

Sedation, Analgesia, Paralysis

making life in the PICU safer, more comfortable, and easier for all.

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Goals of ICU Sedation

Analgesia for painful diseases and procedures

Compliance with controlled ventilation and routine intensive care

Amnesia for the periods of sedation

Reduce the physiologic responses to stress

Avoid complications

How???

Know what you are trying to do

Know your drugs

Know your patient

If you don't know the indications and contraindications to the drug you are considering, and if you are not prepared to deal with complications, *DONT DO IT*.

It is essential to get comfortable with the idea of titrating drugs to effect--there is no "dose".

There are guidelines, but each situation, and each patient will be different. A dose of morphine that wouldn't touch a narcotic tolerant oncology patient could cause life-threatening respiratory depression in an adolescent with a broken arm. Watch the nurses give the drugs, and watch their effect. Keep in mind what the "target" response is. It is the **ONLY** way you will ever be competent to provide adequate analgesia and sedation. **WATCH**, and **PAY ATTENTION**. You will learn something and you will be able to provide better care.

Classes of drugs commonly used in the PICU

Narcotics

Benzodiazepines

Non-steroidal anti-inflammatory agents (Ketorolac)

Ketamine

Propofol

Neuroleptics

Barbiturates

Paralytics-depolarizing and non-depolarizing

Situations in which some combination of the above drugs are commonly needed

Mechanical ventilation, post-operative

Mechanical ventilation, ARDS

Mechanical ventilation, Asthma

Mechanical ventilation, Epiglottitis or croup

Head injury

Post-operative

Chest syndrome

Intubation--various scenarios

Painful procedures--chest tubes, lumbar puncture, bone marrow aspirate, dressing changes, endotracheal tube suctioning

As you think about the drugs you would choose for each situation, think **concretely** about what you are trying to achieve--NO movement whatsoever in the patient with a tenuous airway, analgesia while attempting to allow “wake-up” for extubation post-operatively, etc. Different drugs do different things--often you should use a “balanced” approach.

Basic (very basic) pharmacologic principles

1. Onset of action-- $t_{1/2}$ reflects initial distribution from blood to highly perfused tissues. Clinical onset of action is the time necessary to see effect of the drug.
2. Half life--the time it takes for the concentration of drug to decrease by 1/2. Elimination constant, $K_{el}=0.693 \times T_{1/2}$. ($T_{1/2}$ =redistribution and metabolic clearance)
3. Volume of distribution--relates the amount of drug in the body to the concentration of drug in the blood or plasma--the fluid volume that would be needed to account for all the drug in the body. Small Vd implies that the drug is retained within the vascular compartment, large Vd implies distribution throughout the body of sequestration in certain tissues. $Vd (ml/kg) = \text{Dose} (mg/kg) / \text{concentration at time 0} (mg/ml)$.
4. Clearance--The ability of the body to eliminate a drug, expressed as a volume of blood cleared of drug per unit time. $Cl = Vd \times K_{el}$
4. Metabolism--mostly renal and/or hepatic for most drugs.
5. Bioavailability--the percent of the dose reaching the systemic circulation as unchanged drug following administration by any route.

Opioids (aka narcotics)

Opiates provide both pain relief and sedation. They are the most commonly used class of drugs for analgesia in the PICU. In addition to their analgesic properties, narcotics decrease responsiveness to external stimulation and reduce the level of consciousness. Nevertheless, the sedative properties of narcotics are inferior to those of the benzodiazepines, and amnesia following narcotic administration is incomplete.

	Relative Dose	Elimination $t_{1/2}$	Clearance (ml/kg/min)
<i>morphine</i>	0.1 mg	114 min	14.7
<i>meperidine</i>	1.0 mg	222 min	15.1
<i>fentanyl</i>	1-5 mcg	202 min	11.6
<i>methadone</i>	0.1 mg	15 hours	

Morphine

Minimal direct effect on myocardial performance
Histamine release--may induce hypotension if large doses are given rapidly
Dose related analgesia, sedation, euphoria
Dose related respiratory depression

Meperidine

Respiratory depression similar to other opioids
Normeperidine (metabolite) is epileptogenic
Mild vagolytic
Histamine release and myocardial depression in high doses
Less biliary tract spasm

Fentanyl

Synthetic opioid, highly lipid soluble, short distribution T_{1/2} but long elimination T_{1/2}
Metabolized almost exclusively in the liver, thus may accumulate with altered hepatic blood flow
Provides hemodynamic stability, even in very high doses, and blunts pulmonary vascular responses.
May produce Muscle rigidity ("chest wall rigidity") if given as large fast bolus
Commonly causes lowering of HR (unrelated to pain relief or sedation)

Methadone

Potent analgesic effects, minimal hemodynamic effects
Long half-life
Absorption after oral administration reliably 50-70% that of IV
Sedative and euphoric properties may be less pronounced than those of morphine
Useful for pain control as well as for treating abstinence phenomena.

Untoward Effects of Opioids (aka side effects)

Respiratory depression--All opioids cause dose related respiratory depression by shifting the CO₂ response curve to the right, and abolishing the ventilatory response to hypoxemia. Depending on the drug you can see decreased ventilatory rate or tidal volume (thus, the *rate* may be ok, but the *tidal volume* may be inadequate). Respiratory depression may occur at any age.

Reversal--Naloxone (Narcan)

Full reversal--0.1 mg/kg; >20 kg, 2.0 mg.

"Partial" reversal--titrate to effect--start with 2-10 mcg/kg. Easiest way to do this is to take 0.4 mg (ie, 1 cc of 0.4mg/cc vial) and dilute in 10 cc NS==40mcg/cc. Thus, 1cc per 4 kg body weight equals 10 mcg/kg. Most useful for patients who are expected to have significant residual pain (ie, surgical, chest syndrome, Sickle Cell pain crisis, oncology)

The half life of naloxone is significantly shorter than morphine, demerol, or fentanyl. If there has been a significant overdose, more than one dose will be necessary. A continuous infusion may be needed.

Pruritis--Several of the opioids cause itching, and there is significant inter-patient variability in susceptibility. It may be alleviated by benadryl.

Tolerance and Dependence--Tolerance generally develops after 2-3 days of frequent or continuous usage. Dependence (ie, the potential for withdrawal symptoms) generally develops after 5-7 days of frequent or continuous use. Tolerance is treated by increasing the dose as needed for pain relief. Dependence is treated with gradual withdrawal of the drug, either using the initial drug, or converting to methadone for convenient dosing. Treatment of withdrawal can be difficult if the patient has been receiving narcotics for prolonged periods. In general, the longer the period of treatment, the longer the period of withdrawal needed. Alternatively, one can treat symptoms with alternative drugs (a method usually reserved for those who have a psychological as well as physical dependence on the drug).

Benzodiazepines

Benzodiazepines provide hypnosis, anxiolysis, anterograde amnesia, and anticonvulsant activity. They **DO NOT** provide analgesia. Once more, they *DO NOT* provide analgesia. They are useful for providing sedation and treating seizures, but one must remember to treat pain with an

	Relative Dose	t _{1/2} (redistribution) (min)	t _{1/2} (elimination) (hours)	V _d (Liter/kg)	Clearance (ml/kg/min)
Diazepam	0.3-0.5	30-60	21-37	1.0-1.5	0.2-0.5
Lorazepam	0.05		10-20	0.8-1.3	0.7-1.0
Midazolam	0.15-0.30	6-15	1-4	1.0-1.5	6-8

analgesic

Midazolam has a short onset of action, short duration of action, and relatively short elimination half life. For these reasons, it is useful for short procedures, but inconvenient for prolonged sedation. It may be used as a constant infusion. Continuous administration may result in prolonged sedation even after the infusion is discontinued if the rate of administration is too high. There have also been reports of dystonia and choreoathetosis after midazolam infusion and may represent benzodiazepine withdrawal, persistent effects of the drug, or the combined effect of multiple drugs.

Diazepam has a short onset of action, like midazolam, and slightly longer duration of action, but a long elimination half life. Thus, with repeated doses, it may accumulate.

Lorazepam is less lipid-soluble, and has a longer duration of action with a shorter elimination

half-life, thus is more appropriate than diazepam for prolonged sedation. (Longer duration of action but less risk of accumulation with repeated dosing.)

Untoward Effects of Benzodiazepines

Tolerance--As with the narcotics, dose may need to be increased after 2-3 days

Dependence--Dependence and withdrawal phenomena can be severe. Withdrawal need to be done carefully, looking for signs of withdrawal (tremor, high HR, BP). Too rapid withdrawal in severely dependent patient can cause seizures.

Choreoathetoid movement disorder--Usually improves with time

Personality changes--Usually improves with time, though after long term, high dose use, personality changes may remain apparent to family members for weeks-months.

Respiratory depression--Dose related.

Reversal--Flumazenil--Benzodiazepine receptor antagonist

0.2 mg over 30 sec, may increase dose up to 0.5 mg/minutes. Up to 5 mg total.

Contraindicated--where benzodiazepines have been used to treat seizures, chronic benzodiazepine use, TCA's present, mixed drug overdose.

Ketamine

Ketamine is chemically related to phencyclidine and cyclohexamine. Ketamine hydrochloride is water soluble at commercial concentrations, but is quite lipid soluble as well and quickly crosses the blood-brain barrier.

Pharmacokinetics are very similar in children and adults. With intravenous administration, the distribution half life is less than 30 seconds, the redistribution half life 4.7 minutes, and the elimination half life 2.2 hours. Clinically, one sees peak concentrations within one minute of IV administration, with rapid absorption by the brain and early immediate induction of clinical effects. With redistribution to peripheral tissues, the decrease in CNS levels correlates with resolution of the clinical effect, generally within 15-20 minutes.

The anesthetic state produced by ketamine has been classically described as a functional and electrophysiological dissociation between the thalamocortical and limbic systems. Ketamine is a potent analgesic at sub-anesthetic concentrations, and the effects may be mediated by different mechanisms. Ketamine blocks NMDA receptors, and there is some data that it interacts with opiate receptors as well as CNS muscarinic receptors.

Clinical Effects of Ketamine

CNS

Ketamine produces a dissociative state. Its effect on intracranial pressure remains controversial in practice, but controlled studies in which ventilation was controlled

showed no effect on intracranial pressure. It probably does, however, increase CMRO₂, and hence, use in patients with intracranial injury should probably be avoided if possible.

“Emergence” phenomena are frequently reported after the use of ketamine in older adolescents. Concordant treatment with a benzodiazepine has been shown to prevent the development of unpleasant emergence phenomena.

Cardiovascular System

Ketamine inhibits reuptake of catecholamines in both the peripheral circulation and the CNS in a dose-dependent fashion. It has a direct negative inotropic effect on the myocardium, and a direct vasodilatory action on vascular smooth muscle. This is generally overwhelmed by central sympathetic stimulation that occurs, however, leading to increases in heart rate, systemic arterial pressure, and possibly systemic vascular resistance. The cardiovascular effects of ketamine are attenuated by alpha and beta blocking agents, verapamil, benzodiazepines, and high epidural blockade.

Respiratory effects

Ketamine is a mild respiratory depressant, and there is a dose related increase in respiratory depression with incremental doses of ketamine. In children, respiratory rate, tidal volume, and minute ventilation are unaffected, but the CO₂ response curve is shifted to the right. Ketamine generally preserves airway patency, and protective airway reflexes are not repressed. Transient stridor or laryngospasm are rarely reported, and are associated with coincident respiratory infection. Ketamine increases oral secretions, and this may be more clinically important in those children with upper respiratory infections. Laryngospasm and the potential for emesis/aspiration are more pronounced in infants and patients with a full stomach, hence these patients should be considered at risk for airway compromise.

Ketamine is a potent bronchodilator. The mechanisms of this response is considered to be a combination of drug induced increase in circulating catecholamine, direct smooth muscle dilatation, and inhibition of vagal tone.

Neuromuscular Effects

Ketamine increases skeletal muscle tone, and there are frequently random movements of the head or extremities. Ketamine also appears to potentiate the effects of neuromuscular blocking agents, both depolarizing and non-depolarizing.

Intraocular Pressure

The effects of ketamine on IOP are controversial, and the literature contains various contradictory reports regarding the potential for increased IOP during ketamine anesthesia.

Dosage Recommendations

In the intensive care unit all anesthetic/analgesic/sedative agents should be titrated to

effect, with the unique physiology of each patient kept in mind. This makes dosage recommendations difficult. These children may be compromised from a pulmonary, hemodynamic, or neurologic perspective, and judicious use of any agent is warranted. Ketamine, for example, while supporting hemodynamics in the majority of patients, can cause hypotension if the patient's myocardial reserve is limited. Thus, these recommendations are NOT to be interpreted as policy, but as simple guidelines.

Analgesia-.25-.75 mg/kg IV

Dissociation/anesthesia-1.0-2.0 mg/kg IV in a well hydrated patient with good hemodynamics, 0.25-1.0 mg/kg in a severely dehydrated patient or a patient with compromised myocardial function.

Continuous infusion-1 mg/kg IV followed by 0.5-1.0 mg/kg/hour

Tolerance develops with repeated doses, and the optimal dose will need to be increased. Co-administration of benzodiazepines reduces the incidence of emergence phenomena in older children, but will prolong the duration of sedation. This is not generally problematic in the intensive care setting, but should be considered.

Propofol

Propofol (2,6 diisopropyl phenol, "Diprivan") has low aqueous solubility, and the commercial preparation is a 1% (ie, 10 mg/ml) solution in "intralipid" (ie, 1.2% egg phosphatide, 2.25% glycerol.). It has a rapid onset and short duration of action, and produces respiratory and cardiac depression that is dose related. It is most useful for short procedures or "short" continuous infusions (see below).

Propofol's unique pharmacokinetics are its most attractive feature-rapid onset of hypnosis and rapid resolution of effects after discontinuation of the drug. The distribution of propofol is described by an open three-compartment model: rapid initial distribution from blood to highly perfused tissues (brain, heart, lung, liver)- $t_{1/2}$ 1.8-4.1 min, redistribution and metabolic clearance- $t_{1/2}$ 21 to 69 min, and slow return from poorly perfused tissues to blood- $t_{1/2}$ 184-834 min. Propofol has a large central volume of distribution, is highly protein bound, and has an apparent high volume of distribution at equilibrium.

Propofol is extensively metabolized in the liver and possibly other sites to inactive glucuronide and sulfate conjugates which are excreted in the urine. In adults with renal or hepatic disease, propofol pharmacokinetic parameters are not significantly altered.

Clinical effects are realized within 40 seconds of administration, and emergence occurs within 10 to 30 minutes, depending partially on the length of administration.

Clinical Effects of Propofol

CNS

IV administration of propofol produces hypnosis with minimal excitation, usually within 40

seconds. Propofol is not an analgesic. It appears to decrease ICP, presumably by reducing CBF and increasing cerebrovascular resistance, and also decreases CMRO₂. CPP may be reduced to unacceptable levels. Propofol may be an effective anti-convulsant for status epilepticus unresponsive to other drugs.

Cardiovascular

Propofol may produce hypotension by a direct vasodilatory effect on both arterial and venous beds and by reducing sympathetic tone. High concentrations of propofol have a direct negative inotropic effect. Propofol is thus more likely to induce hypotension in patients with hypovolemia, compromised myocardial function, or vasomotor instability.

Respiratory

Propofol acts as a moderate respiratory depressant, and blunts both hypoxic and hypercapnic ventilatory drive. Minute ventilation, tidal volume, and FRC are all decreased during its use. As well, as high levels, airway protective reflexes are blunted.

Propofol is a mild bronchodilator and pulmonary dilator, but does not affect hypoxic vasoconstriction.

Metabolic

Propofol significantly decreased Vo₂ and Vco₂ in excess of its sedative effects, possibly due to a decrease in cellular metabolism. Serum and urine cortisol levels are decreased, but the adrenal response to ACTH is preserved. Hypothalamic function, thyroid function, or glucose metabolism have not been shown to be affected.

There have been a number of reports of profound metabolic acidosis in children who have received propofol for long term (>24 hours) sedation. The etiology of the metabolic acidosis remains unclear, but probably precludes routine use of propofol for long term sedation in the PICU.

Immunologic

Anaphylaxis has been reported with propofol use. Because of its carrier, it is contraindicated in patients with known hypersensitivity to egg.

Untoward Effects

Pain on injection is relatively common, and can be ameliorated by concomitant injection of 1% lidocaine, generally in a ratio of 1cc lidocaine to 10-20cc propofol.

Hyperlipidemia may occur with long term use.

Green urine (no clinical significance)

Ability to support bacterial growth due to carrier media (thus, should be treated as a sterile injection).

Invitro evidence of inhibition of neutrophil chemotaxis.

Excitatory phenomena when there are low serum levels of drug.

Dosage Recommendations

As with all anesthetics, keep hydration status, vascular tone, and inotropic state in mind. If patient is not intubated, have available equipment to secure an airway.

Induction (ie, intubation): 0.5-1.0 mg/kg (ie, 0.5-1.0cc/10 kg)

Bolus method for short procedures: 0.1-0.5 mg/kg/bolus, every 3-10 minutes.

Maintenance (sedation-OR): 15-100 mcg/kg/min, (ie, 0.075ml/kg/hour to 0.6 ml/kg/hour) start low, increase as necessary. Occasionally need to use up to 300 mcg/kg/min.

ICU sedation: initial 5-10 mcg/kg/min, increase as necessary in 10 mcg /kg/min increments, up to 100 mcg/kg/min.

Muscle Relaxants

Muscle relaxants are used when you need to have the patient NOT MOVE, and to have NO MUSCLE ACTIVITY. They provide ZERO sedation or analgesia. Once more, **ZERO** sedation or analgesia. **DO NOT FORGET.**

Indications for Muscle Relaxants (always relative)

- Intubation

- Mechanical ventilation where risk of extubation is great, or risk of barotrauma is high

- Procedures such as central line placement of biopsy in the intubated patient

- Intractable intracranial hypertension (IF ICP being monitored)

- Reduction of CO₂ production/O₂ consumption (??not clear if this is true)

Depolarizing Neuromuscular Blocker--Succinylcholine

Non-depolarizing neuromuscular blockers

- Pancuronium, vecuronium

- Atracurium, cis-atracurium

- Doxacurium

- Rocuronium

Succinylcholine

“Sux” is loved and hated both. You must understand why before you use it safely. It is a “depolarizing” neuromuscular blocker--it depolarizes the neuromuscular junction by binding the Ach receptor and further transmission of nerve impulses cannot be propagated. It has a **rapid onset of action**--average 45 seconds to achieve intubating conditions, and **short duration of action**--generally 5-8 minutes. It is **vagotonic** and bradycardia is common and may be hemodynamically significant, necessitating premedication with atropine in most cases.

Fasciculations occur in children and adults, are rare in infants. There is a rise in serum K⁺ of 0.5 meq in “normal” patients (those w/o muscle disease), and hence is to be avoided in states of hyperkalemia. The rise in serum K is *massive* in certain pathologic states--burn injury, crush injury, spinal cord injury, certain neuromuscular disease. It is also a triggering agent for malignant hyperthermia (which may be fatal), and patients who are known to have MH, who have a family

history of MH, or who have a condition that puts them at risk for MH should **NEVER** receive sux.

Risk of Hyperkalemia--burn injury, tetanus, spinal cord injury, encephalitis, crush injuries, certain neuromuscular diseases, intra-abdominal sepsis.

Risk of Malignant Hyperthermia--Positive family history, Muscular dystrophies (esp Duchenne), central core myopathy, remember to include “unknown” myopathies.

Other Untoward Effects of Sux:

Jaw stiffness, usually masseter muscle spasm. There is controversy about the relationship of MMM to Malignant hyperthermia.

Arrhythmias--usually vagal in origin. Premedicate with atropine.

Myoglobinemia--Relatively frequent (40 % if given Sux and halothane), occasionally significant enough to produce myoglobinuria.

Increased Intraocular pressure--avoid int eh presence of eye injury.

Inability to intubate--even 5 minutes can be a LONG TIME. Short duration of action is not a license to use sux in a situation when the patient should not be paralysed.

Non-depolarizing Neuromuscular Blockers

These drugs have a longer onset of action and longer duration of action than succinylcholine. They act as competitive antagonists of Ach at the neuromuscular junction. They do not effect potassium and are not MH triggering agents. They differ in their chemical structure, route of metabolism and elimination, onset and duration of action.

	Dose (mg/kg)	onset	Duration	Side Effects	Metablism
Pancuronium	0.1	2 min	4-6 min	tachycardia with bolus use	Renal (60-80%) and biliary excretion
Vecuronium	0.1-0.3	1.5-2 min	20-30 (children) 60-80 (infants)		hepatic metabolism, biliary (80%) and renal (20%) excretion
Atracurium	0.3-0.6	2-3 min	15 min	histamine release (mild)	Hoffman degradation
Rocuronium	0.6-1.2	60sec	60 min		

Problems Associated with Neuromuscular Blocker Use

Loss of a valuable patient monitor--without muscle activity you must depend on vital sign changes to assess pain and anxiety, as well as abdominal assessment.

Fluid retention without muscle activity to stimulate venous and lymphatic drainage.

Long term weakness has been associated with continuous infusions of neuromuscular blocking agents, most commonly the steroid based NMBs (vecuronium) used in conjunction with steroids. There are now reports of significant myopathy associated with Atracurium, however, so the implication of the steroid base as etiologic may not be valid. Excessive blockade should be avoided. This may be accomplished by Train of Four testing, giving drugs as intermittent boluses, or by stopping paralysis on a regular basis and observing the time needed for return of function.

Many antibiotics, especially the aminoglycosides, have neuromuscular blocking properties (complex and varied mechanisms). Aminoglycosides should be avoided if possible if continuous infusions of NMBs are used. If not avoidable, depth of paralysis should be monitored.