sedative hypnotics

dexmedetomidine

general

- Dexmedetomidine is the first selective a2-adrenoreceptor agonist approved for short-term (less than 24 hours) infusion as a sedative for patients receiving mechanical ventilation.

kinetics

- Dosage reduction is recommended with hepatic but not renal impairment.
- Hypotension or bradycardia appears to be most frequent in patients with cardiac conduction defects or hypovolemia. Some patients cannot tolerate the 1 µg/kg loading infusion of dexmedetomidine; for these patients, therapy may be initiated with a maintenance infusion (0.2 to 0.7 µg/kg/hour) that can be titrated to desired effects.

dynamics

- This drug exerts sedative effects via postsynaptic activation of a2-adrenoreceptors in the CNS and analgesic action by inhibiting norepinephrine release presynaptically. In addition, it inhibits sympathetic activity, thereby decreasing blood pressure and heart rate. Dexmedetomidine is eight times more potent than its relative, clonidine, at stimulating a2-adrenoreceptors.

use

- Dexmedetomidine offers several advantages as a sedative in the ICU.
(i) it does not cause significant respiratory depression
(ii) it has a rapid distribution phase (6 minutes) and an elimination half-life of 2 hours. These pharmacokinetic properties permit easy dose titration in response to fluctuating sedative needs.
(iii) Another advantage is the low level of sedation that can be achieved with dexmedetomidine. Patients appear comfortably sedated while undisturbed but can easily be awakened.
- Dexmedetomidine has also been used successfully to ameliorate the hyperadrenergic state of drug withdrawal caused by alcohol, illicit drugs, or long-term sedative-analgesic use in the ICU.
- Because dexmedetomidine is approved for use only for 24 hours, further pharmacokinetic, pharmacodynamic, and clinical research is necessary before it can be recommended for long-term use in ICU patients.

indications

Indication	Comment
Minimize ventilator dysynchrony	Poor synchrony may lead to hypoxemia and dyspnea and is distressing to caregivers. Ventilator adjustment may improve synchrony without medications.
Reduce dyspnea associated with severe acute respiratory failure	Reducing minute ventilation to avoid ventilator-induced lung injury can cause severe dyspnea. Tachypnea with short expiratory times can lead to increased auto-PEEP and hypotension.
Increase tolerance of intubation	A translaryngeal endotracheal tube can cause pain, gagging, and reflexive biting. Local airway anesthesia can reduce the need for sedatives and analgesics.[71]
Reduce anxiety	Acute severe illness possibly leading to disability or death may produce unwanted psychological distress
Reduce recall of ICU symptoms	Recall of distressing symptoms such as severe dyspnea, terror, restraint, or pain can have long-term psychological consequences.[28]
Reduce stress response and oxygen consumption	Reducing unwanted motor activity or respiratory effort can decrease total-body oxygen consumption by 15%.[72]
Reduce elevated intracranial pressure	Coughing, straining, or excessive ventilator dysynchrony can cause dangerous spikes in intracranial pressure.
Reduce pain	Surgical or traumatic wounds, catheter and tube placement, and immobilization usually cause pain.
Prevent removal of life support technology	Removal of an endotracheal tube or vascular catheter can cause death within minutes.
Induce sleep	ICU patients often have abnormal chronobiology cycles associated with delirium and impaired immune function.
Increase efficiency of patient care delivery	Constant visual observation and verbal and tactile patient reassurance may not be possible in understaffed units.
Protect caregivers from violent behaviors	Confused patients can violently assault caregivers.
Adjunct during pharmacologic paralysis	Awareness during pharmacologic paralysis is inhumane and can have long-term psychological consequences.
Treat delirium	Antipsychotics may reduce disorganized thought processes or behavior while the underlying cause of the delirium is treated.
Family considerations	Repeatedly observing the distress of a loved one can cause anguish in family members, who may request that additional sedatives be given to the patient.[23]

presentation in overdose

- Of the sedative medications discussed in this chapter, BZDs and opiates are most likely to be involved in toxic ingestions, either accidental or intended.
- Patients with overdoses from either medication class can present with stupor or coma with hypotension (usually mild and responsive to fluid boluses) and hypotonia.
- Pupil size may be helpful: pupils are pinpoint in opiate ingestion, mid-size in BZD toxicity. Toxicity is usually short-lived and completely reversible unless complications such as anoxic encephalopathy or aspiration pneumonia occur.

opioids

Drug	Equianalgesic Intravenous Dosage	Half-life (h)	Elimination Glucuronidation	Active Metabolites	Special Considerations
Morphine sulfate℞	10 mg Infusion: 0.07-0.5 mg/kg/h	2-3	Reduced in cirrhosis, burns, septic shock, and renal failure	Morphine-3 glucuronide, morphine-6 glucuronides	Histamine release can cause hypotension and cardiovascular instability
Fentanyl	200 µg Infusion: 0.7-10 µg/kg/h	From 0.5-1 to 9-16	Oxidation	None	Rigidity is occasionally seen with high doses; preferred for patients with hemodynamic instability, sensitivity to histamine release, or morphine allergy

therapy for overdose

opioids

- Naloxone can be given as both a diagnostic and therapeutic medication; lack of improvement in level of consciousness or respiratory depression after administration of 10 mg of naloxone (starting with 0.4 mg and giving subsequent doses of 2 mg every few minutes) makes opiate toxicity an unlikely cause of the patient's symptoms.
- If a response is observed, then practitioners should be prepared to administer repeated naloxone boluses every 30 to 60 minutes or to start a continuous infusion at 0.4 to 0.8 mg/hour.
- Occasionally, a patient with opiate overdose develops pulmonary edema requiring mechanical ventilation, but the edema usually resolves within a few days without specific treatment.

benzos

- Flumazenil is a specific antidote for BZD toxicity. A patient's symptoms should improve within a minute after a bolus administration of 0.2 mg and subsequent 0.3-mg doses every 30 seconds.
- Administration of flumazenil to patients receiving chronic BZD therapy may precipitate an unpleasant acute withdrawal syndrome and, theoretically, increase the risk of seizure.
- However, no seizures were observed after flumazenil treatment in 110 patients with suspected BZD overdose, including many patients with polydrug ingestions (e.g., co-ingestion of tricyclic antidepressants).

other agents

Drug	Estimated Comparable Sedative Dose	Onset with Intravenous Administration (min)	Half-life (h)	Active Metabolites	Intravenous Dose	Infusion Dosage Range	Relative Cost/day*
Diazepam℞	5 mg	2-5	20-120	Yes	0.03-0.1 mg/kg q0.5-6h	-	$-$$
Midazolam	2-3 mg	2-5	3-11	Yes	0.02-0.08 mg/kg q0.5-2h	0.04-0.2 mg/kg/h	$$
Propofol℞	50 µg/kg/min	1-2	26-32	None	-	5-80 µg/kg/min	$$$
Dexmedetomidine	0.5 µg/kg/h	5-10	2-7.5	None	-	0.2-0.7 µg/kg/h	$$$
Haloperidol℞	-	3-20	18-54	Yes†	0.03-0.15 mg/kg q0.5-6h	0.04-0.15 mg/kg/h	$$