Peridosing Effects of Surfactant Administration: Treating the Lung Without Harming the Brain

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Disclosure Statement

Dr. Blood’s laboratory has performed preclinical testing of lucinactant (Surfaxin®) for Discovery Laboratories, Inc.
Objectives

- Determine factors that determine the uniformity of surfactant distribution within the lung.
- Identify the effects of surfactant administration on various physiological parameters (brain perfusion and oxygenation).
- Relate the factors which determine pulmonary surfactant distribution to peridosing physiological effects.
Introduction

• One goal of surfactant replacement therapy is to achieve uniform distribution of the surfactant throughout the lung

• Uneven distribution can result in:
  – Volutrauma and barotrauma in the alveoli that receive the surfactant
  – Underutilization of untreated alveoli
Factors Affecting Surfactant Distribution

- Volume instilled
- Rate of instillation
- Surfactant composition and viscosity
- Gravity (infant positioning)
- Ventilation parameters
- Maintenance of positive airway pressure

Two Phases of Surfactant Distribution
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1. Liquid plug propagation
Two Phases of Surfactant Distribution

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Two Phases of Surfactant Distribution

1. Liquid plug propagation

2. Dissipation along surface tension gradients
Two Phases of Surfactant Distribution

1. Liquid plug propagation
2. Dissipation along surface tension gradients
Lack of Liquid Plug
Lack of Liquid Plug
Lack of Liquid Plug
Lack of Liquid Plug
Effect of Tracheal Liquid Plug

- Isolated rat lungs
- Surfactant + radiopaque tracer
- Continuous X-ray video
- Instillation w/ or w/out tracheal liquid plug

# Current Doses and Protocols

<table>
<thead>
<tr>
<th></th>
<th>Survanta® <em>(beractant)</em></th>
<th>Curosurf® <em>(poractant alfa)</em></th>
<th>Infasurf® <em>(calfactant)</em></th>
<th>Surfaxin® <em>(lucinactant)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total phospholipid</strong></td>
<td>100 mg/kg</td>
<td>200 mg/kg</td>
<td>105 mg/kg</td>
<td>174 mg/kg</td>
</tr>
<tr>
<td><strong>Total volume</strong></td>
<td>4 ml/kg</td>
<td>2.5 ml/kg</td>
<td>3 ml/kg</td>
<td>5.8 ml/kg</td>
</tr>
<tr>
<td><strong>Number of aliquots</strong></td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td><strong>Volume/aliquot</strong></td>
<td>1 ml/kg</td>
<td>1.25 ml/kg</td>
<td>1.5 ml/kg</td>
<td>1.45 ml/kg</td>
</tr>
<tr>
<td><strong>Position</strong></td>
<td>Head and foot inclinations, right and left side dependence</td>
<td>No inclination, right and left side dependence</td>
<td>No inclination, position to right and left dependence AFTER instillation</td>
<td>Head inclination, right and left side dependence</td>
</tr>
<tr>
<td><strong>Ventilation</strong></td>
<td>Manual ventilation</td>
<td>40-60 breaths/min</td>
<td>Small bursts with each breath</td>
<td>Mechanical ventilation; PEEP 4-5 cm H₂O</td>
</tr>
</tbody>
</table>
Effect of Instillation Rate

- Intact adult rabbits
- Poractant alfa
- Single bolus = 4 ml/kg over 10 sec
- Infusion = 4 ml/kg over 45 min

Effect of Bolus Volume

- Intact preterm lambs
- Repositioned right/left side between each bolus
- 100 mg/kg beractant

Effect of Volume

- Intact adult rabbits
- 100 mg/kg bovactant
- Single bolus

Effect of Volume

- Intact adult rabbits
- Bovine surfactant
- 5 ml dose was 0.5 ml every 2 min for 20 min
- 50 ml dose was 2.5 ml every 2 min for 40 min

Effect of Maintaining PEEP

- Premature rhesus newborns
- 200 mg of radiolabeled lucinactant
- Two boluses of 2.5 ml/kg
- With or without Bodai adapter to maintain PEEP

So Then More Is Better, Right?

Wait a sec…
What about acute effects on cerebral perfusion?
Possible Acute Effects of Surfactant on Cerebral Perfusion

- Transient hypercapnia-induced cerebral vasodilation
- Pulmonary vasodilation
  - Left-to-right shunt → Cerebral steal effect
- Increased lung volume → decreased venous return
- Pharmacologic
  - Vasoactive components in surfactant affect systemic/cerebral vascular tone?
### Acute Effects of Poractant Alfa on Blood Pressure and Cerebral Perfusion

<table>
<thead>
<tr>
<th></th>
<th>Increase</th>
<th>Decrease</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Arterial Blood Pressure</td>
<td>0</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cerebral Blood Flow Velocity</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Cerebral Oxygenation Status (NIRS)</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Low vs. High Dose Poractant

Internal carotid blood flow velocity

○ = low dose (1.25 ml/kg, n=13)
● = high dose (2.5 ml/kg, n=11)

(Doppler ultrasound)

Change in cerebral blood volume

● = high dose (2.5 ml/kg, n=8)
○ = low dose (1.25 ml/kg, n=5)

(Near infrared spectroscopy)


High vs. Low Dose Poractant

- Infants received initial doses of 100 mg/kg (n=1069) or 200 mg/kg (n=1099)
- No difference in incidence of intraventricular hemorrhage (16.0% in low dose vs 16.6% in high dose)
- High dose group had better oxygenation at 1, 12, and 36 hours

Effect on Cerebral Perfusion - Beractant (4 ml/kg)

14 newborn infants

Multicenter Comparisons of Surfactants With Varying Dose Volumes

Poractant (2.5 ml/kg) vs. Beractant (4 ml/kg)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Poractant Alfa 100 mg/kg (n = 96)</th>
<th>Poractant Alfa 200 mg/kg (n = 99)</th>
<th>Beractant 100 mg/kg (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH grade III–IV</td>
<td>9 (9%)</td>
<td>8 (8%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Infants ≤ 32 wk</td>
<td>(n = 85)</td>
<td>(n = 95)</td>
<td>(n = 90)</td>
</tr>
<tr>
<td>IVH grade III–IV</td>
<td>8 (9%)</td>
<td>7 (7%)</td>
<td>8 (9%)</td>
</tr>
</tbody>
</table>

Poractant (2.5 ml/kg) vs. Lucinactant (5.8 ml/kg)

<table>
<thead>
<tr>
<th>Neuro Scan abnormality</th>
<th>Odds Ratio (95% CI)</th>
<th>Lucinactant Rate (%)</th>
<th>Poractant Rate (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH (overall)</td>
<td>1.06 (0.55, 2.02)</td>
<td>38.7</td>
<td>37.9</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Low Volume vs. High Volume (Poractant vs. Lucinactant)

- Low Volume
  (poractant- 2.5 ml/kg)
- High Volume
  (lucinactant- 5.8 ml/kg)

Low Volume vs. High Volume (Poractant vs. Lucinactant)

6 preterm lambs (n= 6 per group)

- Low Volume (poractant- 2.5 ml/kg)
- High Volume (lucinactant- 5.8 ml/kg)

Low Volume vs. High Volume (Poractant vs. Lucinactant)

6 preterm lambs (n= 6 per group)

Conclusions

• Larger volume of surfactant bolus instillation results in more uniform distribution of the surfactant in the lung.

• There is no convincing evidence that the volume used in any current clinical formulations results in detrimental disturbances in cerebral perfusion.
Future Areas for Study

• Could we give more volume?
• What are the ideal ventilation parameters?
• How will aerosolized surfactant compare?
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QUESTIONS?

New Perspectives in the Management of Neonatal Respiratory Distress Syndrome

A free CE-accredited satellite symposium

Chair: Stephen Welty, MD; Texas Children’s Hospital
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