



PERIOPERATIVE SEDATION AND ANALGESIA

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A Practical Approach to Targeted Sedation and Analgesia for Acute Care Settings



ICU THERAPY

- Sedation
- Weaning from vent
- HOB up 30°.
- Blood Glucose
- PUD Prophylaxis
- DVT Prophylaxis



SEDATION & ANALGESIA IN ACUTE CARE SETTINGS

- Provide adequate pain control¹
- Optimize safety for patients and their caregivers²
- Enhance patient comfort¹
- Facilitate mechanical ventilation³

¹Ely EW, et al. *JAMA*. 2003;289:2983-2991.

²Blanchard AR. *Postgrad Med*. 2002;111:59-74.

³Kress JP, et al. *Am J Respir Crit Care Med*. 2002;166:1024-1028.



SEDATION & ANALGESIA IN ACUTE CARE SETTINGS

- Reduce anxiety¹
- Induce sleep when required¹
- Induce appropriate level of amnesia³

¹Ely EW, et al. *JAMA*. 2003;289:2983-2991.

²Blanchard AR. *Postgrad Med*. 2002;111:59-74.

³Kress JP, et al. *Am J Respir Crit Care Med*. 2002;166:1024-1028.



Goals of Sedation & Analgesia

- Attenuate the harmful adrenergic response^{1,2}
- Improve compliance with care^{1,2}
- Facilitate communication with caregivers and family members^{1,2}
- Avoid or reduce delirium^{1,2,4}

¹Blanchard AR. *Postgrad Med.* 2002;111:59-74.

²Jacobi J, et al. *Crit Care Med.* 2002;30:119-141.

³Dasta JF, et al. *Pharmacotherapy.* 2006;26:798-805.

⁴Ely EW, et al. *JAMA.* 2004;291:1753-1762.



ICU/OR GOALS

- Maximize Therapy
- Move patient along efficiently
- Decide disposition
- When stuck, change direction



SEDATION

- NARCOTICS
 - Primarily analgesic
- BENZODIAZEPINES
 - Sedative/Hypnotic
- ALKYL PHENOL DERIVATIVE
 - Sedative/Hypnotic
- TORADOL
 - Analgesic



SEDATION


- BARBITURATE
 - Sedative/Hypnotic
- NMDA Antagonist
 - Sedative/Anesthetic/Analgesic
- BUTYROPHENONE (Haldol, Respiradol)
- CENTRAL α -2 AGONIST
 - Analgesic and sedative



Overview of Current Sedative and Analgesic Agents

Drug Class	Examples	Year FDA Approved
Opioids	Morphine	Prior to 1938
	Fentanyl	1968
Butyrophenones	Haloperidol	1967
Benzodiazepines	Diazepam	1963
	Lorazepam	1963
	Midazolam	1985
Sedatives/hypnotics	Propofol	1989
α_2 Agonists	Clonidine	1986
	Dexmedetomidine	1999

Comparison of Clinical Effects



	Benzo-diazepines	Propofol	Opioids	Dexmedetomidine	Haloperidol
Sedation	X	X	X	X	X
Alleviate anxiety ^{1,2}	X			X	
Analgesic Properties ¹⁻⁴			X	X	
Promote arousability during sedation ²⁻⁴				X	
Facilitate ventilation during weaning ²⁻⁴				X	
No respiratory depression ¹⁻⁴				X	X
Control delirium ¹⁻⁴				X	X

¹Blanchard AR. *Postgrad Med.* 2002;111:59-74.

²Kamibayashi T, et al *Anesthesiology.* 2000;95:1345-1349.

³Maze M. et al. *Anesthetic Pharmacology: Physiologic Principals and Clinical Practice.* Churchill Livingstone; 2004.

⁴Maze M, et al. *Crit Care Clin.* 2001;4:881.

Comparison of Adverse Effects



	Benzo-diazepines	Propofol	Opioids	Dexmedetomidine	Haloperidol
Prolonged weaning ¹	X	X	X*		
Respiratory depression ¹	X	X	X		
Hypotension ¹⁻³	X	X	X	X	X
Constipation ¹			X		
Deliriogenic	X	X	X		
Tachycardia ¹			Morphine		
Bradycardia ¹			Fentanyl	X	X

*Excluding remifentanyl

¹Harvey MA. *Am J Crit Care*. 1996;5:7-16.

²Aantaa R, et al. *Drugs of the Future*. 1993;18:49-56.

³Maze M. *Crit Care Clin*. 2001;4:881;

Characteristics of an Ideal Sedative

- Rapid onset of action allows rapid recovery after discontinuation¹
- Effective at providing adequate sedation with predictable dose response^{1,2}
- Easy to administer^{1,3}
- Lack of drug accumulation¹
- Few adverse effects¹⁻³
- Minimal adverse interactions with other drugs¹⁻³
- Cost effective³
- Predictable dose response²
- Promotes natural sleep⁴

¹Ostermann ME, et al. *JAMA*. 2000;283:1451-1459.

²Jacobi et al. *Crit Care Med*. 2002;30:119-141.

³Dasta JF, et al. *Pharmacotherapy*. 2006;26:798-805..

⁴Nelson LE, et al. *Anesthesiology*. 2003;98:428-436.

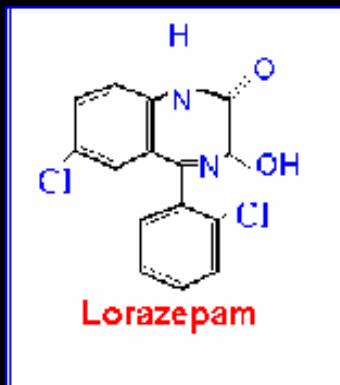
Benzodiazepines - Lorazepam

Clinical Effects

- Sedation, anxiolysis, and amnesia¹
- Commonly used for long-term sedation²

Adverse Effects

- Slower onset of action than midazolam^{2,3}
- Metabolic Acidosis (propylene glycol toxicity)^{4,5}
- Retrograde and anterograde amnesia can exceed desirability⁶
- Delirium⁷



¹Lerch C, et al. *Br Med Bull.* 1999;55:76-95.

²Shafer A. *Crit Care Med.* 1998;26:947-956.

³Wagner BKJ, et al. *Clin Pharmacokinet.* 1997;33:426-453.

⁴Neale BW, et al. *Ann Pharmacother.* 2005;39:1732-1736.

⁵Wilson KC, et al. *Chest.* 2005;128:1674-1681.

⁶Mathew A, et al. *Psychopharmacol.* 2002;16:345-354.

⁷Pandharipande P, et al. *Anesthesiology.* 2006;104:21-26.

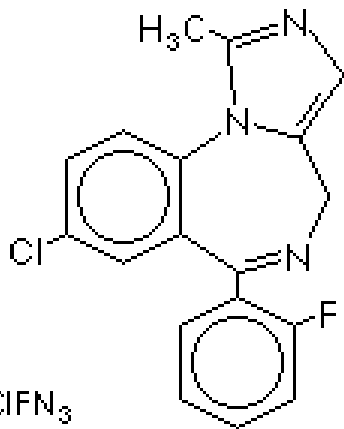
Benzodiazepines - Midazolam

Clinical Effects

- Sedation, anxiolysis, and amnesia¹
- Rapid onset of action intravenously¹

Adverse Effects

- May accumulate in liver and/or renal failure¹
- Anterograde amnesia²
- Prolonged recovery after long-term use³
- Combination with opioids increases hypotensive effects¹
- Respiratory depression⁴
- Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability⁴



C₁₈H₁₃ClFN₃

¹Blanchard AR. *Postgrad Med.* 2002;111:59-74.

²Harvey MA. *Am J Crit Care.* 1996;5:7-16.

³Shafer A. *Crit Care Med.* 1998;26:947-956.

⁴Midazolam [package insert]. Weston, FL: Apotex Corp; 2000.

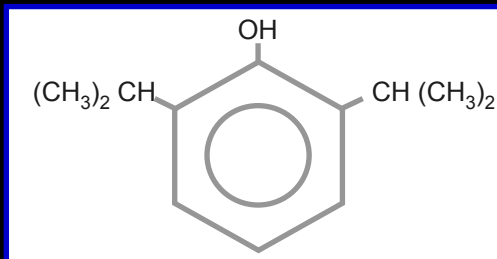
Propofol

Clinical Effects

- Sedation¹
- Hypnosis¹
- Anxiolysis¹
- Muscle relaxation¹
- ↓ ICP¹
- ↓ Cerebral metabolic rate¹
- Antiemetic²

Adverse Effects

- Respiratory depression (exacerbated by opioids)¹
- Hypotension¹
- Decreased myocardial contractility³
- Preservative issues⁴
- Potential for infection⁴
- Tolerance⁵
- Propofol infusion syndrome⁶
- ↑ Serum triglycerides⁴



¹Harvey MA. *Am J Crit Care*. 1996;5:7-16.

²Apfel CC, et al. *Anaesthetist*. 2005;54:201-9.

³Lerch C, et al. *Br Med Bull*. 1999;55:76-95.

⁴Diprivan [package insert]. AstraZeneca Pharmaceuticals; 2004.

⁵Zapantis A, et al. *Crit Care Nurs Clin N Am*. 2005;17:211-223.

⁶Riker RR, et al. *Pharmacotherapy*. 2005;25(5 Pt 2):8S-18S.

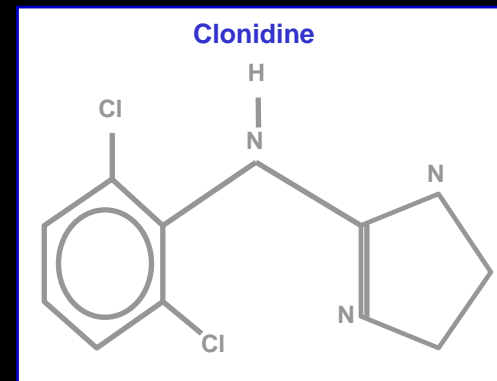
α_2 Agonists: Clonidine

Clinical Effects

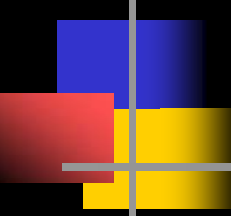
- Antihypertensive^{1,2}
- Analgesia¹
- Anxiolysis¹
- Sedation¹
- ↓ Shivering¹

Adverse Effects

- Bradycardia¹
- Dry mouth¹
- Hypotension³



¹Kamibayashi T, et al. *Anesthesiology*. 2000;93:1345-1349; ²Catapres [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; 2004. ³Nishima K, et al. *Anesthesiology*. 2004;59:323-329.



CENTRAL α -2 AGONIST

- July 29, 2004 — Clonidine effective for reducing perioperative myocardial ischemia - prospective, double-blind, randomized trial published in the August 2004 issue of *Anesthesiology*. The benefit lasted for up to 2 years & similar to that observed for β -blockers.

Clonidine Reduces Perioperative Myocardial Ischemia. CME News Author: Laurie Barclay, MD

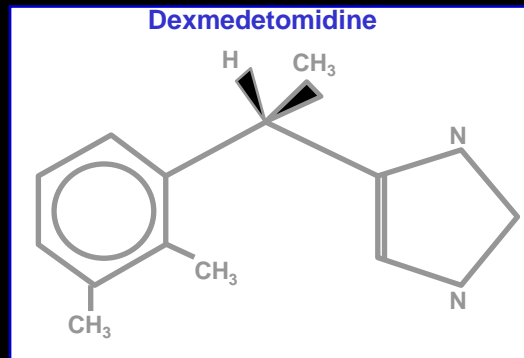
α_2 Agonists: Dexmedetomidine

Clinical Effects

- Antihypertensive^{1,2}
- Sedative^{1,2}
- Analgesic^{1,2}
- ↓ Shivering³
- Anxiolytic effects⁴
- Patient rousability⁴
- Potentiates effects of opioids, sedatives, and anesthetics²
- Decreased sympathetic activity⁵

Adverse Effects

- Bradycardia⁶
- Hypotension⁶
- Dry mouth²
- Vasoconstriction with rapid infusion or at high doses²
- Nausea²



¹Kamibayashi T, et al. *Anesthesiology*. 2000;93:1345-1349.

²Precedex [package insert]. Lake Forest, IL: Hospira Inc; 2004.

³Doufas AG, et al. *Stroke*. 2003;34:1218-1223.

⁴Riker RR, et al. *Pharmacotherapy*. 2005;25(5 Pt 2):8S-18S.

⁵Venn RA, et al. *Brit J Anaesthesia*. 2001;87:684-690.

⁶Shehabi Y, et al. *Intensive Care Med*. 2004;30:2188-2196.



Clinical Characteristics of Dexmedetomidine

- Cooperative sedation¹
- Analgesia^{2,3}
- Organ Protection (ie, neural, renal, cardiac)¹
- Anxiolysis^{2,3}
- Controls hyperadrenergic response to stress¹⁻³
- Reduces shivering³
- Diuretic action⁴
- Mimics Natural Sleep¹

¹Aantaa R, et al. *Drugs of the Future*. 1993;18:49-56.

²Kamibayashi T, et al. *Anesthesiology*. 2000;93:1345-1349.

³Wagner BKJ, et al. *Clin Pharmacokinet*. 1997;33:426-453.

⁴Goodman LS, et al. *The Pharmacological Basis of Therapeutics*. New York, NY: McGraw-Hill;2004:232-235.

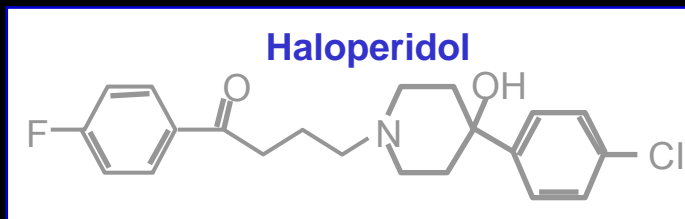
Haloperidol

Clinical Effects

- Hypnotic agent with antipsychotic properties¹
 - For treatment of delirium in critically ill adults¹
- Does not cause respiratory depression¹

Adverse Effects

- Dysphoria²
- Adverse CV effects include QT interval prolongation, extrapyramidal symptoms, neuroleptic malignant syndrome (rare)¹
- Metabolism altered by drug-drug interactions²



¹Harvey MA. *Am J Crit Care*. 1996;5:7-16.

²Crippen DW. *Crit Care Clin*. 1990;6:369-392.

Opioids

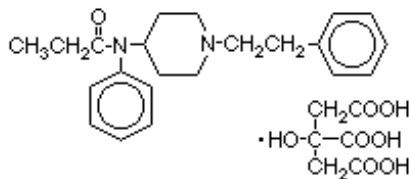
Clinical Effects

- Analgesia¹
- Sedation¹

Adverse Effects

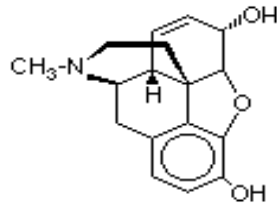
- Respiratory depression^{1,2}
- Hypotension^{1,2}
- Bradycardia^{1,2}
- Constipation¹
- Tolerance¹
- Withdrawal symptoms^{1,2}
- Dysphoria^{3,4}

Fentanyl



$C_{22}H_{28}N_2O \cdot C_6H_8O_7$

Morphine



$C_{17}H_{19}NO_3$

¹Harvey MA. *Am J Crit Care*. 1996;5:7-16.

²Wagner BKJ, et al. *Clin Pharmacokinet*. 1997;33:426-453.

³Dean AJ, et al. *J Psychiatry Neurosci*. 2006;31:38-45.

⁴Gerra G, et al. *Drug Alcohol Depend*. 2004;75:37-45.



DEXMEDETOMIDINE

- Dexmedetomidine: relatively selective α_2 -adrenergic agonist. It is chemically related to clonidine.
- Greater affinity for α_2 -receptors over α_1 -receptors (1,620:1 compared to 200:1 for clonidine).
- *Pediatr Pharm.* 2006;12(1) ©2006 Children's Medical Center, University of Virginia



DEXMEDETOMIDINE

- The sedative & anxiolytic effects result primarily from activity in the locus ceruleus.
- Stimulation of α 2- α receptors here \downarrow central sympathetic output, resulting in \uparrow 'd firing of inhibitory neurons.
- Dexmedetomidine at α 2-adrenergic receptors in the dorsal horn of the spinal cord modulates release of substance P and produces its analgesic effects.[1-3]



DEXMEDETOMIDINE

- *INTERACTIVE* SEDATION!
- DECREASE OPIOID REQUIREMENT
- NO RESPIRATORY DEPRESSION
- SYMPATHOLYTIC

Jorden and Tung, Seminars in Anesthesia, Perioperative Medicine and Pain, Vol 21, No4 (December)2002:pp265-274



DEXMEDETOMIDINE

- DEX acts on the locus coeruleus in PONS.
 - *LC = origin of all CNS NE neurons.*
 - *DECREASE CATECHOLAMINE SURGE*
- With DEX gtt, pt alert, no startle reflexes.
 - participate with procedures
 - enhanced communication
 - *Preservation of cognitive function*
 - *Enhanced communication of sedated patient*
- Pain management improved, ↓ opioid requirement



DEXMEDETOMIDINE

- *decreases* [catecholamine] levels
- *decreases* total body VO_2
- *decreases* myocardial consumption
- *decreases* pain and shivering

- Jorden and Tung, Seminars in Anesthesia, Perioperative Medicine and Pain, Vol 21, No4 (December)2002:pp265-274



“IDEAL PATIENT” for DEX

- MORBID OBESITY
 - Bariatric Surgery
- PULMONARY PT
 - Lung transplant
 - COPD
 - Good analgesia
 - No respiratory depression
- OPIOID TOLERANT PATIENT



“IDEAL PATIENT” for DEX

- Aortic Dissection
 - Esmolol, Nipride and sedative
 - Vs
 - Dexmedetomidine

For decrease HR, BP and sedation

MAINTAINS CORTICAL FUNCTION



“IDEAL”

- MAC
 - Minimize opioids post-op in PACU
 - Especially morbid obesity
- MINIMIZING ILEUS
- PEDS for Offsite anesthesia
- Weaning the agitated patient

Pharmacoeconomic Analysis

Outcomes Analysis in Cardiac Surgery

- 12-month retrospective administrative claims database analysis (2003-2004)¹
- Nationally representative sample of 250 medical and surgical hospitals¹
- Comparison of patients receiving either midazolam plus propofol (M+P, n = 9996) or dexmedetomidine plus M+P (D+M+P, n = 356)¹
 - Patients who were admitted to the hospital for either a cardiovascular valve or vessel procedure¹
 - Patient demographics and outcomes were obtained from the hospital billing claim form, UB-92¹
- Admissions with lengths of stay more than 100 days were excluded from all analyses

Pharmacoeconomic Analysis

Reduced Mean Total TX Charges



- 12-month retrospective administrative claims database analysis¹
- Comparison of patients receiving either midazolam plus propofol (M+P) or dexmedetomidine plus M+P (D+M+P)¹
- The D+M+P cohort showed significant reductions in per patient total charges¹

M+P, n = 9996

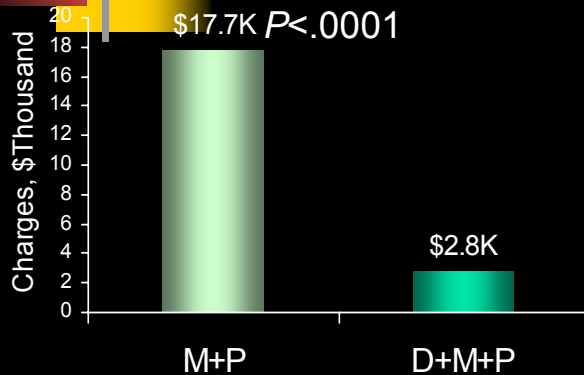
D+M+P, n = 356

¹Dasta JF, et al. *Pharmacotherapy*. 2006;26:798-805.

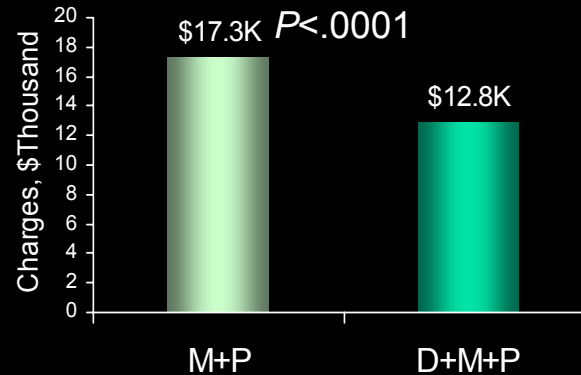
Pharmacoeconomic Analysis

Departmental Treatment Charges

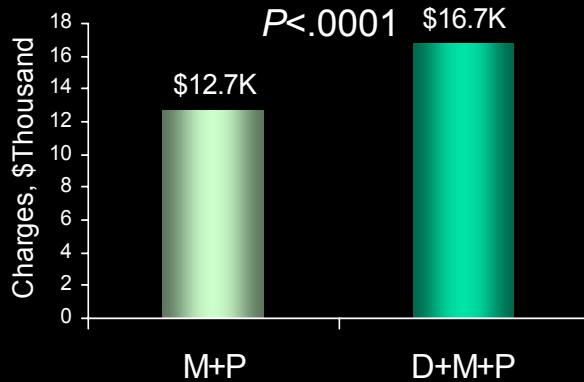
ICU/CCU



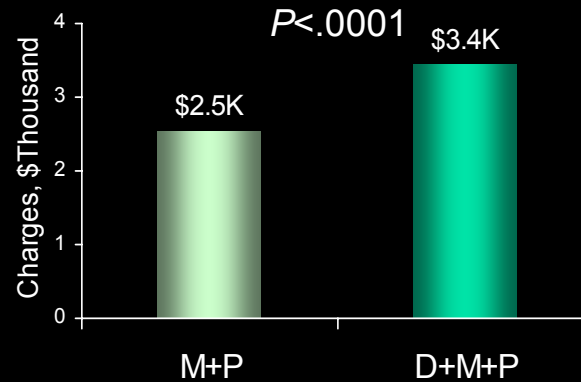
Operating Room



Pharmacy



Anesthesia



Reductions in ICU and OR charges offset increases in other areas

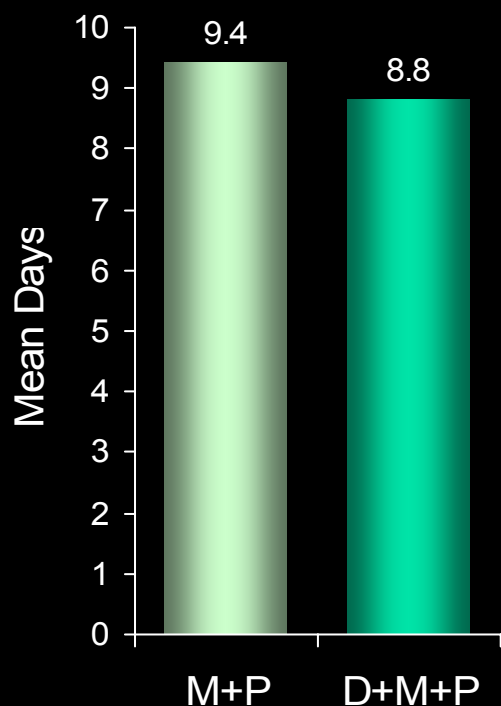
M+P, n = 9996
D+M+P, n = 356

Pharmacoeconomic Analysis

Reduced Hospitalization & Mortality

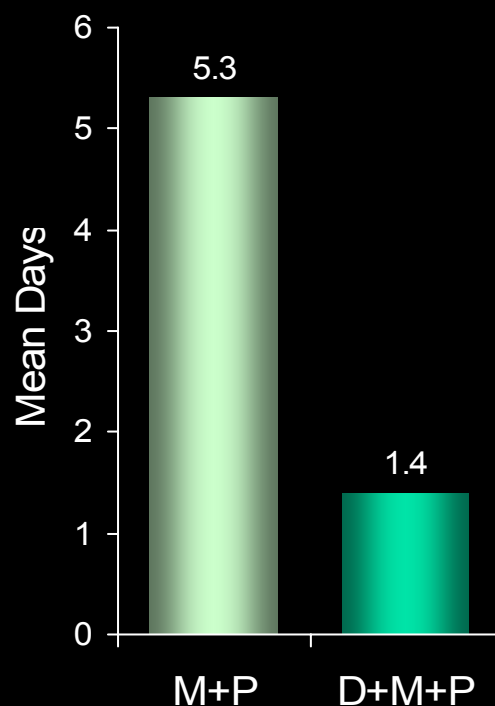
Mean Length of Stay

$P < .0001$



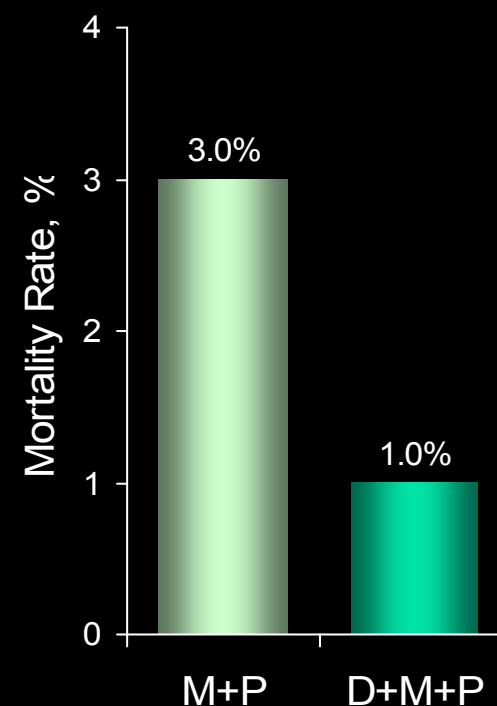
Mean Days in ICU/CCU

$P < .0001$



Mortality Rate

$P = .0142$



M+P, n = 9996
D+M+P, n = 356



Pharmacoeconomic Analysis

Study Limitations

- Dosage
- Duration of therapies
- Influence of practice patterns/institutional variability unknown
- Lack of randomization of patients to treatment introduced risk of selection or channeling bias
- Assigning causality based on results not possible¹



Properties of Dexmedetomidine in Cardiovascular Surgery

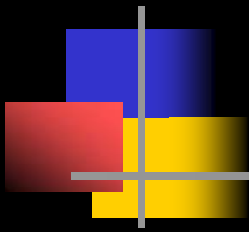
- Lack of respiratory depression
- Cooperative sedation aids in assessing neurophysiological function during vascular procedures such as endarterectomy
- Hemodynamic stabilization is desirable during cardiovascular surgery
- Attenuates hypertension and tachycardia



DEX & CT SURGERY

- Patients receiving dexmedetomidine as part of a sedation regimen for CV surgery appeared to have better hospital outcomes compared with patients receiving a regimen not containing this agent.
- Specifically, a combination of dexmedetomidine, midazolam, and propofol appeared shorten LOS in the ICU or CCU, had shorter overall hospital lengths of stay. Pts were less likely to die in the hospital compared with patients receiving only midazolam and propofol.
- Dasta, et al. Pharmacotherapy. 2006;26(6):798-805.

Properties of Dexmedetomidine in Neurosurgery



- Intraoperative hemodynamic stability¹
- *Lack of respiratory depression*¹
- Patients easily transition from sleep to wakefulness and task performance when aroused, and then back to sleep when not stimulated¹
- Does not increase intracranial pressure¹
- Allows for consistent and reliable somatosensory evoked potential amplitudes or latencies¹

Examples of Cooperative Sedation

Neurological Examples

- Intracranial surgical procedures often require patient cooperation for functional assessment¹
 - The procedure is frequently limited by the location/spatial extent of the lesion and its relationship to functioning tissue¹
 - Surgeons balance the benefits of an aggressive resection with anticipated neurological dysfunction¹
- Intraoperative neurophysiological testing¹
 - Can verify that surgical target has been localized¹
 - Is used to assess the production of an intended functional change¹
- Carotid endarterectomy performed in awake patients allows evaluation of cerebral perfusion by continuous examination of neurologic function²

¹Bekker AY, et al. *Neurosurgery*. 2005; 57(1 Suppl):1-10.

²Bekker AY, et al. *J Neurosurg Anesthesiol*. 2004;16:126-135.

DEX & Cerebral BloodFlow

Clinical Data

- Reduced cerebral blood flow (CBF) has also been demonstrated in human studies¹
 - Reduced CBF may be advantageous for situations such as traumatic brain injury or large brain tumors¹
- No detrimental effect on local brain tissue oxygenation in patients undergoing cerebral vascular surgery¹
- Under normotensive conditions in the setting of compromised cerebral circulation, dexmedetomidine has no apparent adverse effects¹
- It has been shown that dexmedetomidine is suitable for preoperative sedation of patients with subarachnoid hemorrhage (SAH)²

¹Bekker A, Sturaitis MK. *Neurosurgery*. 2005;57:1-10.

²Sato K, et al. *Masui*. 2006;55:51-54.

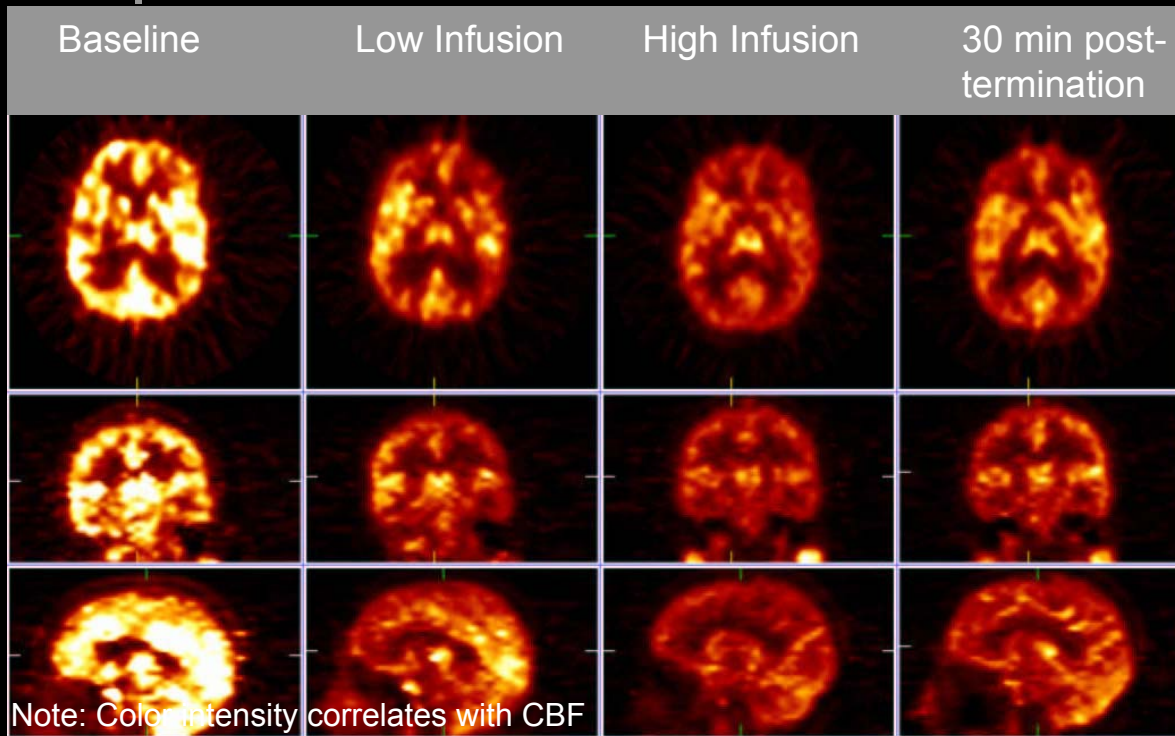
DEX & Cerebral Blood Flow

Cerebral Perfusion in Severe Head Injury

- Prospective study on the effect of dexmedetomidine in patients with severe head injury
 - 12 ICU patients (aged 15 to 64 years)
 - Glasgow Coma Scale ≤ 8
 - Intracranial pressure < 20 mm Hg
 - O₂ saturation monitoring of blood from jugular bulb
- 3 hours of progressive IV dexmedetomidine perfusion (0.2, 0.4, 0.7 mcg/kg/h)
 - All other sedative-analgesic medications previously withdrawn

DEX & Cerebral Blood Flow

Decreased Cerebral Metabolic Rate



- Both low and high doses
 - Reduced global CBF by one third
 - Decreased mean systemic BP, HR, and CO 15% to 20%
 - Increased PaCO₂ no more than 5 mm Hg
- CBF decreased from baseline throughout dexmedetomidine infusion and for at least 30 minutes thereafter



MORBID OBESITY

- **Anesthesia for a patient with morbid obesity using dexmedetomidine without narcotics**
- **Roger E. Hofer, MD et al**
- * From the Departments of Anesthesiology, and Surgery, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minnesota, USA
- *Canadian Journal of Anesthesia* 52:176-180 (2005)



MORBID OBESITY

- Bariatric surgery
 - OSA & pulmonary HTN
 - massive lower extremity lymphedema, and gastroesophageal reflux
- *No epidural*
- GA



BARIATRIC ANESTHESIA

- DEX: a highly selective 2- α agonist
- hypnotic, sedative, sympatholytic, and analgesic properties.2
- *does not cause respiratory depression*, and
- *patients can be easily aroused*,
- *be used even after tracheal extubation*.3,4



BARIATRIC ANESTHESIA

- REASONING: narcotics might cause postoperative respiratory depression, we substituted their intraoperative use with a continuous infusion of dexmedetomidine ($0.7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$)



BARIATRIC ANESTHESIA

- Anesthesia course uneventful
- Intraoperative dex was associated with low anesthetic requirements (0.5 minimum alveolar concentration).
- After completion of the operation *and after tracheal extubation*, the dexmedetomidine infusion was *continued uninterrupted throughout the end of the first postoperative day*.



BARIATRIC ANESTHESIA

- The analgesic effects of dexmedetomidine extended narcotic-sparing effects into the postoperative period;
- Patient had lower narcotic requirements during the first postoperative day [48 mg of morphine by patient-controlled analgesia (PCA)] while still receiving dexmedetomidine, compared to the second postoperative day (morphine 148 mg by PCA) with similar pain scores.



BARIATRIC ANESTHESIA

- Dexmedetomidine: useful anesthetic adjunct for patients susceptible to narcotic-induced respiratory depression.
- In this morbidly obese patient the narcotic-sparing effects of dexmedetomidine were evident both intraoperatively and postoperatively.



BARIATRIC ANESTHESIA

- Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements
- **Conclusion:** Continuous *iv* dexmedetomidine during abdominal surgery provides effective postoperative analgesia, and reduces postoperative morphine requirements without increasing the incidence of side effects.
- Copyright © 2006 European Society of Anaesthesiology
- doi:10.1017/S0265021506000378



PEDIATRIC ANESTHESIA

- Dexmedetomidine for Sedation in the Pediatric Intensive Care Setting
- **Marcia L. Buck, Pharm.D., FCCP**
- **Pediatr
Pharm. 2006;12(1) ©2006 Children's
Medical Center, University of Virginia**
- **Posted 03/13/2006**



PEDIATRIC ANESTHESIA

- Dexmedetomidine offers an additional choice for the sedation of children receiving MV or requiring procedures.
- It may be particularly useful in children with underlying neurologic disorders, who often develop agitation or adverse hemodynamic and respiratory effects with opioids or BZ.



PEDIATRIC ANESTHESIA

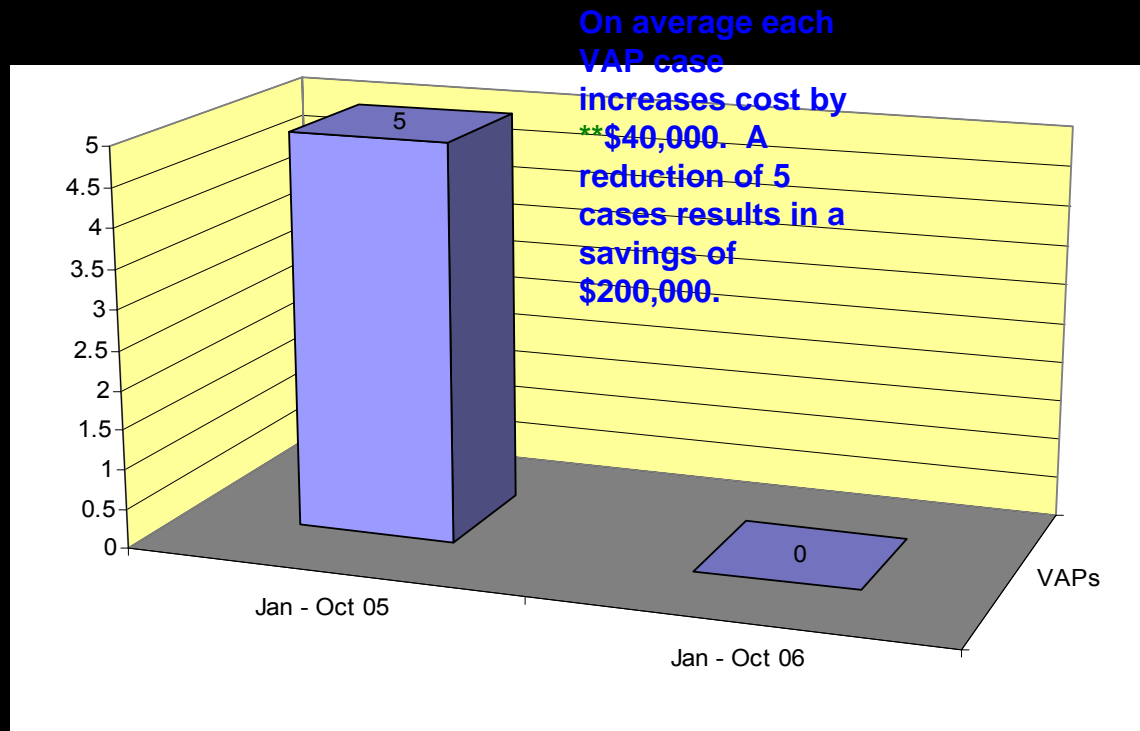
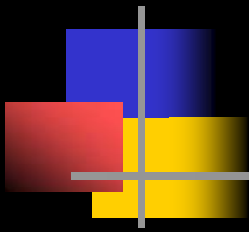
- Dexmedetomidine appears to be well tolerated.
- Potential to cause significant hypotension and should be used only in carefully monitored situations. Additional controlled studies are needed to define the role of dexmedetomidine in the sedation of infants and children.



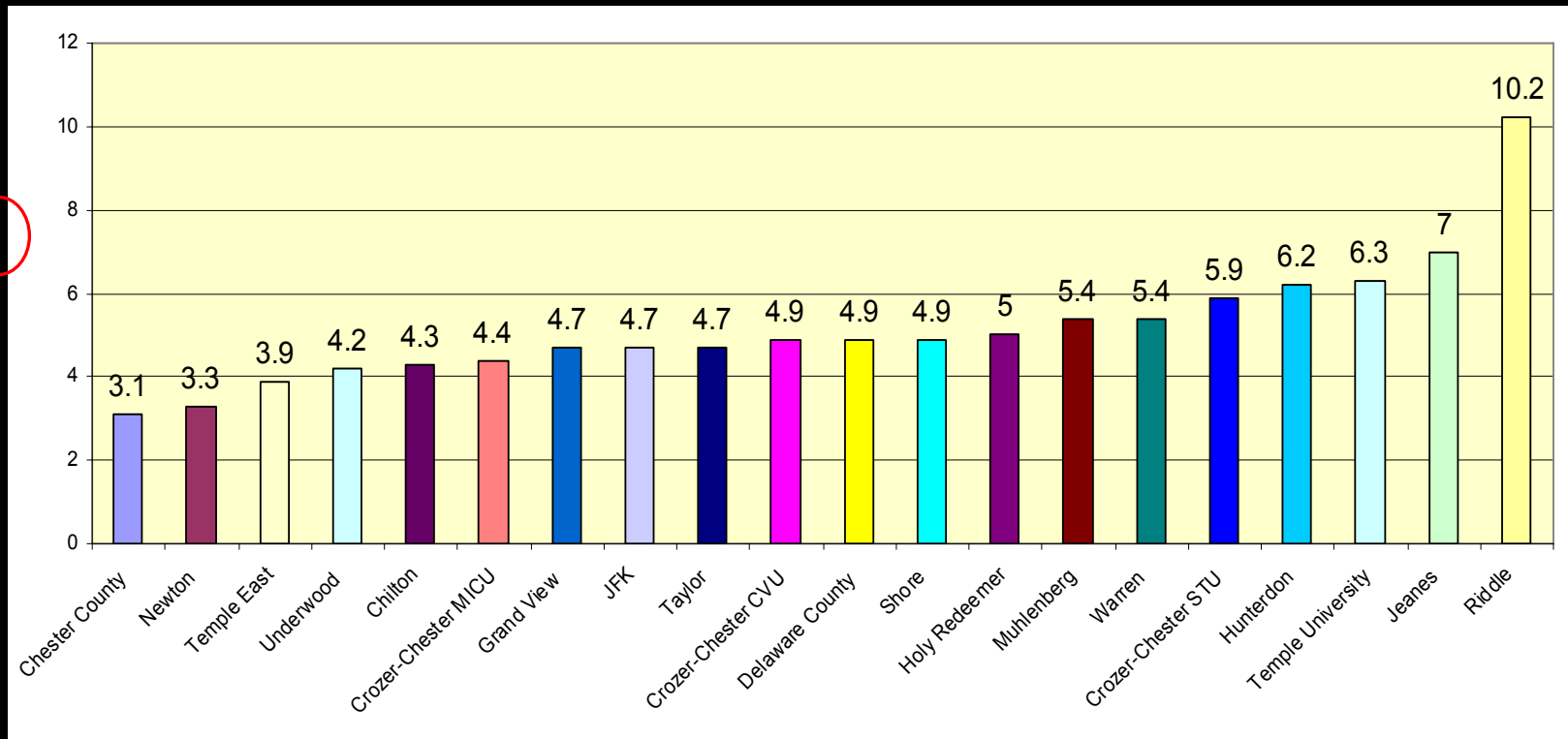
History and Background

- 14 East Coast members, 8 VHA PA members
- 38 reporting ICUs
- Process data collected on every ICU patient once per week
- Outcomes data for unit as a whole completed monthly
- Online data entry and easy reporting module
- Focus on ventilator care, appropriate glucose control, sepsis and infection prevention
- Teams supported with –
 - Conference calls – clinical experts
 - Group coaching
 - Listserv
 - Open data-sharing

The Chester County Hospital VAPs



VHA East Coast Average Days on Mechanical Ventilation (July-Dec 2006)





SUMMARY

- Sedation imperative in acute care setting.
- Analgesia
- Anxiolysis
- Reasonable sedation options
- New sedation options
- Improve consumer satisfaction by keeping patient comfortable.

Physiology of Dexmedetomidine

