

An Update on Alpha 2 Agonists- Where do They Fit into Our Pediatric Anesthesia Practice?

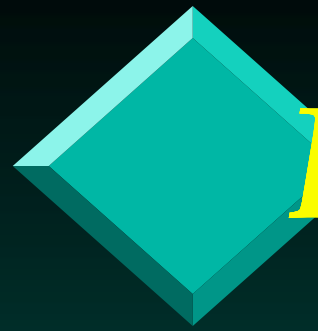
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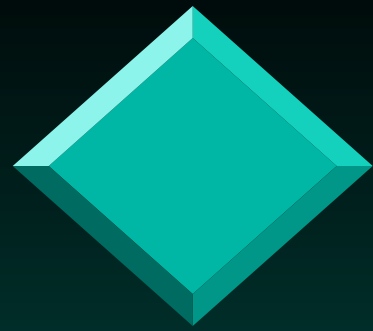
Loma Linda University





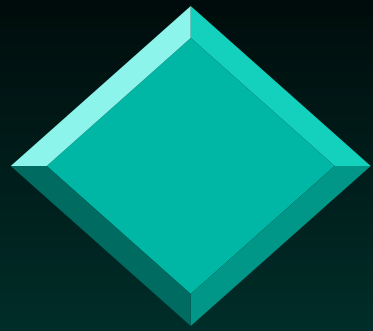
Disclosure Statement

❖ Nothing to Disclose



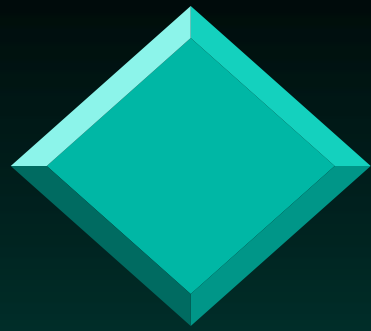
Clonidine

- ❖ Partial agonist, alpha-2 to alpha-1 selectivity ratio of 39
- ❖ Supplied as oral tablets (100, 250, 300 μg), injectable solution (150 $\mu\text{g}/\text{ml}$) and transdermal patch releasing 100, 200, 300 μg over 24 hours



Clonidine Actions - 1

- ❖ CNS - sedation and anxiolysis via oral and neuraxial route
- ❖ CV System
 - Decreased BP by decreased sympathetic outflow
 - Resets baroreflex - decreases HR for a given increase in BP
 - Inhibits SA node firing, prolong PR, AV and QT interval (via vagal effects)



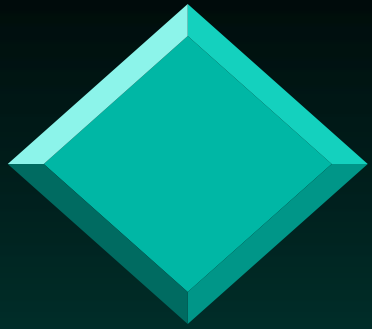
Clonidine Actions - 2

- ❖ **Respiratory** – 300 µg slight decrease in minute ventilation
 - No effect on hypercapnic or hypoxic ventilatory drive
- ❖ **Renal** – decreases secretion of vasopressin
- ❖ **Analgesia** – blocks afferent fibers in peripheral or CNS
 - Modulates efferent pain responses from the brain stem
 - Releases substance P in dorsal horn of SC



Use in the Pediatric Patient

- ❖ Premedication
- ❖ Nausea and vomiting
- ❖ Shivering and delirium
- ❖ Epidural analgesia



Premedication

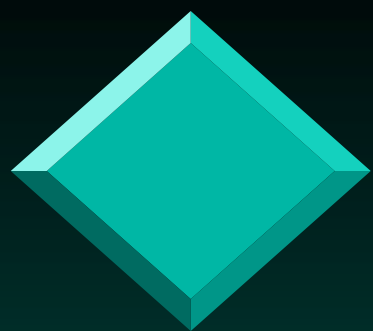
- ❖ Slowly absorbed orally, peak concentrations in 60-90 min
- ❖ Dissolve parenteral formula in apple juice
- ❖ Elimination half life 9 - 12 hours



Comparison of Oral Premedication With Clonidine Vs Midazolam

- ❖ Clonidine 4 mcg/kg vs midazolam 0.5 mg/kg
- ❖ Clonidine - 60 min prior to induction
- ❖ More anxiety on separation and induction
- ❖ Lower intraoperative BP
- ❖ Shorter surgery, anesthesia and emergence times
- ❖ Decreased need for supplemental O₂ in recovery
- ❖ Larger postop opioid requirements
- ❖ Higher pain scores
- ❖ Maximum excitement higher
- ❖ Equal discharge readiness, postop emesis, and 24 hour analgesic requirement.

Fazi LM, et al. Anesth Analg 2001;92:56-61.



Premedication in Children: a Comparison of Oral Midazolam and Clonidine

- ❖ 64 children age 1-6 years
- ❖ Oral midazolam 0.5 mg/kg or oral clonidine 4 µg/kg
- ❖ Onset 30 min with midazolam vs 38 min with clonidine
- ❖ Level of sedation better with clonidine, more emergence agitation in the midazolam group
- ❖ Parental satisfaction was higher in the clonidine group

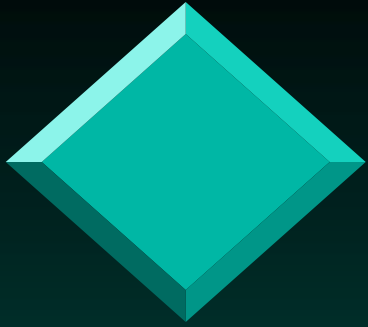
Almenrader N, et al *Pediatric Anesthesia* 2007;17:1143-49



Analgesia for Adenotonsillectomy

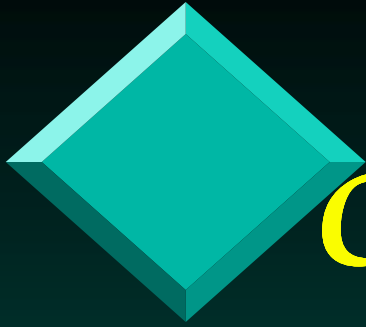
- ❖ Analgesia for adenotonsillectomy
 - 36 children-age 7-12 years of age
 - 4 mcg/kg clonidine 60-90 min preop or fentanyl 3 mcg/kg intraop
 - More sedation in the clonidine group preoperatively but amount of morphine or codeine needed post op was the same

Reimer EJ et al. Can J Anaesth 1998;45:1162-67



Other Uses

- ❖ Nausea and Vomiting - 11% incidence in strabismus surgery patients
 - *Mikawa K et al Can J Anesth 1995;42:977-81*
- ❖ Shivering and delirium
 - Decreased with clonidine either caudal or intravenous 2-3 $\mu\text{g}/\text{kg}$ with sevoflurane anesthesia
 - *Motsch J et al Anesthesiology 1999;91:A1261*
 - *Kulka PJ et al Anesth Analg 2001;93:335-8*



Case Report:

Cardiac arrest in a child with cerebral palsy undergoing sevoflurane induction of anesthesia after preoperative clonidine

Goldfinger MM, Tripi PA

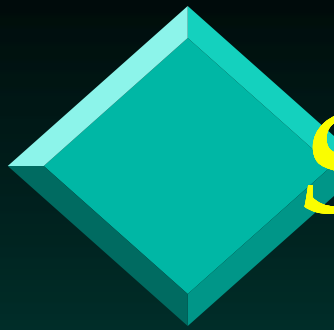
Pediatric Anesthesia 2007;17:270-72



Data

- ❖ 5 year old with CP and seizures for baclofen pump insertion
- ❖ Medications - oral baclofen 15 mg tid, clonidine 0.1 mg at bedtime
- ❖ Cardiac arrest during induction with sevoflurane
- ❖ 3 doses of clonidine had been given over 9 hours prior to surgery (18 ug/kg) recommended dose 5-7 ug/kg/24 hr
- ❖ Severe bradycardia and myocardial depression from combination of clonidine and sevoflurane successfully treated with atropine and epinephrine.

Goldfinger M, et al. Pediatric Anesthesia 2007;17:270-2.



Studies - Caudal Use - 1

Ambulatory Surgery

Duration of Action

Bupivacaine 0.25% (.75 ml/kg)

346 min

1/200,000 epinephrine

300 min

1 μ g/kg clonidine

360 min

2 μ g/kg clonidine

360 min

Mild hypotension but no bradycardia or respiratory depression with clonidine

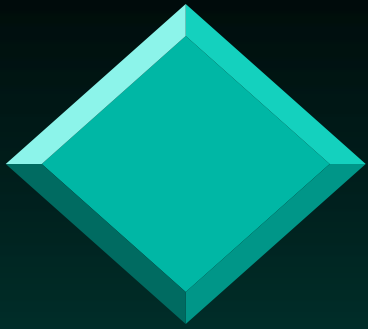
Klimescha W et al Anesth Analg 1998;86:54-61



Epidural Analgesia - Caudal Use - 2

- ❖ Ropivacaine 0.1% (1 ml/kg) with 2 $\mu\text{g}/\text{kg}$ clonidine - better postoperative analgesia than 0.2% ropivacaine (1 ml/kg) - no sedation or motor blockade

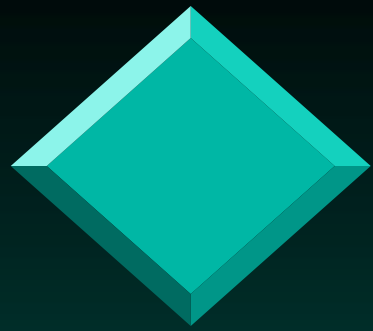
- Ivani G et al Acta Anaesth Scand 2000;44:446-49



Nonopioid additives to local anaesthetics for caudal blockade in children: a systematic review

*Ansermino M, Basu R, Vandebeek C
and Montgomery C*

Paediatric Anaesthesia 2003;13:561-573



Conclusions

- ❖ There is good evidence that addition of clonidine 1-2 $\mu\text{g}/\text{kg}$ to local anesthetics prolongs the duration of caudal analgesia
- ❖ The associated side effects typically mild sedation with doses less than 2 $\mu\text{g}/\text{kg}$ appear to be minimal or beneficial in pediatric patients



Local Anesthetic Concentration?

- ❖ 30 children age 2-8 yrs -1 ml/kg 0.125% bupivacaine with 1/200,000 epinephrine alone or with 2mcg/kg clonidine-no enhancement of postoperative analgesia

Wheeler M et al. Pediatric Anesthesia 2005;15:476-83

- ❖ 36 children age 6 months to 6 yrs -1 ml/kg 0.125% bupivacaine with 2 mcg/kg clonidine or saline-no difference in analgesic duration

Joshi W et al. Pediatric Anesthesia 2004;14:483-6

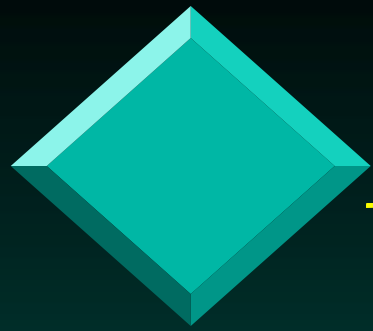
- ❖ 60 children age 1-10 yrs- 1 ml/kg 0.125% bupivacaine and clonidine 2 mcg/kg- duration of analgesia 650 min vs 205 min

Yildiz TS et al. Acta Anaesthesiologica Scand 2006;50:501-4

Continuous Lumbar Epidural

- ❖ Ropivacaine 0.08% (.16 mg/kg/hr) with .08-.12 mcg/kg/hr clonidine vs ropivacaine 0.1% (0.2 mg/kg/hr)
- ❖ Better postoperative analgesia, increased time to first analgesic demand and decreased doses of supplemental analgesia in the first 48 hrs without increase in sedation or other side effects

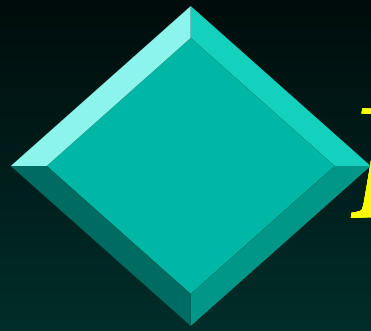
De Negri P et al Anesth Analg 2001;93:71-76



Peripheral Nerve Blockade

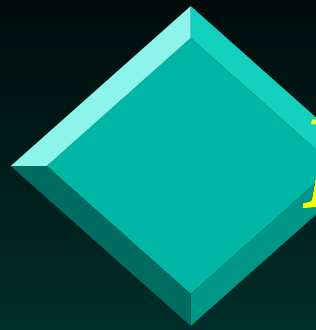
- ❖ 215 children undergoing infraclavicular, lumbar plexus, femoral, fascia iliaca or sciatic nerve block
- ❖ Adding clonidine 1 ug/kg to bupivacaine(.1-.25%) or ropivacaine(.1-.2%) extended the sensory block by 4-5 hours but also increased the incidence of motor blocks.

Cucchiaro G, Ganesh A. Anesth Analg 2007;104:532-7.



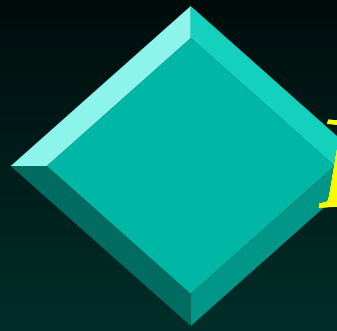
Dexmedetomidine

- ❖ Eight times more specific for alpha-2 adenoreceptors than clonidine
- ❖ Sedation in ICU
- ❖ IV use only (being investigated in humans for epidural use)
- ❖ Dose 1.0 $\mu\text{g}/\text{kg}$ for 10 min then 0.2-0.7 $\mu\text{g}/\text{kg}/\text{hr}$ – distribution half life 9 min – elimination half life – 2 hours



Dexmedetomidine Actions - 1

- ❖ CNS – sedation and anxiolysis – decreased use of midazolam, decreases MAC by 90%
 - *Aho M et al Anesth Analg 1992;75:940-46*
- ❖ Respiratory – 2 µg/kg bolus increased PCO₂ by 4.2 mm Hg, decreased minute ventilation by 20%, minimal changes in frequency
 - *Belleville JP et al Anesthesiology 1992;77:1125-33*



Dexmedetomidine Actions - 2

- ❖ Analgesia - reduced morphine requirements by 50% in patients mechanically ventilated and intubated

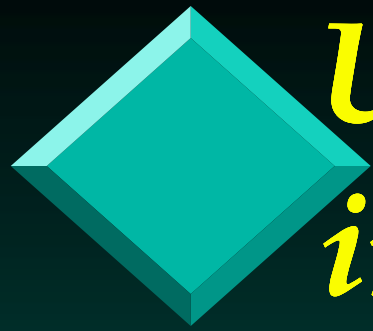
Venn RM et al Anaesthesia 1999;54:1136-42



Pharmacology of Dexmedetomidine in Children

- ❖ 36 children age 2-12 years for GU/GI/Plastic surgery
- ❖ Bolus of $1\mu\text{g}/\text{kg}/\text{hr}$ over 10 minutes (total $6\mu\text{g}/\text{kg}$)
- ❖ Pharmacodynamic responses: heart rate and systolic BP decreases were similar to adults except for early transient increase in SBP in one patient.
- ❖ Elimination half life was 110 min (1.8 hr) similar to adults

Petroz GC et al. Anesthesiology 2006;105:1098-1110



Use of Dexmedetomidine in the Pediatric Patient

- ❖ Sedation and anxiolysis in intubated patients
- ❖ Premedication
- ❖ Controlled hypotension
- ❖ Sedation for invasive and noninvasive procedures
- ❖ Emergence agitation
- ❖ Shivering



Sedation and Anxiolysis in Intubated Patients

- ❖ 0.25 µg/kg/hr dexmedetomidine equal to 0.2 mg/kg/hr midazolam. Less morphine supplementation, better sedation with fewer changes in infusion rate
- ❖ Bridge to weaning - decreases use of opioids and other sedatives that cause respiratory depression.

Tobias JP, et al. Paediatric Anaesthesia 2002;12:171-175.

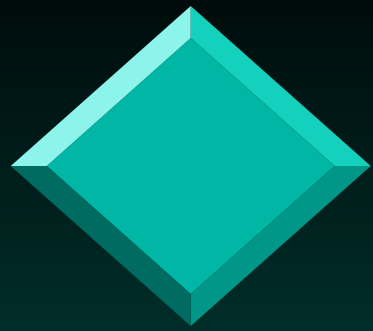
- ❖ Watch with concomitant digoxin use in infants - bradycardia.



Dexmedetomidine Use After Cardiac and Thoracic Surgery

- ❖ 33 patients - age 1-8 years, spontaneously breathing mechanically ventilated patients
- ❖ Dexmedetomidine infusion - 0.2-0.25 ug/kg/hr (average 0.3 ± 0.05 ug/kg/hr)
- ❖ Rescue medications were fentanyl, morphine, midazolam (49 doses given)
- ❖ Children < 1 year required higher dexmedetomidine infusion rates - 0.4 ug/kg/hr, more rescue medications
- ❖ Sedation was achieved in 93% with analgesia in 83%
- ❖ Hypotension was seen in 15% with a trend toward lower heart rates.

Chrysostomou C, et al. Pediatr Crit Care Med 2006;7:126-31.



Premedication

- ❖ 18 patients (18-38 yrs) given placebo, intranasal dexmedetomidine 1 μ g/kg or intranasal dexmedetomidine 1.5 μ g/kg
- ❖ Onset 45 min with a peak effect at 90-105 min
- ❖ Both doses produced equal sedation with decreases in BIS, SBP DBP and heart rate

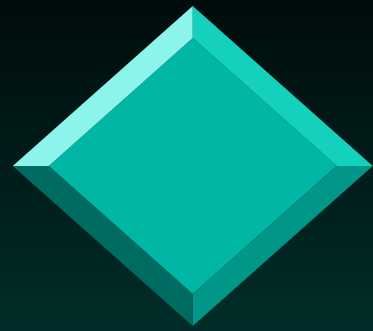
Yuen VN et al. *Anesth Analg* 2007;105:374-80



Awake Craniotomy

- ❖ 2 patients, age 16 years for seizure focus resection, weight 55-65 kg
- ❖ Fentanyl (25-50 ug), propofol 100-200 mg/kg/min and dexmedetomidine 0.2-0.4 ug/kg/hr
- ❖ Asleep part of procedure - dexmedetomidine 0.2-0.7 ug/kg/hr
- ❖ Awake part of procedure 0.1-0.2 ug/kg/hr
- ❖ Supplemented with local infiltration and N blocks during opening skin and bone flap.
- ❖ May replace propofol 100 ug/kg/min and remifentaniol 0.5-2.0 ug/kg/min.

Everett LL, et al. Pediatric Anesthesia 2006;16:338-42.

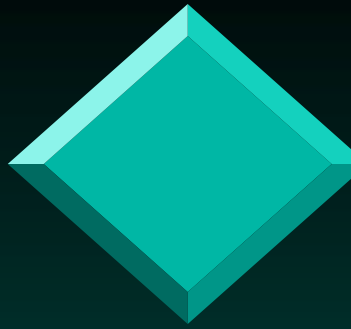


Controlled Hypotension

❖ Spinal instrumentation and fusion

- Isoflurane (0.2-0.3%) in 50% N₂O/O₂
- Remifentanil 0.2-0.3 µg/kg/min
- Dexmedetomidine 0.2 µg/kg/hr initial infusion 0.5-0.7 µg/kg/hr
- MAP 55-65 mmHg - Decreased HR
- Decreased β blocker use, good SSEP, decreased HPV, decreased cerebral vasodilatation, decreased tachycardia than with nitroprusside use

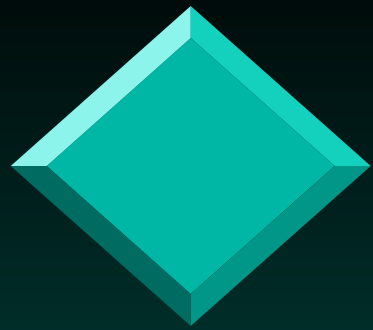
Tobias JD et al Paediatric Anaesthesia, 12.171-175



*Case report:
Dexmedetomidine as a
total intravenous
anesthetic in infants*

Shukry M, Kennedy K.

Pediatric Anesthesia 2007;17:581-3



Data

- ❖ 4 infants, 2 wks-11 months for direct laryngoscopy and bronchoscopy
- ❖ Dexmedetomidine - 1 ug/kg/min until surgically fit status (total dose 2-5 ug/kg)
- ❖ Glottis topicalized with 1% lidocaine (5 mg/kg total dose)
- ❖ One patient needed propofol bolus 3.7 mg/kg

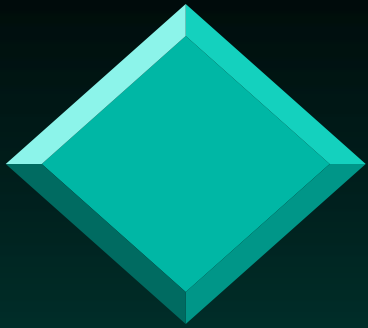
Shukry M, et al. Pediatric Anesthesia 2007;17:581-3.



Dexmedetomidine - Ketamine and Propofol - Ketamine for Cardiac Catheterization

- ❖ Group I - 22 children - bolus 1 ug/kg dexmedetomidine and ketamine 1 mg/kg over 10 min followed by infusion of dexmedetomidine 0.7 ug/kg/hr and ketamine 1 mg/kg/hr
- ❖ Group II - 25 children - 1 mg/kg propofol and 1 mg/kg ketamine followed by an infusion of 100 ug/kg/min propofol and 1 mg/kg/hr ketamine
- ❖ Recovery time longer and lower HR in Group I as well as more bolus ketamine 1 mg/kg needed to obtain sedation.

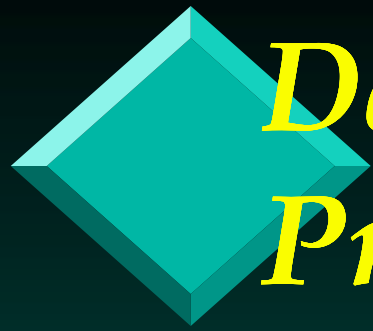
Tosun Z, et al. J Cardiothorac Vasc Anesth 2006;20:515-9.



Dexmedetomidine and CT Scan

- ❖ 62 children-mean age 2.8 yrs (6mo-9.7 yrs)
- ❖ Dexmedetomidine loading dose of 2 $\mu\text{g}/\text{kg}$ over 10 min followed by an infusion of 1 $\mu\text{g}/\text{kg}/\text{hr}$
- ❖ Mean loading dose was 2.2 $\mu\text{g}/\text{kg}$ with 52 patients needing only 2 $\mu\text{g}/\text{kg}$ to complete the scan
- ❖ Time to achieve sedation was 6-20 min, decreased HR and BP occurred but no treatment necessary
- ❖ 3 $\mu\text{g}/\text{kg}$ over 10 min is needed to achieve a rapid onset and high efficacy rate

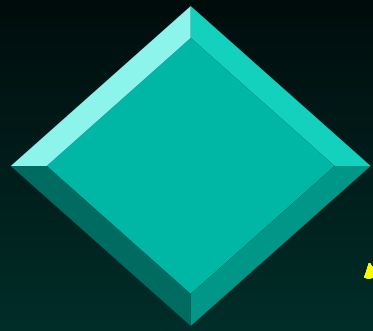
Mason KP, et al Anesth Analg 2006;103:57-62



Dexmedetomidine or Propofol for MRI Imaging

- ❖ Group D - 30 children - dexmedetomidine 1 ug/kg following continuous infusion of 0.5 ug/kg/hr
- ❖ Group P - 30 children - propofol 3 mg/kg followed by continuous infusion of 100 ug/kg/min
- ❖ Adequate sedation in both groups
- ❖ Propofol faster anesthetic induction and recovery but more hypotension and desaturation.

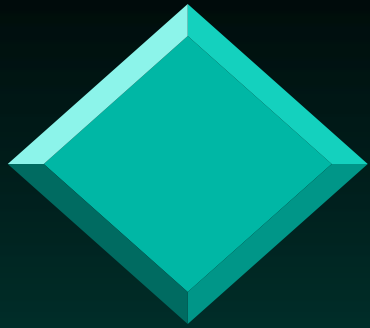
Koroglu A, et al. Anesth Analg 2006;103:63-7.



Dexmedetomidine Sedation for the Adolescent Patient Undergoing MRI

- ❖ 31 patients -mean 13 yrs (10-28.3 yrs)
- ❖ 2 $\mu\text{g}/\text{kg}$ over 10 minutes repeated up to 3 times followed by an infusion of 1 $\mu\text{g}/\text{kg}/\text{hr}$ till completion of the scan
- ❖ 14.6 min to achieve sedation-36 min scans(total time for administration was 61.4 min)-discharge in 45 min
- ❖ Advantageous for the older, heavier, challenging patient-short half life and faster recovery than hypnotics

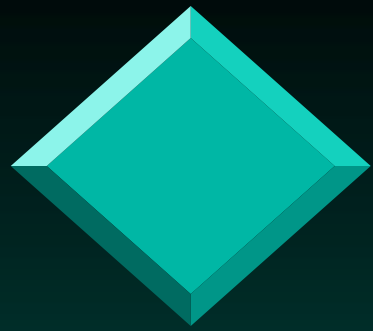
Mason KP, et al Anesthesiology 2007;107:A1407



Monitored Anesthesia Care for MRI

- ❖ Three children with Trisomy 21 and OSA for MRI of upper airway
- ❖ Ketamine bolus of 1 mg/kg and dexmedetomidine 1 μ g/kg followed by infusion of dexmedetomidine 1 μ g/kg/hr
- ❖ Effective sedation, hypercarbia ($P_E\text{CO}_2$ 49-52) and one airway obstruction that responded to repositioning of the airway

Luscri N et al. Pediatric Anesthesia 2006;16:782-6



Dexmedetomidine and Radiation Therapy

- ❖ Daily radiation for brain tumor needed for 12 days
- ❖ Bolus $1\mu\text{g}/\text{kg}$ over 10 minutes followed by continuous infusion of $0.7\mu\text{g}/\text{kg}$ per hour
- ❖ 30% oxygen delivered via NC, endtidal CO_2 monitored
- ❖ No apnea, hypoventilation or hypoxemia
- ❖ Discharged home after 30 minutes

Shukry M et al, 2003 SPA/JSPA Joint Meeting



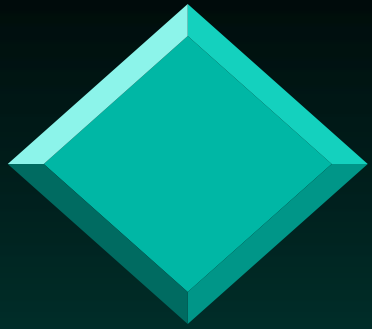
Emergence Agitation

- ❖ Single dose of IV dexmedetomidine, 0.3 $\mu\text{g}/\text{kg}$ after induction and maintenance of anesthesia with sevoflurane plus caudal blockade
- ❖ Decreased emergence agitation with no adverse effects

Ibacache ME et al. Anesth Analg 2004;98:60-3

- ❖ Single dose of IV dexmedetomidine, 1 $\mu\text{g}/\text{kg}$ during sevoflurane anesthesia for MRI decreased emergence agitation from 47.6% to 4.8%

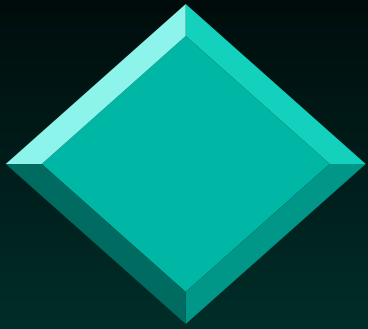
Isik B et al. Pediatric Anesthesia 2006;16:748-53



Emergence Agitation-2

- ❖ **Dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$ decreased agitation due to sedation and analgesia in tonsillectomy patients**

Guler G et al. Pediatric Anesthesia 2005;15:762-6



Dexmedetomidine for Treatment of Post Anesthesia Shivering in Children

- ❖ 24 children (7-16 years) with shivering
- ❖ Dexmedetomidine 0.5 ug/kg over 3-5 min
- ❖ All had cessation of shivering in 5 min (onset 3.5 + 0.9 min)
- ❖ No shivering recurred

Easley RB, et al. Pediatric Anesthesia 2007;17:341-6.

