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# Inhalational Anesthesia: Basic Pharmacology, End Organ Effects, and Applications in the Treatment of Status Asthmaticus

**Joseph D. Tobias, MD**[1]

**Abstract**

The potent inhalational anesthetic agents are used on a daily basis to provide intraoperative anesthesia. Given their beneficial effects on airway tone and reactivity, they also have a role in the treatment of status asthmaticus that is refractory to standard therapy. Although generally not of clinical significance, these agents can affect various physiological functions. The potent inhalational anesthetic agents decrease mean arterial pressure and myocardial contractility. The decrease in mean arterial pressure reduces renal and hepatic blood flow. Secondary effects on end-organ function may result from the metabolism of these agents and the release of inorganic fluoride. The following article reviews the history of inhalational anesthesia, the physical structure of the inhalational anesthetic agents, their end-organ effects, reports of their use for the treatment of refractory status asthmaticus in the intensive care unit (ICU) patient, and special considerations for their administration in this setting including equipment for their delivery, scavenging, and monitoring.

**Keywords**

inhalational anesthsia, status asthmaticus, mechanical ventilation, bronchospasm

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## Introduction

Intraoperatively, a key component of most general anesthetics includes the administration of one of the potent inhalational anesthetic agents (isoflurane, sevoflurane, or desflurane). These agents are capable of providing the required components of general anesthesia including amnesia, analgesia, skeletal muscle relaxation, and control of the sympathetic nervous system. Additionally, they are generally well tolerated with limited effects on end-organ function. In addition to their general anesthetic effects, the potent inhalational anesthetic agents have beneficial physiologic effects including dilatation of airway smooth musculature and reversal of bronchospasm. Given these effects, they are occasionally used in both adult and pediatric patients in the intensive care unit (ICU) setting as a therapeutic maneuver to treat intractable status asthmaticus that is resistant to conventional therapy. The following article reviews the history of inhalational anesthesia, the physical structure of the inhalational anesthetic agents, their end-organ effects, reports of their use for the treatment of refractory status asthmaticus in the ICU patient, and special considerations for their administration in this setting.

## The History of Inhalational Anesthesia

The clinical practice of inhalational anesthesia began more than 150 years ago in the 1840s with the demonstration of the efficacy of diethyl ether by Drs Long and Morton and nitrous oxide ($N_2O$) by Horace Wells. Although these agents were effective and for the first time allowed the performance of major surgical procedures, drawbacks including $N_2O$'s lack of potency, flammability of the other agents, their adverse effect profile, and the unfavorable pharmacokinetics of ether and chloroform mandated the development of alternative agents. In the 1940s, advances in physical and experimental chemistry as off-shoots of nuclear research led to advancements in fluorine chemistry and the subsequent development of efficient and cost-effective ways of incorporating fluorine into the chemical structure of various molecules. These advances led to the next generation of inhalational anesthetic agents including trichloroethylene. Although these agents were less flammable, there were still significant adverse end-organ effects including hepatotoxicity and neurotoxicity in addition to problems with slow recovery. In 1946, Robbins

[1] Departments of Anesthesiology and Pediatrics, University of Missouri, Columbia, Missouri

**Corresponding Author:**
Joseph D. Tobias, MD; University of Missouri, Department of Anesthesiology, 3W-27G HSC, Columbia, MO 65212
Email: Tobiasj@health.missouri.edu

reported the initial work with a series of fluorinated hydrocarbons that led to the eventual synthesis of agents with clinical applications.[1,2] Fluroxene (2,2,2-trifluoroethyl vinyl ether), a fluorinated hydrocarbon, was eventually synthesized in 1951 and became the first of the fluorinated hydrocarbons to be widely used in clinical practice.[3] Despite having significant advantages over the original inhalational anesthetic agents, this agent was still not optimal. Its adverse effect profile including the potential to precipitate ventricular dysrhythmias, nausea and vomiting, and hepatotoxicity encouraged the ongoing search for better agents.[4-6]

Halothane, a halogenated alkane, was synthesized by Suckling in the United Kingdom in the early 1950s and introduced into clinical practice in 1956.[7] Its favorable properties including its non-flammability, favorable blood:gas partition coefficient, rapidity of onset during inhalation induction, bronchodilatory properties, relative cardiovascular stability, non-pungency, and decreased incidence of nausea and vomiting compared to its predecessors quickly led to its widespread use in general anesthetic practice. However, its potential to elicit an immune-mediated hepatotoxicity pushed the ongoing development of newer agents with less hepatotoxicity. The 1970s and 1980s saw significant work with the development of specific methyl-ethyl ethers in an attempt to replace halothane. The methyl-ethyl ethers were chosen over many other compounds as they were stable, non-flammable, and effective general anesthetic agents. The substitution of other halides with fluorine led to greater stability and lower tissue solubility. This work led to the development of the modern class of the potent inhalational anesthetic agents including enflurane, isoflurane, and eventually desflurane. The latter agents combined with the reintroduction of sevoflurane into clinical practice in the early 1990s comprise the currently used class of potent inhalational anesthetic agents.

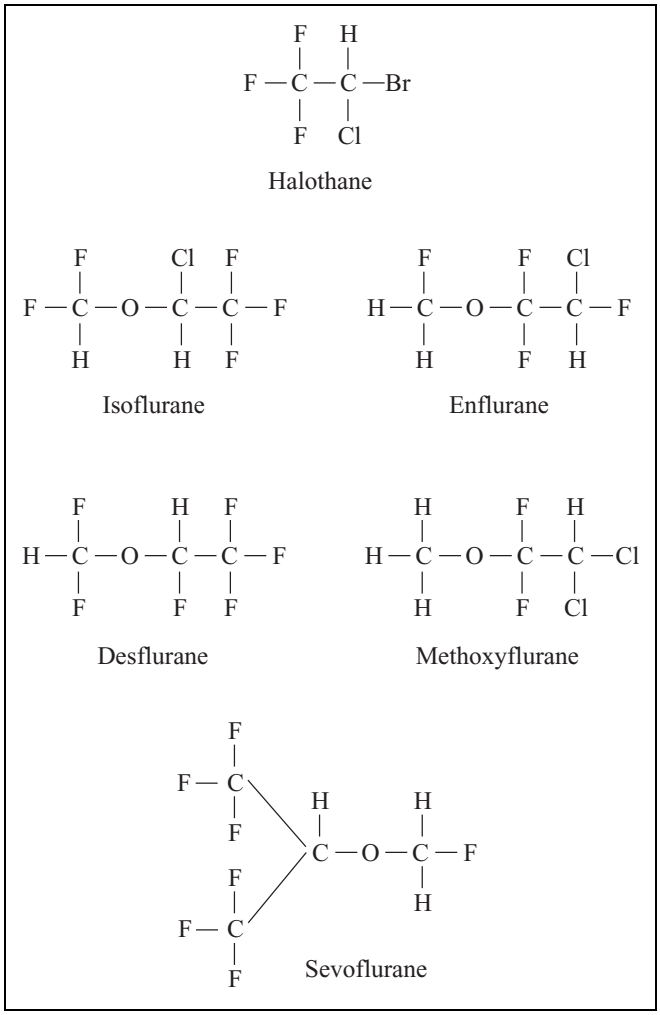


**Figure 1.** Chemical structures of nitrous oxide and the potent inhalational anesthetic agents. The potent inhalational anesthetic agents can be classified into 2 major groups: alkanes such as halothane and ethers. The ethers are further subdivided into methyl, ethyl ethers (isoflurane, desflurane, methoxyflurane, and enflurane) and methyl, isopropyl ethers (sevoflurane).

## Basic Principles of Inhalational Anesthesia

### *Chemical Structure*

The potent inhalational anesthetic agents can be divided into 2 chemical classes, alkanes and ethers (Figure 1). Halothane is an alkane (a 2-carbon chain) while enflurane, isoflurane, desflurane, and sevoflurane are ethers. The first 3 are substituted, methyl-ethyl ethers while sevoflurane is a methyl-isopropyl ether. Variations in the physical and chemical properties such as blood:gas solubility, blood:fat solubility, and potency of the ether compounds are controlled by the substitution of halides (fluoride or chlorine) instead of hydrogen atoms around the carbon molecules. All of the potent inhalational agents fall under the category of volatile liquids, meaning that they have the potential to transform into a vapor. This potential is termed the vapor pressure and varies from agent to agent (Tables 1 and 2). This is one of the previously mentioned physical properties that are determined by the halide substitution around the carbon atoms. Given the volatile nature of these compounds, they can be delivered as a gas to the patient via a vaporizer that allows the adjustment of the inspired concentration of the agent. Given the differences in the vapor pressure among the different potent inhalational anesthetic agents; in the practice of modern anesthesia, there is a specific vaporizer for each of the inhalational anesthetic agent. These vaporizers are calibrated for the specific anesthetic agent. They are termed variable bypass vaporizers in that when the vaporizer is set in the 0% position, all of the gas flow is diverted around the vaporizer and therefore none of the agent is delivered. As the concentration is increased, part of the gas flow depending on the vapor pressure and the inspired concentration desired, is allowed to pass over the inhalational anesthetic agent. This gas flow equilibrates rapidly with the inhalational anesthetic agent and is then added to the gas flow that bypasses the vaporizer thereby delivering the concentration that is set on the vaporizer dial.

**Table 1.** Physical Properties of the Inhalational Anesthetic Agents

| Inhalational anesthetic agent | Vapor pressure (mm Hg @ 20°C) | Blood:gas partition coefficient @ 37°C | MAC (minimum alveolar concentration) |
|---|---|---|---|
| Halothane | 243 | 2.54 | 0.76% |
| Enflurane | 175 | 1.91 | 1.7% |
| Isoflurane | 238 | 1.46 | 1.2% |
| Sevoflurane | 160 | 0.69 | 2% |
| Desflurane | 664 | 0.42 | 6% |

**Table 2.** A Comparison of Isoflurane, Desflurane, and Sevoflurane

| Property | Isoflurane | Desflurane | Sevoflurane |
|---|---|---|---|
| ICU experience | Significant | Limited | Limited |
| Blood:gas partition coefficient | 1.46 | 0.42 | 0.69 |
| MAC | 1.2% | 6% | 2% |
| Onset | Slow | Rapid | Rapid |
| Hemodynamic effects | Decreased SVR with reflex tachycardia; increased cardiac output | Decreased SVR with reflex tachycardia; increased cardiac output | Decreased mean arterial pressure and decreased heart rate |
| Stimulation of the sympathetic nervous system | Minimal | Significant with high concentration or rapid changes in inspired concentration | Minimal |
| Arrhythmogenicity | Limited | Limited | Limited |
| Direct airway irritant effects | Moderate | Significant | Minimal |
| Metabolism | 0.2% | Less than 1% | 5%-10% |
| Metabolic products | TFA | TFA | Compound A, fluoride |
| Cost | Low | Moderate-high | Moderate-high |

NOTES: MAC = minimum alveolar concentration; SVR = systemic vascular resistance; TFA = triflouroacetic acid.

## *Uptake and Distribution*

As volatile liquids, one unique aspect of the potent inhalational anesthetic agents is their administration via the respiratory tract. The onset and duration of action are determined by what is known as the blood:gas solubility coefficient. This coefficient is a reflection of the solubility of these agents in the blood and describes how the anesthetic agent distributes or partitions itself between the blood and the alveoli (Table 1). An agent with a high blood:gas partition coefficient is highly soluble in the blood and will have a slower onset and longer duration of action than an agent with a low blood:gas solubility coefficient. With a low blood:gas solubility coefficient, less of the agent is dissolved in the blood and therefore less is carried away from the alveoli and the brain to the vessel-rich group. With a low blood:gas partition coefficient, the alveolar concentration increases rapidly. The end-capillary venous blood leaving the lungs equilibrates rapidly with the alveolar concentration of the agent. This blood enters the left atrium and becomes the arterial blood leaving the left ventricle. The arterial blood concentration rapidly equilibrates with the brain tissue to provide the anesthetic effect. Given this pattern of uptake and distribution, the increase in the alveolar concentration parallels the brain tissue concentration. Desflurane has the lowest blood:gas solubility coefficient and therefore the most rapid onset and offset, followed in order by sevoflurane, isoflurane, enflurane, and halothane (Table 1). Halothane and sevoflurane are less irritating to the airway than the other agents (isoflurane, desflurane, and enflurane) and therefore are used for the inhalation induction of anesthesia in pediatric and adult patients when intravenous access is not available. Given its limited effects on myocardial contractility and lower blood:gas partition coefficient when compared with halothane, sevoflurane has become the preferred agent for the inhalational induction of anesthesia with halothane no longer manufactured in the United States.

## *Potency (MAC)*

Another feature that varies from agent to agent is their potency. When dealing with the inhalational anesthetic agents, potency is measured by minimum alveolar concentration (MAC). Minimum alveolar concentration is defined as the alveolar concentration of the agent (expressed as a percentage) that is required to prevent one-half of patients from moving in response to a surgical stimulus (Table 1). Obviously, intraoperatively it would be unacceptable for 50% of the patients to move in response to a surgical incision and therefore, greater than 1 MAC of an agent is used or other agents (opioids, propofol) that decrease MAC are combined with the inhalational anesthetic agents. The most potent agents have the lowest MAC. Halothane is the most potent with a MAC of 0.76%, followed by isoflurane (1.2%), enflurane (1.7%), sevoflurane (2%), and desflurane (6%). Medications (opioids, $\alpha_2$-adrenergic agonists,

benzodiazepines), associated conditions (pregnancy), comorbid disease processes (central nervous system [CNS] disorders), and age affect MAC. Minimum alveolar concentration is lower in preterm infants, increases in term infants, and then decreases slightly with advancing age, with a small bump or increase during puberty.[8,9] Although MAC is an important concept as it provides an estimation of the potency of the drug, when these agents are used in the treatment of status asthmaticus, the potent inhalational anesthetic agents are generally titrated based on the desired clinical response (bronchodilatation) rather than using MAC. Additionally, the inspired concentration may be started at a relatively high level (3-4 MAC) to rapidly obtain a high alveolar concentration and thereby achieve the desired clinical response. When used in the ICU setting or the operating room (OR), another term that may be used is MAC-hours. This describes not only the concentration of the agent that is delivered but also the duration of administration. For example, as the MAC of isoflurane is 1.2%, if one were to deliver 1.8%, this would be 1.5 MAC. If 1.8% isoflurane were delivered for 2 hours, this would equate to 3 MAC-hours or 1.5 MAC of the agent for 2 hours.

## End-Organ Effects

Although these agents are non-specific bronchodilators and generally effective in the treatment of bronchospasm, especially when used in high concentrations, adverse effects on other end-organs may occur and must be considered into the risk:benefit ratio when the decision is made to use these agents in the ICU setting.

### *Central Nervous System Effects*

The inhalational agents provide all of the prerequisites of a general anesthetic including sedation and amnesia. They cause a dose-related decrease in CNS activity, reduce the cerebral metabolic rate for oxygen, and depress electroencephalographic (EEG) activity. There is an initial decrease in the amplitude and frequency of the electroencephalograph (EEG) during the administration of sub-MAC concentrations that progresses to increasing periods of electrical silence (burst suppression) as the concentration is increased to 2-3 MAC. Given these effects, they are used everyday in ORs throughout the world and also occasionally to provide sedation during mechanical ventilation in the ICU setting.[10-13] Enflurane and sevoflurane can activate the EEG and produce EEG evidence of epileptiform activity at higher concentrations.[14] The EEG changes are also occasionally accompanied by clinical manifestations of seizure activity. These problems occur more commonly with hyperventilation and hypocarbia, generally occur only during the induction of anesthesia or with rapid increases in the alveolar concentration of the agent, and result in no clinical sequelae. All of the potent inhalational anesthetic agents increase cerebral blood flow (CBF) in a dose-dependent manner by cerebral vasodilatation and a reduction of cerebral vascular resistance. With altered intracranial compliance, these changes can elevate intracranial pressure (ICP). The effect on ICP is least with isoflurane and can be blunted by hyperventilation and by limiting the concentration to 1.0 MAC.[15,16]

### *Cardiovascular System*

The effects on hemodynamic function are also dose-related with a decrease of mean arterial pressure (MAP), myocardial contractility, and myocardial oxygen consumption. The decrease in MAP may also result in a reduction of renal and hepatic blood flow. The potential for these agents to depress cardiovascular function is illustrated by the fact that until its production ceased, halothane represented the number 1 cause of perioperative cardiac arrest in infants and children.[17] Changes in heart rate, cardiac output, and systemic vascular resistance vary from agent to agent. Isoflurane and desflurane result primarily in systemic vasodilatation that results in varying degrees of reflex tachycardia while a decrease in heart rate occurs with sevoflurane and halothane. A rapid increase in the inspired concentration of desflurane may stimulate the sympathetic nervous system, further increasing heart rate. As the primary hemodynamic effects of isoflurane and desflurane are peripheral vasodilatation, there is a decrease in afterload that increases cardiac output as opposed to the decrease in cardiac output that occurs with sevoflurane, halothane, or enflurane. Reflex tachycardia can increase myocardial oxygen demand while vasodilatation may lower diastolic blood pressure, thereby reducing myocardial perfusion pressure. It has also been suggested that coronary vasodilatation related to isoflurane may result in a coronary steal phenomenon in patients with areas of fixed coronary stenosis. These effects may lead to an imbalance in the myocardial oxygen delivery:demand ratio in susceptible patients. Therefore, in the ICU setting, isoflurane and desflurane should be used cautiously in patients at risk for myocardial ischemia or in patients who are unable to tolerate tachycardia and a decrease in systemic vascular resistance. A separate concern exists with halothane related to its alkane structure as it can sensitize the myocardium to the arrhythmogenic effects of catecholamines. These issues are of particular concern when combined with other predisposing factors including hypercarbia, other medications (aminophylline), or high circulating catecholamine levels.

### *Respiratory System*

The potent inhalational anesthetic agents result in a dose-related depression of respiratory function. As with the hemodynamic effects, these are modified by the coadministration of other medications and associated comorbid diseases. With increasing anesthetic depth, there is a progressive decrease in alveolar ventilation mediated by a reduction of tidal volume. This results in an increase in $Paco_2$ during spontaneous ventilation. The inhalational anesthetic agents also inhibit the normal ventilatory responses to hypercarbia and hypoxia by a rightward shift of the response curves. Oxygenation may be further affected by inhibition of hypoxic pulmonary vasoconstriction.[18] Beneficial airway effects including bronchodilatation

make them effective for the treatment of refractory status asthmaticus. Postulated mechanisms include β-adrenergic receptor stimulation, direct relaxation of bronchial smooth muscle, inhibition of the release of bronchoactive mediators, antagonism of the effects of histamine and/or methacholine, or depression of vagally-mediated reflexes.[19,20] More recently, it has been suggested that the potent inhalational anesthetic agents may result in bronchodilatation via an epithelial-dependent mechanism that involves either nitric oxide or a member of the prostanoid family.[21,22] The end result of these effects is the decreased availability of cytosolic calcium or decreased binding of calcium to regulatory proteins resulting in smooth muscle relaxation. In an animal model of chronic allergic asthma, the beneficial effects of sevoflurane on airway resistance and compliance relate not only to changes at the airway level but also in the lung periphery.[23] Although the bronchodilatory properties are shared by all of the potent inhalational anesthetic agents, they may be greatest with halothane while desflurane's bronchodilatory effects may be inadequate to compensate for its direct irritant effects on the airway.[24,25]

## Hepatic Effects

As with any medication, the potential for adverse effects must consider not only the parent compound, but also the metabolic products. For the potent inhalational anesthetic agents, metabolic fate is determined by their chemical structure. Metabolism of these agents is mediated by the hepatic $P_{450}$ system. In all, 15% to 20% of halothane is metabolized compared to 5% to 10% of sevoflurane, 2% to 3% of enflurane, 0.2% of isoflurane, and less than 0.1% of desflurane. Hepatotoxicity related to an immune-mediated reaction is most commonly encountered following exposure to halothane, given its greater degree of metabolism, but has also been reported with enflurane, isoflurane, or desflurane.[26-28] Hepatotoxicity is related to an immune-mediated hepatitis from the metabolic product, trifluroacetic acid (TFA). Trifluroacetic acid acts as a hapten, binding to hepatocytes and thereby incites an immune reaction. Although 5% to 10% of sevoflurane is metabolized, its metabolic pathway is different from the other agents and does not result in the production of TFA and thereby does not cause an immune-mediated hepatitis.[29]

The hepatotoxicity may present as either a mild or a fulminant form. As hepatic injury is more common with halothane than with the other 3 agents (enflurane, isoflurane, and desflurane), the majority of the literature and data regarding hepatoxicity of inhalational anesthesia relates to halothane. It is not known if these data can be universally applied to the other 3 agents. Mild injury affects 20% of adults who receive halothane while the fulminant form (halothane hepatitis) occurs in 1 of every 10 000 adult patients. The fulminant form manifests as massive hepatic necrosis that has a mortality rate of 50% to 75%. Up to 95% of the patients who develop the fulminant form have had a prior exposure to halothane. The most important risk factor for anesthesia-induced hepatotoxicity is prior anesthetic exposure. Other risk factors include female gender, middle age, obesity, and the ingestion of medications or toxins (chronic ethanol ingestion), which stimulate the hepatic microsomal enzymes. Given these concerns, halothane is not recommended for adult use but had been a popular agent for inhalation induction in pediatric anesthesia given its lack of airway pungency and because halothane hepatitis is rare in children (1/200 000).[30] When concerns arise regarding the presence of hepatotoxicity related to one of the potent inhalational anesthetic agents, serum can be sent to specialized centers to determine the presence of antibodies against TFA.

## Renal Effects

The potent inhalational anesthetic agents also have the potential for nephrotoxicity related either to release of fluoride during metabolism of the parent compound or from the metabolic byproducts. Issues related to fluoride are most prominent with enflurane as it has the greatest fluoride content and also undergoes significant metabolism (2% to 3%). Plasma fluoride concentrations and therefore the risks of toxicity also relate to the duration of administration.[31,32] The renal effects of plasma fluoride concentrations $\geq$50 μmol/L include a decreased glomerular filtration rate and renal tubular resistance to vasopressin resulting in nephrogenic diabetes insipidus. Fluoride issues are not present with isoflurane and desflurane given the low fluoride content and their limited metabolism. Theoretical concerns exist with sevoflurane anesthesia not only because of the release of fluoride during metabolism but also because of the production of a vinyl ether known as compound A. Although high levels of serum fluoride have been demonstrated with the prolonged intraoperative administration of sevoflurane, clinical signs of nephrotoxicity are rare. This is postulated to be the result of the low blood:gas partition coefficient of sevoflurane and its rapid elimination from the body as well as the fact that sevoflurane does not undergo primary renal metabolism and therefore there is no local renal release of fluoride.

Compound A is produced during the metabolism of sevoflurane and its interaction with the $CO_2$ absorbent (soda lime) of the anesthesia machine.[33,34] The safe concentration of compound A is unknown in humans as is the mechanism of renal injury.[35] Compound A concentrations are increased by a high inspired concentration of sevoflurane, low fresh gas flows, increasing temperatures, decreased water content of the $CO_2$ absorbent, and high concentrations of potassium or sodium hydroxides in the $CO_2$ absorbent. To date, there are no data regarding compound A concentrations during the prolonged administration of sevoflurane in the ICU setting. However, given that $CO_2$ absorbers are not generally used when the potent inhalational anesthetic agents are administered in the ICU setting (see below), this may limit the concerns regarding compound A.

## Miscellaneous Issues

The potent inhalational anesthetic agents are triggering agents for malignant hyperthermia, a rare although potentially fatal inherited disorder of muscle metabolism. Additional concerns

include cost issues and alterations of the metabolism of other medications. Aside from the specialized equipment for delivery, scavenging, and monitoring of the agent (see below), the daily cost for the agent itself can range from US $50 to $150 per day depending on the inspired concentration, the size of the patient, and the fresh gas flow rate through the ventilator. The potent inhalational agents alter hepatic blood flow and may impact the metabolism of several medications including local anesthetic agents, lidocaine, ?-adrenergic antagonist, and benzodiazepines.[36] They also depress neuromuscular activity and enhance the effect of the neuromuscular blocking agents.

## Applications in the Treatment of Status Asthmaticus

### *Status Asthmaticus (Adult Patients)*

Reports of the treatment of status asthmaticus with general anesthetic agents including tribomethanol, cyclopropane, and ether first appeared in the 1930s.[37-39] These reports were followed in the late 1970s and early 1980s by the initial reports of the use of halothane for the treatment of adults requiring mechanical ventilation for refractory status asthmaticus.[40-43] In 1984, Schwartz et al reported the successful use of halothane to treat refractory status asthmaticus in 2 adult patients.[43] The first patient was a 32-year-old woman with status asthmaticus precipitated by a preceding viral illness. The bronchospasm failed to improve despite treatment with an inhaled β-adrenergic agonist, subcutaneous epinephrine and terbutaline, intravenous aminophylline, hydrocortisone, and endotracheal intubation and mechanical ventilation. After mechanical ventilation, her arterial blood gases (ABG) deteriorated to a pH of 7.17 and a $Paco_2$ of 58 mm Hg and she required an inspired oxygen concentration ($Fio_2$) of 0.9 to maintain adequate arterial oxygenation. Halothane was subsequently administered in an inspired concentration of 0.3% to 0.5% and within 30 minutes, there was an improvement in her bronchospasm as manifested by a decreased peak inflating pressure (data not given), decreased wheezing, and improved air exchange. Follow-up ABG analysis revealed a decreasing $Paco_2$ to 43 mm Hg and then 34 mm Hg over the next 90 minutes. The halothane was discontinued and her trachea was extubated within 24 hours. The second patient was a 24-year-old man with status asthmaticus who failed to respond to subcutaneous epinephrine and terbutaline, an inhaled ß-adrenergic agonist, and aminophylline. An initial ABG revealed pH 6.94, $Paco_2$ 123 mm Hg, and $Pao_2$ 61 mm Hg. His trachea was intubated and mechanical ventilation initiated. Despite this, his bronchospasm persisted and 1 hour following endotracheal intubation, halothane was administered (concentration not specified). There was a rapid improvement with decreased peak inflating pressures (PIP), improved air exchange on clinical examination, and improved ABGs. His trachea was extubated after 45 minutes of halothane.

Two groups of investigators have presented larger case series with the use of halothane for the treatment of status asthmasticus.[44,45] Rosseell et al retrospectively reviewed their experience over a 3-year period and reported the outcome of 5 patients who received halothane.[44] Prior to the use of halothane, the patients had received standardized therapy that included methylprednisolone, aminophylline, sympathomimetic agents, and sodium bicarbonate. A total of 22 patients required endotracheal intubation, 5 of whom received halothane in a concentration varying from 0.2% to 1.5%. The 5 patients who received halothane had a marked reduction in PIP and improvements in resistance within 30 to 60 minutes. One patient had multiple premature ventricular contractions that required a lidocaine infusion and 3 patients required dopamine (2-10 μg/kg per minute) to treat hypotension. There was a moderate increase in hepatocellular enzymes without jaundice in 3 patients. One of the patients died after the halothane was discontinued. This patient had required cardiopulmonary resuscitation prior to admission to the ICU. At the time of his death, the patient's respiratory status was stable, but he developed ventricular fibrillation and could not be resuscitated.

Saulinier et al collected respiratory and hemodynamic data before and 30 minutes after the administration of 1% halothane to 12 adults receiving standard therapy including mechanical ventilation for status asthmaticus.[45] During the administration of halothane, no other therapeutic interventions were added or adjusted. Respiratory data demonstrated improved compliance and resistance as manifested by a decrease in PIP from $55 \pm 8.4$ to $47 \pm 7.9$ cm $H_2O$ ($P < .001$), decreased deadspace with a decrease in the $V_D/V_T$ ratio from $0.77 \pm 0.087$ to $0.72 \pm 0.089$% ($p < .005$), increased pH from $7.21 \pm 0.09$ to $7.25 \pm 0.086$ ($P < .001$), decreased $Paco_2$ from $82 \pm 24.8$ to $73 \pm 20.8$ mm Hg ($P < .001$). No change in oxygenation was noted ($Pao_2$ $145 \pm 65.5$ vs $146 \pm 57.8$ mm Hg). Hemodynamic data revealed statistically significant decreases in mean arterial pressure ($94 \pm 22.8$ to $76 \pm 12.7$ mm Hg), heart rate, right atrial pressure, mean pulmonary artery pressure, and wedge pressure. No change was noted in cardiac index, systolic stroke index, systemic vascular resistance, and left ventricular stroke work index.

Two anecdotal reports regarding the use of halothane for status asthmaticus stand out as somewhat different from the rest.[42,46] Raine et al reported the successful use of halothane to treat status asthmaticus precipitated by the administration of the β-adrenergic antagonist, nadolol.[42] As opposed to other reports that describe the use of halothane with endotracheal intubation and mechanical ventilation, Padkin et al described the successful administration of a subanesthetic dose of halothane using a close-fitting face mask during spontaneous ventilation.[46] The authors suggested that the use of halothane avoided the need for endotracheal intubation and mechanical ventilation.

With the introduction of the methyl-ethyl ether class of potent inhalational anesthetic agents (isoflurane and enflurane) into anesthetic practice, their use in the ICU in the treatment of status asthmaticus also began. The interest in their use in this setting was encouraged by concerns regarding the potential deleterious physiologic effects of halothane including

myocardial depression and provocation of arrhythmias.[43] General efficacy in the treatment of status asthmaticus with a limited adverse effect profile was reported with these agents in isolated case reports involving 1 or 2 patients.[47-51] Of note in these reports is that 1 patient who failed to respond to enflurane subsequently responded to halothane.[50] In this same patient, in addition to issues related to the arrhythmogenic effects of halothane, a metabolic encephalopathy related to increased bromide levels from halothane metabolism was also noted. In a similar case report, Parnass et al noted what they called a partial response to enflurane and therefore switched to isoflurane.[49] Within 30 minutes of administering enflurane, they noted a decrease in the resistance to mechanical ventilation with a decrease in the PIP from 60-70 to 38 cm $H_2O$ and improvement in ABG values. However, no further improvement was noted over the next hour and the patient was switched to 1% isoflurane. Fifteen minutes later, they noted a decrease in the PIP to 27 cm $H_2O$ and cessation of wheezing.

### *Status Asthmaticus (Pediatric Patients)*

As with the adult population, the reports regarding the use of the potent inhalational anesthetic agents for the treatment of refractory status asthmaticus in infants and children are generally anecdotal, including the use of either halothane or isoflurane.[52-57] As part of a cohort of 10 patients who received isoflurane for sedation during mechanical ventilation, Arnold et al reported that 4 of the patients received isoflurane not only for sedation, but also for bronchodilatation in the treatment of status asthmaticus.[58] No additional details regarding the effects of isoflurane on airway compliance and resistance were provided. However, details regarding potential adverse effects can be obtained from their series, which outlined the prolonged administration of isoflurane to 10 pediatric patients, ranging in age from 3 weeks to 19 years. The duration of isoflurane administration ranged from 29 to 769 hours (245 $\pm$ 225 hours) and the MAC-hours ranged from 13 to 497 (131 $\pm$ 154 MAC-hours). There were no differences in blood urea nitrogen, serum creatinine, osmolality, bilirubin, and alanine aminotransferase when comparing time 0 and 96 hours in the 5 patients who received isoflurane for at least 96 MAC-hours. The plasma fluoride concentration directly correlated with the duration of isoflurane administration. The peak concentration averaged 11.0 $\pm$ 6.4 μmol/L with a high value of 26.1 μmol/L after 441 MAC-hours of isoflurane. One patient developed hemodynamic instability that responded to fluid administration. Five patients, who had received greater than 70 MAC-hours of isoflurane, developed agitation and non-purposeful movements after its discontinuation, thereby suggesting the potential for tolerance and withdrawal phenomenon with these agents. The same authors subsequently reported a case of tolerance to isoflurane in a 4-year-old who received isoflurane for sedation during mechanical ventilation while other authors have reported similar withdrawal phenomena.[59-62]

Wheeler et al presented the largest case series regarding the use of the potent inhalational anesthetic agents in the treatment of status asthmaticus in infants and children.[63] When conventional therapy for status asthmaticus failed or was associated with adverse effects, isoflurane was administered to 6 patients ranging in age from 14 months to 15 years. In all 6 patients, there was a decreased PIP, increased pH, and decreased $Paco_2$. The authors also presented their protocol for the use of isoflurane in this scenario with entry criteria that included patients who were intubated and mechanically ventilated with status asthmaticus with a PIP $\geq$ 40 cm $H_2O$ and who had failed therapy with intravenous corticosteroids, magnesium, anticholinergic agents, and terbutaline at $\geq$ 5 μg/kg per minute. They used a Servo 900D ventilator with an attached vaporizer to deliver therapy starting at an inspired concentration of 1% to 2% and adjusting this by 0.1% every 5 to 10 minutes with the goal of achieving adequate ventilation with a PIP $\leq$ 35 cm $H_2O$. They also recommended discontinuing neuromuscular blocking agents and intravenous sedatives once the isoflurane concentration is at 1%. Other therapies for status asthmaticus were continued. Recommended monitoring included an end-tidal $CO_2$ device, central venous and arterial catheters, and consideration of the use of in-line monitoring of the isoflurane concentration.

The latest addition to the potent inhalational anesthetic class of drugs are desflurane and sevoflurane. Unlike the other agents, sevoflurane is a substituted methyl, isopropyl ether. Given its rapid onset, limited airway pungency, and limited effects on hemodynamic function, it has replaced halothane as the drug of choice for the inhalational induction of anesthesia. Recently, Watanabe et al. reported the use of sevoflurane to treat status asthmaticus in a 3-month-old boy.[64] Following an examination of the airway in the OR, which revealed mild laryngomalacia, the patient's trachea was extubated. He immediately developed severe bronchospasm and required reintubation and postoperative mechanical ventilation. The following day, conventional therapies including aminophylline, hydrocortisone, inhaled β-adrenergic agonists failed, and there was an increase in the PIP to 50 to 60 cm $H_2O$ and a decrease in the oxygen saturation to 60%. Therapy with sevoflurane was initiated, which resulted in improvements in his resistance and compliance. However, attempts to wean the sevoflurane resulted in a deterioration in his condition. After 94 hours of therapy, it was possible to wean the patient from sevoflurane. During therapy, a mild increase in hepatic enzymes was noted. A serum fluoride concentration on day 3 was 24.2 μmol/L.

## Special Aspects of Delivery in the ICU Setting

The administration of the potent inhalational anesthetic agents in the ICU setting can be fraught with logistical problems. For a full discussion of these issues, delivery techniques, scavenging, and monitoring, the reader is referred to the recent review by Tobias.[65] Although ORs have the equipment needed for the delivery of the potent inhalational anesthetic agents, it is generally neither feasible to move such critically ill patients nor to occupy an OR for a prolonged period of time with an ICU patient. In addition to the technical aspects of delivering and

scavenging these agents, as these agents are considered general anesthetic agents, one must also investigate hospital and state physician and nursing regulations regarding who is allowed to administer and monitor these agents. It is generally recommended that a formal hospital policy be developed, which outline such issues prior to the use of the potent inhalational anesthetic agents in the ICU setting.

## Delivery Techniques

In general, the options include bringing an OR anesthesia machine into the ICU or modifying an ICU ventilator to accommodate the vaporizer. Although a standard anesthesia machine provides a quick, easy, and effective means of delivering the inhalational anesthetic agent, there are significant limitations of the ventilators on these machines and they may not have the capabilities and options that are present on ICU ventilators. Given these concerns, techniques have been developed to allow for the use of the inhalational anesthetic agents with standard ICU ventilators. Options include the use of a draw-over vaporizer placed into the inspiratory limb of the ventilatory, delivery of the anesthetic gases from a vaporizer into the inspiratory limb, addition of the vaporizer gas flow into the low pressure inlet of a Servo 900C ventilator, or configuration of the Servo 900C to hold a vaporizer in-line distal to the oxygen blender. Draw-over vaporizers add the anesthetic agent to the gas (generally air), which is drawn through the vaporizer by the patient's own spontaneous inspiratory effort. These vaporizers are used in emergency situations or areas where there is no availability of pressurized gases. McIndoe et al evaluated the efficacy of two of these vaporizers (The Ohmeda TEC, Ohmeda, United Kingdom, and the Oxford Miniature Vaporizer, Penlon Ltd, United Kingdom) when placed in the inspiratory limb of the ICU ventilator circuit so that the entire tidal breath passed through the vaporizer.[66] The Ohmeda TEC delivered a predictable concentration only when the PIP was 20 cm $H_2O$ or less while the Oxford Miniature Vaporizer remained unaffected by PIP increases. The authors concluded that at all tidal volumes, inspiratory pressures, and inspired concentrations, the Oxford Miniature Vaporizer performed in a predictable fashion while the Ohmeda TEC vaporizer did not.

A second method of delivery is to add flow from the vaporizer into the inspiratory limb of the ventilatory circuit. An air/oxygen blender and vaporizer are set up separately from the ICU ventilator and the output from the vaporizer is added to the inspiratory circuit using a Y-piece attachment. Depending on the flow rate from the vaporizer and the mode of ventilation, the added flow may alter the delivered tidal volumes or PIP. Additionally, if the patient is breathing spontaneously, the inspired concentration of the potent inhalational anesthetic agent will be affected by changes in minute ventilation. With either of these 2 techniques, draw-over vaporizer or addition of the anesthetic agent to the inspiratory limb, as the inspired concentration of the agent can be quite variable, it is mandatory to monitor the inspired concentration using a gas monitor (see below). Other centers have used a Servo 900C ventilator with gas flow from the vaporizer directed into the low pressure inlet or have fit a vaporizer onto the ventilator in-line distal to the oxygen blender. Although modifications of the air/oxygen blender on the Servo 900C is feasible to allow the delivery of the potent inhalational anesthetic agents, such modifications cannot be safely performed with the Servo 300 ventilator. Additionally, when the anesthetic agents are added into the inspiratory limb or the low pressure inlet, the added gas flow may alter the $Fio_2$ unless the $Fio_2$ of the added gas is equal to the $F_iO_2$ provided by the ventilator. Therefore, continuous in-line monitoring of $F_iO_2$ distal to site of introduction of the inhalational anesthetic agent is necessary to ensure the delivery of the desired $Fio_2$.

Given these problems, novel devices to deliver these agents are being investigated and developed. One such device, the Anesthetic Conserving Device or "AnaConDa®" (ACD, Hudson RCI, Upllands Väsby, Sweden) is a modified heat-moisture exchanger with a deadspace of approximately 100 mL. The device is placed between the Y-piece of the ventilator circuit and the 15 mm adaptor of the endotracheal tube (ETT). There is a port just proximal to the ETT attachment site which allows gas sampling for monitoring the concentration of the agent. The device is non-specific and any potent inhalational anesthetic agent can be infused into the device onto the evaporator rod via a syringe pump. The inspired concentration is titrated by adjusting the infusion rate on the syringe pump based on the manufacturer's recommendations. Exhaled agent is adsorbed onto the lipophilic carbon particle filter in the device and redelivered to the patient thereby limiting environmental pollution (see below). The performance and working characteristics of the device have been investigated in adults in both the OR and the ICU setting.[67-69] Anecdotal experience with the ACD has also been reported in 3 pediatric patients.[70] Dead space issues with the device were noted in 1 patient who weighed 20 kg and the device had to be placed in the inspiratory limb of the ventilator circuit instead of just proximal to the ETT. A recent bench and clinical study evaluating the device's performance has raised some potential safety issues that warrant further evaluation.[71]

## Environmental Pollution and Scavenging

With the administration of these agents outside of the OR, attention must also be directed toward the control of residual environmental concentrations given the potential for adverse effects on cognitive function or health. The regulations regarding standards for the environmental concentrations vary from country to country. In the United States, the standard according to the American Society of Anesthesiologists is that the level of the inhalational anesthetic agent should be less than 2 ppm when used alone and less than 0.5 ppm when used in conjunction with $N_2O$. When using an ICU ventilator, the exhaled breath is vented to the environment. To avoid environmental pollution options include use of a device that adsorbs the exhaled anesthetic agent or connection of the exhalation port of the ventilator to a suction apparatus. There are various commercially available devices such as the Aldasorber (Cardiff

Aldasorber, Chartan Aldred, Workship, United Kingdom) which contain activated charcoal to adsorb the exhaled agent.[72] These devices can be modified to fit the exhalation port of the ventilator. Alternatively, tubing can be connected from the exhalation port of the ventilator to the central suction system. Regardless of the device used, obstruction to the exhalation port must be avoided as inadvertent PEEP and barotrauma may occur. When these scavenging systems are in place, evaluations of ICU contamination during the administration of isoflurane for sedation have failed to demonstrate environmental pollution.[73] The effect of the ACD on the environmental concentration of anesthetic gases has also been investigated.[74] Ambient isoflurane concentrations were below internationally recommended peak, long-term exposure limits with a mean of 0.1 $\pm$ 0.2 ppm and a maximum value of 0.5 ppm. Environmental pollution may also occur when the patient is disconnected from the ventilator for suctioning or other care. Closed suctioning devices can be used to avoid the need to disconnect the patient from the ventilator.

Equipment for monitoring the inspired concentration of the agent is also recommended. Such monitoring is definitely required if delivery techniques are used in which the vaporizer setting does not equal the inspired concentration as when the vaporizer output is added to the inspiratory limb or the low pressure inlet of the Servo 900C ventilator.

## Summary

The potent inhalational anesthetic agents are used on a daily basis to provide intraoperative anesthesia. Given their beneficial effects on airway tone and reactivity, they also have a role in the treatment of status asthmaticus that is refractory to standard therapy. The anecdotal reports in both adult and pediatric patients have demonstrated a universally beneficial effect on airway resistance and compliance. Additionally, the adverse effect profile of the most commonly used agent, isoflurane, is limited. Isoflurane undergoes limited metabolism, has a limited risk of hepatitis, does not result in toxic plasma fluoride concentrations even with prolonged administration, and has limited effects on hemodynamic function. Additionally, it remains the least expensive of the agents in current clinical use (isoflurane, desflurane, and sevoflurane). With prolonged administration, tolerance and withdrawal may occur. Other factors that should be addressed when these agents are administered outside of the OR include delivery, monitoring, and scavenging techniques.

The potent inhalational anesthetic agents may be effective for the patient with status asthmaticus that fails to respond to conventional therapy including β-adrenergic agonists (intravenous and inhaled), anticholinergic agents, corticosteroids, and magnesium or when therapy with these agents is limited by adverse effects. Although Wheeler et al[63] suggest that this therapy be initiated when mechanical ventilation requires a PIP $\geq$ 40 cm $H_2O$; given the risk for barotrauma in these patients, it may be acceptable to initiate this therapy at a lower PIP (30-35 cm $H_2O$) if no response to other therapies is noted. Given the large clinical experience with isoflurane and the above-outlined issues with desflurane and sevoflurane, it appears that isoflurane remains the agent of choice. Therapy can be initiated with an inspired concentration of 1% to 2% with incremental adjustments of 0.1% every 5 to 10 minutes with the goal of achieving adequate ventilation with a PIP $\leq$ 30 cm $H_2O$. Once a response is noted, neuromuscular blocking agents and intravenous sedative agents can be discontinued provided that the expired isoflurane concentration is $\geq$1%. Other therapies for status asthmaticus should be continued with the goal of discontinuing the inhalational anesthetic agent once the acute episode of bronchospasm has resolved. Monitoring during this therapy should include an end-tidal $CO_2$ device and in-line monitoring of the isoflurane concentration. Although generally effective, adverse hemodynamic effects of this therapy may occur. Although the results in the literature are generally favorable, one of the significant limitations of retrospective case reports and case series is that there may be an under-reporting of therapeutic failures. Given that, prospective trials are needed to fully determine the role of these agents in the treatment of status asthmaticus.

## References


1. Vitcha JF. A history of Forane. *Anesthesiology*. 1971;35(1):4-7.
2. Robbins J. Preliminary studies of the activity of fluorinated hydrocarbons. *J Pharmacol Exp Ther*. 1946;86(2):197-200.
3. Krantz JC Jr, Carr J, Lu G, Bell FK. Anesthesia. XL. The anesthetic action of trifluoroethyl vinyl ether. *J Pharmacol Exp Ther*. 1953;108(4):488-495.
4. Tucker WK, Munson ES, Holaday DA, Fiserova-Bergerova V, Turner BM. Hepatorenal toxicity following fluroxene anesthesia. *Anesthesiology*. 1973;39(1):104-107.
5. Johnston RR, Cromwell TH, Eger EI 2nd, Cullen D, Stevens WC, Joas T. The toxicity of fluroxene in animals and man. *Anesthesiology*. 1973;38(4):313-319.
6. Harris JA, Cromwell TH. Jaundice following fluroxene anesthesia. *Anesthesiology*. 1972;37(4):462-463.
7. Raventos J. Action of fluothane: new volatile anesthetic. *Br J Pharmacol Chemother*. 1956;11(4):394-410.
8. Le Dez KM, Lerman J. The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. *Anesthesiology*. 1987;67(3):301-307.
9. Gregory G, Eger EI 2nd, Munson ES. The relationship between age and halothane requirement in man. *Anesthesiology*. 1969;30(5):488-491.
10. Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. *BMJ*. 1989;298(6683):1277-1280.
11. Millane TA, Bennett ED, Grounds RM. Isoflurane and propofol for long-term sedation in the intensive care unit. A crossover study. *Anaesthesia*. 1992;47(9):768-774.
12. Meiser A, Sirtl C, Bellgardt M, et al. Desflurane compared with propofol for postoperative sedation in the intensive care unit. *Br J Anaesth*. 2003;90(3):273-280.
13. Breheny FX, Kendall PA. Use of isoflurane for sedation in the intensive care. *Crit Care Med*. 1992;20(7):1062-1064.

14. Constant I, Seeman R, Murat I. Sevoflurane and epileptiform EEG changes. *Pediatr Anesth*. 2005;15(4):266-274.
15. Sponheim S, Skraastad Ø, Helseth E, Due-Tønnesen B, Aamodt G, Breivik H. Effects of 0.5 and 1.0 MAC isoflurane, sevoflurane and desflurane on intracranial and cerebral perfusion pressures in children. *Acta Anaesthesiol Scand*. 2003;47(8):932-938.
16. Adams RW, Cucchiara RF, Gronert GA, Messick JM, Michenfelder JD. Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. *Anesthesiology*. 1981;54(2):97-99.
17. Morray JP, Geiduschek JM, Ramamoorthy C, et al. Anesthesia-related cardiac arrest in children: initial findings of the Pediatric Perioperative Cardiac Arrest (POCA) Registry. *Anesthesiology*. 2000;93(1):6-14.
18. Benumof JL, Augustine SD, Gibbons JA. Halothane and isoflurane only slightly impair arterial oxygenation during one lung ventilation in patients undergoing thoracotomy. *Anesthesiology*. 1987;67(6):910-915.
19. Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H. Mechanism of action of inhalational anesthesia on airways. *Anesthesiology*. 1982;56(2):107-111.
20. Warner DO, Vettermann J, Brichant JF, Rehder K. Direct and neurally mediated effects of halothane on pulmonary resistance in vivo. *Anesthesiology*. 1990;72(6):1057-1063.
21. Park KW, Dai HB, Lowenstein E, et al. Isoflurane and halothane mediated dilation of the distal bronchi in the rat depends on the epithelium. *Anesthesiology*. 1997;86(5):1078-1087; discussion 23A-24A.
22. Park KW, Dai HB, Lowenstein E, Sellke FW. Epithelial dependence of the bronchodilatory effect of sevoflurane and desflurane in the rat distal bronchi. *Anesth Analg*. 1998;86(3):646-651.
23. Burburan SM, Xisto DG, Ferreira HC, et al. Lung mechanics and morphology during sevoflurane anesthesia in a model of chronic allergic asthma. *Anesth Analg*. 2007;104(3):631-637.
24. Katoh T, Ikeda K. A comparison of sevoflurane with halothane, enflurane, and isoflurane on bronchoconstriction caused by histamine. *Can J Anaesth*. 1994;41(12):1214-1219.
25. von Ungern-Sternberg BS, Saudan S, Petak F, Hantos Z, Habre W. Desflurane but not sevoflurane impairs airway and respiratory tissue mechanics in children with susceptible airways. *Anesthesiology*. 2008;108(2):216-224.
26. Satoh H, Gillette JR, Takemura T, et al. Investigation of the immunological basis of halothane-induced hepatotoxicity. *Adv Exp Med Biol*. 1986;197:657-773.
27. Kenna JG, Neuberger J, Williams R. Evidence for expression in human liver of halothane-induced neoantigens recognized by antibodies in sera from patients with halothane hepatitis. *Hepatology*. 1988;8(6):1635-1641.
28. Kenna JG, Jones RM. The organ toxicity of inhaled anesthetics. *Anesth Analg*. 1995;81(6 suppl):S51-S66.
29. Brown BR Jr, Gandolfi AJ. Adverse effects of volatile anesthetics. *Br J Anaesth*. 1987;59(1):14-23.
30. Wark HJ. Postoperative jaundice in children. The influence of halothane. *Anaesthesia*. 1983;38(3):237-242.
31. Mazze RI, Calverley RK, Smith NT. Inorganic fluoride nephrotoxicity: prolonged enflurane and halothane anesthesia in volunteers. *Anesthesiology*. 1977;46(4):265-271.
32. Spencer EM, Willatts SM, Prys-Roberts C. Plasma inorganic fluoride concentrations during and after prolonged (greater than 24 h) isoflurane sedation: effect on renal function. *Anesth Analg*. 1991;73(6):731-737.
33. Morio M, Fujii K, Satoh N, et al. Reaction of sevoflurane and its degradation products with soda lime. Toxicity of the byproducts. *Anesthesiology*. 1992;77(6):1155-1164.
34. Frink EJ Jr, Malan TP, Morgan SE, Brown EA, Malcomson M, Brown BR Jr. Quantification of the degradation products of sevoflurane in two $CO_2$ absorbents during low-flow anesthesia in surgical patients. *Anesthesiology*. 1992;77(6):1064-1069.
35. Mazze RI. The safety of sevoflurane in humans. *Anesthesiology*. 1992;77(6):1062-1063.
36. Reilly CS, Wood AJ, Koshakji RP, Wood M. The effect of halothane on drug disposition: contribution of changes in intrinsic drug metabolizing capacity and hepatic blood flow. *Anesthesiology*. 1985;63(1):70-76.
37. Fuchs AM. Interruption of asthmatic crisis by tribomethanol (Avertin). *J Allergy*. 1937;8(7):340-346.
38. Meyer NE, Schotz S. Relief of severe intractable bronchial asthma with cyclopropane anesthesia: report of case. *J Allergy*. 1939;10(4):239-240.
39. Robertson CE, Steedman D, Sinclair CJ, Brown D, Malcolm-Smith N. Use of ether in life-threatening acute severe asthma. *Lancet*. 1985;1(8422):187-188.
40. Colaco CM, Crago RR, Weisbert A. Halothane for status asthmaticus in the intensive care unit—a case report. *Can Anaesth Soc J*. 1978;25(4):329-330.
41. Genestal M, Jorda MF, Guittard P, Caval E, Cathala B, Lareng L. Treatment of a case of status asthmaticus with halothane [in French]. *Nouv Presse Med*. 1980;9(44):3360-3361.
42. Raine JM, Palazzo MG, Kerr JH, Sleight P. Near-fatal bronchospasm after oral nadolol in a young asthmatic and response to ventilation with halothane. *Br Med J (Clin Res Ed)*. 1981;282(6263):548-549.
43. Schwartz SH. Treatment of status asthmaticus with halothane. *JAMA*. 1984;251(20):2688-2689.
44. Rosseel P, Lauwers LF, Baute L. Halothane treatment in life-threatening asthma. *Intensive Care Med*. 1985;11(5):241-246.
45. Saulnier FF, Durocher AV, Deturck RA, Lefèbvre MC, Wattel FE. Respiratory and hemodynamic effects of halothane in status asthmaticus. *Intensive Care Med*. 1990;16(2):104-107.
46. Padkin AJ, Baigel G, Morgan GA. Halothane treatment of severe asthma to avoid mechanical ventilation. *Anaesthesia*. 1997;52(10):994-997.
47. Bierman MI, Brown M, Muren O, Keenan RL, Glauser FL. Prolonged isoflurane anesthesia in status asthmaticus. *Crit Care Med*. 1986;14(9):832-833.
48. Revell S, Greenhalgh D, Absalom SR, Soni N. Isoflurane in the treatment of asthma. *Anaesthesia*. 1988;43(6):477-479.
49. Parnass SM, Feld JM, Chamberlin WH, Segil LJ. Status asthmaticus treated with isoflurane and enflurane. *Anesth Analg*. 1987;66(2):193-195.
50. Echeverrria M, Gelb AW, Wexler HR, Ahmad D, Kenefick P. Enflurane and halothane in status asthmaticus. *Chest*. 1986;89(1):152-154.

51. Mutlu GM, Factor P, Schwartz DE, Sznajder JI. Severe status asthmaticus: management with permissive hypercapnia and inhalation anesthesia. *Crit Care Med*. 2002;30(2):477-480.
52. O'Rourke PP, Crone RK. Halothane in status asthmaticus. *Crit Care Med*. 1982;10(5):341-343.
53. Johnston RG, Noseworthy TW, Friesen EG, Yule HA, Shustack A. Isoflurane therapy for status asthmaticus in children and adults. *Chest*. 1990;97(3):698-701.
54. Revell S, Greenhalgh D, Absalom SR, Soni N. Isoflurane in the treatment of asthma. *Anaesthesia*. 1988;43(6):477-479.
55. Restrepo RD, Pettignano R, DeMeuse P. Halothane, an infrequently used drug in the treatment of pediatric status asthmaticus: a case report. *J Asthma*. 2005;42(8):649-651.
56. Otto RW, Fireman P. Isoflurane anesthesia for the treatment of refractory status asthmaticus. *Ann Allergy*. 1991;66(4):305-309.
57. Tobias JD, Garrett JS. Therapeutic options for severe, refractory status asthmaticus: inhalational anaesthetic agents, extracorporeal membrane oxygenation, and helium/oxygen ventilation. *Paediatr Anaesth*. 1997;7(1):47-57.
58. Arnold JH, Truog RD, Rice SA. Prolonged administration of isoflurane to pediatric patients during mechanical ventilation. *Anesth Analg*. 1993;76(3):520-526.
59. Arnold JH, Truog RD, Molengraft JA. Tolerance to isoflurane during prolonged administration. *Anesthesiology*. 1993;78(5):985-988.
60. Kelsall AW, Ross-Russell R, Herrick MJ. Reversible neurologic dysfunction following isoflurane sedation in pediatric intensive care. *Crit Care Med*. 1994;22(6):1032-1034.
61. Smith RA, Winter PM, Smith M, Eger EI 2nd. Tolerance to and dependence on inhalational anesthetics. *Anesthesiology*. 1979;50(6):505-509.
62. Huhges J, Leach HJ, Choonara I. Hallucinations on withdrawal of isoflurane used as sedation. *Acta Paediatr*. 1993;82(10):885-886.
63. Wheeler DS, Clapp CR, Ponaman ML, Bsn HM, Poss B. Isoflurane therapy for status asthmaticus in children: a case series and protocol. *Pediatr Crit Care Med*. 2000;1(1):55-59.
64. Watanabe K, Mizutani T, Yamashita S, Tatekawa Y, Jinbo T, Tanaka M. Prolonged sevoflurane inhalation therapy for status asthmaticus in an infant. *Pediatr Anesth*. 2008;18(6):543-545.
65. Tobias JD. Therapeutic applications and uses of inhalational anesthesia in the pediatric intensive care unit. *Pediatr Crit Care Med*. 2008;9(2):169-179.
66. McIndoe AK, Steward P, Wilson IH. Drawover vaporizers for sedation in intensive care. *Intensive Care Med*. 1997;23(6):704-707.
67. Tempia A, Olivei MC, Calza E, et al. The anesthetic conserving device compared with conventional circle system used under different flow conditions for inhaled anesthesia. *Anesth Analg*. 2003;96(4):1056-1061.
68. Enluynd M, Lambert H, Wiklund L. The sevoflurane saving capacity of a new anaesthetic agent conserving device compared with a low flow circle system. *Acta Anaesthesiol Scand*. 2002;46(5):506-511.
69. Sackey PV, Martling CR, Granath F, Radell PJ. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. *Crit Care Med*. 2004;32(11):2241-2246.
70. Sackey PV, Martling CR, Radell PJ. Three cases of PICU sedation with isoflurane delivered by the 'AnaConDa®'. *Pediatr Anesth*. 2005;15(10):879-885.
71. Berton J, Sargntini C, Nguyen JL, et al. AnaConDa® reflection filter: bench and patient evaluation of safety and volatile anesthetic conservation. *Anesth Analg*. 2007;104(1):130-134.
72. Vaughan RS, Mapleson WW, Mushin WW. Prevention of pollution of operating theatres with halothane vapour by adsorption with activated charcoal. *Br Med J*. 1973;1(5855):727-729.
73. Coleman MA, Coles S, Lytle T, Bennetts FE. Prevention of atmospheric contamination during isoflurane sedation. *Clin Intensive Care*. 1994;5(5):217-220.
74. Sackey PV, Martling CR, Nise G, Radell PJ. Ambient isoflurane pollution and isoflurane consumption during intensive care unit sedation with the Anesthetic Conserving Device. *Crit Care Med*. 2005;33(3):585-590.