

ABSITE CORNER

Common sedative agents: An overview

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GENERAL INFORMATION

ABSITE CORNER is a section of OPUS 12 Scientist dedicated to brief topic reviews geared toward resident preparation for the American Board of Surgery In-Training Examination. Each quarterly edition of OPUS 12 Scientist will contain one or two condensed overviews, accompanied by a list of selected references. Resident contributions via regular article submission process are welcome, subject to Editorial Board and Section Editor approval.

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LORAZEPAM

Lorazepam is an intermediate-acting benzodiazepine. It is used for short-term relief of anxiety. It is also useful as a first-line anticonvulsant in the setting of seizures and/or status epilepticus. Lorazepam is the preferred agent for long-term sedation in the intensive care unit (ICU). Lorazepam's anticonvulsant and central nervous system (CNS) depressant effects are also useful for the prevention and treatment of alcohol withdrawal symptoms.

Lorazepam has a half-life of 10-20 hours. It can be administered orally, intravenously, intramuscularly, or transdermally. It is metabolized via hepatic glucuronidation and undergoes renal excretion. Lorazepam has poor lipid solubility and a high degree of protein binding (85-90%). It is thought to have high affinity for GABA receptors, which helps explain its amnestic properties.

The recommended initial adult daily oral dosage is 2 mg in divided doses of 0.5-1.0 mg. The daily dose should be gradually increased or decreased by 0.5-1.0 mg based on patient response and tolerance. The usual daily dosage is between 2-3 mg. Dosages higher than 3 mg can be used, especially in long-term administration of lorazepam.

Lorazepam infusion can be useful in long-term ICU sedation. However, one must remember that renal impairment and advanced patient age may cause abnormally prolonged duration of action. The starting dose in the elderly (>65 years old) population should not exceed 0.5 mg and should be very carefully and gradually titrated. Lorazepam overdose can be treated with flumazenil.

The most common side effects associated with lorazepam use include: (a) sedation – reported in 1 of 6 people; (b) weakness; (c) unsteadiness/ataxia; (d) feeling of depression; (e) disorientation; (f) headache; (g) sleep disturbance – especially in the ICU; (h) respiratory failure; and (i) withdrawal. There are also case reports of renal toxicity and lactic acidosis related to propylene glycol, a component of the intravenous lorazepam formulation. Concurrent use with alcohol may lead to fatal respiratory depression. Of note,

lorazepam is classified as category D drug in the setting of pregnancy. Benzodiazepine use in pregnancy, especially in high doses, may result in significant perinatal problems (**see below**).

MIDAZOLAM

Midazolam is a short-acting benzodiazepine used to relieve anxiety before operative procedures and to facilitate sedation in the acute procedural setting. Midazolam can also be used to induce loss of consciousness before and during surgery. It has sedative, hypnotic, anxiolytic, and amnestic properties.

Midazolam has a short elimination half-life (1.8-6.4 hours). Its metabolism is primarily hepatic, with renal excretion. Midazolam is metabolized mostly by cytochrome P450-3A4, and agents that affect this system will affect midazolam action. Midazolam acts on benzodiazepine receptors, which enhance the binding of GABA to GABA_A receptor, causing CNS inhibition. It can be administered orally, intramuscularly, or intravenously.

Midazolam is indicated for: (a) preoperative sedation, anxiolysis and amnesia; (b) treatment of seizures and/or status epilepticus; (c) sedation, anxiolysis and amnesia prior to endoscopic procedures; (d) general anesthesia in combination with other agents. Continuous intravenous infusion of midazolam has been used for sedation of intubated patients in the ICU.

Preoperative sedation with midazolam is given intramuscularly at 70-80 mcg/kg approximately 30-60 minutes before general anesthesia. For conscious sedation, intravenous midazolam can be administered starting with doses of 0.5 mg, and titrating slowly to desired effect. Total doses of >2.5 mg should not be exceeded over any two-minute period. For induction of general anesthesia, intravenous midazolam (150-350 mcg/kg) should be given over 30 seconds, and may be followed with additional 25% of the initial dose, if needed, few minutes after the initial injection.

Midazolam dosage should be reduced for patients who are older than 55 years, premedicated, debilitated, or have severe systemic disease. In the pediatric population, preoperative sedation may require anywhere between 80-200 mcg/kg and general anesthesia may require anywhere between 50-200 mcg/kg.

Side effects of midazolam include hypotension, bradycardia, respiratory depression, impaired motor function, coma and withdrawal symptoms. Midazolam overdose can be treated with flumazenil. Midazolam administered regularly during pregnancy may result in reduced IQ, neurodevelopmental problems, physical malformations, and withdrawal symptoms. Newborns may show hypotonia, poor feeding, apnea, cyanosis, floppy infant syndrome.

PROPOFOL

Propofol (2,6-diisopropylphenol) is a short-acting intravenous anesthetic agent. It can be used for induction and/or maintenance of general anesthesia. It is also used in the ICU as a sedative agent

for intubated, mechanically ventilated patients. It can be utilized in the short procedure setting, including endoscopic procedures. Propofol provides no analgesia or muscle relaxing properties.

The commercial preparation consists of 1% propofol, 10% soybean oil, 1.2% purified egg phospholipid (emulsifier), 2.25% of glycerol as a tonicity agent, and sodium hydroxide to adjust the pH. Propofol emulsion is an opaque white fluid (i.e., the 'milk of anesthesia'). Propofol is highly protein bound *in vivo*. It is metabolized by hepatic glucuronidation. Its rapid rate of clearance suggests non-hepatic metabolism as well. Its mechanism of action is not precisely known, but the primary effect may be potentiation of GABA_A receptor, possibly by slowing the channel closing time. The endocannabinoid system may also contribute to propofol's anesthetic action. The elimination half-life is 2-24 hours, but the duration of action is much shorter (minutes) because propofol is rapidly distributed into peripheral tissues.

Propofol is perfectly suited as a quick 'on/off' agent in the setting of head injury, where it allows for periodic 'awakenings' followed by rapid re-institution of sedation. It may also offer some neuroprotection. In terms of dosing, anesthesia induction in adults (<55 years old) is given at 2.0-2.5 mg/kg. In elderly patients (>65 years old) propofol induction is given at 1.0-1.5 mg/kg. Propofol maintenance anesthesia is dosed at 100-200 mcg/kg/min in adults and 50-100 mcg/kg/min for geriatric patients. For ventilated ICU patients, the dose is titrated between 5-50 mcg/kg/min.

Side effects of propofol include: (a) hypotension; (b) transient apnea following induction doses; (c) pain at the injection site – can be mitigated by pretreatment with lidocaine; (d) significant variability in dose-response among patients; (e) rare dystonia; (f) mild myoclonic movements; (g) pancreatitis due to the high lipid content of the propofol carrier medium – seen in chronic administration; (h) hallucinations; (i) seizures – very rare; (j) thrombophlebitis. A rare, but serious, side effect of propofol is the **propofol infusion syndrome**. This potentially lethal metabolic disorder (severe metabolic/lactic acidosis) has been reported in ICU patients after prolonged high-dose infusion of propofol, usually in conjunction with catecholamines and/or corticosteroids.

KETAMINE

Ketamine is a unique sedative agent – a **dissociative** anesthetic. Ketamine does not induce significant respiratory depression. It has hypnotic, analgesic and amnestic effects – a unique combination of clinical features. Ketamine is a co-analgesic, being most effective when combined with low-dose opioids.

Ketamine is classified as an NMDA receptor antagonist, along with phencyclidine (PCP). There are two stereoisomers of ketamine, (S)-ketamine and (R)-ketamine. The (S)-ketamine has a stronger affinity for the PCP site on NMDA receptor as well as greater analgesic effect than (R)-ketamine. Ketamine is usually given intravenously or intramuscularly, but it can be effective

when insufflated, smoked, or taken orally. Its half-life is approximately 2.5-3.0 hours and excretion is 90% renal. The usual intravenous dose of ketamine is 1.0-4.5 mg/kg, which produces surgical anesthesia within 30 seconds after injection. Intramuscular doses, from primarily pediatric experience, produce surgical anesthesia within 3-4 minutes in doses of 6.5-13 mg/kg. Intravenous ketamine anesthetic effect usually lasts 5-10 minutes and intramuscular ketamine effect usually lasts 12-25 minutes.

Ketamine has a variety of clinical effects, including: (a) analgesia, (b) anesthesia, (c) hallucinations, (d) neurotoxicity, (e) arterial hypertension, and (f) bronchodilation. In contrast to the smooth induction of anesthesia, the patient may be agitated on recovery – a phenomenon called **emergence delirium** (disorientation, restlessness, and crying). Patients may experience unpleasant, vivid dreams up to 24 hours post-ketamine administration. The use of benzodiazepines as premedication and providing an undisturbed recovery may help reduce these side effects. Ketamine infusion may be used in small doses (0.1–0.5 mg/kg/hour) in the setting of regional pain syndromes (including reflex sympathetic dystrophy). Here, ketamine provides selective pain relief without prolonged sedation or respiratory depression.

Ketamine causes elevations in intracranial pressure and should not be used in patients who sustained a head injury. There may be an increased risk of cardiac ischemia with ketamine use. Ketamine may also lower the seizure threshold.

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