Neonatal Sedation

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Responses to Pain - Newborns learn quickly
- Taddio et al. 2002 JAMA. IDM’s compared to normal newborns for response to painful stimuli.
- Higher VAS during skin alcohol prep.
- More grimacing and crying during venipuncture
- Conclusion: Newborns anticipate pain and are more expressive when they have previous exposure.

Long-term Pain Effects
- Tolmson Stevens (1996) evaluated 4 week old 28 weekers and compared them to 32 weekers.
- Decreased behavioral responses and increased cardiovascular responses were noted.
- Differences primarily were related total number of invasive procedures - not other clinical factors.

Developmental Issues in Pain Pharmacology
- Enzyme systems in the liver are not fully developed until 3-6 months of age.
- Glomerular filtration rate is very low at birth. Reaches near adult level by 6 months.
- Higher percentage of body weight is water.
- Reduced levels of a-1 glycoprotein
- Diminished ventilatory responses to hypoxia.
- Immature blood brain barrier
Best Option

- Swaddling
- Feeding
- “Shrink Wrapping” - proprietary name
  MedVac - is actually a bean bag that conforms to baby and allows stabilization

Neonatal Sedation Risk

- PSRC Data and others indicate neonates are (in fact) our highest risk population for sedation.

Pulmonary Complications

**Methods**: The Pediatric Sedation Research Consortium (PSRC) ran 24 participating institutions and multidisciplinary memberships. Neurologists detailed records of all sedations performed. From 9/2004 to 8/2005, 13,778 sedations were reported. Patients were stratified by health status using the American Society of Anesthesiologists (ASA) classification system (ASA I-II vs. ASA III-IV) and by age. A pulmonary complication was defined as any incident, stabilization, unachoeldr breathing episode or medication. Generalized linear models with Poisson errors were used to estimate relative risk of a complication with focus on effects of age and ASA status. Clustering by institution was incorporated into variance estimates. Procedures were categorized as radiologic (62%), invasive/laparoscopic (8%), nasal (7%), transcutaneous (4%), endoscopic (7%), neurologic (5%) and other (5%).

**Results**: There were 330 (2.3%) pulmonary complications. These were more common for ASA status II. Among ASA I-II patients, the highest complication rate was in patients < 6 months old (3.3%).

**Conclusions**: Children with ASA II have a greater risk of pulmonary complications during sedation. ASA I-II patients < 6 months old may also have higher risk. Further work is needed to understand the etiology of the complications.
Issues Relating Neurotoxicity and Anesthetic Exposure

- Mounting evidence in neonatal Rat pups that exposure to sedatives and anesthetics at early ages may lead to neuroapoptosis and resultant brain injury - uncertain application to humans - but concerning.

Sedative Anesthetic Toxicity

- Very recent demographic data may link learning disabilities to exposure to anesthetics/sedatives at early ages.

If We Have to Sedate……

- Chloral Hydrate
- Midazolam
- Ketamine
- Dexmedetomidine
- Propofol

Chloral Hydrate

- Beauve - Ped Anesthesia 2008 - looked at 25 neonates for MRI scan.
- 12 Fed and swaddled - 13 sedated with chloral hydrate.
The Pro

- Chloral Hydrate Babies - quicker to the scanner - slightly more success.
- Authors argue for efficiency CH could be useful.
- No data on recovery offered.

Chloral Hydrate - the Con

- Allegart et. al. reported on monitoring babies during and after CH sedation - Pediatric Anesthesia 2008
- Success documented but......
- Sedation could be documented for up to 12 hours.
- Decreased oral intake and increased # of bradycardia events - study terminated.

Midazolam

- Extensive history of use for sedation in the ICN Aranda 2005 Clin Ther.
- Little information on procedural sedation for neonates.

Dartmouth Experience - Midazolam in Neonates

- Ongoing observational experience in the MRI scanner.
- MRI scanner team - does not like failure rate with feeding/swaddling strategy.
- Our protocol - give midazolam small doses - .025mg/kg every 3-4 minutes until sleep sedation is induced.

Midazolam Dartmouth Experience

- After sedation is induced, with all monitors in place, baby is wrapped in warm blankets - no further meds given.
- Neonates - 96% wake up with movement taking them off of the MRI table.
- Less than 5% have required repeat doses.
Dexmedetomidine

- Almost no information on this drug in neonates for procedural sedation.
- Growing experience in pediatric procedural sedation in general.
- ADVANTAGE - so far this drug has not been implicated in neuro-apoptosis!!

DEX Kinetics

- Metabolism in the liver - dose reduction for patients with liver impairment is indicated - think Neonates.
- Elimination through kidneys - elimination 1/2 life is 2 hours, α half life is 6 minutes - likely longer in neonates.

DEX Effects

- Anxiolytic, hypnotic, and analgesic effects are noted roughly in that order - onset is variable depending on dosing - next slide
- Little if any depression of respiratory drive is noted. Quite safe from this perspective - RN delivered sedation is well reported with this drug.

Dosing DEX

- Initial bolus dose = .2-1 mcg/kg over 10 minutes followed by an infusion of .25 - 1.0 mcg/kg/hour.
- Dosing for children has been described - at much higher bolus and infusion rates. Bolus doses as high as 2-3 mcg/kg - more efficacy and more adverse effects - more on that later.....

DEX side effects:

- Hypertension due to α-1 peripheral stimulation
- Initial infusion may be accompanied by a hypertensive response.
- Hypertension may be minimized by slowing infusion to 20 minutes or eliminating it completely.
- Note - Glycopyrrolate treatment of bradycardia may result in hypertension.
DEX side effects

- Note - glycopyrrolate TX for bradycardia can result in significant hypertensive response!

DEX Side Effects

- Bradycardia is well reported by multiple investigators. Importance of this finding is currently a matter of discussion. Appears to be a dose related phenomenon. *Mason 2008*
- HR decreases into the 60-70 bpm range are not common but well described with 2mcg/kg bolus. Particularly problematic in patients receiving Digoxin or those with conduction blocks. *Berkenbosch 2003*

DEX Side effects

- Hammer et. al. 2008 - 12 patients evaluated 5-17 YO undergoing ablation TX under DEX sedation 1 mcg/kg followed by 0.7mcg/kg/hour.
- HR decreased while BP increased on average. Decrease SA nodal and AV nodal function noted.

DEX Side Effects

- Hypotension has also been noted - somewhat dose related, not as marked as bradycardia, and generally not requiring treatment.
DEX Procedural Sedation.

- Mason et al. - series of observation reports from the sedation database at BCH.
- Report of 62 children undergoing CT scans. Much higher doses used - 2 mcg/kg load followed by 1 mcg/kg/hour. 16% required repeat bolus.

Mason DEX Reports

- 18% bradycardia rate and as much as 30% BP decrease.
- No adverse outcomes.
- Authors suggestion - perhaps in this scenario - no need to worry about this finding as we would with ill children.

Mason Studies Cont.

- High dose DEX evaluated for 747 MRI scans.
- Loading dose = 3 mcg/kg with maint 2 mcg/kg/hour. Success in 91-98% of cases.
- Bradycardia noted in 16% sometimes severe - BP never down more than 20% - Ox sats - always good.

DEXMEDETOMIDINE FOR PEDIATRIC PROCEDURAL SEDATION – RESULTS FROM THE PEDIATRIC SEDATION RESEARCH CONSORTIUM

John W Berkenbosch MD, Nina Lubisch ARNP, Susan Gallagher BS, Joseph P Cravero MD and the Pediatric Sedation Research Consortium.
**RESULTS DEMOGRAPHICS**

- **1102 sedations**, 3 Institutions (653/448/1)
  - Total 56,702 total sedations (1.9% of total)
- Age: 59±45 mos, weight: 22.7±16.4 kg
- ASA I=436, ASA II=363, ASA III=285
- Co-morbidities in 582 (53%)

**Primary diagnoses:**
- Neurologic (n=696), Hem-Onc (n=151)

**Primary procedures = radiology (n=1023)**
- MRI (n=794), CT (n=171), nuc med (n=61)

**RESULTS OUTCOMES**

<table>
<thead>
<tr>
<th>Complication</th>
<th>#</th>
<th>%</th>
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<tbody>
<tr>
<td>Inadequate</td>
<td>31</td>
<td>2.8</td>
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<tr>
<td>&gt;30% S/S</td>
<td>18</td>
<td>1.6</td>
</tr>
<tr>
<td>Prolonged</td>
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<td>0.9</td>
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<tr>
<td>Respiratory</td>
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<tr>
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</tbody>
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- **Conditions produced:**
  - Ideal (1038, 94.2%)
  - Suboptimal (57, 5.2%)
- **Failures (n=7, 0.6%)**
  - Inadequate (n=2)
  - Complications (n=2)
  - Unrelated (n=3)
- **Level of Care (n=2)**
  - PICU (n=2)
  - Underlying Dx (n=2)

**More on DEX and Procedural Sedation...**

- At lower doses 1.5 mcg/kg bolus - unacceptable rates of movement during MRI were recorded. Fewer hemodynamic findings and no respiratory depression. *Heard 2007.*
- When compared to Propofol by these investigators - no diff in respiratory findings and longer recovery for DEX.

**DEX Procedural Sedation Summary**

- Generally effective, but less efficient than Propofol.
- Higher doses than generally recommended are needed - evidence evolving.
- Expect little respiratory depression, but bradycardia and hypotension occur - ? importance.

**Propofol Neonatal Sedation - Metabolism**

- No question that propofol clearance is significantly different in neonates compared to adults.
- Glucuronidation is limited - hydroxilation dominates - quite different from adults.
- Clearance is very diminished and is extremely variable.
- Drug accumulation - much more likely.
Allometric Relationships Between the Pharmacokinetics of Propofol in Rats, Children and Adults.
Knibbe et al.

Maturational Kinetics of Single Intravenous Bolus of Propofol
Allegaert et al.

Pharmacokinetics of Propofol Infusions in Critically Ill Neonates, Infants, and Children in an Intensive Care Unit
Propofol
- Response to single dose propofol in children is predicted by allometric models.
- No neonatal allometric model.
- Prolonged emergence after infusion is not predicted by allometric model.

Summary
- Imprinting of Pain and Stress likely has long term effects on neonates.
- Neonates - highest risk sedation subgroup.
- Little data on specific sedation drugs in neonates.
- Non-sedation techniques - progressing.

Summary
- Chlora Hydrate - works but long "tail".
- Midaz - IV titration in small doses.
- Dexmedetomidine - promising but side effects need to be evaluated.
- Propofol - definitely different drug dynamics in Neonates.