Recent Observations in Surfactant Pharmacology: Translational Impact for Neonatal Care

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Thomas Jefferson School of Medicine
Temple University School of Medicine

Hot Topics
Satellite Symposium

Recent Observations in Surfactant Pharmacology: Translational Impact for Neonatal Care

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Background

Kurt Von Neergaard (1929)

First Observations

Von Neergaard, 1929.

Disclosure

- I have disclosed the following financial relationship -
  - Discovery Laboratories, Inc. – Consultant

Background

- Kurt Von Neergaard (1929).
- Clements to Avery & Mead (1959) advanced the study of surface tension and tied this deficiency to RDS.
- Research on lung surface lining (surfactant) lead to a therapeutic intervention exogenous “surfactant replacement therapy (SRT)”.
- Laboratories studied the impact of animal-derived surfactants, which contain surfactant protein (SP-B) and foreign proteins that are potentially immunogenic.
- Other investigators explored the use of synthetic surfactants (controlled formulation and stability; reduce possible inflammatory responses to animal-derived materials and improve production and product availability).

SP-B-B

C. Cochrane

Simplified Peptide Structure
Recent Observations in Surfactant Pharmacology: Translational Impact for Neonatal Care

Preclinical Studies of Lucinactant (KL₄)

- Numerous preclinical studies have demonstrated that lucinactant has significant pharmacologic activity involving pulmonary surface tension-lowering ability, improving lung function and oxygenation comparable to commercially available pulmonary surfactants.

- Lucinactant has been shown to possess anti-inflammatory and anti-microbial activity, and is resistant to inhibition by plasma proteins and oxidants when compared with other surfactants.

Methods

- Exposed to hyperoxia for 24 or 72 hrs
  - 60% O₂
  - 5% CO₂

- ASF collected for protein analysis

- Cells harvested for histology and viability analysis

Physiologic Outcomes

**Cell Viability**

- Saline
- Lucinactant
- Beractant

**TER**

- Saline
- Lucinactant
- Beractant

Inflammatory Mediators

**IL-6**

- Saline
- Lucinactant
- Beractant

**IL-8**

- Saline
- Lucinactant
- Beractant

Methods

- Human airway epithelial cell culture
  - Calu-3 monolayers
  - Air-liquid interface

- Treated with
  - Normal Saline
  - Lucinactant (Surfaxin®, Discovery Labs, Inc.)
  - Beractant (Survanta®, Abbott Labs, Inc.)

Recent Observations in Surfactant Pharmacology: Translational Impact for Neonatal Care

**Aerosolized Lucinactant**
- Initial aerosol delivery studies focused on commercially available aerosol generators.
- After testing of these devices in the first aerosol lucinactant study in humans, it became apparent that these commercial devices were suboptimal.
- Engineering efforts were refocused on an alternate aerosol generator capable of delivering highly concentrated, aerosolized, active surfactant to patients in sufficient amounts for an efficacious response within a relatively short period of time.
- These efforts led to novel aerosol generation technology, the capillary aerosol generator (CAG). Characterization of pre- and post-aerosolization of the drug showed that CAG aerosolized lucinactant retained both its chemical composition and surface tension-lowering properties.

**Aerosolized lucinactant chromatographic profiles - pre and post-aerosolization**

**Dilution curve on PBS pre and post-aerosolization**

**Delivery of Aerosolized Medication to Ventilated Patients is Currently Quite Inefficient**
- Most research today is on improving aerosol generation, or emitted dose
- Higher losses of aerosol occurs during breathing cycle
- Only 1% of nominal dose is delivered to ventilated infants

**AFECTAIR improves aerosol entrainment into the ventilator bias flow**

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AFECTAIR improves aerosol entrainment into the ventilator bias flow


Aerosolized surfactants and RDS

Animal Models
Rey-Santano C et al., EPAS 2012.
Mielgo V et al., EPAS 2012.

Clinical

Summary to Date:

- Comparable surface tension activity.
- Controlled formulation consistency and stability.
- Improved production and product availability.
- Anti-inflammatory and antimicrobial activity.
- Resistant to inhibition by plasma proteins and oxidants when compared with other surfactants.
- Aerosol capability with non-invasive respiratory support.

Thank You!
Attempts to Minimize Invasiveness during the Acute Period: Where do we go from Here?

Jan Mazela
Poznan University of Medical Sciences, Poznan, Poland

Disclosure

• Consultant to Discovery Laboratories, Inc.
• Co-inventor of Afectair, aerosol delivery system owned by Discovery Laboratories, Inc.

Background

Surfactant therapy

Recommended
1. Surfactant therapy should be started from birth in all babies at risk of RDS, with those ≤32 weeks' gestation who do not have MV, until their clinical status can be assessed (A).

Mechanical Ventilation

Recommended
1. MV should be used to support babies when other methods of respiratory support have failed (B). Duration of MV should be limited to reduce plateau effect on lung (C).

Effective Perinatal Intensive Care in Europe: Translating knowledge into evidence-based practice
Attempts to Minimize Invasiveness during the Acute Period: Where do we go from Here?

Jan Mazela, M.D., Ph.D.

Management of neonatal respiratory failure in Europe

Jan Mazela, Mercedes Bonet, Aurélie Piedvache, Ole Pryds, Patrick Truffert, Pierre-Henri Jarreau, Jennifer Zeitlin

on behalf of the EPICE Research Group

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Exogenous Surfactant Therapy

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Alternative Strategies for Surfactant Administration

- Kribs et al developed direct catheter SRT in Germany (MIST=LISA):
  - placed on Single Nasopharyngeal (SNP) Tube and CPAP or IMV
  - small feeding tube placed below the cords
  - surfactant instilled slowly in synchrony with breathing
- Dargaville et al in Australia has described using an angiocatheter #16 passed through the cords an instilling surfactant at 1-3 cm below the cords
- RCT LMA trial on going but generally available in infants > 1200 g (Roberts K et al...)

Kribs, A et al, Acta Paediatr 2008; 97: 293
Dargaville et al, Neonatology 2012; 101: 326

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EPICE project

19 EU regions from 11 EU countries
Population based, prospective study with 2 year follow-up 2011-2012
All infants born between 22 and 31 weeks
Multidisciplinary teams:
obstetricians, pediatricians, epidemiologists, health care providers

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Surfactant administration

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LISA = MIST

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Attempts to Minimize Invasiveness during the Acute Period:
Where do we go from Here?

Jan Mazela, M.D., Ph.D.

LISA = MIST


Intubation still required...

Endotracheal Intubation Attempts During Neonatal Resuscitation: Success Rates, duration and Adverse Effects

- 62% of intubations were successful; consultants (86%), fellows (78%) & residents (24%).
- More senior doctors intubated more rapidly

49% of infants deteriorated during intubation attempts.
SpO2 fell by ≥ 10% in 12/25
HR fell by ≥ 10% in 4/25

O’Donnell CPF et al. Pediatr. 117 No. 1 January 2006, pp. e16-e21

Aerosolized surfactants – clinical studies

The only study utilized single naso-pharyngeal (SNP) tube for CPAP and aerosol delivery

<table>
<thead>
<tr>
<th>Surfactant Method</th>
<th>Population Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorch G Alveofact® Jet nebulizer 150 mg x 2 SNP tube CPAP</td>
<td>A-a O2 gradient, PCO2 &amp; Silverman score improved</td>
</tr>
<tr>
<td>Arroe M Exosurf® Side stream nebulizer prongs CPAP</td>
<td>23-36 wks No significant benefits</td>
</tr>
<tr>
<td>Berggren E Curosurf® Jet nebulizer IF CPAP</td>
<td>27-34 wks No significant benefits</td>
</tr>
<tr>
<td>Finer N Aerosurf® Aeroneb Pro® prongs CPAP</td>
<td>28-32 wks Procedure safe</td>
</tr>
</tbody>
</table>

QUESTION: Was the right patient interface used?
QUESTION: Was the right nebulizer used?

Mazela et al, Curr Opin Pediatr 2007; 19: 155

Multicenter pilot study of aerosolized KL₄ surfactant delivered via nCPAP (KL₄-CPAP-01 Phase 2A)

- Results:

| Adverse Experience During Initial Aerosol Dosing | Percentage (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen desaturation</td>
<td>4.5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4.3</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>3.8</td>
</tr>
<tr>
<td>Gastric distension</td>
<td>2.4</td>
</tr>
<tr>
<td>Nasal irritation</td>
<td>1.1</td>
</tr>
<tr>
<td>Apnea</td>
<td>0</td>
</tr>
</tbody>
</table>

Average reduction dispersion volume per treatment/EADF.

- Treatment safe – no SAE related to dosing
- No need for intubation related to treatment
- Nebulizer showed significant device to device variability in output rate – need to develop more reliable aerosol generator


CureNeb study

- Moderately preterm infants (29° – 33°), n=64 with FiO₂ = 0.22-0.3, < 4h of life
  - Poractant alfa (Curosurf, Chiesi)
    - 200 mg/kg 1st Dose (nominal during ~20 min.)
    - 100 mg/kg 2nd Dose if required after 12 h
  - VM (Pari e-Flow, PARI) nebuliser combined with bubble CPAP via face mask

Significant reduction in CPAP failure in 1st 72h

Pillow J, Minoschinski S, et al. PAS 2013
Attempts to Minimize Invasiveness during the Acute Period: Where do we go from Here?

Jan Mazela, M.D., Ph.D.

CureNeb study

Primary Outcome: Failed CPAP in 1st 72 h

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nebulised</th>
</tr>
</thead>
<tbody>
<tr>
<td>29-31w</td>
<td>13/19</td>
<td>11/21</td>
</tr>
<tr>
<td>32-33w</td>
<td>10/13</td>
<td>1/11</td>
</tr>
</tbody>
</table>

RR: 0.860 (0.399 to 1.854)  p=0.984
RR: 0.118 (0.178 to 0.784)  p=0.004

Primary Outcome: Failed CPAP in 1st 72 h

Ongoing clinical study phase II and III

- 26-32 wga on nCPAP:
  - Treatment group:
    - CAG with Afectair® for aerosol generation and delivery
    - KL4 surfactant
  - Control group: initial CPAP with standard approach

Take Home...

- Perinatal factors such as: cesarean section, presence of preeclampsia, low gestational age and Apgar score below 7 identify infants likely to experience nCPAP failure. When adjusted for center and region prenatal steroids and CPAP experience play a role as well
- INSURE is not influencing effectiveness of nCPAP when used as a rescue mode
- When using less invasive surf administration give Caffeine Citrate first!
- Bright future – aerosolized surfactant administration with optimized nebulizer, delivery system and patient interface
New Directions:
Respiratory Support in Neonates

Martin Keszler, M.D.
Professor of Pediatrics
Brown University
Women and Infants Hospital of Rhode Island

Rationale for Closed Loop Automatic Control

• NB respiratory function is labile
• Human response to perturbations is:
  – Inconsistent
  – Intermittent
  – Subject to bias
  – But adaptable and intelligent
• Automated systems are:
  – Consistent
  – Continuous
  – Objective
  – But rote, do not adapt and subject to artifact

Modalities of Closed Loop Control

• Automated FiO2 control
• Mandatory Minute Ventilation (MMV)
• Neutrally Adjusted Respiratory Assist (NAVA)
• Proportional Assist Ventilation (PAV)
• Volume targeted ventilation
  – VG
  – PRVC
  – VTV

Closed Loop O2 Control

Closed Loop Automated FiO2 Control
New Directions: Respiratory Support in Neonates

Martin Keszler, M.D.

Volume Guarantee
Principles of Operation

The PIP (“working pressure”) is servo-regulated within preset limits (“pressure limit”) to achieve VT that is set by the user. Regulation of PIP is in response to exhaled VT to minimize artifact due to ETT leak. Breath terminates if 130% of TVt, reached.

Benefits of VG
- Maintenance of (relatively) constant tidal volume
- Prevention of volutrauma and hypocapnia due to:
  - Surfactant administration
  - Lung volume recruitment
  - Clearance of lung fluid
- Automatic lowering of pressure support level during weaning
- Compensation for variable respiratory drive
  - stabilization of tidal volume and minute ventilation due to changes of respiratory drive (periodic breathing)

PLV vs. VTV Meta-analysis: Duration of MV

<table>
<thead>
<tr>
<th>Study</th>
<th>VTV</th>
<th>PLV</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Angio 2006</td>
<td>28±24</td>
<td>24±23</td>
<td>3.6 (3.1, 10.3)</td>
<td></td>
</tr>
<tr>
<td>Guven 2013</td>
<td>3.0±7</td>
<td>6.9±8</td>
<td>-3.9 (7.4, -0.5)</td>
<td></td>
</tr>
<tr>
<td>Keszler 2014</td>
<td>4.5±7</td>
<td>15±18</td>
<td>-11.1 (-24.8, 2.6)</td>
<td></td>
</tr>
<tr>
<td>Lista 2014</td>
<td>8.8±3</td>
<td>12.3±3</td>
<td>-3.5 (-5.1, -1.9)</td>
<td></td>
</tr>
<tr>
<td>Liu 2011</td>
<td>4.8±1</td>
<td>6.5±2</td>
<td>-1.7 (-2.5, -0.9)</td>
<td></td>
</tr>
<tr>
<td>Piotrowski 1997</td>
<td>6.7±5</td>
<td>13±15</td>
<td>-6.3 (-12.9, 0.3)</td>
<td></td>
</tr>
<tr>
<td>Singh 2016</td>
<td>8.4±13</td>
<td>9.7±14</td>
<td>-1.3 (-6.8, 4.2)</td>
<td></td>
</tr>
<tr>
<td>Sinha 1997</td>
<td>5.1±3</td>
<td>6.7±6</td>
<td>-1.6 (-4.0, 0.8)</td>
<td></td>
</tr>
<tr>
<td>Zhou 2007</td>
<td>9.3±2</td>
<td>9.8±2</td>
<td>-0.5 (-2.1, 1.1)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8.7±7.5</td>
<td>11.5±15.6</td>
<td>-2.0 (-3.1, -0.9)</td>
<td></td>
</tr>
</tbody>
</table>

PLV vs. VTV Meta-analysis: BPD

<table>
<thead>
<tr>
<th>Study</th>
<th>VTV</th>
<th>PLV</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Angio 2006</td>
<td>27/93</td>
<td>32/92</td>
<td>0.83 (0.55-1.27)</td>
<td></td>
</tr>
<tr>
<td>Duman 2012</td>
<td>3/23</td>
<td>7/22</td>
<td>0.41 (0.12-1.39)</td>
<td></td>
</tr>
<tr>
<td>Guven 2013</td>
<td>2/42</td>
<td>9/30</td>
<td>0.16 (0.04-0.68)</td>
<td></td>
</tr>
<tr>
<td>Keszler 2014</td>
<td>2/9</td>
<td>5/9</td>
<td>0.40 (0.10-1.55)</td>
<td></td>
</tr>
<tr>
<td>Lista 2014</td>
<td>3/30</td>
<td>4/23</td>
<td>0.57 (0.14-2.32)</td>
<td></td>
</tr>
<tr>
<td>Nafday 2005</td>
<td>2/16</td>
<td>4/18</td>
<td>0.56 (0.12-2.67)</td>
<td></td>
</tr>
<tr>
<td>Singh 2016</td>
<td>16/57</td>
<td>17/52</td>
<td>0.86 (0.49-1.52)</td>
<td></td>
</tr>
<tr>
<td>Sinha 1997</td>
<td>1/25</td>
<td>6/25</td>
<td>0.17 (0.02-1.29)</td>
<td></td>
</tr>
<tr>
<td>Zhou 2007</td>
<td>2/15</td>
<td>5/15</td>
<td>0.40 (0.09-1.75)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>58/310</td>
<td>89/286</td>
<td>0.61 (0.46-0.82)</td>
<td></td>
</tr>
</tbody>
</table>

PLV vs. VTV MAA: Other Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>No. of Subjects</th>
<th>RR (95% CI) or Mean diff (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any IVH</td>
<td>11</td>
<td>759</td>
<td>0.65 (0.42-0.99)</td>
</tr>
<tr>
<td>Cystic PVL</td>
<td>7</td>
<td>531</td>
<td>0.33 (0.15-0.72)</td>
</tr>
<tr>
<td>Grade 3-4 IVH</td>
<td>11</td>
<td>707</td>
<td>0.55 (0.39-0.79)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>8</td>
<td>595</td>
<td>0.46 (0.25-0.86)</td>
</tr>
<tr>
<td>Any hypocapnia</td>
<td>2</td>
<td>58</td>
<td>0.56 (0.33-0.96)</td>
</tr>
<tr>
<td>Failure of assigned mode</td>
<td>4</td>
<td>405</td>
<td>0.64 (0.43-0.94)</td>
</tr>
<tr>
<td>Length of suppl. Oxygen (d)</td>
<td>2</td>
<td>133</td>
<td>-1.68 (-2.510-0.88)</td>
</tr>
</tbody>
</table>
New Directions:
Respiratory Support in Neonates

The benefits of VTV cannot be realized without ensuring that the tidal volume is evenly distributed throughout an “open lung”!!!

Where does the air go with PPV?

Compliant chest wall
Limited muscle strength
C-section/absence of labor
Respiratory depression
Impaired ability to establish FRC

SI in preterm rabbits

te-Pas, et al, Pediatric Res 2009

RCT of SI + PEEP vs PEEP

<table>
<thead>
<tr>
<th></th>
<th>SI + PEEP n=104</th>
<th>PEEP n=103</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubated in DR</td>
<td>17%</td>
<td>36%</td>
<td>0.002</td>
</tr>
<tr>
<td>Length of RS (d)</td>
<td>2.7 [0.5-10]</td>
<td>4.3 [0.5-20]</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;1 dose of Surf</td>
<td>10%</td>
<td>21%</td>
<td>0.02</td>
</tr>
<tr>
<td>Survival</td>
<td>98%</td>
<td>96%</td>
<td>0.4</td>
</tr>
<tr>
<td>BPD</td>
<td>22%</td>
<td>34%</td>
<td>0.05</td>
</tr>
<tr>
<td>IVH 3-4/PVL</td>
<td>9%</td>
<td>8%</td>
<td>0.4</td>
</tr>
</tbody>
</table>
New Directions:
Respiratory Support in Neonates

Sustained Lung Inflation in DR: 25 cm H2O for 15 s
Lista, et al, Neonatology 2010

<table>
<thead>
<tr>
<th></th>
<th>SI group</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 89)</td>
<td>(n = 119)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSURE</td>
<td>14 (16)</td>
<td>3 (3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>45 (51)</td>
<td>90 (76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>duration, days</td>
<td>5 ± 11</td>
<td>11 ± 19</td>
<td>0.0008</td>
</tr>
<tr>
<td>Exclusive NCPAP</td>
<td>44 (49)</td>
<td>29 (24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Surfactant</td>
<td>40 (45)</td>
<td>73 (61)</td>
<td>0.027</td>
</tr>
<tr>
<td>O2 therapy</td>
<td>89 (100)</td>
<td>119 (100)</td>
<td>N/A</td>
</tr>
<tr>
<td>duration, days</td>
<td>21 ± 27</td>
<td>31 ± 31</td>
<td>0.016</td>
</tr>
<tr>
<td>Postnatal steroids</td>
<td>9 (10)</td>
<td>30 (25)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>8 (9)</td>
<td>10 (8)</td>
<td>0.920</td>
</tr>
<tr>
<td>PDA</td>
<td>24 (27)</td>
<td>29 (24)</td>
<td>0.791</td>
</tr>
<tr>
<td>BPD</td>
<td>6 (7)</td>
<td>25 (25)</td>
<td>0.004</td>
</tr>
<tr>
<td>Grade 3–IVH</td>
<td>1 (1)</td>
<td>5 (4)</td>
<td>0.372</td>
</tr>
<tr>
<td>PVL</td>
<td>4 (4)</td>
<td>11 (9)</td>
<td>0.299</td>
</tr>
</tbody>
</table>

Italian Multicenter RCT
Lista, et al, PAS 2014

<table>
<thead>
<tr>
<th></th>
<th>Control (N=143)</th>
<th>SI (N=148)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>894±247</td>
<td>893±241</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>GA (wk)</td>
<td>26.8±1.2</td>
<td>26.8±1.1</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>MV in 1st 72h - no. (%)</td>
<td>93 (65)</td>
<td>79 (53)</td>
<td>0.04</td>
<td>0.57 (0.33-0.96)</td>
</tr>
<tr>
<td>Surfactant – no. (%)</td>
<td>110 (77)</td>
<td>109 (74)</td>
<td>0.52</td>
<td>0.88 (0.50-1.56)</td>
</tr>
<tr>
<td>Any MV – no. (%)</td>
<td>98 (69)</td>
<td>88 (59)</td>
<td>0.11</td>
<td>0.68 (0.41-1.13)</td>
</tr>
<tr>
<td>BPD – no. (%)</td>
<td>50 (35)</td>
<td>57 (39)</td>
<td>0.42</td>
<td>1.14 (0.78-1.69)</td>
</tr>
<tr>
<td>Death – no. (%)</td>
<td>12 (8)</td>
<td>17 (11)</td>
<td>0.40</td>
<td>1.39 (0.66-2.93)</td>
</tr>
<tr>
<td>Ptx - no. (%)</td>
<td>2 (1)</td>
<td>9 (6)</td>
<td>0.06</td>
<td>4.57 (0.97-21.50)</td>
</tr>
</tbody>
</table>

Sustained inflation to Aerate Infants’ Lungs (SAIL) Trial
Pts: H. Kirpalani, M. Keszler
P. Davi, S. Ratcliffe
Co Is: J. Davis, S. Donn, N. Finer, H. Hummler, R. Steinhorn, G. Lista, A. tePas

Stay tuned! Results in 4 years 😊