Dexmedetomidine: What is its role in the pediatric cardiac patient?

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I TOLD YOU I'M NOT SICK! WHAT'S THAT? WILL IT HURT?
IT'S A TONGUE DEPRESSOR. IT WON'T HURT AT ALL.
WHAT'S THAT? WILL IT HURT?
IT'S A STETHOSCOPE. IT WON'T HURT AT ALL.
WHAT'S THAT? WILL IT HURT?
IT'S A CATTLE PROD. IT HURTS A LITTLE LESS THAN A BRANDING IRON.
LITTLE KIDS HAVE NO SENSE OF HUMOR.
Panacea – goddess of all cures
Woodcut by Veronese physician Joseph Gazola, 1716
Asclepius and the family
Dexmedetomidine

- Maybe not a panacea.
- But a useful tool in the anesthetic and critical care management of children with congenital heart disease
Disclosures
Objectives

• Participants will:
  • Understand the pharmacology of dexmedetomidine
  • Discuss the clinical utility of dexmedetomidine in the pediatric cardiac patient population
  • Recognize the limitations of using dexmedetomidine in children with congenital heart disease
  • Explore potential benefits of dexmedetomidine as presented in basic science literature
Dexmedetomidine

• $\alpha_2$-adrenergic receptor agonist
• $\alpha_2: \alpha_1$ selective binding $1600:1$
  – 7x more selective than clonidine

• $\alpha$ phase, redistribution half-life = 7 mins
• $B$ phase, terminal elimination half life = 2 hrs
• Clearance 15 mL/kg/min
• Shorter half-life than clonidine
  – Allows for infusion titration
Dexmedetomidine

- Hepatic metabolism – similar to morphine and acetaminophen
  - Inactive metabolites
  - 85% glucuronidation
    - Uridine-5-diphosphate (UDP)-glucuronyltransferase
    - 15% cytochrome p450
- Maturation of clearance at 1 year of age
  - 85% of adult clearance
PK considerations in CHD children

• Clearance increases
  – Weight, age, single ventricle physiology

• Clearance decreases
  – Total cardiopulmonary bypass time

  • Potts, *Ped Anesth*, 2009
  • Su, *Anes & Anal*, 2010
Cellular Mechanism of the $\alpha_2$-Adrenergic Agonists

- Alpha-2 receptor provides negative feedback to inhibit NE release
- Decrease sympathetic response
- Clinical effectiveness tied to selectivity for alpha-2
Cellular Mechanism of the $\alpha_2$-Adrenergic Agonists

- Alpha-2 agonist binds to receptor
- G-protein coupling
- Decrease cell membrane potential
  - Decrease Ca influx
  - Increase K efflux
- Hyperpolarized membrane less likely to fire
- Noradrenergic neuron does not release NE, inhibiting histamine release
- SLEEP

![Diagram showing the cellular mechanism of alpha-2 adrenergic agonists](image)
End organ effects of Dexmedetomidine

- Neurologic
- Hemodynamics
- Respiratory
End Organ Effects - Neurologic

• Sedation via selective binding $\alpha_2$ receptors in the locus ceruleus
  – Decreased noradrenergic output $\rightarrow$ increased GABA firing
  – Natural, non-REM sleep
    • Animal studies
    • Pediatric EEG

End Organ Effects - Neurologic

- No effect on ICP
- Decrease CBF, CMRO2
- Possible neuroprotection during ischemia
- Preserves SSEP, MEP
- Thermoregulation
  - Decreases shivering, heat production, lipolysis
End Organ Effect - CV

- Cardiovascular effects via central and peripheral adrenoreceptors
- Hypotension
- Hypertension
- Bradycardia
- Electrophysiology
- PA Pressures
End Organ Effect - CV

• Hypotension
  – Low dose causes sympatholysis
  – Up to 30% from baseline
  – Dose/Bolus association
  – Attenuated with dose of Ketamine

• Hypertension
  – Large dose causing peripheral vasoconstriction
  – Bolus dose/frequency
  – More frequent in infants
  – Transient, self-resolving (30 mins)
End Organ Effect - Bradycardia

- Decrease up to 30% of baseline with loading dose
- More common in infants
- Ketamine may attenuate response
- Glycopyrrolate
  - Pretreatment does not attenuate
  - Treatment may cause significant hypertension
- Caution
  - AV node dysfunction
  - Sinus node dysfunction
  - HR altering drugs: \( B \)-blockers, digoxin
- Treatment (when present with hypotension, decreased perfusion)
  - Discontinue drug
  - Stimulation
  - Inotropic agents
End Organ Effect - Respiratory

- Maintains airway patency
- Maintains ventilation
- Respiratory rate, SaO2, EtCO2 all remain unchanged
- Makes the drug very attractive in the ICU and for procedural sedation
• FDA approval in adults (December 1999)
  – mechanically ventilated ICU patients, 24 hours
  – monitored anesthesia care
• Currently labeled dosing for ICU sedation
  – loading dose: 1.0 µg/kg over 10 minutes
  – maintenance dose: 0.2 to 0.7 µg/kg/hr
• 2008 FDA added surgical/medical procedures in adults without intubation outside the OR

• Not approved for children
  – Retrospective cohort, 1260 CABG/valve surgery pts.
  – 50% perioperative infusion of dexmedetomidine
  – Mortality % (AOR)

<table>
<thead>
<tr>
<th></th>
<th>In-Hospital</th>
<th>30 Day</th>
<th>1 year</th>
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<tbody>
<tr>
<td>Non Dexmed</td>
<td>4.59</td>
<td>5.12</td>
<td>7.95</td>
</tr>
<tr>
<td>Dexmed</td>
<td>1.23 (0.34)</td>
<td>3.17 (0.39)</td>
<td>3.17 (0.47)</td>
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  – $\alpha_2$-AR agonists reduced mortality and myocardial ischemia; RR 0.66 and 0.68

• Barr, et al. *CCM*, 2013
  – New SCCM guidelines favoring use of non-benzodiazepine and non-opioid drugs, including dexmedetomidine, for ICU sedation.
  – Category B evidence of improve outcomes, decreased delirium
Use in pediatric cardiac patients

- Preoperative sedative
- Procedural sedation
- Anesthesia management during surgical repair of CHD
- Anesthesia management during cardiac catheterization
- CICU sedation
- Anti-arrhythmia therapy
- Treatment of post-anesthesia shivering
• Chrysostomou, “Use of dexmedetomidine in children after cardiac and thoracic surgery,” PCCM 2006

• Chrysostomou, “Dexmedetomidine use in a pediatric cardiac intensive care unit: Can we use it in infants after cardiac surgery?” PCCM 2009

• Lam, “Hemodynamic effects of dexmedetomidine in critically ill neonates and infants with heart disease,” Ped Cardio 2012

• Lam, “Safety and efficacy of dexmedetomidine in children with heart failure,” Ped Cardio 2013
Prospective Study
- 3 cohorts of 12 infants (1-24 mos.)
- Loading dose 0.35/0.7/1 mcg/kg over 10 mins
- gtt 0.25/0.5/0.75 mcg/kg/hr

Results
- Deeper sedation
- Less supplementation
- 31 extubated on dexmed
  - Decreased time to extubation with higher dosing
  - Decrease HR – not clinically significant
  - Dose dependent
  - No difference in MAP from baseline

Conclusion
- Improved sedation
- Successful extubation
- Hemodynamically safe
The Use of Dexametomidine in Pediatric Cardiac Surgery

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We tested dexametomidine, an α2 agonist, for its ability to decrease heart rate, arterial blood pressure, and neuroendocrine response during pediatric cardiac surgery. In a randomized, placebo-controlled study, 30 pediatric patients undergoing open heart surgery were randomly assigned to one of two equal groups. The control group received saline, whereas the treatment group (DEX group) received an initial bolus dose of dexametomidine (0.5 μg/kg) over 10 min, followed immediately by a continuous infusion of 0.5 μg/kg·h. Arterial blood pressure, heart rate, and sequential concentrations of circulating cortisol, epinephrine, norepinephrine, and blood glucose were measured relative to baseline, arterial blood pressure and heart rate decreased significantly after the administration of dexametomidine through skin incision. In the control group, patients' heart rate and arterial blood pressure measurements increased after skin incision until the end of bypass (p < 0.05). In both groups, plasma cortisol, epinephrine, norepinephrine, and blood glucose increased significantly relative to baseline, after incision, and after bypass. However, the values were significantly higher in the control group compared with the DEX group (p < 0.01). In conclusion, intraoperative dexametomidine infusion attenuated the hemodynamic and neuroendocrine response to surgical trauma and cardiopulmonary bypass in pediatric patients undergoing corrective surgery for congenital heart disease.

[From Anesth 2006;58(5):52-6]

The stress response is the term given to the hormonal and metabolic changes that occur after injury or trauma. This is part of a systemic reaction to injury that encompasses a wide range of endocrinological, immunological, and hematological effects. It is initially by neural activation of the hypothalamic-pituitary-adrenal axis (1). The stress response to surgery is characterized by increased secretion of pituitary hormone and activation of the sympathetic nervous system (2, 3). Attenuation of the cardiovascular, neuroendocrine, and inflammatory responses to surgery may improve outcome by beneficial effects on organ function (3-6).

Dexametomidine is a highly specific, potent, and selective α2-adrenoceptor agonist (5). It has a relatively high ratio of α2/β1 activity (460:1 as compared to 220:1 for clonidine) (6) and is therefore considered a full agonist of the α2 receptor. This ratio ensures that its potent action is selective for the central nervous system, without unwanted cardiovascular effects from α2 receptor activation (6). Dexametomidine has activity at the imidazoline receptors involved in central arterial blood pressure control (7, 8). It causes a dose-dependent decrease in mean arterial blood pressure (MAP) and heart rate (HR) (9) and a reduction in sympathetic nervous system activity (9, 10). Dexametomidine is an imidazoline compound, and therefore, it has the potential to exert similar inhibitory effects to etomidate on cortisol synthesis (11).

This is the first study to report the sympatholytic effects of a continuous intraoperative infusion of dexametomidine on cardiovascular function and stress hormones (cortisol and catecholamine) in pediatric cardiac surgery patients. The hypothesis that dexametomidine would attenuate the increase in HR, MAP, and plasma catecholamine concentration in pediatric patients undergoing corrective surgery for congenital heart disease was investigated.

METHODS

After approval of the local Ethics Committee and obtaining written informed consent from the guardians of all patients, the study was designed to include 30 patients, aged 1-6 yr, scheduled for congenital heart disease repair surgery using cardiopulmonary bypass (CPB) between January 2004 and September 2004. Patients undergoing re-operations, deep hypothermia, those with low cardiac output, and those with nonpalpable peripheral pulses before surgery (e.g., accompanying congestive
In the cath lab

- Provides good level of sedation when compared to propofol.
- Maintains airway patency and spontaneous ventilation
- May require propofol rescue bolus

Munro, *Ped Anesth*, 2006
Dexmedetomidine + Ketamine
Mester, AJ of Ther, 2008

- **Bolus**
  - Dexmedetomidine 1 mcg/kg
  - Ketamine 2 mg/kg

- **Infusion**
  - 2 mcg/kg/hr → 1 mcg/kg/hr

- **Rescue**
  - Ketamine 0.5 mcg/kg

- 16 patients
- Balanced hemodynamics
  - No clinical change in HR or BP
  - Opposing effects of the 2 drugs
- No change in respiratory parameters
- No movement to local infiltration
- Rescue
  - 3/16 required ketamine
Safe in pulmonary HTN

• 21 OHT patients, 21 PHTN patients
• 10 minute infusion dose
  – 1, 0.75, 0.5 mcg/kg
• HD response
  – Decrease HR
  – Increase MAP, SVRI
  – Small increase PAP in OHT, not seen in PHTN
  – No change in PVRi
• $\alpha_2$ vasoconstrictor effect seen in peripheral vasculature, does not appear active in pulmonary vasculature

The Hemodynamic Response to Dexmedetomidine Loading Dose in Children With and Without Pulmonary Hypertension

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BACKGROUND: Dexmedetomidine, an $\alpha_2$ receptor agonist, is widely used in children with cardiac disease. Significant hemodynamic responses, including systemic and pulmonary vasodilation, have been reported after dexmedetomidine administration. Our primary goal of this prospective, observational study was to quantify the effects of dexmedetomidine initial loading dose (0.75 mcg/kg over 10 minutes) on mean pulmonary artery pressure (MPAP) in children with and without pulmonary hypertension.

METHODS: Subjects were children undergoing cardiac catheterization for other routine surgeries or after cardiac transplantation (n = 21). Patients with pulmonary hypertension (n = 21). After anesthesia induction with sevoflurane and fentanyl boluses, sevoflurane was discontinued and dexmedetomidine was administered with an initial 0.75 mcg/kg (0.5 mcg/kg) dose followed by a second dose of 0.75 mcg/kg every 5 minutes and a third dose of 0.5 mcg/kg. Measurements were made at baseline and 10 minutes after the initiation of infusion.

RESULTS: Mean hemodynamic responses were similar in the two groups with and without pulmonary hypertension. Hemodynamic responses included decreases in heart rate, mean arterial blood pressure, and systemic vascular resistance. Pulmonary vascular resistance was unchanged in patients with pulmonary hypertension, whereas mean pulmonary artery pressure decreased significantly in children with pulmonary hypertension.

CONCLUSION: Dexmedetomidine initial loading doses were associated with significant systemic vasoconstriction and hypotension, but a similar response was not observed in the pulmonary vasculature, even in children with pulmonary hypertension. Dexmedetomidine does not appear to be contraindicated in children with pulmonary hypertension. (Anesth Analg 2015;120:80-89)
• Anti-arrhythmic properties of dexmedetomidine
• Chrysostomou, et al, Children’s Hospital of Pittsburgh
• Decrease incidence and successful treatment
  – SVT
  – A-flutter
  – V-tach
  – JET
  – sinus tachycardia
Proposed antiarrhythmic mechanism

Tobias & Chrysostomou, *Ped Cardio, 2013*
The effects of dexmedetomidine on cardiac electrophysiology in children


• 12 children with SVT presenting for EPS
• 1 mcg/kg 10 mins, 0.7 mcg/kg/hr

• Results
  – Increased sinus node cycle length
  – Increased sinus node recovery time
  – AV node depression
    • Wenckebach cycle length prolongation
    • Prolong PR interval

• Avoid in EPS
• Caution in patient at risk for heart block, bradycardia
Other clinical uses

- Preoperative sedation
- Treatment of post-anesthesia shivering
- Procedural sedation
- MRI, radiology
- Anterior mediastinal mass
- Difficult airway
- Bronchoscopy
- Sedated echocardiography
- Sleep studies
- EEG
- Narcotic withdrawal
- Emergence delirium
Organ protection?

• Decrease post-bypass acute kidney injury (adults)

• Protection against contrast induced nephropathy by decreasing endothelin-1 and renin
  Bayram, *Ped Anes*, 2014
Organ Protection?

• Decrease in histological inflammation and multiple inflammatory molecules in VILI (dogs)

• Inhibit inflammation in lung of septic rats by suppressing TRL4/NF-κB pathway, decrease IL-6 and TNF-α (rats)
  Wu, *Mediators Inflamm*, 2013

• Decrease mortality and inhibit pro-inflammatory cytokines during polymicrobial sepsis (mice)
  Xu, *Inflamm Res*, 2013

• Protective mechanism against ischemia-reperfusion lung injury (rats)
Neuroprotection

• $\alpha_2$-AR thought to play trophic role in CNS signaling
• Isoflurane caused apoptosis and cognitive dysfunction in neonatal rats
• Inhibition of isoflurane-induced apoptosis
• Preserved long-term memory and cognitive function
Which do you choose?