Neonatal Sedation

Joseph Cravero MD

First Question – Does Pain/Stress Control Matter? – Especially in very young patients. Really?

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.

Long-term Pain Effects

- Taddio et al. (1995) - Circumcision in neonates associated with increased behavioral responsiveness to vaccination at 4-6 months of age.
- Ramsay and Lewis (1995) - Stressful conditions at birth associated with increased salivary cortisol responses to vaccination at 4-6 months.

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.

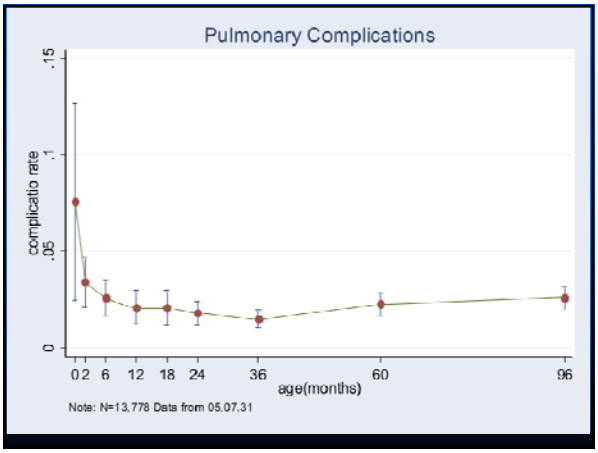
Pulmonary Complications

Methods : The Pediatric Sedation Research Consortium (PSRC) has 24 participating institutions and multidisciplinary membership. Members submit detailed records of all sedations performed. From 8/2004 to 8/2005, 13,778 sedations were recorded. Patients were stratified by health status using the American Society of Anesthesiologists (ASA) classification system [(ASA I-II) vs. (ASA III-V)] and by age. A pulmonary complication was defined as any apnea, desaturation, unexpected bag mask ventilation or intubation. 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 (61%), invasive/surgical (8%), GI (7%), heme/onc (6%), orthopedic (7%), neurologic (6%) and other (5%).

Pulmonary Complications

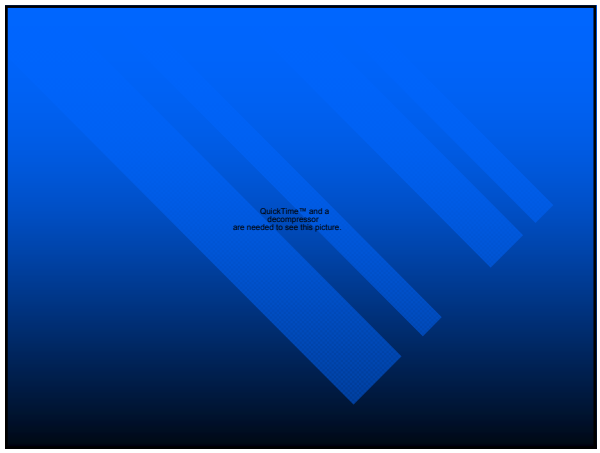
Results : There were 308 (2.2%) pulmonary complications. These were more common for ASA status ≥III. Among ASA I-II patients, the highest complication rate was in patients ≤ 6 months old (3.3 %)

Conclusions: Children with ASA ≥III 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 exact etiology of the complications.



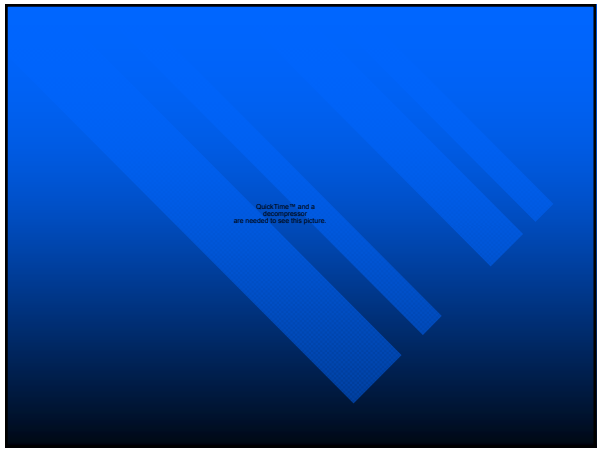
Issues Relating Neurotoxicity an Anesthetic Exposure

- 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.

QuickTime™ and a
decompressor
are needed to see this picture.

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

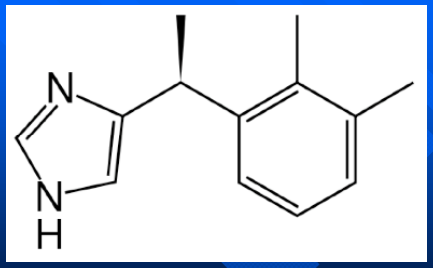
- Ongoing observational experience in the MRI scanner.
- MRI scanner team - does not like failure rate with feeding/swaddling strategy.
- Our protocol - give midazolam small doses - .025mg/kg every 3-4 minutes until sleep sedation is induced.

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 = .2-1mcg/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.

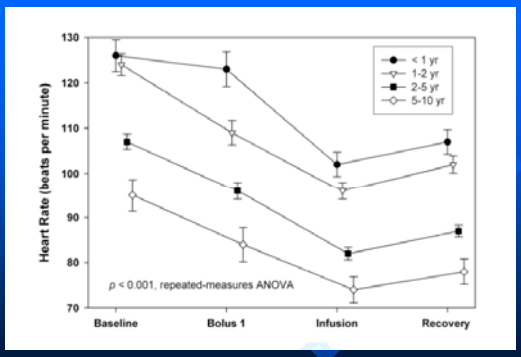
DEX Side Effects

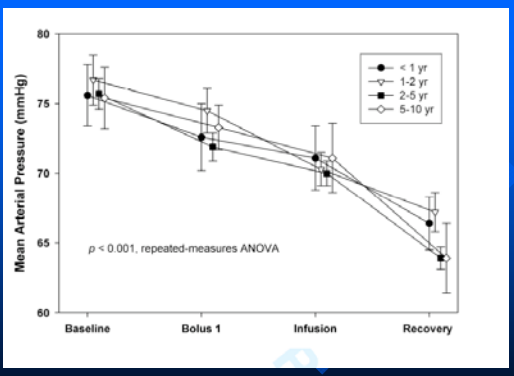
- Hypotension has also been noted - somewhat dose related, not as marked as bradycardia, and generally not requiring treatment.

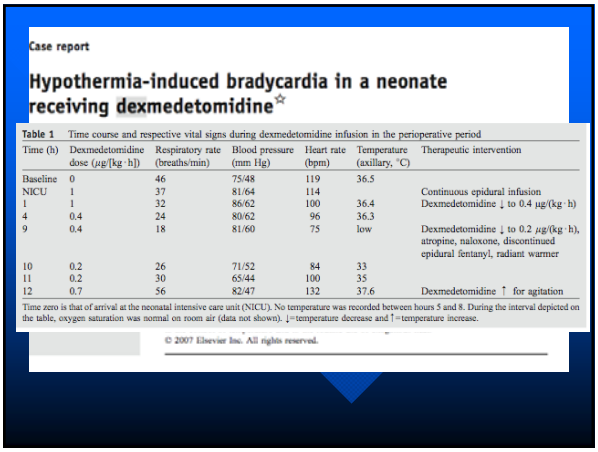
Table 3. Percent Changes From Baseline in Heart Rate and Mean Arterial Pressure

		Decreases			Increases		
Heart Rate	*n*	<15%	15-30%	>30%	<15%	15-30%	>30%
Bolus 1	222	86 (39)	61 (28)	20 (9)	39 (18)	12 (5)	4 (2)
Infusion	198	45 (23)	106 (54)	39 (20)	7 (4)	1 (0.5)	0 (0)
MAP							
Bolus 1	222	110 (50)	36 (16)	3 (1)	47 (22)	21 (9)	5 (2)
Infusion	198	70 (35)	48 (24)	13 (7)	46 (23)	16 (8)	5 (3)

Data represent number of patients with percentage in parentheses.







Case report

Hypothermia-induced bradycardia in a neonate receiving dexmedetomidine☆

Table 1 Time course and respective vital signs during dexmedetomidine infusion in the perioperative period

Time (h)	Dexmedetomidine dose (μg/[kg·h])	Respiratory rate (breaths/min)	Blood pressure (mm Hg)	Heart rate (bpm)	Temperature (axillary, °C)	Therapeutic intervention
Baseline	0	46	75/48	119	36.5	
NICU	1	37	81/64	114		Continuous epidural infusion
1	1	32	86/62	100	36.4	Dexmedetomidine ↓ to 0.4 μg/(kg·h)
4	0.4	24	80/62	96	36.3	
9	0.4	18	81/60	75	low	Dexmedetomidine ↓ to 0.2 μg/(kg·h), atropine, naloxone, discontinued epidural fentanyl, radiant warmer
10	0.2	26	71/52	84	33	
11	0.2	30	65/44	100	35	
12	0.7	56	82/47	132	37.6	Dexmedetomidine ↑ for agitation

Time zero is that of arrival at the neonatal intensive care unit (NICU). No temperature was recorded between hours 5 and 8. During the interval depicted on the table, oxygen saturation was normal on room air (data not shown). ↓=temperature decrease and ↑=temperature increase.

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, ASAIII=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
SEDATION/MEDICATIONS

	Overall (n=1102)	Dex alone (n=192)	Dex + Midaz (n=910)
Dose (ug/kg)	2.8±2.2	**3.2±1.8***	2.6±1.4
Recovery (min)	62.1±33.6	**50.6±25.0***	64.6±34.6
Ideal/suboptimal	1038/64	176/13	862/47
Complications	73 (6.6%)	61 (6.7%)	12 (6.3%)
CV/resp complic	22 (2.0%)	18 (2.0%)	4 (2.1%)

* p<0.0001 compared to dex + midazolam group

RESULTS
OUTCOMES

Complication	#	%
Inad/agitation	31	2.8
>30% ¯ VS	18	1.6
Prolonged	10	0.9
Respiratory	5	0.5
Nausea/vomit	5	0.5
Seizure	1	0.1

- 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 invesitigators - 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.

QuickTime™ and a
decompressor
are needed to see this picture.

Br J Clin Pharmacol 59:705-711, 2005.

Allometric relationships between the pharmacokinetics of propofol in rats, children and adults

Catherijne A. J. Knibbe,[1] Klaas P. Zuideveld,[1,4] Leon P. H. J. Aarts,[3] Paul F. M. Kuks[1] & Meindert Danhof[2]
[1]Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, [2]The Leiden/Amsterdam Centre for Drug Research, Division of Pharmacology, University of Leiden, Leiden and [3]Department of Anaesthesiology and Intensive Care, St Antonius Hospital, Nieuwegein, the Netherlands

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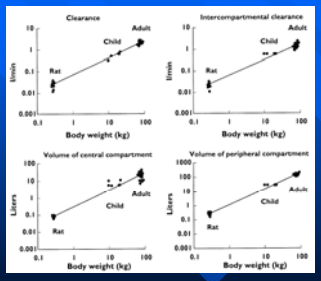
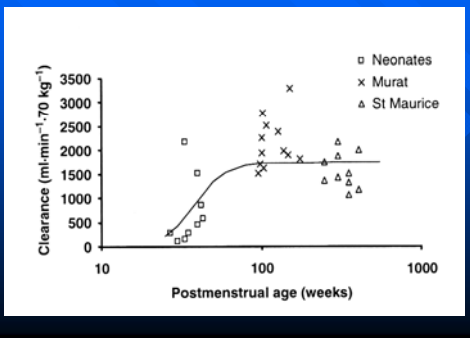


Maturational Kinetics of Single Intravenous Bolus of Propofol
Allegaert et al.
Ped Anesth. 17:1028-1034, 2007.



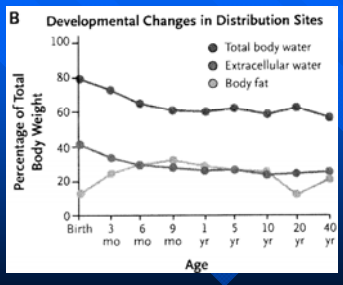
Anesthesiology 2002; 97:1393–1400

Pharmacokinetics of Propofol Infusions in Critically Ill Neonates, Infants, and Children in an Intensive Care Unit

Ann E. Rigby-Jones, B.Sc.,* Judith A. Nolan, M.R.C.P., F.R.C.A.,† Melanie J. Priston, Ph.D.,‡ Peter M. C. Wright, M.D., Ph.D., F.C.A., R.C.S.I.,§ J. Robert Sneyd, M.D., F.R.C.A.,‖ Andrew R. Wolf, M.D., F.R.C.A.#

" large, slowly equilibrating, deep compartment causing full recovery to be considerably delayed"

Kearns et al. NEJM 349:1157-1167, 2003



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

- Chloral 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.