Pulmonary Administration of Gentamicin During Liquid Ventilation in a Newborn Lamb Lung Injury Model

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ABSTRACT. Objectives. Newborns with pulmonary infection frequently present with acute lung injury leading to ventilation/perfusion abnormalities in which intravenous delivery of antibiotics to the lung can be suboptimal. Tidal liquid ventilation (TLV) has been shown to be an effective means for delivering drugs directly to the pulmonary system. The objective of this study was to compare, with lung injury, antibiotic delivery achieved by conventional techniques (gas ventilation and intravenous gentamicin) with that using pulmonary administration of drug (PAD) during TLV.

Methods. Twelve newborn lambs with an acid lung injury were randomized to receive gentamicin either intravenously during gas ventilation or via PAD during TLV using LiquiVent (Alliance Pharmaceutical Corporation, San Diego, CA, and Hoechst-Marion Roussel, Bridgewater, NJ) perfluorochemical. Gentamicin (5 mg/kg) was administered over 1 minute, and serum levels were obtained at 15-minute intervals. Arterial blood gases and pulmonary mechanics were measured. Ventilation efficiency index and arterial/alveolar oxygen ratio were calculated. Lung-tissue gentamicin levels were measured 4 hours after administration and corrected to dry weight.

Results. Serum gentamicin levels were similar in both groups. Lung gentamicin levels (µg/g) were significantly higher for TLV. Also, TLV resulted in significantly more of the total delivered dose in the lung after 4 hours. Ventilation efficiency index and arterial/alveolar oxygen ratios were significantly higher for TLV.

Conclusions. In this lung injury model, both methods achieved equivalent serum gentamicin levels with higher lung levels using PAD during TLV. This study suggests that TLV may provide an effective vehicle for gentamicin delivery in infants with severe pulmonary infection and ventilation/perfusion abnormalities. Pediatrics 1997; 100(5). URL: http://www.pediatrics.org/cgi/content/full/100/5/e5; perfluorochemical, liquid ventilation, gentamicin, newborn, lung injury, pulmonary administration of drug, antibiotic, intratracheal.

ABBREVIATIONS. IV, intravenous; LV, liquid ventilation; PFC, perfluorochemical; PAD, pulmonary administration of drug; TLV, tidal liquid ventilation; GV, gas ventilation; PaO2, arterial partial pressure of oxygen; Ce, dynamic lung compliance; Fio2, fraction of inspired oxygen; MAP, mean arterial (blood) pressure; VEI, ventilation efficiency index; a/A, arterial/alveolar (oxygen ratio); PaCO2, partial pressure of carbon dioxide; Po2, partial pressure of oxygen; V/Q, ventilation/perfusion.

Newborn infants with pulmonary infection frequently present with an acute lung injury leading to ventilation and perfusion abnormalities. In the presence of irregular pulmonary perfusion, intravenous (IV) delivery of antibiotics to the lung can be less than optimal. However, the circulation is currently the only viable route by which to attack pulmonary infections.

Direct delivery to the pulmonary system can be effective for several types of drugs by utilizing aerosolization or direct endotracheal tube delivery. For example, bronchodilators1,2 and many resuscitation drugs3 are effectively delivered in this way. More recently it has been proposed that nebulization may be a preferable route of delivery for corticosteroids4 and diuretic5,6 therapy in the neonate. However, the need for higher drug doses, problems related to particle size, and distribution of drug to the lung periphery can hinder the effectiveness and/or usefulness of this type of drug delivery.7–10

Liquid ventilation (LV), while providing a revolutionary mode for respiratory support, has also been shown experimentally to be an effective alternative means for drug administration.11–13 For example, priscoline and gentamicin have been delivered to the uninjured lung of full-term animals and preterm animals with respiratory distress syndrome more effectively in this way as compared with IV administration.11,13 Some of the same physical properties that enable perfluorochemical (PFC) liquids to behave as a medium for total respiratory support make them advantageous for pulmonary administration of drugs (PAD). Biochemical inertness precludes any interaction with the drug, low surface tension enhances distribution of the drug, and high respiratory gas solubility supports gas exchange during delivery of the drug. Also, with the ability of PFC LV to improve ventilation-perfusion matching,14 drug exposure to the circulation is optimized and therapeutic serum drug levels can be achieved.

Pulmonary infection is a common malady seen in the intensive care nursery. It can be seen in prema-
ture infants with immature defense mechanisms, infants requiring ventilatory support, and infants who have prolonged hospitalization. These infants may benefit not only from LV, but also from direct PADs, particularly antibiotics.

In this study we evaluated and compared serum uptake and lung uptake and distribution of gentamicin using PFC as a vehicle for pulmonary drug delivery during tidal liquid ventilation (TLV) as compared with that of conventional IV administration during gas ventilation (GV) in the lung-injured newborn lamb. We hypothesized that an equal dose of gentamicin delivered to the injured newborn lung via PAD during TLV would result in similar serum levels and higher lung tissue levels compared with IV administration during GV.

METHODS

Animal Preparation

Twelve full-term newborn lambs (mean weight, 4.8 ± 0.35 kg; <1 week of age) were studied and managed according to the National Institutes of Health Regulations and the Guiding Principles in the Care and Use of Animals of the American Physiological Society. The study was performed with the approval of the institutional animal care committee. Animals were anesthetized with sodium pentobarbital (20 to 30 mg/kg). Arterial and venous catheters were placed in the carotid artery and jugular vein. The trachea was cannulated with a 5.0 Hi-Lo Jet (Mallinckrodt Medical, St Louis, MO) endotracheal tube. This tube has a side-port catheter at midlength that was used to administer the drug during TLV. This port was also used for airway pressure measurement during LV. Lambs were paralyzed with pancuronium bromide, 0.1 mg/kg/h, and ventilation was supported with using a Harvard Small Animal Ventilator (Harvard Apparatus, Inc, South Natick, MA). Anesthesia was maintained using sodium pentobarbital (10 mg/kg/h).

Experimental Procedures and Protocol

Lung Injury

A lung injury model was created in newborn lambs to cause pathophysiological perturbations experienced by infants including: 1) pulmonary hypoperfusion secondary to hypoxia and pulmonary hypertension, and 2) maldistribution of ventilation attributable to consolidation and pulmonary edema. This injury was intended to produce a situation of severe ventilation-perfusion mismatch simulating the lung condition of the newborn with pneumonia, adult respiratory distress syndrome, or neonatal respiratory distress syndrome complicated by pneumonia. Saline was acidified using hydrochloric acid to achieve a pH in the range of 1.6 to 1.8. This solution was warmed to 37°C and used to lavage the lung. The fluid was instilled by gravity using approximately 20 cm H₂O pressure to fill the lung, and immediately after instillation, gravity was used to empty the lung. Serial lavages (10 mL/kg/lavage) were performed to establish an injury defined as a 50% decrease from baseline of both empty the lung. Serial lavages (10 mL/kg/lavage) were performed to

GV (n = 6)

GV was achieved using a volume-limited gas ventilator at a breathing frequency of 50 to 60 breaths/minute and pressures of ≤40/8 cm H₂O and FIO₂ = 1.0.

In both groups, ventilation strategy was adjusted as dictated by arterial blood gas data obtained to achieve the best possible gas exchange. Infusion of sodium bicarbonate or THAM (trisethanamine, Abbott Laboratories, Chicago, IL) was used to correct metabolic acidosis. Dopamine and dobutamine (≤20 µg/kg/min) were used if necessary to maintain mean arterial blood pressure (MAP) values >50 mm Hg.

Drug Delivery

Gentamicin sulfate (5 mg/kg) was diluted with normal saline to a total volume of 5 mL. During GV, this dose was administered via continuous IV injection for 1 minute. During TLV, this dose was administered intratracheally via the midlength catheter port of the endotracheal tube in five 1-mL bolus aliquots during each inspiratory, directly into the PFC liquid stream, throughout five consecutive tidal breaths. This multiple bolus technique was used in an attempt to enhance mixing of the drug with the inspiratory PFC liquid stream while duplicating the delivery time of the IV administration. Lambs were studied for 4 hours postgentamicin administration.

Measurements

Arterial pressure was measured (Statham P23Db transducer and Hewlett Packard [Andover, MA] cardiorespiratory monitor-Model 78910A) and arterial blood gases (Radiometer [Copenhagen, Denmark] ABL 330) were obtained throughout the study. Dynamic lung compliance measurements (PEDS Lab, Medical Associated Services, Hatfield, PA) were performed during GV. Ventilation efficiency index (VEI) and arterial-alveolar (a/A) ratios were calculated to normalize for variations in different ventilation strategies and relate ventilatory support to alveolar ventilation, and to assess oxygenation requirements, respectively.

VEI was determined as previously described:19

\[ \text{VEI} = \frac{V_A}{\Delta P \times f} \]  \hspace{1cm} (1)

where \( \Delta P = P_{\text{insp}} - P_{\text{exp,f}} \) is ventilator rate and \( V_A = \frac{V_{CO2}}{P_{alveolar}/760 \text{ mm Hg}} \).

Assuming \( V_{CO2} \) (CO₂ production) as 5 mL/kg/min, then \( V_A = \frac{3800}{P_{alveolar}} \). Therefore,

\[ \text{VEI} = \frac{3800}{\Delta P \times f \times P_{alveolar}} \]  \hspace{1cm} (2)

Note that normal VEI = 0.3 mL/mm Hg/kg, a/A ratio was determined as:

\[ \frac{P_{alveolar}}{V_{alveolar}} \]  \hspace{1cm} (3)

where

Alveolar \( P_{CO2} = [P_{FIO2} \times (P_{atm} - P_{H2O})] \)

\[ \frac{P_{\text{PAO2}}}{R} + \frac{P_{\text{Paco2}} \times F_{\text{IO2}} \times (1 - R)}{R} \]  \hspace{1cm} (4)

\( P_{\text{Fio2}} \) is inspired oxygen concentration, \( P_{atm} \) is atmospheric pressure (760 mm Hg), \( P_{H2O} \) is water vapor pressure (47 mm Hg), \( R \) is respiratory exchange ratio, and \( P_{\text{Paco2}} \) is the partial pressure of carbon dioxide in the alveolus, which is assumed to be equal to the partial pressure of carbon dioxide in the blood.

For \( R \) equal to 1.0, Equation 4 reduces to the following:

\[ \frac{P_{\text{alveolar}}}{{P_{\text{Fio2}}} - P_{\text{H2O}}} - P_{\text{Paco2}} \]  \hspace{1cm} (5)

Note: Water vapor pressure is not considered during TLV because water and water vapor are not miscible with PFC.

Gentamicin Assays

Blood samples for gentamicin assay were obtained before administration of gentamicin and at 15-minute intervals after the administration of gentamicin throughout the study. The blood was collected in glass tubes without anticoagulant and allowed to clot. The tubes were centrifuged and the serum removed for assay.

At the end of each experiment, heart and lungs were block-dissected. Using the main pulmonary artery, the pulmonary vasculature was perfused with 200 mL of normal saline to remove residual intravascular blood. Individual lobe weights were obtained. Representative sections of each lobe of the lung were dissected (five to eight sections/lobe using a predetermined lung
matrix), weighed, and homogenized in 15 mL of a buffered phosphate solution (pH 7.4). The homogenate was centrifuged and the supernatant assayed for gentamicin.

Assay of gentamicin levels in both serum and tissue was performed using a fluorescent polarization method. Tissue levels were normalized to dry lung weight. Large airways were not included in lung samples. The absolute gentamicin concentration for each lobe was then used to calculate a percentage representing the fraction of the total gentamicin dose that was delivered to each lobe.

Data Analysis

Results are presented as mean ± SE. Values for CL and PaO₂ before and after injury were compared using one-way analysis of variance. Gentamicin blood and tissue levels and blood gas data were analyzed using two-way analysis of variance to evaluate differences as a function of time and method of administration. Statistical differences were analyzed further using a Bonferroni post hoc. A P value ≤.05 indicated statistical significance.

RESULTS

Lung Injury

Figures 1A and B show preinjury and postinjury CL and PaO₂ measurements. Preinjury values for CL and PaO₂ were not significantly different between groups. A total of two to seven lavages were required to cause a 50% decrease in CL and at least a 50% decrease in PaO₂ with this injury. Approximately 75% of the lavage fluid was recovered. Similar decreases in both CL and PaO₂ were attained for both groups of animals. One animal in the GV group died 3 hours after gentamicin was given.

Gas Exchange and Blood Pressure

Mean values (±SE) for VEI and a/A ratio throughout the time for both groups are presented in Table 1 and Table 2. Postinjury values for VEI (GV, 0.078 ± 0.017; TLV, 0.072 ± 0.017) and a/A ratio (GV, 0.13 ± 0.034; TLV, 0.22 ± 0.063) were not significantly different between groups. Animals supported with TLV after injury had significantly higher a/A ratios (P < .001) and VEI values (P < .001) as compared with those supported with GV. There was no significant difference in either a/A
ratios or VEI values as a function of time for either group.

After the injury, vasopressors and/or volume boluses were necessary in most animals to maintain MAP values greater than 50 mm Hg. The mean MAP values during the time after injury for each group were: GV = 57.3 ± 2.44 mm Hg; TLV = 56.5 ± 3.46 mm Hg. There was no significant difference between MAP for the two groups throughout this time. In addition, there was no difference in the amount of vascular support between groups.

Gentamicin Serum Levels

Figure 2 shows the serum gentamicin levels obtained as a function of time. Serum levels were highest at 15 minutes after gentamicin administration and were not significantly different between delivery modes. There was a progressive, significant, and comparable decline in mean serum drug level throughout time in both groups. The mean serum value at 15 minutes after administration for all animals was 10.1 ± 1.44 μg/mL and after 4 hours was 3.0 ± 0.197 μg/mL. In the GV group, 15 minutes after IV administration, mean serum level was 12.2 ± 1.45 μg/mL, and after 4 hours was 2.7 ± 0.22 μg/mL. In the TLV group, mean serum level was 8.0 ± 2.31 μg/mL after 15 minutes and 3.3 ± 0.287 μg/mL after 4 hours.

Gentamicin Lung Tissue Levels

Table 3 summarizes intralobar and whole lung tissue gentamicin levels 4 hours after drug administration for each group of animals. During TLV, administering gentamicin via PAD resulted in significantly higher (P < .01) mean lung tissue concentrations for the entire lung as compared with IV administration with GV.

Figure 3 depicts the distribution of lung tissue gentamicin levels expressed as a percentage of the total delivered drug in the lung 4 hours after administration. Gentamicin concentrations seem to be relatively higher in the right lung compared with the left lung when using PAD during TLV. However, this difference did not reach statistical significance.

**DISCUSSION**

The results of this study demonstrate that pulmonary administration of an equal dose of gentamicin during TLV is an effective means to achieve higher
Using PAD when compared with IV administration.\textsuperscript{13} Immature lamb with respiratory distress during TLV lung in the full-term lamb and to the lung of an can be more effectively delivered to the uninjured
tissue. Aminoglycosides protect lung epithelial cells against

TABLE 3. Gentamicin Lung Tissue Levels (\(\mu g/g\))\textsuperscript{*}

<table>
<thead>
<tr>
<th>Lung Lobe</th>
<th>Intravenous Administration (Gas Ventilation)</th>
<th>Pulmonary Administration (Total Liquid Ventilation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial apical</td>
<td>16.9 ± 2.3</td>
<td>38.8 ± 15.2</td>
</tr>
<tr>
<td>Right upper</td>
<td>21.8 ± 2.9</td>
<td>42.1 ± 13.6</td>
</tr>
<tr>
<td>Right middle</td>
<td>17.7 ± 3.3</td>
<td>53.9 ± 18.7</td>
</tr>
<tr>
<td>Right lower</td>
<td>14.6 ± 1.2</td>
<td>30.2 ± 8.3</td>
</tr>
<tr>
<td>Left upper</td>
<td>16.4 ± 3.3</td>
<td>25.7 ± 8.3</td>
</tr>
<tr>
<td>Left lower</td>
<td>18.5 ± 2.6</td>
<td>18.6 ± 2.9</td>
</tr>
<tr>
<td>Mean</td>
<td>17.7 ± 1.1</td>
<td>34.9 ± 5.0</td>
</tr>
</tbody>
</table>

\textsuperscript{*} These gentamicin levels (mean ± SE) in lung tissue, expressed as micrograms of gentamicin per gram of dry lung across lobes, compare levels following intravenous administration during gas ventilation with those following pulmonary administration of drug during tidal liquid ventilation.

\(\dagger\) \(P < .005\), pulmonary administration of drug versus intravenously.

(approximately 2 times) lung tissue gentamicin levels in the injured newborn lung 4 hours after dosing compared with conventional IV administration during GV, while achieving comparable and therapeutic serum levels. A significantly greater percentage (approximately 5 times) of total drug administered after PAD was found in the lung after 4 hours compared with that achieved with IV administration. Concomitantly, PAD with TLV resulted in lung tissue levels 10 times that of serum levels 4 hours after dosing. Furthermore, TLV demonstrated more effective respiratory support for this injury model compared with conventional GV.

Improved delivery of an antibiotic to the injured or infected lung using pulmonary delivery is of great clinical importance. In the intensive care nursery setting, the concern for and presence of pulmonary infection is ubiquitous. It can be seen in infants requiring ventilatory support, premature infants with immature defense mechanisms, and infants who have prolonged hospitalization. These infants may benefit not only from LV, but also from PFC facilitated delivery of drugs, particularly antibiotics.

Selection of an antibiotic depends on the sensitivity of the microorganism. Those infections caused by Gram-negative bacilli often require use of an aminoglycoside. Gentamicin is a widely used aminoglycoside in the newborn intensive care setting as the clinician is often interested in treating or covering for infections produced by \textit{Escherichia coli}, \textit{Klebsiella pneumoniae}, \textit{Pseudomonas} sp, or \textit{Serratia} sp. Also, gentamicin may be used to act synergistically with ampicillin against certain Gram-positive infections.

Previous work has demonstrated that gentamicin can be more effectively delivered to the uninjured lung in the full-term lamb and to the lung of an immature lamb with respiratory distress during TLV using PAD when compared with IV administration.\textsuperscript{13} That is, lung tissue gentamicin levels were significantly higher after PAD. Also, pulmonary distribution of drug was similar with both modes of administration. Given the ventilation/perfusion (V/Q) disturbances that exist with pulmonary infections in the newborn as well as in those neonatal conditions predisposing to pulmonary infection, the effectiveness of this mode of therapy compared with conventional therapy needed to be evaluated in an injured newborn lung model. This is the first study to look at pulmonary administration of an antibiotic during LV using an injured lung model.

For the neonate with respiratory tract infection, successful treatment depends not only on immune defenses both systemically and locally, but also on the ability of therapeudic intervention to optimize the delivery of an appropriate antimicrobial agent to the site of infection in concentrations that exceed those needed to inhibit bacterial growth. For intraparenchymal lung infections, monitoring of serum antibiotic levels can closely approximate antibiotic concentrations in alveolar and interstitial fluids.\textsuperscript{21} However, these measurements may not imply adequate therapy for pneumonia. Many pneumonias represent a mixture of purulent tracheobronchitis plus parenchymal infection. The intubated patient in particular can have large areas of infected respiratory tissues in the airways, far from alveolar and interstitial fluids. Consequently, serum antibiotic levels may be misleading in assessment of the adequacy of antibiotic delivery.

The concept of a blood-bronchus barrier has been used to describe the problems of antibiotic delivery into the respiratory tract.\textsuperscript{21} Parenteral antibiotics are often associated with low antimicrobial activity in bronchial secretions.\textsuperscript{22} Pennington\textsuperscript{21} studied gentamicin in bronchial secretions and found that 1 hour after IV infusion, bronchial levels were approximately 45% of serum levels and that these levels may not reach the minimum inhibitory concentration required by the pathogen involved. In addition, an antibiotic that reaches bronchial secretions can be inhibited by local conditions of inflammation.\textsuperscript{23–25} These circumstances can demand high serum levels that carry associated renal toxicity and otoxicity. The fact that it is difficult to permeate the respiratory system with IV gentamicin is of particular concern in the presence of consolidated pulmonary infection with associated V/Q abnormalities and decreased pulmonary perfusion to affected parenchyma. Concern escalates for the neonate in this situation who is further compromised by an immature immune response. It is intriguing to consider direct pulmonary delivery.

For many types of drugs, direct endotracheal tube administration is an approved delivery mode, especially for naloxone, atropine, diazepam, epinephrine, and lidocaine.\textsuperscript{3} Endotracheal tube administration often requires the use of higher drug doses (compared with IV),\textsuperscript{8} which can create airway irritation and interfere with gas exchange.

Aerosolization, compared with endotracheal delivery, may allow the use of less drug and may yield more uniform distribution, but efficacy still depends on peripheral delivery.\textsuperscript{10,26} Bronchodilators are routinely nebulized to the pulmonary system, however, antibiotic solutions are more viscous than water or saline and thus more difficult to nebulize.\textsuperscript{3} Experimental and clinical data support the delivery of antibiotics to the respiratory tract.\textsuperscript{25,27–30} In addition, there is evidence that direct pulmonary exposure to aminoglycosides protects lung epithelial cells against
oxidant injury. Aerolized aminoglycosides have yielded inconsistent yet encouraging results for patients with cystic fibrosis. Ramsey et al. have shown safety and efficacy with short-term administration of aerosolized tobramycin in stable cystic fibrosis patients using 1800 mg/day, which can be up to 5 to 10 times the IV dose. A prevailing problem when evaluating the usefulness of aerosol therapy is the estimation of the dose of medication actually delivered to the patient’s lungs, which depends on many variables including nebulizer type and output, particle size, and patient breathing pattern. In addition, the presence of uneven distribution of ventilation attributable to severe airway obstruction or mucus hypersecretion can further limit the usefulness of aerosols and prevent them from reaching the appropriate receptor sites in the lung. Poor peripheral lung delivery with aerosolization is reflected in very low serum aminoglycoside levels.

Using TLV to deliver gentamicin to a newborn lung with profound V/Q abnormalities, we have shown significantly higher lung tissue concentrations as well as therapeutic serum levels comparable to those obtained with the same dose administered intravenously. The distribution of drug across lung lobes seems relatively uniform for IV delivery and seems relatively higher in the right lung for PAD during TLV. Although not reaching statistical significance, this trend may be the result of subtle differences in animal position during delivery or perhaps attributable to subtle differences in the flow mechanisms during delivery given that an aqueous drug solution is not dissolved in the PFC liquid during delivery. Future development of a suitable emulsion/suspension of drug in PFC may improve the distribution pattern of pulmonary drug delivery during TLV.

With regard to the total delivered dose of gentamicin, the data (Fig 3) reveal that by 4 hours the majority of drug delivered by either technique has ultimately been delivered to the systemic circulation. As the antibiotic is continually cleared from the circulation, the antibiotic concentration within the lung after PAD should likewise be continually declining as the antibiotic follows the concentration gradient from the lung into the circulation. Because equal doses were given and yielded comparable serum levels throughout time with significantly different lung levels, we speculate that drug exposure to tissues other than the lung may be less after PAD. Further studies would need to define the pharmacokinetics involved with this type of drug delivery, particularly with regard to lung levels throughout time. PAD delivery of an antibiotic for pulmonary infection may allow decreased dose and/or increased dosing interval, which in turn may decrease systemic exposure and the risk of associated toxicities.

Although all newborns with pulmonary infections will not require mechanical ventilation, those who do may sometimes be served by TLV, and in those cases, PAD delivery of antibiotics seems to offer the advantage of higher lung tissue levels than those of IV. Whether the higher lung tissue levels of gentamicin that we have demonstrated can affect on the morbidity and mortality of these infants beyond that of TLV remains to be seen.

We believe that in the injured lung with ventilation and perfusion abnormalities, TLV can provide improved distribution of ventilation and improved pulmonary blood flow providing not only superior ventilatory support, but also a mode for improved antibiotic delivery, resulting in higher drug levels in the injured lung. Newborns with severe ventilation and perfusion abnormalities may not only benefit from TLV, but in the presence of pulmonary infection, may benefit from this unique method for pulmonary administration of antibiotic.
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