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Beneficial effects of a novel anti-hypoxemic agent, TEI-7322, on bleomycin-induced experimental hypoxemia in rats

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Abstract

Almitrine bismesylate is known to be an anti-hypoxemic agent that acts via the enhancement of hypoxic pulmonary vasoconstriction. However, screening for this class of compounds has been minimal, owing, in part, to a lack of convenient hypoxemic models in small animals. The present study was designed to establish a convenient model of hypoxemia induced by bleomycin and to evaluate anti-hypoxemic agents including a newly synthesized compound, TEI-7322, 2-allylamino-4-*tert*-butylamino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine hydrochloride by using this model. Bleomycin was intratracheally instilled into rats. After 3 weeks, the arterial blood gas pressures were monitored in the animals in the conscious state. Then, prednisolone, doxapram, almitrine or TEI-7322 was administered to the bleomycin-treated rats to monitor changes in arterial blood gas pressures. Bleomycin-treated rats showed a decrease in the arterial blood O_2 pressure (PaO_2). The blood CO_2 pressure ($PaCO_2$) increased, along with an increase in the alveolar-arterial oxygen difference ($AaDO_2$). These blood gas pressures in bleomycin-treated rats were not affected by treatment with prednisolone. Doxapram decreased the $PaCO_2$ but did not change the PaO_2. However, administration of almitrine or TEI-7322 significantly improved the PaO_2 of bleomycin-treated rats with a decrease in the $PaCO_2$. In conclusion, (1) bleomycin-induced lung injury causes hypoxemia in rats, probably resulting from ventilation-perfusion inequality; thus this model may be useful for evaluating anti-hypoxemic agents; and (2) TEI-7322, as well as almitrine, showed anti-hypoxemic effects in this model with different properties from those of doxapram, possibly due to improvement of ventilation-perfusion inequality, indicating that TEI-7322 may be a potent candidate for the treatment of hypoxemia.

Keywords: Bleomycin; Experimental hypoxemia; Prednisolone; Doxapram; Almitrine; TEI-7322

1. Introduction

Arterial hypoxemia is a critical problem for patients with respiratory failure accompanied by chronic obstructive pulmonary diseases (Gross, 1990). Although a considerable number of therapies for arterial hypoxemia have been tried, none are yet satisfactory (Ziment, 1978). Almitrine bismesylate is known to enhance hypoxic pulmonary vasoconstriction and to improve the ventilation-perfusion inequality (Dull et al., 1983; Mélot et al., 1983; Romaldini et al., 1983), and has been used as an anti-hypoxemic agent (Magnussen, 1985; Magnussen et al., 1987; Radenbach et al., 1987). However, screening of this class of compounds has been minimal, owing, in part, to a lack of hypoxemic models in small conscious animals. The effectiveness of almitrine in improving the arterial blood O_2 pressure (PaO_2) has been mainly investigated by intravenous administration of the drug to anesthetized dogs (Romaldini et al., 1983; Hughes et al., 1986; Nakanishi et al., 1988). However, this procedure may be unsuitable for screening of anti-hypoxemic agents, particularly those to be tested by oral administration. Therefore, convenient hypoxemic models in small animals are needed in order to estimate the in vivo effectiveness of such drugs.

Bleomycin, an antineoplastic compound consisting of a mixture of cytotoxic glycopeptides, is well known to cause lung fibrosis in human subjects (DeLena et al.,

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1972). Intratracheal administration of bleomycin has been often used to make a model of pulmonary injury in addition to fibrosis (Snider et al., 1978). However, little information is available about the arterial blood gas pressures in bleomycin-treated small animals. The present study was undertaken to analyze the arterial blood gas pressure in conscious rats and to establish a convenient model of hypoxemia induced by bleomycin. In addition, we investigated the influence of some anti-hypoxemic agents on this model and found that a newly synthesized compound, 2-allylamino-4-*tert*-butylamino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine hydrochloride, TEI-7322, displayed a potent anti-hypoxemic effect comparable to that of almitrine.

2. Materials and methods

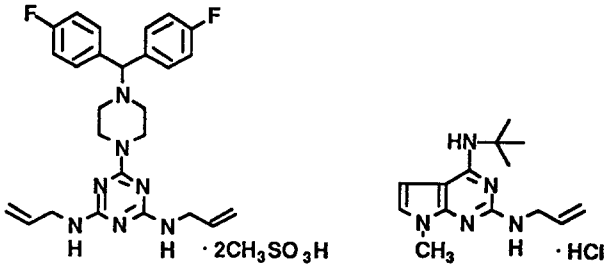
2.1. Experimental animals

Male Sprague-Dawley rats, 6 weeks of age (Charles River Japan, Kanagawa, Japan), were used for all of the experiments. The animals were kept in an air-conditioned room and given standard chow and water ad libitum for the duration of the study. All animal studies were approved by the Institutional Animal Care and Use Committee and performed in accordance with their guidelines.

2.2. Materials

Almitrine bismesylate and TEI-7322 were synthesized in our laboratory. The structures of these compounds are shown in Fig. 1.

Doxapram hydrochloride (Dopram) was purchased from Kissei Pharmaceuticals Co. (Nagano, Japan). Ketamine hydrochloride and halothane were obtained from Sankyo Co. (Tokyo, Japan) and Hoechst Japan (Tokyo, Japan), respectively. Prednisolone and bleomycin hydrochloride were purchased from Wako Pure Chemical Industries (Osaka, Japan).



(A) (B)

Fig. 1. Chemical structures of almitrine bismesylate (A) and TEI-7322, 2-allylamino-4-*tert*-butylamino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine hydrochloride (B).

2.3. Bleomycin-induced lung injury

Bleomycin, dissolved in physiological saline, was intratracheally instilled at a dose of 4.5 mg/kg per 0.75 ml into rats anesthetized by an intraperitoneal injection of ketamine hydrochloride (7.5 mg/kg). Some animals were administered physiological saline alone in the same manner. 3 weeks after bleomycin or saline instillation, the rats were fasted for 18 h and then anesthetized with halothane. An intraarterial catheter was placed into the femoral artery and then subcutaneously tunneled to the back of each rat in order to obtain arterial blood samples. The PaO_2 and the arterial blood CO_2 pressures ($PaCO_2$) were analyzed by a blood gas analyzer (Ciba-Corning Diagnostics Corp., Blood Gas System 278, Medfield, MA, USA). The alveolar-arterial O_2 pressure difference ($AaDO_2$), a convenient parameter for pulmonary gas exchange, was calculated as follows (Kryger, 1990; West et al., 1990):

$$AaDO_2(\text{mmHg}) = 150 - 1.25 \times PaCO_2 - PaO_2$$

An impairment of pulmonary gas exchange, such as ventilation-perfusion inequality and/or diffusion impairment, induces an increase in the $AaDO_2$ (Cerretelli and di Prampero, 1991; Hoppin, 1991).

In four rats from each of the saline- and bleomycin-treated groups, the lungs were removed and fixed by airway infusion of 10% buffered formalin solution (pH 7.4) at a pressure of 25 cmH_2O for a few days. Sections of paraffin-embedded tissue were cut at 3 μm, and stained with hematoxylin and eosin for histopathological examination by light microscopy.

2.4. Treatment of animals with anti-hypoxemic agents

The effects of several compounds on the arterial gas pressures of bleomycin-treated rats were investigated as follows: after the arterial blood gas pressures had been monitored, the bleomycin-treated animals were

Table 1
Arterial blood gas pressures in bleomycin-treated rats

Instillation	*n*	Blood gas pressures (mmHg)		
		PaO_2	$PaCO_2$	$AaDO_2$
Bleomycin	8	72.4±2.4 [b]	35.6±1.4 [a]	33.1±2.6 [b]
Saline	4	96.1±2.4	30.6±1.4	15.6±1.4

Bleomycin dissolved in saline (4.5 mg/kg per 0.75 ml) or saline alone was intratracheally instilled into rats under ketamine hydrochloride anesthesia. The arterial blood gas pressures were analyzed 3 weeks after the administration of bleomycin or saline. Data are expressed as means ± S.E.M. [a] $P < 0.05$ and [b] $P < 0.001$: statistically different from saline-treated rats (Student's *t*-test).

Table 2
Effects of prednisolone on bleomycin-induced hypoxemia

Treatment	Dose (mg/kg, p.o.)	n	Changes in blood gas pressures (mmHg)		
			ΔPaO_2	$\Delta PaCO_2$	$\Delta AaDO_2$
120 min					
Control		3	−0.4 ± 1.4	−1.4 ± 1.0	2.2 ± 0.3
Prednisolone	10	5	0.0 ± 1.1	−1.8 ± 1.0	2.3 ± 0.9
240 min					
Control		4	−3.6 ± 1.3	−1.7 ± 1.7	0.0 ± 3.0
Prednisolone	10	5	−0.9 ± 1.1	−1.8 ± 1.4	3.1 ± 2.1

Prednisolone (10 mg/kg) or vehicle (5% gum Arabic solution) was orally administered to bleomycin-induced hypoxemic rats. The arterial blood gas pressures were analyzed at 120 and 240 min after dosing with prednisolone. Data are presented as changes in the arterial blood gas pressures after dosing and expressed as means ± S.E.M. The results were statistically evaluated by Student's *t*-test).

divided into several groups, to which prednisolone (10 mg/kg), almitrine (3 and 10 mg/kg) or TEI-7322 (3, 10 and 30 mg/kg) was then orally administered. Each drug, suspended in 5% gum Arabic solution, was given at a constant volume of 5 ml/kg. The arterial blood gases were analyzed at 120 or 240 min after dosing. In some animals, an intravenous catheter was placed into a femoral vein and then subcutaneously tunneled to the back, by which doxapram hydrochloride (3 and 10 mg/kg) was intravenously infused at a constant rate of 2 ml/h for 10 min by a syringe pump (Razel Scientific Instruments, Stamford, CT, USA). The arterial blood gases were analyzed 0, 10 and 20 min after the end of infusion. The data are presented as the differences in the blood gas pressures before and after administration of the agents.

In four rats 120 min after the administration of 10 mg/kg of TEI-7322, sections of lungs were prepared and stained with hematoxylin and eosin for histopathological examination by light microscopy as described above.

2.5. Statistical analyses

For evaluation of the data, Student's *t*-test was performed for differences in body weights and in blood gas pressures between bleomycin- and saline-treated rats and for differences in the blood gas pressures of bleomycin-treated rats between vehicle- and prednisolone-administered animals. For evaluation of the effects of several doses of doxapram, almitrine or TEI-7322 on the blood gas pressures, Dunnett's multiple range test was performed. The results are expressed as the means ± S.E.M.

3. Results

3.1. Bleomycin-induced lung injury

Bleomycin-treated rats showed a significant suppression of body weight increase (213.8 ± 18.5 g) compared

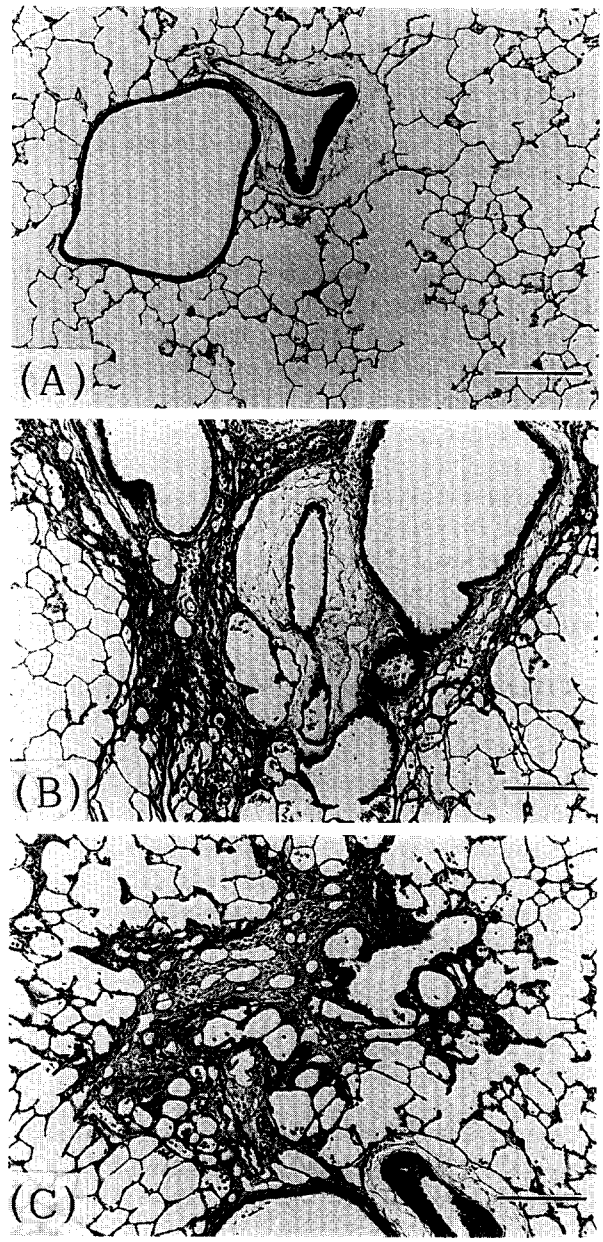


Fig. 2. Histopathological observation of the lungs of a physiological saline-treated rat (A) or a bleomycin-treated rat also given vehicle (5% gum Arabic solution) (B) or 10 mg/kg of TEI-7322 (C). (HE staining, bar = 0.2 mm)

Table 3
Effects of doxapram on bleomycin-induced hypoxemia

Treatment	Dose (mg/kg, i.v.)	n	Changes in blood gas pressures (mmHg)		
			ΔPaO_2	$\Delta PaCO_2$	$\Delta AaDO_2$
0 min					
Control		7	−2.6 ± 1.9	−2.2 ± 0.8	5.3 ± 1.7
Doxapram	3	7	−3.1 ± 1.6	−5.2 ± 0.9 [b]	9.6 ± 1.5 [a]
	10	7	−0.1 ± 2.5	−4.4 ± 1.1	5.6 ± 2.1
10 min					
Control		7	−0.9 ± 2.6	−4.0 ± 1.0	5.9 ± 1.7
Doxapram	3	7	−4.0 ± 2.2	−4.1 ± 0.5	9.0 ± 1.8
	10	7	−0.4 ± 2.2	−3.0 ± 0.7	4.1 ± 2.0
20 min					
Control		7	−1.6 ± 1.8	−2.7 ± 1.1	4.9 ± 1.4
Doxapram	3	7	−3.9 ± 1.8	−3.1 ± 1.1	7.8 ± 0.9
	10	7	−0.4 ± 2.3	−2.3 ± 0.9	3.3 ± 2.2

Doxapram hydrochloride was intravenously infused into bleomycin-induced hypoxemic rats at doses of 3 and 10 mg/kg at a constant rate of 2 ml/h for 10 min by a syringe pump. The arterial blood gas pressures were analyzed 0, 10 and 20 min after the end of infusion. Data are presented as changes in the blood gas pressures after dosing and expressed as means ± S.E.M. [a] $P < 0.1$ and [b] $P < 0.05$: statistically different from the control (Dunnett's multiple test).

with that of saline-treated rats (309.8 ± 9.0 g) 3 weeks after drug administration ($P < 0.01$). At this time, in the bleomycin-treated rats the PaO_2 was significantly decreased, and the $PaCO_2$ was increased with a significant increase in the $AaDO_2$ (Table 1).

Histopathological study of the lungs of bleomycin-treated rats showed perivascular edema, peribronchial edema, and alveolar wall thickening focally distributed throughout the lungs with inflammatory cell infiltration and mild fibrosis. In contrast, no remarkable alterations were observed in the lungs of the physiological saline-treated rats (Fig. 2).

3.2. Effects of prednisolone on bleomycin-induced hypoxemia

The effects of several compounds on the arterial blood gas pressures of bleomycin-induced hypoxemic rats were investigated. Oral administration of prednisolone, an anti-inflammatory steroid, caused no obvious change in the arterial blood gas pressures at a dose of 10 mg/kg, even 240 min after administration (Table 2).

3.3. Effects of doxapram on bleomycin-induced hypoxemia

A peripheral chemoreceptor stimulant, doxapram, decreased the $PaCO_2$ without affecting the PaO_2, resulting in a tendency to increase the $AaDO_2$, when infused intravenously at a dose of 3 mg/kg (Table 3). The decreased $PaCO_2$ was quickly reversed 10 min after the end of infusion. At a dose of 10 mg/kg, doxapram did not affect either blood gas pressure.

3.4. Effects of almitrine on bleomycin-induced hypoxemia

Almitrine induced a dose-dependent increase in the PaO_2 and a decrease in the $PaCO_2$ 120 min after administration (Fig. 3). Almitrine at a dose of 10 mg/kg caused significant changes in the PaO_2 and $PaCO_2$ (9.3 ± 2.9 and −5.3 ± 1.9 mmHg, respectively) and

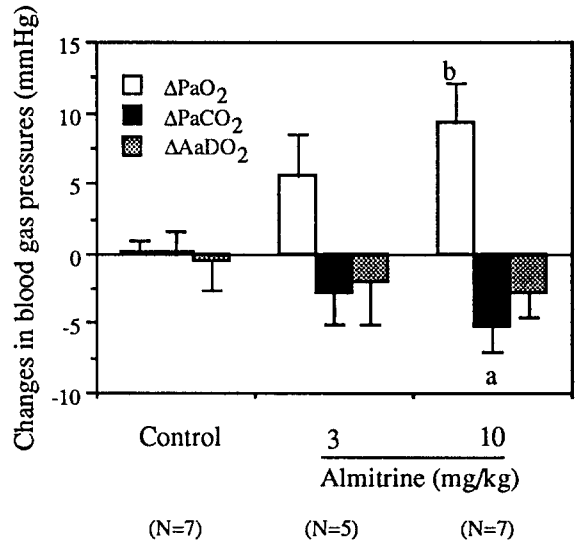


Fig. 3. Effects of almitrine on bleomycin-induced hypoxemia. Almitrine (3 and 10 mg/kg) or vehicle (5% gum Arabic solution) was orally administered to bleomycin-induced hypoxemic rats. The arterial blood gas pressures were analyzed again 120 min after dosing with almitrine. Data are presented as changes in the PaO_2 (open columns), $PaCO_2$ (black columns) and $AaDO_2$ (grey columns) after dosing and expressed as means ± S.E.M. [a] $P < 0.05$ and [b] $P < 0.01$: statistically different from the control (Dunnett's multiple test).

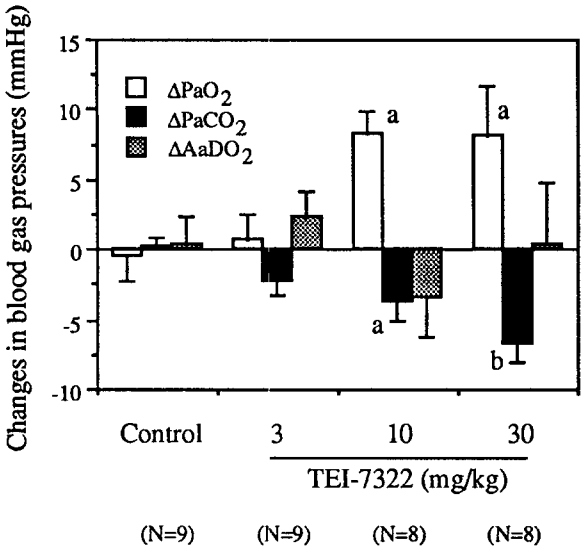


Fig. 4. Effects of TEI-7322 on bleomycin-induced hypoxemia. TEI-7322 (3, 10 and 30 mg/kg) or vehicle (5% gum Arabic solution) was orally administered to bleomycin-induced hypoxemic rats. The arterial blood gas pressures were analyzed again 120 min after dosing with TEI-7322. Data are presented as changes in the PaO_2 (open columns), $PaCO_2$ (black columns) and $AaDO_2$ (grey columns) after dosing and expressed as means ± S.E.M. $^aP < 0.05$ and $^bP < 0.001$: statistically different from the control (Dunnett's multiple test).

showed a tendency to decrease the $AaDO_2$ (-2.8 ± 2.0 mmHg), although this decrease was not statistically significant.

3.5. Effects of TEI-7322 on bleomycin-induced hypoxemia

Significant changes in the blood gas pressures were also observed in the rats treated with TEI-7322 (Fig. 4). TEI-7322 at doses of 10 and 30 mg/kg significantly increased the PaO_2 (8.2 ± 1.7 and 8.1 ± 3.6 mmHg, respectively) and decreased the $PaCO_2$ (-3.7 ± 1.3 and -6.7 ± 1.4 mmHg, respectively). At the dose of 10 mg/kg, TEI-7322 showed a tendency to decrease the $AaDO_2$ (-3.5 ± 2.7 mmHg), although this decrease was not statistically significant.

TEI-7322 at a dose of 10 mg/kg did not affect the histopathological appearance of bleomycin-induced lesions at 120 min after the administration of the drug (Fig. 2).

4. Discussion

In the present study, we established a convenient model of hypoxemia induced by bleomycin in rats, in which arterial blood gas pressure was monitored with the animals in the conscious state. In addition, we found that the newly synthesized TEI-7322, as well as almitrine, showed anti-hypoxemic effects on this model.

Administration of bleomycin is known to induce pulmonary injury and is used as a pulmonary fibrosis model (Snider et al., 1978). However, the arterial blood gas pressures of animals with bleomycin-induced pulmonary injury have been little investigated, particularly in small animals. The present study showed that intratracheal administration of bleomycin at a dose of 4.5 mg/kg to rats caused a remarkable decrease in the PaO_2 and an increase in the $PaCO_2$ with a significant increase in the $AaDO_2$ 3 weeks after the treatment. The decrease in the PaO_2 with a significant increase in the $PaCO_2$ (hypercapnia) is considered to be derived from alveolar hypoventilation (Hlastala, 1991). The significant increase in the $AaDO_2$ indicates an impairment of pulmonary gas exchange, such as ventilation-perfusion inequality and/or diffusion impairment (Cerretelli and Di Prampero, 1991; Hoppin, 1991). Recently, a significant deterioration of hypoxic pulmonary vasoconstriction was reported to occur in bleomycin-induced lung injury in rats (McCormack et al., 1992). The histopathological observations for the bleomycin-instilled lung suggested that the ventilation-perfusion inequality may be derived from reduced hypoxic pulmonary vasoconstriction due to focal, not homogeneous, alveolar wall thickening. Therefore, the bleomycin-induced hypoxemia in this model may result from, at least in part, hypoxic pulmonary vasoconstriction disorders as well as alveolar hypoventilation.

It is reported that bleomycin-induced lung fibrosis can be inhibited by anti-inflammatory drugs such as Mn-superoxide dismutase (Parizada et al., 1991), dimethyl sulfoxide (Pepin and Langner, 1985), deferoxamine (Chandler et al., 1988), indomethacin (Thrall et al., 1979) and truncated secretory leukoprotease inhibitor (Mitsuhashi et al., 1994), as long as these agents are administered before or in the acute phase just after the treatment with bleomycin. To exclude the possibility that the bleomycin-induced hypoxemia might have been caused by the on-going inflammation in the lung in the sub-acute phase, we tested an anti-inflammatory steroid, prednisolone in the bleomycin-induced hypoxemic rats. A single dose of prednisolone, failed to improve the blood gas pressures of the bleomycin-induced hypoxemic rats even at a dose of 10 mg/kg at 240 min after administration. Prednisolone is thought to exert its anti-inflammatory action in rats at this dose and the time of evaluation (DiMartino et al., 1989). These findings indicate that the bleomycin-induced hypoxemia in the sub-acute phase may be a result of the established fibrotic changes with focal alveolar wall thickening, but not of the on-going inflammation in the lungs.

To further characterize the bleomycin-induced hypoxemic model in rats, we also tested the effects of

almitrine and doxapram. Almitrine is reported to improve the PaO_2 through stimulation of peripheral chemoreceptors (Laubie and Schmitt, 1980; Laubie et al., 1983) and enhancement of hypoxic pulmonary vasoconstriction (Bee et al., 1983; Romaldini et al., 1983; Hughes et al., 1986; Nakanishi et al., 1988). So, we administered this compound to the bleomycin-induced hypoxemic rats. In this model, almitrine showed a significant anti-hypoxemic action in addition to its anti-hypercapnic action. One can assume that this anti-hypoxemic effect resulted from two independent actions, namely, enhancement of hypoxic pulmonary vasoconstriction and stimulation of ventilation. In order to clarify the dominant action underlying the anti-hypoxemic effect in this model, we examined the effect of doxapram, because this drug is reported to stimulate peripheral chemoreceptors without affecting hypoxic pulmonary vasoconstriction (Kuga and Naito, 1973; Kubota et al., 1974; Mitchell and Herbert, 1975). Intravenously administered doxapram decreased the $PaCO_2$ without affecting the PaO_2, resulting in a tendency to further increase the $AaDO_2$ in this model. At a dose of 10 mg/kg, doxapram did not affect the blood gas pressures. When the bleomycin-induced hypoxemic rats were treated with 10 mg/kg of doxapram, the $PaCO_2$ was decreased in some rats but increased in others, suggesting that the dose of 10 mg/kg of doxapram might be excessive. In fact, all the rats showed an increase in the $PaCO_2$ (17.0 ± 10.9 mmHg) after the treatment with 30 mg/kg of doxapram. These results indicate that stimulated ventilation could not cause an increase in the PaO_2 in this model probably because of diffusion impairment (Magnussen et al., 1987), and suggest that the anti-hypoxemic effect of almitrine may be mainly derived from enhancement of hypoxic pulmonary vasoconstriction.

Recently, hypoxemia induced in guinea pigs by oleic acid was reported as a convenient hypoxemic model (Moriuchi and Yuizono, 1994). Although this model is useful in screening for anti-hypoxemic compounds, how and to what extent almitrine affects this hypoxemia has not been investigated. Almitrine had no effect on the PaO_2 in oleic acid-induced acute lung injury in dogs (Leeman et al., 1988, 1992a), in spite of the observation that ventilation-perfusion inequality as a result of decreased hypoxic pulmonary vasoconstriction was present in this acute lung injury (Yamaguchi et al., 1991, Leeman et al., 1992b). In these models, intravenously administered oleic acid may affect the pulmonary vessels from the inside of the lumen and injure the endothelium (Chelucci et al., 1991; Velazquez et al., 1991), resulting in alteration of the responsiveness of the vessels. Leeman et al. (1992a) speculated that the oleic acid-induced lung injury altered the pulmonary vascular response to almitrine, transforming a specific vasoconstriction during hypoxia in intact lungs into a nonspecific vasoconstriction in diseased lungs. Therefore, in the oleic acid-induced hypoxemic model in guinea pigs, it might be difficult to evaluate the effects of almitrine and its related anti-hypoxemic compounds. In contrast, in bleomycin-induced lung injury, the vascular endothelium appears intact and is unaffected by bleomycin (Crouch et al., 1991; McCormack et al., 1992).

TEI-7322, which is synthesized in our laboratory, also showed anti-hypoxemic potency, but without any beneficial effect on histopathological changes. TEI-7322 at doses of 10 and 30 mg/kg significantly increased the PaO_2 and decreased the $PaCO_2$. Its mode of action and efficacy were comparable to those of almitrine and differed from those of doxapram. Therefore, TEI-7322 may possess the ability to both stimulate ventilation and increase hypoxic pulmonary vasoconstriction as well as almitrine does. However, in the present study, neither TEI-7322 nor almitrine significantly decreased the $AaDO_2$. In this model, the bleomycin-induced increase in the $AaDO_2$ is thought to result from both ventilation-perfusion inequality and diffusion impairment. Therefore, the anti-hypoxemic effects of TEI-7322 and almitrine based on the increase in hypoxic pulmonary vasoconstriction might be weakened by stronger diffusion impairment. Furthermore, in this model, alveolar hypoventilation is thought to result in an increase in the $PaCO_2$, which may be susceptible to stimulation of ventilation by TEI-7322 and almitrine. Because of these anti-hypercapnic effects, the anti-hypoxemic effects of TEI-7322 and almitrine might not lead to a remarkable decrease in the $AaDO_2$, as long as it is calculated from the PaO_2 and $PaCO_2$ in this model. Besides, our studies have shown that TEI-7322 possesses a beneficial action in hypoxemic rats with either glass bead-induced obstructive respiratory failure (Okada et al., 1994) or acetic acid-induced lung injury (Kadota et al., 1994). In these hypoxemic models, hypercapnia was not observed, and TEI-7322 increased the PaO_2 and decreased the $PaCO_2$ with a significant decrease in the $AaDO_2$. In contrast, doxapram increased the PaO_2 and decreased the $PaCO_2$, but did not show any beneficial effect on $AaDO_2$ in these models. These results also support that TEI-7322 possesses an anti-hypoxemic effect at least similar to that of almitrine and has different properties from those of doxapram. To reveal the mechanisms of action of TEI-7322 with respect to its anti-hypoxemic effect, we are now directly evaluating the effect of this series of compounds on the hypoxia-induced pulmonary vasoconstriction in perfused rat lungs in vitro as well as on the ventilation-perfusion inequality by the multiple inert gas washout method (Wagner et al., 1974) in dogs.

In conclusion, (1) bleomycin-induced lung injury caused hypoxemia in rats, probably resulting, in part,

from ventilation-perfusion inequality, which may have come from decreased hypoxic pulmonary vasoconstriction derived from focal alveolar wall thickening; thus this model may be useful for evaluating anti-hypoxemic agents; and (2) TEI-7322, as well as almitrine, showed anti-hypoxemic effects in this model with different properties from those of doxapram, possibly due to improvement of the ventilation-perfusion inequality, suggesting therefore that this compound may become an orally effective alternative for the treatment of hypoxemia.

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