Dexmedetomidine: Clinical Applications, Mechanisms of Action and New Developments

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Dexmedetomidine: Sedative and Neuroprotective Mechanisms of Action

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Dexmedetomidine, the D-enantiomer of medetomidine, is among the most potent sedative drugs known. It is also one of the best understood in terms of its molecular and cellular mechanisms. Its sedative (and probably its neuroprotective) effects are mediated by subtype A of the α_2 adrenergic receptor, a G-protein-coupled receptor. Acting as an agonist at this receptor, dexmedetomidine causes numerous intracellular changes that lead, generally speaking, to reduced neuronal excitability. These intracellular eeffects are mediated by a reduction in cyclic AMP concentrations. I will outline the genetic evidence that the α_{2A} adrenergic receptor is the key target for dexmedetomidine. At the cellular level, there is good evidence that dexmedetomidine causes its sedative effects by acting on neuronal pathways in the brain that mediate natural sleep and arousal. The similarities between the EEG patterns of natural sleep and dexmedetomidine sedation will be discussed. I will present the evidence that contrasts the actions of dexmedetomidine with other sedative agents that may account for the arousable nature of the sedation with dexmedetomidine. Although currently used only as a sedative/analgesic, dexmedetomidine may provide some protection over the reported neurotoxicity caused by certain anesthetics in neonates. I will briefly discuss this aspect of dexmedetomidine pharmacology. If time allows I will discuss the synergy that occurs between dexmedetomidine and other sedative/hypnotic drugs.

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The effect of dexmedetomidine on the Airway

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General anesthetics and sedatives attenuate upper airway muscle activity, rendering the airway vulnerable to obstruction. In contrast to other sedative agents, dexmedetomidine has been shown to have sedative properties that parallel natural non-rapid eye movement sleep, without significant respiratory depression. These advantages make dexmedetomidine an attractive agent for non-invasive procedural sedation in children. A few case reports have documented the benefits of using dexmedetomidine as a sedative and anesthetic in patients with obstructive sleep apnea (OSA) because of its lack of associated respiratory depression. It is unlikely that the putative benefits of dexmedetomidine are related solely to its lack of respiratory depression, as spontaneous respiration can be maintained with other anesthetics as well.

Our experience with dexmedetomidine in children with OSA for MRI sleep study suggests that it provides an acceptable level of sedation/anesthesia for MRI sleep studies in children with OSA and makes it possible to complete to successfully complete the study in the majority of children with resorting to the use of artificial airways. We have found that sedation with dexmedetomidine has greatly decreased the need for artificial airway adjuncts compared to propofol and pentobarbital, our previous agents of choice, and has made it possible to complete MR airway studies with fewer interruptions, especially in children with severe OSA. In a recent retrospective descriptive study we reviewed the records of 52 children receiving dexmedetomidine and 30 children receiving propofol for anesthesia during MRI sleep studies between July 2006 and March 2008 .The results showed that out of 82 children, MRI sleep studies were successfully completed without the use of artificial airways in 46 children (88.5%) in the dexmedetomidine group *versus* 21 children (70%) in the propofol group.

We recently explored the effect of increasing doses of dexmedetomidine on upper airway in children without OSA. Dexmedetomidine was administered to 23 children scheduled for Magnetic Resonance Imaging of the brain while breathing spontaneously *via* the native airway(study under publication). Static axial and dynamic sagittal midline Magnetic Resonance ciné images of the upper airway were obtained during low (1 mcg kg^{-1} h^{-1}) and high (3 mcg kg^{-1} h^{-1}) doses of dexmedetomidine. The results showed that upper airway changes associated with increasing doses of dexmedetomidine in children with no obstructive sleep apnea are small in magnitude and do not appear to be associated with clinical signs of airway obstruction. Even though these changes are small, all precautions to manage airway obstruction should be taken when dexmedetomidine is used for sedation. The effect of dexmedetomidine on airway morphology in children with OSA is still unknown. Currently we are examining the effect both dexmedetomidine and propofol on upper airway morphology in children with OSA.

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Dexmedetomidine in the ICU: Sedation Strategies and Cardiac Effects

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Dexmedetomidine is mainly an alpha-2 adrenoreceptor agonist with an effect for both the central and peripheral receptors. Due to its effect on these receptors, as well as an effect on imidazoline receptors, it has the potential for substantial cardiac and vascular effects. Dexmedetomidine kinetics follow a "triphasic" effect. With a distribution t ½ of about 6 mins after a loading dose, there is an initial unopposed effect on the peripheral alpha receptors which is associated with increased systemic vascular resistance (SVR) and blood pressure. Subsequently the effect on the central alpha-2 receptors, which is associated with sympatholysis, predominates and this is associated with decreased SVR. The third phase is only seen if dexmedetomidine is used in very high doses, usually > 2 mcg/kg/hr, and is associated with a predominant peripheral effect and thus increased SVR. The effect on the pulmonary vascular bed is less studied, but mostly it seems to follow a similar pattern as with the effect on the SVR. Though initial studies erroneously "concluded" that dexmedetomidine increases PVR by 150%, these studies did not take into consideration the proportional and simultaneous elevation in the SVR. In a recent pediatric study, it was actually demonstrated that conventional doses of dexmedetomidine are associated with a decrease in the PAP and a decrease in the PAP / SBP ratio (1, 2).

Despite the sympatholytic properties, so far studies have not demonstrated any direct negative inotropic effect from dexmedetomidine. On the contrary in a recent pediatric study, echocardiographic assessment of the ventricular function remained unchanged before and after dexmedetomidine (2). Nonetheless, it is important to note that a temporary reduction in

the cardiac output can be seen, especially during the loading phase via an increase in the SVR or during significant associated bradycardia. Therefore caution is warranted in patients with already tenuous cardiac output.

Though there are several concerns with the potential effect of dexmedetomidine on the cardiac conduction tissue, at conventional doses dexmedetomidine appears to have a wide safety margin. Other than the expected 10-30% decrease in the heart rate, the effects on the PR, QRS and QTc intervals are not significant. A recent pediatric study compared patients who received dexmedetomidine and patient who did not after cardiac surgery. No difference was found in the aforementioned ECG intervals (3). In a previous smaller study however, there was a small but statistical difference in the QTc in PR intervals (4). Overall vigilance should still be used when administered in conjunction with other negative chronotropic or inotropic agents.

A recent off label novel use, is in patients with supraventricular tachyarrhythmias. Though the mechanism of action remains largely unknown, dexmedetomidine has been shown to have promising anti-arrhythmic effects. In the only study so far (as well as from institutional experience) dexmedetomidine has been used successfully to treat and potentially prevent typical re-entry SVT, junctional ectopic tachycardia, atrial ectopic tachycardia and with less success atrial flutter / fibrillation. So far the experience with this off label use is promising, and importantly it appears to have less major adverse effects than e.g. adenosine for SVT (5). In some of the latest and ongoing studies, dexmedetomidine is being investigated for its potential effect in decreasing the inflammatory response to sepsis, cardiopulmonary bypass etc. So far data show that administration of dexmedetomidine is associated with a tendency towards a decrease inflammatory response and a decrease in the incidence of adverse clinical outcomes associated with inflammation, e.g. ventilatory support, capillary leak syndrome, arrhythmias, length of stay etc.

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Dexmedetomidine Sedation for Pediatric Sedation

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Sedation for radiological imaging studies encompasses the majority of all sedation related procedures outside of the intensive care unit. Neonates, infants, children, some adolescents and some neurologically compromised adults usually require some form of sedation or anxiolysis to accomplish an imaging study. Until the past decade, radiologists assumed responsibility for these sedation services.

Computerized tomography (CT) was introduced into clinical practice in the 1970's, with the Nobel Prize awarded to its inventors in 1979. Chloral hydrate, synthesized in 1832 and pentobarbital, synthesized in 1928, soon replaced DPT (Demerol-Medperidine, Phenergan-Promethazine and Thorazine-Chlorpromazine) because of their comparatively reduced incidence of respiratory depression. (1-2)

In 1990, commercial MRI was introduced and soon fentanyl, etomidate, ketamine and midazolam were trialled and abandoned because of untoward side effects. (3-5)

Propofol was introduced for MRI in the early 1990's and still represents an area of controversy between anesthesiologists and non-anesthesiologists with respect to whom should be qualified for administration in areas outside of the operating room. (6-14) Despite an appeal from the American Society of Gastroenterologists (ACG) in 2005 to the Food and Drug Administration (FDA) for removal of the warning in the propofol package insert cautioning its use "For general anesthesia or monitored anesthesia care (MAC) sedation….administered only by persons trained in the administration of general anesthesia", the package insert would remain unchanged. (15)

Dexmedetomidine is unique in that it can produce varying depths of sedation which resemble natural, non -rapid eye movement (REM) Stage 2 sleep with respect to cardiovascular, electroencephalogram (EEG) and respiratory effects. (16-21) In 2005, the application of dexmedetomidine sedation for radiological imaging was introduced to the pediatric community. It offered the advantage of minimal to negligible risk of apnea or respiratory depression. (16, 22-24) In 2008, it was approved by the FDA for adult sedation in areas outside of the operating room. Mason et al. trialled dexmedetomidine sedation with higher doses than FDA recommended and had success for CT scans. At these doses, a decrease in heart rate and mean arterial blood pressure were observed, still within normal range for age, along with a 16% incidence of sinus arrhythmia. This study suggested that higher dosages of dexmedetomidine could produce successful imaging conditions for short studies, with average recovery times of 32 minutes. (25)

Heard et al. later confirmed that the lower dosing regimen for dexmedetomidine would not prove successful for MRI when used alone, but could be successful when coupled with.1 mg/kg IV midazolam. (26) At higher doses (3 mcg/kg bolus, 2 mcg/kg/hr infusion), dexmedetomidine as the sole agent was successful for 97.6% of 747 children undergoing MRI. In 16% the heart rate decreased below 20% of age adjusted clinical normal values, with mean arterial blood pressures remaining within 20% of age adjusted norms. (27) A larger study with these higher dexmedetomidine doses in 250 children for CT studies revealed similar hemodynamic responses. (28) Unless bradycardia is associated with hypotension, the routine administration of glycopyrrolate should be avoided, for fear of extreme hypertension. (29) Recent studies indicate that hypertension can occur with dexmedetomidine when used in

higher doses for MRI sedation. There may be a relationship between dosing and occurrence of hypertension in this patient population. (30)

The experience with dexmedetomidine is still in its infancy. It is important to recognize that not every child is an appropriate candidate for dexmedetomidine sedation. The potential application of dexmedetomidine sedation has yet to be fully explored. Its failure to suppress seizure activity on EEG may expand its usage to sedation for those children who are unable to tolerate an unsedated EEG. (21) Its ability to simulate natural sleep conditions may also lend itself to being an appropriate sedative for studies which require natural sleep conditions. The analgesic properties have yet to be fully explored and will affect our application of dexmedetomidine sedation for painful procedures. The dosing of dexmedetomidine in the pediatric population will hopefully be better understood someday after more safety and outcome data are collected and evaluated within the framework of dexmedetomidine blood concentration at the higher dosages. It is only with a better understanding of the pharmacokinetic and pharmacodynamic profile that we will have a better idea of the potential applications, limitations and risks.

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Point-Counterpoint Session: Dexmedetomidine versus Propofol: Clinical limitations, advantages and disadvantages

(Gregory Hammer, MD and Joseph Tobias, MD)

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Dexmedetomidine represents a new class of agent which, although only FDA-approved for use in adults, has been shown to be efficacious in several different clinical scenarios in infants and children including sedation during mechanical ventilation, procedural sedation, supplementation of postoperative analgesia, prevention of emergence delirium, and treatment of withdrawal.[1] Dexmedetomidine and clonidine are members of the imidazole subclass which exhibits a high

ratio of specificity for the α_2 versus the α_1 receptor. Clonidine exhibits an α_2:α_1 specificity ratio of 200:1 while that of dexmedetomidine is 1600:1 thereby making it a complete agonist at the α_2-adrenergic receptor.[1] Dexmedetomidine has a short half-life (2-3 hours vs. 12-24 hours for clonidine) and is commercially available for intravenous administration. The pharmacokinetics of dexmedetomidine are stable throughout the age ranges of the pediatric population.[2]

Given the lack of a perfect agent for sedation, dexmedetomidine has been accepted in the pediatric antesthesia and critical care population as a potential alternative to commonly used agents such as benzodiazepines, barbiturates, and propofol. Central CNS stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the *locus cereleus* in the brainstem play a prominent role in the sedation and anxiolysis produced by dexmedetomidine. Decreased noradrenergic output from the *locus cereleus* allows for increased firing of inhibitory neurons, most importantly the γ-amino butyric acid (GABA) system. Primary analgesic effects and potentiation of opioid-induced analgesia result from the activation of α_2-adrenergic receptors in the dorsal horn of the spinal cord and the inhibition of substance P release. These interactions with central nervous system (CNS) and spinal cord α_2-adrenergic receptors mediate dexmedetomidine's primary physiologic effects including sedation, anxiolysis, analgesia, a decrease of the minimum alveolar concentration (MAC) of inhalational anesthetic agents, decreased renin and vasopressin levels leading to diuresis, blunting of the sympathetic nervous system, and lowering of HR and BP. A significant advantage of dexmedetomidine over other agents commonly used for ICU sedation include a limited effect on normal sleep cycles thereby decreasing the potential for delirium and its resultant effects on ICU moribidity and mortality. Additionally, when used in the arena of procedural sedation or during spontaneous ventilation in other clinical scenarios, dexmedetomidine has limited effects on ventilator function with a decreased incidence of airway and respiratory events when compared with propofol.[3-5] Although dexmedetomidine does possess negative chronotropic effects, in the majority of patients, the resultant lowering of HR have limited clinical effects. Additionally, these properties have been used as a therapeutic agent in patients with tachy-arrhythmias following surgery for congenital heart disease. The beneficial physiologic effects of dexmedetomidine carry over to the CNS where dexmedetomidine has been shown to lower cerebral blood flow and cerebral metabolic rate for oxygen and to provide neuroprotective effects during hypoxic-ischemic events.[6,7] Dexmedetomidine does not affect ICP and unlike many other agents, dexmedetomidine does not accelerate apoptosis in the neonatal period.[8-10] Given these beneficial effects, the clinical uses of dexmedetomidine are likely to continue to increase and expand in the pediatric population.

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The Limitations of Dexmedetomidine in Infants and Children

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The off-label use of dexmedetomidine (DEX) in neonates, infants and children as an adjunct to general anesthetic agents during surgery as well as for sedation during diagnostic procedures, in the perioperative period and in the pediatric ICU has become common. The benefits of DEX are significant but adverse effects with this novel agent are also common. An effect of DEX that is often desirable during and after surgery is the decrease in sympathetic outflow from the brain, resulting in a decrease in heart rate and blood pressure. Additional benefits include sedation, an opioid sparing effect and the lack of associated respiratory depression. There are, however, potentially adverse hemodynamic effects of the drug, including bradycardia, hypertension and hypotension. In addition, DEX is associated with a relatively slow offset; recovery in the PACU following surgery or diagnostic and therapeutic procedures may be prolonged.

The use of DEX during pediatric cardiac surgery has been reported.[i] While the negative chronotropic effect of DEX may be beneficial in adults with coronary artery disease, it remains uncertain whether this represents an advantage in neonates and infants undergoing cardiac surgery. In the latter population, drugs such as dopamine, dobutamine and epinephrine are commonly used following cardiopulmonary bypass for inotropy and in order to maintain the heart rate in the range of 120 to 140 bpm. Atrioventricular pacing may be used when the heart rate is below 100 – 120 bpm despite these agents. It may be illogical to infuse DEX, with its effect of decreasing endogenous catecholamine secretion, while at the same time administering catecholamines for their inotropic and chronotropic effects. Instead, cardiac anesthesiologists and intensivists might consider what degree of sympathetic tone is desirable for a particular patient according to their underlying physiology. In patients in whom diminished levels of circulating catecholamines are desirable, including those with coronary insufficiency, the use of DEX may be beneficial. On the other hand, in neonates and infants exposed to prolonged cardiopulmonary bypass, aortic cross-clamping and ventricular incisions, for whom exogenous catecholamine administration is planned, DEX may not be an appropriate drug. Other adverse effects of DEX include depression of sinus and AV nodal

function, leading to bradycardia and possibly causing or prolonging heart block in at-risk patients in the cardiac OR and ICU.[ii]

DEX has been used as a pre-medication via the intranasal route.[iii] When compared to midazolam, separation from parents was equally well accepted but patients premedicated with DEX more frequently became distressed during induction of anesthesia. This is consistent with the more arousable state during DEX sedation compared with benzodiazepine or propofol sedation. The facilitated arousal associated with DEX may be an advantage in cooperative adults, but this feature may require that large doses of DEX or combination with midazolam, propofol or ketamine be used for procedural sedation in children.[iv] In order to limit the dose of DEX needed to sedate children for MRI (and, presumably, shorten recovery time associated with high doses), it has been combined with a single dose of midazolam; when this combination was compared with propofol, recovery was nevertheless prolonged.[v] When combined with ketamine for cardiac catheterization, children were less well sedated and had longer recovery times compared with the combination of propofol and ketamine.[vi] The contribution of DEX when combined with propofol for procedural sedation in children is questionable.[vii]

DEX is another useful tool in the toolbox of pediatric anesthesiologists and intensivists given that the potential drawbacks of the drug are considered.

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[vii] Hammer GB, Sam WJ, Chen MI, Golianu B, Drover DR: Determination of the pharmacodynamic interaction of propofol and dexmedetomidine during esophagogastroduodenoscopy in children. *Pediatr Anesth* 2009;19:138-44.

Mechanistic Approach to Use of Dexmedetomidine

Julie Finkel, MD, Children's National Medical Center, Washington D.C.,

A Mechanistic Approach to Defining Strategies for the use of Dexmedetomidine in Infants and Children

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Introduction

- Widely used, off-label use as adjunct in the peri-operative period
- Sedative/hypnotic
- Analgesic
- Anxiolytic
- Sympatholytic

Intra-operative Applications

- Provides superior post-operative analgesia compared with morphine
  Arain et al. Anesth. Analg 2004; 98: 153-158
- Profound opioid sparing properties
- PONV
  Benedetti et al. Anesthesiology2005; 18:616-613
- Role as sole agent controversial

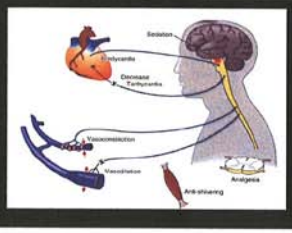
Introduction

- Review mechanisms
- Pharmacology
- Intra-operative applications

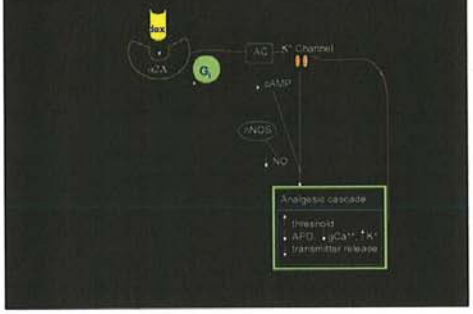
Alpha-2 Agonists

	Clonidine	Dexmedetomidine
$\alpha 2 : \alpha 1$	220:1	1620:1
$t\frac{1}{2}\ \beta$ (h)	6-10	2-3
MAC reduction	48%	90%

Primary Alpha$_2$ Sites of Action

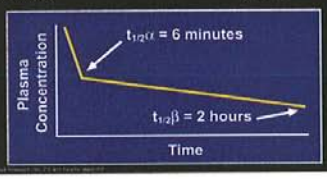


Alpha2-adrenergic Analgesic Cascade

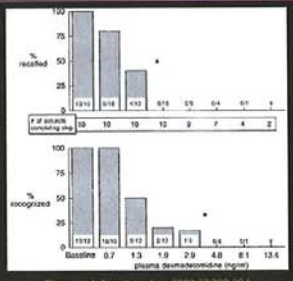


Pharmacokinectics

- Zero order kinetics
- Distribution $t_{1/2\alpha}$ 6 minutes
- Terminal elimination $t_{1/2\beta}$ 2 hours
- Steady-state volume of distribution 118 liters
- Clearance 39 L/h

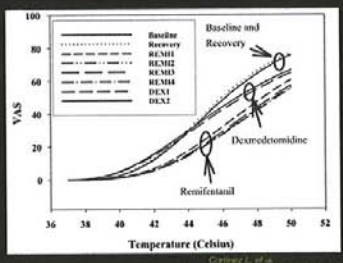


Dexmedetomidine and Recall



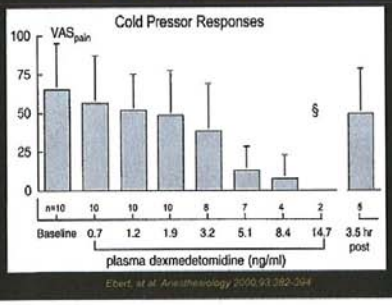
Ebert, et al. Anesthesiology 2000;93:382-394

Stimulus Dependent Analgesia: Heat Pain



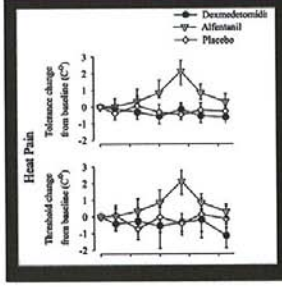
Cortínez L, et al. Anesthesiology 2004;101:1377-83

Stimulus Dependent Analgesia: Cold Pain



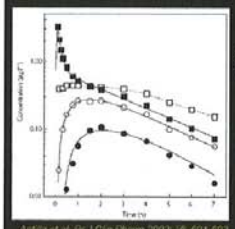
Ebert, et al. Anesthesiology 2000;93:382-394

Dexmedetomidine vs. Alfentanil
Heat Pain



Angst, et al. Anesthesiology 2004; 101:744-52

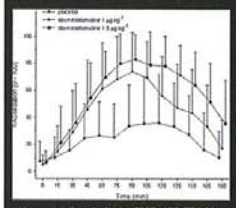
Bioavailability of Dexmedetomidine after Extravascular Doses



single 2.0 μg kg−1 dose. i.v. ( ); i.m. ( ); buccal (o)

Anttila et al. Br J Clin Pharm 2003; 56: 691-693

Sedative and Analgesic Effects of Intranasal Dexmedetomidine



- 0, 1, and 1.5μg/kg compared (100 μg/ml concentration)
- Onset 45 min
- Peak 90-150min
- No impact on pressure pain

Yuen et al. Anesth Analg. 2007; 105: 374-80

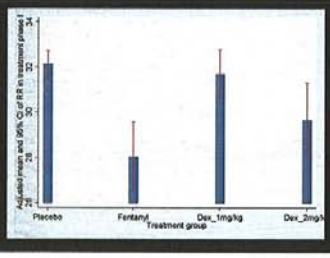
Intranasal Dexmedetomidine for BMT

- 100 patients ages 6mos to 6 years
- 4 groups: dex 1 and 2 μg/kg, fent 2 μg/kg and placebo given immediately after inhalation induction with sevoflurane.
- Hemodynamic and recovery characteristics

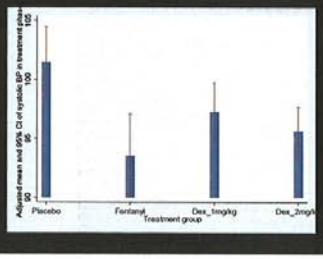
Preliminary Analysis IN Dexmedetomidine

- Dex 1 and 2 not significantly different than fentanyl in terms of agitation and pain
- No difference in vomiting between groups
- Dex 2 stayed longer in PACU

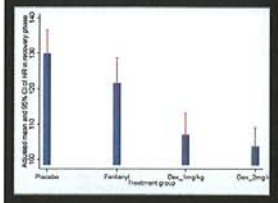
Preliminary Analysis IN Dex: RR Dexmedetomidine vs. Fentanyl p=0.004



Preliminary Analysis IN Dex: SBP Dex vs. Fentanyl P=0.027

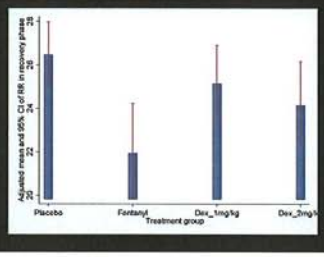


Preliminary Analysis IN Dex: PACU HR

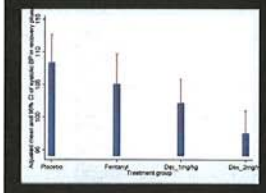


- Placebo vs. Dex p=0.000
- Dex vs. Fentanyl p=0.07

Preliminary Analysis IN Dex: PACU RR Dex vs. Fentanyl p=0.007

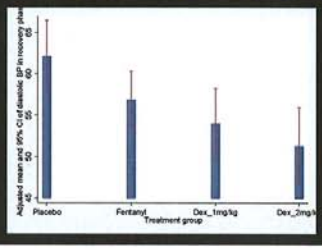


Preliminary Analysis IN Dex: PACU SBP



- Dex 1 vs. Dex 2 p=0.046
- Dex vs. Placebo p=0.021
- Dex 2 vs Placebo p=0.003
- Dex 2 vs. Fent p=0.008

Preliminary Analysis IN Dex: PACU DBP Dex vs. Placebo p= 0.000



IN Dexmedetomidine: Preliminary Conclusions

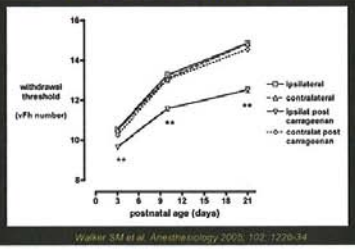
- Dexmedetomidine significantly less impact on RR both intra-op and in PACU
- SBP significantly decreased in dex 2 vs fent group in PACU
- Fent and dex provided similar impact on mitigation agitation and pain compared with placebo

Response to Dexmedetomidine is Developmentally Regulated

- Sensory processing P3, P10 and P21 rat pups
- Reversal of inflammatory hyperalgesia
- Sedation
- Epidural vs. systemic administration compared

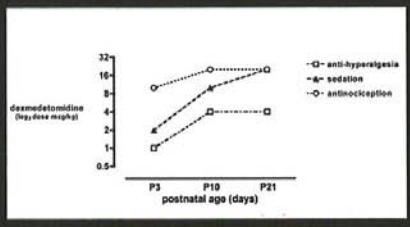
Walker SM et al. Anesthesiology 2005; 102: 1226-34

Response to Dexmedetomidine is Developmentally Regulated: Mechanical Withdrawal Thresholds



Walker SM et al. Anesthesiology 2005; 102: 1228-34

Response to Dexmedetomidine is Developmentally Regulated



Walker SM et al. Anesthesiology 2005; 102: 1228-34

Developmental Implications for Dexmedetomidine

- Increased functional sensitivity in youngest pups
- Therapeutic window is narrow in early development

Dexmedetomidine: Epidural Administration

- Effect is spinally mediated
- In all age groups, max epidural dose had no effect when given systemically
- Epidural dex is rapidly absorbed into the CSF and reaches binding sites in the SC
- Epidural:systemic potency is 1:5

Asano et al. Anesth Analg 2000; 90: 400-7

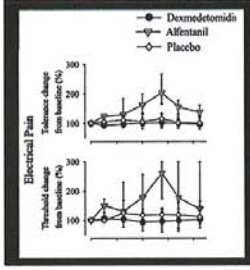
Future Directions: Neuraxial Administration

- Spares supraspinal and systemic sites from extensive drug exposure
- Produce profound analgesia without sedation

Summary

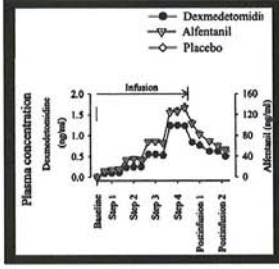
- Preliminary data suggest that dex has a significant potential role as an anesthetic adjunct
- PK/PD relationships need to be further defined
- Controlled clinical trials are required to establish efficacy and risk-benefit profile of systemic and neuraxial applications

Dex vs. Alfentanil
5Hz Frequency Pain



Angst, et al. Anesthesiology 2004; 101:744-52

Dex vs. Alfentanil
Heat/5Hz Frequency Pain



Angst, et al. Anesthesiology 2004; 101:744-52

Dex for Pediatric Tonsillectomy

- Single dose of dexmedetomidine vs. fentanyl on emergence and recovery characteristics
- 100 children aged 2-12y
- Randomized to receive a single IV dose of fentanyl 1mg/kg, fentanyl 2mg/kg, dex 2mg/kg, dex 4mg/kg administered over 10min immediately after induction

Dex for Pediatric Tonsillectomy

- Times to emergence
- Recovery characteristics
- Hemodynamic parameters

Dex for Pediatric Tonsillectomy: Emergence and Recovery

	Fent 1	Fent 2	Dex 2	Dex 4	P value
Time to emergence mean (SD) sec	306±152	397±210	375±223	490±361	0.0389
Incidence of pain in PACU (%)	25	18	7	7	0.000
Pain score > 6 (%)	15	9	4	1	0.000
Incidence of agitation in PACU (%)	25	24	14	12	0.000
Agitation score > 2 (%)	15	14	5	4	0.003
Time to 1st morphine dose mean (SD) min	19±25	44±61	61±89	138±123	0.0004

Dex for Pediatric Tonsillectomy: Emergence and Recovery

	Fent 1	Fent 2	Dex 2	Dex 4	P value
Nausea PACU (%)	5	3	2	0	0.147
Retching PACU (%)	5	3	2	1	0.361
Vomiting PACU (%)	3	3	0	2	0.420
Morphine PACU (%)	19	16	13	14	0.555
LOS in PACU mean (SD) min	54.2±13	66.4±27	66.9±23.7	81.6±33	0.0015

Dex for Pediatric Tonsillectomy: Hemodynamic Responses

	Fent 1	Fent 2	Dex 2	Dex 4	P value
Light anesthesia (HR and BP 20% ↑ baseline (%)	9	7	0	1	**0.002**
Incidence of hypertension (%)	23	18	11	14	**0.017**
Incidence of hypotension (%)	3	5	9	8	0.100
Incidence of tachycardia (%)	18	17	5	9	**0.002**
Incidence of bradycardia (%)	3	3	9	12	**0.003**

Dex for Pediatric Tonsillectomy: PACU Pain and Sedation Characteristics

	Dex 2	Dex 4	P value
Time to emergence mean (SD) sec	375±223	490±363	0.1571
LOS in PACU mean (SD) min	66.9±23.7	81.6±33	**0.0311**
Incidence of pain in PACU (%)	14	14	0.853
Pain score ≥6 (%)	8	2	0.129
Incidence of agitation in PACU (%)	28	24	0.371
Agitation score ≥2 (%)	10	8	0.611
Time to 1st morphine dose mean (SD) min	61±9	137±123	0.0683

Dex Analgesic Ceiling Effect?

- Preliminary evidence in pediatric surgical population

Awake Craniotomy

- Dexmedetomidine was used as a primary anesthetic for brain mapping of the cortical speech area.
- The asleep-awake-sleep technique provided adequate sedation and analgesia throughout the surgery
- Allowed the patient to complete neuropsychological tests.

Arol et al. J Neurosurg Anesthesiol 2003; 15:263-266

Spinal Fusion Surgery

- Opioid sparing
- Propofol sparing

Ngweniyama et al. Pediatric Anesthesia 2008; 18: 1190-195

- Does not affect neurophysiologic monitoring when given in combination with remifentanil and propofol or remifentanil and desflurane.

Tobias et al. Pediatric Anesthesia 2008; 18:1082-1088
Bala et al. Anesthesiology 2008; 109: 417-25

Dexmedetomidine: Transmucosal Applications

- Buccal absorption is 82%

Anttila et al. Br J Clin Pharm 2003; 56: 691-693

- IN well tolerated by adults for sedation
- Comparable to oral midazolam for preoperative sedation