Selective Pulmonary Vasodilation Induced by Aerosolized Zaprinast

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Background: Zaprinast, an inhibitor of guanosine-3',5'-cyclic monophosphate (cGMP)-selective phosphodiesterase, augments smooth muscle relaxation induced by endothelium-dependent vasodilators (including inhaled nitric oxide [NO]). The present study was designed to examine the effects of inhaled nebulized zaprinast, alone, and combined with inhaled NO.

Methods: Eight awake lambs with U46619-induced pulmonary hypertension sequentially breathed two concentrations of NO (5 and 20 ppm), followed by inhalation of aerosols generated from solutions containing four concentrations of zaprinast (10, 20, 30, and 50 mg/ml). The delivered doses of nebulized zaprinast at each concentration (mean ± SD) were 0.23 ± 0.06 mg·kg⁻¹·min⁻¹, 0.49 ± 0.14 mg·kg⁻¹·min⁻¹, 0.71 ± 0.24 mg·kg⁻¹·min⁻¹, and 1.20 ± 0.98 mg·kg⁻¹·min⁻¹, respectively. Each lamb also breathed NO (5 and 20 ppm) and zaprinast (0.23 ± 0.06 mg·kg⁻¹·min⁻¹) in combination after a 2-h recovery period.

Results: Inhaled NO selectively dilated the pulmonary vasculature. Inhaled zaprinast selectively dilated the pulmonary circulation and potentiated and prolonged the pulmonary vasodilating effects of inhaled NO. The net transpulmonary release of cGMP was increased by inhalation of NO, zaprinast, or both. The duration of the vasodilation induced by zaprinast inhalation was greater than that induced by NO inhalation.

Conclusions: Aerosolization of a cGMP-selective phosphodiesterase inhibitor alone or combined with NO may be a useful noninvasive therapeutic method to treat acute or chronic pulmonary hypertension. (Key words: Guanosine-3',5'-cyclic monophosphate phosphodiesterase; inhaled nitric oxide; nitric oxide toxicity; plasma guanosine-3',5'-cyclic monophosphate levels; pulmonary hypertension.)

NITRIC oxide (NO) is produced in endothelial cells from L-arginine by the enzyme NO synthase. Nitric oxide rapidly diffuses to the subjacent smooth muscle cell, where it activates soluble guanylate cyclase and increases the intracellular concentration of guanosine-3',5'-cyclic monophosphate (cGMP).1-6 Cyclic GMP initiates a cascade of events that lead to smooth muscle relaxation and is rapidly hydrolyzed and inactivated within the smooth muscle cell by phosphodiesterases.7,8

Zaprinast, an inhibitor of the type 5 class of phosphodiesterases, selectively blocks the hydrolysis of cGMP with minimal effects on the breakdown of adenosine-3',5'-cyclic monophosphate.9-13 Intravenous administration of low doses of zaprinast selectively decreases pulmonary artery resistance in newborn14 and fetal lambs15,16 with acute pulmonary hypertension. Vasodilator responses to infusions of endothelium-dependent vasodilators and nitrovasodilators are enhanced and prolonged by zaprinast in newborn lambs14 and in the isolated cat lobar artery.10 We and others recently reported the potentiation and prolongation of the pulmonary vasodilating effects of inhaled NO by intravenous zaprinast in lambs.15,17

These studies have suggested that the vasodilating
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effects of zaprinast, either alone or combined with inhaled NO, are relatively specific for the pulmonary circulation.\textsuperscript{14,15,17,18} However, it has also been noted that intravenous administration of zaprinast or dipyriramole, another less specific inhibitor of cGMP hydrolysis, dilate the systemic circulation at moderate to high doses.\textsuperscript{14–16,19} This potential for systemic vasodilation produced by cGMP-specific phosphodiesterase inhibitors may limit the therapeutic application of these agents to critically ill patients. Intravenous administration of a phosphodiesterase inhibitor may also dilate lung vessels in shunting regions and augment hypoxemia. In general, inhalational therapy has several well-established advantages over the oral and intravenous routes, including the low incidence of systemic side effects, the increased local efficacy of smaller inhaled drug doses, and their selective delivery to ventilated regions of the lung.\textsuperscript{20} To examine the effect of inhaled a type 5 phosphodiesterase inhibitor on the pulmonary vasculature, we administered aerosolized zaprinast into the lungs of awake lambs with pulmonary hypertension induced by a U\textsubscript{46}619 infusion. Evidence is presented that low doses of aerosolized zaprinast selectively dilate the pulmonary vasculature and that the aerosolized phosphodiesterase inhibitor augments and prolongs the pulmonary vasodilator effects of inhaled NO.

Materials and Methods

These investigations were approved by the Subcommittee for Research Animal Care of the Massachusetts General Hospital, Boston, Massachusetts.

Animal Preparation

Eight Suffolk lambs weighing 20–25 kg were anesthetized by inhalation of halothane in oxygen. Their tracheas were intubated and their lungs mechanically ventilated at 15 breaths/min and 15 ml/kg tidal volume with a large animal ventilator (Harvard Apparatus, Na
tick, MA). A 7-French thermodilution pulmonary artery catheter (Edwards Laboratories, Santa Ana, CA) was placed in the right external jugular vein through an 8-French introducer (Cordis, Miami, FL). The femoral artery was cannulated with a polyvinyl chloride catheter (2-mm inner diameter) advanced 30 cm into the aorta for continuous arterial pressure monitoring and arterial blood sampling. A tracheostomy was performed and an 8-mm inner diameter cuffed tracheostomy tube (Portex, Keene, NH) was inserted to allow spontaneous ventila-
tion. Studies began 3 h after emergence from general anesthesia if the following exclusion criteria did not occur: a peripheral white blood cell count <4,000 or >12,000 mm\textsuperscript{3}, mean a pulmonary artery pressure (PAP) >20 mmHg, or a core temperature >40°C. The lambs were housed in a Babraham cage with free access to food and water.

Hemodynamic Measurements

Systemic arterial pressure (SAP), PAP, and central venous pressure were measured continuously and pulmonary artery wedge pressure was measured intermittently using calibrated pressure transducers (Cobe Laboratories, Lakewood, CO) zeroed at the mid-chest level and continuously recorded on a thermal chart recorder (Mark 10-1; Western Graphitec, Irvine, CA). Thermodilution cardiac output was measured as the average of two determinations after injection of 5 ml 0°C Ringer’s lactate solution. Pulmonary vascular resistance (PVR) and systemic vascular resistance were computed using standard formulas. After baseline measurements, an intravenous infusion of the potent pulmonary vasoconstrictor U\textsubscript{46}619, a stable endoperoxide analog of thromboxane (9,11-Dideoxy-11α,9α-epoxymethano-prosta
glandin F\textsubscript{2α}), was administered at a rate of 0.5–1.0 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} and was titrated to achieve a mean PAP of 50 mmHg. The change of mean PAP (ΔPAP) from the baseline level of U\textsubscript{46}619-induced pulmonary hypertension was calculated by subtracting the mean PAP during inhalation of NO or aerosolized zaprinast from the baseline level of pulmonary hypertension. The duration of the pulmonary vasodilator response to inhalation of NO or zaprinast was determined by measuring the elapsed time from the discontinuation of inhalation of NO or zaprinast until the mean PAP returned to its preinhalation baseline value and was expressed as the halftime of this vasoconstrictor response.

Delivery of Nitric Oxide and Zaprinast

During the study, the tracheostomy tube was connected to a circuit consisting of a 54 reservoir bag and a two-way non-rebreathing valve (Hans Rudolph, Kansas City, MO) to separate inspired from expired gas. Oxygen and nitrogen were mixed to produce an inspired fraction of oxygen of 0.6–0.7. Nitric oxide gas (800 ppm in nitrogen; Airco, Riverton, NJ) was introduced into the inspiratory limb of the breathing circuit immediately before the reservoir bag. The aerosols of zaprinast were produced using an oxygen-powered nebulizer (Aero Tech II; CIS-US, Bedford, MA) inserted into
the inspiratory limb of the circuit just after the reservoir bag. The oxygen flow supplied to the nebulizer chamber was kept constant at a flow rate of 10 l/min in all experiments. The inspired fraction of oxygen was measured (oxygen meter =5590; Hudson, Temecula, CA) just distal to the insertion point of the nebulizer. The concentration of NO was continuously measured by chemiluminescence (model 14A; Thermo Environmental Instruments, Franklin, MA) at the inspiratory side of the two-way valve. The exhaled gases, as well as those discharged from the chemiluminescence analyzer, were scavenged using a Venturi exhalation trap maintained at negative atmospheric pressure by the laboratory's central vacuum system. The ambient NO/NO₂ levels, as measured intermittently by chemiluminescence, did not increase during the experiments.

**Protocol**

**Dose–Response Study of Intermittent Inhalation of Nitric Oxide, Zaprinast, or Both during U46619-induced Pulmonary Hypertension.** Incremental NO inhalations at 5 and 20 parts per million by volume (ppm) were administered for 6 min separated by 6-min NO-free intervals. All parameters returned to baseline values within these 6 min. Twenty minutes after the last NO inhalation, sequential zaprinast aerosol inhalations at doses of 0.23 ± 0.06, 0.49 ± 0.14, 0.71 ± 0.24, and 1.20 ± 0.98 mg·kg⁻¹·min⁻¹ were administered to lambs for 10 min, allowing 60-min intervals between doses. The aerosols were generated from the solutions of zaprinast at concentrations of 10, 20, 30, and 50 mg/ml, respectively. The amount of zaprinast that was nebulized was measured by weighing the nebulizer before and after each administration. This interval between administration of aerosolized zaprinast was chosen based on a preliminary study in which all hemodynamic parameters returned to baseline within this time and did not measurably affect the duration or magnitude of the response to subsequent exposures (data not shown). Two hours after the last dose of zaprinast was inhaled alone, zaprinast (0.23 ± 0.06 mg·kg⁻¹·min⁻¹) was inhaled with 5 and 20 ppm NO for 10 min with a 60-minute interval between doses.

**Measurements of Transpulmonary Difference of Plasma Guanosine-3′,5′-Cyclic Monophosphate Levels.** To estimate the quantity of cGMP released by the lung into pulmonary venous blood during each treatment, arterial and mixed venous plasma cGMP concentrations were measured in each lamb. Blood samples were obtained at baseline and at the end of each treatment. The transpulmonary difference was expressed as the aortic minus the pulmonary arterial plasma cGMP concentration. Cyclic GMP levels were determined using a radioimmunoassay (Biomedical Technologies, Stoughton, MA) according to the previously described method. The cGMP concentrations in the blood samples were expressed as picomoles per milliliter of plasma.

**Chemicals**

Zaprinast (2-o-propoxyphenyl-8-azapurin-6-one) was donated by Rhone-Poulenc Rorer (Dagenham, Essex, UK). The stock solution of zaprinast was prepared in 0.05 N NaOH. This stock solution was diluted with normal saline to a final concentration of 10, 20, 30, and 50 mg/ml just before use. Immediately before the study, 5 mg U46619 was dissolved in 50 ml Ringer’s lactate solution.

**Data Analysis**

The changes of mean PAP, PVR, SAP, and systemic vascular resistance are expressed as the difference between the stable baseline pulmonary hypertension value and the lowest value recorded during each treatment. The half-time of the vasodilator response was determined by measuring the elapsed time from the termination of each treatment to the time when the mean PAP returned to a value half-way between the lowest mean PAP value recorded during the treatment and the baseline pulmonary hypertension value. All data are presented as means ± SD. Data were analyzed using a paired t test or an analysis of variance with repeated measures followed by Student-Newman-Keuls post hoc testing for multiple comparisons. P < 0.05 was the criterion for significance.

**Results**

**Hemodynamic Effects of Inhaled Zaprinast, Nitric Oxide Gas, or Both**

Table 1 shows the changes of PAP, SAP, PVR, and systemic vascular resistance during each treatment. At each dose level, NO inhalation produced a prompt and stable reduction of the level of pulmonary hypertension (fig. 1) without any effects on mean SAP and systemic vascular resistance. The onset of pulmonary vasodilatation occurred within seconds after beginning NO inhalation, and the vasodilator effect was maximal within 3 min. The previous level of pulmonary vasoconstriction
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Table 1. Hemodynamic Effects of Inhaled NO and/or Inhaled Zaprinast

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>NO</th>
<th>NO 20 ppm</th>
<th>NO 5 ppm</th>
<th>ZAP</th>
<th>ZAP 10 ppm</th>
<th>ZAP 10 mg/ml</th>
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<tr>
<td>PHTN (mmHg/L-min)</td>
<td>19 ± 3</td>
<td>29 ± 6</td>
<td>32 ± 3</td>
<td>23 ± 3</td>
<td>22 ± 3</td>
<td>20 ± 3</td>
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<tr>
<td>PVR (mmHg/L-min)</td>
<td>1.78 ± 0.71</td>
<td>1.90 ± 1.36</td>
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<tr>
<td>SAP (mmHg/L-min)</td>
<td>121 ± 14</td>
<td>121 ± 14</td>
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<tr>
<td>SVR (mmHg/L-min)</td>
<td>35.8 ± 8.7</td>
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<tr>
<td>PVR (mmHg/L-min)</td>
<td>3.9 ± 1.2</td>
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<td>3.9 ± 1.2</td>
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<tr>
<td>CO (L/min)</td>
<td>3.1 ± 1.4</td>
<td>3.1 ± 1.4</td>
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Data are mean ± SD.

Fig. 1. Percentage changes of pulmonary arterial pressure and systemic arterial pressure during inhalation of nitric oxide, zaprinast, or both aerosols. NO = nitric oxide; ZAP = zaprinast; PAP = pulmonary arterial pressure; SAP = systemic arterial pressure. n = 8 in groups of NO 5, NO 20, ZAP 10, ZAP 20. n = 6 in groups of ZAP 30, NO5/Zap10, NO20/Zap10. n = 4 in the ZAP 50 group. Values are reported as means ± SD. *Significant reduction from the values at pulmonary hypertension (P < 0.05). #Significantly different from the value at NO 5 (P < 0.05) and from ZAP10 (P < 0.01).

Inhalation of zaprinast at doses of 0.49 ± 0.14 and 0.71 ± 0.24 mg·kg⁻¹·min⁻¹ selectively decreased PAP and PVR without reducing SAP or systemic vascular resistance (fig. 1). At the highest dose, inhalation of zaprinast at 1.20 ± 0.98 mg·kg⁻¹·min⁻¹ further decreased PAP and PVR, but SAP was also significantly decreased. The duration of the pulmonary vasodilator response to zaprinast was significantly longer than the duration of vasodilation induced by inhaled NO (fig. 2).

Inhalation NO gas (5 ppm) combined with nebulized zaprinast (0.23 ± 0.06 mg·kg⁻¹·min⁻¹) produced a greater reduction of PAP and PVR than either agent alone (fig. 1, table 1). The duration of the vasodilator response to the combination of NO and zaprinast inhalation was longer than that of the response to inhaled NO alone (fig. 2). Administration of aerosolized solvent (0.05 N NaOH in saline) did not exert any measurable effects on systemic or pulmonary hemodynamics or alter the dose-response to inhaled NO (data not shown).

Transpulmonary Difference of Plasma Guanosine-3',5'-Cyclic Monophosphate Concentration during the Inhalation of Nitric Oxide, Zaprinast, or Both

The transpulmonary difference in cGMP concentrations (∆cGMP) increased during inhalation of 20 ppm NO (fig. 3). Inhalation of zaprinast caused a marked

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increase in ΔcGMP at 0.71 ± 0.24 mg·kg⁻¹·min⁻¹ and 1.20 ± 0.98 mg·kg⁻¹·min⁻¹. The increase of ΔcGMP during inhalation of NO (5 ppm) combined with zaprinast (0.23 ± 0.06 mg·kg⁻¹·min⁻¹) was significantly greater than those occurring during inhalation of either agent alone (fig. 3).

Discussion

This study shows that inhalation of an aerosol containing zaprinast, an inhibitor of type 5 cGMP-specific phosphodiesterase, at doses up to 0.71 ± 0.24 mg·kg⁻¹·min⁻¹ caused pulmonary vasodilation without decreasing systemic arterial pressure in a lamb model of acute pulmonary hypertension. The duration of pulmonary vasodilation induced by aerosolized zaprinast was dose dependent and was significantly longer than that of inhaled NO at the two NO concentrations that we tested.

Intravenous administration of zaprinast has been shown to cause systemic and pulmonary vasodilation in rats and lambs. Although the vasorelaxing effect of low doses of zaprinast is relatively selective for the pulmonary circulation, systemic vasodilation has been reported with moderate to higher doses of zaprinast. Administering drugs by inhalation has the advantage of presenting high concentrations selectively to the airways and pulmonary circulation, preferentially target getting well-ventilated lung regions. Inhaled NO improves pulmonary gas exchange in patients with acute respiratory distress syndrome. Although inhaled prostacyclin selectively dilates the pulmonary circulation during hypoxic pulmonary hypertension in a canine model and improves gas exchange in patients with acute respiratory failure, when inhaled in larger quantities, prostacyclin can produce systemic hypotension. Similarly, in the present study, inhalation of a zaprinast aerosol up to a dose of 0.71 ± 0.24 mg·kg⁻¹·min⁻¹ selectively attenuated U46619-induced pulmonary hypertension. However, when inhaling a higher dose of zaprinast at 1.20 ± 0.98 and 2.51 ± 2.02 mg·kg⁻¹·min⁻¹ (data not shown), marked systemic vasodilation was produced. Because inhaled zaprinast appears well absorbed via the airway, it can circulate to systemic vessels and reduce systemic vascular tone at high inhaled doses.

It is a general rule that therapeutic aerosols must reach the lungs to be "effective." Although we carefully measured the quantity of zaprinast that was aerosolized, we do not know the precise amount of zaprinast that actually reached the lungs. Only a portion of the zaprinast that was aerosolized was actually deposited in the respiratory tract, because percentages of the drug dose (typically >50%) are not released from the nebulizer (being permanently trapped on baffles and internal tubing walls), and some of the drug is "rained-out" in

![Graph of duration of vasodilating response to inhaled NO, aerosolized zaprinast, or both.](image)

![Graph of transpulmonary difference of plasma cGMP concentration during inhalations of NO, zaprinast, or both.](image)
the respiratory circuit and in the conducting airways, and some is simply exhaled by the lambs.\textsuperscript{20} Therefore, we cannot accurately compare the doses of zaprinast that are required for pulmonary vasodilation delivered by intravenous or inhalational routes. In general, <10% of drugs administered \textit{via} air-driven nebulizers are deposited in the lungs.\textsuperscript{20} If we assume that 10% of the zaprinast that was inhaled by the lambs in 10 min was deposited in the lungs, the total "effective" amount of zaprinast may be 0.23, 0.49, 0.71, and 1.20 mg/kg at doses of 0.23 ± 0.06, 0.49 ± 0.14, 0.71 ± 0.24, and 1.20 ± 0.98 mg·kg\textsuperscript{-1}·min\textsuperscript{-1}, respectively. The magnitude of reduction of PAP with inhaled zaprinast at a dose of 0.49 ± 0.14 mg·kg\textsuperscript{-1}·min\textsuperscript{-1} given in 10 min (15.2%) is comparable to that of a previous study in which the PAP of a newborn lamb was decreased by about 12% with an intravenous infusion of 1 mg/kg zaprinast in 5 min.\textsuperscript{14} If these assumptions were correct, the total "effective" dose ratio of the inhalation compared with the intravenous zaprinast to achieve the similar reduction of PAP would be <0.5, suggesting that inhaled zaprinast is at least twice as effective as intravenous zaprinast as a selective pulmonary vasodilator.

The vasodilating effects of zaprinast are attributable to stabilization of cGMP produced in response to activators of guanylate cyclases, such as NO and natriuretic peptides.\textsuperscript{20} It is therefore likely that, when endogenous NO production is impaired, such as in primary pulmonary hypertension,\textsuperscript{27} inhaled zaprinast alone may not be an effective pulmonary vasodilator. This potential problem may be circumvented by coadministration of inhaled NO and aerosolized zaprinast. Therefore we investigated the pulmonary vasodilator effects of inhaled NO and aerosolized zaprinast.

Inhalation of aerosolized zaprinast at a dose of 0.23 ± 0.06 mg·kg\textsuperscript{-1}·min\textsuperscript{-1} potentiated and prolonged the pulmonary vasodilation caused by inhaling NO at 5 and 20 ppm. We previously reported that an infusion of intravenous zaprinast at 0.1 mg·kg\textsuperscript{-1}·min\textsuperscript{-1} markedly prolonged and moderately potentiated the pulmonary vasodilating effects of inhaled NO.\textsuperscript{17} The duration of pulmonary vasodilation induced by the combination of inhaled NO and aerosolized zaprinast was similar to that induced by combining inhaled NO with intravenous zaprinast. However, the magnitude of potentiation of the pulmonary vasodilating effects of inhaled NO was greater when combined with aerosolized zaprinast than with intravenous zaprinast.

The duration of the vasodilation caused by breathing an aerosol of zaprinast is markedly longer than that of inhaled NO alone. Furthermore, the duration of pulmonary vasodilation caused by the combined inhalation of aerosolized zaprinast at 0.23 ± 0.06 mg·kg\textsuperscript{-1}·min\textsuperscript{-1} and NO at 5 and 20 ppm was greater than that induced by either agent alone. If we assume the deposition rate of zaprinast aerosol in the lungs to be 10%, effectively deposited aerosolized zaprinast that was generated at 0.23 ± 0.06 mg·kg\textsuperscript{-1}·min\textsuperscript{-1} would be 0.02 mg·kg\textsuperscript{-1}·min\textsuperscript{-1}. Compared with our previous study in which we used 0.1 mg·kg\textsuperscript{-1}·min\textsuperscript{-1} intravenous zaprinast to achieve about 500% prolongation of the duration of the pulmonary vasodilating effects of inhaled NO,\textsuperscript{17} only one fifth the dose of zaprinast was needed \textit{via} inhalational routes to achieve a greater prolongation and potentiation of the pulmonary vasodilating effects of inhaled NO. These data support our hypothesis that the vasodilating effects of inhaled NO are potentiated and prolonged more effectively with inhaled aerosolized zaprinast than the intravenous administration of zaprinast.

The transpulmonary plasma cGMP difference was increased during the inhalation of NO, zaprinast, or both. A marked increase of ΔcGMP was observed during inhalation of aerosolized zaprinast at concentrations ≥30 mg/ml (fig. 3). It is likely that pulmonary vascular cells make an important contribution to plasma cGMP levels. However, other sources of cGMP, such as circulating blood cells and cardiac tissues, cannot be excluded. In isolated cultured cells, cGMP release is correlated with intracellular cGMP concentrations.\textsuperscript{28,29} Although cGMP is an intracellular second messenger, and the precise source of plasma cGMP is unknown, our study demonstrates a temporal correlation between transpulmonary plasma cGMP difference and pulmonary vasodilation. These observations support the hypothesis that zaprinast augments the pulmonary vasodilating effects of inhaled NO by increasing intracellular cGMP levels in pulmonary vascular smooth muscle cells.

Although the current study demonstrated selective pulmonary vasodilation in a model of acute pulmonary hypertension in which healthy lambs inhaled a zaprinast aerosol, the clinical applicability of these observations for patients with lung disease is uncertain. For example, in persons with sepsis and acute respiratory distress syndrome associated with increased NO production, systemic absorption of even small amounts of a PDE5 inhibitor may precipitate unacceptable hypotension. Because healthy lambs with intact lungs were studied, we could not assess the effects of zaprinast aerosols on oxygenation and gas exchange. Further studies using
animal models of lung injury and sepsis will provide important information about the safety and efficacy of inhaled zaprinast in acute respiratory distress syndrome.

In conclusion, this study shows that inhalation of nebulized zaprinast, a cGMP-selective phosphodiesterase inhibitor, causes selective pulmonary vasodilation. The duration of vasodilation with zaprinast inhalation is dose dependent and significantly longer than that of inhaled NO. Inhaled zaprinast also markedly potentiates and prolongs the duration of the pulmonary vasodilating action of inhaled NO without altering its pulmonary vascular selectivity. The data also demonstrate that zaprinast inhalation augments net transpulmonary cGMP release during NO inhalation. Inhalation of a nebulized cGMP-selective phosphodiesterase inhibitor alone or combined with NO may be a useful and noninvasive therapy to treat acute and chronic pulmonary hypertension.

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