

**Sedation, Analgesia, and Paralysis
in the Intensive Care Unit**
Cathy L. Lawson, PharmD, BCPS
Hina N. Patel, PharmD, BCPS

I. Benzodiazepines

- A. Used to relieve anxiety/agitation, prevent withdrawal (alcohol, benzodiazepine), treat seizures/status epilepticus, provide sedation/promote sleep, amnestic effects and in conjunction with patients receiving neuromuscular blocking agents (NMBAs) since they possess no analgesic or sedative properties.
- B. Midazolam may be used for the short-term (<72 hours) treatment of anxiety. Long term administration results in a prolongation of the clinical effects of the drug.
- C. Lorazepam is the preferred agent for the prolonged treatment (>72 hours) of anxiety in the critically ill adult¹. Compared with midazolam, it has a slower onset of action, causes less hypotension, is equally effective and has a longer duration of action.

Benzodiazepine	Onset of Action	Half-life	Active Metabolites
Diazepam (Valium®)	very fast	10 – 80 hours	yes
Chlordiazepoxide (Librium®)	intermediate	5 – 30 hours	yes
Clonazepam (Klonopin®)	intermediate	18 – 50 hours	no
Lorazepam (Ativan®)	fast	10 – 20 hours	no
Midazolam (Versed®)	very fast	1 – 5 hours	no

- D. Benzodiazepines may be given as needed (PRN) IV boluses, as scheduled IV boluses, as a continuous infusion or orally scheduled around the clock.
- E. Adverse effects include oversedation, prolonged sedation and hypotension. Some patients may exhibit a paradoxical reaction. Benzodiazepines have little effect on respiratory drive when given in therapeutic doses.

II. Opioid Analgesics

- A. Primarily used to relieve pain, but also exhibits some sedative properties. May be used to decrease the discomfort or cough associated with endotracheal tube placement and suction. Is used in conjunction with NMBAs since they possess no analgesic or sedative properties.
- B. Morphine is the preferred analgesic agent for critically ill patients.¹ Fentanyl is used primarily in the MICU because it is less likely to produce cardiovascular side effects such as hypotension and is no more expensive than morphine. It may be used safely in patients with an allergy to morphine.
- C. Meperidine (Demerol®) is not recommended because the active metabolite (normeperidine) may accumulate (especially in patients with renal insufficiency) and produce central nervous system excitation.
- D. Adverse effects of opioids include respiratory depression, hypotension (secondary to direct vasodilation and histamine release) and gastrointestinal slowing.

Opioid	Onset of Action	Duration of Action	Equipotent Dose
Fentanyl	7 – 8 minutes	1 – 2 hours	0.1 mg
Hydromorphone (Dilaudid®)	15 – 30 minutes	4 – 5 hours	1.5 mg
Meperidine (Demerol)	10 – 45 minutes	2 – 4 hours	75 mg
Methadone	30 – 60 minutes	4 – 8 hours	10 mg
Morphine	15 – minutes	3 – 7 hours	10 mg

III. Propofol

- A. Primarily used for the short-term (<72 hours) treatment of anxiety. The manufacturer recommends that propofol not be infused for longer than 5 days without providing a drug holiday. This recommendation is based upon the fact that the new formulation contains disodium edetate, a potential chelator of trace elements (zinc), to retard the rate of growth of microorganisms in the event of accidental contamination.
- B. Has no analgesic effect. Bolus doses may cause hypotension especially when used in combination with opioids or benzodiazepines.
- C. Continuous infusion dosing: begin at 5 µg/kg/min and titrate to patient response. Usual dosage range for ICU sedation: 5 to 50 µg/kg/min. Doses up to 200 µg/kg/min have been used in the ICU setting.
- D. Is formulated in a 10% lipid base. Provides 1.1 Kcal/ml. Should not be used in patients with a history with an allergy to eggs.
- E. Adverse effects include hypotension, bradycardia and myocardial depression.

IV. Dexmedetomidine (Precedex®)

- A. Indicated for sedation and treatment of anxiety of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. It should be administered by continuous infusion **not to exceed 24 hours**.
- B. A specific and selective α₂-adrenergic agonist therefore having clinical actions similar to clonidine but with greater affinity for the α₂-adrenergic receptor. Has some analgesic effects with no effects on respiratory drive.
- C. Bolus dosing: give 1 µg/kg over 10 minutes using an infusion pump. Continuous infusion dosing: 0.2 to 0.7 µg/kg/hr.
- D. Adverse effects include hypotension, bradycardia and nausea.

V. Haloperidol (Haldol)

- A. Preferred agent for treatment of delirium in critically ill adults.
- B. A high potency neuroleptic agent. When compared with low potency neuroleptic agents (chlorpromazine), it has less anticholinergic effects and causes less hypotension (less likely to cause α-adrenergic blockade). Also, it has very little effect on respiratory drive.
- C. Proposed dosage regimens for intravenous haloperidol administration⁶⁻⁷:

Initial Dose	Bolus Frequency	Bolus Dose	Maintenance Dose
Mild agitation: 1 – 3 mg IV moderate agitation: 5 – 7 mg IV severe agitation: ≥ 10 mg IV	first bolus after initial dose is in 10 minutes if agitation persists; boluses should be repeated every 20 minutes	first bolus at 10 minutes is the same as the initial dose, then double dose at every 20 minute interval	schedule at routine times rather than as needed (PRN) intervals
Mild agitation: 0.5 – 2 mg IV moderate agitation: 5-10 mg IV severe agitation: ≥ 10 mg IV	every 15 to 20 minutes	double dose until goal of treatment is attained	Schedule at routine times rather than as needed (PRN) intervals

- D. Adverse effects include extrapyramidal symptoms (EPS) and neuroleptic malignant syndrome (NMS). It appears that the incidence of NMS is less with intravenous administration of haloperidol. Tardive dyskinesia (TD) rarely associated with short-term therapy use. Many prolong the QT interval.

VI. Neuromuscular Blocking Agents (NMBAs)

- A. Primarily used in the ICU to assist with mechanical ventilation and facilitate endotracheal intubation. May also be used to minimize oxygen consumption or to treat life-threatening agitation refractory to aggressive sedation and analgesic therapy.
- B. Depolarizing agents bind to and stimulate the acetylcholine receptor, initially causing the muscle to depolarize, then occupies the receptor site longer than acetylcholine. Termination of action is by plasma acetylcholinesterase.
- C. Non-depolarizing agents compete for the acetylcholine receptor site.
- D. When selecting an appropriate NMBA, several factors should be taken into account:
1. duration of procedure (duration of action)
 2. need for quick endotracheal intubation (onset of action)
 3. adverse effect profile (hemodynamic stability, histamine release)
 4. route of elimination (especially in patients with renal or hepatic insufficiency)
 5. concurrent medications/drug interactions
 6. cost
- E. Monitoring
1. To evaluate the need for continued NMBA, the infusion should be discontinued daily at 0800
 2. Patients receiving NMBAs should be appropriately assessed for the degree of blockade that is being sustained. Direct observation along with peripheral nerve (Train-of-Four) stimulation is recommended to decrease the likelihood of prolonged paralysis/myopathy.

Comparative Properties of Non-Depolarizing Neuromuscular Blocking Agents.

Agent	Chemical Classification	Onset of Action (minutes)	Duration of Action (minutes)	Mode of Elimination
Atracurium (Tracrium®)	benzylisoquinoline	2 – 4	30 – 40	Hoffman degradation
Cisatracurium (Nimbex®)	benzylisoquinoline	2 – 3	40 – 60	Hoffman degradation
Doxacurium (Nuromax®)	benzylisoquinoline	4 – 6	90 – 120	renal and liver
Mivacurium (Mivacron®)	benzylisoquinoline	2 – 4	12 – 18	hydrolysis by plasma esterases
Pancuronium (Pavulon®)	steroid	4 – 6	120 – 180	renal and liver
Pipecuronium (Arduan®)	steroid	2 – 4	80 – 100	renal and liver
Rocuronium (Zemuron®)	steroid	1 – 2	30 – 40	renal and liver
Vecuronium (Norcuron®)	steroid	2 – 4	30 – 40	renal and liver

Factors affecting the activity of neuromuscular blocking agents.

Potentiating Factors

Drugs

Aminoglycosides
Beta-adrenergic blockers
Bretylium
Calcium channel blockers
Clindamycin
Cyclophosphamide
Cyclosporine
Dantrolene
Halogenated anesthetics
Lithium
Local anesthetics
Mineralocorticoids
Quinidine
Procainamide
Vancomycin

Clinical

Acidosis
Acute intermittent porphyria
Hepatic failure
Hypermagnesemia
Hypocalcemia
Hypokalemia
Hyponatremia
Hypothermia
Neuromuscular diseases
Renal failure

Inhibiting Factors

Drugs

Anticholinesterase Agents
Azathioprine
Carbamazepine
Phenytoin
Ranitidine
Theophylline

Clinical

Alkalosis
Demyelinating lesions
Diabetes mellitus
Hypercalcemia
Peripheral neuropathies

References

1. Shapiro BA, Warren J, Egol AB, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. *Crit Care Med* 1995;23:1596-600.
2. Jacobi J et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002;30:119-41.
3. Luer J. Sedation and chemical relaxation in critical pulmonary illness: suggestions for patient assessment and monitoring. *AACN Clinical Issues* 1995;6:333-43.
4. Cherny NI. Opioid analgesics: comparative features and prescribing guidelines. *Drugs* 1996;51:713-37.
5. Mirenda J, Broyles G. Propofol as used for sedation in the ICU. *Chest* 1995;108:539-48.
6. Precedex® Package Insert. Abbott Laboratories Inc. Chicago, Ill. September 2000.
7. Fish DN. Treatment of delirium in the critically ill patient. *Clinical Pharmacy* 1991;10:456-64.
8. Ziehm SR. Intravenous haloperidol for tranquilization in critical care patients: a review and critique. *AACN Clinical Issues* 1991;2:765-77.
9. Shapiro BA, Warren J, Egol AB, et al. Practice parameters for sustained neuromuscular blockade in the adult critically ill patient: an executive summary. *Crit Care Med* 1995;23:1601-5.
10. Society of Critical Care Medicine and American Society of Health-System Pharmacists. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Am J Health-Syst Pharm.* 2001;59:179-95.
11. Hunter JM. New neuromuscular blocking drugs. *N Engl J Med* 1995; 332:1691-9.
12. Watling SM, Dasta JF. Prolonged paralysis in intensive care unit patients after the use of neuromuscular blocking agents: a review of the literature. *Crit Care Med* 1994;22:884-93.
13. Fischer JR, Baer RK. Acute myopathy associated with combined use of corticosteroids and neuromuscular blocking agents. *Ann Pharmacotherapy* 1996;30:1437-45.

Other Suggested Readings

Kress JP, Pohlman AS, Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Eng J Med* 2000;342:1471-77.