Aerosolized Iloprost Customized for the Critically Ill

Keith W Harris DO, Thomas G O’Riordan MD, and Gerald C Smaldone MD PhD

BACKGROUND: Aerosolized iloprost, an inhaled synthetic analogue of prostacyclin, is an approved therapy for stage III and IV pulmonary hypertension. However, currently iloprost is delivered via a device that requires a clinically stable patient who can use a hand-held nebulizer. We designed separate aerosol delivery systems to nebulize iloprost to critically ill patients during (1) mechanical ventilation and (2) spontaneous breathing that requires a high fraction of inspired oxygen. The goal was to deliver doses similar to the currently approved high-efficiency I-neb nebulizer system. METHODS: For the intubated patient we used the high-efficiency AeroTech II jet nebulizer and a breath-actuated ventilator circuit, without humidification. For spontaneous breathing, our delivery system consisted of a Pulmanex Hi-Ox disposable oxygen mask and an AeroTech II nebulizer. With a nebulizer charge of 20 μg, the drug presented to the patient (inhaled mass) was captured on a filter and analyzed using radioactivity (technetium-99m). The accuracy of the radiolabel was quantified by directly measuring iloprost with high-performance liquid chromatography and comparing the results. A cascade impactor measured particle distribution. RESULTS: A line of identity confirmed that the radiolabel accurately represented the drug. The mean ± SD inhaled mass was 6.02 ± 0.87 μg (n = 5) on the ventilator and 3.77 ± 0.46 μg (n = 5) during spontaneous ventilation. The mass median aerodynamic diameter and fine-particle fraction were 0.7 μm, 0.99, and 0.7 μm, 0.99, respectively. CONCLUSIONS: Clinically effective doses of iloprost can be delivered to patients who require high-flow oxygen or mechanical ventilation. Key words: pulmonary arterial hypertension, hypoxemia, iloprost. [Respir Care 2007;52(11):1507–1509. © 2007 Daedalus Enterprises]

Introduction

Pulmonary arterial hypertension can be effectively treated with aerosolized iloprost (Ventavis, CoTherix, San Francisco, California), which is an inhaled synthetic analogue of prostacyclin.1,2 The aerosol is approved for delivery via a hand-held nebulizer, the I-neb (Respironics, Cedar Grove, New Jersey). The usual delivered dose (approximately 5 μg) is generated from a 20-μg vial (15 μg is deliberately discarded within the device). The I-neb, however, is not designed for use with mechanical ventilation or with high concentrations of oxygen. We designed aerosol delivery systems for these applications, studied the systems in vitro, and compared the results to published data for iloprost delivery with the I-neb.

Methods

To quantify aerosolized iloprost we established the accuracy of the radiolabel, technetium-99m. First, a measured quantity of technetium-99m activity was added to a 20-μg vial of iloprost. Then, precise amounts of the radioactive solution were separated via pipette into separate glass flasks (range 1–20 μg), and each was filled to 30 cc with assay buffer (33% methanol). Radioactivity and time were recorded, and a predicted amount of drug was determined based on a percentage of the initial iloprost vial. The samples were analyzed via high-performance liquid chromatography (Cardinal Health method ATM-CTB-M0001.01, Respironics [UK] Ltd, Chichester UK). The amount of drug predicted by radioactivity was plotted...
against the high-performance liquid chromatography results. Data are shown in Figure 1. The line of identity is closely approximated.

We designed 2 configurations to measure the amount of aerosolized iloprost delivered to a critically ill patient. The first system simulated an intubated patient. This configuration combined a high-efficiency nebulizer (AeroTech II, CIS-US, Bedford, Massachusetts) with a breath-actuated ventilator circuit without humidification (Fig. 2). The circuit was completed with a ventilator test lung (Michigan Instruments, Grand Rapids, Michigan). A patient’s average pattern of breathing was represented with a pressure-control setting of 24 cm H₂O, positive end-expiratory pressure of 10 cm H₂O, inspiratory time of 3 s (inspiratory-expiratory ratio 1.5:1.0), respiratory rate of 12 breaths/min, and 100% oxygen. The ventilator used was an Evita 2 (Dräger, Telford, Pennsylvania). The nebulizer was charged with 20 μg of iloprost (a standard dose) and run to completion. Droplets of aerosolized iloprost were radiolabeled with technetium-99m. The particles that exited the endotracheal tube were captured by the filter and measured in a well counter. Aerodynamic particle distribution was measured via cascade impactor placed between the ETT and the inhaled mass filter.

For the severely hypoxic, spontaneously breathing patient, we attached an AeroTech II nebulizer to a Pulmanex Hi-Ox disposable oxygen mask (Viasys Healthcare, Conshohocken, Pennsylvania). This circuit provides simultaneous high-flow oxygen and aerosol therapy to the patient. The delivery system was positioned on an adult mannequin head with a filter placed behind the mouth and connected to a piston pump to simulate spontaneous breathing (Fig. 3). The pump was set to a respiratory rate of 20 breaths/min, a tidal volume of 500 mL, and a duty cycle of 0.5. Once again, the nebulizer was charged with 20 μg of iloprost and run to completion. The same methods were used to radiolabel the droplets. This process was also repeated 5 times. A cascade impactor was also used in this
Table 1. Drug Delivery and Aerodynamic Diameter of Iloprost Aerosols

<table>
<thead>
<tr>
<th>Ventilation Type</th>
<th>Inhaled Mass (µg) (n = 5)</th>
<th>MMAD (µm) (n = 1)</th>
<th>FPF (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
<td>6.02 ± 0.87</td>
<td>0.7</td>
<td>0.99</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>3.77 ± 0.46</td>
<td>0.7</td>
<td>0.99</td>
</tr>
<tr>
<td>I-neb published data</td>
<td>4.8–5.2</td>
<td>2.1</td>
<td>0.82</td>
</tr>
</tbody>
</table>

MMAD = mass median aerodynamic diameter  FPF = fine-particle fraction

Results

The mean ± SD iloprost delivery was 6.0 ± 0.9 µg (n = 5) while intubated and 3.8 ± 0.5 µg (n = 5) during spontaneous ventilation (Table 1). The mass median aerodynamic diameter (MMAD) and fine-particle fraction were also measured for both the ventilator and face mask experiments (MMAD 0.7 µm and fine-particle fraction 0.99 for both systems). Table 1 also lists reported values for the I-neb.

Discussion

Iloprost is currently approved in the United States for treatment of stage III or IV pulmonary arterial hypertension. The drug is delivered by the I-neb (formerly the Prodose), which is designed for the spontaneously breathing patient and therefore not compatible with mechanical ventilation. Further, the closed inhalation mouthpiece does not facilitate high-flow oxygen supplementation. However, the I-neb incorporates a computer algorithm (Adaptive Aerosol Delivery) that provides control of drug delivery and ensures the inhalation of a clinically effective dose reported to range from 4.8 µg to 5.2 µg. Conventional nebulizers cannot reliably provide dose control in that narrow range. Our bench data demonstrate that by optimizing the ventilator circuit and spontaneous breathing apparatus a similar amount of drug can be delivered to a critically ill patient in these clinical situations. Though we did not test individual factors (eg, type of ventilator, breathing pattern, humidification) that determine delivery of iloprost, we used our experience with in vitro and in vivo delivery of aerosolized antibiotics to design our system for intubated patients. We have previously shown that choice of nebulizer, breath actuation, and discontinuance of humidification are key factors for antibiotics, and we applied those principles to the present study. Based on our findings and our experience with antibiotics, it is unlikely that aerosol delivery will vary considerably with other breathing patterns, as long as the nebulizer, nebulizer actuation, and humidification are controlled.

Our data indicate that the particle distributions for both the ventilator and spontaneous breathing apparatus are ideal for deep lung deposition (see Table 1). Our MMADs are smaller than those reported for I-neb. It is likely that this observation results from various factors, but the AeroTech II MMAD is representative of previous values measured in our laboratory for the AeroTech II nebulizer. Both the I-neb and AeroTech II distributions are in the so-called “respirable range,” but it is possible that deposition in patients who use the AeroTech II will be more peripheral in the lung. Anecdotally, the aerosols described in our bench study were well tolerated in a single patient with severe pulmonary hypertension and hypoxia. That patient was treated compassionately with aerosolized iloprost, with the systems described in this paper.

Conclusions

Though there have been other prostacyclin therapies described in the literature, including case reports of intubated cardiac surgery patients who received iloprost for post-surgical pulmonary hypertension, none of those reports measured delivered drug or described the delivery circuits in detail. Furthermore, the use of iloprost concurrently with high-flow oxygen has not been described. Iloprost is currently not approved for the aforementioned applications. Our in vitro data are not supported by formal clinical investigations. We have simply demonstrated that a comparable amount of drug to the approved nebulizer can be delivered when measured in the laboratory.

REFERENCES