

Review Article

General Anesthesia in Cardiac Surgery: A Review of Drugs and Practices

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Abstract: General anesthesia is defined as complete anesthesia affecting the entire body with loss of consciousness, analgesia, amnesia, and muscle relaxation. There is a wide spectrum of agents able to partially or completely induce general anesthesia. Presently, there is not a single universally accepted technique for anesthetic management during cardiac surgery. Instead, the drugs and combinations of drugs used are derived from the pathophysiologic state of the patient and individual preference and experience of the anesthesiologist. According to the definition of general anesthesia, current practices consist of four main components: hypnosis, analgesia, amnesia, and muscle relax-

ation. Although many of the agents highlighted in this review are capable of producing more than one of these effects, it is logical that drugs producing these effects are given in combination to achieve the most beneficial effect. This review features a discussion of currently used anesthetic drugs and clinical practices of general anesthesia during cardiac surgery. The information in this particular review is derived from textbooks, current literature, and personal experience, and is designed as a general overview of anesthesia during cardiac surgery. **Keywords:** anesthesia, cardiac, surgery, drugs. *JECT. 2005;37:227–235*

General anesthesia is defined as complete anesthesia, affecting the entire body with loss of consciousness, analgesia, amnesia, and muscle relaxation. There is a wide spectrum of agents able to partially or completely induce general anesthesia. Although the cellular and molecular mechanisms of some of these agents, such as opioids, are well defined, the mechanisms of other anesthetics, such as inhaled agents, are not. Presently, there is not a single universally accepted technique for anesthetic management during cardiac surgery. Instead, the drugs and combinations of drugs used are based upon the pathophysiological state of the patient and individual preference and experience of the anesthesiologist.

According to the definition of general anesthesia, current practices consist of four main components: hypnosis, analgesia, amnesia, and muscle relaxation. Although many

of the agents highlighted in this review are capable of producing more than one of these effects, it is logical that drugs producing these effects are given in combination to achieve the most beneficial effect. For example, inhaled anesthetics alone are capable of producing all of the conditions necessary to safely anesthetize the patient during cardiac surgery (1). However, because of their cardiodepressive effects, they are commonly used in low doses in combination with intravenous agents capable of producing the initial hypnosis. The analgesic and muscle relaxation requirements during cardiac surgery usually are supplemented by use of narcotics and muscle relaxants, especially during moments of high stimulation, such as intubation or sternal opening. Amnestic agents are sometimes difficult to separate from hypnotic agents, although some hypnotics such as benzodiazepines, demonstrate more notable amnestic properties than others. In addition to the requirements of general anesthesia, management of general anesthesia in cardiac surgery should also attempt to preserve myocardial function, prevent ischemia, and maintain stable hemodynamics.

This review features a discussion of currently used anesthetic drugs and clinical practices of general anesthesia during cardiac surgery. Table 1 shows the basic pharma-

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Table 1. Anesthesia-related effects of specific drugs.

Drug	Hypnosis	Analgesia	Amnesia	Muscle Relaxation
Volatile anesthetics	↑	↑	↑	↑
Barbiturates	↑↑	NC	↑	NC
Ketamine	↑↑	↑	↑↑	NC
Propofol	↑↑	↑	↑	↑
Etomidate	↑↑	↑	NC	NC
Benzodiazepines	↑↑	NC	↑↑	NC
Opioids	↑	↑↑	NC	↓
Succinylcholine	NC	NC	NC	↑↑
Nondepolarizing neuromuscular blockers	NC	NC	NC	↑↑

Arrows indicate degree of increase or decrease, NC indicates no change.

cological effects of the drugs in this review. It must be noted that this review will focus on adult cardiac anesthesia. However, the anesthetic care of pediatric and the geriatric patients may vary greatly from the healthy normal adult patient. The information in this review is derived from textbooks, current literature, and personal experience. For a more detailed overview of agents commonly used in cardiac anesthesia, see the textbooks *Clinical Anesthesiology* (Lange Medical Books) by G.E. Morgan, Jr., M.S. Mikhail, and M.J. Murray and *A Practical Approach to Cardiac Anesthesia* (Lippincott, Williams, and Wilkins) by F.H. Hensley, Jr. and D.H. Martin.

EFFECTS OF CARDIOPULMONARY BYPASS (CPB) ON PHARMACOKINETICS

CPB during cardiac surgery is associated with alterations in the absorption, distribution, metabolism, and elimination of drugs (2,3). Upon initiation of CPB, hemodilution leads to alterations in regional blood flow and also the dilution of serum-binding proteins. The dilution of serum-binding proteins leads to an increase in the fraction of unbound drug, favoring distribution of the drug from the serum to the tissues and lowering serum concentrations. A good correlation has been shown between the decrease in albumin concentration and the decrease in drug serum concentrations (2). Because of changes in regional blood flow and dilution of serum binding proteins, the amount of unbound drug reaching the tissues can be greatly altered during CPB.

Most drugs are eliminated by the lungs, kidneys, or liver. During CPB, there is often a decrease in blood flow to each of these organs which can cause decreased elimination of drugs. Also, because hypothermia during CPB, elimination also can be reduced as a result of the reduced renal and hepatic enzyme function. The affects of CPB on drug concentration are difficult to predict because on one hand, there is a decrease in drug serum concentrations caused by diluted serum binding proteins and, on the other hand, there is likely decreased elimination (2). Also,

pharmacokinetic analysis is best performed under steady-state conditions, which normally are not met during CPB.

Sedative Hypnotics

Inhalational Anesthetics: Three potent volatile inhalational agents, isoflurane, desflurane, and sevoflurane, and one gas, nitrous oxide, are commonly used at the present time. Halothane and enflurane are inhalational agents that have been used historically but are rarely used currently in adult cardiac surgery.

The potency and dosage of inhalational anesthetics are defined according to the minimal alveolar concentration (MAC). MAC represents the alveolar concentration of anesthetic at which 50% of patients are unresponsive to a painful surgical stimulus. For determination of MAC in humans, the usual stimulus used is skin incision. At a level of $1.3 \times \text{MAC}$, 95% of patients are unresponsive to painful stimuli. The idea of measuring MAC is that after a period of equilibration, the alveolar concentration is equal to that in the blood and the brain. The rate of induction, changes in anesthetic depth, and recovery of inhalational anesthetics are related to the blood:gas solubility ratio. In general, the higher the blood:gas solubility, the slower the response to inhalational anesthetics.

There does not seem to be a single theory capable of precisely explaining the effects of inhalational anesthetics. Instead, several theories have been proposed to describe how these agents work (4). Some reports suggest that, similar to other anesthetics, there is a direct protein-receptor interaction that causes changes in the activity of neurotransmitters (5). In contrast, others suggest that the actions of volatile anesthetics are related to the lipid solubility of the agents (6). Central to this theory is the idea that nonspecific anesthetic binding to hydrophobic sites on the phospholipid bilayer of neuronal membranes may expand the bilayer beyond a critical amount which alters membrane function. Yet another theory suggests that the anesthetic effects may be partly caused by the increase of glutamate uptake in astrocytes (7). Realistically, the exact mechanism is likely a combination of all of these actions.

Despite the lack of knowledge regarding cellular and molecular mechanisms of these agents, the physiological and pharmacological effects of these agents have been well documented, contributing to their use in clinical anesthesia. Most of these volatile agents cause some degree of myocardial depression, skeletal muscle relaxation, and an increase in renal vascular tone and hepatic blood flow (1). Volatile anesthetics may reduce ischemic myocardial damage similar to ischemic preconditioning (8–10). The degree of myocardial protection and the deleterious outcomes of inhalational agents are variable and depend on the specific agent and the concentration used. Table 2 shows the main pharmacological nonanesthetic effects of each of these drugs (11).

Also important to the discussion of volatile anesthetics

Table 2. Clinical pharmacology of inhalational anesthetics.

Effects	Nitrous Oxide	Halothane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Cardiovascular						
Blood pressure	NC	↓↓	↓↓	↓↓	↓↓	↓
Heart rate	NC	↓	↑	↑	NC or ↑	NC
SVR	NC	NC	↓	↓↓	↓↓	↓
Cardiac output	NC	↓	↓↓	NC	NC or ↓	↓
Respiratory						
Tidal volume	↓	↓↓	↓↓	↓↓	↓	↓
Respiratory rate	↑	↑↑	↑↑	↑	↑	↑
Cerebral blood flow	↑	↑↑	↑	↑	↑	↑
Intracranial pressure	↑	↑↑	↑↑	↑	↑	↑
Renal blood flow	↓↓	↓↓	↓↓	↓↓	↓	↓
Hepatic blood flow	↓	↓↓	↓↓	↓	↓	↓
Neuromuscular nondepolarizing blockade	↑	↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑

Arrows indicate degree of increase or decrease, NC indicates no change. Adapted from *Clinical Anesthesiology*, 3rd ed. Morgan, Mikhail, and Murray (1).

SVR, systemic vascular resistance.

is malignant hyperthermia (MH). Volatile anesthetics as well as the neuromuscular blocker succinylcholine can exacerbate MH in susceptible individuals (12). MH is an autosomal-dominant inherited disorder of skeletal muscle characterized by hyperthermia, muscle rigidity, hypercapnia, tachycardia, and myoglobinuria, which may be detected soon after administration. This disease is caused by a pathological increase in calcium release from the sarcoplasmic reticulum. The incidence of the disease is relatively rare (0.002% of adults); however, the anesthesiologist must screen patients for risk of MH. Currently, there is no simple test to diagnose MH. The gold standard of MH diagnosis is the caffeine-halothane contracture test, which measures elevated contracture of muscle biopsies after the exposure to caffeine and halothane (13). This test may be conducted in susceptible patients because of the potential impact on other family members who may carry the MH gene (14). Patient history of myalgias, myoglobinuria, caffeine intolerance, tendency to fever, and family history of MH or intolerance to triggering agents are all signs that may indicate MH susceptibility. If a patient is susceptible to MH and a biopsy contracture test has not been performed, a nontriggering technique should be used. The anesthesia vaporizer should be carefully washed to remove traces of triggering agents, and the use of disposable circuits is recommended if possible. Fortunately, in the case of unexpected MH, it has been shown that the use of dantrolene, an inhibitor of sarcoplasmic calcium release, has decreased mortality from 70% to 80% to less than 10% (12).

Nitrous Oxide: Nitrous oxide, or “laughing gas,” is a general inhalational anesthetic that is sometimes used in the prebypass period of adult cardiac surgery. However, it is generally not used during bypass because of its extremely high blood solubility and ability to expand air

bubbles (15). Occasionally, the use of nitrous oxide is preferred because of its ability to increase the effectiveness of other volatile agents (16) and because of its rapid onset and elimination. Nitrous oxide can be used to increase pulmonary vascular pressures and is contraindicated in patients with pulmonary hypertension. Although nitrous oxide has some ability to directly depress myocardial contractility, cardiac function is essentially unchanged as a result of the stimulation of catecholamines. Aside from the risk of air emboli, the major disadvantages to the use of nitrous oxide include increased systemic vascular resistance. With chronic exposure, there is also an increased risk of bone marrow depression and neuropathy (17,18).

Halothane: Halothane is a very inexpensive halogenated alkane whose popularity has decreased dramatically in recent years because of titration difficulties and potential hepatic toxicity. In general halothane, like most volatile anesthetics, causes a dose-dependent reduction in arterial blood pressure and cardiac output. Unique to halothane is the decreased heart rate as the carotid baroreceptor reflex is blunted. Although halothane is also a coronary vasodilator, the drop in systemic arterial pressure causes a decrease in coronary blood flow. However, because of the lower metabolic demand of the myocardium, coronary oxygen supply generally is preserved. Halothane also has been shown to sensitize the myocardium to catecholamines, leading to arrhythmias; therefore, epinephrine and norepinephrine are used with caution in patients anesthetized with halothane. Halothane generally causes rapid shallow breathing and, unlike nitrous oxide, minute ventilation decrease and CO₂ levels increase. Historically, halothane has been used to reverse asthma-induced bronchospasm (19) because of its bronchodilator effects, which also are seen with all other halogenated inhalational agents. Similar to other inhalational agents,

halothane causes dilation of cerebral vessels, increased cerebral flow, and loss of cerebral vessel autoregulation.

There has been ongoing discussion regarding the hepatic effects of halothane. Like most other inhalational agents, halothane causes a decrease in hepatic flow. Hepatotoxicity also has been documented with the use of halothane (20). There are two types of halothane hepatitis. Type I halothane hepatitis is a mild form that occurs in approximately 20% of patients and is characterized by slight elevations in serum aminotransferase. Type II halothane hepatitis occurs in approximately 1 in 35,000 patients (20) and is characterized by severe disturbance in liver function and liver necrosis. Type II halothane hepatitis is considered immune-mediated, as serum from these patients contain immunoglobins against liver microsomal proteins (20). Those at most risk for halothane hepatotoxicity are obese females and those with a prior exposure to halothane. In patients with repeated exposure to halothane within 1 month, the incidence rises to 1 in 3000 (20).

Enflurane: Enflurane is a halogenated ether with characteristics typical of other volatile anesthetics. It is similar to halothane in most respects, including its respiratory, renal, and hepatic effects. Unlike halothane, enflurane decreases systemic vascular resistance resulting in a compensatory increase in heart rate. Cerebral blood flow and intracranial pressure are increased with the use of enflurane, and this agent can actually increase cerebrospinal fluid secretion. During deep anesthesia, enflurane can lower seizure threshold; therefore, this agent should be used with caution in those with seizure disorders. Also, because a fluoride metabolite of enflurane is nephrotoxic with prolonged use, it should be used with caution in patients with renal insufficiency. However, it is likely that this fluoride metabolite reaches toxic levels in most cases.

Isoflurane: Isoflurane is a chemical isomer of enflurane and is currently one of the most commonly used volatile anesthetic in cardiac surgery. Its popularity has stemmed partly from its minimal cardiac effects when compared with older agents. Because of its pungency and airway irritation, it is not a good agent for inhalational induction; therefore, induction of anesthesia usually is accomplished with an intravenous agent. Also contributing to the popularity of this drug is its protective effects on the brain by reducing cerebral metabolic oxygen requirements to the point of an isoelectric electroencephalogram.

Although arterial and systemic blood pressure decline with the use of isoflurane, cardiac output is preserved as the result of an active carotid baroreceptor reflex and decreased afterload. In fact, in contrast to other volatile agents isoflurane may result in the greatest decrease in systemic vascular resistance. Respiratory depression of isoflurane is similar to that observed with other volatile anesthetics. Isoflurane is also comparable with other volatile anesthetics in terms of renal and hepatic effects. Be-

cause isoflurane is an isomer of enflurane, it may be expected that the same nephrotoxic fluoride metabolite of enflurane may be problematic with isoflurane. However, this metabolite is of less concern with isoflurane because it undergoes significantly less metabolism.

Central to the ongoing debate involving the use of isoflurane in cardiac surgery is the issue of coronary steal. Coronary steal occurs when blood is redistributed away from a poorly perfused region of the myocardium to an area that is adequately perfused. Many early studies linked isoflurane to coronary steal (21,22) are inconclusive. This idea was re-examined by Slogoff et al. (23) years later using more than 1000 patients undergoing coronary artery bypass graft surgery. Patients were randomized to receive one of four volatile anesthetics. It was found that there was no increased risk of ischemic episodes with the use of isoflurane compared with other agents. Currently, there is no convincing evidence that isoflurane should be avoided in patients with coronary artery disease.

Desflurane: The structure and clinical effects of desflurane are remarkably similar to that of isoflurane. However, the substitution of a fluoride atom for a chloride causes desflurane to boil near room temperature. Also, desflurane can interact with desiccated carbon dioxide absorbent, such as soda lime, to produce toxic carbon monoxide (24). This also has been demonstrated with other inhalational agents but it is most dramatic with desflurane. Desflurane has a very low blood:gas solubility; therefore, anesthetic depth can be titrated quickly, resulting in a rapid emergence from the anesthetized state. Desflurane has a very short duration of action and relatively low potency when compared with other agents, although its potency is high enough to provide general anesthesia in the presence of high concentrations of oxygen. Although the cardiovascular, respiratory, renal, and hepatic effects are somewhat similar to those typical of volatile anesthetics, desflurane is the least metabolized inhalational agent. However, if the concentration of desflurane is increased too rapidly, it can cause temporary sympathetic activation, which is clinically significant in cardiac patients. Desflurane is a pungent agent, resulting in coughing and laryngospasm when used for inhalational induction, and induction normally is accomplished with an intravenous agent. Desflurane use does not seem to be associated with renal or hepatic dysfunction.

Sevoflurane: Sevoflurane is the newest of the volatile anesthetics that is frequently used because of its nonpungency and relatively rapid increases in alveolar concentration. Also, sevoflurane has been shown to limit myocardial damage and preserve ventricular function better than intravenous agents (8,9). However, with this agent cardiac output is not maintained seen with isoflurane and desflurane. An advantage of sevoflurane over isoflurane is the lack of evidence of coronary steal. Sevoflurane also has

bronchodilatory effects that are useful in preventing bronchospasm, similar to isoflurane and other agents. Also similar to isoflurane is its depression of cerebral metabolic requirements; thus, it is capable of protecting the brain from ischemia. Although normal hepatic blood flow and hepatic function is maintained with sevoflurane, this agent may have deleterious effects on renal function because of decreased blood flow and the nephrotoxic effects of fluoride and compound A (released when sevoflurane is exposed to carbon dioxide absorbants), which occurs with prolonged exposure. Interestingly, sevoflurane degradation caused by the interaction with desiccated carbon dioxide absorbant has been associated with fires (25).

Intravenous Agents

Barbiturates: The major use of barbiturates in cardiac surgery is as intravenous induction agents, and only the ultra-short acting agents are used for this purpose. In this group are thiopental and methohexital. The short duration of these agents is caused by rapid redistribution and not elimination; therefore, if given in large doses or as an infusion, their effect is prolonged. Pentobarbital is of intermediate duration and is sometimes used in cardiac surgery to induce barbiturate coma. Barbiturates are hypnotic drugs that act to depress the metabolic demands of the brain to provide protection during periods of ischemia. They are considered ultra-short acting induction agents and are considered the gold standard for neuroprotection against which other newer agents are compared (26). It has been shown that barbiturates can decrease cerebral metabolic oxygen consumption as much as 45% at 37°C and up to 80% at 18°C (26). These drugs can induce mild sedation, complete general anesthesia, or barbiturate coma like that induced during circulatory arrest (27). Barbiturates suppress acetylcholine neurotransmission and enhance the transmission of inhibitory neurotransmitters, such as γ -aminobutyric acid (GABA). The hypnotic potency, anticonvulsant activity, and time-to-peak concentrations of the barbiturates can vary dramatically dependent on structure. Thiopental, the most popular barbiturate in cardiac surgery, is characterized by the rapid onset and its reputation for safe use in hemodynamically stable patients. However, most cardiac patients are not hemodynamically stable, making its use limited.

Depression of the medullary vasomotor center with barbiturates causes a dramatic decrease in blood pressure and an elevation in heart rate, provided that the carotid baroreceptor reflex is active. The cardiovascular effects of barbiturates are largely dependent upon this reflex, and changes in intravascular volume can produce marked effects on cardiovascular function. In comparison with other intravenous anesthetic agents, the circulatory depression with barbiturates is intermediate; however, these agents can cause dramatic respiratory depression and laryngeal spasm (27).

Barbiturates are capable of dramatically lowering cerebral oxygen requirements; therefore, the decrease in cerebral blood flow typically is not problematic. In fact, these agents are used to protect the brain during deep hypothermic circulatory arrest (26). However, it must be noted that barbiturates do not have analgesic effects and therefore must be used in conjunction with other agents. Although renal and hepatic blood flows are decreased by these agents, they generally are not associated with dysfunction of these organs. All barbiturates are metabolized by the liver and generally excreted by the kidney.

Ketamine: Ketamine is similar to other hypnotics in that its effects are modulated to a large degree by blocking excitatory neurotransmission in the brain. However, unlike many general anesthetics, which work on GABA receptors, ketamine is an antagonist at the *N*-methyl-D-aspartate (i.e., NMDA) glutamate receptor, which possesses most of the analgesic, amnestic, and neuroprotective effect. Ketamine is known to produce a unique state known as dissociative anesthesia which causes the patient to appear conscious but unable to respond to stimuli. Also, the administration of ketamine may be associated with adverse psychological effects, especially when not co-administered with benzodiazepines. Ketamine is extensively redistributed, metabolized by CYP450 in the liver, and eliminated by the kidney. Pharmacokinetically, ketamine has short distribution and elimination half-lives; therefore, this agent can produce unconsciousness quite rapidly (28). Norketamine, the primary metabolite of ketamine, is one third to one fifth as potent as the parent molecule and may be involved in the prolonged analgesic actions of this drug (28). Aside from its hypnotic effects, ketamine is capable of producing a great degree of amnesia and analgesia.

Ketamine is a unique agent in that it has the ability to increase heart rate, mean arterial pressure, and plasma catecholamines via changes in sympathetic stimulation. As the result of these effects, ketamine is sometimes used in patients with depressed cardiovascular function. Ketamine can be problematic in patients with ischemic disease because the sympathetic adrenergic stimulation may increase myocardial oxygen demands beyond the capacity of coronary blood flow. Ketamine also may increase pulmonary vascular resistance, and it provides a greater degree of bronchodilation than most intravenous anesthetics making its use beneficial in patients with asthma (28). Ketamine is known to increase cerebral blood flow and cerebral oxygen consumption; therefore, this drug is used with caution in patients with elevated intracranial pressure.

Propofol: Like many other intravenous agents, propofol involves a positive modulation of the inhibitory function of the neurotransmitter GABA. Propofol can cause pain on injection because of its formulation, which consists of

an emulsion containing egg lecithin and soybean oil for intravenous administration, and its use is contraindicated in patients with hypersensitivity to these components. Propofol is lipid-soluble, resulting in its ability to cross the blood-brain barrier with a rapid onset of action, with induction occurring within 40 seconds (29). Although much more expensive than traditional hypnotics, propofol is becoming a common choice among anesthesiologists because of rapid emergence from sedation attributable to its fast metabolism, thus facilitating early extubation (30). Propofol also is preferred for its lack of a hangover effect during recovery and is considered as an alternative to thiopental for intravenous induction (29).

Propofol decreases heart rate, blood pressure, and myocardial function in a dose-dependent manner. Heart rate and blood pressure can decrease as much as 20% with this agent, although these depressant effects seem to be transient (29). Unless decreased blood pressure is desired, the use of propofol for induction of anesthesia may have no benefit over etomidate (31). Propofol also causes a mild dose-dependent respiratory depressant effect and has a mild bronchodilator effect. Propofol is used safely in patients with increased intracranial pressure because intracranial pressure is maintained at normal levels or even decreased. The net effects of propofol include decreases in intracranial pressure, cerebral oxygen requirements, and cerebral perfusion pressure, therefore this agent is a candidate for neuroprotection (32).

Etomidate: Etomidate works by depressing the reticular activating system and mimics the actions of GABA. It is structurally unrelated to other anesthetics and consists of a carboxylated imidazole ring. Etomidate is primarily used as an induction agent of general anesthesia; however, it is associated with pain when injected into peripheral veins. Similarly to thiopental and other anesthetics, its redistribution into peripheral tissues is responsible for emergence from sedation. However, etomidate is unique in its potency, which is 25 times greater than that of thiopental (31). The cardiovascular and respiratory effects of etomidate are virtually negligible, with slight decreases in blood pressure and ventilation. Etomidate causes virtually no cardiac depression in healthy patients but can cause indirect cardiac depression in compromised patients (33). Etomidate decreases intracranial pressure and also decreases the cerebral metabolic rate. Despite the lack of solid evidence of cerebral protective effects, it often is used for cerebral protection (32). Although etomidate causes little cardiorespiratory effects, it has been shown to induce myoclonic movements in 60–80% of patients (34). However, pretreatment with agents such as sufentanil may reduce myoclonus (35). Etomidate also is capable of causing temporary adrenal suppression with a single induction dose.

Benzodiazepines: Benzodiazepines such as midazolam and lorazepam generally are used to reduce anxiety and

provide amnesia. Benzodiazepines bind directly to their receptors in the central nervous system to enhance inhibitory effects of neurotransmitters such as GABA. Benzodiazepines consist of a benzene ring and a diazepine ring in which substitutions may contribute to changes in potency. Benzodiazepines undergo metabolism in the liver and generally are excreted by the kidney. However, these processes generally are slow resulting in a long half-life.

The beneficial effects of benzodiazepines include a reduction in cerebral oxygen demand and amnestic, sedative, and anxiolytic properties with no analgesia. Compared with thiopental, benzodiazepines have less cardiorespiratory effects that include a slight decrease in cardiac output and blood pressure (36). These effects are more pronounced when used in conjunction with narcotics. Benzodiazepines also are considered safer than thiopental in patients with heart disease (36). Although respiratory suppression with benzodiazepines is often mild, it can be severe even with small dosage especially in the elderly and when co-administered with narcotics. These patients must be monitored carefully. Midazolam is considered an excellent choice for premedication because of its amnestic and anxiolytic effects. However, lorazepam is a popular alternative because of its high potency and longer duration of action.

Amnesiacs

Amnesia, or loss of memory, is not necessarily a product of hypnosis, or sedation. Although many of the drugs capable of producing hypnosis also produce amnestic effects, this is not always the case. If special attention is not given to induce amnesia there is an associated risk of patient recall, which is common with hypnosis produced by pure narcotics. Drugs such as ketamine and benzodiazepines are commonly used intravenous agents that are preferred for their amnestic properties. However, ketamine has limited use in the adult cardiac patient due to its cardiovascular effects. Potent inhalational agents reliably produce amnesia when administered at levels greater than 0.5–0.6 MAC.

Analgesics

Opioids: Opioids are defined as any derivative, natural or synthetic, of opium or morphine or any substance that has their effects. Narcotics have potent analgesic effects associated with significant changes in mood and behavior, and the potential for dependence and tolerance after repeated administration. The most commonly used opioids in cardiac surgery are fentanyl, sufentanil, and remifentanyl. Morphine is still considered the prototype opioid agent against which other agents are compared, but its use has declined due to histamine release and hypotension at higher doses (e.g., 1 mg/kg). Pharmacokinetic properties of these agents are shown in Table 3.

Table 3. Pharmacokinetics of opioids in adults.

Drug	Lipid Solubility	Half-life (hours)	Vd (L)	Clearance (L/min)
Morphine	1.4	1.7	200	1.2
Fentanyl	816	3.6	335	1.53
Sufentanil	1757	10.8	339	0.9
Ramifentanyl	NA	10–20 minutes	25–62	3–4

Lipid solubility, octanol/water partition coefficient; Vd, steady-state volume of distribution. Adapted from *Cardiac Anesthesia*, 4th ed, Kaplan, Reich, and Konstadt.

Clearly the most beneficial effect of opioids is analgesia, and these drugs also cause mild sedation. Narcotics are poor hypnotics and generally are used in conjunction with other agents such as benzodiazepines or inhalational agents to induce general anesthesia. However, in the late 1960s and early 1970s, Lowenstein et al. reported “narcotic-based,” or high-dose narcotic anesthesia in which morphine was used solely to induce general “anesthesia” (37,38). It is now known that high-dose narcotic anesthesia has the advantage of hemodynamic stability and lack of myocardial depression but that mechanical ventilation is necessary after surgery because of high levels of respiratory depression. Although opioids can undoubtedly induce unconsciousness, they cannot induce complete general anesthesia. This is evidenced by the fact that opioids are capable of decreasing the MAC of inhalational drugs by only 65–70% (39); therefore, they should be used in combination with other agents. Interestingly, the use of high-dose anesthesia has not been associated with increased morbidity or mortality when compared with alternate methods (40,41).

There are three main opioid receptors (μ , κ , and δ), each with their own subgroups and each coupled to gamma-proteins. These receptors share significant sequence homology and each is coupled to adenylate cyclase. The μ - and κ -opioid receptors have been localized to areas of the brain associated with neuronal pain pathways. In contrast, δ -opioid receptors have not been found in the brain but are found in many other organs, with the highest levels found in the heart (42). However, the direct effects of opioids on the heart have not been well documented. In a recent comprehensive review, it was concluded that at clinically relevant doses, the cardiovascular actions of morphine and related narcotic analgesics are limited (42). Activation of opioid receptors inhibits the release and response to stimulatory neurotransmitters at neurons associated with pain. Fentanyl and sufentanil are very lipid-soluble and therefore easily penetrate the blood brain barrier resulting in a rapid onset and short duration. However, although less lipid-soluble, remifentanyl has the quickest onset and shortest duration. Opioids are metabolized by the liver and excreted by the kidneys with the exception of remifentanyl, whose ultra-short duration is

due to metabolism by nonspecific esterases. The side effects of opioids are generally respiratory depression, muscle rigidity, and lack of reliable amnesia. The side effects of opioids can be reversed with naloxone, an opioid antagonist, but this reversal agent will also antagonize analgesic effects.

Muscle Relaxants

Neuromuscular blocking agents, or muscle relaxants, are administered to facilitate intubation and surgical exposure and prevent patient movement during periods of high stimulation of the patient. It is important to discontinue neuromuscular blockade before cessation of general anesthesia because otherwise the patient would be awake but paralyzed, resulting in extreme dysphoria. Muscle relaxants in this review fall into one of two categories: depolarizing and nondepolarizing. Table 3 shows pharmacological characteristics of common muscle relaxants (43).

Succinylcholine: Succinylcholine, an acetylcholine receptor agonist, is a depolarizing muscle relaxant that consists of two acetylcholine molecules joined together by a carbon bond. It is the only depolarizing muscle relaxant currently used. Although the initial effect of succinylcholine is neuromuscular activation, the drug’s duration desensitizes the acetylcholine receptor resulting in relaxation. Succinylcholine has a short duration of action (5–15 minutes) and the fastest onset (60–90 seconds) of all the muscle relaxants. The major drawbacks to use of succinylcholine are increases in serum potassium and like volatile anesthetics, the risk of malignant hyperthermia (12). This increase in serum potassium is a concern in patients with high baseline levels and in patients suffering from burns, spinal cord injury, massive trauma, prolonged ICU stay, and in patients with certain myopathies. Because this drug is metabolized by endogenous cholinesterases, low levels of cholinesterases or abnormal cholinesterases will cause a prolongation of the duration of the paralytic effects of this drug.

Nondepolarizing Muscle Relaxants: Since the advent of succinylcholine, the focus of neuromuscular blockade drugs development has been to develop a neuromuscular blocker with the pharmacokinetics of succinylcholine without the adverse side effects which accompany its use. Thus far, this search has been unsuccessful. The newer neuromuscular blocking drugs such as vecuronium and cis-atracurium are nondepolarizing agents that are competitive antagonists of acetylcholine at the nicotinic acetylcholine receptor at the motor end-plate. There are a wide variety of nondepolarizing muscle relaxants on today’s market. The newest of these agents have virtually no cardiovascular side effects, and the pharmacological and pathological properties associated with drugs in this category are greatly variable (Table 4).

Table 4. Characteristics of neuromuscular-blocking drugs.

Drug	Dose (mg/kg)	Onset (min)	Duration (min)	Effects on HR	Effects on BP	Effects on CO	Renal Elimination
Succinylcholine	1.5	1–1.5	5–15	+	+	0	0%
Pancuronium (Pavulon®)	0.1	3–5	180–240	++	+	+	70%
Vecuronium (Norcuron®)	0.1	2–3	75–120	0	0	0	15%
Cis-atracurium (Nimbex®)	0.2	2–3	60–90	0	0	0	<5%
Doxicurium	0.06	3–5	180–240	0	0	0	75%
Rocuronium (Zemuron®)	0.6	1–2	45–90	0	0	0	0%
Mivacurium (Mivacron®)	0.2	2–3	15–40	0	0	0	<5%

Dose shown is the dose used for intubation. HR, heart rate; BP, blood pressure; CO, cardiac output. Adapted from *Cardiac Surgery in the Adult*, 2nd ed. McGraw/Hill, 2003.

CONCLUSION

General anesthesia is more than simply the appearance of an “unconscious” patient. Each of the four main components of general anesthesia must be provided with caution. The most logical approach to induction and maintenance of general anesthesia is a combination of drugs, both inhaled and intravenous, with specific actions. Although there is no general consensus among anesthesiologists to provide a universal protocol, a careful consideration of each drug and associated effects on the body as a whole is essential to providing proper care to the cardiac patient.

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