Inhaled Therapies for Pulmonary Hypertension

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The inhaled route has a number of attractive features for treatment of pulmonary hypertension, including delivery of drug directly to the target organ, thus enhancing pulmonary specificity and reducing systemic adverse effects. It can also improve ventilation/perfusion matching by dilating vessels supplying ventilated regions, thus improving gas exchange. Furthermore, it can achieve higher local drug concentrations at a lower overall dose, potentially reducing drug cost. Accordingly, a number of inhaled agents have been developed to treat pulmonary hypertension. Most in current use are prostacyclins, including epoprostenol, which has been cleared for intravenous applications but is used off-label in acute care settings as a continuously nebulized medication. Aerosolized iloprost and treprostinil are both prostacyclins that have been cleared by the FDA to treat pulmonary arterial hypertension (PAH). Both require frequent administration (6 and 4 times daily, respectively), and both have a tendency to cause airway symptoms, including cough and wheeze, which can lead to intolerance. These agents cannot be used to substitute for the infused routes of prostacyclin because they do not permit delivery of medication at high doses. Inhaled nitric oxide (INO) is cleared for the treatment of primary pulmonary hypertension in newborns. It is also used off-label to test acute vasoreactivity in PAH during right-heart catheterization and to treat acute right-heart failure in hospitalized patients. In addition, some studies on long-term application of INO either have been recently completed with results pending or are under consideration. In the future, because of its inherent advantages in targeting the lung, the inhaled route is likely to be tested using a variety of small molecules that show promise as PAH therapies. *Key words: inhaled route; aerosol therapies; pulmonary hypertension; pulmonary arterial hypertension; inhaled nitric oxide.* [Respir Care 2015;60(6):794–805. © 2015 Daedalus Enterprises]

Introduction

Rather than discuss aerosol therapies per se, we will address inhaled therapies for pulmonary hypertension generally because inhaled nitric oxide (INO) is used diagnostically, has therapeutic potential in pulmonary hypertension, and is a gas rather than an aerosol. However, aerosols will be the focus of our discussion because 2 have been cleared to treat pulmonary arterial hypertension (PAH).

Before examining inhaled therapies for pulmonary hypertension, we will first provide an overview of pulmonary hypertension, which is defined as a mean pulmonary arterial pressure of $\geq$ 25 mm Hg. The World Symposium on Pulmonary Hypertension, most recently held in Nice, France, in 2013,[1] has classified pulmonary hypertension into 5 groups. Group 1 PAH requires a pulmonary artery wedge pressure of $\leq$ 15 mm Hg and increased pulmonary vascular resistance (PVR), calculated as the difference between the mean pulmonary arterial pressure and pulmonary artery wedge pressure divided by the cardiac output. Group 1 consists of idiopathic PAH (formerly called primary pulmonary hypertension) and associated forms of pulmonary hypertension (formerly called secondary pulmonary hypertension). PAH may be associated with connective tissue disease (especially scleroderma), congenital cardiac shunts, portal hypertension, human immunodeficiency virus, and toxins like fenfluramine and methamphetamine.

Group 2 is the most prevalent form of pulmonary hypertension and is related to left-heart disease (systolic, diastolic, or valvular). In Group 2 pulmonary hypertension, the filling pressure of the left heart (pulmonary artery wedge pressure) is $>$ 15 mm Hg. To maintain the transpulmonary pressure gradient (mean pulmonary arterial pressure $-$ pulmonary artery wedge pressure), the mean pulmonary arterial pressure must rise at least concomitantly. In most patients, the mean pulmonary arterial pressure increases passively in proportion to the rise in the pulmonary artery wedge pressure, giving rise to post-capillary pulmonary hypertension. In some patients, the pulmonary arteries undergo remodeling and constriction, resulting in an elevated pre-capillary resistance, thus contributing to combined pre- and post-capillary pulmonary hypertension. In this instance, the mean pulmonary arterial pressure can be substantially higher than what would be expected from the increase in pulmonary artery wedge pressure alone.

Group 3 is pulmonary hypertension associated with chronic hypoxemia or parenchymal lung disease, including COPD, interstitial lung disease, particularly idiopathic pulmonary fibrosis, and obstructive sleep apnea. Group 4 is chronic thromboembolic pulmonary hypertension, caused by thromboemboli accumulating in the pulmonary arteries and failing to resolve. Finally, Group 5 is a miscellaneous category. Currently, sarcoidosis- and sickle cell-related pulmonary hypertension are in this category, along with a number of other unusual causes.

Over the past 20 years, the FDA has cleared 9 therapies for PAH. These therapies target one of 3 main signaling pathways: prostacyclin, NO, and endothelin. The first clinically available drug was epoprostenol, a prostacyclin analogue. Endogenous prostacyclins are derived from arachidonic acid, which signals through the prostacyclin receptor, stimulating adenylate cyclase to generate cyclic adenosine monophosphate (cAMP). This intracellular second messenger mediates vasodilatation and inhibition of cell proliferation and has antiplatelet actions. The second pathway of interest is NO. NO is a potent endogenous vasodilator that activates guanylyl cyclase to release cyclic guanosine monophosphate (cGMP), which has actions similar to those of cAMP. Finally, endothelin receptor antagonists attenuate the influence of the excess endothelin-1 signal observed in PAH. All of the available therapies for pulmonary hypertension have been cleared for Group 1 PAH, with one also approved for patients with Group 4 chronic thromboembolic pulmonary hypertension.

We discuss the advantages and disadvantages of the inhalation route generally and then examine each of the available inhaled therapies individually according to their biochemical pathway, reviewing their pharmacology, indications, evidence for efficacy, practical applications, and limitations.

Advantages and Disadvantages of Inhaled Therapies for Pulmonary Hypertension

The inhaled route offers several significant advantages over systemic routes of drug administration (Table 1). First, it delivers medication directly to the diseased organ, enabling higher doses locally with less systemic toxicity. This can minimize systemic hypotension, a common limitation in acutely ill patients, because most of the drugs are systemic and pulmonary vasodilators. Second, inhaled va-

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Table 1. Advantages and Disadvantages of the Inhaled Route for Administration of Pulmonary Hypertension Medications

Advantages	Disadvantages
Local delivery, potentially higher concentration of medication in the target organ	Irritant effects on airways
Avoidance of systemic adverse effects, including systemic hypotension	Limitation of medication dose due to airway symptoms
Delivery to ventilated areas, vasodilatation improves $\dot{V}/\dot{Q}$ and gas exchange	Delivery systems can be cumbersome and time-consuming
Potentially lower total dose of medication with lower cost	May be very costly

$\dot{V}/\dot{Q}$ = ventilation/perfusion ratio

Table 2. Advantages and Disadvantages of Nitric Oxide as an Inhaled Agent to Treat Pulmonary Hypertension

Advantages	Disadvantages
Odorless and colorless	Administration technology very expensive at present
Rapid-acting, full response usually within minutes	Short duration of effect necessitates continuous administration if used long-term
Rapid offset, very safe	Requires cumbersome portable tanks for out-patient use at present*
Short exposure time suitable for busy catheterization lab setting	Withdrawal syndrome consisting of deterioration of hemodynamics and gas exchange poses a potential impediment to long-term use
No systemic adverse effects due to immediate inactivation by combining with hemoglobin to form methemoglobin	

* More portable technology is currently in development.

sodilators are likely to improve or at least have fewer adverse effects on gas exchange compared with other systemic routes of administration. This is because they are delivered to ventilated areas, where their vasodilatory action can enhance blood flow to ventilated regions, enhancing ventilation/perfusion matching. On the other hand, systemically delivered vasodilators indiscriminately dilate the pulmonary arterial bed, leading to blunted (or blocked) hypoxic vasoconstriction with enhanced blood flow to poorly ventilated areas, impairing gas exchange. Third, by delivering drug directly to the target organ, inhalation may permit reduction of the total medication dose, potentially lowering cost.

The inhaled route also has significant disadvantages. Intolerance of inhaled drug administration due to sensitization or direct irritant effects of the medications (or the excipients) on the airways may result in cough or even bronchospasm. Also, control over drug dosing is less precise due to variability in breathing patterns and the difficulty in determining exactly how much medication reaches the target regions of the lung. Delivery systems may also be cumbersome and difficult to operate, introducing the potential for error and inaccurate dose administration. This, coupled with cost considerations, may limit practical application of inhaled drugs in the out-patient setting.

The Prostacyclin Pathway

Epoprostenol

Prostacyclins, discovered in 1976 by the Nobel Prize winner John Vane, are derived from arachidonic acid via the action of prostacyclin synthase.[2] Originally characterized by their potent vasodilatory activity, they have since been shown to have antiproliferative, pro-apoptotic, and antithrombotic properties.[3,4] The first prostacyclin cleared by the FDA for the treatment of PAH was epoprostenol in 1995, which was administered by continuous intravenous infusion. In the pivotal randomized clinical trial, epoprostenol improved exercise capacity as well as survival (the only pulmonary hypertension drug shown to do so in a randomized trial).[5] Today, it remains a commonly prescribed agent for the treatment of advanced PAH.

Although epoprostenol was approved for continuous intravenous infusion, the intravenous formulation can be aerosolized and used therapeutically off-label. One of the limitations of epoprostenol (intravenous and nebulized) is its very short half-life (3–5 min). As a result, it requires continuous nebulization, rendering it impracticable for long-term application. However, for short-term in-hospital applications, it has advantages over the intravenous route, including less adverse effects on gas exchange or systemic blood pressure, making it attractive for treatment of pulmonary hypertensive crises or vasodilator testing. Notably, even though epoprostenol is very expensive when used as a long-term continuous infusion, for short-term acute care applications, it is much cheaper than INO (see below).

No large randomized trials have yet evaluated the application of inhaled epoprostenol in subjects with pulmonary hypertensive crises, but one small study examined its short-term effects on hemodynamics and gas exchange in a group of subjects with pulmonary hypertension following surgery, including cardiac procedures and lung transplantation or resection (Table 2).[6] After 4–6 h of inhaled epoprostenol, the mean pulmonary arterial pressure fell significantly, cardiac output rose, and the P_{aO_2}/F_{IO_2} oxygenation index tended to rise. Furthermore, there was less effect on the mean systemic arterial pressure than on the mean pulmonary arterial pressure, indicating pulmonary selectivity. Although this study suggested that inhaled

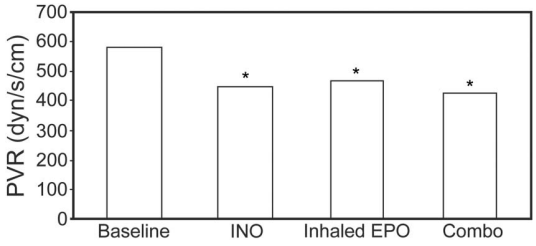

Fig. 1. Pulmonary vascular resistance (PVR; dyn/s/cm) at baseline and after exposure to inhaled nitric oxide (INO; 20 ppm) for 10 min, inhaled epoprostenol (EPO; 50 μg/min) for 10 min, and the combination (Combo). * $P < .05$ versus baseline. From Reference 7, with permission.

epoprostenol may be helpful in such perioperative settings, controlled trials are indicated to establish efficacy.

For short-term use, inhaled epoprostenol is a less expensive alternative to INO. To define the relative therapeutic benefits of these 2 agents, we compared them in a randomized short-term crossover trial (Fig. 1).[7] During 10-min exposures between 10-min washout periods, we compared INO (20 ppm) and inhaled epoprostenol (50 μg/min) administered via a vibrating mesh nebulizer (Aerogen, Dublin, Ireland). Both agents reduced PVR by ~20%. Interestingly, there were no significant systemic hemodynamic differences between the agents, and there was no additive effect (beneficial or detrimental) when delivered in combination. These data support the concept that inhaled epoprostenol is a suitable alternative to INO.

For these vasodilator trials performed on awake, nonintubated subjects, we used a face mask with a well-sealed air cushion (Vital Signs, Totowa, New Jersey) and administered the aerosol via a T-connector in a single-tube circuit with a filter for exhaled gas to prevent epoprostenol aerosol from dispersing into the atmosphere. Although a mouthpiece might be more efficient for aerosol delivery, the use of sedation in the catheterization laboratory and the need for multiple hours or even days of administration in the ICU render the mouthpiece impractical for most of these applications. For mechanical ventilation via endotracheal tubes, we administered the aerosol via the inhalation limb of the ventilator circuit, downstream from the humidifier. We also placed a filter (Respirgard II, Vital Signs) in the exhalation tubing to prevent entry of epoprostenol into the exhalation circuitry of the ventilator, where it can be damaging. We changed the filter every 4 h to prevent saturation and increased backpressure. Our institution now uses inhaled epoprostenol instead of INO in postoperative patients, and we have seen an ~90% drop in respiratory therapy costs related to INO (personal communication, 2015, Joseph Curro RRT MEd, Tufts Medical Center). Additional details on inhaled epoprostenol administration are given in Table 3.

Iloprost

Iloprost is an alternative prostacyclin that was first used clinically in Europe, where it is available in some countries by inhalation as well as intravenously. It was cleared in the United States for inhalation in 2004. It has a longer half-life than epoprostenol (7–8 min) and a half-life of pharmacodynamic activity of ~0.5 h.[8] Although this necessitates frequent treatments (at least 6 times/d), iloprost is approved for long-term use in out-patients.

Iloprost was approved based on the Aerosolized Iloprost Randomized (AIR) Trial performed in Germany, which enrolled 203 subjects, roughly two thirds with idiopathic PAH and the remainder with chronic thromboembolic pulmonary hypertension.[9] Subjects self-administered treatments an average of 7.8 times/d and realized a highly significant placebo-subtracted improvement in 6-min walk distance (6MWD) of 36 m ($P = .004$) (Fig. 2). In addition, the primary outcome variable (a combination of improvement in New York Heart Association [NYHA] functional class of at least 1 and in 6MWD of at least 10% and no deterioration or death) occurred in 16.8% of treated subjects and only 4.9% of controls ($P = .07$). In addition, significantly more iloprost-treated subjects improved their NYHA class, quality-of-life, and dyspnea scores. Of concern, subjects in the iloprost group more often had syncope considered serious, mainly during exertion in the morning. This was thought to be possibly related to the lengthy period without medication during sleeping hours.

In subjects with pulmonary fibrosis and pulmonary hypertension, iloprost, in contrast to an infused prostacyclin, had more pulmonary specificity and was less likely to increase shunt fraction.[10] In a group of 22 children, one third were intolerant of inhaled iloprost because of adverse airway effects, including cough and bronchospasm.[11] Only 9 subjects tolerated longer-term use, but there were favorable outcomes in these, including improved functional capacity. Some evidence supports the use of iloprost as a vasodilator in the acute setting. In a nonrandomized cohort of 22 mechanically ventilated subjects with residual pulmonary hypertension post-thromboendarterectomy, inhaled iloprost reduced PVR by 33% in half of the subjects compared with no change in the other half, who received only inhaled saline.[12] Iloprost (25 μg) was added to normal saline to achieve a volume of 2 mL and was administered over 15 min by jet nebulizer via the ventilator's inspiratory limb.

Inhaled iloprost is administered using the I-neb aerosolized adaptive delivery system (Philips Respironics, Murrysville, Pennsylvania), which adapts to patient breathing patterns to optimize drug delivery (Fig. 3). However, it must be held parallel to the surface of the ground and requires a predictable breathing pattern, which some patients find challenging. Furthermore, it can take up to 10 min

Table 3. Applications of Currently Available Inhaled Therapies for Pulmonary Hypertension

Agent	Indications	Dose	Cost	Outcomes	Adverse Effects
Nitric oxide	PPHN	5–40 ppm	$100–400/h	Decreased mean pulmonary artery pressure, PVR, improved O_2, increased 6MWD	Possible withdrawal
	Vasoreactivity testing*	For 10 min			
	Hypertensive crises	For hours to days			
	Long-term use for PAH	For months to years			
Epoprostenol	Vasoreactivity testing*	50 μg/min via mask	$36/vial	Decreased mean pulmonary artery pressure, PVR	Possible withdrawal, cough, headache, jaw ache, nausea, diarrhea
	Hypertensive crises*	For 10 min or hours to days			
Iloprost	Group 1 PAH to improve exercise tolerance and symptoms, avoid deterioration	2.5 or 5 μg/dose, 6–9 times/d	$70,000/y	Decreased mean pulmonary artery pressure, increased 6MWD	Cough, wheeze, headache, flushing, trismus, nausea, diarrhea, syncope
Treprostinil	Group 1 PAH to improve exercise ability	3–9 puffs, 4 times/d*	$100,000/y	Increased 6MWD	Cough, wheeze, headache, throat, irritation, nausea, diarrhea, syncope

* Off-label application.
PPHN = persistent pulmonary hypertension of the newborn
PAH = pulmonary arterial hypertension
PVR = pulmonary vascular resistance
6MWD = 6-min walk distance

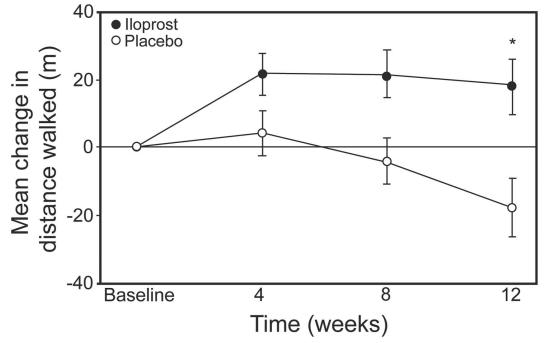

Fig. 2. Iloprost effect on 6-min walk distance in the 12-week Aerosolized Iloprost Randomized (AIR) Trial. * $P = .004$. From Reference 9, with permission.

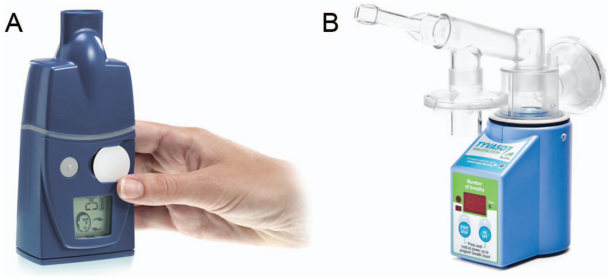

Fig. 3. A: I-neb, courtesy Philips Respironics. B: TD-100, courtesy United Therapeutics.

(or sometimes more) to administer each dose and requires daily cleaning and maintenance. Many patients find this cumbersome and have difficulty keeping up with the recommended 6 doses/d. The Venta nebulizer is an alternative device used more often in Europe. Inhaled iloprost is usually prescribed for out-patients with moderate-to-severe PAH who are not deemed to be sick enough for, are poor candidates for, or have declined infusion therapy. It is supplied by specialty pharmacies that employ specialized nurses to educate patients on proper application of the device (see Table 3).

In summary, inhaled iloprost is effective in patients with idiopathic PAH in improving exercise capacity and dyspnea. The inhaled route is associated with fewer adverse effects on gas exchange or systemic symptoms and hemodynamics compared with intravenous drug delivery. Despite these benefits, application of inhaled iloprost has been limited due to frequent airway symptoms and the significant time investment required for compliance with recommended dose frequency and for maintenance of the nebulizer apparatus. Finally, given that the estimated half-life of action is in the range of 0.5 h even with 6–9 times daily dosing, patients using it are not exposed to active drug most of the time.[8]

Treprostinil

Treprostinil, another prostacyclin analogue, was first cleared for subcutaneous use in 2002, intravenous use in 2007, and inhalation in 2011. Compared with other commercially available prostacyclins, treprostinil has the longest half-life (3–4 h), which translates to a longer dosing interval when administered by inhalation.[13] Inhaled treprostinil was cleared by the FDA in 2011 based on the results of the TRIUMPH I (Double Blind Placebo Controlled Clinical Investigation Into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients With Severe Pulmo-

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