ROCKY MOUNTAIN
SEDATION
EDUCATION • TRAINING • SAFETY

SEDATION PHARMACOLOGY STUDY GUIDE

Continuum of Depth of Sedation

	Minimal Sedation/ Anxiolysis	**Moderate Sedation/ Analgesia *"Conscious Sedation"***	**Deep Sedation/ Analgesia**	**General Anesthesia**
Responsiveness	Normal response to verbal stimulation	Purposeful** response to verbal or tactile stimulation	Purposeful** response following repeated or painful stimulation	Un-arousable: even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous Ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular Function	Unaffected	Usually maintained	Usually maintained	May be impaired

Committee of Origin: Quality Management and Departmental Administration ASA House of Delegates

Minimal Sedation (Anxiolysis)

- Drug-induced state during which patients respond normally to verbal commands. Although cognitive function and physical coordination may be impaired, airway reflexes, and ventilatory and cardiovascular functions are unaffected.

Moderate Sedation/Analgesia ("Conscious Sedation")

- Drug-induced depression of consciousness during which patients respond purposefully** to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Deep Sedation/Analgesia

- Drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully** following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General Anesthesia

- Drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation **should be able to rescue** patients whose level of sedation becomes deeper than initially intended. Individuals administering Moderate Sedation/Analgesia ("Conscious Sedation") **should be able to rescue** patients who enter a state of Deep Sedation/Analgesia, while those administering Deep Sedation/Analgesia **should be able to rescue** patients who enter a state of General Anesthesia.

*** Rescue of a patient from a deeper level of sedation than intended is an intervention by a practitioner proficient in airway management and advanced life support. The qualified practitioner corrects adverse physiologic consequences of the deeper-than-intended level of sedation (such as hypoventilation, hypoxia and hypotension) and returns the patient to the originally intended level of sedation. It is not appropriate to continue the procedure at an unintended level of sedation.

** Reflex withdrawal from a painful stimulus is **NOT** considered a purposeful response.

SEDATIVES AND ANALGESICS

Benzodiazepines

Clinical Effect:

a. Antianxiety
b. Amnesia – ante grade
c. Sedation
d. Centrally medicated muscle relaxation
e. Antiseizure effect
f. No analgesia

Mechanisms of Action:
Benzodiazepine receptor binding facilitates Gamma – aminobutyric Acid receptor binding which increases the conductance of chloride ions across the cell membrane.

Discussion:
Benzodiazepines interact with specific receptors in the central nervous system, particularly in the cerebral cortex. Benzodiazepine-receptor binding enhances the inhibitory effects of various neurotransmitters. For example, benzodiazepine-receptor binding facilitates aminobutyric acid receptor binding, which increases the membrane conductance of chloride ions. This causes a change in membrane polarization that inhibits normal neuronal function. Flumazenil (an imidazobenzodiazepine) is a specific benzodiazepine receptor antagonist that effectively reverses most of the central nervous system effect of benzodiazepines.

Biotransformation:
The benzodiazepines rely upon the liver for biotransformation into water-soluble glucuronide end products. The phase I metabolites of diazepam are pharmacologically active. Slow hepatic extraction and a large volume of distribution result in a long elimination half-life for diazepam (30 hours). Although lorazepam also has a low hepatic extraction ratio, its lower lipid solubility limits its volume of distribution, resulting in a shorter elimination half-life (15 hours). Nonetheless, the clinical duration of lorazepam is often quite prolonged owing to a very high receptor affinity. In contrast, midazolam shares diazepam's volume of distribution, but its elimination half-life (2 hours) is the shortest of the group because of its high hepatic extraction ratio.

Excretion:
The metabolites of benzodiazepine biotransformation are excreted chiefly in the urine. Enterohepatic circulation produces a secondary peak in diazepam plasma concentration 6 – 12 hours following administration.

Effects on Organ Systems:

Cardiovascular:

The benzodiazepines display minimal cardiovascular depressant effects even at induction doses. Arterial blood pressure, cardiac output, and peripheral vascular resistance usually decline slightly, while heart rate sometimes rises. Midazolam tends to reduce blood pressure and peripheral vascular resistance more than does diazepam.

Respiratory:

- Depresses the ventilatory response to CO2
- Intravenous doses may cause apnea
- Potent synergistic apnea effect with all opiates
- Discussion: Benzodiazepines depress the ventilator response to CO2. This depression is usually insignificant unless the drugs are administered intravenously or in association with other respiratory depressants. Although apnea may be less common than following barbiturate induction, even small intravenous doses of diazepam and midazolam have resulted in respiratory arrest. The steep dose-response curve, slightly prolonged onset (compared to thiopental or diazepam), and high potency of midazolam necessitate careful titration to avoid over dosage and apnea. Ventilation must be monitored in all patients receiving intravenous benzodiazepines, and resuscitating equipment must be immediately available.

Cerebral:

Benzodiazepines reduce cerebral oxygen consumption, cerebral blood flow, and intracranial pressure but not to the extent the barbiturates do. They are very effective in preventing and controlling grand mal seizures. Oral sedative doses often produce antegrade amnesia, a useful premedication property. The mild muscle-relaxant properties of these drugs is mediated at the spinal cord level, not at the neuromuscular junction. The antianxiety, amnesic, and sedative effects seen at low doses progress to stupor and unconsciousness at induction doses. Compared to thiopental, induction with benzodiazepines is associated with a slower loss of consciousness and a longer recovery. Benzodiazepines have no direct analgesic properties.

Adverse Reactions:

In general, benzodiazepines are safe and effective in the short term, although cognitive impairments and paradoxical effects such as aggression or behavioral disinhibition occasionally occur. A minority react reverse and contrary to what would normally be expected. For example, a state of panic may worsen considerably following intake of a benzodiazepine. Long-term use is controversial due to concerns about adverse psychological and physical effects, increased questioning of effectiveness, and, because benzodiazepines are prone to cause tolerance, physical dependence, and, upon cessation of use after long-term use, a withdrawal syndrome. Due to adverse effects associated with the long-term use of benzodiazepines, withdrawal from benzodiazepines, in general, leads to improved physical and mental health. The elderly are at an increased risk of suffering from both short- and long-term adverse effects, including an associated roughly 50% increase in the risk of dementia.

Drug Interactions:

- Cimetidine binds to cytochrome P-450 and reduces the metabolism of diazepam.
- Erythromycin inhibits midazolam metabolism.
- Benzodiazepines reduce the minimum alveolar concentration of volatile anesthetics as much as 30%.
- Ethanol potentiates the sedative effects of the benzodiazepines.
- Opiates: Synergistic respiratory depressant effect

Benzodiazepine Oral Agents

BENZODIAZEPINE	COMMON NAME	PEAK ONSET (hours)	ELIMINATION t 1/2	INDICATED USE	TYPICAL DOSE
Alprazolam	Xanax	1-2	9–20 hours	Anxiolytic	0.5 mg
Chlordiazepoxide	Librium	1.5-4	5–30 hours	Anxiolytic	25 mg
Clonazepam	Klonopin	1-4	18–50 hours	Anxiolytic Anticonvulsant	0.5 mg
Diazepam	Valium	1-1.5	20–100	Anxiolytic Anticonvulsant Muscle relaxant	10 mg
Lorazepam	Ativan	2-4	10–20 hours	Anxiolytic Anticonvulsant	1 mg
Midazolam	Versed	0.25-0.5	3 hours	Hypnotic Anticonvulsant	7.5 mg
Triazolam	Halcion	0.25	2 hours	Hypnotic	0.25 mg

Dosing

AGENT	USE	ROUTE/DOSE
Diazepam (Valium)	Premedication Sedation Induction	Oral: .2 mg/Kg Oral: .4 mg/Kg IV: .3 mg/Kg
Midazolam (Versed)	Premedication Sedation Induction	Oral: .5 mg/Kg-max 20mg Oral: .5 mg/Kg IV: .01 mg/Kg IV: .1 mg/Kg
Lorazepam (Ativan)	Premedication Sedation	Oral: .05 mg/Kg Oral: .05 mg/Kg
Alprazolam (Xanax)	Premedication Sedation	Oral: .5 mg x 1 Oral: 1mg x 1

Pharmacokinetics

AGENT	ROUTE/PEAK ONSET	ELIMINATION t1/2 (active metabolite)
Diazepam (Valium)	ORAL / 35 minutes	100 hours – average
Midazolam (Versed)	ORAL / 15 minutes	6 hours – average
Lorazepam (Ativan)	ORAL / 30 minutes	20 hours – average

Flumazenil: Flumazenil is a benzodiazepine antagonist. It works by blocking receptors in the brain and central nervous system that benzodiazepines need to reach to be active, which helps reduce drowsiness and sedation.

EMERGENCY REVERSAL AGENT	INCREMENTAL DOSES	MAXIMUM OFFICE BASED DOSE
Flumazenil	.2 mg every minute until reaching the desired degree of reversal	1.0 mg

Opioids

Clinical Effects:
Opioids are among the world's oldest known drugs; the therapeutic use of the opium poppy predates recorded history. The analgesic (painkiller) effects of opioids are due to decreased perception of pain, decreased reaction to pain as well as increased pain tolerance.

Mechanisms of Action:
Opioids bind to specific receptors located throughout the central nervous system and other tissues. Four major types of opioid receptor have been identified: mu, kappa, delta, and sigma. While opioids provide some degree of sedation, they are most effective at producing analgesia. The pharmacodynamic properties of specific opioids depend upon which receptor is bound, the binding affinity, and whether the receptor is activated. See Table below. Although both opioid agonists and antagonists bind to opioid receptors, only agonists are capable of receptor activation. Agonist-antagonists (eg. nalbuphine, nalorphine, butorphanol, and pentazocine) are drugs that have opposite actions at different receptor types.

Opioid-receptor activation inhibits the presynaptic release and postsynaptic response to excitatory neurotransmitters (eg, acetylcholine, substance P) from nociceptive neurons. The cellular mechanism for this neuromodulation may involve alterations in potassium and calcium ion conductance. Transmission of pain impulses can be interrupted at the level of the dorsal horn of the spinal cord with intrathecal or epidural administration of opioids. Modulation of a descending inhibitory pathway from the periaqueductal gray through the nucleus raphe magnus to the dorsal horn of the spinal cord may also play a role in opioid analgesia. Although opioids exert their greatest effect within the central nervous system, opioid receptors have also been isolated from somatic and sympathetic peripheral nerves.

Opioid Receptors

RECEPTOR	CLINICAL EFFECT	OPIATE
Mu	Respiratory Depression	Morphine Fentanyl Hydrocodone Oxycodone
Kappa	Sedation	Morphine Fentanyl Hydrocodone Oxycodone
Delta	Analgesia	Morphine Fentanyl Hydrocodone Oxycodone
Sigma	Dysphoria	Fentanyl Hydromorphine Oxycodone Hydrocodone Sufentanyal

Effects on Organ Systems:

Cardiovascular:

In general, opioids do not seriously impair cardiovascular function. Meperidine tends to increase heart rate (it is structurally similar to atropine), while high doses of morphine, fentanyl, Sufentanil, and Alfentanil are associates with a vagusmediated bradycardia. With the exception of Meperidine, the opioids do not depress cardiac contractility. Meperidine and morphine evoke histamine release in some individuals that can lead to profound drops in arterial blood pressure and systemic vascular resistance. The effects of histamine release can be minimized in susceptible patients by slow opioid infusion, adequate intravascular volume, or pretreatment with H1 and H2 histamine antagonists.

Respiratory:

Opioids depress ventilation, particularly respiratory rate. Resting PaCO2 increases and the response to a CO2 challenge is blunted, resulting in a shift of the CO2 response curve downward and to the right. These effects are mediated through the respiratory centers in the brainstem. The apneic threshold – the highest PaCO2 at which a patient remains apneic – is elevated, and hypoxic drive is decreased. Morphine and meperidine can cause histamine-induced bronchospasm in susceptible patients. Opioids (particularly fentanyl, Sufentanil, and Alfentanil) can induce chest wall rigidity severe enough to prevent adequate ventilation. This centrally mediated muscle contraction is most frequent after large drug boluses and is effectively treated with muscle relaxants. Opioids can effectively blunt the bronchoconstrictive response to airway stimulation such as that occurring during intubation.

Cerebral:

Potent analgesia: Intravenous opioids have been the mainstay of pain control for more than a century. Mild to moderate dose dependent sedation occurs with all opiates . Unlike barbiturates or benzodiazepines, relatively large doses of opioids are required to render patients unconscious. Stimulation of the medullary chemoreceptor trigger zone is responsible for a high incidence of nausea and vomiting. **Regardless of the dose, opioids do not reliably produce amnesia.** Physical dependence is a significant problem associated with repeated opioid administration.

Adverse reactions/ Side effects:

- Sedation - can also be an indication
- Respiratory depression
- Constipation
- Strong sense of euphoria.
- Opioids can cause cough suppression, which can be both an indication for opioid administration or an unintended side effect.
- Opioid dependence can develop with ongoing administration, leading to a withdrawal syndrome with abrupt discontinuation.

Drug Interactions:

- The combination of opioids – particularly meperidine – and monoamie oxidase inhibitory may result in respiratory arrest, hypertension or hypotension, coma, and hyperpyrexia. The cause of this dramatic interaction is not understood.
- Barbiturates, benzodiazepines, and other central nervous system depressants can have synergistic cardiovascular, respiratory, and sedative effects with opioids.
- The biotransformation of Alfentanil, but not Sufentanil, may be impaired following a 7-day course of erythromycin, leading to prolonged sedation and respiratory depression.

Dosing Profile

OPIOID	ROUTE	DOSE
Morphine	IM	.2 mg/Kg
Morphine	IV	.05 mg/Kg
Fentanyl	Intranasal	.25 mcg/Kg
	IM	1 mcg/Kg
	IV	.25 mcg/Kg increments
Hydrocodone	Oral	5-10 mg PO
Oxycodone	Oral	5-10 mg PO
Morphine	Oral	3-5 mg PO
Hydromorphone	Oral	2-4 mg PO

Narcan (naloxone) is indicated for the complete or partial reversal of opioid depression. Narcan (naloxone) prevents or reverses the effects of opioids including respiratory depression and sedation. Narcan is essentially a pure opioid antagonist. It blocks the action of opioids at the receptor - opioid interface through binding.

Emergency Reversal

EMERGENCY REVERSAL AGENT	INCREMENTAL DOSES	MAXIMUM OFFICE BASED DOSE
Naloxone	**IV:** .04 mg every 3 minutes until adequate ventilation and alertness are achieved **IM:** 2x the above dose	.4 mg

Ketamine

Mechanisms of Action:

Ketamine has multiple effects throughout the central nervous system, including blocking polysynaptic reflexes in the spinal cord and inhibiting excitatory neurotransmitter effects in selected areas of the brain. In contract to the depression of the reticular activating system induced by the barbiturates, ketamine functionally "dissociates" the thalamus (which relays sensory impulses from the reticular activating system to the cerebral cortex) from the limbic cortex (which is involved with the awareness of sensation). While some brain neurons are inhibited, others are tonically excited. Clinically, this state of **dissociative anesthesia** causes the patient to appear conscious (eg, eye opening, swallowing, muscle contracture) but unable to process or respond to sensory input. The existence of specific ketamine receptors and interactions with opioid receptors has been postulated.

Effects on Organ Systems:

Cardiovascular:

In sharp contrast to other anesthetic agents, ketamine increases arterial blood pressure, heart rate, and cardiac output. These indirect cardiovascular effects are due to central stimulation of the sympathetic nervous system. Accompanying these changes are increases in pulmonary artery pressure and myocardial work. For these reasons, ketamine should be avoided in patients with coronary artery disease, uncontrolled hypertension, congestive heart failure, and arterial aneurysms. The direct myocardial depressant effects of large doses of ketamine are unmasked by sympathetic blockade (eg, spinal cord transection) or exhaustion of catecholamine stores (eg, severe end-stage shock). On the other hand, ketamine's indirect stimulatory effects are often beneficial to patients with acute hypovolemic shock.

Respiratory:

Ventilatory drive is minimally affected by the customary induction doses of ketamine, although rapid intravenous bolus administration or pretreatment with opioids occasionally produces apnea. Ketamine is a potent bronchodilator, making it a good induction agent for asthmatic patients. Although upper airway reflexes remain largely intact, patients at increased risk for aspiration pneumonia should be intubated. The increased salivation associated with ketamine can be attenuated by premedication with an anticholinergic agent.

Cerebral:

Consistent with its cardiovascular effects, ketamine increases cerebral oxygen consumption, cerebral blood flow, and intracranial pressure. These effects preclude its use in patients with space occupying intracranial lesions. Myoclonic activity is associated with increased subcortical electrical activity, which is not apparent on surface electroencephalography. Undesirable psychotomimetic side effects (eg, illusions, disturbing dreams, and delirium) during emergence and recovery are less common in children and in patients premedicated with benzodiazepines. Of the nonvolatile agents, ketamine may be the closes to being a "complete" anesthetic since it induces analgesia, amnesia, and unconsciousness.

Drug Interactions:

a. Diazepam attenuates ketamine's cardiostimulatory effects and prolongs its elimination half-life.
b. Propranolol, phenoxybenzamine, and other sympathetic antagonists unmask the direct myocardial depressant effects of ketamine.
c. Ketamine produces myocardial depression when given to patients anesthetized with halothane or, to a lesser extent, other volatile anesthetics.
d. Lithium may prolong the duration of action of ketamine.

Dosing:

To prevent dysphoria, pre-medicate with 2.5 mg of midazolam

Dosing

Agent	**Use**	**Route**	**Dose**
Ketamine	Sedation	IV IM	5-10 mg every 20 minutes with a maximum total of 50 mg .5 mg/kg X 1

Propofol

Mechanisms of Action:
The mechanism by which propofol induces a state of general anesthesia may involve facilitation of inhibitory neurotransmission mediated by aminobutyric acid.

Effects on Organ Systems:

Cardiovascular:

The major cardiovascular effect of propofol is a decrease in arterial blood pressure owing to a drop in systemic vascular resistance, cardiac contractility, and preload. Hypotension is more pronounced than with thiopental but is usually reversed by the stimulation accompanying laryngoscopy and intubation. Factors exacerbating the hypotension include large doses, rapid injection, and old age. Propofol markedly impairs the normal arterial baroreflex response to hypotension.

Respiratory:

Propofol is a profound respiratory depressant that usually causes apnea following an induction dose. Even when used for conscious sedation, propofol infusion inhibits hypoxic ventilatory drive and depresses the normal response to hypercarbia. Propofol-induced depression of upper airway reflexes exceeds that of thiopental and can prove helpful during intubation or laryngeal mask placement in the absence of paralysis.

Cerebral:

Propofol decreases cerebral blood flow and intracranial pressure. In patients with elevated intracranial pressure, propofol can cause a critical reduction in cerebral perfusion pressure (<50 mm Hg) unless steps are taken to support mean arterial blood pressure. Propofol and thiopental probably provide a similar degree of cerebral protection during focal ischemia. **A unique characteristic of propofol is its antiemetic and antipruritic properties.** Propofol does not have anticonvulsant properties.
IV administration is occasionally accompanied by excitatory phenomena such as muscle twitching, spontaneous movement, or hiccupping.

Dosing

Agent	Use	Route	Dose
Propofol	Sedation	IV	25-100 mcg/kg/min