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Intravenous Almitrine Bismesylate Reversibly Induces Lactic Acidosis and Hepatic Dysfunction in Patients with Acute Lung Injury

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Background: **Intravenous almitrine, which augments hypoxic pulmonary vasoconstriction, is used for short-term improvement of arterial oxygenation. However, recent research has suggested a potentially harmful effect on lactate metabolism and hepatic function.**

Methods: **Arterial oxygenation, hemodynamic parameters, plasma lactate, and hepatic function were monitored prospectively in 25 patients with acute lung injury (defined as a ratio of arterial oxygen pressure to inspiratory oxygen fraction ≤ 150 mmHg) who where treated with intravenous almitrine. In 21 of 25 patients, acute lung injury was related to primary lung lesions, including pneumonia, postcardiosurgical atelectasis, and lung contusions.**

Results: **Intravenous almitrine increased the ratio of arterial oxygen pressure to inspiratory oxygen fraction from 93 ± 33 mmHg to 207 ± 107 mmHg (mean ± SD). In eight patients (three men), the plasma lactate concentration increased by an average of +3.5 ± 1.8 mM, and the *p*H and bicarbonate concentration both decreased during the first 24 h of treatment. In this group of patients, the total bilirubin concentration was elevated before almitrine administration, and the results of other hepatic function tests, such as aspartate aminotransferase, alanine aminotransferase, and prothrombin time, were altered by almitrine administration. Therefore, intravenous almitrine was discontinued. Lactic acidosis and hepatic dysfunction improved. In the other 17 patients (14 men), the plasma lactate concentration and the hepatic function tests remained unaltered during intravenous almitrine therapy for >60 h. Univariate and multivariate analyses revealed that an abnormal plasma concentration of total bilirubin before almitrine administration and female gender were the two factors significantly linked with lactic acidosis during almitrine infusion.**

Conclusions: **This study confirms that intravenous almitrine greatly improves arterial oxygenation in patients with acute lung injury but may also induce lactic acidosis and hepatic dysfunction. The coexistence of lactic acidosis and hepatic dysfunction in the same patients strongly suggests that the liver is the primary source of intravenous almitrine-induced lactic acidosis. (Key words: Acute respiratory distress syndrome; hypoxic pulmonary vasoconstriction; inhaled nitric oxide; liver function.)**

ORAL almitrine bismesylate has been used for many years to improve gas exchange in patients with chronic obstructive pulmonary disease. Although the mechanism of action of almitrine is uncertain, two clinical effects have been well documented: (1) an improvement of minute ventilation in spontaneously breathing patients with a decreased pressure of carbon dioxide in arterial blood *via* a stimulation of the chemoreflex and (2) a vasoconstrictor effect on pulmonary vessels that apparently predominates in hypoxic zones, improving the ventilation–perfusion matching, oxygen pressure in arterial blood (Pa_{O_2}) and decreasing the venous admixture (for a review, see references 1 and 2). Many side effects have been reported after prolonged oral treatment, including increased dyspnea, gastrointestinal upset, and peripheral neuropathy that affects the myelinated fibers of the lower limbs.[2,3] In addition, the association of weight loss and worsening pulmonary hypertension has reduced considerably the use of almitrine for the long-term treatment of patients with chronic obstructive pulmonary disease.

Intravenous almitrine has been used successfully for short-term improvement of Pa_{O_2} in patients with acute respiratory failure.[4,5] At low doses ($<10\ \mu g \cdot kg^{-1} \cdot min^{-1}$), intravenous almitrine alone improves intrapulmonary shunt.[1] Such improvement in Pa_{O_2} has been attributed to an intrapulmonary blood flow redistribution from the poorly ventilated zones toward the normal

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zones.[5,6] Such redistribution has been related to a preferential pulmonary vascular contraction in hypoxic zones. The recent development of inhaled therapies, such as nitric oxide (NO) and prostacyclin, to manipulate the flow component of the ventilation–perfusion ratio prompted us and others[7–9] to combine these therapies with almitrine to optimize the Pa_{O_2} of severely hypoxic patients. However, such improvement in the ratio of Pa_{O_2} to the inspiratory fraction of oxygen (FI_{O_2}) might be "cosmetic," because most deaths after acute respiratory distress syndrome (ARDS) were related to multiple organ failure.[10] Accordingly, the use of potentially toxic substances, such as inhaled NO or almitrine must be balanced in terms of the benefit-to-risk ratio. Scant information exists regarding side effects of short-term intravenous almitrine treatment in patients in the intensive care unit. Sicsic *et al.*[11] reported severe hepatic cytolysis during intravenous almitrine treatment in a patient with posttraumatic ARDS. In the current article, we report the use of almitrine in 25 consecutive patients with acute lung injury (ALI). Almitrine was associated with lactic acidosis and impaired results of hepatic function tests in 30% of the patients. These two side effects were reversed after almitrine was discontinued.

Methods

Patients

This survey was approved by the human ethics committee of the institute, and written consent was obtained from patients or the next of kin. Twenty-five consecutive tracheally intubated and ventilated (volume-cycled) patients with severe ALI, defined as a Pa_{O_2}:FI_{O_2} ratio $\leq$150 mmHg, and treated with almitrine after therapeutic optimization (see therapeutic strategy) were included prospectively. Among these, eight had ARDS (Murray score >2.5) based on classic criteria, including bilateral lung infiltrates shown on a chest roentgenograph and a thoracic computed tomograph and an absence of cardiac failure assessed by echocardiography, a pulmonary artery occlusion pressure <18 mmHg, or both.[12] The 17 other patients had focal lung lesions that involved <50% of the total lung surface, as judged by four independent, blinded observers by chest roentgenography and computed tomographic assessment of parenchymal consolidation.

Measurements

Twelve patients had an oximetric thermodilution pulmonary artery catheter (Abbott Laboratories, Chicago, IL) placed that allowed measurement of mean pulmonary arterial, right atrial, and pulmonary artery occlusion pressures. The other 13 patients were monitored using central venous catheters and transesophageal descending aortic flow velocity (ODM 2; Abbott Laboratories, Rungis, France).[13] In all patients, arterial pressure was measured *via* arterial catheter (Seldicath catheter; Plastimed Laboratories, St. Leu la Forêt, France). Arterial blood sampling allowed determination of arterial blood gases (ABL 300; Radiometer, Copenhagen, Denmark), prothrombin time (%), the coagulation factors II, V, and VII, aspartate aminotransferase (AST, n < 35 IU/l), alanine aminotransferase (ALT, n < 56 IU/l), total bilirubin (n < 17 μM), alkaline phosphatase (n < 115 IU/l), glucose (n, 4–5.5 mM) and lactate (n < 2 mM, $\pm$0.06 mM at the precision test; Ektachem 700, Kodak, Rochester, NY). The cumulative dose of almitrine, the Logistic Organ Dysfunction System score,[14] and the Simplified Acute Physiology Score II[15] (both scores performed at the time of almitrine administration) were calculated also.

Therapeutic Strategy

Patients with compromised arterial oxygenation were administered intravenous almitrine after preliminary therapeutic optimization that consisted of adequate fluid resuscitation (based on filling pressures and mixed venous oxygen saturation), appropriate use of vasoactive drugs to maintain blood pressure, determination of the best positive end-expiratory pressure level based on oxygen transport when it was available, and administration of inhaled NO at a dose of 4–15 ppm, as previously described.[7,12] Inhaled NO was administered continuously *via* fenestrated silicone catheter (1.3 mm diameter; Vygon, Paris, France) positioned within the endotracheal tube, at a flow rate adapted to provide a therapeutic fraction of 4–15 ppm. Potential NO toxicity was assessed by (1) the methemoglobin level determined daily by spectrophotometry (OSM2 Hemoximeter, Radiometer), which was consistently <1.5%, and by (2) NO and nitrogen dioxide (NO_2) levels in both the inspired and expired limbs of the ventilator, measured twice a day by chemiluminescence (EcoPhysic, Massy, France). The NO_2 level was always <100 ppb.

When the Pa_{O_2}:FI_{O_2} ratio remained $\leq$ 150 mmHg after these modalities were used, patients were administered a continuous infusion of intravenous almitrine (Servier, Suresnes, France) through a central catheter. The dose of almitrine was titrated from 2–8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to achieve the best Pa_{O_2}:FI_{O_2} ratio with the minimal amount

of almitrine.[1] Hemodynamic and biologic parameters were recorded before the administration of almitrine (T0) and every 12 h for 60 h in all patients (T12 to T60).

For the patients whose lactate concentration increased by more than +2 mM during the first 24 h of almitrine administration, almitrine was discontinued at 24 h (T24). For the other patients, in whom the plasma lactate concentration remained stable between T0 and T24, almitrine administration was continued at the same infusion rate for at least 36 h more (until T60). In all patients, NO inhalation was maintained at least until T60.

Statistical Analysis

Mean values between groups were compared using two-way analysis of variance for subsequent measures. Intragroup comparisons were made using the Newman-Keuls test. Data are expressed as mean ± SD, and $P < 0.05$ was considered significant.

Potential univariate correlates of lactic acidosis were identified by chi-squared analysis for qualitative parameters and by the Mann–Whitney U test for quantitative parameters. Considering the small sample size, a logistic exact procedure was used for multivariate analysis (LogXact, Cytel Software).

Results

Table 1 summarizes selected clinical characteristics of the 25 patients at the time of intravenous almitrine administration. The mean Logistic Organ Dysfunction System score was 5 ± 3, the Simplified Acute Physiology Score II was 34 ± 10, and the Pa_{O_2}: FI_{O_2} ratio was 93 ± 33 mmHg for the 25 patients. The causes of ALI were related mainly to primary lung lesions (21 of 25 patients), including pneumonia (n = 7), postcardiosurgical atelectesia (n = 6), and lung contusions after thoracic trauma (n = 4).

Intravenous almitrine enhanced the Pa_{O_2}:FI_{O_2} ratio by more than two times in the 25 patients included in our survey (table 2, fig. 1). The improvement in the Pa_{O_2}:FI_{O_2} ratio was associated with an increased systolic pulmonary arterial pressure in the 12 patients with pulmonary artery catheters. The other measured hemodynamic parameters, including cardiac output, remained unchanged.

Eight patients had increased plasma lactate concentration during the first 24 h of intravenous almitrine administration—a +3.5 ± 1.8 mM increase compared with T0; these patients were included in a group labeled "high lactate" (HL group, figs. 1 and 2). Figures 1 and 2 show that plasma lactate increased at 12 h and peaked at T24. Intravenous almitrine discontinuation in the HL group at T24 was followed by a decrease in plasma lactate level that returned to normal in all patients within 36 h. In parallel, the *p*H and the bicarbonate concentration decreased during intravenous almitrine infusion and returned to normal at T60. In contrast, intravenous almitrine did not alter the *p*H, the bicarbonate concentration, or the plasma lactate level between T0 and T60 in the 17 other patients who were included in the low-lactate group (LL group).

Impaired hepatic function also was observed in the HL group 24 h after intravenous administration of almitrine (fig. 2, table 3). The AST and ALT serum concentrations increased, whereas prothrombin time and factor VII decreased in the HL group. When intravenous almitrine was discontinued, factor VII returned to normal within 36 h, whereas the AST serum concentration and the prothrombin time remained altered, slowly improving in the next 3 or 4 days (data not shown). Total bilirubin, glucose, and alkaline phosphatase concentrations remained stable after almitrine administration in both groups, despite a greater baseline bilirubin level in the HL group. Intravenous almitrine did not alter hepatic function tests throughout the 60 h of observation in the LL group.

The amount of almitrine administered was greater in the HL group than in the LL group during the first 24 h (459 ± 155 mg for the HL group and 370 ± 113 mg for the LL group; $P < 0.05$) but was less over the 60 h because almitrine was discontinued in the HL group (459 ± 55 mg for the HL group and 911 ± 361 mg for the LL group, $P < 0.005$).

Figure 2 shows that despite the difference in plasma lactate concentrations and the hepatic function tests between the HL and LL groups, intravenous almitrine induced a similar improvement in the Pa_{O_2}:FI_{O_2} ratio in both groups. Although almitrine was discontinued in the HL group at T24, the improvement in the Pa_{O_2}:FI_{O_2} ratio lasted until T60 in the two groups.

Univariate analysis revealed that the level of bilirubin before almitrine administration and patient gender were predictive factors for the occurrence of lactic acidosis after almitrine administration, whereas age, catecholamine treatment, Logistic Organ Dysfunction System score, Simplified Acute Physiology Score II, and cause of ALI (ARDS *vs.* non-ARDS) were not. Therefore, as shown in figure 3, female patients were at high risk for the occurrence of lactic acidosis; five of eight were in the HL

Table 1. Clinical Characteristics of Patients with Acute Lung Injury

Patient Number	Age (yr)/Gender	Diagnosis for Hypoxemia	LODS	SAPS II	Pa_{O_2}:FI_{O_2}	Drugs	Outcome	Cause of Death
HL group								
1	57/F	*Proteus* pneumonia	4	33	150	E	Alive	
2	62/F	Post cardiosurgical atelectesia	7	42	70	D + NE	Alive	
3	34/M	Post cardiosurgical atelectesia	5	40	66		Alive	
4	72/F	*Pseudomonas aeruginosa* pneumonia	6	47	136		Alive	
5	38/F	*Legionella* pneumonia	4	23	89		Alive	
6	41/M	Lung hemorrhage	5	40	88		Dead	Massive hemoptysis
7	32/M	Lung contusion	8	45	72		Alive	
8	20/F	Fat embolism	3	34	66		Dead	Sepsis
Mean ± SEM	45 ± 18 (F = 5, M = 3)		5 ± 2	37 ± 9	92 ± 33			
LL group								
1	24/M	*Legionella* pneumonia	1	14	139		Dead	Sepsis
2	45/M	Lung contusion	8	51	59		Alive	
3	69/M	Post cardiosurgical atelectasia	4	31	66		Alive	
4	49/M	Post cardiosurgical atelectasia	6	36	71		Alive	
5	63/M	Post cardiosurgical atelectasia	8	41	144	NE	Alive	
6	49/M	Gastric aspiration	3	29	110		Alive	
7	31/M	Lung contusion	4	32	140		Alive	
8	33/M	Lung contusion	1	18	58		Alive	
9	18/M	Gastric aspiration	3	25	53		Alive	
10	51/F	*Pneumococcal* pneumonia	1	27	52		Alive	
11	39/M	Sepsis	9	48	65		Alive	
12	30/F	*Pseudomonas aeruginosa* pneumonia	10	50	74	E	Dead	Sepsis
13	46/M	Sepsis	6	33	120		Alive	
14	48/M	Post cardiosurgical atelectasia	1	23	141		Alive	
15	53/M	Sepsis	4	27	82		Dead	Sepsis
16	31/M	Sepsis	8	46	85	E	Alive	
17	38/F	*Pneumococcal* pneumonia	8	36	118		Alive	
Mean ± SEM	42 ±14 (F = 3, M = 14)		5 ± 3	33 ± 11	93 ± 35			

D = dobutamine; E = epinephrine; NE = norepinephrine.

group. In contrast, all male patients with normal initial levels of bilirubin were in the LL group (10 of 10). Initial bilirubin level and gender both were also found to be predictive factors when used in the multiple logistic exact model. In this case, the exact odds ratio for gender was 2.46 ($P = 0.038$), and the β parameter for bilirubin (exact assumption) was 0.056 ($P = 0.01$).

Discussion

Intravenous almitrine consistently improved the Pa_{O_2}:FI_{O_2} ratio in patients with ALI. Intravenous almitrine was also associated with lactic acidosis and impaired hepatic function in 30% (n = 8) of our patients. Lactic acidosis and hepatic dysfunction appeared within 12 h of almi-

Table 2. Hemodynamic and Respiratory Effects of Almitrine

	n	Before Almitrine Administration	T12	T24
MAP (mmHg)	25	75 ± 11	71 ± 12	71 ± 12
PAPs (mmHg)	12	41 ± 13	45 ± 14*	46 ± 11*
PAPm (mmHg)	12	31 ± 10	33 ± 10	32 ± 8
PAPd (mmHg)	12	23 ± 5	24 ± 8	24 ± 6
CO (L/min)	12	5.8 ± 1.0	5.9 ± 1.1	6.3 ± 1.1
RAP	25	10 ± 4	10 ± 4	10 ± 4
PAoP	12	12 ± 2	13 ± 2	12 ± 2
Pa_{O_2}/FI_{O_2} (Torr)	25	93 ± 33	207 ± 113†	217 ± 107†
Pa_{CO_2} (Torr)	25	42 ± 10	41 ± 11	43 ± 11

Data were recorded before and 12 and 24 h after almitrine administration (T12 and T24, respectively). Twelve patients had a pulmonary artery catheter (HL group, n = 6; LL group, n = 6). No difference was observed between the HL and LL groups; data were therefore pooled. MAP = mean arterial pressure; PAPs = systolic pulmonary arterial pressure; m = mean; d = diastolic; CO = cardiac output; RAP = right atrial pressure; PAoP = pulmonary artery occlusion pressure.

* $P < 0.05$ *versus* before.

† $P < 0.001$ *versus* before.

trine administration and were reversed after drug discontinuation. In contrast, in the other 70% (n = 17) of patients, intravenous almitrine induced no change in any of the measured biologic parameters.

Effects of Almitrine on Arterial Oxygenation

Acute lung injury is characterized by impaired gas exchange caused by maldistribution of ventilation:perfusion ratios. The recent introduction of intravenous almitrine and inhaled NO dramatically modified the therapeutic management of hypoxemia in patients with ALI.[1,8,9] In our patients with ALI, the introduction of intravenous almitrine after therapeutic optimization, which included inhaled NO, increased the $Pa_{O_2}:FI_{O_2}$ ratio within 12 h from 93 ± 7 mmHg to 207 ± 23 mmHg ($P < 0.001$). Improvement of the $Pa_{O_2}:FI_{O_2}$ ratio was observed in every patient observed, regardless of plasma lactate concentration and hepatic dysfunction.

Interestingly, the $Pa_{O_2}:FI_{O_2}$ ratio remained greater at T24 and T60 than at T0 in the HL group, even after almitrine was discontinued (fig. 2). This may be explained by the pharmacologic properties of almitrine:[1,2] (1) almitrine is highly bound (>99%) to low-density lipoprotein and its half-life is >24 h in humans; (2) hydroxy metabolites of almitrine show almitrine-like activity; and (3) because almitrine is mainly metabolized by the liver and excreted in bile, hepatic dysfunction in the HL group further prolonged almitrine and the half-lives of its metabolites, as previously described.[16]

Lactic Acidosis

Disturbances of acid–base equilibrium and particularly lactic acidosis are among the most frequent metabolic disorders seen in the intensive care unit. Hyperlactatemia may result from decreased lactate clearance, from increased lactate production related to any cause of local anaerobic metabolism or cellular dysfunction, or from both.

Much of the lactate produced by the body is cleared by the liver by gluconeogenesis and oxidative phosphorylation.[17] In our study, the coexistence of hyperlactatemia and hepatic dysfunction, in the HL group, suggests an impaired hepatic lactate clearance as a mechanism of hyperlactatemia. The lung, which is another site of mammalian lactate metabolism, may account for the origin of hyperlactatemia. Because lactate is a preferential energetic substrate for rat and Wedded seal lungs,[18,19] almitrine might have reduced the lactate lung uptake in our patients. More realistically, inflamed lungs may produce more lactate in the presence of almitrine. Such an hypothesis is confirmed by recent data about lung lactate production in critically ill patients.[20]

Other organs, such as the brain and the gut, and the erythrocytes are major lactate producers,[17] both in physiologic and pathophysiologic conditions. In our study,

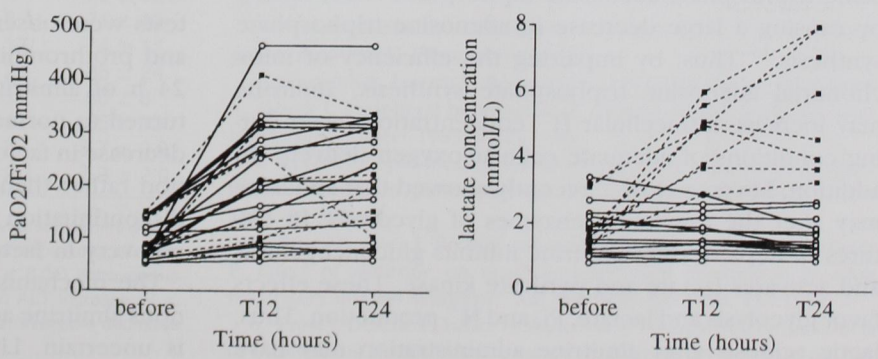

Fig. 1. Individual data for the ratio of arterial oxygen pressure to inspiratory oxygen fraction ($Pa_{O_2}:FI_{O_2}$) and plasma lactate concentration. The dashed line represents patients from the high-lactate group, and the solid line represents patients from the low-lactate group.

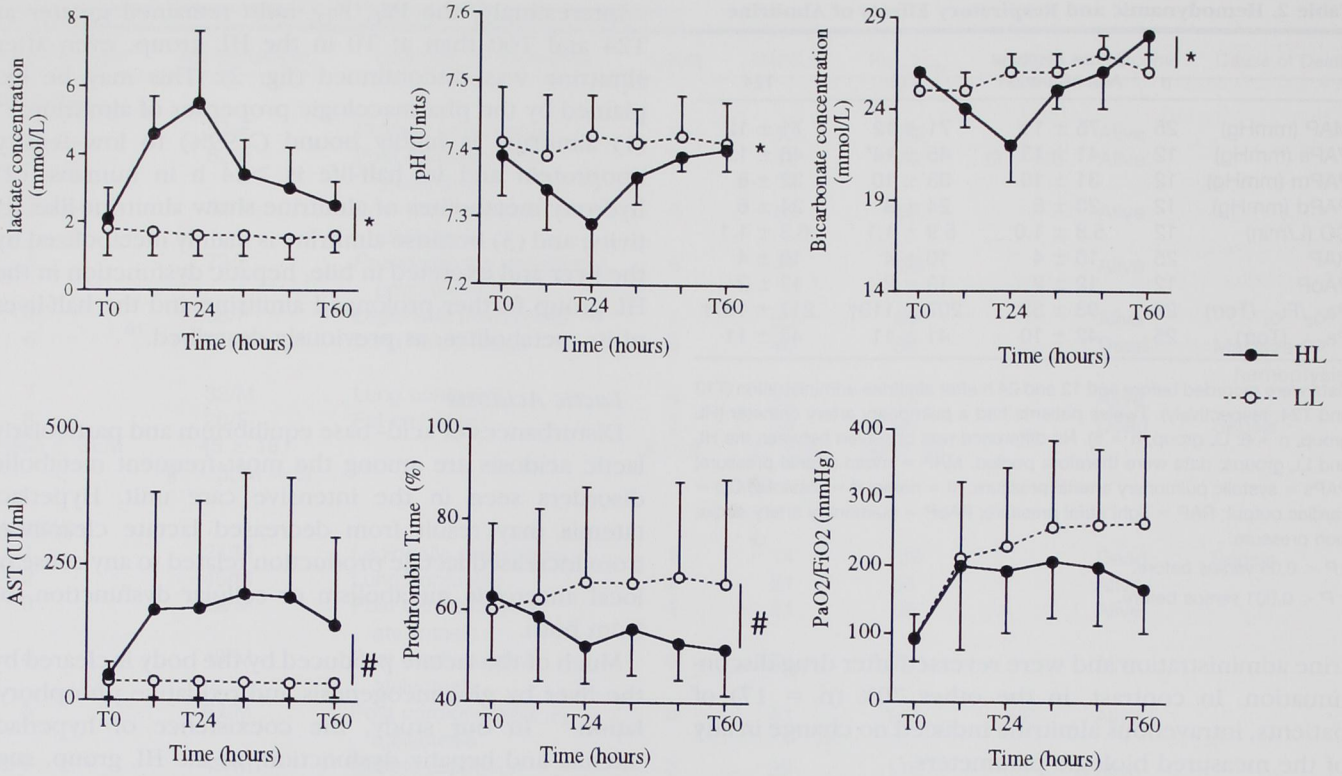

Fig. 2. Lactic acidosis and hepatic dysfunction follows almitrine administration in the high-lactate group; *$P < 0.01$ and #$P < 0.03$, both by two-way analysis of variance for repeated measures. Almitrine improves the ratio of arterial oxygen pressure to the inspiratory oxygen fraction Pa_{O_2}:Fi_{O_2} during time in both the high-lactate and the low-lactate groups ($P < 0.001$). Although almitrine was discontinued at 24 h (T24), no difference was found between the high- and low-lactate groups.

almitrine-induced hyperlactatemia was associated with a decrease in *p*H and bicarbonate concentration. This acidosis probably is related to mitochondrial dysfunction, which is known to induce an accumulation of Pi and H^+.[17] Almitrine may affect mitochondrial function by reducing oxygen delivery to certain organs, but more likely by acting directly on mitochondrial adenosine triphosphatase activity, as previously suggested by several authors.[21–23] In mitochondria that are isolated from bovine heart and rat liver, almitrine decreased the adenosine triphosphate:adenosine diphosphate ratio, mainly by causing a large decrease in adenosine triphosphate synthesis.[23] Thus, by impairing the efficiency of mitochondrial adenosine triphosphate synthesis, almitrine may increase intracellular H^+ concentration, even during conditions of adequate cellular oxygen delivery. In addition, Leverve *et al.*[22] recently showed that almitrine may alter the regulatory enzymes of glycolysis. In cultures of hepatocytes, almitrine inhibits gluconeogenesis and activates lactate and pyruvate kinase. These effects favor glycolysis and lactate, Pi, and H^+ production. Thus, lactic acidosis after almitrine administration may have been related, at least in part, to a direct intracellular effect of almitrine on glucose metabolism and mitochondrial function.

Alterations of Hepatic Function Tests

A preliminary report recently described an alteration in hepatic function tests in a patient with ARDS who was treated with almitrine.[11] It showed an increase in AST plasma concentrations to levels >1,000 IU/l that decreased as soon as almitrine was discontinued. In our study, similar alterations in results of hepatic function tests were observed. The AST and ALT levels increased and prothrombin time and factor VII decreased within 24 h of almitrine administration, and these values returned to normal after almitrine was discontinued. The decrease in factor VII is related to a true hepatic dysfunction rather than to a vitamin K deficiency, because the discontinuation of almitrine was followed by a quick recovery in factor VII level.

The mechanism of hepatic dysfunction after intravenous almitrine administration in patients in the HL group is uncertain. Liver injury is unlikely to be related to

hemodynamic alterations because no difference was observed before and after almitrine administration, except for an increase in pulmonary artery systolic pressure (table 1). In addition, no difference was observed between the HL and LL groups. Hepatic dysfunction may have been related to a local vasoconstrictor effect of the almitrine on hepatic vessels, to a direct, and potentially toxic, effect of almitrine on hepatocyte, or to both.[22] These effects may have been amplified by the impaired hepatic excretion of bilirubin seen before intravenous almitrine administration in the HL group.

In conclusion, our survey shows that a great improvement in the Pa_{O_2}:FI_{O_2} ratio in all patients with ALI who were treated using intravenous almitrine. No alteration in plasma lactate concentration or in results of hepatic function tests were seen in most of these patients during the first 60 h of treatment. However, in some patients with abnormal plasma bilirubin concentrations, an almitrine improvement in arterial oxygenation was associated with lactic acidosis and an alteration in hepatic function test results. Although lactic acidosis and hepatic dysfunction returned to normal after intravenous almitrine was discontinued, arterial oxygenation remained improved for at least 36 h more. Therefore, we suggest

Table 3. Hepatic Parameters before and 24 h and 60 h after Almitrine Administration (T24 and T60, respectively) in Both HL and LL Groups

	Group	Before Almitrine Administration	T24	T60
ALT (IU/l)	HL	32 ± 11	96 ± 136	103 ± 128
	LL	25 ± 10	23 ± 5	25 ± 9
Total bilirubin (μM)	HL	49 ± 54*	57 ± 66	59 ± 64
	LL	15 ± 12	17 ± 22	13 ± 12
Alkaline phosphatase (IU/l)	HL	79 ± 22	93 ± 42	111 ± 39
	LL	76 ± 39	80 ± 64	90 ± 91
Factor II (%)	HL	73 ± 10	68 ± 8	78 ± 12
	LL	67 ± 8	68 ± 5	71 ± 12
Factor V (%)	HL	80 ± 15	71 ± 17	74 ± 17
	LL	75 ± 13	82 ± 23	86 ± 24
Factor VII (%)	HL	64 ± 15	41 ± 12	66 ± 8
	LL	58 ± 14	58 ± 17	65 ± 13
Glucose (mM)	HL	7.9 ± 3.0	8.4 ± 3.1	8.7 ± 2.9
	LL	8.4 ± 3.4	7.7 ± 2.3	7.9 ± 2.0

At T60 the LL group was still under almitrine treatment, whereas almitrine was stopped at T24 in the HL group. Before almitrine administration, total bilirubin was greater in the HL group than in the LL group (*$P < 0.01$). Intravenous almitrine administration induced in the HL group (a) an ALT increase ($P < 0.05$, two-way ANOVA for repeated measures) and (b) a reversible decrease of factor VII ($P < 0.01$).

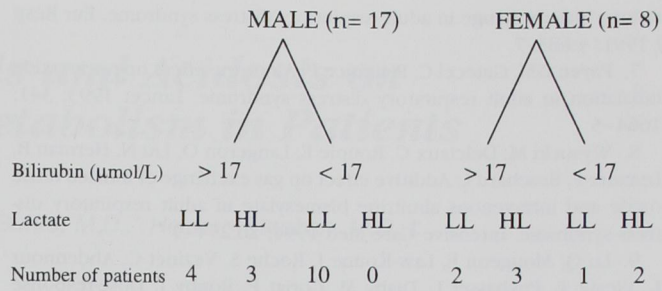

Fig. 3. Patient gender and total bilirubin plasma concentration before almitrine administration were predictive factors for the occurrence of lactic acidosis.

that almitrine should be administered in short infusions of 12–24 h every 2 or 3 days. Consequently, the cumulative dose of almitrine would be reduced with a potential reduction in toxicity but with a sustained arterial oxygenation improvement. The intracellular mechanism of almitrine-induced hepatic dysfunction remains unclear, and more clinical and experimental studies are necessary. However, we recommend that the lactate concentration be monitored, that biologic hepatic function tests be performed every 12 h during the first 24–48 h of almitrine administration, and that the almitrine infusion be discontinued in cases of severe alteration. The bilirubin concentration before almitrine treatment and patient gender were predictive factors of the occurrence of lactic acidosis and hepatic dysfunction. This association should be confirmed by a larger study.

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