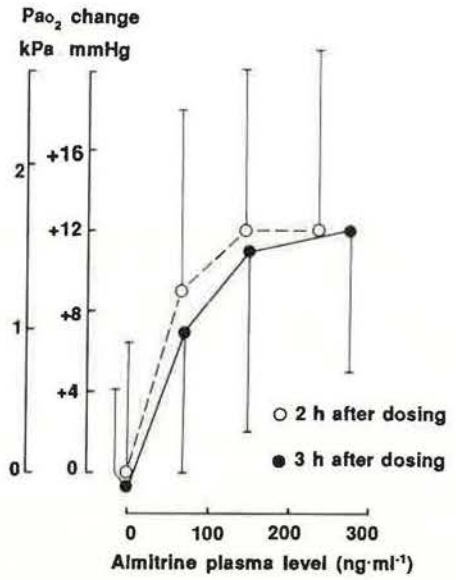

Fig. 2. – Relationship between mean ΔPao_2 and mean almitrine plasma level 2 and 3 h after a single oral intake in sixteen COPD patients. The table shows the mean values and the figure a plot with SD.

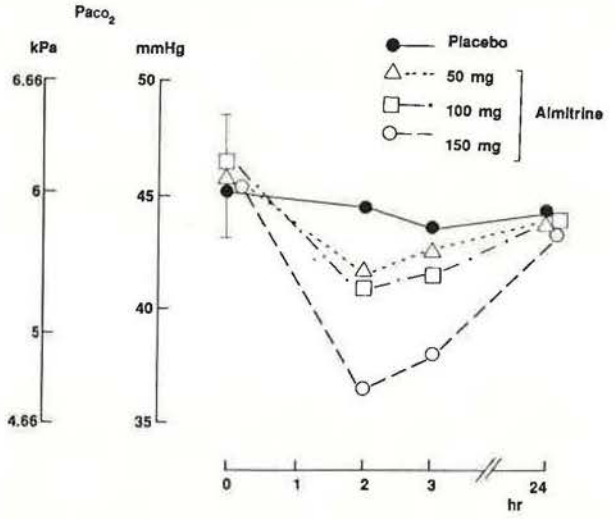

Fig. 3. – Mean $Paco_2$ in sixteen COPD patients before and after single oral intake of almitrine bismesylate 50 (Δ), 100 (□), or 150 mg (○) versus placebo (●).

Pharmacokinetics

Mean almitrine plasma concentration *vs* time curves following oral administration of almitrine bismesylate 50, 100 and 150 mg in our sixteen COPD patients are shown in figure 5. Whatever the dose, mean time to peak plasma level (t_{max}) was around 3 h after drug intake. For a given dose and time, there were large interindividual variations in plasma almitrine levels. No correlation was found between C_{max} and body weight of our patients.

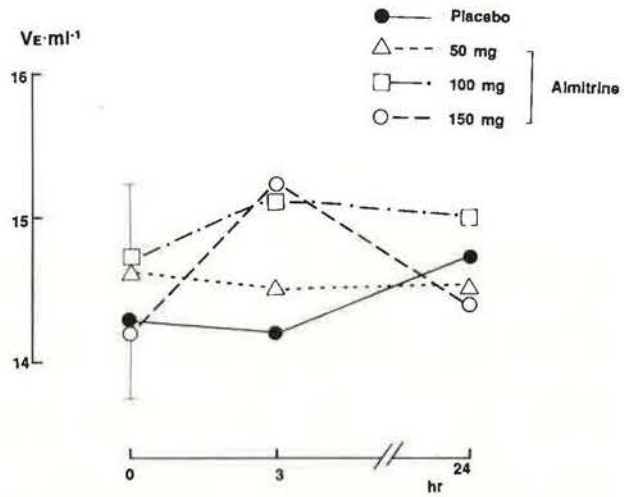

Fig. 4. – Mean resting ventilation in sixteen COPD patients before and after a single oral intake of almitrine bismesylate 50 (Δ), 100 (○) or 150 mg (○) *versus* placebo (●).

Table 2 summarizes means±SD of the pharmacokinetic parameters. In the range of doses studied, mean C_{max} and area under the curve (AUC) correlated linearly with dose. Total plasma clearance and terminal half-life of almitrine were not significantly changed with increasing dose. The volume of distribution was slightly different between doses ($p<0.01$). The higher value calculated after a 100 mg dose is probably without pharmacokinetic significance since there was no overall trend with dose. The value of the terminal half-life between the different doses ranged from 116–140 h, *i.e.* 5–6 days. This long terminal half-life may explain why a residual plasma concentration of almitrine of 5–10 $ng \cdot ml^{-1}$ was measured in some of the patients just before subsequent intake of the drug.

Discussion

This study confirms that oral administration of almitrine bismesylate (50 or 100 mg) improves blood gases in the majority of COPD patients without significantly changing minute ventilation, as has been observed by others under identical conditions [4, 16], or in patients under mechanical ventilation [5]. A dose-related Pao_2 increase was noted in more than 80% of our patients, with a mean increase of about 1.5 kPa (11 mmHg), 2 or 3 h after intake of almitrine 100 mg. Almitrine 150 mg caused only a negligible additional increase in Pao_2 which was associated with a significant increase in ventilation and decrease in $Paco_2$.

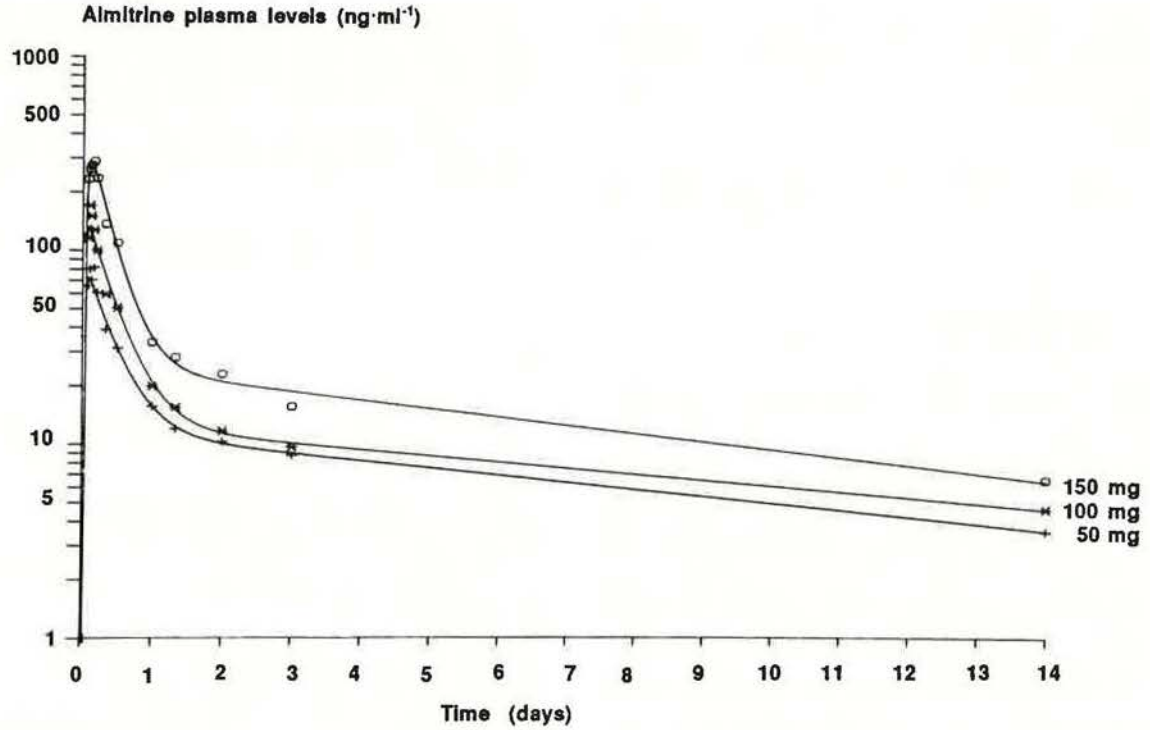

Fig. 5. – Mean almitrine plasma levels in sixteen COPD patients before and after a single oral intake of almitrine bismesylate at different doses.

Table 2. – Mean±SD pharmacokinetic parameters of almitrine following oral administration of 50, 100, 150 mg of almitrine bismesylate.

		50 mg	100 mg	150 mg	
C_{max}	ng·ml^{-1}	110.3±47.3	194.5±139.0	378.9±118.4	p<0.001†
T_{max}	h	3.06±1.08	2.91±0.95	3.03±1.12	NS
AUC	ng·ml^{-1}·h	3617.9±2453.3	4308.5±3047.6	7775.8±3824.9	p<0.001†±
CL	*l*·h^{-1}	15.81±11.13	25.7±16.9	17.52±8.09	NS
V	*l*	1821.8±822.8	3398.6±1738.8	2475.3±1253.9	p<0.01
$t_{0.5,z}$	h	139.6±121.3	135.9±105.4	115.9±63.6	NS

The relationships betweem C_{max} or AUC and dose are, respectively: $C_{max}=1.26\ Dose^{1.10}$ and $AUC=150.8\ Dose^{0.73}$ with the two exponents non-significantly different from 1. C_{max}: maximal plasma concentration; t_{max}: time to peak plasma level; AUC: area under plasma concentration *vs* time curve; CL: plasma clearance; $t_{0.5,z}$: plasma half-life; NS: non-significant.

Although the aim of this study was not to investigate the mode of action of almitrine, our results seem consistent with its proposed mechanisms of action. Almitrine at doses ≤1.5 mg·kg^{-1} improves pulmonary gas exchange in hypoxaemic COPD patients by a reduction of alveolar ventilation perfusion ($\dot{V}A/\dot{Q}$) distribution inequalities [5, 16, 17]. At higher doses, almitrine also stimulates external ventilation through stimulation of peripheral chemoreceptors [1, 3]. Our study shows that almitrine causes a submaximal Pao_2 improvement 2 and 3 h after a single 100 mg oral dose in COPD patients, but also that there are large inter-individual variations in the response ranging from 0–2.7 kPa (0–20 mmHg) in our sixteen patients. Similar observations have been reported by others [18–20] and it is now recognized that at least 20% of COPD patients will not respond to almitrine even following chronic administration [21–23]. In a recent Vectarion International Multicentre Study (VIMS) report [24], 55% of patients receiving almitrine bismesylate 100 mg per day for twelve months were considered as good responders, *i.e.* showing a Pao_2 increase of at least 0.7 kPa (5 mmHg).

It is still impossible to predict which COPD patients will respond to almitrine. Unresponsiveness has not yet been studied in relation to the severity of respiratory

insufficiency, pulmonary hypertension or chemoreceptor sensitivity. Our three patients who did not respond to almitrine 50 mg were no different in any of the measured clinical and laboratory parameters from the responders.

This study shows that unresponsiveness is not due to poor absorption of the drug. Indeed, the patient who did not respond to almitrine 150 mg had a normal plasma level 3 h after oral intake. Other patients responded well in spite of much lower plasma almitrine levels.

This dose-response study shows that Pao_2 increases proportionally to plasma almitrine concentration with a submaximal effect around 100 and 150 $ng \cdot ml^{-1}$, 2 and 3 h after administration. Our pharmacokinetic results show that C_{max} and AUC correlate linearly with dose and that almitrine half-life in plasma is 5–6 days, which may possibly account for some residual effect on Pao_2 24 h after administration. This half-life is longer than previously described in healthy subjects after single oral administration. It may be explained by a longer sampling time than in previous studies. Indeed, in normal volunteers, terminal half-lives of 30–35 h are found with a 48 h sampling and 40–45 h with a 72 h sampling [9]. Therefore, the results of this study do not necessarily suggest that almitrine elimination from plasma is different in patients with COPD in comparison with healthy subjects. A progressive increase of plasma levels may thus be expected with chronic administration of almitrine over the initial period of treatment, as already demonstrated in long-term clinical studies [22, 25], and the pharmacokinetics of the drug might best be studied after repeated oral administration. In conclusion, almitrine 50 and 100 mg causes a dose-related Pao_2 increase without change of ventilation, in most hypoxaemic COPD patients, 2 and 3 h after single oral dose administration. Almitrine 150 mg increases ventilation and decreases $Paco_2$ but gives only a negligible additional Pao_2 improvement compared to 100 mg. Mean Pao_2 increase correlates with plasma almitrine level up to about 150 $ng \cdot ml^{-1}$ plasma, when a maximal or near maximal Pao_2 effect of about 1.5 kPa (11 mmHg) is reached.

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Etude dose-réponse et étude pharmacocinétique du bismesylate d'almitrine après administration orale unique dans les bronchopneumopathies chroniques obstructives. Th. Bury, J.P. Jeannot, J.C. Ansquer, M. Radermecker.

RÉSUMÉ: Pour définir mieux les relations dose-effet et la pharmacocinétique de l'almitrine, nous avons administré à 16 patients BPCO hypoxémiques en état stable, au cours d'une étude en double aveugle et randomisée, des doses uniques orales de 50, 100, 150 mg ou de placebo, à des intervalles de 2 semaines. Nous avons mesuré la ventilation au repos, les gaz du sang artériel et les niveaux plasmatiques d'almitrine. L'administration de placebo n'a entraîné aucune modification significative des gaz du sang ou de la ventilation, alors que les doses de 50 et de 100 mg d'almitrine entraînaient une amélioration significative de la Pao_2, liée à la dose chez 13 des 16 patients. La dose de 150 mg d'Almitrine n'ajoute que peu ou pas d'amélioration de la Pao_2 par rapport à la prise de 100 mg. La Pao_2 revient à des valeurs quasi basales après 24 h. Deux des 3 patients n'ayant pas répondu à la prise de 50 mg ont répondu aux doses de 100 et de 150 mg d'almitrine seulement, alors quele troisième n'a pas répondu du tout. L'augmentation moyenne de Pao_2 chez les 16 patients est de 7 (0.9 kPa), 11 (1.5 kPa) et 12 (1.6 kPa) mm Hg 3 heures après l'administration de 50, 100 et 150 mg respectivement. Nous avons a observé, après la dose de 150 mg, une diminution moyenne significative de 7 mm Hg (0.9 kPa) de $Paco_2$ et une augmentation de ventilation d'un litre par minute. La concentration plasmatique moyenne maximale d'almitrine et la surface la courbe sont en corrélation linéaire avec la dose. La relation entre l'augmentation moyenne de Pao_2 et le taux plasmatique moyen d'almitrine est curvilinéaire, la courbe s'aplatissant au-delà des niveaux plasmatiques de 150 ng·ml. La demi-vie plasmatique terminale de l'almitrine est de l'ordre de 116 à 140 heures. En conclusion, une augmentation maximale ou quasi maximale de Pao_2 de l'ordre de 11 mm Hg (1.5 kPa) se produit chez la plupart des BPCO hypoxémiques, sans modification de la ventilation externe, 2 et 3 h. après prise unique orale de 100 mg de bismesylate d'almitrine, correspondant à un taux plasmatique moyen d'environ 150 ng·ml.
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