Therapeutic applications and uses of inhalational anesthesia in the pediatric intensive care unit*

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Objective: **To review the physical properties, end-organ effects, therapeutic applications, and delivery techniques of inhalational anesthetic agents in the pediatric intensive care unit.**

Data Source: **A computerized, bibliographic search regarding intensive care unit applications of inhalational anesthetic agents.**

Main Results: **Although the end-organ effects of inhalational anesthetic agents vary depending on the agent, general effects include a dose-related depression of ventilatory and cardiovascular function. With increasing anesthetic depth, there is a decrease in alveolar ventilation with a reduction in tidal volume and an increase in $Paco_2$ in spontaneously breathing patients. 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. Beneficial effects include sedation, amnesia, and anxiolysis, making these agents effective for sedation during mechanical ventilation. Bronchodilatory and anticonvulsant properties have led to their use as therapeutic agents in patients with refractory status asthmaticus and epilepticus. Issues regarding their delivery in the intensive care unit include equipment for their delivery, scavenging, and monitoring.**

Conclusions: **The literature contains reports of the therapeutic use of the potent inhalational anesthetic agents in the pediatric intensive care unit. Potential applications include sedation during mechanical ventilation as well as therapeutic use for the treatment of status asthmaticus and epilepticus. (Pediatr Crit Care Med 2008; 9:169–179)**

Key Words: inhalational anesthesia; isoflurane sedation; status asthmaticus; status epilepticus

During the intraoperative period, general anesthesia is frequently induced and maintained by the administration of inhalational anesthetic agents (halothane, isoflurane, sevoflurane, or desflurane). These agents provide the key components of general anesthesia, including amnesia, analgesia, skeletal muscle relaxation, and control of the sympathetic nervous system, with limited and generally well-tolerated effects on end-organ function. In addition to their general anesthetic effects, the potent inhalational anesthetic agents have beneficial physiologic effects, including suppression of seizure foci and dilation of airway smooth musculature. Given these effects, these agents are occasionally used in the pediatric intensive care unit (PICU) to provide sedation during mechanical ventilation or to treat status epilepticus and status asthmaticus that are refractory to conventional therapies. This article reviews the physical structure of the inhalational anesthetic agents, their end-organ effects, reports of their applications in the PICU patient, and special considerations for their administration in the PICU.

Principles of Inhalational Anesthesia

Chemical Structure. The inhalational anesthetic agents include N_2O and the potent inhalational agents (halothane, enflurane, isoflurane, sevoflurane, and desflurane). As the PICU applications of N_2O are limited, it will not be discussed further. The potent inhalational anesthetic agents consist of two chemically distinct classes. Halothane is an alkane (a two-carbon chain), while the other four agents (enflurane, isoflurane, desflurane, and sevoflurane) are ethers, the first three being substituted methylethyl ethers and sevoflurane being a methylisopropyl ether (Fig. 1). The substitution of fluoride or chlorine for the various hydrogen atoms around the carbon molecules can significantly affect the physical properties of these agents, altering their blood/gas solubility, blood/fat solubility, and potency. These agents are volatile liquids; their potential to transform into a vapor is termed *vapor pressure* (Table 1). In clinical practice, the potent inhalational agents are administered to the patient via a vaporizer, which allows the inspired concentration of the agent to be increased or decreased by adjusting the dial. As the concentration on the dial is increased, more of the fresh gas flow is diverted into the vaporizer, thereby increasing the output of the agent and its inspired concentration (variable bypass, flow-over vaporizer). Because the vapor pressures vary, there is a specific vaporizer for each of the inhalational anesthetic agents.

Uptake and Distribution. A unique aspect of the inhalational anesthetic agents is their administration via the respiratory tract. The onset and duration of action of the agent are determined by its blood/gas solubility coefficient. This coefficient describes how the anesthetic partitions itself between the blood and the alveolar gas. An agent with a high blood/gas solubility (partition) coefficient has a slower

*See also p. 233.

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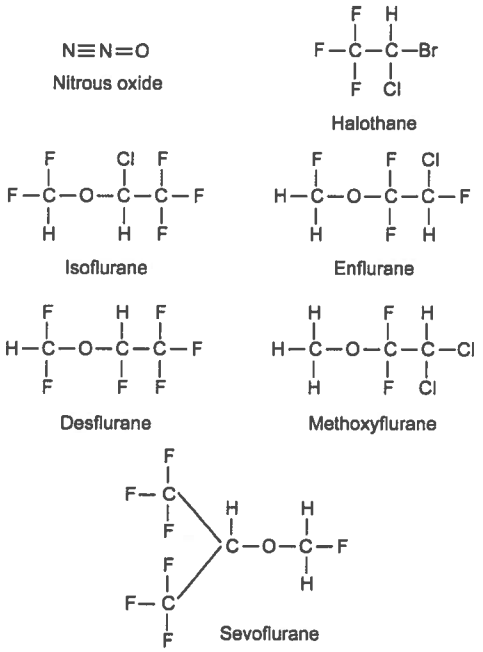

Figure 1. Molecular structure of the inhalational anesthetic agents.

Table 1. Physical properties of the inhalational anesthetic agents

Inhalational Anesthetic Agent	Vapor Pressure, mm Hg at 20°C	Blood/Gas Partition Coefficient at 37°C	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

onset of action and a longer duration of action upon discontinuation than an agent with a low blood/gas solubility coefficient. In addition, the depth of anesthesia can be adjusted more quickly with an agent that has a low blood/gas solubility coefficient. Of the potent inhalation agents, 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). The lower solubility in blood allows the alveolar concentration of the agent and hence the brain concentration of the agent to increase more rapidly than agents with a higher solubility in blood. Following their administration from the vaporizer, the inhalational anesthetic agents are taken up from the alveoli into the blood based on their blood/gas partition coefficient, the blood flow through the lungs (cardiac output), the distribution of blood flow to the various tissue beds, and their solubility in these tissues (blood/tissue solubility coefficient). The end-capillary venous blood from the lungs, which becomes the arterial blood leaving the left ventricle, rapidly equilibrates with the alveolar concentration. In turn, the arterial concentration equilibrates with the brain tissue to provide the anesthetic effect. The increase in the alveolar concentration should be thought of as paralleling the brain tissue concentration. This occurs given the high blood flow to the brain compared with other organs. Agents that are relatively insoluble in blood (desflurane and sevoflurane) result in a more rapid rise in the alveolar concentration and the most rapid onset of action.

The increase in the alveolar concentration is dependent on the difference between the delivery of the agent to and its removal from the alveolus. Delivery is controlled by the inspired concentration of the agent and the patient's minute ventilation. The removal of these agents from the alveoli is dependent on the solubility of the agent in the blood, the pulmonary blood flow, and the concentration of the agent in the mixed venous blood. Although in the majority of patients, pulmonary blood flow equates with cardiac output, the rise in the alveolar concentration of the agent may be altered in patients with congenital heart disease and right-to-left or left-to-right shunts. In the setting of a left-to-right shunt, blood with a high concentration of the inhaled anesthetic agent is recirculated through the lungs, increasing the mixed venous oxygen tension more rapidly than the normal state, thereby accelerating the rise in the alveolar concentration and thereby the onset of action of the agent. In the setting of a right-to-left shunt, the opposite effect occurs with a delayed onset of action of these agents.

Potency (Minimum Alveolar Concentration). Potency is measured by minimum alveolar concentration (MAC), or the concentration of the agent that is required to prevent 50% of patients from moving in response to a surgical stimulus (Table 1). The lower the MAC of an agent, the more potent is the gas. Halothane is the most potent of the inhalational anesthetic agents (MAC 0.76%), followed by isoflurane (1.2%), enflurane (1.7%), sevoflurane (2%), and desflurane (6%). Other medications (opioids, α_2-adrenergic agonists, benzodiazepines) and associated conditions (pregnancy or central nervous system disorders) can affect MAC. MAC varies with age, being lower in preterm infants, increasing in term infants, and then decreasing slightly with advancing age (1, 2). Since it is not desirable to have 50% of patients moving during surgical procedures, a higher concentration of the anesthetic agent (1.5–2.0 MAC) may be used intraoperatively or an agent with 1.0–1.5 MAC may be combined with N_2O, opioids, or intravenous anesthetic agents. In the PICU, the concentration required to achieve the desired effect will vary depending on the clinical scenario, the patient's status, and the duration of administration.

End-Organ Effects

The inhalational agents provide all of the prerequisites of a general anesthetic. How the potent inhalational anesthetic agents work has not been fully determined, although recent work suggests that they stabilize critical proteins, possibly receptors of neurotransmitters (3). The inhalational anesthetic agents are nonflammable and nonexplosive in clinical concentrations. Halothane and sevoflurane are less pungent to the air-

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way 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. The evaluation of the etiology of cardiac arrest during general anesthesia in infants and children has implicated halothane as the primary agent responsible for many of the events (4).

The inhalational anesthetic agents result in a dose-related depression of ventilatory and cardiovascular function. These effects are modified by comorbid disease processes and the coadministration of other medications. At increasing anesthetic depth, there is a progressive decrease in alveolar ventilation with a reduction of tidal volume and an increase in $Paco_2$ in spontaneously breathing patients. The inhalational anesthetic agents also interfere with the normal ventilatory responses to hypercarbia and hypoxia and inhibit mucociliary function. Oxygenation may also be affected, especially in patients with pulmonary parenchymal disease or atelectasis from inhibition of hypoxic pulmonary vasoconstriction (5). Beneficial airway effects include a direct effect on bronchial smooth muscle with bronchodilatation, making the inhalational anesthetic agents effective in treating refractory status asthmaticus (discussed subsequently). These effects are related to both a depression of airway reflexes and direct effects on the airway smooth musculature (6, 7). Although these effects are shared by all of the potent inhalational anesthetic agents, animal data suggest that these effects may be greatest with halothane (8).

The potent inhalational anesthetic agents decrease mean arterial pressure, myocardial contractility, and myocardial oxygen consumption in a dose-dependent fashion. The decrease in mean arterial pressure reduces renal and hepatic blood flow. Changes in cardiac output, systemic vascular resistance, and heart rate vary from agent to agent. Isoflurane and desflurane result primarily in vasodilatation with reflex tachycardia, while a decrease in heart rate occurs with sevoflurane and halothane. Rapid increases in the inspired concentration of desflurane may stimulate the sympathetic nervous system and further increase heart rate. As the primary hemodynamic effects of isoflurane and desflurane are peripheral vasodilatation, there is a decrease in afterload, which 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. Theoretical concerns have been raised regarding the potential for a coronary steal phenomenon with agents that result primarily in vasodilatation. These effects have the potential to lead to an imbalance in the myocardial oxygen delivery/demand ratio in susceptible patients. 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. This may also be a consideration in patients with residual or palliated congenital heart disease in whom alterations in the systemic and pulmonary vascular resistance may alter the ratio of pulmonary to systemic blood flow.

Halothane, because of its alkane structure, sensitizes the myocardium to catecholamines and predisposes to dysrhythmias, especially with associated hypercarbia, when used in conjunction with other medications (aminophylline), or in the presence of high circulating catecholamine levels. The latter may occur when anesthetized patients receive epinephrine-containing local anesthetic agents. The inhalational anesthetic agents cause a dose-related decrease in central nervous system activity, reduce the cerebral metabolic rate for oxygen, and depress electroencephalographic (EEG) activity. Enflurane and sevoflurane can activate the EEG and produce EEG evidence of epileptiform activity at higher concentrations (9). The EEG changes are also occasionally accompanied by clinical manifestations of seizure activity. Such problems are more common with hyperventilation and the development of hypocarbia and generally occur only during the induction of anesthesia or rapid changes in the alveolar concentration of the agent. No clinical sequelae have been reported from these issues. All of the potent inhalational anesthetic agents increase cerebral blood flow in a dose-dependent manner via a reduction in cerebral vascular resistance, which can lead to an elevation of intracranial pressure (ICP) in patients with compromised intracranial compliance. Additionally, the hemodynamic effects may lower mean arterial pressure, which coupled with the increase in ICP may further decrease cerebral perfusion pressure (10). The effect on ICP is least with isoflurane and can be blunted by hyperventilation and hypocarbia ($Paco_2$ of 25–30 mm Hg) and by limiting the concentration to 1.0 MAC (11).

The inhalational anesthetic agents depress neuromuscular activity and enhance the effect of the neuromuscular blocking agents. They are triggering agents for malignant hyperthermia, a rare albeit potentially fatal inherited disorder of muscle metabolism. The chemical structure of the agent determines its metabolic fate. In addition to the parent compound, products produced during metabolism by the P_{450} system may be responsible for toxicity. Fifteen to twenty percent of halothane is recovered as metabolites compared with 5% to 10% of sevoflurane, 2% to 3% of enflurane, 0.2% of isoflurane, and $<0.1\%$ of desflurane. Hepatotoxicity can occur due to an immune-mediated reaction following exposure to halothane, enflurane, isoflurane, or desflurane (12–14). The metabolic product trifluoroacetic acid can act as a hapten, binding to hepatocytes and inducing an immune-mediated hepatitis. Although described primarily with halothane, given its higher rate of metabolism and greater production of trifluoroacetic acid, there have been anecdotal reports of hepatitis with all of the agents except sevoflurane (1, 15). 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 trifluoroacetic acid. Two types of hepatotoxicity, a mild and a fulminant form, have been described. The mild injury affects 20% of adults who receive halothane, while the fulminant form (halothane hepatitis) occurs in one of every 10,000 adult patients. Patients with the fulminant form develop a massive hepatic necrosis with a mortality rate of 50% to 75%. Most of these patients (up to 95%) have had a prior exposure to halothane. The most important predictive factor for anesthesia-induced hepatotoxicity is prior anesthetic exposure. Other risk factors include female gender, middle age, and obesity. Chronic ethanol ingestion and isoniazid use increase enzyme levels responsible for the metabolism of the inhalational anesthetic agents and may also increase the risk. Given

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these concerns, halothane is not recommended for adult use but remains popular in pediatric anesthesia because halothane hepatitis is rare in children (1 in 200,000) (16). Because cross-sensitization may occur, all of the inhalational anesthetic agents should be avoided in patients who have unexplained postoperative hepatic injury.

The inhalational anesthetic agents may also have the potential for nephrotoxicity related either to the release of fluoride during metabolism of the parent compound or to the production of toxic metabolic byproducts. Prolonged enflurane anesthesia may result in a diminished renal concentrating ability because of the renal effects of fluoride released during enflurane metabolism. Although a limited amount of enflurane is metabolized, its content of fluoride is high enough that even with a relatively low metabolic rate, serum fluoride concentrations increase with prolonged administration (17). Fluoride concentrations >50 μmol/L can result in a decreased glomerular filtration rate and renal tubular resistance to vasopressin (nephrogenic diabetes insipidus). Theoretical concerns have also been raised regarding sevoflurane anesthesia, not only because of the release of fluoride during metabolism with prolonged administration but also because of the production of a vinyl ether known as compound A. Although high levels of serum fluoride occur following 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 (unlike methoxyflurane) 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 reaction with the CO_2 absorbent (soda lime) of the anesthesia machine (18, 19). The safe concentration of compound A is unknown in humans as is the mechanism of renal injury (20). 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. No data are available regarding compound A concentrations during the prolonged administration of sevoflurane in the PICU. However, given that CO_2 absorbers are not generally used when the potent inhalational anesthetic agents are administered in the intensive care unit (ICU), there are likely to be no concerns regarding compound A although fluoride concentrations may increase.

Additional concerns with the inhalational anesthetic agents include cost and alterations of the metabolism of other medications. In addition to the cost of the specialized equipment needed to deliver and monitor the agent (discussed later), the daily cost for isoflurane can range from $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 inhalational agents alter hepatic blood flow and thereby the metabolism of several medications, including lidocaine, β-adrenergic antagonists, benzodiazepines, and local anesthetic agents, which may be administered in the PICU (21). These potential interactions and their clinical effects must be considered when pharmacologic agents are coadministered during the use of the inhalational anesthetic agents in the PICU.

Applications in the PICU

Procedural Sedation. There are limited reports regarding the use of inhalational anesthetic agents for procedural sedation with novel delivery devices. Several studies demonstrated the efficacy of methoxyflurane as an agent for procedural sedation in various clinical scenarios (22–24). Babl et al. (23) reported the successful use of methoxyflurane as a prehospital analgesic in a cohort of 105 patients who ranged in age from 15 months to 17 yrs (median 15 yrs). Methoxyflurane was administered by paramedics during the prehospital period using a Penthrox inhaler (Medical Developments International, Victoria, Australia), a tubular, handheld device that is primed with liquid methoxyflurane (3 mL) and provides 25–30 mins of administration. Recent awareness of the device has increased given its use to provide analgesia following an injury of a participant of the reality TV show, Survivor (http://www.cbs.com/primetime/survivor2/show/episode06/story.html). Methoxyflurane was used as a general anesthetic agent and for procedural sedation during the 1960s and 1970s. However, with the development of newer agents and recognition of its potential for nephrotoxicity (free chloride and oxalic acid are released during metabolism and can result in renal failure), its use decreased markedly in the United States. Given these concerns, methoxyflurane is no longer available for clinical use in the United States. The technique of methoxyflurane using the Penthrox inhaler is licensed in Australia for self-administration to conscious, stable patients with trauma-associated pain and for procedural sedation.

Sevoflurane has also been administered outside of the operating room (OR) for procedural sedation. Sury et al. (25) administered sevoflurane via nasal cannula to provide sedation during magnetic resonance imaging in 13 infants with a median postconceptual gestational age of 46 wks (range, 40–70 wks) and a median weight of 4.4 kg (range, 3.3–6.5 kg). Sevoflurane was delivered from a standard anesthesia machine vaporizer using a flow rate of 2 L/min and delivered via nasal cannulae. The technique was successful in 12 infants using a median maximum inspired sevoflurane concentration of 4% (range, 4% to 8%). One infant desaturated to 85% and required repositioning of the head to maintain a clear airway.

Sedation During Mechanical Ventilation. Favorable experiences have been reported with the use of inhalational anesthetic agents for sedation during mechanical ventilation in adult ICU patients (26–29). Although many of these studies are relatively recent, the technique is not necessarily a novel idea. In 1969, Prys-Roberts et al. (30) reported the efficacy of these agents in adults to provide sedation during mechanical ventilation and to control the autonomic hyperactivity associated with tetanus. Kong et al. (26) randomized 60 adults to receive isoflurane or midazolam for sedation during mechanical ventilation during a 24-hr study period. The adequacy of sedation was assessed using a 6-point scale assessed at hourly intervals, and supplemental sedation was provided with bolus doses of morphine (0.05 mg/kg). Isoflurane was administered at a concentration varying from 0.1% to 0.6% (mean concentration of 0.21%), while midazolam was administered as a continuous infusion of 0.1–0.2 mg/kg/hr. No difference in hemodynamic variables was noted between the two groups. Patients receiving isoflurane achieved satisfactory sedation 86% of the time compared with 64% of the time with midazolam. A more rapid weaning from mechanical ventilation was noted in patients receiving isoflurane. Millane et al. (27) reported

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equal efficacy when comparing propofol with isoflurane for sedation during mechanical ventilation in adults, while Meiser et al. (28) reported shorter and more rapid emergence times when comparing desflurane with propofol. The latter report also suggested that despite concerns regarding the cost of the potent inhalational anesthetic agents, there was a significant cost savings with desflurane (95 vs. 171 euros per day with desflurane vs. propofol). Limitation in the amount of desflurane required was achieved by using a fresh gas flow rate of only 1 L/min.

Other investigators have focused on the potential end-organ effects with the prolonged administration of inhalational anesthetic agents in the ICU (31–33). In adults randomized to receive midazolam or isoflurane (0.1% to 0.6%), plasma fluoride concentrations increased from a mean of 3.1 μmol/L to 20.0 μmol/L 48 hrs after starting isoflurane. Fluoride concentrations continued to increase to a peak of 25.3 μmol/L at 16 hrs after discontinuation of isoflurane and then declined with a half-life of 111 hrs. In patients receiving midazolam, serum fluoride concentrations increased from 4.2 μmol/L to a peak of 6.8 μmol/L at 12 hrs after starting sedation. Despite the increase in serum fluoride concentrations, no effect was noted on urinary electrolytes, urine osmolarity, and creatinine clearance. The authors noted that based on the number of MAC-hours of isoflurane received by their patients, larger than expected increases in the serum fluoride concentration occurred in their cohort of critically ill patients. The authors postulated that the metabolism of isoflurane may be altered in this subpopulation. In addition to effects on renal function, the effects on hepatic function have also been investigated in the adult ICU population (32). No significant increase was noted in plasma aspartate aminotransferase, alanine aminotransferase, and glutathione transferase levels during the administration of isoflurane for sedation in adults during mechanical ventilation. Additionally, no difference was noted between patients receiving isoflurane and those receiving midazolam.

Arnold et al. (34) reported their experience with isoflurane for sedation during mechanical ventilation in ten pediatric patients, ranging in age from 3 wks to 19 yrs. The duration of isoflurane administration ranged from 29 to 769 hrs (245 ± 225 hrs), and the MAC-hours ranged from 13 to 497 (131 ± 154 MAC-hours). Isoflurane was started at 0.5% and adjusted in 0.2% increments as needed. There was adequate sedation 75% of the time, excessive sedation 4% of the time, and inadequate sedation 21% of the time. In the five patients who received isoflurane for ≥96 MAC-hours, there were no differences in blood urea nitrogen, serum creatinine, osmolality, bilirubin, and alanine aminotransferase between time 0 and 96 hrs. The duration of isoflurane administration correlated directly with the plasma fluoride concentration. The peak serum fluoride concentration averaged 11.0 ± 6.4 μmol/L, with a high value of 26.1 μmol/L after 441 MAC-hours of isoflurane. One patient developed hemodynamic instability, which responded to fluid administration. Although the technique was chosen because of data suggesting that tolerance and withdrawal phenomena would not be an issue (35), five patients, who had received >70 MAC-hours, had agitation and nonpurposeful movements after discontinuing isoflurane. The same authors subsequently reported a case of tolerance to isoflurane in a 4-yr-old who received isoflurane for sedation during mechanical ventilation (36). Similarly, Hughes et al. (37) reported hallucinations after 4 days of isoflurane in an unspecified concentration for sedation during mechanical ventilation in a 7-yr-old boy.

Kelsall et al. (38) retrospectively reviewed their experience with isoflurane sedation in children with upper airway issues (laryngotracheobronchitis or epiglottitis) requiring endotracheal intubation and mechanical ventilation. Twelve of 29 patients (41%) received isoflurane for sedation in a concentration ranging from 0.25% to 1.5%. Although isoflurane was effective, the authors reported reversible neurologic dysfunction (ataxia, agitation, hallucinations, and confusion) after cessation of isoflurane. No such problems were noted in the patients who did not receive isoflurane and in patients who received isoflurane for ≤15 hrs.

Atkinson et al. (39) used isoflurane to supplement fentanyl anesthesia during repair of congenital diaphragmatic hernia in 13 infants supported with extracorporeal membrane oxygenation. Seven patients received fentanyl (22 μg/kg/hr by continuous infusion with supplemental doses as needed during the surgical procedure) and vecuronium for neuromuscular blockade, while six received isoflurane through the extracorporeal membrane oxygenation circuit in addition to fentanyl. A free-standing vaporizer was inserted into the fresh gas flow input of the extracorporeal membrane oxygenation circuit. Gases exiting the oxygenator were collected in a semirigid plastic cover and evacuated using the wall suction. The inspired concentration of isoflurane was adjusted from 0.5% to 1.5% as needed to control hemodynamic responses to the surgical procedure. Patients receiving only fentanyl had higher maximum blood pressure and higher heart rate responses during the procedure than patients receiving isoflurane in addition to fentanyl. All of the infants who received only fentanyl required the addition of sodium nitroprusside to control blood pressure during the procedure compared with one of six who received isoflurane.

Status Asthmaticus. Reports of the treatment of status asthmaticus with general anesthetic agents including tribomethanol, cyclopropane, and ether first appeared in the 1930s (40–42). These reports were followed by the use of the modern-day inhalational anesthetic agents for the treatment of adults requiring mechanical ventilation for refractory status asthmaticus (43–45). To date, the information regarding the impact of the potent inhalational anesthetic agents on children with refractory status asthmaticus remains primarily anecdotal (46–50). The previously discussed study of Arnold et al. (34) included four pediatric patients who received isoflurane for sedation and bronchodilatation during mechanical ventilation during the treatment of status asthmaticus. However, no additional details were provided regarding the effects of isoflurane on airway compliance/resistance. Wheeler et al. (51) reported the largest case series to date regarding the use of the potent inhalational anesthetic agents in the treatment of status asthmaticus. Isoflurane was used successfully in six patients, ranging in age from 14 months to 15 yrs, after conventional therapy failed. The authors also presented their protocol for the use of isoflurane in this scenario with entry criteria that included intubated and mechanically ventilated patients with status asthmaticus with a peak inspiratory pressure (PIP) ≥40 cm H_2O who fail therapy with intravenous corticosteroids, magnesium, anticholinergic agents, and terbutaline at ≥5 μg/kg/min. The authors 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%

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every 5–10 mins with the goal of achieving adequate ventilation with a PIP ≤35 cm H_2O. They also recommended discontinuing neuromuscular blocking agents and intravenous sedatives once the isoflurane concentration was at 1%. The authors advised that other therapies for status asthmaticus be continued because their mechanism of action is different from the inhalational anesthetic agents. The authors recommended monitoring with an end-tidal CO_2 device, invasive central venous and arterial catheters, and consideration of the use of inline monitoring of isoflurane concentration.

Status Epilepticus. The potent inhalational anesthetic agents produce dose-dependent changes in the EEG with an initial decrease in the amplitude and frequency of the EEG during the administration of sub-MAC concentrations, which progresses to increasing periods of electrical silence (burst suppression) as the concentration is increased to 2% to 2.5%. Patients with a history of epilepsy have fewer epileptogenic spikes during general anesthesia with halothane or enflurane than during the normal awake or asleep state (52). In this same population, epileptogenic spikes induced by the administration of etomidate were suppressed by the inhalational anesthetic agents. The potential role of these agents in the treatment of status epilepticus (SE) is also supported by animal studies. Both sevoflurane and isoflurane at 1 MAC have been shown to suppress bupivacaine-induced seizures in rats (53).

In clinical practice, treatment protocols for refractory SE frequently mention the use of general anesthesia with the inhalational anesthetic agents (54, 55). As with the reports of the use of inhalational anesthesia for the treatment of refractory status asthmaticus, many of the reports regarding the use of these agents for SE are primarily anecdotal and include a limited number of pediatric patients (56–62). The first report of the use of isoflurane for the treatment of SE in a pediatric patient was published in 1985 (60). Although SE was controlled with a pentobarbital infusion, attempts to taper the infusion led to the recurrence of seizure activity. During the third attempt to wean the pentobarbital infusion, isoflurane was administered when seizures recurred. At an end-tidal isoflurane concentration of 0.8%, seizure activity ceased. Isoflurane was administered for 48 hrs, after which time the seizure activity was controlled with a combination of several intravenous medications. During isoflurane, blood pressure support with phenylephrine and isotonic fluids was required. The authors cited logistic problems with the use of the inhalational anesthetic agents outside of the OR, and for their patient they maintained "continuous anesthetist presence," which they noted was expensive and not reimbursed by third-party payers. The authors recommended consideration of isoflurane only in patients who fail intravenous general anesthetic agents or manifest adverse hemodynamic effects from their administration.

The same authors subsequently reported the largest clinical series (six patients ranging in age from 2 to 13 yrs) of the use of inhalational anesthetic agents in the treatment of SE in children (61). The etiology of the SE included organophosphate toxicity (n = 1), status post hepatic transplantation (n = 1), status post arteriovenous malformation resection (n = 2), and idiopathic (n = 2). In all patients, conventional therapy with at least phenobarbital, phenytoin, and benzodiazepines failed to control SE. Isoflurane controlled SE in all patients, the only adverse effect being hypotension, which was treated with isotonic fluids and vasopressors.

Special Aspects of Delivery in the PICU

The most difficult problems in using the inhalational anesthetic agents in the PICU are logistical. Although ORs are well equipped to provide the necessary equipment for the delivery of these agents, the PICU may not be. Problems of delivery and scavenging have led some authors to recommend that patients requiring such therapy may be best cared for in the operating or recovery room (44). However, this is neither feasible nor practical in most centers, and therefore techniques have been developed that allow for the use of these agents in the ICU (discussed subsequently). Aside from the technical aspects of delivering and scavenging these agents, because these agents are considered general anesthetics, hospital and state physician and nursing regulations may restrict those who are allowed to administer, monitor, and even adjust the inspired concentration of the medication. Changes in the inspired concentration may need to be made by physicians or members of the anesthesiology staff, thereby raising staffing issues. As there are likely to be national, regional, and local differences in such regulations, it is recommended that before the use of the inhalational anesthetic agents in the PICU, these issues be investigated and addressed in a formal hospital policy. Additionally, initial and ongoing in-service training of the staff is helpful to provide background information regarding the rationale for the use of such therapy and the potential adverse effects associated with it. Consideration should be given to designating a member of the anesthesiology department to answer questions and provide consultation as needed. Some authors also have suggested that an anesthesiologist be present at all times (60).

Delivery Techniques. In many of the cases reported in the literature, a standard anesthesia machine and ventilator are brought from the OR to the ICU (28). Although the use of an OR anesthesia provides a quick and effective way to deliver the inhalational anesthetic agent, OR ventilators may not have the capabilities and ventilation options that are present on standard ICU ventilators. Although the ventilators on anesthesia machines may parallel the working variables of ICU ventilation with options such as pressure- or volume-limited ventilation, means to control the inspiratory time, delivery of effective positive end-expiratory pressure, and even pressure-supported modes, newer modes of ventilation such as pressure-regulated, volume-controlled ventilation and changes in the inspiratory flow pattern are not available. Likewise, the alarm systems and monitoring capabilities of OR ventilators may not be equivalent to the features available on ICU ventilators. A hybrid answer in some centers has been to use the Servo 900D anesthesia machine (Fig. 2), which although manufactured for use in the OR is similar to the Servo 900C ICU ventilator. On the Servo 900D anesthesia machine/ventilator, the vaporizer is inline, immediately distal from the air/oxygen blender before the working circuitry of the ventilator. Therefore, it allows the delivery of a set concentration of the inhalational anesthetic agent regardless of changes in ventilatory settings. However, the Servo 900D has limited ventilator capabilities as it functions only in the volume-limited mode with the tidal volume extrapolated by setting the minute ventilation and the respiratory rate. Given such concerns and the familiarity of ICU physicians with standard ICU ventilators, several op-

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tions have been developed to allow for the use of the inhalational anesthetic agents with standard ICU ventilators.

In emergency situations or areas where there is no availability of pressurized gases, specialized anesthetic vaporizers known as "draw-over vaporizers" have been used. These vaporizers add anesthetic agent to the gas (generally air) that is drawn through the vaporizer by the patient's own spontaneous inspiratory effort. McIndoe et al. (63) devised a model to evaluate the efficacy of two of these vaporizers (the Ohmeda TEC, Ohmeda, UK, and the Oxford Miniature Vaporizer, Penlon Ltd, UK) when placed in the inspiratory limb of the ICU ventilator circuit so that the entire tidal breath passed through the vaporizer. The Ohmeda TEC delivered a predictable concentration only when the PIP was 20 cm H_2O, 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 (27). For this purpose, 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 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 two techniques (using a draw-over vaporizer or adding flow from the vaporizer into the inspiratory limb) 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 (discussed later).

Given concerns about alterations in ventilatory variables and variability in the inspired concentration of the agent when gas flow is added to the inspiratory limb of the ventilatory circuit, other centers have used a Servo 900C ventilator. For this purpose, two options are reported in the literature. A Servo 900C can be fitted in the same manner as a Servo 900D with an anesthetic vaporizer (50). The gas flow from the air/oxygen blender passes through the vaporizer and then into the ventilator circuitry, thereby allowing for alterations in ventilatory mode and tidal volume without changes in the inspired concentration of the inhalational anesthetic agent. Alternatively, the gas flow from a standard OR vaporizer can be directed into the low-pressure inlet on the side of the Servo 900C ventilator (Fig. 3). This technique uses the Servo 900C ventilator with options for both volume- and pressure-limited modes of ventilation and prevents alterations in tidal volume or airway pressures as the anesthetic agent is delivered to the working circuitry of the ventilator. However, as the agent is added to the standard gas flow of the ventilator, alterations in the minute ventilation will affect the inspired concentration of the inhalational anesthetic agent. Given the variability in the inspired concentration of the inhalational agent when this technique is used, in-line gas monitoring is also suggested. Although modifications of the air/oxygen blender on the Servo 900C are feasible to allow the delivery of the potent inhalational anesthetic agents, such modifications cannot be safely performed with the Servo 300 ventilator.

Given the problems with the devices and techniques available to deliver the inhalational anesthetic agents in the ICU, novel means of delivering these agents are needed. An additional problem is that many of the techniques that have been described also require high gas flows and therefore result in the consumption of significant quantities of the potent inhalational anesthetic agents, thereby increasing the cost of this therapy. The Anesthetic Conserving Device (AnaConDa or ACD, Hudson RCI, Upllands Väsby, Sweden) (Fig. 4) is a modified heat-moisture exchanger with a deadspace of 100 mL that may allow a simplified means of administering the potent inhalational anesthetic agents in the ICU. The device is placed between the Y-piece of the ventilator circuit and the 15-mm

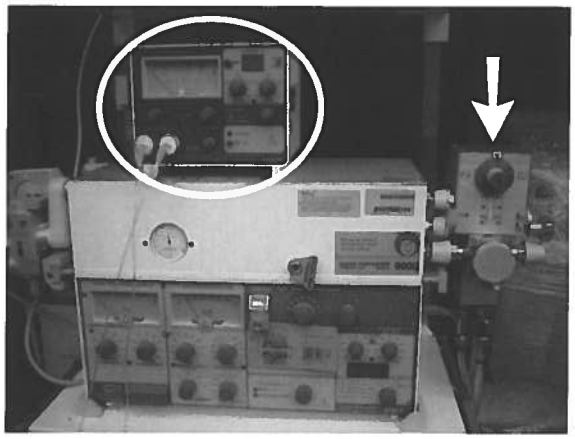

Figure 2. The Servo 900D anesthesia machine. The vaporizer is in-line immediately distal to the oxygen blender (*arrow*), and there is a gas monitor to measure the end-tidal concentration of the agent on top (*circle*).

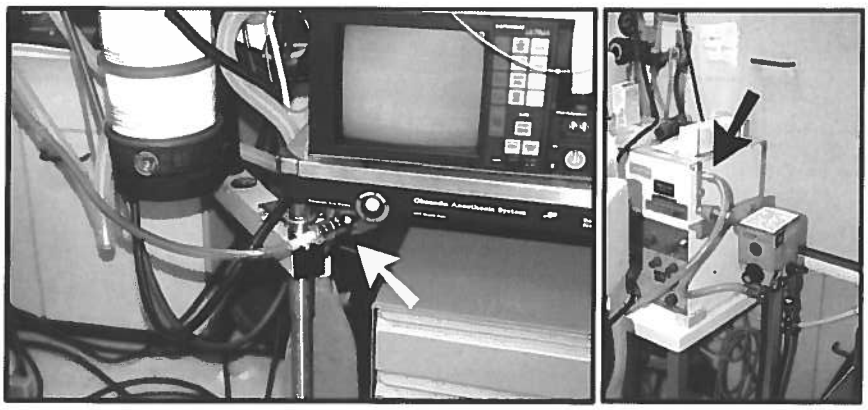

Figure 3. Tubing directs the gas from the common gas outlet of the anesthesia machine (*white arrow*) to the low-pressure inlet on the side of the Servo 900C ventilator (*black arrow*).

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adaptor of the endotracheal tube. There is also a port at the end of the device just proximal to its attachment to the endotracheal tube which allows gas sampling and monitoring of the agent concentration. Any of the inhalational anesthetic agents can be infused into the device and onto the evaporator rod via a syringe pump and delivered to the patient. The desired inspired concentration is titrated by adjusting the infusion rate on the syringe pump based on the manufacturer's recommendations. Exhaled isoflurane is adsorbed to the lipophilic carbon particle filter in the device and redelivered to the patient, thereby limiting environmental pollution.

Although the efficacy of the ACD in delivering the inhalational anesthetic agents has been demonstrated in the OR (64, 65), a bench and clinical study evaluating its performance has raised several issues that warrant further evaluation (66). Using a lung-analog model, changes in anesthetic output following changes in the isoflurane infusion rate and ventilatory variables were evaluated. There was a linear relationship between the isoflurane infusion rate and the delivered anesthetic concentration when the ventilator variables were held constant. Likewise, no change in output was noted with alterations in positive end-expiratory pressure and inspiratory times. A change in tidal volume was identified as the single most important variable affecting output from the ACD. Increasing the respiratory rate while holding the minute ventilation constant resulted in an increased concentration, whereas increasing the tidal volume without changing the respiratory rate resulted in decreased output. The authors also noted alterations in the delivered concentration based on alterations in the fresh gas flow. Other potential safety issues included an increase in the delivered concentration related to gravity-induced flow of the anesthetic agent during syringe changes when the syringe was disconnected 30 cm above the filter, while a reverse-flow effect decreased the inspired concentration when the disconnection was performed 30 cm below the filter. The authors also cautioned that the Luer-lock fitted agent infusion catheter was no different from that used for standard intravenous tubing.

Sackey et al. (67) evaluated the ACD in the ICU in 40 adult patients requiring sedation for >12 hrs. The patients were randomized to sedation with isoflurane administered with the ACD or a continuous infusion of midazolam. The inspired isoflurane concentration was started at 0.5% (infusion rate on the syringe pump of 1–3.5 mL/hr according to the manufacturer's recommendations), while midazolam was infused at 0.02–0.05 mg/kg/hr. The infusion rates were adjusted as needed and opioids were administered for analgesia. The percentage of time within the desired level of sedation was similar between the two groups (54% with isoflurane and 59% with midazolam) with no difference in opioid requirements or the need for bolus doses of sedative agents. The time to extubation (10 ± 5 vs. 252 ± 271 mins) and the time to follow verbal commands (10 ± 8 vs. 110 ± 132 mins) were shorter with isoflurane than with midazolam. Two adverse effects were reported with the ACD. One patient developed a high (1%) end-tidal concentration of isoflurane after changing the ACD. The ACD was removed from the ventilator circuit, the end-tidal concentration decreased to the desired level, and the isoflurane was resumed. In a second patient, an increased infusion requirement to maintain the desired concentration of isoflurane was noted. The ACD was changed earlier than per protocol (daily), and the infusion rate to achieve the desired inspired concentration returned to normal. The authors speculated that the copious secretions from the patient had nearly occluded the evaporator rod of the ACD. Isoflurane-sedated patients had normal urine volumes and creatinine clearances. The inorganic fluoride concentration was >50 μmol/L in three patients with a maximum value of 64 μmol/L during isoflurane sedation.

The same investigators conducted a prospective evaluation of 15 adult patients sedated with the ACD to determine isoflurane consumption and environmental pollution (68). In ten patients there was active scavenging of waste gases from the ventilator, while none was performed in the other five patients. Continuous monitoring of the ambient isoflurane concentration was performed using spectrophotometry. Ambient isoflurane concentrations were below internationally recommended peak, long-term exposure limits with a mean of 0.1 ± 0.2 ppm and a maximum value of 0.5 ppm. Isoflurane peaks during nursing procedures were short-lived, of low amplitude, and infrequent. During the study period, there were only two episodes with an ambient isoflurane concentration ≥2 ppm for >10 mins and two episodes with a concentration ≥5 ppm for >1 min. Isoflurane requirements averaged 2.1 ± 1.0 mL/hr, approximately one fourth that previously reported with the administration of isoflurane from a vaporizer.

Anecdotal experience with the ACD has also been reported in three pediatric patients who required sedation during mechanical ventilation or in the treatment of status epilepticus (69). Effective sedation was achieved with isoflurane concentrations of 0.3% to 0.4% while 0.9% was required to control status epilepticus. In two patients, who weighed 30 and 40 kg, respectively, the ACD was placed distal to the Y-piece as described in the adult population. In the third pa-

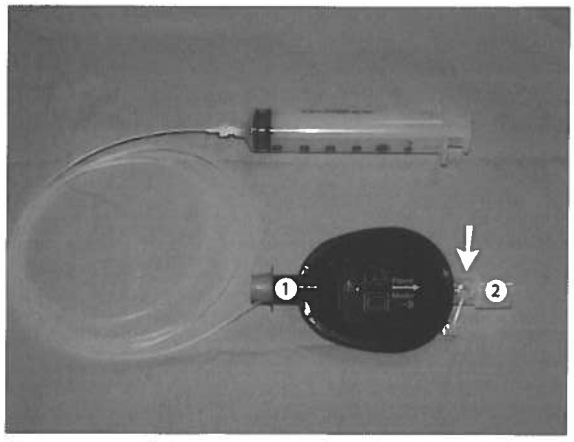

Figure 4. The Anesthetic Conserving Device (AnaConDa or ACD, Hudson RCI, Upllands Väsby, Sweden) is a modified heat-moisture exchanger that allows the administration of inhalational anesthetic agents in the ICU. The device is connected to the Y-piece of the ventilator circuit at *point 1* and to the 15-mm adaptor of the endotracheal tube at *point 2*. There is also a port at the end of the device (just proximal to its attachment to the endotracheal tube (*arrow*) that allows gas sampling and monitoring of the concentration of the agent. Isoflurane or any other inhalational anesthetic agent is infused into the device using a standard syringe pump.

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tient, who weighed 20 kg, when the ACD was placed in this position, the patient became tachypneic with an increase in his respiratory rate from 25 to 35 breaths/min. Although several ventilatory changes were attempted to compensate for the deadspace added by the ACD, effective ventilation could not be achieved. The ACD was removed and placed into the inspiratory limb of the ventilator circuit. This allowed effective ventilation and delivery of isoflurane; however, the authors commented that by using the ACD in this position, there would be a loss of the rebreathing function of the device and no conservation of isoflurane. There was also an increase in the deadspace of the system, although it was possible to compensate for it with the ACD in the inspiratory limb as opposed to distal to the Y-piece. The authors subsequently cautioned against the use of this device distal to the Y-piece in patients <30 kg until a smaller model becomes available. They suggested that using the device in the inspiratory limb was a simpler technique than bringing a vaporizer into the PICU.

Environmental Pollution and Scavenging. Given the potential for adverse effects on cognitive function or health, there are guidelines to minimize the residual environmental concentrations of inhalational anesthetic agents. In the United States, the standard according to the American Society of Anesthesiologists is that the level of the inhalational anesthetic agent should be <2 ppm when used alone and <0.5 ppm when used in conjunction with N_2O. These stringent guidelines are not universally accepted. In Sweden, the recommended guidelines are for levels <10 ppm for long-term exposure and <20 ppm for short-term exposure, while the United Kingdom recommends levels <50 ppm for long-term exposure (68). While these levels have been shown to have no effect on cognitive function or behavior, there are no data from which to determine whether chronic exposure to low levels of the inhalational anesthetic agent has an adverse effect on other health issues.

Given these concerns, a method to limit environmental pollution is needed in most circumstances. As noted by the study of Sackey et al. (68), environmental pollution with the ACD placed distal to the Y-piece of the circuit is minimal and within the recommended limits in Sweden and the United Kingdom. Although the mean concentrations were low at 0.1 ppm, there were periods of time when the ambient concentration of isoflurane exceeded the limits recommended in the United States, thereby suggesting that even when the ACD is used, scavenging may be required. To deal with such issues, some authors have constructed specific rooms in the ICU with central scavenging systems similar to what is available in the OR (28). Although effective, such redesign and construction are costly and therefore not feasible in most centers.

ICU ventilators do not routinely scavenge exhaled gases; rather, the exhaled breath is vented to the environment. To avoid environmental pollution, options include using a device that adsorbs the exhaled potent inhalational anesthetic agent or connecting the exhalation port of the ventilator to a suction apparatus. Various commercially available devices include the Aldasorber (Cardiff Aldasorber, Chartan Aldred, Workship, UK), which contains activated charcoal to adsorb the exhaled agent (70). Such devices were formerly used most commonly in the OR before the availability of central scavenging systems. These devices can be modified to fit the exhalation port of the ventilator (38). Alternatively, tubing can be connected from the exhalation port of the ventilator to the central suction system. Johnston et al. (50) suggested connecting the exhaust port of the ventilator to a t-piece that is attached to a 3-L self-inflating anesthesia bag. Wall suction is then applied to the distal end of the t-piece and adjusted so that the 3-L bag partially fills with each breath. Other authors have suggested surrounding the exhalation port with a semirigid container, which is then connected to the wall suction (39). Regardless of the device used, obstruction to the exhalation port must be avoided because inadvertent positive end-expiratory pressure and barotrauma may occur if emptying of the ventilator is obstructed. When these scavenging systems are in place, evaluations of ICU contamination during the administration of isoflurane for sedation have failed to demonstrate environmental pollution (71, 72).

Environmental pollution may also occur when the patient is disconnected from the ventilator for nursing care including suctioning. To eliminate such issues, closed suctioning devices can be used to avoid the need to disconnect the patient from the ventilator. Alternatively, a bronchoscopy adaptor can be placed between the end of the endotracheal tube and the ventilator circuit to allow access for suctioning without the need to disconnect the patient from the ventilator (60). As exhalation of the potent inhalational anesthetic agent may be ongoing for hours following their use, scavenging should be continued for 2–4 hrs following discontinuation of the potent inhalational anesthetic agent. Specialized equipment to monitor the inspired concentration of the agent is also required. Such monitoring is especially 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. In these cases, the dial setting on the vaporizer will not equal the delivered concentration, and changes in minute ventilation can change the inspired concentration. Monitoring devices are routinely available in all ORs and are compact enough that they can easily be moved into the ICU.

Summary

The inhalational anesthetic agents are used daily to provide intraoperative anesthesia. Although these agents can have adverse end-organ effects including a dose-related depression of ventilatory and cardiovascular function, nephrotoxicity, and vasodilatation leading to increased ICP in the majority of patients, these agents are well tolerated. Given their beneficial physiologic effects (sedation, analgesia, bronchodilation, neuroprotection, and anticonvulsant properties), there may be a role for these agents in the ICU not only for sedation but also to treat status asthmaticus and status epilepticus. Isoflurane remains the agent used most commonly for ICU interventions given its limited metabolism, limited end-organ toxicity profile, and cost compared with the other available agents.

Factors that may limit the use of these agents outside of the OR include issues regarding delivery, monitoring, and scavenging. Options for their delivery in the ICU include use of a standard anesthesia machine including the Servo 900D, modification of an ICU ventilator with the addition of a vaporizer, addition of the agent to inspiratory limb of the ventilator circuit, or use of the ACD. Additional concerns include scavenging to avoid environmental pollution and the need to monitor the inspired concentration of the agent. With such caveats in mind, the inhalational anesthetic agents may have a therapeutic role in the PICU. Given the

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current medicolegal environment in the United States, I suggest ongoing pediatric anesthesiology consultation when these agents are used in the PICU. However, each hospital and PICU should develop its own protocols according to local and state regulations when these agents are used for therapeutic effects outside of the OR. As the reported experience with these agents in the PICU is limited, future prospective trials are needed to clearly delineate the role of these agents in patient care.

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