Aerosolized Prostacyclln

In Search of the Ideal Pulmonary Vasodilator

The requirements of an ideal pulmonary vasodilator include efficacy, selectivity, safety, and cost. Selectivity has been elusive. For decades, physicians caring for children and adults with pulmonary hypertension—either primary or secondary to lung disease, congenital heart disease, or congenital diaphragmatic hernia—have searched for an agent that would selectively decrease pulmonary vascular resistance. There is a twofold requirement for selectivity. Pulmonary vasodilators should not cause systemic hypotension (selective for the pulmonary circulation) nor should they increase intrapulmonary shunt (selective for that part of the pulmonary circulation that serves ventilated lung units). There are no therapeutic agents, however, that selectively dilate any part of the circulation, if they get there. A strategy to prevent vasodilators from getting there led to the search for short biologic half-life agents that act in the pulmonary circulation and are destroyed or diluted before they reach the systemic circulation. This strategy was coupled with delivery into the pulmonary artery with the hope that the effect was local and dissipated by the time the systemic circulation was reached. Short half-life agents have included adenosine triphosphate and prostaglandins. Intrapulmonary injection has been tried with tolazoline, hydralazine, and prostacyclin, among others. None has proved selective for the pulmonary circulation. In addition, they all increase blood flow to nonventilated lung, increase shunt, and risk decreasing oxygen delivery.

Nitric oxide can be delivered only by inhalation. The use of nitric oxide made it clear that double selectivity could be achieved. Because nitric oxide binds to hemoglobin and is rapidly inactivated, it has no systemic effect. Because it is delivered to ventilated lung regions, it has the effect of increasing blood flow to precisely where it is wanted. Nitric oxide is close to being an ideal pulmonary vasodilator. Unfortunately, a complex and expensive technology, dedicated to its use, is necessary to ensure safe and effective use. In addition, the occurrence of toxic metabolites with therapeutic doses and methemoglobinemia raises the question, “Are there alternatives?”

The concept of delivering vasodilators to ventilated alveoli suggested that aerosolized vasodilators could, like nitric oxide, selectively affect the pulmonary circulation. Two case reports in this issue of the Journal describe the use of aerosolized prostacyclin in four children with pulmonary hypertension. Pappert et al. from a group who advocate the use of inhaled nitric oxide in acute respiratory distress syndrome (ARDS), report the use of aerosolized prostacyclin in three children with ARDS, whereas Zwisler et al. describe its use in an infant with congenital heart disease and pulmonary hypertension. The salutary effects of a selective pulmonary vasodilator—decreased pulmonary vascular resistance without systemic hypotension and an improved PaO2/FiO2 ratio, comparable to that seen with inhaled nitric oxide—are reported. These reports are similar to published reports about adults with ARDS.

Prostacyclin’s physiologic role has been eclipsed by the avalanche of interest in nitric oxide. Prostacyclin is a ubiquitous, potent vasodilator released primarily from endothelial cells but also from other cell types. It is critical for maintaining low pulmonary vascular resistance and plays a major role in the transitional circulation. In the lung, both ventilation and hypoxia increase its secretion. It was first used intravenously to treat a child with pulmonary hypertension in 1980. Prostacyclin spontaneously hydrolyzes at physiologic pH into an inactive metabolite (6-keto-prostaglandin F1α), and has a half-life of 2–3 min. Prostacyclin is reasonably stable in aerosol (in the appropriate buffer approximately 12 h) and can be delivered to the site of action: ventilated lung. Prostacyclin acts by binding to cell surface prostacyclin receptors to activate adenylyl cyclase (probably via a G protein). Cyclic adenosine monophosphate activates protein kinase A to express its effects, including decreased free intracellular calcium in vascular smooth muscle causing vasorelaxation. Prostacyclin also stimulates endothelial release of nitric oxide. These interactions between nitric oxide and prostacyclin suggest that, when used in combination, their effect may be more than additive.
Prostacyclin may be best known for its antithrombotic and disaggregatory effects on platelets. In the lung affected by ARDS, prostacyclin prevents thrombosis and may prevent the endarteritis obliterans commonly seen at postmortem examination. Significant systemic absorption, theoretically, may lead to a coagulopathy in these critically ill patients.

Does aerosolized prostacyclin have any drawbacks? It is not licensed for use in the United States, and neither is nitric oxide. Systemic effects (hypotension and tachycardia), not evident in these reports, have been reported only with aerosol doses 100 times greater than those reported here.9 Pappert et al.‘s data have an interesting finding. The largest improvement in the PaO₂/FIO₂ ratio did not occur at the minimum pulmonary artery pressure (PAP) in any child. In one, intrapulmonary shunt was greatest at the lowest PAP. This finding suggests that, at doses that maximally decreased PAP, vasodilation occurred in nonventilated areas and worsened shunt. This could have occurred by either prostacyclin penetration to nonventilated areas or absorption of prostacyclin with a downstream effect in the pulmonary circulation within nonventilated areas. Titration to optimal oxygen delivery, not minimum PAP, may be necessary for prostacyclin.

Are there drawbacks of the aerosolized inhalation approach? Aerosolization is technologically widely available and useful for a wide range of other therapies. Ultrasound aerosolization is preferred to jet nebulization because of the smaller particle size and avoidance of high gas flows. The uncertainties of aerosolized dosing are a concern, but titration to effect is a familiar strategy. Another consideration is the effect of vasodilators on the airway epithelium and smooth muscle. There is some evidence that airway dilation occurs with nitric oxide.10 Some vasodilator prostaglandins, for example, prostaglandin E₂, are bronchodilators.11 There is conflicting evidence whether prostacyclin is a bronchoconstrictor, but certainly it is not a bronchodilator.12 Can altered airway resistance occur by an effect independent of airway smooth muscle responses? Dilution of blood vessels located in the submucosa and airway wall reduces airway caliber. Enlargement of the submucosal vascular plexus is a factor in cardiac asthma.13 Increased airway resistance has been reported with aerosolized vasodilators, including nitroglycerin.14 So far, the limited clinical data have not revealed altered airway resistance with aerosolized prostacyclin, but this has been measured only by relatively crude techniques. With increased pulmonary administration of vasodilators, the possibility of increased airway resistance should be remembered.

Regarding safety, because nitric oxide is a highly toxic molecule, the body has well developed defense mechanisms to contain it. Its rate and duration of action are limited to microns and seconds. Methemoglobinemia remains a concern. The result of an unintended excessive dose of inhaled nitric oxide would be (and has been) catastrophic.15 Pulmonary effects of prolonged administration are unknown but potentially deleterious. The higher oxides of nitrogen (peroxynitrite, nitrogen dioxide) formed from nitric oxide, especially in the presence of high concentrations of oxygen and superoxide radicals, are highly toxic molecules. These could inactivate surfactant, damage endothelial and type II cells, and amplify lung injury, particularly in the setting of ARDS, even with low-dose nitric oxide.15,16 Prostacyclin, on the other hand, has multiple salutary effects. It has a much longer duration of action and wide-ranging autocrine, paracrine, and endocrine effects. It has no known toxic effects or toxic metabolites. The result of an overdose is reversible hypotension. If aerosolized prostacyclin proves as efficacious as nitric oxide, cost and convenience will decide which will find the widest application.

The use of inhaled nitric oxide has reminded us of something significant: the route of delivery can be as important as the drug of choice. We can expect to see other vasodilators applied in this fashion. Pulmonary administration addresses the issue of selectivity. Efficacy, safety, and cost will decide the drug of choice.

Randall C. Wetzel, M.B., B.S., F.C.C.M., F.A.A.P.
Anesthesiology and Critical Care Medicine
The Johns Hopkins Hospital
600 North Wolfe Street
Baltimore, Maryland 21287-3711

References