ICU Pharmacology

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ICU Pharmacology

- Sedatives
- Analgesics
- Paralytics
- Pressors

Sedation

- Relieve pain, decrease anxiety and agitation, provide amnesia, reduce patient-ventilator dysynchrony, decrease respiratory muscle oxygen consumption, facilitate nursing care.
- May prolong mechanical ventilation and increase costs.

Goals of Sedation

- Old- Obtundation
- New- Sleepy but arousable patient
- Almost always a combination of anxiolytics and analgesics.

What is Agitation?

- Pain
- Patient-ventilator interactions
- Encephalopathy
- Withdrawal
- Anxiety
- Delirium
- Fear
- Sleep deprivation
- Depression
- ICU psychosis

Benzodiazepines

- Act as sedative, hypnotic, amnestic, anticonvulsant, anxiolytic.
- No analgesia.
- Develop tolerance.
- Synergistic effect with opiates.
- Lipid soluble, metabolized in the liver, excreted in the urine.
- Interact with erythro, propranolol, theo

Benzodiazepines

- Diazepam (Valium)
  - Repeated dosing leads to accumulation
  - Difficult to use in continuous infusion
- Lorazepam (Ativan)
  - Slowest onset, longest acting
  - Metabolism least affected by liver disease
- Midazolam (Versed)
  - Fast onset, short duration
  - Accumulates when given in infusion >48 hours.

	Onset	Peak	Equiv. dose
Diazepam (valium)	1-3 min	3-4 min	2-5 mg
Lorazepam (ativan)	5-15 min	15-20 min	1-2 mg
Midazolam (versed)	1-3 min	5-30 min	1-5 mg

Propofol

- Sedative, anesthetic, amnestic, anticonvulsant
- Respiratory and CV depression
- Highly lipid soluble
- Rapid onset, short duration
  - Onset <1 min, peak 2 min, duration 4-8 min
- Clearance not changed in liver or kidney disease.

Propofol- Side effects

- Apnea, unpredictable respiratory depression
  - May not be all that unpredictable
  - Use only in mechanically ventilated patients
- Hypotension
  - First described in post-op cardiac patients
- Increased triglycerides
  - 1% solution of 10% intralipids
  - Daily tubing changes, dedicated port

Propofol Infusion Syndrome

- Rare and often fatal syndrome described in critically ill children undergoing long-term propofol infusion at high doses
- Cardiac failure, bradycardia, rhabdomyolysis, severe metabolic acidosis and renal failure
- Supportive treatments with catecholamines and corticosteroids act as triggering factor, as can higher doses (> 5 mg/kg/hr), prolonged (>48 h) infusions, use in patients with acute neurological or inflammatory illnesses.

Etomidate

- Sedative, anesthetic
- Used in rapid sequence intubation
- Advantages
  - Rapid onset of action (<60 sec)
  - Reliable pharmacokinetics
  - Cardiovascular stability
- Disadvantages
  - Inhibits adrenal steroidogenesis
    - Etomidate eliminates the adrenal's response to adrenocorticotropin hormone through inhibition of 11-β-hydroxylase, the same enzyme implicated in sepsis-associated adrenal dysfunction

Dexmedetomidine (Precedex)

- $\alpha 2$ agonist, acts of receptors in locus ceruleus and spinal cord
- Sedation through endogenous sleep promoting pathways, analgesia through spinal cord pathways
- No respiratory depression, some bradycardia and vasodilation
- Approved for brief post-op sedation

Butyrophenones

- Haldol
  - Anti-psychotic tranquilizer
  - Slow onset (20 min)
  - Not approved for IV use, but is probably safe
  - No respiratory depression or hypotension.
  - Useful in agitated, delirious, psychotic patients
  - Side effects- QT prolongation, NMS, EPS

Sedation studies

- Propofol vs. midazolam
  - Similar times to sedation, faster wake-up time with propofol AJRCCM, 15:1012, 1996.
- Nursing implemented sedation protocol
  - ↓ duration of mech vent, ↓ ICU stay, ↓trach rate Crit Care Med 27:2609, 1999.
- Daily interruption of sedation
  - ↓ duration of mech vent, ↓ ICU LOS, hosp LOS NEJM 342:1471, 2000.

Sedation studies (cont.)

- Dexmedetomidine vs. midazolam
  - Using Precedex at higher doses and for longer than approved, end point was light sedation. Precedex had less delirium, shorter LOS. Riker RR. JAMA 301(5):489-499, 2009.
- No sedation for critically ill patients receiving mechanical ventilation
  - It's an option in some patients. Lancet 375: 475-480, 2010.

Monitoring Sedation

- Many scoring systems, none are validated.
- Sedation-Agitation Score (SAS)
  - +2: Dangerously agitated, does not follow commands, thrashing, pulling at tubes or catheters
  - +1: Agitated, but follow commands, asynchronous breathing, persistent coughing or choking
  - 0: Calm and follows commands
  - -1: Deep sedation, awakens only to noxious stimuli
  - -2: Over-sedation, unresponsive to any stimuli

Pain in the ICU

- Pain leads to a stress response which causes:
  - Catabolism
  - Ileus
  - ADH release
  - Immune dysregulation
  - Hypercoaguable state

Pain in the ICU

- What causes pain in the ICU?
  - Lines
  - Tubes
  - Underlying illness
  - Interventions
  - Everything else

Analgesics

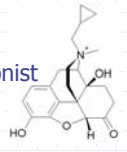
- Relieve Pain
- Opioides
- Non-opiodes
- Can be given PRN or continuous infusion
  - PRN avoids over sedation, but also has peaks and valleys and is more labor intensive.

Opiodes

- Metabolized by the liver, excreted in the urine.
  - Morphine- Potential for histamine release and hypotension.
  - Fentanyl- Lipid soluble, 100X potency of Morphine, more rapid onset, no histamine release, slightly more expensive.
  - Demerol- Not a good analgesic, potential for abuse, hallucinations, metabolites build up and can lead to seizures.

Opiodes

- Adverse effects
  - Respiratory depression
  - Hypotension (sympatholysis, histamine release)
  - Decreased GI motility (peripheral effect)
  - Pruritis
- Methylnaltrexone
  - Peripherally acting μ-opoid antagonist



Non-opiodes

- Ketamine
  - Analog of phencyclidine, sedative and anesthetic, dissociative anesthesia.
  - Potent bronchodilator, hypertension, hypertonicity, hallucinations, nightmares.
  - Bad side effects can be limited by using with benzos, using at lower doses
  - Emergence phenomena in anesthesia doses
    - 12% of patients
    - Varies from pleasant dream-like state to hallucinations to delirium, confusion, irrational behavior

Non-opiodes

- Ketorolac
  - NSAID
  - Limited efficacy (post-op ortho)
  - Synergistic with opiodes
  - No respiratory depression
  - Increased side effects in the critically ill
  - Renal failure, thrombocytopenia, gastritis

Paralytics

- Paralyze skeletal muscle at the neuromuscular junction.
- They do not provide any analgesia or sedation.
- Prevent examination of the CNS
- Increase risks of DVT, pressure ulcers, nerve compression syndromes.

Use of Paralytics

- Intubation
- Facilitation of mechanical ventilation
- Preventing increases in ICP
- Decreasing metabolic demands (shivering)
- Decreasing lactic acidosis in tetanus, NMS.

Paralytics

- Depolarizing agents
  - Succinylcholine
- Non-depolarizing agents
  - Pancuronium
  - Vecuronium
  - Atracurium

Paralytics

Drug	Onset	Duration	Route of elimination	Adjust for renal	Adjust for liver
Succinylcholine	1-1.5 min	5-10 min	acetylcholinesterase	No	Yes
Pancuronium	1.5-2 min	60 min	85% kidney	Yes	Yes
Vecuronium	1.5 min	30 min	biliary, liver, kidney	No	Yes
Atracurium	2 min	30 min	Plasma (Hoffman)	No	No
Rocuronium	1 min	30-60 min	Hepatic	No	Yes
Tubocurare	6 min	80 min	90% kidney	Yes	Yes

Paralytics

Drug	Advantages	Side effects
Succinylcholine	rapid onset, short acting	↑K, ICP, IOP
Pancuronium	Inexpensive, long acting	tachycardia
Vecuronium	Less CV effects	bradycardia
Atracurium	Hoffman elim	rash, histamine release
Rocuronium	No hemodynamic effects	expensive

Complications of Paralysis

- Persistent neuromuscular blockade
  - Drug accumulation in critically ill patients
  - Renal failure and >48 hr infusions raise risk

Post-paralytic syndrome

- Acute myopathy that persists after NMB is gone
- Flaccid paralysis, decreased DTRs, normal sensation, increased CPKs.
- May happen with any of the paralytics
- Combining NMB with high dose steroids may raise the risk.

Monitoring Paralysis

- Observe for movement
- Twitch monitoring, train of four, peripheral nerve stimulation.

Shock

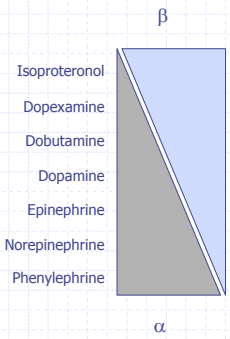
- Hypoperfusion of multiple organ systems.
- May present as tachycardia, tachypnea, altered mental status, decreased urine output, lactic acidosis.
- Not all hypotension is shock and not all shock has hypotension.

Shock

- Rapidity of diagnosis is key.
- The types:
  - Hypovolemic/ hemorrhagic
  - Cardiogenic
  - High output
- Fluid bolus is almost always the correct initial therapy.

Pressors

- β_1 myocardium- ↑ contractility
- β_2 arterioles- vasodilation
- β_1 SA node- ↑ chronotropy
- β_2 lungs- bronchodilation
- α peripheral- vasoconstriction



Dopamine (Intropin)

- Dopaminergic {Renal} (2-4 mcg/kg/min)- increase in mesenteric blood flow
- β (5-10 mcg/kg/min)- modest positive ionotrope
- α (10-20 mcg/kg/min) vasoconstriction

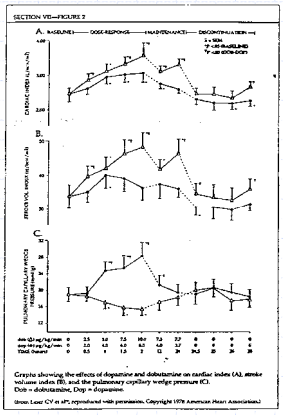
Dopamine

- "Renal dose" dopamine probably only transiently increases u/o without changing clearance.
- Newer studies suggest it may impair mesenteric perfusion more than norepi
- Use is falling out of favor
- Adverse effects- tachyarrhythmias .

Dobutamine (Dobutrex)

- Primarily β1, mild β2.
- Dose dependent increase in stroke volume, accompanied by decreased filling pressures.
- SVR may decrease, baroreceptor mediated in response to ↑ SV.
- BP may or may not change, depending on disease state.

Dopamine vs. Dobutamine in cardiogenic shock



Dobutamine

- Useful in right and left heart failure.
- May be useful in septic shock.
- Dose- 5-15 mcg/kg/min.
- Adverse effects- tachyarrhythmias.

PDE Inhibitors

- Amrinone, Milrinone
- Positive ionotrope and vasodilator (systemic and pulmonary).
- Little effect on heart rate.
- Uses- CHF
- AE- arrhythmogenic, thrombocytopenia
- Milrinone dosing- 50mcg/kg bolus, 0.375-0.5 mcg/kg/min infusion.

Norepinephrine (Levophed)

- Potent α and β agent
- Vasoconstriction (that tends to spare the brain and heart).
- Good agent to $\uparrow$SVR in high output shock.
- May cause decreased perfusion of kidneys, mesenteric bed (least of all α agents).
- Can cause reflex bradycardia (vagal).

Phenylephrine (Neosynephrine)

- Strong, pure α agent.
- Vasoconstriction with minimal $\uparrow$ in heart rate or contractility.
  - Often causes reflex bradycardia
- Does not spare the heart or brain.
- BP at the expense of perfusion.

Epinephrine

- β and α agent.
- More mesenteric ischemia than norepi.
- May have more right heart effects.
- Some effects on metabolic rate, inflammation (Use in anaphylaxis)
- AE- Arrhythmogenic, coronary ischemia, renal vasoconstriction, ↑ metabolic rate.

Ephedrine

- Releases tissue stores of epinephrine.
- Longer lasting, less potent than epi.
- Used mostly by anesthesiologists.
- 5-25 mg IVP.

Vasopressin

- Made in hypothalamus, stored in anterior pituitary. Released in response to hypovolemia, increased osmolality
- V1 receptors on vascular smooth muscles
- Vasoconstrictor that may be useful in septic shock, when added to norepi in fluid resuscitated patients.
- Unclear role in other shock states.
- .01 to .04 units/min

Labetolol (Normodyne)

- α_1 and non-selective β blocker.
- Dose related decrease in SVR and BP without tachycardia.
- Does not ↑ICP
- Useful in the treatment of hypertensive emergencies, aortic dissection.
- Bolus= 20mg, infusion= 2mg/min.

Nitroglycerine

- Venodilator at low doses (<40mcg/min)
- Arteriolar dilation at high doses (>200 mcg/min).
- Rapid onset, short duration, tolerance.
- AE- inhibits platelet aggregation, ↑ ICP, headache.

Nitroprusside (Nipride)

- Balanced vasodilator
- Rapid onset, short elimination time
- Useful in hypertensive emergency, severe CHF, aortic dissection
- Accumulates in renal and liver dysfunction.
- Toxicity= CN poisoning (decreased CO, lactic acidosis, seizures).

Nitroprusside

- Dosing- 0.2- 10 mcg/kg/min
- Other AE- ↑ ICP

Types of Shock

- Hypovolemic
- Cardiogenic
- High output

Hypovolemic Shock

- Cold and clammy, thready pulse, clear lungs.
- GI bleeds, trauma, dehydration.
- Treatment-Volume, volume, volume

Cardiogenic Shock

- Cold and clammy, thready pulse, crackles, S3.
- Left heart failure, right heart failure, valvular disease.
- Treatment- preload reduction(diuretics), afterload reduction (ACE-I), increase contractility (PDE inhibitor, dobutamine)

High Output Shock

- Warm and well perfused, bounding pulses
- Sepsis, sepsis, sepsis, and then other things
- Treatment- Volume first, then norepi, vasopressin or dobutamine as second agent.