Pharmacodynamics and Pharmacokinetics of Inhaled Iloprost, Aerosolized by Three Different Devices, in Severe Pulmonary Hypertension*

Horst Olschewski, MD, PhD; Beate Rohde, MD; Jürgen Behr, MD, PhD; Ralph Ewert, MD, PhD; Tobias Gessler, MD; H. Ardeschir Ghofrani, MD; and Thomas Schmehl, PhD

Background: **Inhalation of iloprost, a stable prostacyclin analog, is an effective therapy for pulmonary hypertension with few side effects. This approach may, however, be handicapped by limitations of currently available nebulization devices. We assessed whether the physical characterization of a device is sufficient to predict drug deposition and pharmacologic effects.**
Methods: **We investigated the effects of a standardized iloprost aerosol dose (5 μg; inhaled within approximately 10 min) in 12 patients with severe pulmonary hypertension in a crossover design employing three well-characterized nebulizers. The nebulizers use different techniques to increase efficiency and alveolar targeting (Ilo-Neb/Aerotrap [Nebu-Tec; Elsenfeld, Germany], Ventstream [MedicAid; Bognor Regis, UK], and HaloLite [Profile Therapeutics; Bognor Regis, UK]). Measurements were performed using a Swan-Ganz catheter and determination of arterial iloprost plasma levels.**
Results: **During inhalation of iloprost, the pulmonary vascular resistance decreased substantially (baseline, approximately 1,250 dyne·s·cm^{-5}; decrease, − 35.5 to − 38.0%) and pulmonary artery pressure decreased substantially (baseline, approximately 58 mm Hg; decline, − 18.4 to −21.8%), whereas the systemic arterial pressure was largely unaffected. Cardiac output and mixed venous and arterial oxygen saturation displayed a marked increase. The pharmacodynamic profiles with the three devices were superimposable. Moreover, rapid entry of iloprost into the systemic circulation was noted, peaking immediately after termination of the inhalation maneuver, with very similar maximum serum concentrations (158 pg/mL, 155 pg/mL, and 157 pg/mL), and half-lives of serum levels (6.5 min, 9.4 min, and 7.7 min) for the three nebulizers, respectively. Interestingly, the "half-life" of the pharmacodynamic effects in the pulmonary vasculature (*eg*, decrease in pulmonary vascular resistance, ranging between 21 and 25 min) clearly outlasted this serum level-based pharmacokinetic half-life.**
Conclusions: **A standardized dose of aerosolized iloprost delivered by different nebulizer types induces comparable pharmacodynamic and pharmacokinetic responses. Pulmonary vasodilation, persisting after disappearance of the drug from the systemic circulation, supports the hypothesis that local drug deposition largely contributes to the preferential pulmonary vasodilation in response to inhaled iloprost.** ***(CHEST 2003; 124:1294–1304)***

Key words: iloprost; nebulization device; pulmonary hypertension

Abbreviations: ANOVA = analysis of variance; AUC = area under the serum level-time curve; AUCt0-tlast = area under the serum level-time curve calculated from the start of inhalation to the last sampling time point; Cmax = maximum serum concentration; NO = nitric oxide; PAP = pulmonary artery pressure; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; Sa_{O_2} = arterial oxygen saturation; SAP = systemic artery pressure; Sv_{O_2} = mixed venous oxygen saturation; SVR = systemic vascular resistance

Primary pulmonary hypertension (PPH) is a severe disabling disease with a poor prognosis.[1] Long-term infusion of prostacyclin was the first therapy shown to be lifesaving in a controlled study,[2] and such efficacy may also exist for patients with the scleroderma spectrum of diseases,[3] and other diseases associated with severe pulmonary arterial hypertension.[4,5] However, this approach is hampered by the lack of pulmonary selectivity of the vasodilatory effect of prostacyclin causing systemic side effects such as pain and systemic hypotension,[6] by ventilation-perfusion mismatch in predisposed patients,[7–9] as well as by infectious complications due to the continuous use of an IV line.[6] Inhalation of

nitric oxide (NO) is selective for the lung vasculature, but its pulmonary vasodilatory potency is lower than that of prostacyclin,[10–12] and interruption of NO inhalation may provoke a rebound hypertensive crisis due to the very short half-life of this agent.[13,14]

As an alternative approach, repetitive aerosol delivery of iloprost, a stable prostacyclin analog, has been used to treat pulmonary hypertension and proved to be efficacious in a double-blind, placebo-controlled study.[15] In PPH and other forms of precapillary pulmonary hypertension, it was demonstrated that nebulized iloprost decreases pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP), concomitant with an increase in cardiac output, in the absence of significant systemic arterial pressure drop and ventilation-perfusion mismatch.[9,16–18] Rescue administration of inhaled iloprost was undertaken in progressive right-heart failure due to severe pulmonary hypertension,[19,20] and currently available data from a 2-year study with iloprost aerosolization suggest beneficial long-term effects with minor side effects.[21]

The aerosol approach is, however, handicapped by limitations of the currently available nebulization devices. Substantial loss of the aerosolized drug in the device is a common finding, resulting in major and possibly variable differences between the dose delivered into the device, the nebulized dose, and the inhaled dose. Droplet size and aerosol concentration during the inhalation phase may determine the extent and the site of pulmonary drug deposition, and thus on delivery of the inhaled agent to the pulmonary vasculature.

In the present study, we investigated the pharmacokinetics and the pharmacodynamic effects of inhaled iloprost in patients with severe pulmonary hypertension. Three different jet nebulizers manufactured for alveolar drug delivery were employed. The first, coupled with a reservoir for alveolar targeting (Ilo-Neb/Aerotrap; Nebu-Tec; Elsenfeld, Germany) has been widely employed in long-term iloprost nebulization including the open-label, 2-year study in Germany.[21] Due to the reservoir, this device is relatively large. Additionally, considerable amounts of aerosol are deposited inside the device, resulting in an efficiency (inhaled dose/filling dose) of only approximately 13%. The second nebulizer uses the Venturi effect to boost aerosol production during inspiration (Ventstream; MedicAid; Bognor Regis, UK) and is much smaller as it does not need a reservoir, but loses efficiency due to internal drug deposition and high filling volumes (efficiency approximately 15%). The third nebulizer employs a microchip technique for delivery of an aerosol pulse during the first half of the inhaled tidal volume, and was used in the pivotal trial showing clinical efficacy of inhaled iloprost.[15] It combines increased efficiency (approximately 25%) with exact aerosol dosing independent of the breathing pattern (HaloLite; Profile Therapeutics; Bognor Regis, UK).

The dosing regimen for each nebulizer was adjusted to deliver a total amount of 5 μg of iloprost to the respiratory tract of the patients (calculated for entry at mouthpiece) during an inhalation maneuver lasting approximately 10 min, based on preceding biophysical characterization of these devices.[22] Following such a standardized procedure, the pharmacodynamic effects of inhaled iloprost were found to be virtually superimposable for all devices tested. Moreover, this was also true for the kinetics of iloprost appearance and disappearance in the systemic circulation in response to its aerosol delivery. Interestingly, the serum levels of inhaled iloprost declined much more rapidly than the pulmonary vasodilatory effect, which suggests prolonged local vasorelaxant potency of the aerosolized agent not reflected by the time course of serum levels.

Materials and Methods

Patients

A total of 12 patients (aged > 18 years) with PPH or secondary pulmonary hypertension were enrolled in the study. The patients had been treated for at least 3 months with six iloprost inhalations per day in three experienced German centers for pulmonary hypertension. Only patients who were known to respond to iloprost inhalation with a decrease of PVR of at least 20% were included. Patients with renal or severe hepatic impairment, thromboembolic disease, bleeding disorders, significant restrictive or obstructive lung diseases, pulmonary venous hypertension, and diseases directly affecting the pulmonary vessels, according to the new diagnostic World Health Organization classification,[23] were excluded from the study. The patients gave written informed consent before participation in the trial. The study protocol was reviewed and approved by the local ethics committees of the participating centers.

*From the Department of Internal Medicine (Drs. Olschewski, Gessler, Ghofrani, and Schmehl), Justus-Liebig-University, Giessen; Schering AG (Dr. Rohde), Berlin; Ludwig-Maximilians-University (Dr. Behr), Munich; and Deutsches Herzzentrum (Dr. Ewert), Berlin, Germany.
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Drs. Olschewski, Gessler, and Schmehl are consultants for Schering AG and NebuTec Company. Dr. Rohde is an employee of Schering AG.
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Correspondence to: Horst Olschewski, MD, PhD, Department of Internal Medicine II, University Hospital, Klinikstrasse 36, D-35392 Giessen; Germany; e-mail horst.olschewski@innere.med.uni-giessen.de

Nebulizing Devices

Three different jet nebulizer systems were used: (1) Ilo-Neb combined with the Aerotrap reservoir, and the Pulmocar Akku compressor (Sanesco Medizintechnik; Vienna, Austria); (2) Ventstream combined with the Freeway Lite compressor (MedicAid); and (3) HaloLite. On the basis of preceding *in vitro* characterization of the aerosols delivered by each device,[22] the volume of the iloprost solution to be filled into the nebulizer and the concentration of the iloprost solution were adjusted for each device to provide a total dose of 5 μg of iloprost delivered at the mouthpiece within a comparable time span. The physical characteristics of the nebulizers and the dose regimens are depicted in Table 1. Accordingly, the inhalation time was defined to be 12 min and 10 min for the IloNeb and the Ventstream nebulizers, respectively. In contrast, the nebulization time of the HaloLite system is not prefixed, because this device stops automatically when the inhalation of the prescribed dose is completed. The basis of this system is a breath-by-breath measurement and summing up of the total inhaled quantity. Inhalation times for the HaloLite nebulizer were thus variable, depending on the breathing pattern of the patient, with an average of approximately 11 min. The iloprost solution administered with the nebulizer was prepared immediately before use, according to written detailed dosing instructions.

Study Conduct

A randomized, open-label, multicenter, crossover trial design was used with six sequences, three treatments and three periods (also known as Williams design). Each patient was randomly assigned to one of the six possible sequences of treatments. The iloprost aerosol (total dose of 5 μg at the mouthpiece) was administered by three subsequent inhalations using the three different devices in randomized order. Every treatment was followed by a washout time of 2 h. All treatments were administered on a single day during a previously scheduled right-heart catheterization. For safety reasons, the following inhalation stop criteria were defined: (1) decrease of mean systemic BP to < 65 mm Hg or by $> 10\%$ of baseline for at least 2 min, (2) decrease of arterial oxygen saturation (Sa_{O_2}) by $> 5\%$ for at least 2 min, (3) severe headache, and/or (4) local intolerability of the aerosol.

Before inhalations were started, a Swan-Ganz catheter (Baxter Edwards; Deerfield, IL) and an arterial line were inserted. A fiberoptic thermodilution pulmonary artery catheter was used for measuring PAP, pulmonary artery wedge pressure, central venous pressure, and cardiac output. The arterial line was used for continuous measurement of systemic arterial pressure (SAP) and drawing arterial blood samples for blood gas analysis and measurement of iloprost serum levels. For assessment of Po_2, Pa_{O_2}, and Pa_{CO_2}, as well as Sa_{O_2} and mixed venous oxygen saturation (Sv_{O_2}), venous and arterial blood samples were withdrawn at baseline, at end of inhalation, and 30 min, 60 min, and 120 min after the end of inhalation. Hemodynamics and drug concentrations were measured simultaneously. Additionally, hemodynamics were assessed 5 min and 15 min after the end of inhalation, and drug concentrations were measured 2 min, 5 min, and 15 min after the end of inhalation.

Measurement of Iloprost Concentrations

Serum levels of iloprost were measured using a specific and sensitive radioimmunoassay with a quantitation limit of 25 pg/mL. The assay was validated using human samples and gas chromatography coupled with mass spectrometer as an alternative analysis procedure.[24]

Pharmacokinetic Evaluation

Pharmacokinetic parameters were obtained from the individual serum level-time curves using the TOPFIT program, Version 2.1 (Goedecke AG, Schering AG, Thomae GmbH; Freiburg, Germany). Maximum serum concentration (Cmax) and time to reach Cmax were directly taken from the data. The area under the serum level-time curve (AUC) was calculated according to the linear trapezoidal rule from the start of inhalation to the last sampling time point (AUCt0-tlast), which was calculated with concentrations above the limit of quantitation (AUCt0-tlast) and the partial area from the last sampling time point to the respective next sampling time point for which the concentration was set at zero. This method of extrapolating AUC was chosen because AUC measured at the start of inhalation to infinity could not be obtained in all cases due to the rapid decrease of iloprost serum levels after the end of inhalation. In assessments with quantifiable iloprost serum levels in the last blood sample of treatment periods 1 and 2, only AUCt0-tlast could be calculated and was used for subsequent statistical evaluation. Patient 11 was excluded from evaluation of treatment 2 (Ventstream device) because no drug exposure was achieved due to a technical problem during inhalation.

For further characterization of the pharmacokinetics of inhaled iloprost, the half-life ($t_{1/2}$) of the iloprost serum level decrease was calculated by means of regression analysis of the mean serum level-time curve between the end of inhalation and 30 min after end of inhalation in a semilogarithmic plot (λ = slope of regression line): $t_{1/2} = 2/\lambda$. Accordingly, the "half-life" of the pharmacodynamic effect was calculated, employing the iloprost-induced decrease in PVR. Calculation was performed by means of regression analysis of the time curves of absolute changes of PVR compared to baseline between the time point of maximum effect and 30 min after end of inhalation in a semilogarithmic plot (λ = slope of regression line): $t_{1/2} = 2/\lambda$.

Table 1—*Baseline Characteristics of the Different Nebulization Devices: Related Dosing Regimens**

Characteristics	Ilo-Neb	Ventstream	HaloLite
In vitro characteristics of nebulizing devices (tidal volume 0.67 L, 15 cycles per min)			
Particle size (MMAD), μm	3.5	3.8	4.3
Mass flow (output rate of the nebulizer), μL/min	28	65	62
Dosing regimens for delivery of 5 μg of iloprost at the mouthpiece			
Iloprost concentration of the inhalation solution, μg/mL	15	8	10
Volume filled into the inhalation device, mL	4	5	2.5
Inhalation time, min	12	10	approximately 11†

*MMAD = mass median aerodynamic diameter.
†Delivered according to the breathing pattern of the patient (average inhalation time of approximately 11 min in the present study).

Statistics

The target variables were the maximum percentage changes in the hemodynamic variables in response to iloprost inhalation and the pharmacokinetic variables Cmax and AUC. Analysis of variance (ANOVA) for a mixed linear model using fixed effects (period, treatment, and first-order carryover) as well as random subject effect was performed to compare the target variables. Two-sided tests and confidence intervals were adjusted for three multiple comparisons according to Tukey-Kramer. The multiple significance (confidence) level was set at 0.05 (0.95) for each target variable. There was no adjustment for multiple end points.

Results

Nine female and four male patients (aged 26 to 71 years) were included in the study. Twelve of them completed the trial. One male patient was prematurely withdrawn due to an exclusion criterion that became evident immediately after start of the first treatment (mean SAP < 65 mm Hg). Eleven of the 12 patients had PPH, and 1 patient presented with isolated pulmonary hypertension with CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia without lung fibrosis or major inner organ involvement). Body weight ranged between 41 kg and 86 kg.

In 33 of 36 inhalation maneuvers, the aerosolization was entirely finished; in three cases, it was stopped prematurely (although close to the predefined end of inhalation) due to a decrease in mean systemic BP by > 10% of baseline for > 2 min. The patients did not experience any subjective adverse events.

Iloprost inhalation caused an average PVR decrease of 35.5 to 38.0% compared to baseline, with a maximum effect either immediately at the end of inhalation, or within 5 min (Table 2, Fig 1). The PVR decrease was paralleled by an average decrease in mean PAP of 18.4 to 21.8%, and an average increase in cardiac output of 30.6 to 37.1%. The SAP showed only some marginal decrease, while systemic vascular resistance (SVR) changes were noted in parallel with the changes in cardiac output (Fig 2, *top*, *A*, and *center*, *B*; Table 2). The PVR/SVR ratio indicated a more pronounced effect of iloprost inhalation on the PVR than on the SVR (Fig 2, *bottom*, *C*).

Heart rate was not significantly changed (data not given), and no relevant arrhythmia was noted. The mean Sa_{O_2} and mean Sv_{O_2} increased in response to iloprost inhalation (Fig 3; Table 2). A critical decrease in Sa_{O_2} (> 5% compared to baseline) did not occur in any patient.

Iloprost serum levels became rapidly detectable with all three devices employed (Fig 4). Serum concentrations reached a maximum either at the end of inhalation or within the following 5 min (Fig 4; Table 2). Beyond 30 min after the end of inhalation, quantifiable serum levels of iloprost were detected in only 3 of the 12 patients. Cmax and AUC values were comparable using the different nebulizers (Table 2). After reaching an early concentration peak, iloprost serum levels rapidly decreased with a half-life of 6.5 to 9.4 min (Table 3). In contrast, the half-life of the pharmacodynamic effect, as calculated from the PVR decrease, ranged between 21 min and 25 min.

When statistical analysis (ANOVA) was applied to the hemodynamic and pharmacokinetic responses to iloprost inhalations performed with the different devices, no significant differences between the devices were revealed, except for a slightly more pronounced SAP decrease shortly after iloprost inhalation using the HaloLite compared to the IloNeb system (Table 4). However, this was not associated with any typical complaints and not considered clinically significant in any case.

The iloprost aerosol administration was well tolerated by the patients irrespective of the nebulization device employed. Minor adverse events such as transient headache and flush were noted with similar frequencies with all devices: headache occurred in 4 patients, 3 patients, and 4 patients following inhala-

Table 2—*Maximum Hemodynamic Effects, Cmax, and AUC After Inhalation of Iloprost Using Different Nebulization Devices

Effects	Ilo-Neb (n = 12)	Ventstream (n = 12)	HaloLite (n = 12)
Maximum PVR change, %	− 36.4 ± 4.8	− 36.9 ± 3.9	− 38.0 ± 4.9
Maximum mean PAP change, %	− 21.8 ± 3.9	− 18.5 ± 3.8	− 20.7 ± 3.9
Maximum cardiac output change, %	30.6 ± 7.7	33.3 ± 7.0	36.2 ± 10.0
Maximum Sv_{O_2} change, %	19.2 ± 5.6	14.1 ± 6.1	22.2 ± 9.1
Maximum mean SAP change, %	− 2.3 ± 2.2	− 3.0 ± 2.8	− 7.8 ± 2.4
Maximum SVR change, %	− 17.0 ± 4.7	− 18.8 ± 7.0	− 24.6 ± 5.7
Cmax, pg/mL	158 ± 20	155 ± 20†	157 ± 18
AUC, pg/h/mL	49.0 ± 9.9	54.2 ± 13.6†	47.8 ± 10.2

*Data are presented as mean ± SEM.
†n = 11.

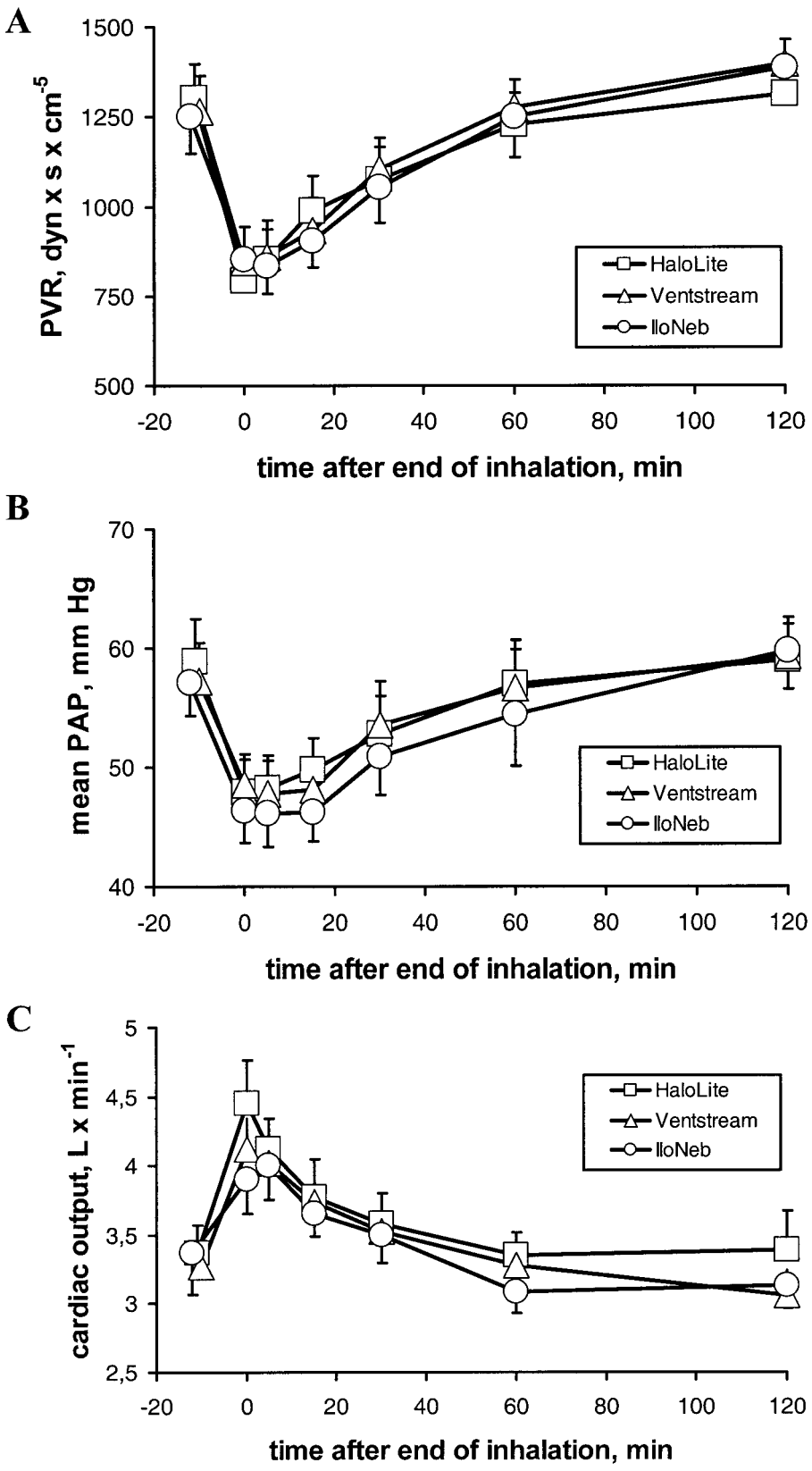

FIGURE 1. Time course of pulmonary hemodynamic variables in response to iloprost inhalation. In 12 patients with severe pulmonary hypertension, 5 μg of iloprost was inhaled employing three different nebulization devices. Time was set at zero at the end of the inhalation maneuver. Data are given as mean ± SEM.

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