Chapter 10
Inhalational Agents: What Volatile Inhalational Agents Are and How to Use Them in the ICU Setting

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Introduction

Inhalational agents have played a pivotal role in anesthesia history. The first publicly demonstrated anesthetic of the modern era, diethyl ether, was an inhalational anesthetic. Volatile anesthetics play a significant role in clinical anesthesia throughout the world and are administered routinely by anesthesiologists using anesthesia machines. Technological advances have permitted volatile anesthetic administration to migrate to nontraditional areas outside of the operating room, such as the critical care unit. The development of specialized equipment such as Anesthetic Converting Device (AnaConDa; Sedana Medical, Uppsala, Sweden), which is a miniature vaporizer consisting of an antiviral and antibacterial humidifying filter, in addition to an activated charcoal membrane that allows for absorption and reuse of the anesthesia, has allowed for the use of anesthetic gases with critical care unit ventilators.

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Principles of Inhalational Agents

Inhalational anesthetic agents, which remain the principle amnestic agents used in the operating room for general anesthesia, provide unique advantages secondary to their distinctive pharmacokinetic and pharmacodynamic principles. The three volatile agents most commonly used in the USA are isoflurane, desflurane, and sevoflurane, all of which are halogenated hydrocarbons. Sevoflurane is a fluorinated methyl isopropyl ether. Isoflurane and desflurane are both methyl ethyl ethers, with desflurane differing from isoflurane by only one atom. Halogenation affords all three of these agents superior stability and less flammability compared to ether.

The inhalational mechanism of drug delivery is particularly unique. The pharmacokinetics of these agents depends upon physical properties such as partial pressure, vapor pressure, and solubility. Furthermore, uptake, distribution, and clearance are all directly dependent on alveolar ventilation and cardiac output.

The partial pressure of a gas is the fractional contribution that it makes to the overall pressure of all combined gases, which at sea level totals 760 mmHg. 1.4% isoflurane thus achieves a partial pressure of 10.64 at barometric pressure (1.4% × 760 mm Hg = 10.64 mm Hg). The partial pressure that is achieved in the alveoli (PA), which itself is dependent on inspired concentration, atmospheric pressure, and uptake into the blood, ultimately results in equilibration with arterial partial pressure (Pa) secondary to thermodynamic force that causes movement down a pressure gradient. Pa then in turn equilibrates with the central nervous system tissue (PCNS). Equilibrium results when the partial pressure gradients between PA, Pa, and PCNS equalize and achieve steady state. The goal of inhalational anesthesia is to obtain a certain partial pressure of the agent in the CNS that provides the desired effect. On account of differing solubility coefficients between tissues, at equilibrium where PA = Pa = PCNS, the actual concentration in the tissues will differ between the alveoli, arterial blood, and CNS. PA is thus an accurate and titratable measure of PCNS and thus also anesthetic plane and makes volatile anesthetics quickly and easily titratable.

The solubility of each anesthetic agent determines how readily Pa will equilibrate with PA. The blood-gas partition coefficient denotes solubility and is the ratio of the concentrations between the two states at equilibrium, i.e., an equal partial pressure. The greater the relative solubility of a volatile agent in blood as compared to the alveolar gas, the more molecules of anesthetic agent must dissolve in the blood to produce equilibration between PA and Pa. Thus, as solubility increases, uptake and time to equilibrium are both increased and induction of anesthesia slows. Likewise, as arterial blood reaches peripheral organs, tissues with high tissue-blood coefficients require more molecules (and more time) for equilibrium [1]:

$$\text{Uptake} = P\left(A - v\right) \times \text{gamma} \times \text{CO}$$

Minimum Alveolar Concentration

The minimum alveolar concentration (MAC) is used as a standard indicator of depth of anesthesia and also demonstrates the agent's relative potency [1]. 1 MAC is defined as the minimum alveolar concentration at sea level (1 atmosphere) at which 50% of patients do not move in response to a surgical incision. It is important to remember that MAC is defined by muscle immobility, which is an effect at the level of the spinal cord. This alveolar concentration corresponds to an alveolar partial pressure, which at steady state produces a partial pressure in the brain that results in immobility and amnesia. For example, 1 MAC of sevoflurane is 2.1% (2.1% × 760 = 15.96). The more potent the agent, the lower the alveolar concentration needed to achieve 1 MAC (Table 10.1). 1.14% isoflurane produces the same effect as 6% desflurane, thus indicating isoflurane is significantly more potent. MAC is highest at 6 months and then decreases with age. The duration of administration does not alter MAC [2].

Uptake and Distribution

The speed at which depth of anesthesia is achieved corresponds to the rate of rise of PA/PI (inspired partial pressure). The rate of PA rise is influenced both by anesthetic inflow into the alveoli and by anesthetic uptake into the alveolar capillary vessels. High delivery and low uptake increase this rate of rise. High PI, increased alveolar ventilation, low dead space, and low FRC all increase the rapidity of volatile anesthetic onset by increasing the rate of PA rise. Factors that increase blood uptake lower the rate of PA increase, and thus onset is slowed because the goal PA takes longer to achieve. These factors include high cardiac output, high agent solubility, and high alveolar to venous partial pressure differences [3].

There are a number of other factors that also contribute to duration of onset. Left to right shunting usually does not alter anesthetic uptake or speed of induction significantly provided cerebral perfusion is not decreased to a degree that delivery of volatile agent to the brain is decreased. Right to left shunting slows induction as less arterial blood has the opportunity to equilibrate with the PA.

Table 10.1 Properties of modern volatile anesthetics

Common anesthetics	Blood-gas partition coefficient	Minimum alveolar concentration (MAC)
Sevoflurane	0.63	2.05
Isoflurane	1.4	1.14
Desflurane	0.42	6

Concentration Effect

There are two notable pharmacokinetic principles of volatile anesthetics that also impact the speed of induction: concentration effect and second-gas effect. Concentration effect describes the impact of the inspired partial pressure on the rate of PA rise. The phenomenon describes how, after volatile absorption from the alveoli to the blood, the resulting absence of gas is replaced by an even higher (less diluted by dead space) inspired concentration of anesthetic, thus leading to higher PAs. The higher the PI, the faster the PA will rise secondary to this effect. The second-gas effect describes a unique phenomenon that occurs with the use of two agents especially with one being nitrous oxide which has a very rapid uptake. As nitrous oxide is rapidly absorbed by the blood with each breath, additional volatile agent is brought into the alveoli from the conducting airways leading to higher PA and thus faster anesthetic onset.

Delivery of the Agent

Anesthesia Machine Direct Delivery

Anesthesia machines combine the ability to mechanically ventilate and administer volatile anesthetics in a closed-loop system that reduces both the amount of anesthetic consumed and environmentally wasted. If an anesthesia machine is chosen to deliver volatile anesthetics in the ICU setting, the vaporizer attached to the machine is the mechanism by which anesthetic dose is determined. Anesthetic vapor is mixed with a combination of air, oxygen, and potentially nitrous oxide. The circle system of an anesthesia machine allows the patient's expired gas to be reused after the chemical elimination of carbon dioxide, and thus very little gas is wasted. Because at room temperature inhalational anesthetics are liquids, a vaporizer device is needed to accurately add the desired amount of anesthetic vapor to the gas flow, which is then delivered to the patient via spontaneous or mechanical ventilation. Unfortunately, anesthesia machine ventilators are generally limited in their modes and in their ability to deliver precise volumes and pressures in small children.

Alternatively, the anesthesia machine can be used to deliver the desired volatile concentration and FiO_2 to a separate, more sophisticated ventilator; however most ventilators require a higher driving pressure than this method would provide. There are special ICU ventilators that have a vaporizer in circuit with a high driving pressure gas input as well as some that utilize a circle system to reduce agent wastage. Delivery of the inhaled anesthetic drugs requires a vaporizer. A scavenging system is required to prevent environmental contamination. Continuous end-tidal concentration monitoring is utilized to monitor cerebral concentration. This can be achieved with the use of an anesthesia machine or a vaporizing device dedicated for use with an ICU ventilator such as the AnaConDa (Anesthesia Conserving Device, Sedana Medical, Sweden), MIRUS (Pall Medical, Germany), or RIVAL

(Reflector-In-line Vaporizer Anesthesia application, Thornhill Medical, Toronto, Canada) [4]. The AnaConDa system is a modified heat moisture exchanger that has been developed to allow the use of inhalational agents such as sevoflurane and isoflurane in the ICU without requiring high fresh gas flows or specialized ventilators. The device features a syringe pump that delivers isoflurane or sevoflurane to a small carbon-fiber device which goes in-line with a traditional ICU ventilator, and carbon dioxide absorbers and circle systems are not required. In many ways, this can be considered a disposable anesthetic vaporizer. The device can be used with common intensive care unit ventilators and is inserted between the Y-piece and the patient. Liquid isoflurane or sevoflurane are delivered by a syringe pump. Majority of anesthetic exhaled by the patient is absorbed by a reflector and resupplied during the next inspiration. The newer MIRUS system also uses a reflector and can deliver desflurane. RIVAL is the first commercial available in-line vaporizer in North America and Europe. RIVAL is described as an in-line vaporizer that can be placed on the inspiratory limb circuit and allows for changes of inspired concentrations of inhalational anesthetics independent of inspired gas flow or minute ventilation which may potentially lead to the higher efficiency and versatility of anesthetic delivery [5].

Necessary Equipment and Preparation

Continuous monitoring of inspired and expired volatile anesthetic concentration is vital in order to safely administer an appropriate dose of the drug. Errors may occur with the vaporizer itself whereby more or less anesthetic is actually delivered relative to what is dialed on the device. Waste gas scavenging is also important as Occupational Safety and Health Administration (OSHA) allows a maximum of 2 ppm for occupational exposure to these volatile agents. If a closed or semi-closed system is used to deliver volatile gases, expired carbon dioxide must be removed from the circuit prior to delivering the recycled gases back to the patient. This is achieved via one of several different carbon dioxide absorbents, each of which works by a similar though unique chemical reaction. Calcium hydroxide (Ca(OH)2) is the principal chemical in all available carbon dioxide (CO_2) absorbents and is combined with various catalysts. These catalysts can react with inhaled anesthetics to produce various undesirable byproducts, including carbon monoxide and compound A. Sevoflurane in particular is known to produce compound A, and thus flow rates must be at least 2 L/min per manufacturer recommendations to prevent compound A accumulation and the associated potential renal injury, though no studies have found this to be clinically significant. As these reactions are exothermic, the avoidance of thermal injury is necessary. Carbon monoxide production is most associated with desflurane and occurs most significantly when the absorbent becomes desiccated. Knowledgeable practitioners and trained staff are essential for safe delivery and quick recognition of adverse side effects such as cardiorespiratory depression. The ability to recognize and immediately treat malignant hyperthermia must also be readily available as discussed later in the chapter.

Clinical Effects of Inhalational Anesthetics

Volatile anesthetics exert dose-dependent physiological changes throughout the body, which requires an extensive understanding when used in the clinical setting.

Circulatory System

A common effect of volatile agents is relaxing vascular smooth muscle leading to a decrease in systemic vascular resistance. This will ultimately lead to a dose-related decrease in mean arterial pressure, but only minimal changes will occur to cardiac inotropy in the adult population. The neonatal myocardium is more sensitive to inhalational anesthetics and may exhibit a greater decrease in contractility.

Enflurane, isoflurane, and desflurane result in 5–10% increases in HR from baseline, while sevoflurane does not usually exhibit until doses of 1.5 MAC [2]. These increases in heart rate are likely secondary to a reflex tachycardia from noxious stimuli on the airway receptors or activation of the sympathetic nervous system. Halothane reduces the arrhythmogenic threshold for epinephrine or increases the heart's sensitivity to catecholamines and causes ventricular dysrhythmias. Sevoflurane, isoflurane, and desflurane do not demonstrate the same dysrythmogenicity [3, 6]. Inhalational agents diminish the baroreceptor reflex during general anesthesia, with halothane and enflurane more than depression of the reflex than isoflurane or sevoflurane. The baroreflex returns to normal the quickest with the use of sevoflurane.

Volatile anesthetics can decrease oxygen consumption up to 15% during general anesthesia, as well as redistribute cardiac output. Blood flow is decreased to the liver, gut, and kidneys, while flow to the brain, skin, and muscle remains essentially unchanged [2].

Nitrous oxide is frequently combined with volatile anesthetics during general anesthesia and has unique cardiovascular actions. When combined with volatile anesthetics, both systemic vascular resistance and blood pressure are greater than without the nitrous oxide. This change is thought concentration, as well as the decrease in dose of the simultaneous administration of the volatile anesthetic [2].

Cerebral

All the potent inhalational anesthetics are dose-dependent cerebral vasodilators. They reduce cerebral metabolic rate but can increase cerebral blood flow and intracranial pressure by blunting cerebral autoregulation. This occurs by the uncoupling of cerebral blood flow and metabolism. Cerebral blood flow increases more significantly at concentrations greater than one MAC, thus further increasing ICP [7].

Volatiles cause characteristic changes in EEG. As depth of anesthesia increases, periods of electrical silence become more frequent, with an isoelectric pattern occurring at a range of 1.5–2.0 MAC. All volatiles depress the amplitude and increase the latency of somatosensory evoked potentials. Increasing MAC to 1 may abolish evoked potentials [6].

Hepatic

Volatile anesthetics undergo very little hepatic metabolism and minimally effect hepatic function. The best known potentially hepatotoxic drug is halothane causing "halothane hepatitis." This hepatitis can manifest as either a mild, self-limited form with no evidence of liver failure or a more severe, fulminant hepatitis that is most likely immune-mediated. Isoflurane, desflurane, and enflurane have been associated with acute hepatic failure, but the incidences attributed to them have been very small. Risk factors for developing volatile anesthetic-associated hepatitis include female gender, obesity, age, and, most importantly, a history of prior exposure [2].

Neuromuscular

Inhalational agents induce relaxation of both skeletal and smooth muscle by blocking nicotinic acetylcholine receptors at the neuromuscular junction. They may potentiate the required dose of a neuromuscular blocking agent, though it may not be sufficient to prevent patient movement in response to all noxious stimuli.

While smooth muscle relaxation may be beneficial in certain situations, it may also prove to be detrimental in others, for instance, it can cause nausea, emesis, or ileus from gastrointestinal smooth muscle relaxation [7].

Pulmonary

All volatile anesthetics affect ventilation in a dose-dependent manner. They increase respiratory rate and decrease tidal volume with minimal effects on decreasing minute ventilation until higher inspired concentrations of the gases are reached. The net ventilatory mechanics are also impacted by inhaled anesthetics. Functional residual capacity is decreased during general anesthesia from a decrease in the intercostal muscle tone, cephalad displacement of the diaphragm position and inward displacement of the rib cage [6], and the onset of phasic expiratory activity of respiratory muscles [2]. The decrease in FRC can lead to symptomatic hypoxemia that is overcome by positive pressure ventilation.

While volatiles affect vascular smooth muscle, they have very little effect on pulmonary vascular resistance. Modern volatile agents do inhibit hypoxic pulmonary vasoconstriction at high concentrations, thereby increasing V/Q mismatch, which may result in hypoxia.

Inhaled anesthetics have been used to treat status asthmaticus when conventional treatment fails. This works as an effective treatment as volatiles relax smooth muscle in the airway by decreasing smooth muscle tone from $beta_2$ receptor activation, inhibition of acetylcholine and histamine, and blocking of hypocapnic bronchoconstriction [2, 3]. The bronchodilating effect may be lessened when the bronchial epithelium is damaged, as seen in asthmatics or patients with respiratory viruses. Isoflurane and desflurane are more irritating to the airways than sevoflurane and can produce airway irritation and, in the instance of desflurane, can increase airway resistance. This irritation may lead to coughing or laryngospasm. Sevoflurane's less noxious properties make it the volatile agent of choice for an inhalation induction of general anesthesia, though isoflurane and desflurane are used for maintenance of anesthesia without increased incidence of airway irritation [2].

Volatile anesthetics reduce ciliary movement and alter the characteristics of mucus that can result in inadequate clearing of secretions, mucus plugging, atelectasis, and hypoxemia.

Biotransformation and Toxicity of Inhalational Anesthetic Agents

Comparing currently used anesthetics, sevoflurane is prone to significant biodegradation, followed by isoflurane and desflurane (Table 10.2). The biodegradation pathways of isoflurane and desflurane are closely related. Both isoflurane and desflurane involve cytochrome P450 2E1 enzymes that insert an active oxygen atom, producing HCl (isoflurane), HF (desflurane), and an unstable product that degrades to trifluoroacetic acid, carbon dioxide, fluoride ions, and water. Sevoflurane is also metabolized via cytochrome P450 2E1 oxidative biodegradation, producing carbon dioxide, inorganic fluoride, and hexafluoroisopropanol. Biodegradation is mostly found in the liver and only insignificantly in the kidney [8].

Table 10.2 Biodegradation of modern volatile anesthetics

Common anesthetics	% of metabolism
Sevoflurane	5–8
Isoflurane	0–0.2
Desflurane	0–0.02

Isoflurane

In adult population, there has been controversy regarding the use of isoflurane in patients with coronary artery disease because of the possibility of "coronary steal," which is diversion of blood from areas of the myocardium with inadequate perfusion to the myocardium with more adequate perfusion. However, this has not been shown to be clinically significant. Isoflurane exposure has also been demonstrated to induce cognitive decline in mice. Exposure of cultured human cells to isoflurane has been reported to induce apoptosis as well as accumulation and aggregation of amyloid beta protein. However, no clear link between clinical exposure to isoflurane and cognitive decline or dementia in humans has been established. The results from observational studies of anesthetic exposure in children have been mixed, and more preclinical and clinical studies are required to determine whether anesthetics cause injury to humans.

Sevoflurane

Sevoflurane metabolites include fluoride ($F-$), which has the potential to cause high-output renal failure. However, because of sevoflurane's low blood-gas solubility and its rapid elimination, fluoride concentrations fall very quickly after surgery, and renal toxicity from fluoride does not occur. The interaction of sevoflurane with dry carbon dioxide absorbents produces a chemical toxic to rats called "compound A." Larger amounts of breakdown products are produced at very low fresh gas flows, as a result of increased temperature of the soda lime, and when the soda lime is desiccated. Compound A causes serious injury to kidneys in rats but is not proven to cause the same in humans [9].

Desflurane

Desflurane is minimally metabolized. The interaction of desflurane with dry CO_2 absorbents produces carbon monoxide and possibly results in increased levels of blood carboxyhemoglobin. The major clinical drawbacks of desflurane are its airway pungency and cardiovascular reactivity making it difficult to use in pediatric population.

Table 10.3 Use of volatile anesthetics outside of the operating room

Advantages	Disadvantages
Bronchodilation	Nausea, vomiting
Anticonvulsant	Specialized equipment
Potential lung and myocardial protection	Cardiorespiratory depression
Minimal drug tolerance/tachyphylaxis or withdrawal	Nephrotoxicity
Postoperative sedation	Immunomodulation
Ease of titrating depth of sedation	Neuroapoptosis
Insignificant end organ metabolism	Malignant hyperthermia

Advantages of Inhalational Anesthetic Use in the PICU

The advantages of inhalational anesthetics in the critical care setting include improved management of status epilepticus, bronchospastic airway diseases such as status asthmaticus, alternative to traditional sedation practices, and potential for myocardial and lung protection (Table 10.3).

Status Epilepticus

Status epilepticus is a potentially life-threatening medical emergency. The definition of status epilepticus historically has been variable, though its current definition is accepted as continuous seizures lasting more than 5 minutes or intermittent seizures for 30 minutes without recovery in between seizures. Approximately 10–20% of children with epilepsy will have at least one instance of status epilepticus [10]. Refractory status epilepticus is when there is clinical or EEG evidence of seizures after 60 minutes despite treatment with a first-line anticonvulsant (benzodiazepine) and second-line anticonvulsant medications (i.e., fosphenytoin, phenytoin, phenobarbital, valproate, levetiracetam). Superrefractory status epilepticus is a refractory status epilepticus that persists or recurs after 24 hours of general anesthesia [11]. General anesthesia for refractory seizures may be achieved using intravenous (IV) agents or inhalational agents with the goal of burst suppression. IV anesthetic agents include pentobarbital, midazolam, or propofol. The use of IV anesthetic agents is typically limited by side effects and complications. It should be noted that propofol, while used in the adult population, has less utility in the pediatric population due to the risk of propofol infusion syndrome [11] and is contraindicated in the setting of a ketogenic diet. While the use of inhaled volatile anesthetics is not always included in the treatment algorithm for refractory status epilepticus, its use has been described in the literature since as early as the 1960s [12], and modern-day volatiles have been reported since the 1980s [13, 14]. Volatile agents are oftentimes considered the last resort after the failure of IV anesthetic agents. Their use in the ICU is limited by the ability to safely deliver the gas with appropriately trained personnel. Inhaled anesthetic agents have a marked advantage in the ability to provide almost immediate

control of seizure activity. Retrospective reports have demonstrated isoflurane was effective in almost immediately stopping long-standing superrefractory status epilepticus [14, 15]. Another distinct advantage of inhaled volatile anesthetic gases is the ease at which they are measured and titrated. The minimum alveolar concentration of isoflurane required to achieve burst suppression is between 1.5% and 2%. In conjunction with continuous EEG monitoring, inhaled anesthetics are easily titratable to maintain the minimum concentration required for burst suppression. Even in prolonged use, there do not seem to be long-standing adverse effects on hepatic or renal function [15, 16]. There is not good evidence for how long to continue burst suppression under inhalational anesthesia. The time should be used to optimize antiepileptic therapy and identify and treat underlying etiologies. Much of the evidence supporting the efficacy of volatile anesthetics in arresting refractory status epilepticus is limited to case reports or series. Ideally, larger prospective randomized controlled trials would help identify the role in which volatile anesthesia should play in the management of status epilepticus.

Bronchospastic Airway Disease and Status Asthmaticus

Status asthmaticus is a life-threatening refractory asthma exacerbation that can result in respiratory failure and death. Standard treatment of status asthmaticus includes oxygen, inhaled short-acting beta agonists, corticosteroids, anticholinergics such as ipratropium, and intravenous magnesium sulfate. Subsequent treatment may include methylxanthines, noninvasive positive pressure ventilation, heliox, ketamine, nebulized epinephrine, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [17, 18]. Inhaled volatile anesthetics are effective bronchodilators with halothane reported in the literature to successfully treat refractory severe status asthmaticus dating as far back as the 1930s with cyclopropane [19] and 1970s and 1980s with halothane [20, 21]. Since that time, there have been several case reports noting treatment of status asthmaticus with modern-day anesthetics including isoflurane or sevoflurane when conventional therapy has failed [22]. Several larger retrospective reviews have also reported successful treatment of severe asthma with isoflurane that was refractory to traditional management in pediatric and adult patients [23, 24]. Multiple reviews report improvement of pH and PCO_2 after initiation of inhaled volatile anesthetic therapy in the setting of status asthmaticus [23, 24]. Because the patients require mechanical ventilation for long-term delivery of inhaled anesthetics, volatile anesthesia has the added benefit of providing necessary sedation, reducing or eliminating the need for intravenous sedation. To date, much of the evidence supporting the effective use of volatile anesthesia for status asthmaticus is anecdotal and limited to case reports or case series. There may be a role for volatile anesthetics in the treatment of refractory status asthmaticus that fails to respond to conventional therapy. Ideally, randomized controlled trials would help further elucidate the role that inhaled volatile anesthetics should play in the treatment of refractory status asthmaticus.

Alternative Sedation Option for ICU Sedation

Approximately 85% of ICU undergoing mechanical ventilation or invasive procedures undergo sedation [25]. The most commonly used agents are intravenous and include benzodiazepines and propofol in conjunction with opioids. Ketamine, barbiturates, and dexmedetomidine are also utilized [25]. No intravenous sedation agent is ideal. Benzodiazepines may be associated with tolerance, withdrawal, or neuropsychiatric disorders (depression, anxiety, posttraumatic stress disorder) [26, 27]. Propofol may be associated with propofol infusion syndrome (potentially fatal complication as a result of prolonged propofol infusion), resulting in metabolic acidosis, rhabdomyolysis, hyperlipidemia, cardiac and renal failure [28], hypertriglyceridemia, and pancreatitis. Along with opioids, propofol and benzodiazepines rely on the liver and kidney for elimination [29]. Certain benzodiazepines have active metabolites. Both undersedation and oversedation are problematic with IV agents. Inhaled volatile agents have been used in the operating room for surgical anesthesia for over a century. As discussed previously, over the last few decades, they have also been used on occasion in the pediatric and adult critical care setting for the treatment of refractory status asthmaticus and epilepticus when conventional therapy has failed. More recently, investigation into its use as a sedative agent outside of the operating room has increased interest. Volatile anesthetic agents have distinct advantages in that they are easily measured and titratable, have a rapid onset of action, lack tolerance or tachyphylaxis, exhibit rapid offset with pulmonary elimination, and have low hepatic metabolism and no significant metabolites [30]. The ability to measure end-tidal concentration of inhaled volatile gases helps prevent over- or undersedation. Rapid washin and washout of gases contribute to its titratability. These both contribute to faster emergence times as compared to intravenous agents. In the adult literature, several trials have demonstrated that in short-term postoperative sedation, inhaled volatile sedation has shorter times to extubation when compared to midazolam or propofol [31–33]. Similar results have been demonstrated with longer-term sedation trials [34, 35]. Mesnil et al. also demonstrated that the sevoflurane group had a reduction in morphine consumption 24 h post extubation as compared to the midazolam and propofol groups, suggesting a possible benefit of opioid sparing when inhaled volatile agents are used for sedation [35].

There may be a role for the use of inhaled volatile agents for sedation in the critical care setting. Trials are currently underway examining the use of volatile agents for long-term sedation in North America (VALTS) and Germany (IsoConDa) [4]. Prior to adopting widespread use of volatile sedation in the ICU setting, the safety, efficacy, and benefit over traditional intravenous sedation must be demonstrated. In addition to this, safe delivery with specialized devices and appropriately trained practitioners and personnel remains a large obstacle.

Potential Myocardial and Lung Protection Properties

Pharmacologic conditioning of the heart occurs when exposure to a particular drug protects the heart from ischemia or reperfusion injury. Preconditioning occurs when the protective effect follows exposure prior to the ischemic event; postconditioning occurs when the protective effect takes place when exposure occurs immediately following the ischemic event. Volatile anesthetic agents appear to be a class of drugs that demonstrate pre- and postconditioning in animal models [36, 37]. There appears to be a benefit of using volatile agents during cardiac surgery; however, there was no difference in myocardial ischemia during noncardiac surgery when comparing volatile agents to total intravenous anesthesia [38]. In one pediatric study of children undergoing ventricular septal defect repairs, preconditioning with volatiles demonstrated decreased creatinine kinase MB (CK MB) release. It showed a trend to decrease inotropic support and ventilation and intensive care unit duration; however it was not statistically significant [39].

In addition to potential cardioprotection, volatile anesthetics have demonstrated protection on other organ systems including the lungs. In rodent models, sevoflurane was shown to suppress inflammation [41], and isoflurane decreased lung injury and vascular leakage [40]. Most of the clinical data in humans regarding pulmonary protection rely on intraoperative exposure to volatile anesthetics. When compared to propofol, patients under one-lung ventilation anesthetized with volatile anesthetics had decreased markers of inflammation [41] and reduced adverse events including pneumonia, atelectasis, pleural effusion, and bronchopulmonary fistula [42]. A prospective analysis of data on 124,497 patients over an 8-year period found that higher intraoperative inhalational anesthetic dose was associated with a lower odds of postoperative respiratory complications and also with a lower 30-day mortality [43].

While preclinical evidence for the role of volatile anesthetics in cardiac conditioning and lung protection is compelling, further investigation into the role volatile agents may play in clinically relevant cardiac and pulmonary protection is necessary, especially in the pediatric population.

Disadvantages of Inhalational Anesthetic Use in the PICU

There is growing interest for the use of potent inhaled anesthetics outside the operating room especially in the ICU. The disadvantages of volatile anesthetic (Table 10.3) use in the ICU include cost, equipment needs, cardiorespiratory depression, side effect profile of the volatile anesthetics, malignant hyperthermia (MH), immunomodulatory effects, and neurocognitive dysfunction.

Specialized Equipment

The primary limitation to the use of inhalational anesthetics in the PICU setting traditionally has been related to practical difficulties associated with administration of inhaled anesthetic agents outside of the operating room. These difficulties include problems with administration, monitoring, and gas scavenging. Routine use has been limited by the requirement of vaporizers, specially adapted ventilators and high flow respiratory circuits resulting in high agent consumption, costs, and concerns about environmental contamination. Inhalational anesthetic implementation in the ICU requires engineering upgrade of a significant part of the ICU for gas-scavenging infrastructure and technical investments such as the filters, delivery pumps, and gas analyzer. The availability of miniature vaporizers, such as the Anesthesia Conserving Device (AnaConDa; Sedana Medical, Uppsala, Sweden) and the more recently introduced MIRUS system (Pall Medical, Dreieich, Germany), has attempted to simplify bedside volatile anesthetic administration [44]. AnaConDa is the most studied and widely used heat moisture exchanger in the world. Unfortunately it does add 100 ml to the dead space in the ventilator circuit, which may result in hypercapnia especially during weaning from mechanical ventilation [34]. Another potential problem is inadvertent intravenous injection as the Luer-lock anesthetic infusion line has a similar appearance to intravenous infusion lines [45]. Additionally, workplace contamination may occur during refilling of the syringes and loss of anesthetic to the environment during frequent tracheal tube suctioning. Currently, the MIRUS device and AnaConDa are available in very limited countries and have not been approved for use in the USA. The implementation of inhaled anesthetics in critical care setting requires an important educational intervention directed at the physicians, nurses, and respiratory therapists. Knowledge about agents has to be maintained round the clock across all shifts and staff rotations.

Cardiorespiratory Depression

Volatile anesthetics universally produce concentration-dependent myocardial depression. This is due primarily to altered Ca^{2+} entry and sarcoplasmic reticulum Ca^{2+} handling [46]. The negative inotropy is compounded by decreases in systemic vascular resistance (SVR) by isoflurane, desflurane, and sevoflurane to further reduce blood pressure. Reduction in SVR is most prominent with isoflurane, supporting the theory of coronary steal phenomenon in patients with coronary artery disease. All volatile anesthetics prolong the QT interval, potentially increasing the risk of torsades de pointes polymorphic ventricular tachycardia. Volatile anesthetics also cause dose-dependent respiratory depression. Inhalational anesthetics significantly affect respiration in infants and children in a dose-dependent fashion via effects on the respiratory center, chest wall muscles, and reflex responses. Isoflurane, sevoflurane, and desflurane depress ventilatory drive and response to CO_2, resulting in a dose-dependent decrease in alveolar ventilation mainly through reduction in tidal volume,

while the respiratory rate is maintained or slightly increased. The increased respiratory rate during inhalational anesthesia has been attributed to sensitization of the stretch receptors within the lung as well as possible central effects. Even at subanesthetic concentrations, it blunts the hypoxic and hypercarbic ventilatory responses.

Adverse Effects of Inhalational Agents

Some of the adverse effects of inhalational anesthetics include nephrotoxicity, hepatotoxicity, and nausea and vomiting. Inhalational anesthetics affect renal function potentially due to four possible mechanisms: cardiovascular, autonomic, neuroendocrine, and metabolic. Metabolic mechanism is a serious clinical concern that has led to renal dysfunction after inhalational anesthesia. Metabolism of inhalational anesthetics releases inorganic fluoride that has been postulated to cause renal dysfunction. A second theoretical cause of sevoflurane-associated renal dysfunction is compound A, a product of alkaline hydrolysis of sevoflurane in the presence of CO_2 absorbents. In vivo, sevoflurane is metabolized by microsomal CYP IIE1 isozyme in both the liver and kidneys. The peak plasma concentration of inorganic fluoride is proportional to the duration of exposure to sevoflurane in children [8]. However, studies have failed to show any evidence of nephrotoxicity with prolonged volatile use, even in the setting of high fluoride levels.

Isoflurane, sevoflurane, and desflurane have also been associated with transient hepatic dysfunction and raised transaminase enzymes. This severe form involves massive hepatic necrosis that can lead to death. The mechanism for this severe injury is immunologic, requiring prior exposure to a volatile anesthetic. Isoflurane and desflurane all undergo oxidative metabolism by cytochrome P450 enzymes to produce trifluoroacetate. The trifluoroacetate can bind covalently to hepatocyte proteins. The trifluoroacetyl-hepatocyte moieties can act as haptens, which the body recognizes as foreign and to which the immune system forms antibodies. Subsequent exposure to any anesthetic capable of producing trifluoroacetate may provoke an immune response, leading to severe hepatic necrosis [47].

The use of volatile anesthetics is associated with a twofold increase in the risk of PONV, with risk increasing in a dose-dependent manner, and no significant difference in incidence with different volatile anesthetics [48]. The exact nature of vomiting pathways is complex and also not fully understood, but a number of pathophysiological mechanisms known to cause nausea or vomiting have been identified. The main coordinator is the vomiting center, a collection of neurons located in the medulla oblongata. Such structures include the chemoreceptor trigger zone (CRTZ), located at the caudal end of the fourth ventricle in the area postrema, and the nucleus tractus solitarius (NTS), located in the area postrema and lower pons. The CRTZ receives input from vagal afferents in the gastrointestinal tract, and it can also detect emetogenic toxins, metabolites, and drugs circulating in the blood and cerebrospinal fluid due to its lack of the blood-brain barrier. The CRTZ projects neurons to the NTS, which receives input from vagal afferents and from the vestibular and limbic systems. The NTS triggers vomiting by stimulating the rostral

nucleus, the nucleus ambiguous, the ventral respiratory group, and the dorsal motor nucleus of the vagus. PONV is also linked to several other stimuli, including opioids, volatile anesthetics, anxiety, adverse drug reactions, and motion. Multiple neurotransmitter pathways are implicated in the physiology of nausea and vomiting [49]. Enterochromaffin cells in the gastrointestinal tract release serotonin, and the vagus nerve communicates with the CRTZ via 5-HT3 receptors. The CRTZ communicates with the NTS primarily via dopamine-2 (D2) receptors. The vestibular system, which detects changes in equilibrium, communicates with the NTS via histamine-1 (H1) and acetylcholine (mACh). Anticipatory or anxiety-induced nausea and vomiting appears to originate in the cerebral cortex, which communicates directly with the NTS via several types of neuroreceptors [49]. Therefore, antiemetic drugs have been developed to target these specific receptors. Given that available antiemetic drugs work on different receptor classes, multiple antiemetics can be safely and effectively combined to reduce the risk of PONV in high-risk patients.

Malignant Hyperthermia (MH)

Malignant hyperthermia (MH) is a rare (1 in 50,000 to 100,000) pharmacogenetic disorder of skeletal muscle triggered in susceptible individuals by all volatile inhalational anesthetics. In addition to volatile agents, depolarizing skeletal muscle relaxants such as succinylcholine can also trigger MH. This syndrome has been linked to mutation in the type 1 ryanodine receptor (RyR1) in more than 50% of cases studied to date. Signs of MH include tachycardia, increased expired CO_2, muscle rigidity, and increased temperature and are related to increased metabolism (hypermetabolic state). The key aspects of management include discontinuation of volatile anesthetics and succinylcholine, immediate administration of intravenous dantrolene, and treatment of potentially life-threatening electrolyte abnormalities such as hyperkalemia. The Malignant Hyperthermia Association of the United States (MHAUS) provides detailed treatment recommendations on its website http://www.mhaus.org/healthcare-professionals. MHAUS also maintains a 24-hour hotline for emergency advice (1-800-644-9737 in the USA; 001-209-417-3722 outside of the USA). Dantrolene markedly attenuates the loss of calcium from sarcoplasmic reticulum, restoring the metabolism to normal and reversing the signs of metabolic stimulation. This can be difficult to diagnose in the critically ill patient in the ICU setting due to other comorbidities [50]. Use of volatile anesthetics requires staff education, malignant hyperthermia protocol adoption, and dantrolene availability to manage this rare medical emergency.

Immunomodulatory Effects

Volatile anesthetics have long been known to moderately suppress the immune system. Numerous studies have investigated whether this suppression increased the risk of postoperative wound infection, and no correlation was ever identified.

Although specific targets of volatile anesthetics in the immune system have not been well defined, molecular and cellular events involved in immunomodulation by volatile anesthetics have been identified, including a reduction in the number of immune cells due to cell death and the suppression of immune activities. Whether this immunosuppression hinders the host's ability to kill malignant cells liberated during surgical manipulation has become a question of research interest. There have been mixed results in rat models. Theoretically, many perioperative factors potentially suppress the host immunity and augment the cancer cells, leading to the growth of minimally residual tumor cells and recurrence of cancer. Some studies have reported potentially harmful immunosuppression or cancer cell augmentation after anesthesia with volatile anesthetics [51, 52]. Other identified co-founding factors have shown intermittent association with poor outcomes, including surgical stress response, hypotension, hypothermia, hyperglycemia, blood transfusions, glucocorticoids, and NSAIDs [51]. Well-controlled randomized clinical trials are needed, although isolating effects of volatile anesthetics from other factors in a perioperative setting remains challenging. Future studies should take into consideration the surgical procedures involved, the anesthetics and other medications used, and the time dependence in immunomodulation and resolution.

Neurocognition Effects

Over the last decade, the safety of the anesthetic agents has come under scrutiny after the realization that immature animals demonstrate neurodegeneration and long-lasting neurocognitive and behavioral deficiencies and elderly animals have learning and memory impairment after exposure to general anesthesia [53]. All of the commonly used anesthetic and sedative agent classes bind either to the GABA receptor or to the N-methyl-D-aspartate receptor (NMDA – a subtype of the glutamate receptor) to produce their anesthetic and sedative effects. Evidence from animal studies suggests that most general anesthetics which block NMDA receptor or bind GABA receptors trigger neuroapoptosis or programmed cell death in the developing brain. These agents include inhalational anesthetics which bind to GABA receptors. NMDA-binding agents include nitrous oxide and ketamine.

In immature rodents and monkeys at critical developmental periods, exposure to either NMDA receptor blockers or GABAergic agents can lead to increased apoptosis [54]. The effects are dose dependent and seen over particular periods of early development. There is some evidence that rodents exposed to anesthesia during infancy have delayed neurobehavioral development. One of the proposed mechanisms for anesthetic-induced neuroapoptosis in the developing brain occurs when binding of GABA and NMDA agents blocks normal neurotransmission in the GABA and glutamate systems, resulting in synaptic deprivation [55, 56]. This in turn leads to the activation of the intrinsic neuroapoptotic cascade due to lack of neuronal stimulation. Mitochondrial disruption occurs as part of this process and can be observed in electron microscopic studies of anesthetic exposure. Caspase 9 is released from the mitochondria, resulting in increased caspase 3 concentrations, inciting the completion of the neuroapoptosis process [55, 56].

The most important human studies to assess the impact of anesthesia on the developing brain include the General Anesthesia Compared to Spinal Anesthesia (GAS) and the Pediatric Anesthesia Neurodevelopmental Assessment (PANDA). The GAS randomized infants undergoing inguinal hernia repair to either an awake-regional technique or a general anesthetic. Secondary outcomes assessed at 2 years of age showed no increased risk of adverse neurodevelopment in children exposed to a general anesthetic [57]. The PANDA study compared children who had undergone inguinal hernia repair with general anesthesia before 3 years of age with an unexposed sibling. No difference in IQ was found between exposed and unexposed siblings [58]. The results from these trials suggest that a short-duration anesthetic in otherwise-healthy children may have limited effects. Nevertheless, the concerns regarding anesthetic neurotoxicity led the US Food and Drug Administration (FDA) to issue a drug safety communication.

In 2017, the US FDA issued a drug safety communication stating that the use of general anesthetic drugs "for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than 3 years" [59]. "Lengthy" is defined as >3 h; this warning has resulted in a labeling change to all common anesthetic drugs binding to GABA and NMDA receptors, including volatile anesthetic agents. Furthermore, US FDA warns that "…we should discuss with parents, caregivers, and pregnant women the benefits, risks, and appropriate timing of surgery or procedures requiring anesthetic and sedation drugs" [59]. The International Anesthesia Research Society, in a collaborative public-private partnership with the FDA, formed SmartTots (Smart Strategies to Reduce Anesthesia Risk in Tots; www.smarttots.org) to coordinate and fund research with the goal of ensuring safe surgery for infants and children who undergo anesthesia and/or sedation.

Conclusions

Volatile agents are a family of inhalational general anesthetics and its use in the ICU setting holds a promising potential. However, additional study and overcoming barriers to ICU adoption need to be addressed before volatiles become routinely used in critical care setting. Current evidence suggests that volatiles have beneficial properties beyond the operating room. To show that volatiles present a clear clinical benefit, larger trials are required to see whether these agents display better sedation ventilation outcomes, cytoprotective properties, and longer-term cognitive effects compared with current intravenous methods. Furthermore, introducing change to existing clinical practice and organizational behaviors and attitudes presents an additional challenge in the ICU settings. Presently, delivery of volatile agents in the ICU is a new approach for many critical care providers who have limited anesthesia training related to volatile delivery. As a result, education and training programs will be necessary to assist intensivists with the learning curve in understanding this group of agents, optimizing complex drug delivery system and avoiding pitfalls. Evolving research will continue to provide insights of whether these agents have new therapeutic indications beyond the operating room.

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