Pharmacology of Sedative-Analgesic Agents: Dexmedetomidine, Remifentanil, Ketamine, Volatile Anesthetics, and the Role of Peripheral Mu Antagonists

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DEXMEDETOMIDINE

Introduction

Dexmedetomidine is a highly selective alpha-2 agonist that provides anxiolysis and cooperative sedation without respiratory depression. It decreases central nervous system (CNS) sympathetic outflow in a dose-dependent manner and has analgesic effects best described as opioid-sparing. There is increasing evidence that dexmedetomidine has organ protective effects against ischemic and hypoxic injury, including cardioprotection, neuroprotection, and renoprotection. After its approval by the Food and Drug Administration (FDA) in 1999, it has become well established in the United States as a sedative-hypnotic agent.

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**Receptor Pharmacology**

Dexmedetomidine is the dextro enantiomer of medetomidine, the methylated derivative of etomidine. Its specificity for the alpha-2 receptor is seven times that of clonidine, with an alpha-2/alpha-1 binding affinity ratio of 1620:1, and its effects are dose-dependently reversed by administration of a selective alpha-2 antagonist such as atipamezole.

Specific alpha-2 receptor subtypes mediate the varied pharmacodynamic effects of dexmedetomidine. For example, agonism at the alpha-2A receptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection, and inhibition of insulin secretion. Agonism at the alpha-2B receptor suppresses shivering centrally, promotes analgesia at spinal cord sites, and induces vasoconstriction in peripheral arteries. The alpha-2C receptor is associated with modulation of cognition, sensory processing, mood- and stimulant-induced locomotor activity, and regulation of epinephrine outflow from the adrenal medulla. Inhibition of norepinephrine release appears to be equally affected by all three alpha-2 receptor subtypes.

Dexmedetomidine also binds to imidazoline receptors, which recognize the imidazoline or oxazoline structure of alpha-2 agonist agents. This activity may explain some of the non-alpha-2 receptor–related effects of this drug class. Imidazoline receptor subtypes have also been identified. Imidazoline-1 receptors modulate blood pressure regulation and have anti-arrhythmic effects. They are found in the ventrolateral medulla and are linked to G-proteins. Imidazoline-2 receptors have been implicated in neuroprotection in a cerebral ischemia model in animals and in generation of memory. They are typically located on the mitochondrial outer membrane and are not G-protein coupled, but may exert their effects by decreasing tissue norepinephrine levels.

**Pharmacokinetics**

After intravenous (IV) injection, dexmedetomidine has an onset of action after approximately 15 minutes. Peak concentrations are usually achieved within 1 hour after continuous IV infusion. Analysis by a 2-compartment model demonstrates rapid distribution away from the CNS, with an alpha half-life ($t_{1/2a}$) of 6 minutes and a terminal elimination half-life ($t_{1/2b}$) of between 2.0 and 2.5 hours. The drug is highly protein-bound, with a 6% free fraction, and has a relatively large steady state volume of distribution ($V_{dss}$, 1.33 L/kg). Except for a larger $V_{dss}$, pharmacokinetics do not appear to be substantially altered in mechanically ventilated patients sedated with dexmedetomidine in an intensive care unit (ICU).

Total plasma clearance of the dexmedetomidine is age independent, thus similar rates of infusion can be used in children and adults to effect a steady state plasma concentration. Plasma protein binding of dexmedetomidine is also similar to adults. In children younger than 2 years of age, the volume of distribution ($V_d$) at steady state ($V_{SS}$) is increased, suggesting that higher doses are required to achieve $V_{SS}$; but $t_{1/2b}$ is prolonged, which may result in increased drug accumulation with time.

Dexmedetomidine is also absorbed systemically through the transdermal, buccal, or intramuscular routes, with a mean bioavailability from the latter 2 routes of 82% and 104% respectively.

Dexmedetomidine is extensively metabolized in the liver through glucuronide conjugation and biotransformation in the cytochrome P450 enzyme system. There are no known active or toxic metabolites. However, hepatic clearance may be decreased by as much as 50% of normal with severe liver disease. Pharmacokinetics are not significantly altered in patients with severe renal impairment, but patients remained...
sedated for longer than normal controls, suggesting an enhanced pharmacodynamic effect, presumably because of the presence of varying degrees of uremic encephalopathy.\textsuperscript{14} Thus, dosages should be decreased in the presence of either hepatic or renal disease. Dexmedetomidine decreases cardiac output in a dose-dependent manner, but the impact of this on clearance does not appear to be clinically relevant.\textsuperscript{15}

**Dosing and Administration**

Phase 1 studies demonstrated that IV doses of dexmedetomidine induced dose-dependent decreases in systolic and diastolic blood pressure and in heart rate and substantial decreases in plasma norepinephrine levels. However, at high-bolus IV doses (50–75 $\mu$g), a transient initial hypertensive response may be seen, presumably because of activation of peripheral vascular alpha-2 receptors before the central sympatholytic effect on the vasomotor center.\textsuperscript{16} There do not appear to be any reflex or drug-induced alterations in plasma renin activity, atrial natriuretic peptide or arginine vasopressin (AVP).\textsuperscript{17} Dexmedetomidine also produces dose-dependent decreases in vigilance and increases in sedation that correlate well with electroencephalogram (EEG)-based spectral entropy monitoring.\textsuperscript{18}

Initial studies that targeted plasma dexmedetomidine levels revealed desirable pharmacodynamic effects between 0.5 and 1.2 ng/mL. Subsequent clinical studies designed to achieve these effects used a loading dose of 1 $\mu$g/kg during a period of 10 minutes, followed by a continuous IV infusion rate of 0.2 to 0.7 $\mu$g/kg/hr, the dosing regimen originally approved by the FDA in 1999.

Studies examining very high dexmedetomidine plasma levels (up to 8.0 ng/mL) demonstrate that the alpha-2C peripheral vasoconstrictor effects become predominant, with increasing systemic vascular resistance and decreasing cardiac index, associated with marked catecholamine suppression and deepening sedation. However, even at these very high plasma levels, there was no clinically significant respiratory depression.\textsuperscript{19} Indeed, when administered as the sole agent, dexmedetomidine appears to be remarkably safe. Case reports of large accidental overdoses of dexmedetomidine (192 $\mu$g loading dose, 2–30 $\mu$g/kg/hr) describe oversedation as the only notable sign, with resolution within an hour of discontinuation.\textsuperscript{20} Moreover, dexmedetomidine has been used safely as the sole agent at high rates of infusion (5–15 $\mu$g/kg/hr) to anesthetize patients with tracheal stenosis while preserving spontaneous ventilation.\textsuperscript{21} In October 2008, the FDA approved an increased dose of dexmedetomidine (up to 1.5 $\mu$g/kg/hr) for surgical procedures.

In contrast, there is a risk for excessive bradycardia and even sinus arrest when dexmedetomidine is administered in combination with sympatholytic or cholinergic agents (eg, beta-blockers, fentanyl, neostigmine), especially if there is concomitant vagal stimulation (eg, sternal separation, laparoscopic insufflation, colonoscopy).\textsuperscript{22–24} Based on preliminary studies, the FDA-approved duration of infusion of dexmedetomidine remains 24 hours. However, there are several studies that have demonstrated safe use for a week or longer in mechanically ventilated critically ill patients.\textsuperscript{25,26} With prolonged administration, tolerance to dexmedetomidine’s hypnotic effects has been demonstrated in animals,\textsuperscript{27} but it does not appear to be clinically significant. Unlike clonidine, cessation of administration does not appear to be associated with rebound hypertension or agitation.

**Pharmacodynamic Effects**

**Sedation: anxiolysis, hypnosis, and amnesia**

As described earlier, dexmedetomidine provides dose-dependent increases in anxiolysis and sedation. However, the quality of sedation appears to be unique in
comparison with GABAergic agents such as midazolam or propofol. Arousability is maintained at deep levels of sedation, with good correlation between the level of sedation (Richmond agitation-sedation scale) and the bispectral (BIS) EEG. Once aroused, subjects perform well on tests of vigilance, such as the critical flicker-fusion frequency. To achieve the same result, infusions of midazolam or propofol must be discontinued. This results in so-called “cooperative sedation,” in that patients can cooperate with ICU nursing, radiologic, and even airway procedures and undertake sophisticated neurologic testing during craniotomies for tumor dissection or stereotactic implantations. In addition, given the demonstrated benefit of daily wake-up trials on outcomes in ICU patients, there appears to be particular value in a drug such as dexmedetomidine that facilitates the arousal and rapid orientation of a sedated patient and then allows the patient to return to a sedated state soon afterward.

Sedation induced by dexmedetomidine has the respiratory pattern and EEG changes commensurate with natural sleep. Dexmedetomidine induces sleep by activating endogenous non-rapid eye movement sleep–promoting pathways. Stimulation of alpha-2A receptors in the nucleus ceruleus inhibits noradrenergic neurons and disinhibits gamma-aminobutyric acid (GABAergic) neurons in the ventrolateral preoptic nucleus (VLPO). In contrast, GABAergic agents, such as propofol or benzodiazepines, directly enhance the inhibitory effects of the GABAergic system at the VLPO. Norepinephrine release from the locus ceruleus remains unaffected, thus leading to less restful sleep. Functional MRI studies show that unlike GABAergic agents, dexmedetomidine preserves a cerebral blood flow pattern akin to natural sleep.

The amnestic effects of dexmedetomidine are far less than the benzodiazepines, which provide profound anterograde amnesia that may contribute to confused states on emergence. In contrast, amnesia is achieved with dexmedetomidine only at high plasma levels (> 1.9 ng/mL), without retrograde amnesia.

**Analgesia**

Dexmedetomidine appears to exert analgesic effects at the spinal cord level and at supraspinal sites. However, there has been considerable debate as to whether its analgesic effects are primary or simply opioid-sparing. Early studies suggested that part of its analgesic benefit might be mediated by attenuation of the affective-motivational component of pain. Nonetheless, in comparison with hypnotic agents such as propofol, or postoperative opioids used alone, dexmedetomidine significantly decreases opioid requirement.

Dexmedetomidine may also provide antinociception through nonspinal mechanisms—intra-articular administration during knee surgery improves postoperative analgesia, with less sedation than the IV route. Suggested mechanisms are activation of alpha-2A receptors, inhibition of the conduction of nerve signals through C and Aδ fibers, and the local release of encephalin.

**Cardiovascular effects**

Dexmedetomidine causes dose-dependent decreases in heart rate and blood pressure, concomitant with decreasing plasma catecholamines. This is of considerable benefit in tachycardiac, hypertensive patients, and dexmedetomidine typically improves hemodynamic stability in the perioperative period. However, these effects may be unwanted in patients with congestive heart failure, whose cardiac output is rate dependent, or with conduction system disease. As mentioned, high-dose boluses may result in a biphasic response, with bradycardia and hypertension consequent to
initial stimulation of peripheral alpha-2B vascular receptors, followed by central sympathectomy and a decline in blood pressure.19

**Respiratory effects**

Unlike opioids, dexmedetomidine is able to achieve its sedative, hypnotic, and analgesic effects without causing any clinically relevant respiratory depression, even when dosed to plasma levels up to 15 times those normally achieved during therapy.19 Compared with remifentanil, hypercapnic arousal is preserved, and the apnea threshold is actually decreased.34 Administration of dexmedetomidine during sevoflurane or desflurane anesthesia with spontaneous ventilation has no effect on end-tidal carbon dioxide.42 Arterial saturation is better preserved with dexmedetomidine than propofol in children undergoing MRI procedures.43 A similar improvement in oxygenation was observed in extubated patients in an ICU.44

In contrast to infusions of opioids, benzodiazepines, or propofol, dexmedetomidine can safely be infused through tracheal extubation and beyond. It has been used successfully to facilitate tracheal extubation in patients who had previously failed extubation because of excessive agitation45,46 and with similar benefit in agitated patients requiring noninvasive ventilation.47 Dexmedetomidine is effective in achieving excellent sedation without respiratory depression during fiberoptic intubation or other difficult airway procedures.21,48–50 Intubating conditions are further enhanced because dexmedetomidine decreases saliva production and airway secretions.1 Despite the lack of respiratory depression, dexmedetomidine was originally approved by the FDA for use in “initially intubated, mechanically ventilated patients,” that is, it had to be started on ventilated patients but could be continued through and beyond tracheal extubation. In October 2008, dexmedetomidine was FDA-approved for procedural sedation in nonintubated patients.

**Metabolic effects**

Dexmedetomidine and other alpha-2 agonists suppress shivering, possibly by their activity at alpha-2B receptors in the hypothalamic thermoregulatory center of the brain.4 Low-dose dexmedetomidine has an additive effect with meperidine on lowering the shivering threshold, when these drugs are combined.51 Dexmedetomidine may be beneficial in decreasing patient discomfort from postoperative shivering52 and controlling shivering that may delay therapeutic hypothermia for acute stroke or CNS injury. However, bradycardia has been noted when dexmedetomidine was added to remifentanil during therapeutic hypothermia in children.53

**Organ protective effects**

The ability of alpha-2 agonists to decrease tachycardia and hypertension suggests that they may play a role in cardioprotection by enhancing myocardial oxygen balance. There is as yet little evidence that dexmedetomidine enhances myocardial ischemic preconditioning or attenuates reperfusion injury. Most of the evidence is inferred; for example, when used after cardiac surgery, dexmedetomidine decreased the incidence of ventricular arrhythmias from 5% to zero, compared with propofol.54

A large European study demonstrated that perioperative infusion of mivazerol, another alpha-2 agonist, significantly decreased cardiac death after vascular surgery in patients with known coronary artery disease.55 A meta-analysis of noncardiac vascular surgery patients receiving any alpha-2 agonist agent demonstrated decreased risk of myocardial infarction and death,56 but a more recent meta-analysis of dexmedetomidine alone on cardiovascular outcomes after noncardiac surgery did not show statistical significance.57 Larger studies are required to clearly establish the cardioprotective effect of dexmedetomidine; they should include patients at
sufficiently high cardiac risk, and the dexmedetomidine infusion should be continued for at least 48 to 72 hours postoperatively.57

There is considerably more experimental evidence that dexmedetomidine has neuroprotective effects by several mechanisms. These include sympatholysis, preconditioning, and attenuation of ischemia-reperfusion injury.58 There is also evidence that dexmedetomidine decreases cerebral blood flow,59,60 but its ratio with cerebral metabolic rate (ie, flow-metabolism coupling) appears to be preserved.61

Alpha-2 adrenergic agonists, such as clonidine, have an established role in the treatment of central hyperadrenergic states induced by withdrawal of drugs, including cocaine, alcohol, or opioids. Numerous case reports of successful treatment of withdrawal using dexmedetomidine have been published,62–69 but to date, no randomized trials have been performed.

The effects of dexmedetomidine on renal function are complex. Alpha-2 agonists exert a diuretic effect by inhibiting the antidiuretic action of AVP at the collecting duct, most likely through alpha-2A receptors, resulting in decreased expression of aquaporin-2 receptors and decreased salt and water reabsorption.70,71 They also enhance osmolal clearance through non–AVP-dependent pathways, possibly mediated by the alpha-2B receptor.72

There is experimental evidence that dexmedetomidine attenuates murine radiocontrast nephropathy by preserving cortical blood flow.73 This mechanism is supported by the observation that dexmedetomidine decreases the renal cortical release of norepinephrine.74 There is also evidence that dexmedetomidine attenuates murine ischemia-reperfusion injury.75 However, prospective human studies establishing a benefit are not yet available.

REMIFENTANIL

Remifentanil is an ultra–short-acting opioid that acts as a mu-receptor agonist; it is 250 times more potent than morphine. In 1996, the FDA approved remifentanil as an analgesic agent for the induction and maintenance of anesthesia. In 2002, the European Medicines Agency approved its use for analgesia in mechanically ventilated adult patients in intensive care for up to 3 days.76 Although remifentanil is used and studied extensively in the operating room, its popularity in the critical care arena is growing.77

The pharmacokinetic profile of remifentanil is unique in its class. Described as a “forgiving opioid,” remifentanil is characterized by a rapid onset and offset.78,79 Infusion of remifentanil has an onset of action of 1 minute78 and rapidly achieves steady-state plasma levels. Its action dissipates within 3 to 10 minutes after discontinuation of an infusion. Remifentanil has a t1/2 β of approximately 10 to 20 minutes and a context sensitive half-time of 3 to 4 minutes, regardless of the duration of infusion.78,80,81

Remifentanil is metabolized directly in the plasma by nonspecific esterases. Its primary metabolite is remifentanil acid, which has negligible pharmacologic activity. Thus, although remifentanil acid is eliminated by the kidneys, remifentanil’s action is not prolonged to a significant extent by renal injury or prolonged infusion in patients in intensive care.82 Dose adjustments are not required in patients with hepatic dysfunction, but patients with liver disease can be more sensitive to the ventilatory depressant effects of remifentanil.76,83,84 In contrast to other opioids such as morphine and fentanyl, which can accumulate in organ dysfunction, continuous infusions of remifentanil are not associated with a prolongation of effect. Several publications report the successful use of a remifentanil infusion for up to 33 days with signs of recovery within 10 minutes of discontinuation of the infusion.76,82,85,86 On the other
hand, inadvertent or sudden discontinuation of remifentanil may result in rapid return of the underlying pain. Thus, a longer-acting opioid should be administered before stopping the remifentanil infusion if it is anticipated that analgesic requirements are ongoing.

Similar to other opioids, remifentanil can cause bradycardia, hypotension, respiratory depression, nausea, and skeletal muscle rigidity. Bolus injections of remifentanil are not recommended because they may cause thoracic muscle rigidity with difficult mask or pressure-controlled ventilation.76

Several cases of acute withdrawal syndrome have been reported after cessation of remifentanil infusions in the ICU. Tachycardia, hypertension, sweating, mydriasis, and myoclonus have occurred within 10 minutes of discontinuation of remifentanil-based sedation. Symptoms persisted after administration of morphine and clonidine and were resolved only after remifentanil was reinitiated.87 Gradual tapering of the infusion from 24 to 48 hours may decrease the incidence of a withdrawal syndrome.87,88

The rapid offset of the analgesic effect of remifentanil has generated considerable interest in its use to shorten mechanical ventilator times in the ICU. A regimen using remifentanil infusion (0.1–0.15 μg/kg/min) with midazolam, added as needed, shortened the duration of prolonged mechanical ventilation by more than 2 days compared with a midazolam infusion with the addition of fentanyl or morphine.85 In a randomized controlled trial, the duration of mechanical ventilation, extubation times, and the interval after extubation to ICU discharge were significantly shorter with remifentanil infusion (0.15 μg/kg/min) compared with morphine infusion.89 When remifentanil-midazolam was compared with sufentanil-midazolam for a median duration of 6 days of mechanical ventilation, mean weaning time was 22 hours compared with 96 hours, even though the sufentanil dose was down-titrated before extubation.90

In contrast, there was no difference in time to tracheal extubation when combined infusions of remifentanil (0.15 μg/kg/min) and propofol were compared with fentanyl and propofol after short-term ventilation (12–72 hours). Moreover, patients who received remifentanil complained of more pain during and after tracheal extubation.91 In a subsequent study by the same group, mechanical ventilation time after cardiac surgery was decreased, and ICU discharge was earlier with a remifentanil-propofol regimen than with a fentanyl-midazolam regimen.92 These two studies suggest that the duration of ventilation was more influenced by the duration of action of the hypnotic agent (midazolam vs propofol) than the opioid (fentanyl vs remifentanil).

Remifentanil has been evaluated in the neurointensive care setting. Because of its short half-life, remifentanil may facilitate frequent awakening to evaluate neurologic and respiratory parameters.76,93 In a study of patients with traumatic brain injury who were mechanically ventilated, intracranial pressure (ICP) and cerebral perfusion pressure were maintained with remifentanil.94 However, in patients with severe traumatic brain injury, even high doses of remifentanil (up to 1.0 μg/kg/min) were insufficient to suppress coughing and elevation of ICP, and increased doses of vasopressor drugs were required to maintain cerebral perfusion pressure.95

KETAMINE

Clinical reports of the use of ketamine, a nonbarbiturate phencyclidine derivative, first appeared more than four decades ago.96 Because it provides analgesia and apparent anesthesia with relative hemodynamic stability, ketamine was considered an ideal “battlefield anesthetic” and was popularized during the Vietnam war.97

Ketamine binds with N-methyl-D-aspartate (NMDA) and sigma opioid receptors to produce intense analgesia and a state termed dissociative anesthesia; patients
become unresponsive to nociceptive stimuli, but may keep their eyes open and maintain their reflexes. Blood pressure is maintained, and spontaneous breathing and laryngeal reflexes are preserved. Ketamine crosses the blood-brain barrier rapidly and reaches maximal effect in 1 minute. The duration of a single dose of ketamine (2 mg/kg IV) is 10 to 15 minutes. Effective plasma levels of ketamine can be achieved by IV, intramuscular, sublingual, or rectal routes, making it a useful agent in pediatric patients.

In comparison to etomidate, propofol, and midazolam, ketamine appears to act as a cardiac stimulant through sympathetic-mediated mechanisms. At clinical concentrations, ketamine has a positive inotropic action and induces vasoconstriction, probably by inhibiting endothelial nitric oxide production, which preserves hemodynamic stability even in septic shock. In animal studies, ketamine acts as a myocardial depressant at very high plasma concentrations, particularly in a catecholamine-depleted state, but this manifestation appears extremely rare in clinical medicine. Although vasoconstriction and inotropy are preferable in certain situations, ketamine increases myocardial oxygen demand, limiting its use in patients with active coronary ischemia. Its sympathomimetic activity is attenuated by concomitant administration of benzodiazepines. Ketamine has bronchodilator activity and may be helpful in the setting of status asthmaticus and bronchospasm, although this benefit may be counteracted by its propensity to increase oral secretions.

Ketamine has antiinflammatory properties. It decreases the formation of the cytokine precursor, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and thereby decreases interleukin-, cytokine-, and endotoxin-induced tumor necrosis factor alpha production.

Ketamine is still used in clinical anesthesia, but its popularity is limited because of its undesirable side-effect profile of hallucinations (during dissociative anesthesia), emergence delirium and unpleasant recall, increased oral secretions, lacrimation, tachycardia, and the potential for exacerbating myocardial ischemia. Clinicians have avoided ketamine in patients at risk for elevated ICP, which may occur in patients who are spontaneously ventilating. This observation contrasts with studies that show that ketamine does not increase cerebral blood flow or ICP if normal carbon dioxide levels are maintained. In combination with benzodiazepines, ketamine prevents increases and decreases in ICP. Hemodynamic variables appear to be preserved in brain or spinal cord injured ICU patients. These results suggest that the depth of sedation is more important than the choice of sedative in the management of elevated ICP.

Concerns for the psychotropic effects of ketamine have restricted its use as a sedative-analgesic in the ICU. However, there is evidence that low-dose (60–120 μg/kg/h) ketamine infusions in combination with opioids may not be associated with untoward effects and may improve outcomes in the critically ill. There are several explanations for this benefit. The analgesic effects of ketamine occur at plasma concentrations lower than those associated with its psychotropic activity, which are in any event attenuated by simultaneous administration of hypnotics such as propofol or midazolam. When patients received ketamine infusions as an adjunct to opioid therapy in the ICU, morphine consumption decreased without adverse side effects. Similar findings were noted in a randomized controlled trial of patients who had cardiac surgery, with improvement in patient satisfaction. Prolonged infusion of opioids, such as fentanyl and morphine, inhibits bowel function and promotes constipation or even prolonged ileus. Ketamine does not inhibit bowel mobility and may reduce the feeding complications associated with opioids.

There are other benefits of concomitant administration of ketamine. Major surgery, burns, trauma, and painful procedures in the ICU induce prolonged noxious stimuli,
which can cause central sensitization and lead to allodynia (a painful response to an innocuous stimulus), hyperalgesia (an exaggerated response to a painful stimulus), and eventually chronic pain syndromes. Opioids themselves can induce hyperalgesia. Ketamine antagonizes the NMDA receptor to block these responses, reducing windup pain and central hyperexcitability. Several studies report that ketamine decreases opioid-induced hyperalgesia. Potentially, ketamine can decrease opioid requirements, tolerance, and prevent chronic pain. In summary, ketamine has regained its popularity as a “battlefield anesthetic” in the Iraq war for the treatment of acute and chronic pain and burns.

There are few reports of adverse long-term psychological sequelae after ketamine. Its administration has actually been associated with a decreased incidence of post-traumatic stress disorder (PTSD) in soldiers in the Iraq war. There is also evidence that a single dose of IV ketamine rapidly improves symptoms in patients with treatment-resistant depression. Because PTSD and depression can occur in patients who are critically ill, randomized controlled trials to investigate ketamine as a novel therapeutic agent would appear to be warranted.

VOLATILE ANESTHETIC AGENTS

Volatile anesthetics such as isoflurane, sevoflurane, and desflurane are in daily use in the operating room in the delivery of general anesthesia. A major advantage of these halogenated ethers is their quick onset, quick offset, and ease of titration in rendering the patient unconscious, immobile, and amnestic. Although volatile anesthetics are generally associated with stable hemodynamics with little variation, dose-dependent vasodilatation, cardiac depression, and arrhythmias can occur. Isoflurane, sevoflurane, and desflurane provide cardioprotection through pharmacologic preconditioning; troponin levels and length of ICU stay are decreased. Volatile anesthetics are also bronchodilators and can be prescribed as therapeutic agents for the treatment of bronchospasm and status asthmaticus.

Administering sedation through the lung is a dependable route for delivery and elimination. Characterized by a steep dose-response curve, inhalation anesthesia offers a more consistent onset time with less variability compared with traditional IV sedation. Because newer volatile anesthetics (eg, isoflurane, sevoflurane, desflurane) are primarily eliminated by the lungs, there is very little accumulation in patients with renal and hepatic dysfunction, and shorter and more predictable emergence times are observed. Potential concerns for the accumulation of inorganic fluorides and possible renal dysfunction have not been realized.

Intensivists use sedation scales to titrate sedatives in the ICU. In contrast, volatile anesthetics can be monitored by their end-tidal concentration or fraction. This allows excellent control of the drug’s actions and can provide a guide to the expected concentration at target organs. In an ICU study, isoflurane end-tidal concentrations correlated with the clinical assessment of sedation depth better than with the BIS index. Adverse effects can be reversed by immediately decreasing the inspired concentration. The term median alveolar concentration (MAC) is defined as the specific vapor end-tidal concentration needed to prevent motor response to a painful stimulus in 50% of subjects; the exact value depends on the potency of the volatile anesthetic. In general, it is recommended that, in the ICU, volatile anesthetics be delivered at an end-tidal concentration of 0.5 MAC.
Several clinical trials have compared volatile anesthetics to IV sedation in critical care. Preliminary studies evaluating isoflurane in the ICU found that it was safe, effective, and associated with shorter emergence times than midazolam or propofol.\textsuperscript{148–150,154} Compared with propofol, sevoflurane sedation was associated with shorter extubation times and length of hospital stay in patients after cardiac surgery.\textsuperscript{151} Similar observations have been made when desflurane was compared with propofol after surgery, and patients appeared to have better cognitive function after emergence.\textsuperscript{138} Long-term (6-month) follow-up of patients found a trend toward fewer hallucinations and delusions if they had received isoflurane versus midazolam sedation in the ICU.\textsuperscript{155}

Given these benefits, a number of major restrictions remain that govern the routine delivery of volatile anesthesia in the ICU—cost, environmental pollution, and the anesthesiologist’s expertise.\textsuperscript{156} The need for a cumbersome circuit to deliver the volatile anesthetic and the uneconomical anesthetic consumption in an open ICU ventilator circuit have limited their effectiveness. Non-rebreathing ICU ventilators require a scavenging system to avoid environmental pollution. Several published studies have used a new and fairly simple device, the “Anesthetic Conserving Device” (AnaConDa, Hudson RCI, Upplands Väsby, Sweden) that allows infusion of liquid volatile anesthetic through the breathing circuit of a standard ICU ventilator. By incorporating a vaporizer chamber with a charcoal reflection filter it creates a semi-closed rebreathing circuit that retains 90% of the inhaled anesthetic. Modifications are still required to enhance safety. Changes in ventilator settings affect the delivery of the anesthetic, and it is possible that the volatile anesthetic syringe could inadvertently be connected to an IV infusion line, but there is little escape of the anesthetic into the atmosphere.\textsuperscript{157}

**PERIPHERAL OPIOID RECEPTOR ANTAGONISTS**

Opioids remain the primary class of analgesic drugs in the ICU and may be infused for many days in critically ill patients. Undesired side effects are legion, and in addition to nausea, vomiting, pruritus, and urinary retention, they include delayed gastric emptying, suppression of bowel motility, constipation, and ileus. Methylnaltrexone and alvimopan are members of a new class of drugs—peripherally acting mu opioid receptor antagonists (PAMORAs). In contrast to naloxone, these medications do not cross the blood-brain barrier to antagonize the central effects of opioids. Instead, they antagonize the peripheral side effects of opioids—notably constipation and ileus—while preserving analgesia. The FDA has approved subcutaneous methylnaltrexone for the relief of opioid-induced constipation and oral alvimopan to facilitate the return of gut dysfunction after anastomotic bowel surgery.

The PAMORAs have the potential to markedly benefit the management of ICU patients, and further trials are warranted. Enteral feeding promotes gut function and the immune system; by delaying gastric emptying, opioids predispose patients to vomiting and pulmonary aspiration. Methylnaltrexone reverses opioid-induced delayed gastric emptying time\textsuperscript{158,159} and thereby may not only decrease aspiration risk but also improve absorption of orally administered medications in the critically ill.\textsuperscript{160}

Opioids enhance the ability of the human immunodeficiency virus (HIV) to enter macrophages by modulating coreceptors such as beta-chemokines and chemokine (C-C motif) receptor 5 (CCR5). This activity is completely reversed by methylnaltrexone, which may be of benefit to HIV patients receiving or abusing opioids.\textsuperscript{161} *Pseudomonas aeruginosa*, a common pathogen in ICU patients, is endowed with mu opioid receptors, which when activated produce factors that enhance gut wall permeability and allow the bacteria to spread systemically. Methylnaltrexone blocks the production
of these factors and may help curtail systemic invasion in patients receiving opioids.  

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