Pain and Sedation Management for Critically Ill Patients: A Rational Approach

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Definitions

Sedation
- The act of calming, especially by the administration of a sedative drug

Hypnosis
- A state of altered consciousness, artificially induced

Analgesia\(^1\)
- A lessening or absence of the sense of pain without loss of consciousness

Amnesia\(^2\)
- The loss or impairment of memory

\(^1\) Stedman’s Medical Dictionary. 1995.
\(^2\) Dorland’s Illustrated Medical Dictionary. 28th ed. 1994.
Definitions

Anxiety\(^1\)
- A state of intense apprehension, uncertainty, and fear

Agitation\(^2\)
- A state of anxiety accompanied by motor restlessness\(^1\)

Delirium\(^1\)
- A temporary state of mental confusion

Psychosis\(^2\)
- A severe mental disorder characterized by loss of contact with reality

Pain !!!
Adverse Effects of Pain

- Psychological
- Respiratory
- Cardiovascular
- Gastro-intestinal
- Neuro-endocrine
- Metabolic
Respiratory Complications

- Painful surgical incision
  - ↓ Diaphragm function
    - ↓ Pulmonary compliance
      - Muscle splinting
      - ↓ Deep coughing
  - Retention of secretion
    - Atelectasis
- Hypoxaemia
- Hypercarbia
- Pneumonia
Cardiovascular Effects

Before .............. After

Supply-Demand Balance and Mismatch
Neuro-endocrine Effects

↑ Sympathetic tone
↑ Hypothalamic stimulation

ACTH*
ADH†
Aldosterone
Angiotensin-II
Catecholamines
Cortisol
Glucagon

Growth hormone
IL-1‡
IL-6§
Renin
Serotonin
TNF||

↓ Insulin & testosterone

↑ Na & water retention
↑ Glucose, free fatty acids and ketone bodies

↑ O2 consumption
Negative nitrogen balance
Assessing Pain

- Faces Pain Rating Scale
- Visual Analog Scale (VAS)
  - No pain ➔ worst pain imaginable
- Hemodynamics
- Pain questionnaire
  - Qualitative aspects
Faces Pain Rating Scale

0: No pain
1: Moderate pain
2: Worst possible pain

Adapted with permission from Chambers, Craig. Pain. 1998;78:29.
Assessment of Pain

Critical Care Medicine 1997;25:1159-1166
Behavioral Indicators

A: No movement
B: Grimacing
C: Vocalization
D: Restless
E: Hesitant
F: Tense
G: Attention seeking
H: Wrinkled forehead
I: Splinting
J: Drawn around eyes
K: Rigid
L: Tearing

Critical Care Medicine 1997;25:1159-1166
Physiological Indicators

A: ↑ Heart rate
B: ↑ BP
C: ↑ RR
D: ↓ BP
E: Perspiration
F: Pallor
G: ↓ RR
H: ↓ HR

Critical Care Medicine 1997;25:1159-1166
Assessing Sedation

- Ramsay Sedation Scale
- Motor Activity Assessment Scale (MAAS)
- Observer’s Assessment of Alertness/Sedation Scale (OAA/SS)
- Riker’s Sedation-Agitation Scale (SAS)
- Sedation monitors
### Ramsay Sedation Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anxious, agitated, or restless</td>
</tr>
<tr>
<td>2</td>
<td>Cooperative, oriented, and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Responds to commands</td>
</tr>
<tr>
<td>4</td>
<td>Asleep, but with brisk response to light glabellar tap or loud auditory stimuli</td>
</tr>
<tr>
<td>5</td>
<td>Asleep, sluggish response to light glabellar tap or loud auditory stimuli</td>
</tr>
<tr>
<td>6</td>
<td>Asleep, no response</td>
</tr>
</tbody>
</table>

Adapted from Ramsay et al. BMJ. 1974;2:656-659.
## The Riker Sedation-Agitation Scale

<table>
<thead>
<tr>
<th>Sedation / Agitation Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dangerous agitation: pulls at ET; tries to remove catheters; limbs over bedrail; strikes staff; thrashes from side to side</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated; does not calm, despite frequent verbal reminding of limits; requires physical constraints; bites ET</td>
</tr>
<tr>
<td>5</td>
<td>Agitated: anxious or mildly agitated; attempts to sit up; calms down to verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm and cooperative: calms, awakens easily; follows commands</td>
</tr>
<tr>
<td>3</td>
<td>Sedated: difficult to arouse; awakens to verbal stimuli or gentle shaking but drifts off again; follows simple commands</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated: arouses to physical stimuli but does not communicate or follow commands; may move spontaneously</td>
</tr>
<tr>
<td>1</td>
<td>Unarousable: minimal or no response to noxious stimuli; does not communicate or follow commands</td>
</tr>
</tbody>
</table>

Factors Provoking Anxiety

- Pain
- Inconsiderate Providers
- Alarms
- Temperature
- Mechanical Devices
- Loss of Control
- Lights
- Nonchanging Environment
- Sleep Deprivation
- Loss of Control
- Surgical Stress
- Temperature
- Noises
- Lights
- Memory Loss
- Confusion

Anxiety in the ICU

- Causes
  - Pain
  - Environment
  - Sleep deprivation
  - Drug withdrawal

- Effects
  - Agitation ➔ delirium ➔ psychosis ➔ PTSD
  - CVS
    - ↑ BP; ↑ HR
  - Sleep deprivation
Sleep Deprivation

Average amount of sleep in the ICU is 1 hour, 51 minutes per 24 hours.

Restorative Properties of Sleep

- Increased rate of healing
  - Promotes anabolism
    - Facilitates growth hormone release
  - Counteracts catabolism
    - Inhibits cortisol release
    - Inhibits catecholamine release

Sleep Deprivation: Infection and Immunity

- Bacterial translocation from the gut\(^1\)
- Septic burden by pathogenic microorganisms and their toxins in tissues\(^1\)
- Changes in the distribution of peripheral leukocytes\(^2\)
  - Reduction in NK cells
- Reduction in phytohemagglutinin-induced lymphocyte DNA synthesis\(^3\)
- Decreases the activity of leukocytes and increases interferon levels\(^3,4\)

Sleep Deprivation: Cardiorespiratory Function

- Human
  - Volunteers
    - Increased pressor response to sympathetic stimulation\(^1\)
    - Changes in cardiovascular responses to simulated orthostasis\(^2\)
  - Patients
    - Increased BP, HR, and urine norepinephrine in hypertensives\(^3\)
    - Increased incidence of cardiovascular events\(^3\)
- Rats
  - Death due to pulmonary edema\(^4\)

Sleep Deprivation: Cognitive Function

- Impaired memory\(^1\)
- Impaired communication skills\(^2\)
- Impaired decision-making\(^3\)
- Confusional state\(^4\)
  - Apathy
  - Delirium

Causes of Sleep Deprivation in the ICU

- Patient-related
  - Pain\(^1\)
  - Anxiety\(^1\)
  - Underlying illness\(^2\)
    - COPD
    - CHF
- Medications\(^2\)
  - Morphine
  - Theophylline
- Environment\(^2\)
  - Noise
  - Light
- Intensity of nursing care and interventions\(^2\)

Risks of Undersedation: Agitated Patients

- Can injure themselves or others
  - Self-extubation, decannulation, wound dehiscence
- ↑ Peripheral oxygen consumption
  - Risks of hypoxemia, organ ischemia
- ↑ Physiologic stress/catecholamine surge
  - Changes in immune response, wound healing, coagulation
  - Disrupted circadian rhythms
- Require more intensive nursing care
  - Restraints
  - Consequences of excessive sedation
- Sleep deprivation and posttraumatic stress disorder (PTSD)
Risks and Consequences of Oversedation

- Respiratory depression
- Hemodynamic instability
- Delayed weaning from ventilator
- Inability to neurologically access CNS-impaired patients
- Aspirational pneumonia
- Increased nursing care and costs
- Pressure injuries, venous stasis, muscle atrophy

The Perfect Sedative in the ICU

- Provides
  - Sedation / Anxiolysis
  - Analgesia
  - Amnesia

- No effect on cardiovascular function
- Rapid onset and offset
- Minimal respiratory depression
- No or inactive metabolites
The Perfect Sedative in the ICU

- No accumulation in renal or hepatic dysfunction
- No interactions with other medications
- No pain on injection
- No associated tolerance or withdrawal
- Safe for all ages with no age-related changes in pharmacokinetics
- Cost-effective

**Does not exist!**
Difficulties with Choice of Sedatives

- Paucity of randomized, controlled studies
- Unconvincing results from studies that have been done
- Pharmacology changes with duration of infusion
  - Initial studies on all these medications done with bolus doses
  - Later studies of infusion over time show striking changes in pharmacokinetics
Can we do it without drugs?..

- Back to the basics
  - Physical contact
  - Environmental factors
  - Effective communication
  - Comfort measures
  - Reorientation techniques
  - Uninterrupted sleep periods

- Technical interventions
  - Mechanical interventions (eg, tube patency)
  - Relaxation techniques (music therapy, therapeutic touch)

- Psychosocial
  - Family visitations and interactions
  - Spiritual contact

Pharmacologic Agents Used for Sedation and Analgesia

- **Analgesics**¹
  - Morphine sulfate
  - Fentanyl

- **NSAIDS**
  - Cox2s – Valdecoxib, Paracoxib

- **Benzodiazepines**¹
  - Lorazepam - Ativan
  - Midazolam - Versed

- **Sedative/hypnotics**¹
  - Propofol - Diprovan

- **Butyrophenones**¹
  - Haloperidol - Haldol

- **α₂ Agonists**²
  - Dexmedetomidine – Precedex

Opioids

**Fentanyl**

\[
\text{C}_{22}\text{H}_{28}\text{N}_{2}\text{O} \cdot \text{C}_{6}\text{H}_{8}\text{O}_7
\]

- 200ug
- 100ug/h
- $26/d

**Morphine**

\[
\text{C}_{17}\text{H}_{19}\text{NO}_{3}
\]

- 10mg
- 5mg/h
- $12/d
Opioids: Clinical Effects

- Analgesia
- Sedation
- Tolerance
- Respiratory depression
- Withdrawal symptoms
- Hypotension
- Bradycardia
- Constipation

Opioids: Clinical Effects

ALVEOLAR VENTILATION ($\dot{V}_f$ / min)

ALVEOLAR PCO$_2$, (torr)

CONTROL

30 MINUTES AFTER 15 mg MORPHINE IV

30 MINUTES AFTER 30 mg MORPHINE IV

Miller, 1986
Opiates: Reversal Agents

- **Naloxone**
  - Nausea and vomiting
  - Tachycardia
  - Hypertension
  - Pulmonary edema
  - Cardiac dysrhythmias
  - Ventricular fibrillation

- **Naltrexone**
  - Effective orally up to 24 hours

- **Nalmefene**
  - Longer duration of action than naloxone
  - Acute pulmonary edema

Theoretical time course of analgesic efficacy of opioid analgesics, local anesthetic, and nonsteroidal anti-inflammatory drugs (NSAIDs) when used as part of a “balanced” analgesic approach to minimizing postoperative discomfort.
Analgesics – Fentanyl vs Morphine

- No comparative studies are available
- Fentanyl would seem to be the better of the two
  - No histamine release – more hemodynamically stable
  - Slightly shorter onset
  - Much shorter half-life
    - 30–60 min vs 2–9 hr
  - No active metabolites
On further examination…

- Fentanyl has a much larger volume of distribution than morphine – its half-life prolongs from 30–60 min to 9–16 hr with prolonged infusion
- Fentanyl exhibits striking tachyphylaxis – dosing requirements increase dramatically with prolonged infusion

Analgesics – Fentanyl vs Morphine

- On further examination...
  - Fentanyl’s hemodynamic stability is due to its lack of histamine release, negative inotropy or vasodilatation
  - Fentanyl is, however, a powerful inhibitor of endogenous catecholamines; this causes severe hypotension in patients whose blood pressure is dependent on endogenous catecholamines
Types of Opioid Utilized

Opioids: Route of Administration

Dosing Schedule

- Dasta et al - prospective observational study*
- Information on prescribing and administering of opioid, benzodiazepine and muscle relaxants
- N=221
- 90% of drug prescribed on PRN basis

*Crit Care Med 1994; 22:974-980
Patient Controlled Analgesia

- Useful in non-critically ill patients
- Stable drug concentration
- Increased patient autonomy
- Better pain control in post-CABG patients†

Patient Controlled Analgesia

- Improved pain satisfaction
- Decreased pain scoring
- Improved SpO₂
- Improved FEV₁
- Improved VC

Epidural Use in the ICU

- Limited clinical data available
- Low et al conducted postal survey*
- Assess the utilization of epidural catheters under various clinical scenarios
- No standard plan of care
- No algorithm for patient variables related to epidural.

Benefits of Epidural in the ICU

- Pain control
- Early mobilization
- Decreased incidence of deep venous thrombosis
- Improved pulmonary mechanics
- Increased splanchnic blood flow
- Decreases duration of post-operative ileus
Chest Wall Trauma

- Chest wall trauma -8% of all trauma admissions
- Marker of severity of injury
- Rib fractures found in 10% of patients after trauma
- Associated with significant morbidity and prolonged ICU stay*

Multiple Rib Fractures

- Systemic Opioids
- Intercostal nerve block
- Inter-pleural analgesia
- Epidural analgesia
- Thoracic paraverterbral block
Contra-indication to Regional But…

- Multiple other injuries
- Haemodynamic instability
- Associated spinal injury
- Mask intra-abdominal injury
- Associated Horner Syndrome makes neuro assessment difficult

Respiratory Complications

Painful surgical incision/ fracture

Diaphragm function

Pulmonary compliance

Muscle splinting

Deep coughing

Retention of secretion

Atelectasis

Hypoxaemia

Hypercarbia

Pneumonia
Ai et al performed randomized controlled study in rabbits*

Saline & lidocaine epidural group

pHi and endotoxin measured

Improvement in pHi in local epidural group

*Anesthesiology 2001;94: 263-9
Epidural and Splanchnic Circulation

- GI system fertile source for inflammatory mediators
- Splanchnic mal-perfusion increases mediator release
- Spackman et al conducted a double blinded randomized controlled study*
- Randomized to morphine and epidural
- Epidural shown to improve splanchnic perfusion
- Widened indication profile

*Intensive Care Med 2000; 26:1638-1645
Cardiovascular Effects

- ↑ Heart Rate
- ↑ Afterload
- ↑ Inotropy

↓ Hemoglobin
↓ Diastolic time
↑ End-diastolic pressure

Epidural → ↑ Pain control

Heart Rate
Afterload
Inotropy

Hemoglobin
Diastolic time
End-diastolic pressure
Not All Good News......
Does Epidural Change Post-Operative Cardiac Outcome?

**NO**
- Baron et al. Anesthesiology 1991; 75: 611-618
- Christopherson et al. Anesthesiology 1993; 79: 422-434

**YES**
Does Epidural Change Post-Operative Cardiac Outcome?

- Controversial
- Improves outcome in high risk patients
- No difference seen in lower risk population
- Insufficient numbers in study
- Highest risk at 72-96 hours post surgery
No Matter What Opioid You Are Using...

- Re-evaluate the need for analgesia before discharge to a regular ward
- 80% of in-hospital Cardiac Arrest are Hypoxic
**NSAIDS**

- Prostaglandin synthesis interference
- Actions: anti-inflammation, antipyresis, analgesia
- Acetaminophen for antipyresis
- Side effects: gastropathy, nephrotoxicity, coagulopathy
- ASA hypersensitivity
The proposed mechanism of action of the nonsteroidal anti-inflammatory drugs (NSAIDs)
NSAIDS in the ICU

■ Analgesic benefits not studied in ICU patients
■ Increased risk of bleeding
■ Increased risk of renal dysfunction
■ Increased incidence of peptic ulcer disease
■ Increased risk of broncho-spasm in patients with aspirin allergy
NSAIDS in the ICU...
Acetaminophen in Cardiac Surgery

- Relatively safe
- No platelet dysfunction
- Minimal renal dysfunction
- Maximum daily dose <4g
- Relative contra-indication in hepatic dysfunction

*Anesth Analg 2002;95: 813-819*
Classes of NSAIDS

- Propionic – ibuprofen, naproxen
- Acetic – indomethicin, tolmetin
- Salicytic – ASA, diflunisal
- Anthranilic – phenylbutazone
- Pyrrolopyroroles – ketorolac
- COX-2 inhibitors – celecoxib, rofecoxib, valdecoxib
COX-2 Inhibitors

- Cyclooxygenase – 1: responsible for cellular functions ("housekeeping" enzyme for platelets, kidneys, and stomach)

- Cyclooxygenase – 2: responsible for inflammatory response and mitogen activity
  - Polyposis prophylaxis
  - Lack of platelet aggregation inhibition
Valdecoxib

- Mechanism of action: NSAID with typical anti-inflammatory, analgesic, antipyretic

- Pharmokinetics
  - Maximal plasma concentrations in 3 hours
  - Bioavailability 83% after po administration
  - No age or gender differences were seen in pharmacokinetics that require dosage adjustment
Selective COX-2 inhibition

Less GI, renal and platelet dysfunction

Opiate sparing

Oral and IV formulation available

Tang et al compared placebo vs. IV parecoxib†

Decreased PCA opioid requirement

No change in pain management or opioid side effect

†Anesthesiology 2002;96:1305-1309
Valdecoxib vs Opioids After Hip Arthroplasty…

- Multicenter, double blind, multidose study
- Placebo, 20mg, 40 mg b.i.d valdecoxib given pre- and post-operatively
- IV-PCA MSO4
- 40% less morphine in treatment groups
- VAS-pain Patient Satisfaction improved in valdecoxib groups
Sedative-Hypnotics

Available Agents

- Propofol
- Midazolam
- Lorazepam
## Propofol

### Advantages
- Sedation\(^1\)
- Hypnosis\(^1\)
- Anxiolysis\(^1\)
- Muscle relaxation\(^1\)
- ↓ ICP\(^1\)
- ↓ Cerebral metabolic rate\(^1\)
- Relief of bronchospasm\(^1\)

### Limitations
- Respiratory depression (enhanced by opioids)\(^1\)
- Hypotension\(^1\)
- Decreased contractility\(^2\)
- Lack of analgesia\(^3\)
- Hypertriglyceridemia\(^1\)
- Preservative issues\(^4\)
- Potential for infection necessitates need for regular changing of lines\(^5\)

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Sedative-Hypnotics

Available Agents

- **Propofol**
  - Ultra short-acting after bolus dose and short-term infusion
  - Short duration of action useful especially for short-term sedation of:
    - intubated patients after surgical procedures
    - the patient with changing neurologic status requiring frequent neurological evaluation
    - the elderly

—continued
Sedative-Hypnotics

Available Agents

- Propofol
  - Negative inotrope, vasodilator – can cause hypotension
  - Infection risk
  - Hyperlipidemia
Increased mortality initially evident in pediatric population

Led to “moratorium” on the use of propofol for pediatric patients by the manufacturer

Later seen in adult patients
Propofol Syndrome

Characterized by:

- Metabolic Acidosis
  - Sometimes with a high anion gap.
  - Sometimes with a lactic acidosis.
  - Many times with an uncharacterized metabolic acidosis.
- Rhabdomyolysis
- Myocardial Dysfunction
- Death
Propofol Syndrome

Characteristics in head injury patients

- Noted 5 fatal cardiac arrests after high dose Propofol infusion
- Reviewed data from 1996-9
  - Of 67 patients – 7 had deaths that seemed consistent with Propofol syndrome
  - Found that patients with doses of Propofol higher than 5 mg/kg/hr had a much higher mortality than if dose was lower

Propofol Syndrome

Possible Etiologies

- Decreased transmembrane electrical potential and alteration of electron transport across inner mitochondrial membrane

- Alteration in microcirculatory blood flow measured via invivo microvideoscopcy of the sublingual microcirculatory network.
  - Koch, M. Crit Care Med 2004; 32(12 suppl): A41
Benzodiazepines: Pharmacodynamics

- Amnesia
- Sedation/anxiolysis
- Anticonvulsant
- Relief of muscle spasm

Midazolam: Clinical Effects

- Sedation, anxiolysis, and amnesia\(^1\)
- Rapid onset of action intravenously\(^1\)
- Possible accumulation in liver failure\(^2\)
- Anterograde amnesia\(^3\)
- Prolonged recovery after long-term use\(^4\)
- Combination with opioids increases hypotensive effects\(^5\)
- Half Life 2.5 Hours

Sedative-Hypnotics

Available Agents

- **Midazolam**
  - Rapid onset of action (usually 2–5 min)
  - Short duration of action after bolus dose (~15 min) due to redistribution
  - Longer-acting after short-term infusion (~1–2 hr)
  - Long half-life after long-term (72 hr) infusion with large inter-patient variability (3–15 hr)

Lorazepam: Clinical Effects

- Sedation, anxiolysis, and amnesia\(^1\)
- Preferred for prolonged sedation\(^2\)
- Slower onset of action than midazolam\(^2,3\)
- Half Life 8-20 Hours
- Less hypotension than with midazolam\(^2\)
- Retrograde and anterograde amnesia

Sedative-Hypnotics

Available Agents

- **Lorazepam**
  - Slow onset of action (10–20 min)
  - Intermediate half-life (6 hr) after bolus dose due to metabolism
  - Longer acting after 72-hr infusion (12–32 hr)
  - Prolongation of effect and decreased drug requirements in the elderly
Sedative-Hypnotics

Lorazepam
Midazolam
Propofol

Infusion Duration (min)

Context Sensitive Half-Time (min)

Benzodiazepines: Reversal Agents

- **Flumazenil**
  - Transiently antagonizes the benzodiazepine component of ventilatory depression and sedation during use with opioids
  - Reverses CNS and circulatory side effects of benzodiazepines within 2 minutes
  - Useful for diagnostic evaluation

One study comparing propofol (P) vs midazolam (M) and lorazepam (L) for ICU Trauma patients

- Randomized, open label — 2 – 4 days
- Over sedation occurred most often with L
- Under sedation occurred most often with P
- Fewest titrations required with M
- Cost P > M > L

Sedative-Hypnotics

Many studies comparing propofol (P) with midazolam (M) for sedation after CABG
- P extubated sooner after d/c than M
- Decreased morphine requirements after P
- Lower PaCO₂ after extubation in P
- Generally similar quality of sedation
- Propofol patients more hypotensive but no difference in cardiac endpoints
- Earlier extubation not followed by earlier ICU discharge
Review article looking at 49 randomized controlled trials  

- The main conclusion — more studies needed
- Propofol is at least as effective as midazolam
- Propofol exhibits a faster time to extubation than midazolam
Other Conclusions

- It is NOT clear that this results in a decrease in total time of ventilation or in a shorter ICU time
- Use of propofol results in more problems with hypotension than midazolam
- No difference was found in comparing midazolam with lorazepam.
Other Conclusions, cont’d.

- Other studies since then have had differing results:
  - Lorazepam is a useful alternative to midazolam, with easier management of sedation level, no difference to awakening, and significant cost savings

Other Conclusions, cont’d.

- Other studies since then have had differing results:
  
  ▪ Significantly delayed emergence from sedation with lorazepam compared with midazolam (15 hr to 31 hr)

Haloperidol: Clinical Effects

- For treatment of delirium in critically ill adults
- Does not cause respiratory depression
- Metabolism altered by drug-drug interactions
- Altered sensory perception (rambling, incoherent speech, disorientation)
- Adverse effects include QT interval prolongation, extrapyramidal symptoms, neuroleptic malignant syndrome (rare)

Neuroleptics

- Haloperidol
  - “Stuns”, does not sedate
  - Indicated for delirium, not sedation
  - No respiratory depression or significant hemodynamic side effects
  - Can cause extrapyramidal symptoms and QT prolongation
  - Can have a prolonged effect when used for a prolonged period of time
### α₂ Agonists

<table>
<thead>
<tr>
<th><strong>Clonidine</strong></th>
<th><strong>Dexmedetomidine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectivity: α₂:α₁ 200:1¹</td>
<td>Selectivity: α₂:α₁ 1620:1³</td>
</tr>
<tr>
<td>t₁/₂ β 10 hrs¹</td>
<td>t₁/₂ β 2 hrs³</td>
</tr>
<tr>
<td>PO, patch, epidural²</td>
<td>Intravenous³</td>
</tr>
<tr>
<td>Antihypertensive¹</td>
<td>Sedative-analgesic³</td>
</tr>
<tr>
<td>Analgesic adjunct¹</td>
<td>Primary sedative</td>
</tr>
<tr>
<td>IV formulation not available in US</td>
<td>Only IV α₂ available in the US</td>
</tr>
</tbody>
</table>

\(\alpha_2\) Agonists: Pharmacodynamics

- Sedation/hypnosis\(^1\)
- Anxiolysis\(^1\)
- Analgesia\(^1\)
- Sympatholysis (BP/HR, NE)\(^1\)
- Reduces shivering\(^2\)
- Neuroprotective effects\(^3\)
- No effect on ICP\(^3\)
- No respiratory depression\(^1\)

α₂-Receptor Subtypes

Physiology of α₂ Adrenoceptors

Alpha-2 agonist

- Dexmedetomodine
  - Sedation and analgesia
  - No (minimal) respiratory depression
  - Causes unique type of sedation that allows for easy arousal with preserved respiratory drive, with quick return to sedated state, without changing infusion rate
  - Has ceiling on dose
    - Package insert dose range 0.2–0.7 µg/kg/hr for 24 hours
    - Doses over 0.7 µg/kg/hr and for longer periods of time now starting to be studied.
    - Causes hypotension, especially with volume depletion and loading dose.
Dexmedetomidine: Prescribing Information

- **Indications**
  - Sedation of initially intubated and MV patients during treatment in OR, Angiography, ICU
  - Sedation and management of agitated patients in ED?
  - Successful weaning of ventilated patients
  - Management of alcohol withdrawal patients

- **Contraindication**
  - Caution in patients with advanced heart block

- **Drug interactions**
  - Vagal effects can be counteracted by IV administration of anticholinergic agents

- **Disease effecting clearance**
  - Clearance is lower in patients with hepatic impairment
Dexmedetomidine

Advantages

- Has sedative, analgesic, and anxiolytic effects
- Respiratory stability
- Predictable hemodynamic response
- Arousable and oriented patient
- No need to discontinue before extubation
- Antishivering

Limitations

- May reduce HR and BP (caution in hypovolemia, shock, and heart block)
- Potentiates effects of opioids, sedatives and anesthetics
- Dry mouth
- Vasoconstriction at high dose

Clinical Strategies for Patient Comfort and Safety in the ICU

- What are the goals of sedation and analgesia?
- Can existing drugs achieve these goals:
  - Alone or in combination?
  - By bolus or infusion?
- Is there an unmet need?
  - Can dexmedetomidine fill it?
- Clinical challenges:
  - What are they and how can we meet them?
Achieving Optimal Patient Comfort in the ICU

- Analgesia
- Anxiolysis
- Sedation
- Hypnosis
- Amnesia
Often a Neglected Problem

Drug therapy within 48 hours in ICU

Is patient comfortable and at goal?

- No
  - Rule out & correct reversible causes
  - Use non-pharmacological treatment and optimize environment

- Yes
  - Reassess goal daily
  - Titrate and taper therapy
  - Consider daily wake-up
  - Taper if > 1wk high dose therapy

- IVP doses > 2 hrs?
  - Consider continuous infusion of opioid

- Use pain scale to assess pain
- Set analgesia goal

**H-D unstable**
- Fentanyl, Hydromorphone
- Morphine
- Repeat until controlled, scheduled and PRN dose

**H-D stable**
- Morphine
- Repeat until controlled, scheduled and PRN dose

*Crit Care Med 2002; 30:119-141*
The Fine Balance in Patient Comfort

Undersedation

Oversedation
The Fine Balance in Patient Comfort

- Anxiety
- Agitation
- Hypertension
- Tachycardia
- Arrhythmias
- Myocardial ischemia
- Wound disruption
- Patient injury
The Fine Balance in Patient Comfort

Depersonalization
Delayed emergence
Delayed weaning
Pressure injury
Venous stasis
Muscle atrophy
Increased cost
Choosing the Right Drug Combination
Sedation

Hypnosis

Anxiolysis

Amnesia

Analgesia

Patient Comfort
Sedation

Dexmedetomidine

Primary

Analgesia

Midazolam

Adjunct

Sedation

R Sladen, ASA 2001
Sedation

Dexmedetomidine

Propofol

Analgesia

Primary

Adjunct

Sedation

R Sladen, ASA 2001
Sedation

Analgesia

Dexmedetomidine

Primary

Fentanyl

Adjunct Analgesia

R Sladen, ASA 2001
Sedation

Analgesia

Dexmedetomidine

Primary

Morphine

Adjunct Analgesia

R Sladen, ASA 2001
Safety and efficacy are no longer sufficient

- Optimal use of limited resources needs to be justified
- Third-party payers and others demand evidence of cost-effective data for new drugs
- What is the added value of the increased costs?

# Costs of Analgesic / Sedative Agents in the ICU

<table>
<thead>
<tr>
<th></th>
<th>Cost per mg</th>
<th>Low Dose - mg/hr -</th>
<th>High Dose - mg/hr -</th>
<th>Low Cost - $ per Day -</th>
<th>High Cost - $ per Day -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.05</td>
<td>1.00</td>
<td>15.00</td>
<td>1.23</td>
<td>18.48</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.37</td>
<td>0.10</td>
<td>2.00</td>
<td>3.29</td>
<td>65.76</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.29</td>
<td>2.00</td>
<td>35.00</td>
<td>13.92</td>
<td>243.60</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.48</td>
<td>0.50</td>
<td>15.00</td>
<td>5.70</td>
<td>171.00</td>
</tr>
<tr>
<td>Propofol</td>
<td>0.04</td>
<td>100.00</td>
<td>350.00</td>
<td>87.82</td>
<td>307.36</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>286.00</td>
<td>0.02</td>
<td>0.05</td>
<td>109.82</td>
<td>336.34</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.53</td>
<td>1.00</td>
<td>15.00</td>
<td>12.77</td>
<td>191.52</td>
</tr>
</tbody>
</table>
Rationale for Economic Evaluations

- Safety and efficacy are no longer sufficient
  - Optimal use of limited resources needs to be justified
  - Third-party payers and others demand evidence of cost-effective data for new drugs
  - What is the added value of the increased costs?

Cost of Undersedation

- Patient discomfort and dissatisfaction
- Long-term psychological effects
- Increased use of paralytic drugs
- Increased metabolic demands
- Associated cardiovascular consequences
Cost of Oversedation

- Unable to adequately examine the patient
- Expensive diagnostic imaging and other tests
- Possible late diagnosis of treatable problems
- Prolonged mechanical ventilation time
- Prolonged stay in the ICU
Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult.


Volume 30, No. 1 2002

28 Recommendations
Goals of Sedation in the ICU

ACCM Guidelines – 2002

- 28 total recommendations
- Analgesia should be provided with IV doses of common opiates (fentanyl, morphine, hydromorphone).
- Fentanyl is preferred for a rapid onset of analgesia in acutely distressed patients.
- Morphine or hydromorphone are preferred for intermittent therapy over fentanyl because of their longer duration of effect.
- Midazolam or diazepam should be used for the rapid sedation of the acutely agitated patient.
- Fentanyl or hydromorphone are preferred for patients with hemodynamic instability or renal insufficiency.
Goals of Sedation in the ICU

ACCM Guidelines – 2002, cont’d.

- Propofol is the preferred sedative when rapid awakening is important (e.g., for neurosurgical assessment or extubation).
- Midazolam is recommended for short-term use only, as it produces unpredictable awakening and time to extubation when infusions continue for more than 48–72 hours.
- Lorazepam is recommended for the sedation of most patients via intermittent IV administration or continuous infusion.
- Triglyceride concentrations should be monitored after 2 days of propofol infusion, and total lipid intake should be included in the nutrition support prescription.

—continued
Goals of Sedation in the ICU

ACCM Guidelines – 2002, cont’d.

- The potential for opiate, benzodiazepine or propofol withdrawal should be considered after high doses or more than approximately 7 days of therapy. The dose should be tapered systematically to prevent withdrawal symptoms.
- Haloperidol is the preferred agent for the treatment of delirium in the critically ill patient.
- Patients should be monitored for ECG changes (QT prolongation and arrhythmias) when receiving haloperidol.

### Effect of Rational Use Guidelines

#### Implementation of Guideline Policy

<table>
<thead>
<tr>
<th></th>
<th>Before (Days)</th>
<th>After (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital LOS</td>
<td>34.3</td>
<td>23.3</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>19.1</td>
<td>9.9</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>13.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

LOS = length of stay.

Assessing the Degree of Sedation: The Riker Sedation-Agitation Scale

<table>
<thead>
<tr>
<th>Sedation / Agitation Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dangerous agitation: pulls at ET; tries to remove catheters; limbs over bedrail; strikes staff; thrashes from side to side</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated; does not calm, despite frequent verbal reminding of limits; requires physical constraints; bites ET</td>
</tr>
<tr>
<td>5</td>
<td>Agitated: anxious or mildly agitated; attempts to sit up; calms down to verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm and cooperative: calms, awakens easily; follows commands</td>
</tr>
<tr>
<td>3</td>
<td>Sedated: difficult to arouse; awakens to verbal stimuli or gentle shaking but drifts off again; follows simple commands</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated: arouses to physical stimuli but does not communicate or follow commands; may move spontaneously</td>
</tr>
<tr>
<td>1</td>
<td>Unarousable: minimal or no response to noxious stimuli; does not communicate or follow commands</td>
</tr>
</tbody>
</table>

Continuous vs Intermittent Sedation in the Patient with Severe Sepsis

- **Continuous sedation** (without active titration or tapering)
  - May prolong mechanical ventilation with:
    - Increased ICU stay
    - Increased risk of nosocomial pneumonia

- **Intermittent sedation**
  - Daily interruption to wakefulness
  - Reduces duration of mechanical ventilation
  - Decreases ICU stay
  - Facilitates examination
  - Reduces diagnostic studies

Prompt Extubation:
Reduced Cost and Length of Stay

Example: CABG (n=100)

- Study arms:
  - Early extubation (1 to 6 hr)
  - Late extubation (12 to 22 hr)

- Results:
  - ↓ total costs by 25%
  - ↓ ICU costs by 53%
  - ↓ hospital and ICU lengths of stay
  - Shifts high ICU costs to lower ward costs
  - Improves resource utilization; increases throughput

In Conclusion…

Nonpharmacologic Treatment
Sleep Promotion
Combination Therapy
Environmental Control
Analgesia
Physician Management
Sedation
Nursing Care
Delirium Control
Future Directions

- Expanded role for dexmedetomidine?
- As medications come off patent:
  - Role for sufentanil in ICU?
  - Role for remifentanil in ICU?
    - Muellejans et al, Crit Care. 2004 Feb
- Constantly changing landscape — some generics get more expensive as time goes on.
- Increased titration of sedatives
Add- on Slides
Dexmedetomidine May Facilitate Early Extubation

- No respiratory depression
- Patient is arousable
- Ablation of neurohormonal stress
- Synergy with anesthetics and analgesics
  - Lower doses of anesthetics and analgesics
- Pain control without the sedating effects of opioids
- Less use of diuretics
- Facilitates daily wake-up for longer term intubated patients

Herr. 2003; in press.
Failure to Wean From the Ventilator: Advantages of Dexmedetomidine

Transitioning from propofol to dexmedetomidine

- Does not cause respiratory depression
- Activates natural sleep pathways; patient is easily aroused
- May facilitate weaning patients off the ventilator
- Maintains adequate sedation and calmness after extubation
- Facilitates assessment of patient comfort and pain levels
Head Injury: Issues

- Difficulty achieving awakening state
  - Increased hippocampal blood flow
  - Release of catecholamines
  - Decreased GABA activity; increased neuronal activity

- The “hyperadrenergic syndrome”
  - Tachycardia
  - Hypertension
  - Hyperventilation
  - Sweating
  - Muscle rigidity
  - Elevated ICP
Head Injury: Sedation

Issues with head injury patients
- Frequently agitated or combative
  - Must be sedated
- Periodic neurologic assessments needed
  - Patient must be cooperative

Use of dexmedetomidine
- Can be used as primary agent
- Provides cooperative sedation
- Titrate to effect
- Blunt hyperadrenergic response
Use of Dexmedetomidine in the Burn Unit

- Alpha-2 agonist effect greatly assists in the management of burn patients; includes blunting of catecholamine surge
- Use in intubated and nonintubated burn patients
- Administer as a standard load once patient is euvolemic (range: 0.4 to 0.7 mcg/kg)
- Lower dose (range) for less severe burns and nonintubated patients
  - 0.2 to 0.4 mcg/kg for routine burn care
  - 0.6 mcg/kg for delicate patients
Dexmedetomidine Protocol for Trauma

- Initiation of dexmedetomidine
  - Loading dose: none
  - Gradual step-up in dose based on heart rate
  - Titrate to sedation scale

- Lower doses (<0.7 mcg/kg/hr)
  - Adequate for non-CNS injury

- Higher doses (<2.0 mcg/kg/hr)
  - Agitation associated with CNS injury
  - Withdrawal from alcohol or other drugs
Alcohol Withdrawal and Trauma

- Spinal cord injury occurs mostly in males who are intoxicated
- Experience agitation; at risk for exacerbating underlying injury
- Benzodiazepines are typically used
  - Intubation and ventilation are often required
- Dexmedetomidine is an alternative
  - Spontaneous breathing
  - Hemodynamic stability
  - Adequate sedation
  - Prevention of autonomic effects of withdrawal
  - Pain control
Summary

- Overall goals of sedation are to increase patient safety and comfort and facilitate management
- Both undersedation and oversedation are associated with deleterious consequences
- Dexmedetomidine can help optimize sedation and patient care via:
  - Unique mechanism of action on natural sleep pathway that permits patients to be well rested yet easily aroused
  - Synergism with other agents, resulting in significant dose reductions
  - Pain control and no respiratory effects
- Keys to success include appropriate patient selection and proper adjustment of protocols
It didn’t work...!