Inhaled Therapies for Pulmonary Hypertension

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Summary

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 ≥ 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 ≤ 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

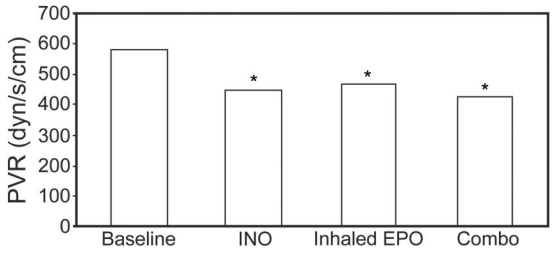

Fig. 1. Pulmonary vascular resistance (PVR; dyn/s/cm) at baseline and after exposure to inhaled nitric oxide (INO; 20 ppm) for 10 min, inhaled epoprostenol (EPO; 50 μg/min) for 10 min, and the combination (Combo). * $P < .05$ versus baseline. From Reference 7, with permission.

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 Vasoreactivity testing* Hypertensive crises Long-term use for PAH	5–40 ppm For 10 min For hours to days For months to years	$100–400/h	Decreased mean pulmonary artery pressure, PVR, improved O_2, increased 6MWD	Possible withdrawal
Epoprostenol	Vasoreactivity testing* Hypertensive crises*	50 μg/min via mask For 10 min or hours to days	$36/vial	Decreased mean pulmonary artery pressure, PVR	Possible withdrawal, cough, headache, jaw ache, nausea, diarrhea
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

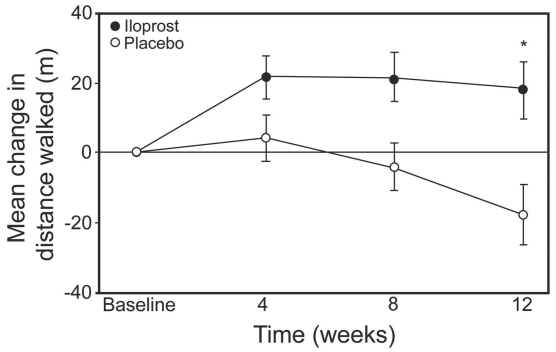

Fig. 2. Iloprost effect on 6-min walk distance in the 12-week Aerosolized Iloprost Randomized (AIR) Trial. * $P = .004$. From Reference 9, with permission.

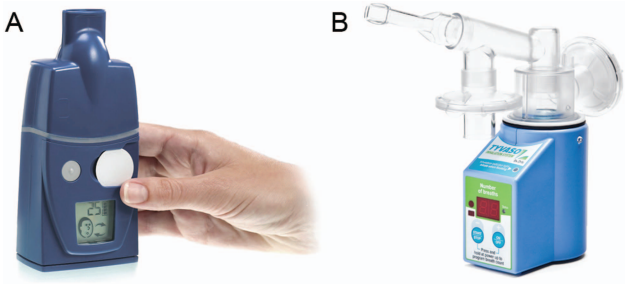

Fig. 3. A: I-neb, courtesy Philips Respironics. B: TD-100, courtesy United Therapeutics.

(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-

nary Arterial Hypertension) Trial, which randomized 235 subjects into inhaled treprostinil versus placebo groups.[14] All subjects were on background monotherapy: approximately two thirds on bosentan and one third on sildenafil. Overall improvement in the median 6MWD was 20 m ($P = <.001$). Post hoc subgroup analyses indicated that the improvement was significant for subjects on background bosentan (25 m) but not for those taking sildenafil (9 m), although the study was not powered adequately for such analysis. Secondary outcomes also showing significant improvements with inhaled treprostinil included N-terminal pro-brain natriuretic peptide and quality of life (Minnesota Living with Heart Failure Questionnaire scale), but no differences were apparent in rate of clinical worsening, dyspnea score, or NYHA functional class. Adverse effects encountered significantly more frequently in the treprostinil group included cough (54 vs 29%), headache (41 vs 23%), and flushing (17 vs 1%). Data for inhaled treprostinil are lacking for pediatric and acute care applications.

Treprostinil aerosol is administered via the Opti-Neb (Teleflex Medical, Reading, Pennsylvania), which, like the I-neb, requires assembly, cleaning, and maintenance (see Fig. 3 and Table 3). However, treprostinil is administered 4 times/d, with up to 12 puffs each time, but less time is needed compared with I-neb treatments, which require many more steady breaths until the treatment is finished. Thus, acceptance of and adherence to the Opti-Neb tends to be better (personal observation). Like iloprost, inhaled treprostinil is prescribed for out-patients, usually as an add-on therapy via specialty pharmacies that provide specialized nurses for teaching and technical support.

Compared with benefits demonstrated with other therapies, inhaled treprostinil is arguably less potent, considering that the improvement in 6MWD was less, and clinical worsening and NYHA end points were not met.[14] On the other hand, it is important to consider that all subjects in the TRIUMPH I Trial were on background therapy, which generally reduces the increase in 6MWD compared with de novo therapy. Furthermore, relatively few events occurred in the control group, making it unlikely that the treatment arm could sufficiently reduce events to achieve a significant benefit for clinical worsening. On the other hand, in a small retrospective cohort (18 subjects) transitioned from infusion prostacyclins to inhaled treprostinil, a minority of subjects deteriorated over the ensuing 7 months, leading the authors to advise caution and close monitoring after such transitions.[15] Conversely, subjects with PAH who were deteriorating on inhaled treprostinil were successfully transitioned to intravenous or subcutaneous treprostinil.[16]

Given the limitations, inhaled iloprost and treprostinil are used less often in the PAH population compared with the oral or infused medications. Their best application appears to be for patients who are already on one or 2 oral agents and have not reached improvement goals, but are not candidates for or have not deteriorated enough to warrant infusion therapy. On the other hand, these therapies would be poor choices for initial therapy because of limited efficacy and cost ($>$ \$100,000/y), and they should not be used as substitutes for infusion therapy when needed to rescue unstable patients.

Nitric Oxide/cGMP Pathway

Nitric Oxide

Nitric oxide is an endogenous vasodilator and maintains low basal tone in vascular beds.[17] It has multiple actions, including antiproliferative and anti-inflammatory effects under physiologic conditions. However, in pathologic states, inducible nitric oxide synthase increases NO release, which can have pro-inflammatory and toxic effects, especially when peroxynitrite is formed by the interaction of NO and superoxide.[18] Nitric oxide is produced by a number of different cell types, but endothelial cells are important sources in the vasculature. It acts very rapidly and is almost immediately inactivated by combining with hemoglobin to form methemoglobin. Accordingly, it has very few systemic adverse effects, which is one of its big advantages (see Table 1).

In adults, INO is used off-label in the catheterization laboratory to test acute pulmonary vasoreactivity, seeking to identify patients who may be long-term responders to calcium channel blocker therapy. According to current practice standards, a positive acute vasodilator response is defined as a fall in mean pulmonary arterial pressure of at least 10 mm Hg to below 40 mm Hg without a reduction in cardiac output.[19] Acute vasoreactivity also has some prognostic significance. Subjects who experience a $>$ 30% drop in PVR have a better prognosis than non-responders.[20] INO is also used quite commonly to treat acute pulmonary hypertensive crises due to conditions such as deteriorating chronic pulmonary hypertension; acute right-heart failure following massive pulmonary embolism, cardiac surgery, and heart or lung transplantation; or after lung resection surgery. Although some reports have demonstrated favorable hemodynamic effects of INO (including decreased mean pulmonary arterial pressure and PVR and increased cardiac output),[21] there are no data from adequately controlled trials to support its routine use in these clinical settings.

NO has 2 main disadvantages. First, it is very expensive as currently formulated. Cost via currently available technology can reach \$12,000/month, which is prohibitive at most institutions. At institutions with a neonatology unit, INO is used for its only FDA-approved application, persistent pulmonary hypertension of the newborn, a rare form of PAH Group 1. In this context, INO use in vasodilator

trials during right-heart catheterization in adults with PAH adds marginally to cost. At institutions lacking neonatology units, however, it is frequently cost-prohibitive, and intravenous or inhaled epoprostenol or older agents such as intravenous adenosine are used more often for vasoreactivity testing. Second, when administration is too rapidly discontinued, patients may experience a withdrawal syndrome, characterized by rebound pulmonary hypertension. In one ICU study on use of INO to treat acute pulmonary hypertensive crises due to a variety of etiologies, two thirds of the subjects encountered withdrawal, and mortality was > 50%.[22] Some evidence suggests that co-administration of sildenafil may be helpful in mitigating the withdrawal.[23]

For in-patient applications of INO, our institution uses the same face mask as that used with inhaled epoprostenol and the INOmax DS (Ikaria, Hampton, New Jersey), which enables the user to quickly and accurately provide INO in doses ranging from 1 to 80 ppm by mixing pressurized NO and oxygen via adjustment of bleeder valves. For vasodilator testing and for most clinical applications, we use 10–20 ppm, concentrations that are generally adequate to bring about maximal vasodilatation.[6] The INOmax also monitors nitrogen dioxide (NO_2) concentration, a toxic metabolite of the reaction between NO and oxygen, to ensure that levels stay below safe limits. Considering that NO concentrations are low and the exposure is brief, we have not seen problems with excessive NO_2 levels during vasoreactivity testing. For pulmonary hypertensive crises, we use the same range of INO concentrations as used for acute vasodilator testing and the same face mask. During use of both INO and inhaled epoprostenol, standard monitoring includes a pulmonary artery catheter, although lowering pulmonary arterial pressure to a desirable level is often not possible, and with applications of INO for more than a few hours, methemoglobin levels should be checked periodically.

In older literature, there are several reports of therapeutic use of INO in out-patients with chronic pulmonary hypertension. These systems use pulsed nasal oxygen devices with compressed tanks containing 80 ppm NO pulsed for 0.1 s via one cannula and providing continuous oxygen via the other. Channick et al[24] reported decreases in mean pulmonary arterial pressure (from 51 to 43 mm Hg) and PVR (from 790 to 620 dyn/s/cm) in subjects with idiopathic PAH using this system. Preston et al[25] reported their experience using a similar system for long-term out-patient INO, demonstrating acute vasoresponsiveness in 7 of 8 subjects with pulmonary hypertension related to sarcoidosis and improvements in 6MWD in all 5 subjects who continued therapy for the subsequent 2–4 months. Further research on and clinical use of long-term INO have been stymied by the high cost and lack of insurance coverage for off-label applications after FDA approval for persistent pulmonary hypertension of the newborn, but interest has resurged recently. We are anxiously awaiting results of a recently completed phase-2 trial sponsored by Ikaria on long-term INO in subjects with Group 1 PAH. Other manufacturers are working on technology that can deliver INO via compact canisters suitable for ambulatory use. GeNO (Cocoa, Florida) is developing a device that generates NO via a chemical reaction from liquid NO_2 and that can provide INO for up to several days from a container that fits in a fanny pack.

INO has an established role as a testing agent for pulmonary vasoreactivity, but its role as a therapeutic agent in either acute or chronic pulmonary hypertension remains to be established. It is used frequently for acute pulmonary hypertensive crises, but without evidence to demonstrate efficacy beyond acute vasodilator effects. For longer-term out-patient applications, it could be used as an add-on therapy that has the potential to improve pulmonary hemodynamics and gas exchange without adversely affecting systemic blood pressure, but we await further investigations on this application.

Sildenafil

Oral sildenafil, approved by the FDA in 2007 for Group 1 PAH, inhibits phosphodiesterase 5, thereby increasing intracellular cGMP levels. Inhaled sildenafil has been tested in animal models. In one study using a lamb pulmonary hypertension model, inhaled sildenafil lowered the mean pulmonary arterial pressure as much as INO up to 20 ppm and had no significant effect on systemic blood pressure.[26] In addition, inhaled sildenafil had an additive effect with INO. Considering that oral sildenafil has relative pulmonary specificity and intravenous sildenafil is commercially available, it is unclear what additional role inhaled sildenafil would play in a clinical setting.

Other Possible Inhaled Therapies for Pulmonary Hypertension

Vasoactive Intestinal Peptide

Vasoactive intestinal peptide was discovered in 1970 by Dr Sami Said,[27] who spent the remainder of his career seeking therapeutic applications for the compound, including for pulmonary hypertension. Originally found in intestinal tissue, it has proved to be a potent systemic and pulmonary vasodilator. In a small cohort of 8 subjects with idiopathic PAH, inhaled vasoactive intestinal peptide showed very impressive favorable effects on pulmonary hemodynamics and exercise capacity.[28] Unfortunately, these promising findings have not been replicated. A more recent preliminary report showed no hemodynamic benefit in a cohort of subjects with PAH,[29] curbing enthusiasm for the drug.

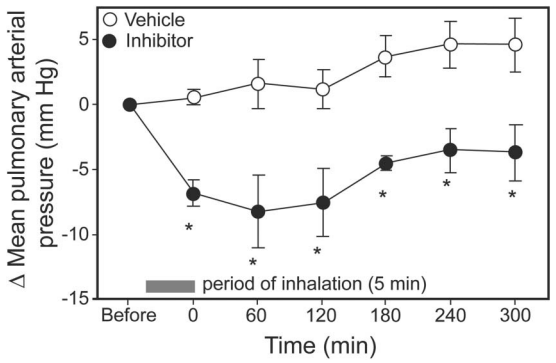

Fig. 4. Change in mean pulmonary arterial pressure after a 5-min inhalation of the Rho kinase inhibitor Y-27632 in rats with hypoxic pulmonary hypertension, with significant reductions lasting for > 4 h. * $P < .05$. Data from Reference 30.

Rho Kinase Inhibitors

Rho kinases are intracellular signaling molecules that regulate vasoconstriction and cell proliferation. They are activated by the RhoA protein after its activation by G protein-coupled receptors. Rho kinase then stimulates myosin light chain, leading to smooth muscle contraction.[30] Inhaled inhibitors of Rho kinase (Y-27632 and fasudil) potently reduced mean pulmonary arterial pressure in several rat models of pulmonary hypertension, virtually normalizing it in chronically hypoxic rats (Fig. 4).[31] These inhaled agents were more potent than INO and were devoid of the systemic hypotensive effects of the oral route of administration. Despite these promising results, these agents have not been tested in humans with pulmonary hypertension.

Tyrosine Kinase Inhibitors

One of the limitations of our current pulmonary hypertension armamentarium is that presently approved drugs act mainly as vasodilators and do not primarily target the pulmonary arterial remodeling characteristic of the disease. This leads to a treatment paradigm that is aimed at stabilization rather than regression of disease. In theory, if we can develop agents that inhibit molecular signaling pathways that regulate proliferation, we might make more progress in treating pulmonary hypertension. Tyrosine kinases such as platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor are signaling molecules that promote cell proliferation in the pulmonary vasculature. Inhibitors of these agents (tyrosine kinase inhibitors) are commercially available, mainly as cancer therapies, and several have been used to treat pulmonary hypertension. Imatinib, approved to treat chronic myelogenous leukemia, was tested in subjects in a randomized controlled trial and significantly improved 6MWD by 23 m in subjects with advanced disease.[32] Enthusiasm for the drug was dampened, however, by a very high dropout rate among subjects receiving active therapy and a high occurrence of subdural hematomas. These collateral effects were likely the result of the pleiotropy of the tyrosine kinase inhibitors, with disrupted signaling in multiple organs giving rise to multiple off-target adverse effects. Accordingly, the drug failed to slow clinical worsening and is unlikely to undergo further development as a possible pulmonary hypertension agent. However, other approaches aimed at inhibiting tyrosine kinases may prove to be promising, including the use of small molecules via the inhaled route to effect more specific inhibition and limit adverse effects on off-target organs.

Summary

Using the inhaled route to deliver therapeutic aerosols and gases to patients with pulmonary hypertension offers potential advantages, including better targeted therapy, that could be more effective, less toxic, and less expensive than other routes. Among available inhaled therapies for adults, INO is used mainly as a diagnostic agent or for short-term acute rescue therapy and has not been approved by the FDA for these applications. Two other therapies, iloprost and treprostinil, are prostacyclin analogues that are effective in improving exercise capacity and are FDA-approved for PAH. However, they have not been as widely used as oral PAH therapies because of limited efficacy and the need for frequent administration. Their usual application is fairly narrow: patients already on one or 2 background therapies who have not achieved desired therapeutic goals but have not deteriorated enough to require infusion prostacyclin therapy. Because it usually reduces systemic adverse effects, the inhaled route remains an attractive option for pulmonary hypertension therapy. We can expect future studies on the use of INO and a variety of other therapies, including targeted small molecules aimed at disrupting cell signaling pathways responsible for vascular constriction and remodeling.

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Discussion

Willson: Very nice presentation. You have this beautiful diagram of 3 different pathways to get to treatment of pulmonary arterial hypertension (PAH). Where does vasoactive intestinal peptide (VIP) fit in that?

Hill: Well, it doesn't fit into any of those pathways. I used that illustration because those are the pathways from which current agents are available, but the VIP pathway is a separate pathway that operates via its own VIP receptor. It has multiple effects, not just cardiovascular, but also gut motility and so forth, so it's a separate pathway. If you look at the diagram, it includes most currently known pathways that impinge on PAH in experimental models; it is daunting. Every month they come out with a new pathway, but we still have only the 3 main ones for our current agents.

*** MacIntyre:** Thanks, Nick. I don't deal with out-patient or even in-patient PAH patients much, but I do deal with postoperative cardiac surgery patients, and the explosive use of INO in my institution for these patients is not a modest cost at all—we're talking $3–4 million per year. Inhaled aerosolized epoprostenol is a viable alternative, and I find it very interesting that we have these 2 drugs in a very expensive market, both of them being used off-label and both of them technically non-reimbursable. Do you see either of these drugs ever going to clinical trials for this indication, or are we just going to be stuck with these off-label battles for the foreseeable future?

Hill: I think we're going to have off-label battles. As I mentioned, in the out-patient arena, there's promise, but in-patient…one of the arms of our study was to look at the acute vasodilator properties of INO versus epoprostenol in the postoperative setting. We got one of our cardiothoracic surgeons involved, and everybody was enthusiastic. Do you know how many subjects we enrolled in that arm? None! And it was because when it came to enrolling subjects, it was always "not this patient, they're too sick," and they wanted to use whatever they wanted to use. I think we're going to run into this problem with any study looking at postoperative subjects. These are also patients who tend to be bowls of fruit from the perspective of putting studies together because there are all kinds of different postoperative scenarios, so I think it's going to be really challenging to do that study.

*** MacIntyre:** I share your thoughts there, and I think it's a very interesting history lesson that INO got into the cardiac surgery unit many years ago because it could reduce pulmonary arterial pressures and was dirt cheap. We were buying it from a local welding company as a matter of fact, and nobody really cared about controlling use because it was so inexpensive and it seemed to work. People literally got hooked on it. Now equipoise is gone, and you're right, trying to do clinical trials on these drugs—unless you're comparing 2 different drugs head to head—I think will be extraordinarily difficult. I don't think anybody's going to put somebody in a placebo trial.

Berlinski: I just want to comment on the device aspect. There are 2 available devices, and I think there's definitely an unmet need for a portable device that will be convenient for patient use. The device used to deliver inhaled treprostinil prostacyclin [therapy] is large. You have to carry a bag with all the parts, and when you assemble it, it takes like 15 parts. It's not an easy task. It's an ultrasonic device, so you add the water, then the cap, then the medicine. The device is not breath-triggered, which is a limitation, and releases the aerosol for 3 seconds at regular intervals. The device used to deliver iloprost has some positive qualities, such as guiding the patient into the appropriate breathing mode to optimize intrapulmonary deposition. I think that aspect needs to be kept in future development, and maybe issues regarding positioning the device and making it easier would probably be an answer to having a better device. There's definitely an unmet need from the device perspective.

Hill: I appreciate those comments from somebody who knows more about the technical aspects than I do, but I couldn't agree with you more based on the feedback I get from patients.

DiBlasi: With regard to devices, I find it particularly interesting that a lot of the drugs you've mentioned in your excellent presentation really are provided with these breath-actuated nebulizers or something that's actuated by a clinician, and it may work wonderfully in these spontaneously breathing patients, but what about when they need to be intubated? We can't use these devices in line because they're large and heavy and unable to synchronize and nebulize with the inhalation of the mechanical ventilator or patient. So what are we left with at that point? Do you have anything to say about that? What type of nebulizers do you use? Just because these drugs are approved with these devices, it doesn't necessarily mean that we can deliver these drugs effectively to intubated patients.

Hill: The only agents that we use at my institution and that I have any experience with are INO, which you can give fairly easily through the appropriate setup in a ventilator, and inhaled epoprostenol, which we've given using the Aeroneb. It's extremely important with inhaled epoprostenol to use a device that delivers the drug reliably in terms of dose and consistency. We have found that the Aeroneb, which uses vibrating mesh technology, works pretty well. When you're giving an intravenous infusion, the concentration of the drug in the solution relative to the concentration in the blood is extremely high, and you're going at very low infusion rates. Just a drop or 2 in excess will make a patient extremely toxic for a while because of overdosing. So with inhaled, you need something that's very reliable, or you risk both under- and overdosing. We have worked this out with our ventilator systems; we administer the aerosolized medication downstream from the humidifier and then place a filter proximal to the exhalation circuit of the ventilator to prevent accumulation of drug, which can damage the exhalation circuitry. It works pretty well. I have no experience with inhaled iloprost, although there are reports of its use via ventilators in the literature. I could find no mention of treprostinil being administered via a ventilator. I think the inhaled epoprostenol approach is fine for patients on mechanical ventilation,

and I don't see that you really need to go to these other formulations because if it's continuous, who cares? They're on a mechanical ventilator, so they're not going anywhere. Once they're extubated, though, you could switch to one of the other agents.

Restrepo: A very nice presentation. My question is that you showed several outcomes that were driven basically by hemodynamic changes and some physiological changes, like walking more, 6MWD, and so on. What do you think is the future in terms of the outcomes that we need to be measuring for these patients? Because maybe you can improve 6MWD, but it doesn't mean that these patients are surviving longer. Based on the data we have on lung transplantation, these patients definitely aren't getting transplanted anymore because some of them get better. What is the future in terms of outcomes?

Hill: You're asking a question that goes well beyond just aerosolized therapy and relates to every agent we use to treat PAH. This has been a hot topic for quite some time. The problem is that we have an orphan disease, we don't have a lot of patients out there, and we have a number of different agents we want to test. Most experts would agree that using survival as a main outcome variable is probably unrealistic because there just aren't enough patients, and there isn't enough time. Instead, studies use combined outcomes, and you may be aware that when the macitentan randomized controlled trial[1] was published, the authors used the term "morbidity and mortality." They didn't actually show any mortality benefit in the trial, but mortality was in their combined end point. The end point included hospitalization, need to add therapy, transplant, death, and then clinical deterioration, which is largely dependent on a decrease in 6MWD. There was a 43% reduction in the occurrence of these morbidity events in this trial; the main driver was clinical deterioration due mainly to a drop in 6MWD, seen in 80% of those with events. So even though people say, "Oh, the 6MWD is no good, we don't want to rely on it anymore as an outcome variable," we're still relying on it as an outcome variable. So this study suggests that patients don't deteriorate as rapidly on PAH drugs, and it seems likely that we're prolonging survival. Some long-term observational studies suggest that average survival is now 6–7 years, up from 3 years when the National Institutes of Health registry was done during the early 1980s, when pharmacotherapies were unavailable. I think that, in the future, we need to have outcomes that get more at the pathophysiology of the disease, some kind of indicator that would work like a biopsy of the lungs so you could look at structural changes. It might be possible with some of the imaging techniques that are used today, for example, molecular labeling with magnetic resonance imaging. So we may get to something like that in the future. Survival by itself, though, I don't see as a realistic outcome.

Restrepo: With all these different pathways and all these different alternatives, are you expecting to see more combination studies that work in different parts of the pathways? And how will these combinations may be impacted by the economics of the issue of implementation in the real world?

Hill: This is an issue that's been kicked back and forth in the field, and it again has to do with the limited resources we have. There are a few combination trials out there that show certain combinations are beneficial. Epoprostenol, for example, was combined with sildenafil and showed a 26-m improvement in 6MWD. There is one very interesting trial known as the AMBITION Trial. The results should be available by the end of the summer. It's the combination of upfront tadalafil and ambrisentan, the phosphodiesterase 5 inhibitor and the endothelin receptor antagonist, respectively, versus each one alone. So it's a 3-armed trial, with no placebo, but it will be very interesting to see whether the upfront combination gives better outcomes. They're using an event-driven design similar to what I described for macitentan. There's a limited number of these trials you can do because they take large numbers of patients and several years to complete, so you have to be very selective about what exactly it is that you want to test. I personally think that we need to look beyond the agents we have and get at more fundamental cellular mechanisms. I also think the inhaled route offers one of the ways we can get around the issues we've had with systemic toxicity.

Hess: I think the issue of appropriate clinical outcomes also applies to the use of these agents in the ICU for mechanically ventilated patients. So we don't have evidence for INO that it improves outcomes other than that it improves physiology, perhaps, for a short period of time. It may drop the pulmonary arterial pressure, and it may make the P_{aO_2} a little better, but we don't have any evidence that patients are more likely to survive. So now we have moved from one unproven agent, INO, to another, inhaled epoprostenol. And what is driving that is cost. I think that some clinicians have gotten confused where they now believe that inhaled epoprostenol is a good thing (maybe it is, and maybe it isn't). I don't think the appropriate studies have been done to know that, and I think we need to recognize that the only reason we are using inhaled epoprostenol instead of INO is because one is really expensive, and the other one is cheaper.

*** MacIntyre:** And, just to re-emphasize, the only reason we ever used INO in adults is because it makes the numbers look better for a short period of time without any impact on any meaningful outcomes.

Hill: I couldn't agree with you more. When this issue comes up, I always recall a study published by Bhorade et al[2] in the Blue Journal about 12 years ago in which the authors administered INO to a group of subjects with what they termed acute right-heart syndrome. What's interesting about this trial is that they divided subjects into NO responders (who had a good hemodynamic response) and nonresponders. Well, guess who had the higher mortality rate by far? The responders. This is reminiscent of the ARMA Trial,[3] too, where the high-stretch group had better oxygenation within the first few days, but had the higher mortality. It may well be a similar phenomenon here that the acute vasodilator response may not be very meaningful when it comes to later outcomes. Also, I didn't mention the withdrawal problem with INO, meaning that blood pressure and gas exchange can become unstable when you stop INO, but it can be a big issue as well.

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