



The Pharmacology Of Intravenous Anesthetic Induction Agents: A Primer

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Intravenous anesthetics are used widely for induction and maintenance of general anesthesia, and for moderate to deep sedation. Various anesthetic drugs are available, each with unique attributes that dictate suitability for specific applications. This review covers basic pharmacology of the IV induction agents relevant to their optimal clinical utilization.

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History and Principles

Whereas inhaled anesthetics are useful for the induction of anesthesia, particularly in the absence of IV access as occurs commonly in pediatric anesthesia, IV anesthetics have become the primary agents for the induction of general anesthesia. The development of IV anesthetics followed the late 19th-century introduction of hollow needles, syringes, and IV fluid therapy, which provided direct access to the bloodstream for the rapid administration of drugs. These innovations paved the way for the introduction of rapidly acting IV anesthetics. Prior to the development of IV anesthetics, induction of general anesthesia required inhalation of gases and vapors (including nitrous oxide, ether, and chloroform) that often resulted in slow, unpleasant, and occasionally dangerous inductions.

Hexobarbital, the first ultrashort-acting barbiturate—and considered to be the first successful and widely used IV anesthetic—was introduced by Weese in Germany in 1932.¹ This was followed in 1935 by the introduction of thiopental by Lundy² in Minnesota and Waters³ in Wisconsin. Thiopental became widely accepted, largely because of the lack of excitatory myoclonic movements that were seen with hexobarbital; 75 years later, thiopental is still in use.

In 1926, Lundy introduced the concept of “balanced anesthesia” to describe a polypharmaceutical combination of premedication, local anesthesia, and general anesthesia to reduce the dose of each agent and thereby improve safety.

This concept has evolved to include the combination of various IV drugs including hypnotics, analgesics, sedatives, and muscle relaxants, often with inhaled anesthetics—a practice that is widely used today. Lundy also recognized the disadvantages of IV barbiturates (in particular, marked cardiovascular depression) that led to continuing efforts to find other induction agents with reduced nonhypnotic side effects. In the absence of an ideal anesthetic devoid of significant side effects, balanced anesthesia allows dose reductions in an effort to minimize toxicity. Indeed, Paracelsus (1493-1541), the “founding father” of toxicology, anticipated the practice of anesthesia with his claim that “All things are poison and nothing is without poison; only the dose permits something not to be poisonous.”

Properties of the Ideal Induction Agent

The goal of inducing anesthesia without significant side effects continues to occupy the minds of anesthetic pharmacologists and clinicians in their efforts to improve the safe practice of anesthesia. General anesthesia, a generalized depression of the central nervous system (CNS), includes amnesia, loss of consciousness (hypnosis), and immobility, often associated with

analgesia and suppression of autonomic reflexes. Properties of the ideal IV anesthetic capable of rapidly inducing hypnosis are delineated in Table 1; no currently available drug achieves these criteria. Indeed, the prospect of developing a single drug that meets these criteria is daunting.

The recognition that general anesthesia is a composite of neuropharmacologic actions involving discrete dose-related actions on multiple receptors located in discreet regions of the CNS⁴ has coincided with a shift toward the titration of individual drugs to target each action/receptor to different degrees (in contrast to the fixed ratios of effects provided by a single drug). Although the mechanisms explaining each component of general anesthesia are unknown, current concepts suggest that amnesia involves actions on synaptic plasticity in the hippocampus, unconsciousness involves disruption of thalamocortical interactions, and immobility involves depression of spinal reflexes.⁵ Progress in neuroscience research and understanding the neuropharmacology of general anesthetics will facilitate further developments in the rational use of existing anesthetics and development of new anesthetics that selectively target one or more of these distinct pathways.

Mechanisms of Action

The primary targets of IV anesthetic agents are ionotropic (ion channel-linked) receptors for the endogenous neurotransmitters glutamate, the principal excitatory transmitter, or γ -aminobutyric acid (GABA), the principal inhibitory transmitter. The GABA_A receptor is a member of the family of ligand-gated ion channels that includes the nicotinic acetylcholine, glycine, and 5-HT₃ serotonin receptors. GABA_A receptors conduct chloride and bicarbonate anions to hyperpolarize the membrane of mature neurons, and are the primary targets for the anesthetic effects (sedation, anxiolysis, hypnosis, amnesia) of all IV anesthetics and sedatives, except ketamine.⁵ Advances in molecular biology and genetic engineering have in recent years allowed identification of the structural requirements and GABA_A receptor subunit specificities for the actions of several IV anesthetic drugs.

Ionotropic glutamate receptors are classified as either *N*-methyl-D-aspartate (NMDA) or non-NMDA types. The NMDA-type glutamate receptor conducts sodium and calcium cations, which depolarize the neuronal membrane and activate multiple intracellular signaling pathways involved in learning and memory, and under pathologic conditions mediate excitotoxic neuronal damage. Noncompetitive blockade of NMDA receptors is the primary mechanism for the dissociative anesthetic ketamine.

Both GABA_A receptor potentiation and NMDA receptor blockade can lead to neurodegeneration and neurocognitive deficits in the developing nervous system in animal models. These findings have led to close scrutiny of anesthetics for possible neurodevelopmental effects in humans.

Table 1. Properties of the Ideal IV Anesthetic Agent

Pharmacodynamic/pharmacokinetic properties
Causes hypnosis and amnesia
Rapid onset (time of one arm-brain circulation)
Rapid metabolism to inactive metabolites
Minimal cardiovascular and respiratory depression
No histamine release or hypersensitivity reactions
Nontoxic, nonmutagenic, noncarcinogenic
No untoward neurologic effects, such as seizures, myoclonus, antanalgesia, neurotoxicity
Other beneficial effects: analgesic, antiemetic, neuroprotection, cardioprotection
Pharmacokinetic-based models to guide accurate dosing
Ability to continuously monitor delivery
Physicochemical properties
Water soluble
Stable formulation, nonpyrogenic
Nonirritating; painless on IV injection
Small volume needed for induction
Inexpensive to prepare and formulate
Antimicrobial preparation

Pharmacokinetic Principles

Appropriate use of IV anesthetics requires an understanding of their pharmacokinetic and pharmacodynamic properties.⁶ The rapid onset and short duration of action of all IV induction anesthetics described below can be explained by their pharmacokinetic properties. These small aromatic or heterocyclic compounds are highly lipophilic, which is a key factor in determining their pharmacokinetic behavior. Following rapid-bolus IV administration, these agents distribute rapidly within the intravascular space and to the highly perfused (vessel-rich) tissues (Figure) that include the brain and spinal cord; the result is a loss of consciousness within the time of one arm-brain circulation (about 20 seconds, depending on the cardiac output). Subsequently, concentrations in the CNS fall rapidly as the drugs redistribute to muscle and, to a much lesser extent, fat. This redistribution is responsible for the short duration of a single-bolus injection. Throughout this period, small but substantial amounts of drug are removed (cleared) by the liver and metabolized.

The action of a single-bolus injection is terminated primarily by redistribution to the much larger compartments that include lean vessel-rich tissues such as muscle. Therefore, the appropriate dose for induction should be calculated based on lean body mass. The high partition coefficient of fat to plasma of the lipophilic anesthetics has little effect on their initial distribution because of the poor perfusion of adipose tissue; however, it provides a large reservoir for delayed drug uptake with prolonged administration.

The redistribution kinetics of these lipophilic drugs leads to substantial uptake into multiple compartments, and this has important implications for offset. Pharmacokinetic modeling of these drugs led to the concept of context-sensitive half time (time to achieve a 50% reduction in concentration after stopping a continuous infusion) to describe the accumulation of lipophilic drugs in more slowly equilibrating compartments that require longer times for elimination. These important effects—that vary considerably between specific drugs (thiopental >> ketamine, propofol > etomidate)—become increasingly evident with prolonged IV infusions, or large cumulative doses. A short duration of action depends on redistribution, which is saturable and limited by the mass of lean tissue. Pharmacokinetic modeling has led to pharmacokinetic/pharmacodynamic-based computer-driven pumps that target effect-site concentrations to improve control of IV drug administration.

IV General Anesthetics

A variety of chemically unrelated, injectable anesthetic drugs of diverse molecular structure are available with differing pharmacologic profiles and side effects. Appropriate drugs are selected based on the anesthetic goals for each patient as dictated by the procedure to be performed and patient-specific pathophysiologic considerations.

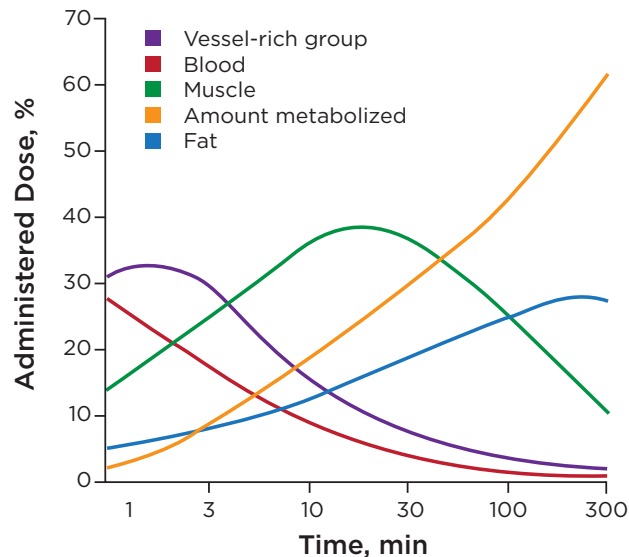


Figure. Uptake and redistribution of an IV bolus of thiopental.

The amount of thiopental in the blood rapidly decreases as drug moves from blood to body tissues. The time to peak tissue levels is a direct function of the tissue capacity for barbiturate uptake relative to blood flow. Redistribution between tissues and metabolism results in removal of tissue contents. Similar pharmacokinetic mechanisms apply to the other IV anesthetics.

From Saidman LJ. Uptake, distribution and elimination of barbiturates. In: Eger EI, ed. *Anesthetic Uptake and Action*. Baltimore, MD: Williams and Wilkins; 1974:264-284. Reprinted with permission.

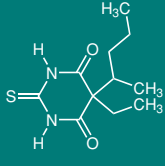
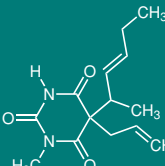
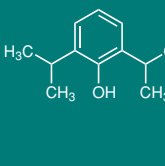
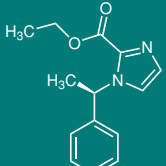
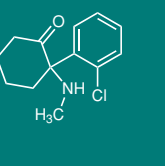
BARBITURATES

Physicochemical Properties

The barbiturates (Table 2) are weak acids that are poorly soluble in water at neutral pH. The most commonly used anesthetic barbiturates, which include thiopental, thiamylal, and methohexital, are formulated as racemic mixtures of their water-soluble sodium salts, and use sodium carbonate to maintain an alkaline pH range of 10 to 11. The alkalinity of these solutions can result in severe tissue damage from extravascular or intra-arterial injections, and will induce precipitation of drugs that are weak bases (eg, vecuronium, rocuronium, lidocaine, labetalol, and morphine).

Barbiturates are classified broadly as thiobarbiturates (sulfur at carbon-2 [C₂]: thiopental, thiamylal) and oxybarbiturates (oxygen at C₂: methohexital). The substitution of sulfur for oxygen at C₂ increases lipophilicity, which results in increased potency, more rapid onset, and shorter duration of action. Alkylation of nitrogen-1 (N₁) also increases lipophilicity and thereby speeds onset, but increases excitatory side effects—as seen with methohexital, a methylated oxybarbiturate.

Table 2. Physicochemical and Pharmacokinetic Properties of Anesthetic Induction Agents

	Thiopental 	Methohexital 	Propofol 	Etomidate 	Ketamine 	
Water solubility	Yes (sodium salt)	Yes (sodium salt)	No	No	Yes	
pK _a	7.6	7.9	11	4.2	7.5	
Volume of distribution (L/kg)	2.4	2.4	4.6	5.4	3	
Clearance (mL/min/kg)	3.4	11	25	21	19	
Protein binding, %	80	85	98	75	12	
Induction dose (mg/kg IV)	Adult	2.5-4.5	1-1.5	1.5-2.5	0.2-0.4 (6-7 PR)	0.5-2 (4-6 IM)
	Children	5-6	1-2 (30 PR)	2-3		
	Infants	7-8	2-3	3-4.5		
Active metabolites	No	No	No	No	Yes (minimal)	

IM, intramuscular; PR, per rectum

Perouansky MA, Hemmings HC Jr. Intravenous anesthetic agents. In: Hemmings HC Jr, Hopkins PM, eds. *Foundations of Anesthesia*. 2nd ed. Philadelphia, PA: Elsevier; 2006:297. Modified and reprinted with permission.

A severe shortage of thiopental caused by manufacturing issues occurred in 2009 and has continued in 2010. A simultaneous shortage of propofol has meant that the choice of induction agents often is dictated by availability rather than pharmacology.

Use for Induction

Considerable information is available concerning the clinical effects of barbiturates, given their widespread use for 75 years.⁷ Until the 1990s, barbiturates were the most popular anesthetic induction agents. Propofol largely has supplanted barbiturates, especially in ambulatory anesthesia.

Following IV injection, thiopental, thiamylal, and methohexital induce anesthesia lasting 4 to 8 minutes. Dose requirements are reduced by pharmacodynamic interactions (opioid, α_2 -adrenergic agonist, benzodiazepine premedication, or acute ethanol intoxication), and by pharmacokinetic effects (anemia, hypoproteinemia, low cardiac output, or shock). Reduced cardiac output prolongs induction, causing higher peak drug levels in the blood, thus decreasing the dose requirement. Methohexital is about 3 times more potent than thiopental, which is slightly less potent than thiamylal. Pain on IV injection is rare with thiopental, but more common with methohexital.

Systemic Effects

Cardiovascular: The principal hemodynamic effects of barbiturates in healthy, normovolemic patients are transient reductions in systemic arterial pressure and cardiac output, increased heart rate, and minimal change in systemic vascular resistance (Table 3). Hypotension results from marked venodilation, with peripheral pooling of blood and decreased cardiac filling pressure that reduces cardiac output.

Usual doses of thiopental produce minimal myocardial depression, although higher doses reduce contractility. An increased heart rate, which is more marked with methohexital than with thiopental, results from baroreceptor reflex-mediated sympathetic stimulation and can partially compensate for the vasodilation and negative inotropic effects.

Thiopental and thiamylal, but not methohexital, can induce histamine release, which exacerbates their cardiovascular effects. The hypotensive effects of barbiturates are more pronounced in patients with hypertension, hypovolemia, valvular or ischemic heart disease, or shock. The hemodynamic effects can be particularly deleterious in conditions that are worsened by reduced preload or tachycardia—such as myocardial ischemia, congestive heart failure, pericardial

tamponade, and valvular heart disease.

Respiratory: Anesthetic barbiturates are potent central respiratory depressants. They produce dose-dependent decreases in both minute volume and tidal volume. The respiratory rate can increase slightly at lower doses. At higher doses, the respiratory rate is reduced, ultimately leading to apnea. The medullary center ventilatory responses to both hypercapnia and hypoxia are depressed. Usual induction doses of barbiturates do not depress laryngeal and tracheal reflexes.

Neurologic: Barbiturates are potent anticonvulsants, providing brain protection and reducing intracranial pressure in patients with intracranial hypertension. Thiopental is the only agent shown to produce long-term cerebral protection in focal ischemia; however, it is ineffective in cerebral resuscitation after global ischemia (cardiac arrest). Like other general anesthetics, it is effective in short-term neuroprotection but improved long-term outcome is difficult to show.

Undesirable CNS effects include paradoxical excitement with small doses (possibly owing to central disinhibition or an analgesic effect in the presence of pain) and involuntary skeletal muscle movements (myoclonus, a central excitatory effect). Methohexital can trigger seizure foci in susceptible patients, an effect used to advantage in epilepsy surgery and for anesthesia in electroconvulsive therapy. Significant effects on neuromuscular transmission or skeletal muscle function do not occur.

Other: Stimulation of the mitochondrial enzyme δ -aminolevulinic acid reductase, the rate-limiting enzyme in porphyrin biosynthesis, can exacerbate acute intermittent porphyria in susceptible patients; therefore, barbiturates are contraindicated in porphyria. Unlike etomidate, barbiturates do not suppress adrenocortical stimulation. Thiopental can be used safely for anesthetic induction in cesarean deliveries; however, doses greater than 8 mg/kg can cause neonatal depression as a result of placental transfer of the drug.

PROPOFOL

Physicochemical Properties

Propofol (2,6-di-isopropylphenol) is an achiral, lipophilic, sterically hindered substituted phenol (Table 2). A very weak acid, it is nonionized at physiologic pH, and very insoluble in water. Because of its poor water solubility, propofol is formulated at 1% (v/v) in an oil/water emulsion containing 10% soybean oil, 1.2% egg lecithin, and 2.25% glycerol (as an osmotic agent) with a pH range of 6.0 to 8.5. The emulsion is an excellent medium for microbial growth, so care must be taken to avoid contamination.

Current formulations include the metal chelator EDTA (Diprivan, AstraZeneca) and benzyl alcohol/sodium benzoate (Hospira) to impede microbial growth. (A third formulation is no longer in production.) A severe shortage of propofol occurred during 2009 and 2010 following a recall of several lots found to contain particulate matter (Hospira) or due to possible microbial

contamination (Teva). This led the FDA to approve the temporary importation of preservative-free propofol (Propoven, APP Pharmaceuticals) to alleviate the shortage.

Fospropofol (Lusedra; Eisai, Inc), a water-soluble methylphosphorylated pro-drug derivative of propofol, which is metabolized to propofol, recently was introduced for moderate IV sedation. However, its slow onset and recovery profile severely limit its usefulness for rapid induction of general anesthesia.

Use for Induction

Rapid redistribution and hepatic elimination result in a rapid return to consciousness with minimal residual effects after typical IV induction doses. Propofol's pharmacokinetic properties and a low incidence of nausea and vomiting make it particularly useful for short procedures and ambulatory surgery.⁸ Propofol's rapid clearance and short context-sensitive half time also make it useful for maintenance of anesthesia by continuous infusion without significant cumulative effects; plasma concentrations decrease rapidly when the infusion is terminated.

Infusion of propofol can be combined with infusions of other short-acting drugs (eg, remifentanyl [Ultiva, Bioniche Pharma], alfentanil, sufentanil) for total IV anesthesia. Propofol exhibits pharmacodynamic synergism with benzodiazepines and opioids (hypnotic effect), which allows a reduction in the propofol dose for induction. Pain on injection is a significant problem with IV propofol. This can be minimized by using larger veins with a rapid carrier infusion rate, by injecting lidocaine before or with the propofol emulsion, or by injecting a synthetic opioid before propofol. Formulation in medium-chain rather than long-chain triglycerides also reduces pain on injection.

Systemic Effects

Cardiovascular: The IV injection of propofol in healthy patients decreases arterial blood pressure by 15% to 40%; reductions in blood pressure generally are greater than with equipotent doses of thiopental (Table 3). Propofol produces significant reductions in systemic vascular resistance and cardiac filling, with little or no direct effect on myocardial contractility. The effect of propofol on heart rate is variable, but in general it produces less tachycardia than thiopental. Propofol resets baroreceptor reflex control of heart rate, resulting in an unchanged heart rate despite reduction of blood pressure; this explains, in part, the greater hypotensive effect of propofol compared with thiopental. The hemodynamic effects of propofol are magnified in hypovolemic or elderly patients and in patients with impaired left ventricular function. These patients benefit from a reduced dose of propofol in conjunction with slow administration and an IV opioid or benzodiazepine to reduce the propofol requirement and minimize cardiovascular effects.

Patients should be adequately hydrated before induction to minimize hypotension. The pressor response to tracheal intubation is less marked and intubating conditions

Table 3. Cardiovascular, Respiratory, and CNS Effects of 4 IV Anesthetics

Function	Thiopental	Propofol	Etomidate	Ketamine
Heart rate	↑	-/↓	-	↑↑
Systemic vascular resistance	-/↓	↓↓	-	-/↑
Cardiac contractility	-/↓	↓	-	↑
Histamine release	↑	-/↑	-	-
Mean arterial pressure	↓	↓↓	-	↑
Respiration	↓↓	↓↓	-/↓	-/↓
Cerebral blood flow	↓	↓	↓	↑
CMRO ₂	↓	↓	↓	-/↑
Intracranial pressure	↓	↓	↓	-/↑
CNS excitation	-/+	+	++	++

CMRO₂, cerebral metabolic rate of oxygen consumption; CNS, central nervous system

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are better due to enhanced relaxation of intrinsic muscle with propofol, compared with barbiturates.

Propofol, in combination with lidocaine and a short-acting opioid (remifentanyl or alfentanil) is particularly useful for tracheal intubation without neuromuscular blockers. Propofol produces a minimal increase in plasma histamine levels. Propofol is not arrhythmogenic and does not sensitize the heart to catecholamines.

Respiratory: Propofol is a potent respiratory depressant and often produces an apneic period of 30 to 60 seconds following a normal induction dose. Hiccough, cough, and laryngospasm are less common than with barbiturates, possibly because of greater depression of laryngeal reflexes. Propofol also causes bronchodilation—in contrast to thiopental and etomidate—which makes it a useful agent for patients with asthma.

Neurologic: Propofol acts as an anticonvulsant and can be used for treating refractory epilepsy (although dystonic movements sometimes are confused with seizure activity). With propofol, excitatory phenomena such as tremor, hypertonus, opisthotonos, and spontaneous or dystonic movements can occur with induction or at emergence from anesthesia. Although propofol can produce electroencephalographic (EEG) burst suppression, it has not been demonstrated to be neuroprotective in clinical practice. Propofol is not likely to induce EEG seizure activity in healthy individuals, but can be epileptogenic in patients who have a seizure disorder. Propofol can shorten the duration of convulsions after electroconvulsive therapy, which can be a therapeutic disadvantage.

Other: Propofol has significant antiemetic activity, even at subanesthetic doses. It also is an effective antipruritic and can be used to relieve pruritus associated

with neuraxial opioids. Propofol is more effective in reducing intraocular pressure than thiopental or etomidate. As with other IV anesthetics, propofol does not trigger malignant hyperthermia. Propofol increases the activity of γ -aminolevulinic acid reductase and is potentially porphyrinogenic; its use has been described in patients with acute intermittent porphyria without producing a porphyric attack, however. Propofol has no direct effect on neuromuscular transmission, nor are there significant interactions between propofol and neuromuscular blocking agents. Propofol has been used successfully in pregnancy and obstetrics, but can cause neonatal depression after prolonged infusion.

As propofol gained acceptance for use as a sedative in intensive care units, reports appeared of adverse reactions, some of them fatal. The constellation of symptoms (metabolic acidosis, lipemic plasma, myocardial failure, hepatomegaly, rhabdomyolysis) was characteristic enough to be described as propofol infusion syndrome. The underlying pathophysiology is not clearly understood.

Both pharmacologic and clinical evidence support the abuse potential of propofol, which produces both pleasurable and euphoric effects with rapid recovery. In contrast to barbiturates, it is not currently regulated as a controlled substance in the United States.

ETOMIDATE

Physicochemical Properties

Etomidate is a carboxylated imidazole derivative (Table 2). A weak base, it is poorly water soluble and currently formulated as a hyperosmotic solution in 35% propylene glycol. Etomidate is prepared as the pharmacologically active *R*(+) stereoisomer.

Use for Induction

A niche has been found for etomidate as an induction agent with fewer cardiovascular and respiratory depressant actions than thiopental.⁹ It is particularly useful for induction in patients with impaired ventricular function or cardiac tamponade, and in cases of hypovolemia. Etomidate is remarkable for its relative lack of cardiovascular effects (Table 3), which has led to its frequent use for tracheal intubation in the emergency room. In healthy individuals or in patients with mild cardiovascular disease, etomidate has minimal effects on heart rate, stroke volume, cardiac output, and ventricular filling pressures. Although arterial blood pressure is minimally affected, it may decrease by up to 20% in patients with valvular heart disease. Pain on injection is common; the use of large veins, a rapid carrier infusion, or opioid premedication decreases the incidence.

Systemic Effects

Cardiovascular: Hemodynamic stability with etomidate results from reduced effects on the sympathetic nervous system and baroreceptor reflex responses. Etomidate produces a smaller change in the supply and demand of myocardial oxygen than does thiopental or ketamine. Etomidate also has a negative inotropic effect that is 2 times lower than an equianesthetic dose of thiopental. Etomidate does not evoke histamine release and is associated with a low incidence of hypersensitivity reactions.

Respiratory: Etomidate causes less respiratory depression than barbiturates. In most patients, minute ventilation and tidal volume are decreased, whereas respiratory rate is increased. Transient apnea can develop, especially in geriatric patients. Etomidate depresses the sensitivity of the medullary respiratory center to carbon dioxide, but ventilation is usually greater at a given P_{aCO_2} than with barbiturates.

Neurologic: Etomidate has effects on the CNS similar to those of barbiturates. Etomidate also decreases the cerebral metabolic rate of oxygen consumption ($CMRO_2$) and cerebral blood flow, and reduces elevated intracranial pressure without reducing arterial blood pressure or cerebral perfusion pressure; this results in an increase in the supply-demand ratio for cerebral oxygen. These properties make etomidate attractive for use in neurosurgical procedures. However, its inhibition of nitric oxide limits its neuroprotective potential in animal models of stroke. Although it has been used to control status epilepticus, etomidate also can activate seizure foci, a property that can be used to facilitate intraoperative localization. Etomidate can precipitate generalized seizure activity in patients with epilepsy, and it does not inhibit evoked seizures in patients undergoing electroconvulsive therapy.

Induction is accompanied by a high incidence (>80% of unpremedicated patients) of excitatory phenomena, including spontaneous muscle movement, hypertonus, and myoclonus. Although such effects can resemble seizure activity, they are associated with epileptiform EEG activity in approximately 20% of patients, probably

a result of disinhibition of subcortical extrapyramidal pathways. The incidence of myoclonus associated with etomidate is reduced by prior therapy with opioids or benzodiazepines.

Other: Etomidate directly suppresses adrenal cortical function, which makes its use controversial. Adrenal suppression following single injections has been reported, and increased mortality is observed in critically ill patients receiving long-term infusions. Etomidate reversibly inhibits the activity of steroid 11β -hydroxylase, a key enzyme in steroid biosynthesis which persists 6 to 8 hours after an induction dose and is unresponsive to adrenocorticotropic hormone. Novel derivatives of etomidate with improved pharmacokinetic properties and reduced inhibition of steroid 11β -hydroxylase have been reported.¹⁰

Nausea and vomiting are more common following induction of anesthesia with etomidate than with other agents. Etomidate is potentially porphyrinogenic and should be avoided in patients with porphyria. There are insufficient data to support the use of etomidate in pregnancy and obstetrics. Etomidate is an inhibitor of plasma cholinesterase and can prolong the action of succinylcholine in patients with cholinesterase deficiency.

KETAMINE

Physicochemical Properties

Ketamine, a weak base, is a partially water-soluble arylcyclohexylamine derivative (Table 2). In the United States, ketamine is formulated as a racemic mixture of 2 enantiomers in aqueous solution with sodium chloride and benzethonium chloride. The *S*(+) enantiomer is about 3 times more potent than the *R*(-) enantiomer in producing anesthesia, and is associated with fewer psychoactive side effects; it therefore has a higher therapeutic index, and is available for use in some countries but not the United States. There are no apparent differences between the enantiomers regarding cardiovascular effects in humans, although some differences have been detected *in vitro*.¹⁰

Use for Induction

Ketamine possesses a number of properties that limit its routine clinical use, although some properties can be advantageous in specific situations.¹¹ The sympathomimetic properties of ketamine give it an important role in the induction of anesthesia under specific conditions. Ketamine is useful in the rapid induction of anesthesia in hemodynamically unstable patients who have acute hypovolemia, hypotension, cardiomyopathy, constrictive pericarditis, or cardiac tamponade, and in patients who have congenital heart disease (with the potential for right-to-left shunting) or bronchospastic disease. Ketamine may be the agent of choice for rapid induction of anesthesia in patients who have acute asthma or cardiac tamponade.

A unique advantage of ketamine is the versatility of administration routes: IV, intramuscular, oral, and rectal. Subanesthetic doses of ketamine by intermittent bolus (0.1-0.5 mg/kg IV) or continuous infusion (10-20 mcg/kg

body weight per minute) can provide sedation and intense analgesia for short painful procedures and as a supplement to regional anesthesia. Ketamine combined with a benzodiazepine is useful in sedation of pediatric patients. Several clinically useful characteristics of ketamine promote its use, including analgesia, bronchodilation, and reduced cardiopulmonary depression.

Systemic Effects

Cardiovascular: The cardiovascular effects of ketamine result primarily from stimulation of the sympathetic nervous system to produce tachycardia and hypertension (Table 3). Ketamine increases atrioventricular conduction time and has a direct myocardial depressant effect; however, these effects usually are masked by the sympathomimetic effect. In patients who have a depletion of catecholamine stores or exhausted compensatory mechanisms of the sympathetic nervous system (ie, critically ill patients or patients in shock), ketamine can have significant hypotensive effects. The cardiostimulatory effects of ketamine include increases in systemic and pulmonary arterial vascular resistance and pressure, heart rate, cardiac output, myocardial oxygen consumption, coronary blood flow, and cardiac work. Thus, ketamine is relatively contraindicated in patients who have coronary artery disease. The hemodynamic effects of ketamine are not related to dose and are usually less pronounced following a second dose. Equianesthetic doses of the S(+) enantiomer might allow for decreased cardiovascular side effects as well as a quicker recovery (because of the reduced dose and more rapid metabolism).

Respiratory: Ketamine does not appreciably depress the ventilatory response to carbon dioxide. Respiratory rate may decrease transiently immediately after induction of anesthesia; apnea is rare. Upper airway reflexes and muscle tone are maintained, but increased salivary and tracheobronchial secretions can lead to cough and laryngospasm such that the coadministration of an antisialagogue is recommended.

The bronchodilatory effect of ketamine is extremely useful in patients with reactive airway disease or bronchospasm. Ketamine is unique in its ability to maintain the functional residual capacity upon induction of anesthesia possibly because of the maintenance of skeletal muscle tone. These properties make it useful in developing countries and under conditions where access to mechanical ventilation and supplemental oxygen are limited.

Neurologic: Ketamine is a potent cerebral vasodilator that increases cerebral blood flow (more than CMRO₂) and intracranial pressure in spontaneously breathing patients; thus, it is relatively contraindicated in neurosurgical procedures. The increase in intracranial pressure can be attenuated by controlled ventilation, hypocapnia, or prior administration of diazepam, thiopental, or propofol. The cerebrovascular effects appear to be direct. Ketamine also produces mydriasis, nystagmus, and excitatory CNS effects. However, ketamine does not appear to lower the seizure threshold in patients who have seizure disorders; its anticonvulsant efficacy has

been demonstrated in animals. Ketamine in low doses might control neurogenic pain and reverse the “wind-up” phenomenon.

Other: Emergence reactions, including delirium, excitement, confusion, euphoria, fear, vivid dreaming, and hallucinations, occur most frequently during the first hour of emergence. The incidence of emergence reactions (10%-30% in adults) is lower in children and elderly patients, and with use of the S(+) enantiomer. Such reactions can be reduced by the coadministration of benzodiazepines with a lower dose of ketamine. Ketamine enhances the action of nondepolarizing neuromuscular blockers—possibly by blocking nicotinic receptors. Ketamine increases muscle tone, but does not trigger malignant hyperthermia. Ketamine can stimulate uterine contraction in the first trimester of pregnancy but has variable effects in the third trimester.

Summary

IV anesthetics provide the most efficient method for the rapid induction of general anesthesia in adults. Rapid uptake and redistribution into the CNS as a result of the agents' high lipophilicity provides for the rapid onset and short duration of effects after bolus administration. None of the currently available agents has the characteristics of an ideal IV anesthetic, largely due to multiple off-target systemic effects. Distinct pharmacologic properties in conjunction with procedure-specific and patient-specific factors guide the selection of IV induction agents that match side effects with overall therapeutic goals.

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