Chapter 6: Hypnotics

Sapan Amin

INTRODUCTION

FOCUS POINTS

1. Body composition is different in children than in adults, with children having a higher proportion of total body water than fat and muscle.
2. Egg allergy does not preclude propofol use (egg lecithin) because the usual allergy is due to egg albumin.
3. Prolonged propofol infusions (24 hours) can lead to propofol infusion syndrome (PRIS), which is a syndrome defined by metabolic acidosis, rhabdomyolysis, lipemia, and hepatomegaly.
4. Among the hypnotics, only ketamine has both amnestic and analgesic properties and is considered the most complete anesthetic.
5. Ketamine should be used with caution in patients that are sympathetically depleted (ICU patients) because it has direct myocardial depressant effects.
6. Etomidate provides hemodynamic stability upon administration but can cause adrenal insufficiency even after a single dose.
7. Midazolam is the most common premedication in adults intravenously, and in children orally.
8. Methohexital can be used for maintenance of anesthesia instead of propofol in patients with mitochondrial disorders. It should be used with caution in patients with seizure history.

Hypnotics are drugs that have dose-dependent effects extending from reduction of anxiety to a sleep-like state. Due to differences in drug distribution between adults and children, dosing needed to exert similar clinical effects may vary. Parameters such as body composition, metabolism, regional blood flow, and clinical state affect distribution and thus effect.

Body composition is different in children than in adults, with children having a higher proportion of total body water than fat and muscle. Total body water is significantly larger in neonates and infants, especially preterm infants. Preterm infants and neonates have other differences in metabolism when compared to older children and adults. They have immature hepatic and renal function and decreased protein binding of drugs.

Regional blood flow plays a significant role in the effects of hypnotic drugs. The brain, heart, and liver are the main organs that first receive the drug. The next group to receive blood flow is the less perfused muscle group. The last group made up of the poorly perfused tissues is fat. Fat in turn acts as a reservoir and can release the drug into the bloodstream, maintaining higher drug concentration levels and prolonging drug effects.

As children get older, the renal and hepatic function increases as a larger fraction of cardiac output goes toward the liver and kidneys. Thus, the half-life of many medications in children over 2 years is shorter than in adults.

Sicker children especially in states of hemodynamic instability may need to have drug dosages reduced and/or given at a slower rate to prevent further cardiovascular deterioration.

As clinicians became more experienced with hypnotic drugs, more drug combinations have been considered to both decrease individual drug doses and improve side effect profile of individual drugs. An example of this is the use of ketamine along with propofol (“ketofol”).

PROPOFOL

Propofol is the most commonly used intravenous induction agent because of its desirable properties of fast onset, clear headedness upon awakening, and less incidence of postoperative nausea and vomiting (infused at a low dose).[1] Propofol is a phenol derivative that is insoluble in water and is dissolved in 1.2% egg lecithin, 10% soybean oil, and 2.25% glycerol. The lipid solution can lead to microbial growth and contains ethylenediaminetetraacetic acid (EDTA) or metabisulfite. Propofol should be administered within 6 hours of opening the vial. An egg allergy does not contraindicate the use of propofol since most egg allergies are due to egg albumin (egg white), and egg lecithin is taken from egg yolk.[2]

Clinical Uses

1. Induction of anesthesia
2. Procedural sedation
3. Laryngospasm to deepen the patient
4. Total intravenous anesthesia (TIVA) or balanced anesthesia (in combination with opioids)
5. Prevention of postoperative nausea and vomiting[3]

Mechanism of Action

Propofol acts by facilitating GABA(A) receptor, which leads to increased influx of chloride ions causing hyperpolarization of neurons rendering them resistant to activation. It is only available for intravenous injection. It is fast-acting with short initial distribution half-life, leading to a quick wake-up. Even after long infusions, it has a relatively short context-sensitive half-time.[4,5] It can cause discomfort when given through a peripheral vein most likely due to the medication's intrinsic properties (pH and emulsion composition), a side effect that may be relieved with the administration through a larger vein or with the addition of lidocaine in advance or administration.

Induction Dose

2.5 to 3.5 mg/kg–higher doses than that of adults are needed[6,7]

Continuous intravenous sedation dose 200 to 300 mg/kg/min when used for TIVA

Elimination

Conjugation occurs in the liver, which leads to inactive metabolites that are renally excreted. Clearance is greater than hepatic blood flow and the high clearance can lead to rapid recovery after infusions.

Medication Profile

1. *Cardiovascular effects*: Propofol decreases blood pressure by lowering systemic vascular resistance, increasing venous capacitance, and decreasing cardiac contractility (decreasing sympathetic tone).[8] Factors associated with hypotension are prematurity, large doses, rapid bolusing, and patients that have poor LV contractility. Fall in systemic vascular resistance can lead to a decreased pulmonary blood flow (Qp<Qs) and arterial desaturation in patients with congenital heart disease that have a cardiac shunt.[9]
2. *Respiratory effects*: Propofol inhibits the response of the respiratory centers to hypercarbia and hypoxia.[10] It causes dose-dependent decrease in tidal volume, minute ventilation, and ventilatory drive and at induction doses extreme respiratory depression leading to apnea. Propofol can cause profound loss of muscle tone in the upper airway causing obstruction, while also depressing airway reflexes, useful in the treatment of laryngospasm. Although it can cause histamine release, it mostly causes bronchodilation and therefore has a lower incidence of wheezing than etomidate or thiopental.

3. *CNS effects*: Propofol decreases cerebral metabolic activity and oxygen demand, causing decreases in cerebral blood flow and intracranial pressure.[11] Due to its effect on blood pressure, leading to hypotension, propofol can lower cerebral perfusion pressure. Cerebral autoregulation and CO_2 vascular reactivity are maintained.[12] Propofol is an excellent hypnotic but a poor analgesic. Propofol has antiepileptic properties and can be used for patients that are acutely seizing and has been used in the treatment of status epilepticus. It has been known to cause dystonia.

Caution

Prolonged propofol infusions (24 hours) can lead to propofol infusion syndrome (PRIS), which is a syndrome defined by metabolic acidosis, rhabdomyolysis, lipemia, hepatomegaly, and possibly an increase in serum lactate and can often times be fatal. It is hypothesized that propofol can cause either direct inhibition of the mitochondrial respiratory chain or deficient mitochondrial fatty acid metabolism.[13] This syndrome has the propensity to occur in patients who are concurrently treated with catecholamines and steroids.[14]

Propofol inhibits multiple mitochondrial pathways and should be used judiciously (single induction dose) in patients with mitochondrial disease.

KETAMINE

Ketamine is a phencyclidine derivative and has multiple effects throughout the central nervous system (CNS).

Clinical Uses

1. *Procedural sedation*: It is used frequently in the emergency department for procedural sedation. When added in a low dose with propofol, it can decrease the respiratory depression associated with propofol.[15]
2. *Induction of general anesthesia*: It is used in patients with increased sympathetic activity whereby the sympathetic reserve is not depleted. It is also used in situations where hemodynamic instability is evident and heart rate is desired to be elevated (ie, hypotension in cardiac tamponade), or when the patient needs to be spontaneously breathing (difficult airway).[16]
3. *Analgesia*: It has been used perioperatively for analgesia in lower doses either as a bolus or as infusion and to decrease opioid requirements and opioid-induced hyperalgesia.[17] It is also used in the treatment of complex regional pain.

Mechanism of Action

It is an NMDA receptor antagonist and primarily works by dissociating the thalamus from the limbic cortex, known as “dissociative anesthesia.” The S(+) isomer has increased potency due to its greater affinity for the NMDA receptor but is unavailable in the United States.

Pharmacokinetics

Absorption

Ketamine is usually given intravenously but can also be administered intramuscularly especially in the case of special needs children or for IV placement when the child is agitated.

Distribution

Ketamine is very lipid soluble, which leads to rapid brain uptake and distribution. Awakening occurs due to redistribution peripherally.

Biotransformation

Ketamine has very high hepatic clearance with an extraction ratio of 0.9. It is biotransformed into different metabolites, one of which is norketamine that exhibits anesthetic activity. Tolerance can develop to ketamine.

Excretion

Ketamine is mostly metabolized in the liver and the products of ketamine biotransformation are excreted renally.

Medication Profile

1. *Cardiovascular effects*: Ketamine causes increased blood pressure, heart rate, and cardiac output. These effects are due to increased sympathetic stimulation and inhibition of norepinephrine reuptake. Ketamine should be given cautiously in patients with uncontrolled hypertension because of its sympathetic tone stimulation. In patients that are sympathetically depleted, ketamine has direct myocardial depressant effects. Although there have been concerns for increased pulmonary vascular resistance due to ketamine, studies suggest that if ventilation is maintained, there is not an increase in pulmonary vascular resistance.[16,18,19]

2. *Respiratory effects*: The respiratory system is minimally affected by doses of ketamine, but rapid IV bolus can still cause apnea. Racemic ketamine is an extremely potent bronchodilator, but the S(+) enantiomer produces minimal bronchodilation. Laryngeal reflexes are usually left intact though laryngospasm may occur due to increased salivation, which can be attenuated with an antisialagogue.

3. *CNS effects*: Ketamine is associated with increased cerebral oxygen demand, and cerebral blood flow. It has been associated with increased intracranial pressure in the past, but more recent data debunked that association. Ketamine increases somatosensory evoked potentials. Patients' eyes may remain open with spontaneous eye movements and nystagmus. Ketamine is the most complete anesthetic in that it provides amnesia as well as analgesia. It causes hallucinations and bad dreams. Hallucinations can be attenuated with a dose of midazolam or propofol.

Caution

Ketamine has a higher incidence of nausea than either propofol or thiopental (barbiturate).

ETOMIDATE

Etomidate works by mimicking the inhibitory effects of GABA. Etomidate binds to GABA(A) receptor and increases the receptor's affinity for GABA. Etomidate contains a carboxylated imidazole ring and is dissolved in propylene glycol for injection. This solution causes pain on injection, which can be pretreated with lidocaine, but is still painful for many.

Pharmacokinetics

Absorption

Available only for intravenous injection with immediate action.

Distribution

Very rapid onset of action due to its lipid solubility and large nonionized fraction at physiological pH. Redistribution is the primary cause of decreasing plasma levels after injection and reawakening.

Biotransformation

Hepatic microsomal enzyme system and plasma esterases rapidly hydrolyze etomidate to an inactive metabolite.

Excretion

Hydrolyzed end products are excreted in the urine.

Medication Profile

1. *Cardiovascular effects*: It is noted to be a very stable cardiovascular induction agent.[20,21] Cardiac output and myocardial contractility usually remain

unhindered.

2. *Respiratory effects*: Ventilation is less affected with etomidate than other induction agents.
3. *CNS effects*: It decreases cerebral metabolic activity, cerebral blood flow, and intracranial pressure. Etomidate increases the evoked potentials of somatosensory evoked potentials (SSEPs).
4. *Endocrine*: Etomidate hinders production of cortisol and aldosterone by reversibly inhibiting enzymes involved in their synthesis (11 beta-hydroxylase). Critically ill patients may be disserviced by etomidate administration, the one induction agent that is considered to maintain hemodynamic stability. Even one dose in pediatric patients produces decreased adrenal function and 11 beta-hydroxylase activity for a minimum of 24 hours.[22–24] Therefore, it is prudent to consider an alternative to etomidate in the critically ill patient.

Caution

Myoclonus can be observed due to disinhibitory effects on the extrapyramidal system.

Postoperative nausea and vomiting are more common than with other induction agents. Etomidate lacks analgesic properties.

DEXMEDETOMIDINE

Dexmedetomidine is a more selective alpha-2 adrenergic agonist and eight times more selective than clonidine. It mimics natural sleep and reduces sympathetic activity. Dexmedetomidine causes analgesia at the level of the spinal cord and hypnosis by stimulation of the locus coeruleus. It is most commonly administered intravenously and intranasally. It undergoes rapid hepatic metabolism by hydroxylation and conjugation.

Clinical Uses

1. *Premedication*: –Intranasal administration 0.5 to 1 mcg/kg.[25]
2. *Procedural sedation for radiological procedures*: MRI/CT (1–2 mcg/kg).
3. Facilitating sedated intubation in children.
4. *As an anesthetic adjunct*: Decreases intraoperative narcotic requirements, helps to maintain spontaneous ventilation.
5. Prophylaxis for or treatment of emergence delirium.

Medication Profile

1. *Cardiovascular effects*: Dexmedetomidine causes decreased HR and increased blood pressure due to increased systemic vascular resistance when given as a bolus. The decreased HR is a response to increased systemic vascular resistance and increased blood pressure most likely due to increased postsynaptic alpha-2 receptor stimulation on vascular smooth muscle.[26] As the central alpha-2 effects take hold, the SVR will come down with a slow increase in the HR.
2. *Respiratory effects*: Dexmedetomidine causes very little respiratory depression and the ventilatory response to hypercarbia is minimal. Upper airway obstruction can occur during sedation.
3. *CNS effects*: Dexmedetomidine decreases cerebral blood flow without significant changes in intracranial hemodynamics.

Caution

Dexmedetomidine's context-sensitive half-time increases considerably with increasing duration of the infusion.

BENZODIAZEPINES

Benzodiazepines are sedative-hypnotics that contain a benzene ring fused with a diazepine ring. The three commonly used benzodiazepines are midazolam (short acting), lorazepam (intermediate acting), and diazepam (long acting).

Midazolam's imidazole ring allows it to be water soluble at low pH.

Diazepam and lorazepam are insoluble in water and therefore are dissolved in propylene glycol which can cause irritation upon injection.

Clinical Uses

1. *Premedication*: Midazolam is the most commonly administered premedication. It is usually given orally in pediatric patients without an intravenous catheter in place. It can also be administered intramuscularly or intranasally. Intranasal administration can be irritating.
2. *Procedural sedation*
3. *Treatment of seizures*: Benzodiazepines all decrease seizure activity and can be used in the treatment of seizures.
4. *Induction of anesthesia:* Infrequent use with the addition of opioids.

Pharmacokinetics

Metabolism

Metabolized by the liver through microsomal oxidation or glucuronide conjugation.

Absorption

Benzodiazepines are administered orally (midazolam 40%, lorazepam/diazepam 90%), intramuscularly, and intravenously.

Distribution

Midazolam is highly lipid soluble, which leads to quick redistribution going from the brain to peripheral inactive sites.

Pharmacodynamics

Benzodiazepines bind to GABA(A) receptor and change the conformation of the GABA receptor causing it to have more affinity for GABA molecules, increasing chloride ions. They have a favorable safety profile with less respiratory and cardiovascular depression when compared to barbiturates and propofol. Benzodiazepines also have a short-acting antagonist (flumazenil) used to reverse sedative effects when needed.

Medication Profile

1. *Cardiovascular effects*: Benzodiazepines can cause peripheral vasodilation with little change in cardiac output. In conjunction with fentanyl they can decrease blood pressure.
2. *Respiratory effects*: They cause a decrease in respiration due to a decrease in response to arterial carbon dioxide.
3. *CNS effects*: Benzodiazepines decrease $CMRO_2$ and cerebral blood flow, but less than barbiturates. They have a ceiling effect and are unable to cause an isoelectric EEG; therefore, they are not used in cerebral protection during focal injuries. They act as antiepileptics and can be used in the treatment of status epilepticus.

Midazolam Dosing

0.3 to 0.5 mg/kg orally (max 10–15 mg).

0.1 mg/kg intravenously.

0.2 mg/kg intranasally/intramuscularly.

Caution

Intravenous induction of general anesthesia takes a much higher dose and is slower than propofol, thiopental, or etomidate. The delayed awakening when compared to other agents makes the use of midazolam or diazepam for induction much less common.

BARBITURATES

Barbiturates used to be the most common intravenous anesthetic drugs prior to the advent of propofol. Barbiturates come from derivatives of barbituric acid. Substitutions at N1, C2, and C5 lead to different properties for each of the drugs in this class. The only intravenous anesthetic commonly used in the United States is methohexital (oxybarbiturate). Barbiturate solutions can precipitate with acidic drugs (non-depolarizing neuromuscular blockers-e.g.-vecuronium, rocuronium, cisatracurium) since they are alkaline with a pH of 10 which in turn can lead to crystallization of intravenous lines. Arterial injection or intravenous infiltration can lead to severe pain and tissue injury.

Clinical Uses

1. *Induction of anesthesia*: The short-acting methohexital can be used for induction of general anesthesia.
2. Total intravenous anesthesia (TIVA).

Pharmacokinetics

Thiopental is highly lipid soluble and its high nonionized fraction leads to rapid uptake in the brain. If there is hypoalbuminemia, hypovolemia, or acidosis, there can be higher concentrations delivered to the brain and heart.

Biotransformation

Hepatic oxidation is the primary route of elimination to inactive water-soluble metabolites which are excreted by the kidneys. The exception to this is phenobarbital which is primarily excreted by renal excretion.

Medication Profile

1. *Cardiovascular effects*: Thiopental tends to cause a reduction in MAP by centrally mediated inhibition of the sympathetic nervous system and direct myocardial inhibition.[27] The reduction in MAP is less than that of propofol.[28] There is vasodilation of the peripheral capacitance vessels due to depression of the medullary vasomotor center. Tachycardia occurs due to reflex response to blood pressure. There may be an exaggerated fall in blood pressure in patients with hypovolemia, congestive heart failure, and beta-blockade.
2. *Respiratory effects*: Depression of the medullary ventilatory center leads to decreased responses to hypercapnia and hypoxia. Barbiturates depress upper airway tone and lead to upper airway obstruction and apnea. Minute ventilation is decreased along with a decrease in tidal volumes and respiratory rate. Thiopental can rarely cause bronchoconstrictive effects (cholinergic nerve stimulation) especially in patients with asthma but methohexital does not share that characteristic.
3. *Cerebral*: Barbiturates decrease cerebral metabolic rate, cerebral blood flow, cerebral blood volume, and intracranial pressure but increase cerebral vasoconstriction. Cerebral perfusion pressure is usually maintained due to a greater reduction of intracranial pressure than mean arterial blood pressure. Barbiturates at higher doses can lead to burst suppression and electrical silence. Barbiturates do not have analgesic properties at induction doses.

Thiopental is mentioned above as one of the representatives of the barbiturate class, but it is NO longer available for use in the United States.

METHOHEXITAL

It is an ultrashort-acting barbiturate with a protein binding of about 70%. It is cleared rapidly by the liver after demethylation and oxidation and

subsequent renal elimination.

Administration: Intravenous, intramuscular, rectal.

Redistribution of methohexital leads to awakening just like thiopental. An induction intravenous dose can lead to reawakening within 5 to10 minutes. It can be given in place of propofol for induction in patients in whom there is possible concern with propofol, eg, mitochondrial disorders, propofol allergy.[29]

Caution

Methohexital potentiates cerebral evoked potentials, decreases seizure threshold, and can cause seizures unlike the other barbiturates.

On IV administration it can cause patients to hiccup, become apneic, and have dystonic movements.

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