PERIOPERATIVE SEDATION AND ANALGESIA

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Director
ICU Department
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

Dorman, Todd
SEDATION & ANALGESIA IN ACUTE CARE SETTINGS

- Provide adequate pain control\(^1\)
- Optimize safety for patients and their caregivers\(^2\)
- Enhance patient comfort\(^1\)
- Facilitate mechanical ventilation\(^3\)

SEDATION & ANALGESIA IN ACUTE CARE SETTINGS

- Reduce anxiety\(^1\)
- Induce sleep when required\(^1\)
- Induce appropriate level of amnesia\(^3\)

Goals of Sedation & Analgesia

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

\textsuperscript{1}Blanchard AR. *Postgrad Med.* 2002;111:59-74.
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 $\alpha$-2 AGONIST
  - Analgesic and sedative
## Overview of Current Sedative and Analgesic Agents

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Year FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids</strong></td>
<td>Morphine</td>
<td>Prior to 1938</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td>1968</td>
</tr>
<tr>
<td><strong>Butyrophenones</strong></td>
<td>Haloperidol</td>
<td>1967</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>Diazepam</td>
<td>1963</td>
</tr>
<tr>
<td></td>
<td>Lorazepam</td>
<td>1963</td>
</tr>
<tr>
<td></td>
<td>Midazolam</td>
<td>1985</td>
</tr>
<tr>
<td><strong>Sedatives/hypnotics</strong></td>
<td>Propofol</td>
<td>1989</td>
</tr>
<tr>
<td><strong>α₂ Agonists</strong></td>
<td>Clonidine</td>
<td>1986</td>
</tr>
<tr>
<td></td>
<td>Dexmedetomidine</td>
<td>1999</td>
</tr>
</tbody>
</table>

http://www.fda.gov/cder/ob/default.htm
## Comparison of Clinical Effects

<table>
<thead>
<tr>
<th></th>
<th>Benzo-diazepines</th>
<th>Propofol</th>
<th>Opioids</th>
<th>Dexmedetomidine</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Alleviate anxiety</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Analgesic Properties</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Promote arousability during</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sedation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facilitate ventilation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>during weaning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No respiratory depression</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control delirium</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

# Comparison of Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Benzo-diazepines</th>
<th>Propofol</th>
<th>Opioids</th>
<th>Dexmedetomidine</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged weaning¹</td>
<td>X</td>
<td>X</td>
<td>X*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory depression¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension¹-³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Constipation¹</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Deliriogenic</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia¹</td>
<td></td>
<td></td>
<td>Morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia¹</td>
<td></td>
<td></td>
<td>Fentanyl</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

¹Excluding remifentanil

¹Harvey MA. Am J Crit Care. 1996;5:7-16.
Characteristics of an Ideal Sedative

- Rapid onset of action allows rapid recovery after discontinuation\(^1\)
- Effective at providing adequate sedation with predictable dose response\(^1,2\)
- Easy to administer\(^1,3\)
- Lack of drug accumulation\(^1\)
- Few adverse effects\(^1-3\)
- Minimal adverse interactions with other drugs\(^1-3\)
- Cost effective\(^3\)
- Predictable dose response\(^2\)
- Promotes natural sleep\(^4\)

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Benzodiazepines - Lorazepam

Clinical Effects

- Sedation, anxiolysis, and amnesia\(^1\)
- Commonly used for long-term sedation\(^2\)

Adverse Effects

- Slower onset of action than midazolam\(^2,3\)
- Metabolic Acidosis (propylene glycol toxicity)\(^4,5\)
- Retrograde and anterograde amnesia can exceed desirability\(^6\)
- Delirium\(^7\)

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Benzodiazepines - Midazolam

Clinical Effects
- Sedation, anxiolysis, and amnesia\(^1\)
- Rapid onset of action intravenously\(^1\)

Adverse Effects
- May accumulate in liver and/or renal failure\(^1\)
- Anterograde amnesia\(^2\)
- Prolonged recovery after long-term use\(^3\)
- Combination with opioids increases hypotensive effects\(^1\)
- Respiratory depression\(^4\)
- Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability\(^4\)

# Propofol

## Clinical Effects
- Sedation\(^1\)
- Hypnosis\(^1\)
- Anxiolysis\(^1\)
- Muscle relaxation\(^1\)
- ↓ ICP\(^1\)
- ↓ Cerebral metabolic rate\(^1\)
- Antiemetic\(^2\)

## Adverse Effects
- Respiratory depression (exacerbated by opioids)\(^1\)
- Hypotension\(^1\)
- Decreased myocardial contractility\(^3\)
- Preservative issues\(^4\)
- Potential for infection\(^4\)
- Tolerance\(^5\)
- Propofol infusion syndrome\(^6\)
- ↑ Serum triglycerides\(^4\)

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\(^{1}\)Harvey MA. *Am J Crit Care*. 1996;5:7-16.


**α₂ Agonists: Clonidine**

**Clinical Effects**
- Antihypertensive\(^1,2\)
- Analgesia\(^1\)
- Anxiolysis\(^1\)
- Sedation\(^1\)
- ↓ Shivering\(^1\)

**Adverse Effects**
- Bradycardia\(^1\)
- Dry mouth\(^1\)
- Hypotension\(^3\)

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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
**α₂ Agonists: Dexmedetomidine**

<table>
<thead>
<tr>
<th>Clinical Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive(^1,2)</td>
<td>Bradycardia(^6)</td>
</tr>
<tr>
<td>Sedative(^1,2)</td>
<td>Hypotension(^6)</td>
</tr>
<tr>
<td>Analgesic(^1,2)</td>
<td>Dry mouth(^2)</td>
</tr>
<tr>
<td>↓ Shivering(^3)</td>
<td>Vasoconstriction with rapid infusion or at high doses(^2)</td>
</tr>
<tr>
<td>Anxiolytic effects(^4)</td>
<td>Nausea(^2)</td>
</tr>
<tr>
<td>Patient rousability(^4)</td>
<td></td>
</tr>
<tr>
<td>Potentiates effects of opioids, sedatives, and anesthetics(^2)</td>
<td></td>
</tr>
<tr>
<td>Decreased sympathetic activity(^5)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Characteristics of Dexmedetomidine

- Cooperative sedation\(^1\)
- Analgesia\(^2,3\)
- Organ Protection (ie, neural, renal, cardiac)\(^1\)
- Anxiolysis\(^2,3\)
- Controls hyperadrenergic response to stress\(^1-3\)
- Reduces shivering\(^3\)
- Diuretic action\(^4\)
- Mimics Natural Sleep\(^1\)

Haloperidol

**Clinical Effects**
- Hypnotic agent with antipsychotic properties
  - For treatment of delirium in critically ill adults
- Does not cause respiratory depression

**Adverse Effects**
- Dysphoria
- Adverse CV effects include QT interval prolongation, extrapyramidal symptoms, neuroleptic malignant syndrome (rare)
- Metabolism altered by drug-drug interactions

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Opioids

Clinical Effects
- Analgesia\(^1\)
- Sedation\(^1\)

Adverse Effects
- Respiratory depression\(^1,2\)
- Hypotension\(^1,2\)
- Bradycardia\(^1,2\)
- Constipation\(^1\)
- Tolerance\(^1\)
- Withdrawal symptoms\(^1,2\)
- Dysphoria\(^3,4\)

\(^1\)Harvey MA. *Am J Crit Care*. 1996;5:7-16.
DEXMEDETOXOMIDINE

- Dexmedetomidine: relatively selective alpha2-adrenergic agonist. It is chemically related to clonidine.

- Greater affinity for $\alpha_2$-receptors over $\alpha_1$-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 $\alpha_2$-receptors here ↓ central sympathetic output, resulting in ↑’d firing of inhibitory neurons.
- Dexmedetomidine at $\alpha$ 2-adrenergic receptors in the dorsal horn of the spinal cord modulates release of substance P and produces its analgesic effects.[1-3]
DEXMEDETOXMIDINE

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

DEX acts on the locus coeruleus in PONS.

- $LC = \text{origin of all CNS NE neurons.}$

- 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

Jorden and Tung
**DEXMEDETOMIDINE**

- decreases [catecholamine] levels
- decreases total body VO$_2$
- decreases myocardial consumption
- decreases pain and shivering

---

“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 hospitals$^1$
  - 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 procedure$^1$
    - Patient demographics and outcomes were obtained from the hospital billing claim form, UB-92$^1$
  - 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 analysis
- Comparison of patients receiving either midazolam plus propofol (M+P) or dexmedetomidine plus M+P (D+M+P)
- The D+M+P cohort showed significant reductions in per patient total charges

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

$106K
$89K

Pharmacoeconomic Analysis

Departmental Treatment Charges

ICU/CCU

<table>
<thead>
<tr>
<th></th>
<th>Charges, $Thousand</th>
</tr>
</thead>
<tbody>
<tr>
<td>M+P</td>
<td>$17.7K</td>
</tr>
<tr>
<td>D+M+P</td>
<td>$2.8K</td>
</tr>
</tbody>
</table>

Operating Room

<table>
<thead>
<tr>
<th></th>
<th>Charges, $Thousand</th>
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<tbody>
<tr>
<td>M+P</td>
<td>$17.3K</td>
</tr>
<tr>
<td>D+M+P</td>
<td>$12.8K</td>
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</tbody>
</table>

Pharmacy

<table>
<thead>
<tr>
<th></th>
<th>Charges, $Thousand</th>
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<tbody>
<tr>
<td>M+P</td>
<td>$12.7K</td>
</tr>
<tr>
<td>D+M+P</td>
<td>$16.7K</td>
</tr>
</tbody>
</table>

Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Charges, $Thousand</th>
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<tbody>
<tr>
<td>M+P</td>
<td>$2.5K</td>
</tr>
<tr>
<td>D+M+P</td>
<td>$3.4K</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th></th>
<th>M+P</th>
<th>D+M+P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.4</td>
<td>8.8</td>
</tr>
</tbody>
</table>

*P < .0001*

**Mean Days in ICU/CCU**

<table>
<thead>
<tr>
<th></th>
<th>M+P</th>
<th>D+M+P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.3</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*P < .0001*

**Mortality Rate**

<table>
<thead>
<tr>
<th></th>
<th>M+P</th>
<th>D+M+P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.0%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

*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 possible

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

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.

Properties of Dexmedetomidine in Neurosurgery

- Intraoperative hemodynamic stability\(^1\)
- *Lack of respiratory depression*\(^1\)
- Patients easily transition from sleep to wakefulness and task performance when aroused, and then back to sleep when not stimulated\(^1\)
- Does not increase intracranial pressure\(^1\)
- Allows for consistent and reliable somatosensory evoked potential amplitudes or latencies\(^1\)

Examples of Cooperative Sedation

Neurological Examples

- Intracranial surgical procedures often require patient cooperation for functional assessment\(^1\)
  - The procedure is frequently limited by the location/spatial extent of the lesion and its relationship to functioning tissue\(^1\)
  - Surgeons balance the benefits of an aggressive resection with anticipated neurological dysfunction\(^1\)
- Intraoperative neurophysiological testing\(^1\)
  - Can verify that surgical target has been localized\(^1\)
  - Is used to assess the production of an intended functional change\(^1\)
- Carotid endarterectomy performed in awake patients allows evaluation of cerebral perfusion by continuous examination of neurologic function\(^2\)

Reduced cerebral blood flow (CBF) has also been demonstrated in human studies\(^1\)
- Reduced CBF may be advantageous for situations such as traumatic brain injury or large brain tumors\(^1\)
- No detrimental effect on local brain tissue oxygenation in patients undergoing cerebral vascular surgery\(^1\)
- Under normotensive conditions in the setting of compromised cerebral circulation, dexmedetomidine has no apparent adverse effects\(^1\)
- It has been shown that dexmedetomidine is suitable for preoperative sedation of patients with subarachnoid hemorrhage (SAH)\(^2\)

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 PaCO$_2$ no more than 5 mm Hg
- **CBF decreased from baseline throughout dexmedetomidine infusion and for at least 30 minutes thereafter**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Low Infusion</th>
<th>High Infusion</th>
<th>30 min post-termination</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Baseline" /></td>
<td><img src="image2" alt="Low Infusion" /></td>
<td><img src="image3" alt="High Infusion" /></td>
<td><img src="image4" alt="30 min post-termination" /></td>
</tr>
</tbody>
</table>

Note: Color intensity correlates with CBF

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
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.\textsuperscript{2}
- does not cause respiratory depression, and
- patients can be easily aroused,
- be used even after tracheal extubation.\textsuperscript{3,4}
REASONING: narcotics might cause postoperative respiratory depression, we substituted their intraoperative use with a continuous infusion of dexmedetomidine (0.7 µg•kg⁻¹•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.
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.
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.

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doi:10.1017/S02650215060000378
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
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.
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

VHA East Coast / PA ICU Program
The Chester County Hospital
VAPs

On average each VAP case increases cost by **$40,000. A reduction of 5 cases results in a savings of $200,000.

Source: IHI
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

α2A, α2C Locus Ceruleus
α2A Brainstem vasomotor center
α2B CNS-based thermoregulatory inhibition

Antishivering

α2B Cerebral vessels and peripheral vasculature

Vasoconstriction

Vasodilation

Bradycardia

Decrease
Tachycardia

Blocks cardioaccelerator nerve

Analgesia

Diuresis