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ZK 36-374, a Stable Analog of Prostacyclin, Prevents Acute Hypoxic Pulmonary Hypertension in the Dog

STEPHEN L. ARCHER, MD, ELLIOT CHESLER, MD, FACC, JAY N. COHN, MD, FACC, E. KENNETH WEIR, MD, FACC

Minneapolis, Minnesota

Vasodilator therapy in pulmonary hypertension is limited by the lack of an agent selective for the pulmonary circulation. The effects of intravenous prostacyclin and two stable prostaglandin analogs, ZK 36-374 and CL 115,347, were assessed on the preconstricted pulmonary vasculature of the anesthetized dog. During hypoxic vasoconstriction ZK 36-374 (0.4 μg/kg per min) markedly reduced pulmonary artery pressure (26 ± 3 to 13 ± 1 mm Hg) ($p < 0.05$) and pulmonary vascular resistance (6.2 ± 1.1 to 2.8 ± 0.2 mm Hg/liter per min) ($p < 0.01$). There was no significant effect on cardiac output, aortic pressure or arterial blood gases. Pulmonary vasoconstriction induced by prostaglandin $F_2\alpha$ was similarly affected by ZK 36-374, and in this instance the aortic pressure was also reduced (158 ± 11 to 129 ± 11 mm Hg) ($p < 0.01$).

ZK 36-374 (0.2 μg/kg per min) was more effective in lowering hypoxic pulmonary vascular resistance (from 6.5 ± 0.6 to 3.0 ± 0.3 mm Hg/liter per min) than was prostacyclin (0.75 μg/kg per min) (from 6.3 ± 0.6 to 4.2 ± 0.4 mm Hg/liter per min) ($p < 0.05$) and resulted in a smaller fall in aortic pressure ($p < 0.05$). CL 115,347 (1.0 μg/kg per min) had no effect on the pulmonary vasculature during normoxia or when preconstricted by prostaglandin $F_2\alpha$ or hypoxia, but reduced aortic pressure and total systemic resistance ($p < 0.05$). It appears to be a selective systemic vasodilator with no pulmonary vascular activity.

ZK 36-374 is an effective agent in reversing pulmonary vasoconstriction in this model and has potentially useful selectivity for the pulmonary circulation. Oral administration is possible.

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Pulmonary hypertension may complicate the management of a variety of cardiopulmonary disorders such as chronic obstructive airways disease, mitral valve disease, left heart failure, thromboembolic disease and left to right intracardiac shunts, or it may occur in isolation (primary pulmonary hypertension). The relative importance of fixed vascular obstruction and vasoconstriction varies with the type and duration of the underlying disease. In some forms of pulmonary hypertension, mechanical obstruction is amenable to surgical correction (for example, mitral valve replacement or pulmonary thromboendarterectomy). However, in most cases the only therapeutic interventions available are anticoagulation, or the use of oxygen or vasodilator agents. The use of vasodilators in patients with pulmonary hypertension has been limited by the lack of an orally active agent that is selective for the pulmonary vasculature. Nonselective vasodilators used in the presence of a fixed pulmonary vascular resistance may result in systemic vasodilation, which is not offset by an increase in cardiac output and can thus cause systemic hypotension.

This study compares the relative selectivity of prostacyclin and two novel prostaglandin analogs on the pulmonary and systemic vasculatures. The short half-life of intravenous prostacyclin makes it useful in assessing the reversible component of pulmonary hypertension, by reducing the risk of prolonged systemic hypotension. Unfortunately, the short half-life, lack of relative selectivity for the pulmonary vasculature and absence of an oral form of prostacyclin prevent its use for long-term treatment. ZK 36-374, a stable carbaprostacyclin analog of prostacyclin, has hemodynamic properties similar to those of the parent compound but can be given orally and has a significantly increased half-life (1,2). CL 115, 347 is a methyl ester of 15-deoxy-16-hydroxy-16-(α/β)-vinyl prostaglandin E_2, which is vasoactive and can be administered orally or topically

From the Department of Medicine, University of Minnesota and the Department of Medicine, Veterans Administration Medical Center, Minneapolis, Minnesota.

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Address for reprints: Stephen L. Archer, MD, Veterans Administration Medical Center (111C), 54th Street and 48th Avenue South, Minneapolis, Minnesota 55417.

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(3). The efficacy of these agents was tested in the model of pulmonary hypertension provided by hypoxia and prostaglandin $F_2\alpha$-induced pulmonary vasoconstriction in the anesthetized dog.

Methods

Experimental procedures. Twenty mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg intravenously), paralyzed with succinyl choline (2 mg/kg intravenously) and ventilated with a Harvard ventilator. A Swan-Ganz catheter was advanced into the pulmonary artery. Two cannulas were placed in the descending aorta and one was placed in the inferior vena cava.

Body temperature was monitored by an esophageal temperature probe (model 43TA, Yellowsprings Instrument Company) and was maintained between 37 and 39°C. Blood pressure was recorded using a Statham P23 transducer connected to a Hewlett Packard 8 channel recorder. Cardiac output was measured by injecting 1 ml of indocyanine green dye (Eastman Kodak) (1.25 mg/ml) into the inferior vena cava and withdrawing blood from the aortic catheter (20 ml/min) through a cuvette densitometer connected to a cardiac output computer (Waters Instrument). Arterial blood gases were measured using a Corning model 168 pH and blood gas analyzer.

Before the experiment an equilibration period was used to establish the appropriate respiratory rate and tidal volume to maintain arterial partial pressure of carbon dioxide (P_{CO_2}) in the range of 35 to 45 mm Hg. The rate and volume were left unchanged during the remainder of the experiment.

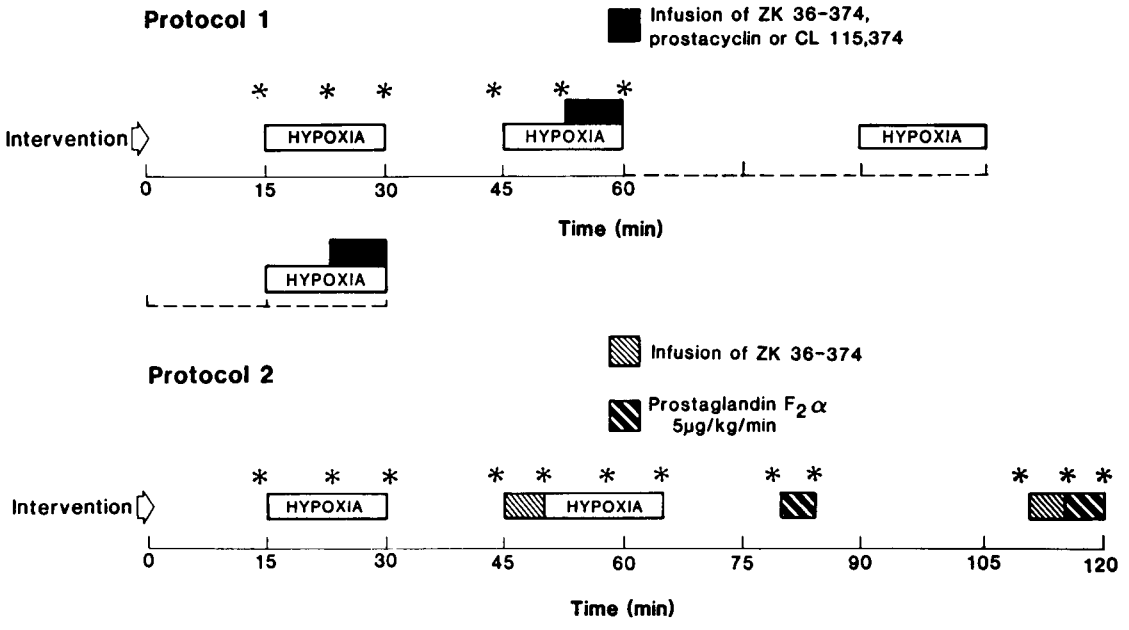
Drugs. Prostacyclin (Sigma), CL 115,347 (American Cyanamid Company) and ZK 36-374 (Schering), were prepared immediately before use by diluting the stock solution with 0.9% saline.

Protocol

Protocol 1. Preliminary experiments were performed to determine doses of each drug that would have significant hemodynamic effects during hypoxia but not induce unacceptable hypotension. The intravenous doses selected were ZK 36-374 (0.2 μg/kg per min × 7 min), prostacyclin (0.75 μg/kg per min for 7 minutes), and CL 115, 347 (1.0 μg/kg per min for 7 min).

After an initial equilibration period, pulmonary vasoconstriction was induced by ventilation with an hypoxic mixture (concentration of expired oxygen in air [FiO_2] 0.1) (Fig. 1). Hemodynamic variables and arterial blood gases were recorded at the end of the normoxic control period and after 8 and 15 minutes of hypoxia. After a further 15 minute normoxic control period another hypoxic challenge was given but this time the drug to be tested was infused during the final 7 minutes of the hypoxic period. Hemodynamic variable and arterial blood gases were measured as before. The drugs were tested in 14 dogs: 6 dogs received CL 115,347 only, 2 dogs received ZK 36-374 only and 6 dogs received ZK 36-374 and prostacyclin. In animals receiving two drugs the order of administration was randomized and hemody-

Figure 1. Schematic representation of experimental protocols 1 and 2. *Hemodynamics and arterial blood gases measured; hypoxia = period of ventilation with FiO_2 0.1. The **broken line** along the time axis reflects the fact that only six dogs received more than one drug (see protocol 1 in Methods).



namic variables were allowed to return to baseline over 30 minutes before the control hypoxic challenge was repeated.

Protocol 2. Protocol 1 demonstrated that CL 115,347 had no activity on the pulmonary vasculature preconstricted by hypoxia and no further testing was performed. ZK 36-374 was tested in six dogs by a second protocol to determine whether its longer half-life would allow infusion of the drugs before a hypoxic challenge and diminish the undesired drop in aortic pressure noted in protocol 1, while still reducing the hypoxic pulmonary hypertension. As before, an initial normoxic control period was followed by a 15 minute hypoxic challenge (FiO_2 0.1) (Fig. 1). Hemodynamic variables and arterial blood gases were measured as in protocol 1. The only drug tested in this protocol was ZK 36-374 (0.4 μg/kg per min intravenously), which was given over the 5 minutes before the next hypoxic period. For comparison with the observations made during hypoxic pulmonary vasoconstriction, protocol 2 also tested ZK 36-374 against pulmonary vasoconstriction induced by prostaglandin $F_2\alpha$ (5μg/kg per min intravenously, for 4 minutes). Hemodynamic variables and arterial blood gases were measured as shown in Figure 1.

Statistical Methods. All values are expressed as mean ± SEM. Intergroup comparisons were made using analysis of variance. Subsequent post hoc analysis was made using Tukey's test. When only two groups were compared, a Student's *t* test was used. Probability values of less than 0.05 were considered statistically significant.

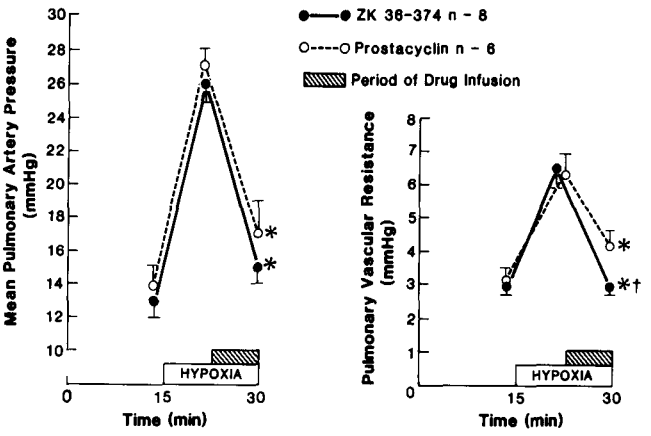


Figure 2. ZK 36-374 lowers pulmonary artery pressure and vascular resistance more than prostacyclin during hypoxic pulmonary vasoconstriction (protocol 1). *p < 0.05: value differs from predrug hypoxic value; †p < 0.05: value obtained during infusion of ZK 36-374 (0.2 μg/kg per min) differs from value obtained during infusion of prostacyclin (0.75 μg/kg per min). Hypoxia = period of ventilation with FiO_2 0.1.

Results

Protocol 1 (Table 1)

Hypoxia elevated the pulmonary artery pressure and resistance at both 8 and 15 minutes of hypoxia ($p < 0.05$ for both). There were no significant differences between the 8

Table 1. Effects of Intravenous Infusion of ZK 36-374, Prostacyclin and CL 115,347 (given by protocol 1) on Hemodynamics During Hypoxia

	Mean Aortic Pressure (mm Hg)	Mean Pulmonary Artery Pressure (mm Hg)	Cardiac Output (liters/min)	Total Systemic Resistance (mm Hg/liter per min)	Pulmonary Vascular Resistance (mm Hg/liter per min)	Arterial Oxygen Tension (mm Hg)
Normoxia	144 ± 5	13 ± 1	3.0 ± 0.4	51 ± 5	2.8 ± 0.2	88 ± 4.0
Hypoxia, 8 min	173 ± 6	26 ± 1	3.4 ± 0.3	54 ± 4	6.2 ± 0.5	32 ± 1
Hypoxia, 15 min	170 ± 6	24 ± 1	3.5 ± 0.3	52 ± 4	5.7 ± 0.4	30 ± 2
Normoxia	143 ± 4	13 ± 1	3.0 ± 0.5	53 ± 5	3.0 ± 0.3	100 ± 1
Hypoxia, 8 min	171 ± 5	26 ± 1	3.5 ± 0.4	59 ± 6	6.5 ± 0.6	34 ± 1
Hypoxia, 15 min/ ZK 36-374 per (0.2 μg/kg per min)	137 ± 7*†	15 ± 1*	3.4 ± 0.5	42 ± 4*	3.0 ± 0.3*†	33 ± 2
Normoxia	150 ± 6	14 ± 1	3.1 ± 0.6	56 ± 8	3.1 ± 0.4	99 ± 3
Hypoxia, 8 min	177 ± 8	27 ± 1	3.6 ± 0.4	54 ± 6	6.3 ± 0.6	33 ± 2
Hypoxia, 15 min/ prostacyclin (0.75 μg/kg per min)	110 ± 19*	17 ± 2*	3.0 ± 0.3	38 ± 5*	4.2 ± 0.4*	33 ± 2
Normoxia	131 ± 4	12 ± 1	3.5 ± 0.3	38 ± 3	2.5 ± 0.2	87 ± 4
Hypoxia, 8 min	152 ± 7	23 ± 3	3.5 ± 0.2	44 ± 2	5.5 ± 0.4	30 ± 2
Hypoxia, 15 min/ CL 115,347 per (1.0 μg/kg per min)	102 ± 5*	25 ± 2	3.7 ± 0.2	28 ± 2*	5.8 ± 0.4	31 ± 2

*p < 0.05, value differs from the 8 minute hypoxic value; †p < 0.05, value obtained during infusion of ZK 36-374 differs from that obtained during infusion of prostacyclin. All values are expressed as the mean and SEM.

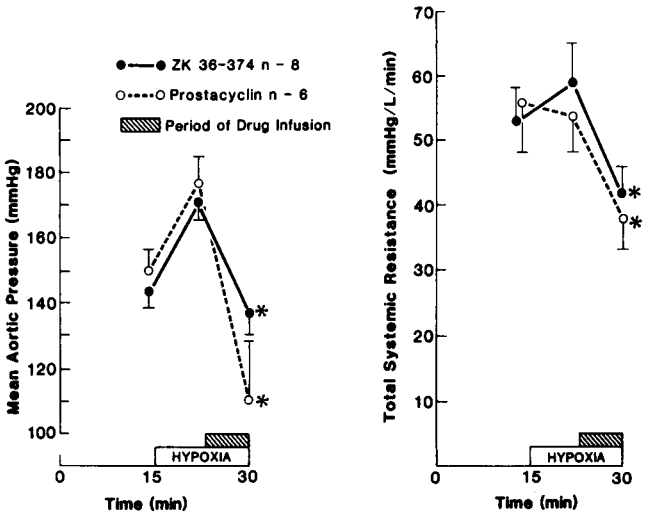


Figure 3. ZK 36-374 and prostacyclin reduce aortic pressure and total systemic resistance during hypoxia (protocol 1).*$p < 0.05$: value differs from hypoxic control value; hypoxia = period of ventilation with FiO_2 0.1.

and 15 minute values for either mean pulmonary artery pressure (26 ± 1 and 24 ± 1 mm Hg, respectively) or pulmonary vascular resistance (6.2 ± 0.5, and 5.7 ± 0.4 mm Hg/liter per min, respectively). The mean aortic pressure was also elevated by hypoxia ($p < 0.05$), but the total systemic resistance was not affected.

Infusion of ZK 36-374 (0.2 μg/kg per min) or prostacyclin (0.75 μg/kg per min) during the final 7 minutes of the hypoxic period lowered the mean aortic pressure, total systemic resistance, mean pulmonary artery pressure and pulmonary vascular resistance measured after 15 minutes of hypoxia compared with the 8 minute hypoxic value ($p < 0.05$ for each). There were no effects on the cardiac output, mean pulmonary wedge pressure or arterial blood gases. The fall in pulmonary vascular resistance was greater with ZK 36-374 (0.2 μg/kg per min) than with prostacyclin at a higher dose (0.75 μg/kg per min) (Fig. 2) despite the fact that prostacyclin tended to lower the absolute mean aortic pressure more than did ZK 36-374 (Fig. 3). In fact the fall in aortic pressure after prostacyclin (−66 ± 15 mm Hg) was greater than that after ZK 36-374 (−34 ± 6 mm Hg) ($p < 0.05$).

CL 115,347 had no effect on the pulmonary vascular hemodynamics during hypoxia, nor did it alter cardiac output, mean pulmonary wedge pressure or arterial blood gases. It did lower the 15 minutes hypoxic value for mean aortic pressure compared with the 8 minute (pre-CL 115,347) hypoxic value (from 152 ± 7 to 102 ± 5 mm Hg) and also lowered the total systemic resistance (from 44 ± 2 to 28 ± 2 mm Hg/liter per min) ($p < 0.05$ for each).

Protocol 2

Hypoxia (Table 2). As in protocol 1, hypoxia alone increased pulmonary artery pressure (from 14 ± 1 to 26 ± 3 mm Hg), pulmonary vascular resistance (from 3.1 ± 0.3 to 6.2 ± 1.1 mm Hg/liter per min) and mean aortic pressure (from 147 ± 5 to 172 ± 7 mm Hg) ($p < 0.05$ for each) compared with normoxic control values. Infusion of ZK 36-374 (0.4 μg/kg per min) during the 5 minutes before hypoxia lowered mean aortic pressure and total systemic resistance ($p < 0.05$ for each) without affecting cardiac output, mean wedge pressure or arterial blood gases. The infusion was stopped at the onset of hypoxia, and the 8 and 15 minute hypoxic values were measured with no drug infusion. At 8 and 15 minutes of hypoxia the mean pulmonary artery pressure and pulmonary vascular resistance were decreased significantly compared with the preceding 8 and 15 minute hypoxic control values. In protocol 2 the mean aortic pressure, measured at 8 minutes of hypoxia, decreased slightly (from 172 ± 7 to 150 ± 7 mm Hg) while the pulmonary vascular resistance returned to

Table 2. Pretreatment With ZK 36-374 Reduces Hypoxic Pulmonary Vasoconstriction (protocol 2)

	Mean Aortic Pressure (mm Hg)	Mean Pulmonary Artery Pressure (mm Hg)	Mean Pulmonary Wedge Pressure (mm Hg)	Cardiac Output (liters/min)	Total Systemic Resistance (mm Hg/liter per min)	Pulmonary Vascular Resistance (mm Hg/liter per min)	Arterial Oxygen Tension (mm Hg)
Normoxia	147 ± 5	14 ± 1	5 ± 1	3.0 ± 0.4	53 ± 8	3.1 ± 0.3	95 ± 2
Hypoxia, 8 min	172 ± 7	26 ± 3	5 ± 1	3.4 ± 0.4	52 ± 5	6.2 ± 1.1	32 ± 1
Hypoxia, 15 min	165 ± 6	24 ± 2	5 ± 1	3.5 ± 0.3	49 ± 5	5.6 ± 0.8	28 ± 1
Normoxic control	138 ± 6	13 ± 1	4 ± 1	2.8 ± 0.4	54 ± 6	3.0 ± 0.1	93 ± 1
5 Min post ZK 36-374 (0.4 μg/kg per min)	94 ± 10‡	11 ± 1	4 ± 1	2.9 ± 0.6	35 ± 3†	2.6 ± 0.2	96 ± 1
Hypoxia, 8 min	150 ± 7	13 ± 1†	4 ± 1	2.9 ± 0.4	55 ± 6	2.8 ± 0.2*	34 ± 1
Hypoxia, 15 min	152 ± 6	16 ± 2*	5 ± 1	3.4 ± 0.3	48 ± 5	3.4 ± 0.4*	30 ± 1

*$p < 0.05$, †$p < 0.01$: value differs from the hypoxic control value; ‡$p < 0.05$ value obtained during infusion of ZK 36-374 differs from that obtained during normoxic control period. All values are expressed as the mean ± SEM.

Table 3. ZK 36-374 Reduces Prostaglandin $F_2\alpha$-Induced Pulmonary Vasoconstriction (protocol 2)

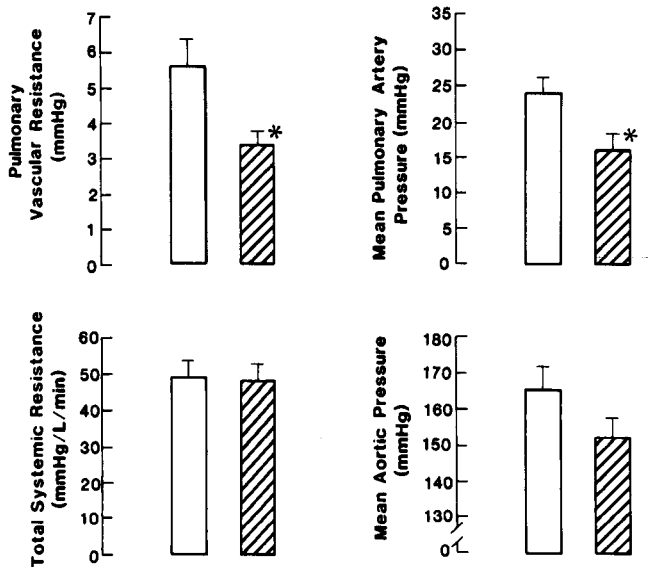
	Mean Aortic Pressure (mm Hg)	Mean Pulmonary Artery Pressure (mm Hg)	Mean Pulmonary Wedge Pressure (mm Hg)	Cardiac Output (liters/min)	Total Systemic Resistance (mm Hg/liter per min)	Pulmonary Vascular Resistance (mm Hg/liter per min)	Arterial Oxygen Tension (mm Hg)
Normoxia	148 ± 6	13 ± 1	5 ± 1	3.0 ± 0.4	53 ± 8	2.7 ± 0.4	93 ± 2
$PGF_2\alpha$ (5 μg/kg per min)	158 ± 11	25 ± 3*	6 ± 1	3.1 ± 0.4	54 ± 6	6.6 ± 1.1*	94 ± 2
Normoxia	134 ± 4	12 ± 1	4 ± 1	2.6 ± 0.4	58 ± 8	3.4 ± 0.2	95 ± 2
5 Min post ZK 36-374 (0.4 μg/kg per min)	97 ± 9†	11 ± 1	4 ± 1	3.2 ± 0.7	33 ± 4†	2.6 ± 0.2	96 ± 1
$PGF_2\alpha$/ZK 36-374	129 ± 11§	15 ± 2§	4 ± 1	2.6 ± 0.5	53 ± 7	4.3 ± 0.4‡	88 ± 6

*$p < 0.05$: value obtained with $PGF_2\alpha$ differs from the normoxic control value; †$p < 0.01$: value following ZK 36-374 differs from normoxic control value; ‡$p < 0.05$, §$p < 0.01$: value following $PGF_2\alpha$ plus ZK 36-374 differs from value following $PGF_1\alpha$ alone. All values are expressed as the mean ± SEM.

normoxic levels (from 6.2 ± 1.1 to 2.8 ± 0.2 mm Hg/liter per min).

Prostaglandin $F_2\alpha$ (Table 3). Prostaglandin $F_2\alpha$ elevated mean pulmonary artery pressure (from 13 ± 1 to 25 ± 3 mm Hg) and pulmonary vascular resistance (from 2.7 ± 0.4 to 6.6 ± 1.1 mm Hg/liter per min) ($p < 0.05$ for each) without affecting cardiac output, mean wedge pressure, mean aortic pressure, total systemic resistance or arterial blood gases. After administration of ZK 36-374 (0.4 μg/kg per min), prostaglandin $F_2\alpha$ caused a smaller rise in mean pulmonary artery pressure (from 11 ± 1 to 15 ± 2 mm Hg) and pulmonary vascular resistance (from 2.6 ± 0.2 to 4.3 ± 0.4) ($p < 0.01$ and <0.05, respectively).

Figure 4. ZK 36-374 (protocol 2) exerts a relatively greater vasodilatory effect on the pulmonary vasculature than on the systemic vasculature during hypoxia. **Open bars** represent the absolute value after 15 minutes of hypoxia without drug. **Hatched bars** represent the absolute value after 15 minutes of hypoxia when preceded by infusion of ZK 36-374. *$p < 0.05$: value differs from hypoxic control value.



Discussion

The treatment of pulmonary hypertension by vasodilator agents is frequently complicated by systemic hypotension because no dilator selective for the pulmonary vasculature is available. Prostacyclin is an endogenous vasodilator that acts on the pulmonary circulation but has a half-life of only 3 minutes and requires intravenous administration (1,4).

ZK 36-374 is a more stable analog of prostacyclin and has a half-life of 13 minutes when given intravenously (5). When given orally to rats it has a bioavailability of 13% (6). Both prostacyclin and ZK 36-374 have been postulated to cause vasodilation by binding to receptors in the arterial wall (7).

CL-115,347 is a prostglandin E_2 analog with systemic antihypertensive activity. It can be given by oral or topical routes (3). When given topically in rats it significantly lowers arterial pressure for 24 hours without inducing tachycardia (3).

Effect of ZK 36-374 on pulmonary hypertension. The present studies show that ZK 36-374 causes a smaller reduction in systemic arterial pressure than does prostacyclin, while producing a greater decrease in hypoxic pulmonary vascular resistance in this model of pulmonary hypertension (Fig. 4). ZK 36-374 reduced hypoxic pulmonary artery pressure and resistance to normoxic levels. The systemic arterial oxygen tension at the end of 15 minutes of hypoxia was not diminished by infusions of either ZK 36-374 or prostacyclin in comparison with hypoxic control values. This suggests that the vasodilation occurred without the increase in venous shunting that has been noted after the use of other vasodilators (8). Infusion of ZK 36-374 also diminished the pulmonary hypertension induced by prostaglandin $F_2\alpha$. CL 115,374 showed selectivity for the systemic circulation in that it reduced systemic arterial pressure and resistance, while pulmonary vascular hemodynamic variables were unchanged during hypoxia.

Previous clinical studies. ZK 36-374 has been used clinically in patients with severe peripheral vascular disease

(5). It was infused over 3 days (0.5 to 4.0 ng/kg per min intravenously). After about 24 hours aortic pressure had decreased 15%, while pulmonary vascular resistance was reduced by 34%. When the dose was increased to 8 ng/kg per min, side effects such as headache, nausea and abdominal pain occurred. One day after the end of the infusion, pulmonary vascular resistance was still low in comparison with the preinfusion level (5). ZK 36-374 has also been shown to reduce platelet aggregation in humans, at a dose (up to 2 ng/kg per min intravenously over 4 hours), which did not alter systemic arterial pressure or heart rate (9).

Implications. While ZK 36-374 is clearly not specific for the pulmonary vasculature, it does represent an improvement in this respect when compared with prostacyclin. The information derived from an acute experiment in healthy, anesthetized dogs should not be directly extrapolated to the long-term therapy of patient with pulmonary hypertension. However, these results, the clinical information already obtained on the infusion of ZK 36-374 in humans and the availability of an oral form suggest that clinical trials of ZK 36-374 for the treatment of pulmonary hypertension may be justified.

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