Propofol: The Workhorse IV Hypnotic

Propofol is the workhorse IV hypnotic for induction, maintenance, and procedural sedation in modern anesthesia practice. Its extremely rapid onset, short context-sensitive half time, and favorable recovery profile make it central to CRNA practice in the OR, PACU, and ICU. Understanding its pharmacology lets you anticipate hemodynamic and respiratory effects, leverage its neuroprotective and antiemetic properties, and avoid serious complications such as propofol infusion syndrome (PRIS).

Learning Objectives

01

Pharmacological Profile

Understand the onset, duration, and recovery profile of propofol

02

Mechanism of Action

Explain the molecular mechanism of action of propofol and relate it to CNS and systemic effects

03

Pharmacokinetics

Interpret the pharmacokinetic profile of propofol, including context-sensitive half time, and apply it to infusion planning

04

Clinical Dosing

Select appropriate doses and infusion ranges for induction, maintenance, and sedation in different patient populations

05

Safety Management

Anticipate, recognize, and manage adverse effects and toxicities, including PRIS and severe hypotension

Mechanism of Action

Propofol produces hypnosis primarily through potentiation of inhibitory neurotransmission in the central nervous system. It acts as a positive allosteric modulator of the GABA-A receptor, which is the main inhibitory receptor in the brain. By enhancing GABA-mediated chloride influx, propofol increases neuronal hyperpolarization and decreases neuronal excitability to produce hypnosis and sedation.

Primary Action

GABA-A receptor: increases receptor opening probability and/or prolongs channel opening, enhancing inhibitory neurotransmission

Additional Actions

Some inhibition of **NMDA** and **nicotinic** acetylcholine receptors; modulation of **glycine** and other ligand-gated channels

Net CNS Effect

Decreased cortical and subcortical activity, reduced cerebral metabolic rate of oxygen ($CMRO_2$), and hypnotic effect ± amnesia

Clinically, this mechanism explains the profound loss of consciousness, EEG slowing, anticonvulsant properties, and the absence of intrinsic analgesia (does not affect pain pathways or opioid receptors).

Pharmacokinetics

Propofol displays multicompartment kinetics with extremely rapid distribution into the brain followed by redistribution to muscle and fat. Its high clearance and short context-sensitive half time support its use in TIVA and titratable sedation.

1

Onset: 30–45 seconds

After IV bolus (one arm–brain circulation time)

2

Distribution: 2–8 minutes

Rapid decline in plasma concentration due to redistribution accounts for short duration after a single bolus

3

3-Compartment Model

Typically described by a 3-compartment model with a large steady-state volume of distribution

4

Protein Binding: ~95–99%

Mainly to albumin and erythrocytes; only the unbound fraction is pharmacologically active. Decreased plasma protein levels (severe ESRD/ESLD; pregnancy) may lower drug binding and increase the free active fraction which can increase clinical effects

Metabolism & Elimination

Metabolism

- Metabolized by **CYP2B6, UGTHP4, and CYP2C6**
- Extensive hepatic metabolism via conjugation (glucuronidation) and hydroxylation to inactive metabolites
- Significant extrahepatic metabolism, especially in the lungs and possibly kidneys, contributes to high clearance
- There are no changes in elimination in patients with severe cirrhosis due to these extrahepatic sites
- **Clearance:** high (approaching or exceeding hepatic blood flow), which helps maintain short context-sensitive half times for many clinical infusion durations

Elimination

- Primarily renal excretion of inactive metabolites; small amounts in bile
- Less than 1% is excreted unchanged
- **Elimination half-life:** 1-2 hours

Context-Sensitive Half Time

After short to moderate infusions (up to several hours), the context-sensitive half time remains relatively short compared with many other IV agents. This supports smooth wake-up and rapid titration for sedation, but very long, high-dose infusions can still lead to prolonged emergence and metabolic complications.

WHAT IS CONTEXT-SENSITIVE HALF TIME?

The traditional idea of half-life—how long it takes for the concentration of a drug in the body to drop by half—does not always apply well to continuous infusions. When a drug is given continuously, the time it takes to clear from the body depends on how long the infusion has been running. To explain this, the concept of context-sensitive half-time was developed. The word "context" refers to the duration of the infusion. Context-sensitive half-time is the amount of time it takes for the plasma drug concentration to decrease by 50% after stopping an infusion. The longer a drug has been infusing, the more it may accumulate in certain tissues, which can lengthen its time to offset. This concept is explored in more detail in the *Pharmacokinetics* Module.

Pharmacodynamics: System Effects

Propofol's PD profile is dominated by strong CNS depression, significant cardiovascular depression, and potent respiratory depression.

Central Nervous System

- Rapid onset hypnosis ± amnesia, but **no analgesia**
- Decreases $CMRO_2$, cerebral blood flow (CBF), and intracranial pressure (ICP) and cerebral perfusion pressure (CPP) while preserving autoregulation and CO_2 reactivity
- Anticonvulsant properties; increases the seizure threshold (makes it harder for a seizure to occur); can be used for refractory status epilepticus
- Antiemetic effect at low doses (e.g. 10-20 mg), reducing postoperative nausea and vomiting (PONV). TIVA instead of inhaled anesthetics can be used in severe PONV patients

Cardiovascular System

- Decreases systemic vascular resistance via arterial and venous vasodilation
- Direct negative inotropic effect reduces myocardial contractility
- Decreases preload and afterload, with a fall in arterial blood pressure after induction
- Blunts baroreflex, so heart rate may not increase appropriately; bradycardia can occur
- Effects are exaggerated in hypovolemic, elderly, cardiac-compromised patients or the co-administration of other agents like high-dose fentanyl

Respiratory System

- Dose-dependent respiratory depression with decreased tidal volume (↓↓) and respiratory rate (↓)
- **Apnea is common after induction doses**, especially when combined with opioids. Depends on dose, speed of injection and patient characteristics
- Decreased ventilatory response to hypercapnia and hypoxia
- Decreases upper airway reflexes, facilitating LMA insertion and endotracheal intubation with less coughing
- Safe for asthmatic patients (propofol or ketamine are preferred for these patients); minimal bronchodilating effect; respiratory resistance is lower and wheezing is decreased compared to etomidate

Other Systems

- Decreases intraocular pressure, helpful in ophthalmic cases if systemic BP is maintained
- Can cause injection site pain (60% incidence), likely due to activation of nociceptive receptors in the venous endothelium and the emulsion itself
- Long infusions may increase serum triglycerides and lead to lipid overload
- Myoclonus (spontaneous excitatory muscle movements) due to selective disinhibition of subcortical centers
- Antipruritic effect (anti-itching) for patients with opioid-induced pruritus
- Easily crosses the placental barrier when given to a parturient and sedative effects can occur in the neonate. May result in lower APGAR scores if given just prior to delivery

Dosage & Administration

Dosing of propofol must be individualized based on age, comorbidities, hemodynamic status, concomitant drugs, and the desired depth of hypnosis or sedation. Always think in mg/kg for bolus and mcg/kg/min for infusions, and always anticipate the hemodynamic consequences before you inject.

Induction of Anesthesia

Healthy adults (ASA I–II): 1.5–2.5 mg/kg IV bolus

Elderly/compromised: 0.5–1.5 mg/kg, administered slowly in small increments (e.g., 20–40 mg at a time) while monitoring BP and responsiveness

Maintenance (TIVA)

Adults with opioid and adjuncts: Approximately 75–150 mcg/kg/min continuous infusion

Elderly/compromised: Start at the lower end of infusion ranges and titrate carefully

Sedation (MAC/Procedural)

Initial bolus: 0.25–0.5 mg/kg

Infusion: 25–100 mcg/kg/min titrated to effect

Pediatric Dosing

Children require relatively higher induction doses due to higher clearance and volume of distribution

Induction: 2.5 to 3.5 mg/kg IV in healthy children

Maintenance: 100-300 mcg/kg/min for TIVA, adjusted to response

30s

Onset of Hypnosis

60-90s

Peak Effect

5-10min

Duration of Single Bolus

Depending on dose and patient factors

Practical Administration Tips

- Use a large vein in the forearm or antecubital fossa to reduce injection pain
- Small bolus of lidocaine (20–50 mg) IV immediately before. Some practitioners will mix lidocaine with propofol but this can cause large lipid droplets to occur in the syringe
- Strict aseptic technique, with infusion lines and vials discarded within recommended time limits to reduce infection risk

Clinical Uses

Propofol's versatility spans induction, maintenance, and sedation across multiple settings.

Induction of General Anesthesia

For nearly all types of surgery

Maintenance of Anesthesia

As part of TIVA, often combined with short-acting opioids and adjuncts

Monitored Anesthesia Care (MAC)

Short procedures including endoscopy, cardioversion, TEE, minor surgical interventions

Out of OR Anesthesia

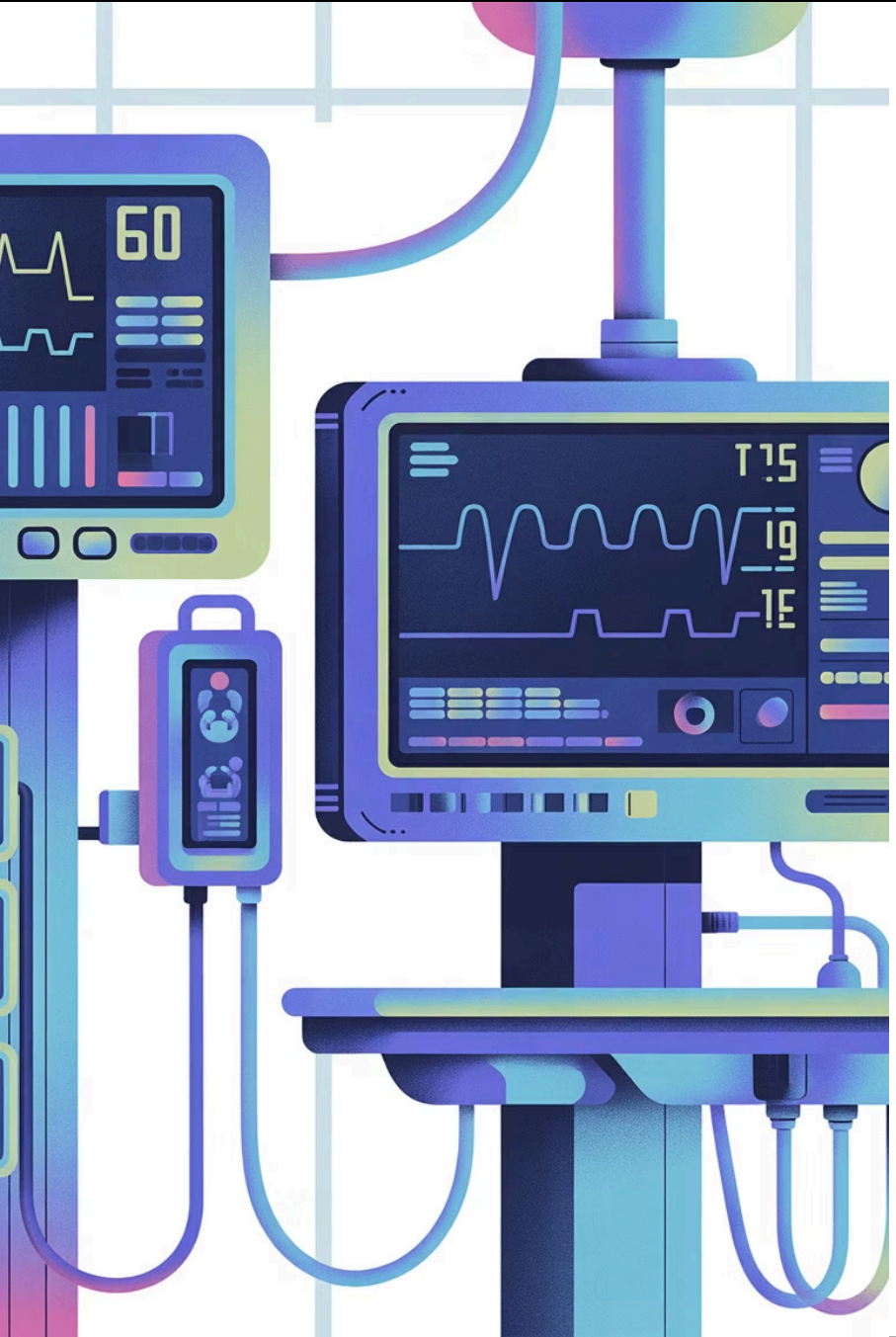
EP lab, IR, CT/MRI procedures

ICU Sedation

For ventilated patients, usually time-limited and carefully monitored for PRIS and hypertriglyceridemia

Adjunct Therapy

PONV prevention/treatment and reduction of opioid-induced pruritus at low doses



Common Adverse Effects

Hypotension

From vasodilation and myocardial depression

Respiratory Depression

Apnea or significant respiratory depression, especially when combined with opioids

Injection Pain

Especially in small hand veins

Myoclonic Movements

Transient myoclonic movements or opisthotonus-like posturing (usually self-limited)

Less Common or Benign Effects

- Mild bradycardia without hypotension
- Green or pink discoloration of urine due to metabolites
- Hypertriglyceridemia with prolonged or high-dose infusions

Propofol Infusion Syndrome (PRIS)

Rare but potentially fatal syndrome associated with prolonged high-dose infusions, especially in critically ill patients and children.

Mechanism

Propofol infusion syndrome is believed to result from **impaired mitochondrial oxidative phosphorylation** and inhibition of **acylcarnitine transferase**, which prevents normal fatty acid transport into mitochondria. This disruption reduces ATP production and promotes a shift to anaerobic metabolism, leading to metabolic acidosis, cardiac failure, and rhabdomyolysis.

Risk Pattern

Doses **≥4 mg/kg/hr (≥67 micrograms/kg/min)** for longer than 24–48 hours, especially with concomitant administration of catecholamines and corticosteroids

Clinical Features

- Metabolic (lactic) acidosis
- Rhabdomyolysis and markedly elevated CK
- Hyperkalemia
- Bradycardia, hypotension, cardiac failure, arrhythmias, and cardiovascular collapse
- Green crystalized urine
- Renal failure, hepatomegaly, elevated LFTs, and lipidemia
- Pulmonary edema

Immediate Discontinuation

Stop propofol immediately

Alternative Sedation

Switch to alternative sedation

Supportive Therapy

Aggressive supportive therapy and organ support: improve gas exchange, cardiac pacing for bradycardia, PDE inhibitors, glucagon, ECMO, CRRT

Allergic Reactions & Infection Risk

Allergic and Anaphylactoid Reactions

- True IgE-mediated allergy is rare but possible
- Reactions may involve hypotension, bronchospasm, and rash or full anaphylaxis

Infection Risk

- The lipid emulsion supports microbial growth
- Contaminated propofol has been implicated in clusters of postoperative infection
- This is preventable with strict aseptic technique, adherence to vial and line change intervals, and avoiding multi-patient use of opened vials

Drug Interactions

- Potent synergy with opioids, benzodiazepines, volatile anesthetics, and other CNS depressants for both hypnosis and respiratory depression
- Concurrent antihypertensives, beta blockers, and vasodilators increase risk of hypotension and bradycardia
- Enzyme-inducing drugs may enhance clearance, increasing infusion requirements, whereas severe hepatic or cardiac failure may reduce clearance

CAN PATIENTS WITH EGG, SOY OR PEANUT ALLERGY HAVE PROPOFOL?

Although propofol contains egg lecithin and soybean oil, there is little evidence that patients with egg, soy, or peanut allergy are at increased risk when receiving propofol. Egg-allergic patients typically react to egg-white proteins, not the egg-yolk lecithin found in propofol, and refined soy oil used in the emulsion has allergenic proteins removed. Similarly, the concern about peanut allergy is based on theoretical cross-reactivity among legumes, but no data support avoiding propofol in peanut-allergic patients. Retrospective data show safe administration in most egg-allergic individuals, with caution only suggested for patients with a history of true egg anaphylaxis. Overall, propofol can generally be used safely in patients with egg, soybean, or peanut allergies.

Citation: Nagelhout (7th ed.), Chapter 9, Page 105

Contraindications & Precautions

Absolute and relative contraindications guide your decision to choose propofol or to modify dosing.

Absolute or Strong Contraindications

- Documented anaphylaxis or serious hypersensitivity to propofol or to components of the formulation
- History of PRIS related to propofol in the same patient
- Formulations containing sodium metabisulfite in sulfite-sensitive patients (more common in asthma patients)
- Disorder of lipid metabolism

Egg and Soy Allergy Considerations

Older formulations led to concern about egg and soy allergies due to egg lecithin and soybean oil in the emulsion. Current evidence suggests that many patients with food allergies to egg or soy tolerate propofol safely, but institutional policies vary and some clinicians still exercise caution in patients with severe anaphylactic food allergy.

Relative Contraindications / Major Precautions

- Marked hypovolemia, cardiogenic shock, or severe systolic dysfunction
- Severe valvular disease, especially aortic stenosis, where sudden afterload drops can be dangerous
- Severe COPD, OSA, or baseline respiratory depression, given high risk of apnea
- Severe hyperlipidemia, or pancreatitis when prolonged infusion is planned
- Pediatrics, particularly for prolonged ICU sedation, due to higher relative PRIS risk
- Pregnancy: crosses the placenta and may cause neonatal depression with induction; brief use for induction is common, but continuous maternal sedation requires careful risk–benefit assessment
- Pediatric patients with cardiac mitochondrial disease may be affected by large doses. Propofol inhibits ATP synthesis (mitochondrial acylcarnitine transferase & oxidative phosphorylation)

Anesthesia Considerations & Clinical Pearls

Propofol is extremely forgiving in healthy adults but can be hazardous in fragile patients. Your practice must be proactive about hemodynamics, airway, and infusion safety.

Hemodynamic Management

- Pre-induction assessment for hypovolemia, sepsis, and cardiac disease is essential
- Consider fluid loading and ready vasopressor support for high-risk patients
- Use reduced doses and slow titration rather than a full rapid bolus in elderly, hypovolemic, or cardiac-compromised patients

Ventilation and Airway

- Be prepared for immediate apnea after induction, especially when combined with opioids
- Ensure functional suction, oxygen source, and airway adjuncts are available before giving the induction dose
- For MAC and procedural sedation, maintain verbal contact, use capnography, and titrate slowly to avoid loss of airway reflexes unless you are prepared to manage the airway

Neurosurgical and Neuro-Critical Care

- Propofol is favorable for controlling ICP and $CMRO_2$ when MAP is maintained
- Common agent for neuroanesthesia and neuro-ICU sedation
- Avoid excessive hypotension that might compromise cerebral perfusion pressure

Monitoring Prolonged Infusions

- Monitor serum triglycerides and signs of metabolic acidosis for ICU patients on longer propofol infusions
- Avoid exceeding high-risk dose thresholds for prolonged periods
- Use alternative sedatives if deep sedation is needed for days

Managing Injection Pain

- Use a large forearm or antecubital vein when possible
- A small IV lidocaine bolus (20–40 mg) with or just before propofol reduces pain
- Slow injection. Make sure the BP cuff doesn't inflate at the same time if on the same side as the IV

Clinical Scenarios

Scenario 1: Induction of Healthy vs Fragile Patients

Question: What would your bolus dose be for a 70 kg patient that is an ASA 1 24-year-old patient vs. a 70 kg 89-year-old patient?

ASA 1, 24-year-old (70 kg): Standard induction dose of 1.5–2.5 mg/kg = approximately 105–175 mg IV bolus. You can push this relatively quickly and expect rapid onset with minimal hemodynamic compromise in a healthy young adult.

ASA 3-4, 89-year-old (70 kg): Reduced dose of 0.5–1.5 mg/kg = approximately 35–105 mg, administered slowly in 20–40 mg increments while continuously monitoring blood pressure and level of consciousness. Consider having vasopressor support ready. The elderly patient has decreased cardiac reserve, possible hypovolemia, and altered pharmacokinetics requiring careful titration.

Scenario 2: Monitored Anesthesia Care

Question: How do you bolus and start your infusion for a MAC case?

Approach: For a typical MAC case (e.g., colonoscopy, minor procedure), start with a small bolus of 0.25–0.5 mg/kg (approximately 20–40 mg for a 70 kg patient) to achieve initial sedation. Assess the patient's response over 1-2 minutes. Then initiate a continuous infusion at 25–75 mcg/kg/min, titrating upward as needed based on patient comfort, procedure requirements, and vital signs. Maintain verbal contact when possible and use capnography to monitor respiratory status. Be prepared to support the airway if sedation deepens unexpectedly.

TIP: If an airway is needed but they are reacting to the insertion, you may need to deepen them further (and worsen their obstruction) just to the the airway in then decreasing the sedation once they are accustomed to the device.

Scenario 3: Out of OR Anesthesia - Endoscopy vs TEE

Question: How do you bolus your propofol for various out of OR procedures?

Endoscopy (e.g. EGD): These procedures typically require deep sedation. Consider a slightly larger initial bolus of 1-1.5 mg/kg (75-150 mg for a 75 kg patient), then start a moderate infusion at 75-150 mcg/kg/min. You want a very short period of apnea (15-30 seconds) while the scope is being inserted

TEE (transesophageal echocardiography): TEE often requires moderate sedation . Use a small initial bolus of 20–40 mg (0.25–0.5 mg/kg), followed by a high infusion of 100-200 mcg/kg/min then titrate down to effect. Monitor closely for apnea and hypotension, especially in patients with cardiac disease. Have airway equipment immediately available and be prepared to provide positive pressure ventilation if needed.

Key Takeaways

Formulation & Pharmacology

Propofol is a sedative-hypnotic in a lipid emulsion, with rapid onset and short context-sensitive half time that support its use for induction, maintenance, and sedation.

Mechanism of Action

It enhances GABA-A activity, producing hypnosis and amnesia but no intrinsic analgesia, while lowering $CMRO_2$, CBF, and ICP.

Major Adverse Effects

Major adverse effects are dose-dependent hypotension and respiratory depression, often exacerbated by hypovolemia, comorbidities, and concurrent CNS depressants.

Dosing Guidelines

Typical adult induction dosing is 1.5–2.5 mg/kg, with lower and more carefully titrated dosing for elderly and hemodynamically unstable patients; TIVA and sedation use weight-based infusions titrated to clinical effect.

PRIS Warning

Propofol infusion syndrome is a rare but life-threatening complication of prolonged high-dose infusions, especially in critically ill patients, and requires high suspicion and immediate discontinuation of the drug.

Infection Prevention

Strict aseptic technique and adherence to discard times are mandatory because the lipid emulsion supports bacterial growth.

References

1. Nagelhout JJ, Elisha S, Heiner JS, eds. *Nurse Anesthesia*. 7th ed. Elsevier; 2022.
2. Flood P, Rathmell JP, Urman RD, eds. *Stoelting's Pharmacology & Physiology in Anesthetic Practice*. 6th ed. Wolters Kluwer; 2021.
3. Katzung BG, ed. *Basic & Clinical Pharmacology*. 14th ed. McGraw-Hill Education; 2018.

This presentation provides a comprehensive overview of propofol pharmacology for CRNA practice. Always consult current clinical guidelines, institutional protocols, and drug references for the most up-to-date information and specific patient care decisions.