Can We Optimize Caffeine Therapy?

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Professor, Pediatrics
Case Western Reserve University
Cleveland, Ohio
Caffeine Therapy

- Where have we been?
- Impact of the CAP Study
- How does caffeine work?
- What has happened?
- What to do now?
Apnoeic Attacks in the Newborn Treated with Aminophylline

“In 10 preterm babies with birthweights ranging from 860 to 2200 gm recurring apnoeic attacks ceased or became infrequent after administration of aminophylline 5 mg suppositories at 6-hourly intervals”.

Kuzemko JA & Paala J: Dept of Paediatrics, Maternity Hospital, Peterborough, 1973
Dear Richard:

I will be happy to answer your questions concerning our apnea protocol. At the present time we are using patients as their own controls and carefully monitoring apnea lasting more than 20 seconds before and after therapy.

We have considered a double blind study, but that is of now difficult to embark upon as our initial results with theophylline have been quite effective.

Sincerely yours,

Joseph B. Warshaw, M.D.
Mean Daily Number of Apneic Episodes

Number of Apneic spells per day

Pre Theophylline
Post Theophylline

Pre Caffeine
Post Caffeine

Uauy, Pediatr 1975
Aranda, J Peds 1977
Caffeine Therapy

- Where have we been?
- **Impact of the CAP Study**
- How does caffeine work?
- What has happened?
- What to do now?
Methylxanthine therapy in premature infants: Sound practice, disaster, or fruitless byway?

Schmidt B: J Pediatr 1999
CAP TRIAL

Schmidt B.
Effect of Caffeine Therapy for Apnea of Prematurity

<table>
<thead>
<tr>
<th></th>
<th>Caffeine Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>postmenstrual age at last use of endotracheal tube</td>
<td>Median</td>
<td>29.1 weeks</td>
</tr>
<tr>
<td>postmenstrual age at last use of supplemental oxygen</td>
<td>Median</td>
<td>33.6 weeks</td>
</tr>
</tbody>
</table>

Schmidt, NEJM 2006
**Caffeine Therapy for Apnea Trial: Outcome at 18-21 Months**

<table>
<thead>
<tr>
<th></th>
<th>Caffeine</th>
<th>Placebo</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or disability</td>
<td>40%</td>
<td>46%</td>
<td>0.77</td>
<td>0.006</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>4.4%</td>
<td>7.3%</td>
<td>0.58</td>
<td>0.009</td>
</tr>
<tr>
<td>MDI&lt;85</td>
<td>34%</td>
<td>38%</td>
<td>0.80</td>
<td>0.035</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>5.1%</td>
<td>7.9%</td>
<td>0.63</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Schmidt B: NEJM 2007*
Efficacy of Xanthine Therapy

“Infants receiving respiratory support derived more neurodevelopmental benefits from caffeine than infants not receiving support.”

“Earlier discontinuation of any positive airway pressure explained 49% of the beneficial long term drug effect.”

Survival Without Disability to Age 5 Years After Neonatal Caffeine Therapy for Apnea of Prematurity

“Neonatal caffeine therapy was no longer associated with a significantly improved rate of survival without disability in children with very low birth weights who were assessed at 5 years.”

Schmidt B: JAMA 2012
Developmental Coordination Disorder

OR [95% CI] = 0.71 [0.52-0.98]

# Rates of Functional Impairment at 11 Years in the CAP Trial

<table>
<thead>
<tr>
<th></th>
<th>Caffeine</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor academic performance</td>
<td>14.4%</td>
<td>13.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Behavior problems</td>
<td>10.9%</td>
<td>8.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Motor impairment</td>
<td>19.7%</td>
<td>27.5%</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

*Schmidt: JAMA Pediatr, 2017*
Caffeine Therapy

- Where have we been?
- Impact of the CAP Study
- How does caffeine work?
- What has happened?
- What to do now?
Proposed Beneficial Effects of Xanthine on BPD

CAFFEINE

Lower concentration

Adenosine receptor blockade
($A_1$, $A_{2A}$, $A_{2B}$, $A_3$)

INCREASSED RESPIRATORY DRIVE

Higher concentration

↑cAMP
(phosphodiesterase inhibition)

INFLAMMATORY RESPONSE MODULATION

BRONCHODILATION
Caffeine Concentration to Activate Molecular Targets

Atik A: NeuroToxicology 2016
CAFFEINE

Adenosine A1 receptor blockade

Increased respiratory drive

Adenosine A2A receptor blockade

GABA inhibition

Inflammatory response inhibited

IMPROVED NEUROMOTOR OUTCOME
Xanthines for Neonatal Apnea

**Physiologic**
- Increased minute ventilation
- Shift of CO$_2$ response curve to left ± increased slope
- Improved pulmonary mechanics
- Decreased hypoxic ventilatory depression
- ?? Greater efficiency of diaphragmatic contraction

**Biochemical**
- Central adenosine receptor subtype antagonism
- ?? Inhibition of phosphodiesterase
Proposed Model for GABA/Adenosine Interaction in Respiratory Regulation

GABAergic neurons

GABAergic neurons

Adenosine

chemosensory neurons

rhythm generating neurons

hypoglossal neurons

phrenic motoneurons

Receptors

- Adenosine $A_{2A}$
- GABA$_A$

Wilson: Resp Physiol Neurobiol 2004
Adenosine $A_1$ receptor blockade

Increased respiratory drive

Adenosine $A_{2A}$ receptor blockade

GABA inhibition

Inflammatory response inhibited

CAFFEINE

IMPROVED NEUROMOTOR OUTCOME
Background: Inconsistent Data!

Protective effects of adenosine $A_{2A}$ receptor agonist in ventilator-induced lung injury in rats

Chronic or high dose acute caffeine treatment protects mice against oleic acid-induced acute lung injury via an adenosine $A_{2A}$ receptor-independent mechanism

Correlation between serum caffeine levels and changes in cytokine profile in a cohort of preterm infants
Prevention of Hyperoxia-mediated Pulmonary Inflammation in Neonatal Rats by Caffeine

“Treatment with caffeine at the beginning of hyperoxia blocked the upregulation of chemokines and proinflammatory cytokines and the influx of myeloid leukocytes seen with high oxygen”.

Weichelt U: Eur Respir J 2013
Methods
Decrease in Respiratory System Resistance at Day 8 after Caffeine in LPS-Exposed Pups

*p<.01 via one way ANOVA (post-hoc)

Köroğlu: Neonatology 2014
Caffeine Prevents Hyperoxia-induced Lung Damage in Preterm Rabbits

Radial alveolar counts

Acute lung inflammation scores

Nagatomo R: Neonatology 2016
CAN CAFFEINE BOOST YOUR BRAIN?

THE EVIDENCE
Multiple studies show that caffeine consumption may cut Alzheimer’s risk.

THE THEORY
Caffeine may block inflammation linked to neurodegenerative diseases, a new University of Illinois study found.
Neuroprotection by Caffeine in Hyperoxia-Induced Neonatal Brain Injury

- Rat pups were pretreated with caffeine and exposed to 80% oxygen for 24-48 hours
- Caffeine...
  - reduced oxidative stress markers
  - promoted anti-oxidative responses
  - downregulated pro-inflammatory cytokines

Caffeine Therapy

- Where have we been?
- Impact of the CAP Study
- How does caffeine work?
- What has happened?
- What to do now?
- When to start?
- When to end?
- How much?
Indications for Caffeine Therapy

Therapeutic
Prophylactic

CAP Trial Survey [2010-2011]

Abu Jawdeh: J Neonat Perinat Med 2013
Early* Caffeine Prophylaxis for VLBW: Pediatrrix Database

*Initiated on day of birth

Jobe AH: J Pediatr 2017
Greenberg J: Personal communication
### Association of Early* Caffeine and Outcome: Retrospective Cohort Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Caffeine Group, Median (IQR)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Discharged receiving oxygen, No. (%)]</td>
<td>Early (n = 3806)</td>
<td>Late (n = 1295)</td>
</tr>
<tr>
<td></td>
<td>931 (24.5)</td>
<td>323 (24.9)</td>
</tr>
<tr>
<td>Duration of oxygen requirement, d</td>
<td>9 (1-43)</td>
<td>8 (1-49)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, d</td>
<td>2 (1-9)</td>
<td>4 (1-23)</td>
</tr>
<tr>
<td>Duration of noninvasive respiratory support, d</td>
<td>1 (1-5)</td>
<td>1 (1-5)</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>52 (27-88)</td>
<td>49 (21-88)</td>
</tr>
<tr>
<td>Discharged receiving caffeine, No. (%)</td>
<td>1386 (35.4)</td>
<td>475 (36.7)</td>
</tr>
</tbody>
</table>

*Within the first two days*  

Lodha A: JAMA Pediatr 2015
Rapid Response of Diaphragm EMG to Caffeine Bolus [10 mg/kg caffeine base]

Kraaijenga JV: J Pediatr 2015
Caffeine to Improve Breathing Effort of Preterm Infants at Birth

<table>
<thead>
<tr>
<th></th>
<th>Caffeine DR group (13 patients)</th>
<th>Caffeine NICU group (10 patients)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1,091 breaths</td>
<td>N=779 breaths</td>
<td></td>
</tr>
<tr>
<td>Minute volume (ml/kg)a</td>
<td>189 ± 74</td>
<td>162 ± 70</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Average inspired tidal volume (ml/kg)b</td>
<td>5.2 (3.9 to 6.4)</td>
<td>4.4 (3.0 to 5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory rate/min at 7–9 min after birtha</td>
<td>35 ± 10</td>
<td>33 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)b</td>
<td>157 (141 to 170)</td>
<td>146 (135–160)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxygen saturation (%) at 7–9 min after birthb</td>
<td>91 (87 to 94)</td>
<td>91 (88 to 94)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Caffeine Decreases Intermittent Hypoxia in Preterm Infants Nearing Term-equivalent Age

Dobson: J Perinatol, 2017
Extubation Failure after High vs Low Caffeine Citrate Maintenance Dosage

Randomized Controlled Trial

Steer P: Arch Dis Child Fetal Neonatal Ed 2004
Caffeine Citrate Dosing Adjustments to Assure Stable Caffeine Concentrations in Preterm Neonates

Koch G: J Pediatr 2017
## Early Caffeine Prophylaxis and Risk of Initial CPAP Failure in VLBW Infants

*Data from 366 NICUs - 2000-2014*

<table>
<thead>
<tr>
<th></th>
<th>Early caffeine DOL 0</th>
<th>Routine caffeine DOL 1-6</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 4528</strong></td>
<td><strong>N = 6605</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPAP failure</td>
<td>990 (22%)</td>
<td>1376 (21%)</td>
<td>1.05 (0.93, 1.18)</td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>683 (15%)</td>
<td>1029 (16%)</td>
<td>1.06 (0.92, 1.21)</td>
</tr>
<tr>
<td>Surfactant therapy</td>
<td>662 (15%)</td>
<td>919 (14%)</td>
<td>1.00 (0.88, 1.15)</td>
</tr>
</tbody>
</table>

# Effect of Early Caffeine on Age of First Successful Extubation [23-30 wk GA]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early caffeine [n=41]</th>
<th>Control* [n=42]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first successful extubation [days]</td>
<td>21 [10 to 41]</td>
<td>20 [9 to 43]</td>
<td>.703</td>
</tr>
</tbody>
</table>

*placebo with caffeine load at extubation

data are median [IQR]

Amaro CM et al: J Pediatr 2018
Caffeine Therapy

- Where have we been?
- Impact of the CAP Study
- How does caffeine work?
- What has happened?
- **What to do now?**
# Neonatal Caffeine Therapy: Unresolved Issues

<table>
<thead>
<tr>
<th></th>
<th><strong>Pro</strong></th>
<th><strong>Con</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early onset</strong></td>
<td>• Improves various morbidities</td>
<td>• Available data are largely based on associations rather than randomized trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• How early is too early?</td>
</tr>
<tr>
<td><strong>Prolongation of therapy</strong></td>
<td>• Decreases duration of intermittent hypoxic episodes</td>
<td>• May provide exposure to unnecessary medication</td>
</tr>
<tr>
<td></td>
<td>• May shorten hospitalization [if discharged on caffeine]</td>
<td>• May prolong hospitalization [if discharged off caffeine]</td>
</tr>
<tr>
<td><strong>Higher doses</strong></td>
<td>• More strongly enhance respiratory neural output</td>
<td>• Adenosine receptor subtype inhibition of inflammation is variable and dose dependent, raising safety concerns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Preliminary report of cerebellar injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Likely need for postnatal dose adjustments</td>
</tr>
</tbody>
</table>