Clinical and economic considerations in the use of inhaled anesthesia from the perspective of health-system pharmacists and anesthesiologists

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Articles based on the proceedings of a symposium held December 8, 2009, during the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada. The content of this supplement was written by a professional writer, Susan R. Dombrowski, M.S., and was reviewed, revised, and approved by the authors. Ms. Dombrowski reports no affiliation with or financial interest in a commercial organization that poses a conflict of interest with this supplement. The activity was supported by an educational grant from Baxter Healthcare Corporation.

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The supplement as a whole provides 2.0 hours (0.2 CEU) of continuing-education credit (ACPE activity 204-000-10-414-H01P, knowledge-based activity).

See page S21 or http://ce.ashp.org to locate the continuing-education learning objectives, self-assessment questions, and instructions covering the articles in this supplement.
Clinical and economic considerations in the use of inhaled anesthesia from the perspective of health-system pharmacists and anesthesiologists

Introduction

Tricia Meyer


Anesthesia practice in the United States has evolved considerably since the 1990s. Anesthesia care providers’ practices involve new technology (implantable pumps for pain control, brain function monitors to indicate depth of anesthesia); increased regulatory oversight (surgical checklists, core measures); and anesthetic agents with faster onset and shorter duration of action (desflurane, sevoflurane). In addition, the surgical landscape has shifted from primarily the inpatient operating room (OR) to the ambulatory setting, with more than 65% of all surgeries being performed in ambulatory surgery centers. This change in the delivery of anesthesia combined with reducing costs, enhancing OR efficiency, and advancing patient safety and satisfaction are current goals for perioperative clinicians.

In order to expedite OR throughput and turnover and minimize delays in patient discharge, new systems, processes, and medications are being developed to improve the overall experience of patients. In the past, patients’ concerns centered on whether they would awaken after surgery. Now, among the major concerns of many patients is the length of the waiting period before surgery, in addition to the outcome of surgery and the potential for postoperative discomfort from pain, nausea, and vomiting. Many institutions have recognized the importance of patient and family satisfaction and have devised ways to ensure that surgical patients and their family members have a positive experience. A perioperative clinician recently used Internet-based Twitter technology to keep family members apprised of a patient’s progress during a surgical procedure.

In recent years, anesthetic agents with a short duration of action (e.g., midazolam, propofol, desflurane, sevoflurane) have been marketed for preoperative and intraoperative use. The use of these agents facilitates fast-track (i.e., expedited) surgery and recovery. Inhaled anesthetic agents are a key component of general anesthesia during surgery, and the new less soluble drugs provide a quicker onset and offset of anesthetic effect. These agents account for a substantial portion of the anesthesia pharmacy drug budget although cost per individual case may be low. The selection of appropriate inhaled anesthesia can facilitate...
smooth emergence from anesthesia and postoperative recovery, and this contributes to patient satisfaction.

Health-system pharmacists can help manage the costs of inhaled anesthesia by reviewing the characteristics and delivery of inhaled agents, quantifying the volume and mix of surgical cases in their institution, and understanding all the components of cost associated with these agents. By collaborating with anesthesia care providers, pharmacists can identify strategies for minimizing inhaled anesthetic expenditures without compromising the patient’s perioperative and recovery experience. Cost containment is only one area for potential collaboration between pharmacists and anesthesia care providers. Pharmacists can also participate in teaching and in the development of practice parameters, quality improvement initiatives, and research protocols involving inhaled anesthetic agents.

The first article in this supplement describes the challenges that health-system pharmacists face in helping to manage the use and costs of inhaled anesthesia agents in the OR. The characteristics of these agents, the basic principles for delivering inhaled anesthesia, and the role of inhaled anesthesia in fast-track recovery after surgery also are discussed. In the second article, the components of and factors contributing to the costs of inhaled anesthesia, basis for quantifying and comparing these costs, and practical strategies for performing pharmacoeconomic analyses and reducing the costs of inhaled anesthesia are addressed.

The third article describes the culture of anesthesia practice; stages, types, and goals of anesthesia; and nomenclature for and factors that can affect the dosing of inhaled anesthesia. The basis for anesthesiologist choices among inhaled anesthesia agents; special considerations in using inhaled anesthesia in bariatric surgery patients, pediatric patients, and cardiac surgery patients; and myths associated with the use of inhaled anesthesia in these and other patient populations are discussed.

References
Managing inhaled anesthesia: Challenges from a health-system pharmacist’s perspective

TRICIA MEYER

Medication use in the operating room (OR) is complex, and managing the medication use process in that environment may present a challenge to health-system pharmacists for several reasons. Many institutions lack an OR pharmacy and an OR pharmacist dedicated to the oversight of medication use in the preoperative, intraoperative, and postoperative setting. Medication use on conventional hospital units involves physician prescribing and pharmacist review, order verification, and dispensing, followed by administration and monitoring of the medication by nursing staff. In the OR, an anesthesiologist assumes most of these responsibilities. The medication use process on a medical unit may take minutes to hours, whereas in the OR the medication use process often takes place within seconds or minutes.

Also contributing to the difficulty of pharmacists’ oversight of medication use in the OR is a lack of familiarity with OR systems, processes, equipment, and personnel. If the hospital does not have a pharmacy OR satellite, pharmacists may find the OR less accessible than patient care areas.

Many medications used in the OR are unique to that setting (e.g., tobramycin in cement used for orthopedic cases, malignant hyperthermia kits). Inhaled anesthetic agents are among these medications.

Purpose. To discuss the challenges that health-system pharmacists face in managing the use and costs of inhaled anesthesia in the operating room (OR), the characteristics of inhaled anesthesia agents, systems for delivering inhaled anesthesia, and the role of inhaled anesthetics in fast-track recovery after surgery.

Summary. Inhaled anesthetic agents are the most common drugs used in general anesthesia and are a substantial part of the anesthetic drug budget in health systems. Challenges for health-system pharmacists in managing costs associated with these agents include the lack of a dedicated OR pharmacy, limited access to the OR, unfamiliarity with some of the medications used in the OR, and difficulty quantifying inhaled anesthetic drug use. The three inhaled anesthesia agents currently used in the United States have proven to be safe and effective. These agents have differences in solubility in blood and tissues, which affect onset, absorption, and excretion. Isoflurane has the highest solubility in blood and tissues, which may result in slower recovery. Lower solubility allows for a faster recovery. The two newest agents on the market, sevoflurane and desflurane, both have low solubility, with desflurane having lower solubility than sevoflurane. Sevoflurane has the advantage of low pungency and is not associated with respiratory irritation. As a cost-savings initiative, the inhalation agents may be used with low flow rates, which minimizes the amount of inhaled anesthetic used. In addition, using the less soluble inhaled anesthetic agents as part of a fast-track approach will accelerate recovery by reducing time to emergence and recovery. This approach can potentially reduce costs to the institution.

Conclusion. Understanding the differences in characteristics and delivery of the inhaled anesthesia agents will enable health-system pharmacists to collaborate with anesthesia care providers to better manage the use and costs of these agents.

Index terms: Anesthetics; Costs; Desflurane; Drug administration; Hospitals; Isoflurane; Pharmaceutical services; Pharmacists, hospital; Pharmacy, institutional, hospital; Sevoflurane; Solubility; Surgery; Toxicity

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Based on the proceedings of a symposium held December 8, 2009, during the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, and supported by an educational grant from Baxter Healthcare Corporation. Dr. Meyer received an honorarium from the American Society of Health-System Pharmacists for her participation in the symposium and for the preparation of this article. Dr. Meyer reports that she serves as a speaker for Baxter Healthcare Corporation.

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The complexity of administering inhaled anesthetics via the anesthesia machine and breathing circuit are not typically part of the pharmacy school curriculum and understanding of the delivery system must be gained “on the job.”

The intensity of medication use in the OR is among the highest of all areas of the hospital. Anesthesia drugs account for 5–13% of the overall drug budget. Many of these medications (e.g., propofol before a generic form became available) are or were at one time among the top 10 or 20 drug expenditures in a pharmacy budget. The inhaled anesthetic agents alone may account for 20% of anesthesia drug expenses, which make them a frequent target for cost-saving initiatives. The cost per case for inhaled anesthetic agents may appear small, but the costs of these agents to the institution can be substantial because of the volume of surgical cases. It is key to consider all of the costs associated with the delivery of inhaled anesthetic agents.

Ordinarily, inhaled anesthetic agents are purchased by the hospital pharmacy department, although anesthesiologists are considered the experts on use of these agents. The use of inhaled anesthetic agents has typically been monitored and managed by anesthesiologists. It is difficult for pharmacists to know whether anesthesiologists are using the agents in a cost-effective manner or in accordance with institutional protocols. Pharmacists can review individual anesthesia records to determine use of the inhaled anesthetic agent; however, the records can be confusing and calculating the amount used can be difficult. Purchasing records often are the most readily available source of information to pharmacists, and these records have limited usefulness. The use of inhaled anesthetic agents (e.g., the choice of agent and flow rate) can vary among practitioners, depending on their individual preferences.

The units of measure used for pricing inhaled anesthesia agents differ from those used for conventional medications. Although they come as liquids, evaluating the price or acquisition cost of the bottle or cost per mL of these agents is not the most appropriate means to determine cost. The volume contained in each individual unit varies by agent and should be considered when calculating cost to the institution.

**Inhaled anesthetic agents**

The first inhaled anesthetic agent, which was synthesized in 1772, was nitrous oxide. The agent was put into clinical use in the early 1840s for its hypnotic and analgesic effects. Similar properties were noted with diethyl ether in 1844. The agent was widely used as an anesthetic for approximately 100 years despite its unpleasant odor, taste, and the delayed postoperative recovery, which also involved significant nausea and vomiting. Today many older patients recall receiving ether for surgeries performed when they were young. In the 1940s, techniques in fluorine chemistry led to the development of halogenated agents with improved stability, potency, and safety. This discovery led to what we consider the modern day inhaled anesthesia agent, as well.

Isoflurane, desflurane, and sevoflurane are halogenated ether-based compounds with many of the characteristics of the ideal inhaled anesthetic agent. Isoflurane is halogenated with fluorine and chlorine (Figure 1), and desflurane and sevoflurane are halogenated with fluorine alone (the only difference between isoflurane and desflurane is the substitution of chlorine on isoflurane with fluorine on desflurane). The fluorination provides increased stability and decreased toxicity and flammability. Halogenation with fluorine increases solubility and potency. Desflurane and sevoflurane are environmentally friendly. Isoflurane is less environ-

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<th>Characteristic</th>
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<th>Sevoflurane</th>
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*At 20°C and 1 atmosphere of pressure.

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**Table 1. Commercially Available Inhaled Anesthesia Products**

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mentally friendly than desflurane and sevoflurane because of the presence of chlorine (compounds with a chlorine moiety have the potential to deplete the atmospheric ozone layer, resulting in greenhouse warming), although its environmental impact is negligible.

Isoflurane, desflurane, and sevoflurane differ in several important characteristics, particularly solubility in blood and tissues, which affects recovery time, and pungency, which manifests as respiratory irritation.6 Compared with desflurane and sevoflurane, isoflurane has a higher solubility in blood and tissues, which may translate into a slower recovery.7,8 Isoflurane has a pungent odor, and patients receiving the agent are at intermediate risk for respiratory irritation.6 This drug would not be used as an induction agent.

Sevoflurane has low solubility in blood and tissues, which allows a rapid recovery.7,8 Sevoflurane has minimal odor, no pungency, and does not cause respiratory irritation.6 Therefore, this agent is an excellent choice for mask induction of anesthesia for both adults and children. For pediatric patients, administration of inhaled anesthetics by mask is preferred to the needle stick required for i.v. anesthetic medications. In contrast, most adults prefer to receive anesthetic agents by the i.v. route rather than by inhalation through a mask. The product labeling for sevoflurane includes a warning that exposure should not exceed 2 MAC hours at flow rates of 1 to <2 L/min, and fresh gas flow rates of <1 L/min are not recommended. The recommendations are intended to minimize exposure to a degradation product known as compound A that has been linked to nephrotoxicity in animals.9

Desflurane has lower blood:gas solubility compared with isoflurane or sevoflurane, which permits tighter control over the level of anesthesia and may provide faster emergence and recovery from anesthesia.7,8 Desflurane is safe to use with a low fresh gas flow rate. It has a pungent odor and is associated with a higher risk for respiratory irritation than sevoflurane and would not be used as an induction agent.6

Desflurane and isoflurane may cause transient increases in heart rate.10 Sevoflurane does not cause the increase in heart rate unless it is administered at higher concentrations. All three agents share a dose-related decrease in arterial blood pressure. Other pharmacologic effects of isoflurane, desflurane, and sevoflurane are similar (Table 2). All three agents can cause respiratory depression, with a decrease in tidal volume and an increase in respiratory rate. These effects are dose dependent. These agents show a mild increase in intracranial pressure and depress cerebral blood flow. Similar effects with these agents are seen in decreased renal blood flow, urinary output, and glomerular filtration rate.10-12
Dynamics of inhaled anesthesia

The goal of inhalation anesthesia is to develop and maintain an anesthetizing partial pressure of the anesthetic agent in the brain. A series of partial pressure gradients is required to drive the inhaled anesthetic agent across barriers to the brain. The gradients begin at the anesthesia machine. The anesthetic gas is inspired into alveolar spaces, where it is driven across another gradient into arterial blood and ultimately to the brain.

The faster an anesthetic agent reaches equilibrium between the gas and liquid phases across these gradients, the faster the onset of action. Agents with low solubility in blood and tissues will equilibrate quickly and produce a rapid onset of effect and offset of effect, with a short wake-up time even after a long duration of administration.

Solubility in blood and tissues can be expressed as partition coefficients. The blood-gas partition coefficient is the ratio of the concentration of an anesthetic agent in blood to the concentration of the agent in the gas phase when equilibrium is reached between the two phases.\(^4,5\) The blood-gas partition coefficient is lowest for desflurane (0.45), followed by sevoflurane (0.65), and highest for isoflurane (1.4).\(^7\) The lower the blood-gas partition coefficient, the lower the gas's affinity for and solubility in blood.

A short duration of anesthetic action could reduce costs if it translates to short stays in the postanesthesia care unit (PACU) and a subsequent decrease in resources such as nursing hours paid to staff recovery areas. A concern for a rapid recovery process would be hemodynamic instability and difficulty maintaining a patent airway. Postanesthesia discharge criteria evaluations are used to decrease the occurrence of adverse events.

The termination of anesthetic effect may be quantified as the time required for the alveolar concentration of the agent to decrease by 90%. This 90% decrement time corresponds to recovery from anesthesia. The 90% decrement times for isoflurane, desflurane, and sevoflurane were compared for various durations of anesthetic administration using a computer model and published pharmacokinetic values.\(^5\) The duration of anesthesia was taken into consideration because it affects the rate at which anesthetic concentrations decrease after discontinuation of anesthesia. The 90% decrement time was lowest for desflurane, intermediate for sevoflurane, and highest for isoflurane, regardless of the duration of anesthesia. The 90% decrement time for desflurane ranged from 5 minutes after 30 minutes of anesthesia to 14 minutes after six hours of anesthesia. In contrast, the 90% decrement time for the highly soluble isoflurane increased markedly as the duration of anesthesia increased beyond a short time, although there was little difference in 90% decrement time between two hours of anesthesia and six hours of anesthesia. The 90% decrement time for sevoflurane was low and approached that of desflurane when the duration of anesthesia was short (i.e., less than two hours), but the 90% decrement time increased markedly as the duration of anesthesia increased, approaching values for isoflurane (i.e., 86 minutes after six hours of isoflurane and 65 minutes after six hours of sevoflurane).

The duration of the surgical procedure and anesthesia may influence the choice among these three inhaled anesthesia agents. Desflurane and sevoflurane have a faster termination of anesthetic effect than isoflurane when the duration of surgery and anesthesia is short.

Delivery systems

The delivery of inhaled anesthesia involves the use of complex machinery that may be unfamiliar to most pharmacists. Inhaled anesthesia delivery systems include an anesthesia machine with a flow meter that regulates the amount of background gases (i.e., oxygen, nitrous oxide, and air), a calibrated vaporizer that heats and vaporizes the liquid anesthetic agent, and a rebreathing circuit with inspiratory and expiratory components.\(^6\) The background gases flow to the vaporizer, where a portion of the background gases enters the vaporizer and picks up the anesthetic vapor. The mixture of anesthetic and background gases is delivered to the patient via a face mask or endotracheal tube. Carbon dioxide is removed from expired gases when they pass through a carbon dioxide absorber in the circuit. Expired gases are then mixed with fresh background gases for rebreathing by the patient. The University of Florida has developed an interactive, Internet-based program with a virtual anesthesia machine to simulate use of this equipment for volatile (i.e., inhaled) anesthesia delivery (http://vam.anest.ufl.edu/). This program is an excellent teaching tool for pharmacy students and residents and pharmacists who are new to OR pharmacy practice.

Gas flow rates are classified as minimal (0.25–0.5 L/min), low (0.5–1.0 L/min), medium (1.0–2.0 L/min), high (2.0–4.0 L/min), and very high (>4 L/min).\(^4\) Very high rates have been used in the past to prevent inadvertent hypoxia and optimize control of the depth of anesthesia.\(^4\) However, lower rates are advantageous because they allow appropriate anesthesia with less anesthetic agent use, thereby minimizing costs, and resulting in minimal escape of anesthetic agent into the environment.\(^1,4\)

Fast-track recovery

Fast-track recovery is an approach to accelerating recovery in which patients who meet certain criteria bypass the phase I PACU and are transferred directly from the OR to a phase II recovery area.\(^3\) This approach may provide cost savings
to the health care system because of the decreased length of stay. It also offers benefits to the patient and his or her family members at institutions where family members are permitted access to the phase II recovery area (family members are typically not allowed in the PACU).

Three types of recovery time can be measured after the use of inhaled anesthesia. Early recovery is the time until patients open their eyes and obey commands. Intermediate recovery is the time until the patient is ready to go home. Late recovery is the time to return to normal activities.

Most patients are eager to complete the recovery process and return home as quickly as possible. The use of inhaled anesthetic agents with a short duration of action as part of a fast-track recovery approach can facilitate that goal.

**Conclusion**

Understanding the differences in characteristics and delivery of the inhaled anesthetic agents will enable health-system pharmacists to collaborate with anesthesia care providers to better manage the use and costs of these agents. Potential benefits include improved patient satisfaction and reduced costs to the health care system.

**References**

Economic considerations in the use of inhaled anesthetic agents

JULIE GOLEMBIEWSKI

Purpose. To describe the components of and factors contributing to the costs of inhaled anesthesia, basis for quantifying and comparing these costs, and practical strategies for performing pharmacoeconomic analyses and reducing the costs of inhaled anesthetic agents.

Summary. Inhaled anesthesia can be costly, and some of the variable costs, including fresh gas flow rates and vaporizer settings, are potential targets for cost savings. The use of a low fresh gas flow rate maximizes rebreathing of exhaled anesthetic gas and is less costly than a high flow rate, but it provides less control of the level of anesthesia. The minimum alveolar concentration (MAC) hour is a measure that can be used to compare the cost of inhaled anesthetic agents at various fresh gas flow rates. Anesthesia records provide a sense of patterns of inhaled anesthetic agent use, but the amount of detail can be limited. Cost savings have resulted from efforts to reduce the direct costs of inhaled anesthetic agents, but reductions in indirect costs through shortened times to patient recovery and discharge following the judicious use of these agents are more difficult to demonstrate. The patient case mix, fresh gas flow rates typically used during inhaled anesthesia, availability and location of vaporizers, and anesthesia care provider preferences and practices should be taken into consideration in pharmacoeconomic evaluations and recommendations for controlling the costs of inhaled anesthesia.

Conclusion. Understanding factors that contribute to the costs of inhaled anesthesia and considering those factors in pharmacoeconomic analyses and recommendations for use of these agents can result in cost savings.

Index terms: Anesthetics; Costs; Drug administration; Pharmacoeconomics; Surgery


The cost of anesthesia care has three main components. Direct costs include the costs of anesthesia agents, other materials, and labor. Indirect costs include the costs related to the consequences of an event. These consequences may be intended or unintended (e.g., a prolonged stay in the operating room [OR] or postanesthesia care unit [PACU]). Intangible costs include the costs related to pain and suffering as a result of illness or treatment. Intangible costs, however, are difficult if not impossible to quantify.

The direct costs of anesthesia care may be divided into fixed costs and variable costs. Costs established in contract negotiations usually are fixed for the duration of the contract. Some variable costs hinge on decisions made by anesthesia care providers, and these variable costs are potential targets for cost savings. An example is the choice of drugs used to provide general anesthesia in patients undergoing surgery or other invasive procedures.

Commonly, the intravenous (i.v.) anesthetics propofol and etomidate are used for induction (to render the patient unconscious). Often these induction agents are immediately followed by succinylcholine or a non-depolarizing neuromuscular blocking agent (e.g., rocuronium) to facilitate intubation. In children, instead of an i.v. agent such as propofol, sevoflurane is commonly used to induce general anesthesia. In both adults and children, inhaled anesthetic agents are the workhorses for maintaining anesthesia, although continuous i.v. infusion of propofol is an alternative to inhaled anesthetic agents. The
recent propofol shortage has caused anesthesia care providers to examine their practices and consider alternatives such as the use of sevoflurane for induction of anesthesia in adults. A variety of other medications may be used intraoperatively to maintain paralysis, modulate blood pressure and heart rate, and provide other desired pharmacologic effects such as amnesia and analgesia. These medications may include nondepolarizing neuromuscular blocking agents (e.g., vecuronium, cisatracurium), reversal agents (e.g., neostigmine and glycopyrrolate), ephedrine, phenylephrine, metoprolol, esmolol, labetalol, fentanyl, midazolam, ketamine, local anesthetics, and antiemetic agents.

Cost of inhaled anesthesia

Inhaled anesthetic agents represent a major portion of anesthesia drug costs. Desflurane and sevoflurane are the most commonly used inhaled anesthetic agents, and they are costly. Four factors contribute to the cost of inhaled anesthetic agents. These agents are commercially available as liquids, and the acquisition cost per milliliter is generally fixed, on the basis of a negotiated contract price. The second cost component is the volume of vapor produced per milliliter of liquid, which also is fixed and is based on the physical and chemical characteristics of the agent. The third cost component is the potency of the anesthetic agent, which varies from one agent to another but is a fixed physical property of the agent. The concentration of the agent required may vary depending on patient characteristics (e.g., age, concurrent medications, temperature) and the depth of anesthesia required for the invasiveness of the surgery being performed. The depth of anesthesia may be increased or decreased at various stages of the surgery, depending on the procedure. The fourth component of the cost of inhaled anesthesia is the amount of anesthetic agent wasted.

The concentration of inhaled anesthetic necessary to provide general anesthesia is quantified by using the concept of minimum alveolar concentration (MAC), which is defined as the alveolar concentration of the inhaled anesthetic agent at 1 atmosphere of pressure that prevents movement in response to a surgical stimulus in 50% of patients. The MAC reflects the dosage of an anesthetic agent required to produce the desired depth of anesthesia. The MAC required varies according to the desired response. For example, an alveolar concentration of 1.2–1.3 MAC is required to consistently prevent patient movement during surgical stimuli (e.g., incision), whereas an alveolar concentration below 0.4–0.5 MAC allows patients to open their eyes on command at the end of surgery. MAC values can be compared among inhaled anesthetic agents; the MAC values for desflurane, sevoflurane, and isoflurane are 6.0%, 2.05%, and 1.15%, respectively.

The amount of inhaled anesthetic agent wasted is directly correlated to the fresh gas flow rate. The use of a high flow rate increases the amount of inhaled anesthetic agent vaporized and decreases rebreathing of exhaled anesthetic gas. This approach provides greater control of the level of anesthesia, but it has a higher cost. The amount of anesthetic gas vaporized exceeds what partitions from the gas phase into the lung and brain tissues, resulting in waste. Excess anesthetic gas ends up being vented into the atmosphere.

In contrast, using a low fresh gas flow rate maximizes rebreathing of exhaled anesthetic gas, minimizes the amount of anesthetic gas vented into the atmosphere, and is less costly than a high flow rate. However, this approach provides less control of the level of anesthesia. A low gas flow rate also may conserve the patient’s expired heat and humidity.

Comparing costs

The costs of an inhaled anesthetic agent can be estimated by calculating the cost per MAC hour, defined as administration of the inhaled anesthetic agent at 1 MAC for one hour. The cost per MAC hour of the agent can be calculated from the concentration (%) of gas delivered (i.e., the vaporizer setting), fresh gas flow rate (FGF in L/min), duration of inhaled anesthetic delivery (60 min), molecular weight (MW in g), cost per mL (in dollars), a factor to account for the molar volume of a gas at 21 °C (2412), and density (D in g/mL). The formula is as follows:

\[
\text{Cost per MAC hour ($)} = \frac{[(\text{Concentration})(\text{FGF})(\text{duration})]}{[(\text{MW})(\text{cost/mL})]/[(2412)(D)]}
\]

For example, the cost per MAC hour of isoflurane at a fresh gas flow rate of 2 L/min is $1.04 based on a concentration of 1.15% for 1 MAC, duration of 60 minutes, MW of 184.5 g, average wholesale cost per mL of $0.15, and density of 1.496 g/mL. Most of the components in the formula used to calculate cost per MAC hour are fixed, except for fresh gas flow rate. The two most commonly used inhaled anesthetic agents, desflurane and sevoflurane, are substantially more expensive than isoflurane at fresh gas flow rates ranging from 1 L/min to 3 L/min (Table 1). The cost per MAC hour of these agents hinges on the fresh gas flow rate; for example, when using average wholesale cost, the cost per MAC hour for desflurane at a typical flow rate of 1 L/min is similar to that of sevoflurane at a typical flow rate of 2 L/min. When institutional acquisition cost is considered, the cost per MAC hour may be higher or lower than when average wholesale cost is used.

Practical experience

The potential cost savings from analyzing and modifying the use
of inhaled anesthetic agents are illustrated by experiences in several health systems. A collaborative effort involving the pharmacy and anesthesia departments to reduce the use of desflurane and increase the use of sevoflurane at Montefiore Medical Center in the Bronx, New York, suggested a potential cost savings of more than $100,000 between March 2007 and April 2008. Isoflurane was the workhorse anesthetic agent at Montefiore, but desflurane and sevoflurane also were used at the medical center. Sevoflurane was more expensive than desflurane when the acquisition costs of the same volume of liquid were compared.

In evaluating the possibility of similar potential savings at one’s own institution, a closer look is warranted. As previously discussed, the cost of an inhaled anesthetic agent is not based solely on acquisition cost. Fresh gas flow rates must be taken into consideration, and these rates often vary considerably according to the inhaled anesthetic agent being administered, current intraoperative conditions, and the anesthesia care provider.

A second consideration is that anesthesia machines vary in terms of the number of vaporizers on the machine. A different vaporizer is required for each inhaled anesthetic agent. Older anesthesia machines may have three vaporizers, but most newer anesthesia machines have two vaporizers (accommodating two agents), and compact anesthesia machines have only one vaporizer (accommodating one agent). Great care and effort are required in switching vaporizers if a patient requires an agent that is not already set up on the machine. Newer anesthesia machines are designed with connectors to prevent errors involving filling the vaporizer with the wrong agent, and the position of the vaporizer is critical during placement, removal, and storage. Spills in the OR and inadvertent exposure of OR personnel to the anesthetic agent also are a concern. To minimize the need to switch vaporizers in anesthesia machines that have two vaporizers, the two most appropriate vaporizers should be placed in the machine. For example, an isoflurane vaporizer may be kept in OR rooms where longer surgeries are performed, a sevoflurane vaporizer kept in OR rooms where children are anesthetized, and vaporizers for sevoflurane and desflurane kept in OR rooms where short surgeries are performed. The choice of vaporizers can therefore vary from one anesthetizing location to another within the institution as well as between institutions.

At Montefiore Medical Center, it appears that sevoflurane and isoflurane vaporizers were selected as the two vaporizers on the anesthesia machine, making the use of desflurane available only on request. At many institutions, however, that may not be appropriate for the type of patients and the surgical procedures performed. Close collaboration between the anesthesia and pharmacy departments is necessary to determine the most appropriate location and choice of vaporizer for each anesthesia machine and anesthetizing location in the institution.

The potential for cost savings from reducing the fresh gas flow rate used for inhaled anesthesia was demonstrated at another institution. At the University of Nebraska Medical Center, the combined costs of desflurane and sevoflurane amounted to $477,000 in fiscal year 2005–2006. The purchase price of the two inhaled anesthetic agents was similar, but the cost per minute was significantly higher for sevoflurane ($0.79) than desflurane ($0.56, p = 0.022), largely because of a higher average fresh gas flow rate and MAC equivalent during induction and maintenance of anesthesia. A potential annual cost savings of $238,500 from reducing the fresh gas flow rate by 50% was projected.

### Analyzing Costs

Anesthesia records are maintained on paper in most health systems, although automated record keeping systems are available in many institutions. It usually is difficult to ascertain from anesthesia records the precise duration of delivery of a particular concentration of an inhaled anesthetic agent. Titration to a desired level of anesthesia typically requires frequent changes in vaporizer settings, and the amount of detail in paper-based anesthesia records is limited. Nevertheless, anesthesia records can be used to obtain a sense of patterns of use (e.g., choice

<table>
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<tbody>
<tr>
<td>Fresh Gas Flow Rate (L/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.52</td>
<td>12.96</td>
<td>6.05</td>
</tr>
<tr>
<td>2</td>
<td>1.04</td>
<td>25.93</td>
<td>12.10</td>
</tr>
<tr>
<td>3</td>
<td>1.56</td>
<td>38.88</td>
<td>18.15</td>
</tr>
</tbody>
</table>

\*MAC = minimum alveolar concentration.
\*All estimated costs per MAC hour are based on a duration of 60 minutes and the following formula: Cost per MAC hour ($) = ([Concentration] × [FGF]) × [duration] × [MW] × [cost/mL] / ([1000] × [D]) where FGF is fresh gas flow rate in L/min, MW = molecular weight in g, cost per mL is in dollars based on average wholesale price, and D = density in g/mL.

- Isoflurane calculations are based on a concentration of 1.15%, molecular weight (MW) of 184.5 g, cost per mL of $0.15, and density of 1.496 g/mL.
- Desflurane calculations are based on a concentration of 6%, MW of 168 g, cost per mL of $0.96, and density of 1.45 g/mL.
- Sevoflurane calculations are based on a concentration of 2.05%, MW of 201 g, cost per mL of $0.90, and density of 1.51 g/mL.
and concentration of agent, rough estimation of MAC hours of use) and fresh gas flow rates. These variables can substantially contribute to the direct costs of anesthesia.

The indirect costs of anesthesia are much more difficult to quantify than the direct costs. In theory, the lower solubility of desflurane and sevoflurane in blood and tissues compared with isoflurane may confer a more rapid emergence from anesthesia and discharge from the PACU, offsetting the higher cost of these agents compared with isoflurane. However, it has been difficult to demonstrate a reduction in the time to PACU discharge from the use of sevoflurane instead of isoflurane after short surgical procedures. In one study, a shorter time to orientation was observed with the use of sevoflurane instead of isoflurane primarily in long (more than three hours) surgical cases. However, the isoflurane had not been titrated downward toward the end of surgery, as is the custom in clinical practice to promote a shorter time to emergence from anesthesia following completion of the surgical procedure. There was no difference in the time to eligibility for discharge between sevoflurane and isoflurane despite failure to titrate isoflurane at the end of surgery in this study.

Several factors should be taken into consideration in pharmacoeconomic evaluations and recommendations for controlling the cost of inhaled anesthetic agents. The surgical case mix (e.g., number of inpatient procedures versus outpatient procedures, children versus adults, normal weight versus morbidly obese patients) and fresh gas flow rates typically used during inhaled anesthesia are among these factors. The role of isoflurane in the institution depends on anesthesiology care provider practices and surgical case mix. The availability and the locations of isoflurane vaporizers also are considerations.

The impact of efforts to promote the cost-effective use of inhaled anesthetic agents can be evaluated by using purchasing records for these agents, which provide a rough measure of usage and cost. Changes in patient case mix or anesthesia care providers’ practices could have an impact on fresh gas flow rates and choice of agent and thus on inhaled anesthetic costs. Auditing anesthesia records is time consuming, especially if records are available only on paper, but it can provide valuable insight into usage patterns and the impact of cost-saving measures for inhaled anesthetic agents.

**Conclusion**

Inhaled anesthetic costs can be substantial. Careful consideration and management of factors that affect the direct and indirect costs of inhaled anesthesia can provide economic benefits.

**References**

An anesthesiologist’s perspective on inhaled anesthesia decision-making

RICHARD CARL PRIELIPP

The operating room (OR) is a unique practice environment, and anesthesiologists practice in a culture that is distinctly different from that of other health care practitioners. Anesthesiology is a hands-on, high-stress specialty that requires considerable experience to achieve excellence. It requires complex monitoring, detailed knowledge of pharmacology, and the ability to manage patients during periods of rapid deterioration. Often, the anesthesiologist may supervise two or more nurse anesthetists. The successful anesthesiologist must be reliable and skilled at communicating with surgeons, OR nursing staff, and ancillary personnel. In the OR, anesthesiologists must be highly vigilant and adept at making rapid decisions about patient care. Being prepared to meet unpredictable patient needs often results in the preparation of drugs and syringes that may not be used. Although some may consider this a waste of medications, having these drugs drawn into syringes facilitates a prompt response to emergencies. Preparedness is vital for patient safety.

Purpose. To describe the culture and content of anesthesia practice; the stages, types, and goals of anesthesia; nomenclature and factors that can affect dosing of inhaled anesthesia; basis for anesthesiologist choices among inhaled anesthesia agents; and special considerations in using inhaled anesthesia in bariatric surgery patients, pediatric patients, and cardiac surgery patients; and to provide insights into myths associated with inhaled anesthesia.

Summary. The practice of anesthesiology requires complex monitoring, detailed knowledge of pharmacology, and the ability to make quick decisions about patient management. Four stages of anesthesia have been characterized on the basis of patient responsiveness to surgical stimuli. The second stage ("excitement") occurs during induction of or emergence from anesthesia; patients in this stage are particularly vulnerable to problems with laryngospasm, airway obstruction, uncontrolled motor movements, regurgitation, vomiting, and aspiration. In the United States, most general anesthesia involves inhaled agents. The minimum alveolar concentration (MAC) of inhaled anesthetic agents, which anesthesiologists use in dosing these drugs, can be affected by age, a variety of medications, and other patient-specific factors. MAC can be thought of as a measure of drug potency. Both MAC and solubility in blood and tissues differ among inhaled anesthetic agents. Agents with low solubility have a rapid onset and offset of effect and may allow for faster recovery. The choice among inhaled anesthetic agents may depend on their solubility, as well as the propensity to cause airway irritation and coughing, drug cost, and characteristics such as patient age, obesity, and duration of surgery. Anesthesia care providers’ experience and habits may also influence drug choice. Emergence delirium (i.e., agitation) can occur with all three inhaled anesthetic agents in common use (isoflurane, desflurane, and sevoflurane). Other potential issues such as hepatotoxicity and nephrotoxicity are of minimal concern with these agents. Using low flow rates of fresh gas is one strategy for minimizing inhaled anesthesia costs, but it is not always feasible.

Conclusion. Experience and careful consideration of the characteristics of inhaled anesthetic agents and surgery- and patient-specific factors allow anesthesia care providers to meet the rapidly changing needs of patients receiving inhaled anesthesia in a safe and cost-effective manner.

Index terms: Age; Anesthetics; Costs; Decision making; Desflurane; Dosage; Drug administration; Drugs; Isoflurane; Obesity; Pediatrics; Pharmacoeconomics; Sevoflurane; Solubility; Surgery; Toxicity


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Stages and types of anesthesia
Several stages of anesthesia were described in the past when diethyl ether was used during spontaneous ventilation for anesthesia, and these stages remain relevant today. Stage 1 involves sensory depression with a mild, early analgesic effect. The patient still opens his or her eyes but may tolerate mild surgical stimuli (e.g., insertion of an intravenous [i.v.] needle or catheter).

Stage 2 is characterized by excitement, with heightened laryngeal reflexes and some skeletal muscle movement. This stage is a vulnerable period that requires considerable anesthesiology expertise to manage. Problems such as laryngospasm, airway obstruction, regurgitation, vomiting, and aspiration may arise in stage 2 during either induction of or emergence from anesthesia.

Stage 3 is a period of operative anesthesia and unresponsiveness to surgical stimulation; the patient will not move (meaningfully) in response to stimuli. Stage 4 reflects physiologic decompensation due to impending anesthesia overdose. This stage is undesirable, and anesthesia care providers go to great lengths to avoid it.

General anesthesia is used in the vast majority (probably around 80%) of cases requiring anesthesia. However, there has been a recent resurgence of interest in regional anesthesia and major neuraxial blocks, partly because these types of anesthesia can be used to provide extended analgesia during the postoperative period. These techniques are particularly valuable for patients undergoing major orthopedic and abdominal bowel procedures because they facilitate early ambulation.

Monitored anesthesia care (i.e., local anesthesia in combination with deep, potent intravenous sedation and analgesia) is another approach used for anesthesia in some patients. Various other combinations of techniques may be used in select anesthesiology applications.

Goals of anesthesia
A key goal in the use of anesthesia is to provide safe conditions for the performance of surgery or ancillary invasive procedures, using drugs with rapid onset and offset of anesthetic effect. Timely discharge from the hospital or ambulatory surgery center is often another important goal. Proactive management of potential barriers to discharge (e.g., postoperative nausea and vomiting [PONV], pain, and urinary retention) will expedite patient discharge. A short length of perioperative or hospital stay has important implications for controlling costs. Minimizing postoperative discomfort (pain and especially nausea and vomiting) contributes to patient satisfaction.

The priority given to the various goals of anesthesia may vary depending on the clinical scenario, but safety is always the highest priority. Anesthesiologists take a zero-tolerance approach to avoidable safety problems in the provision of anesthesia.

Minimum alveolar concentration
Inhaled anesthetic agents are commonly used for general anesthesia. The minimum alveolar concentration (MAC) of an inhaled anesthetic agent (at standard temperature and 1 atmosphere of pressure) that prevents meaningful movement in response to a surgical stimulus in 50% of patients is part of the standard nomenclature used by anesthesiologists to compare the potency of anesthetic agents. MAC values originally were described in animals, but they are now applied to response to skin incision in younger, healthy humans. The response must be meaningful (i.e., a purposeful movement to avoid a painful stimulus rather than a random muscle twitch).

Variations of the MAC also have been used as a quantitative measure. For example, the MAC-BAR is the concentration of an anesthetic agent required to block adrenergic and cardiovascular responses to skin incision. Most of these MAC variations are of less universal clinical utility but are used in research and select applications.

MAC values in the literature are for healthy, young adults, usually approximately 20–40 years of age. Isoflurane has an MAC of 1.15%, and if a healthy, young person receives isoflurane at 1.1%, there is a 50% chance of movement in response to a surgical incision.

The MAC of all inhaled anesthesia gases decreases with patient age. The MAC is highest at approximately six months of age and lowest after the age of 80 years. The MAC decreases by approximately 6% per decade from infancy to old age.

A variety of medications and patient-specific factors can affect MAC (Table 1). Pregnancy is a particularly relevant factor in the use of inhaled anesthesia. Some factors (including alcohol or other drug ingestions) increase or decrease the MAC depending on whether exposure is chronic or acute.

Inhaled anesthesia agents
The inhalation anesthetic agents are chemically in the methyl-ethyl or isopropyl ether class and thus have an intrinsic aroma by nature of their ether biochemistry. Thus, the more pleasant odor of one particular agent—sevoflurane—is more readily accepted by patients, especially children. The pleasant odor can actually distract children during inhalation induction and act to divert their attention away from other potentially scary elements within the operating room.

The ideal inhaled anesthetic agent is nonflammable and nontoxic and provides amnesia, muscle relaxation, and analgesia. The agent is easily administered, provides rapid induction of and emergence from anesthesia, has a pleasant odor, and is devoid of toxic metabolic byproducts. The three
commonly used inhaled anesthetic agents—isoﬂurane, desﬂurane, and sevoﬂurane—are ﬂuorinated ethers, so ﬂammability is not a concern. These agents all provide anesthesia, albeit at different concentrations. However, the concentration required is not a major focus in the anesthesiologist’s decision-making process.

The three inhaled anesthetic agents have similar pharmacology because of their similar chemical structure. They all depress myocardial contractility and ventilation, but they also relax bronchial muscles and dilate the bronchioles, which is beneﬁcial.8 The mild muscle relaxation produced by inhaled anesthetic agents augments the neuromuscular blockade produced by the muscle relaxants used during surgery. Inhaled anesthetic agents also increase cerebral blood ﬂow and decrease cerebral metabolic rate of oxygen consumption, which are of importance in neuroanesthesia cases.9 The agents generally are nontoxic, but they promote PONV.10

The choice among the three available inhaled anesthetic agents by anesthesiologists and nurse anesthetists is based on a host of factors, sometimes including subliminal ones such as experience with a particular agent. Their preferences for a particular agent may reﬂect habits established during their training or early in their practices. Convenience is another factor that may contribute to the choice of an agent, because most newer anesthesia machines may accommodate only one or two vaporizers, and the use of an anesthetic agent not already set up on the machine requires switching vaporizers. Switching vaporizers can be inconvenient and maybe reduce efﬁciency in the OR. Lack of familiarity with the differences between anesthetic agents also may be a factor in decisions about which agent to use.

Legitimate reasons for choosing among the inhaled anesthetic agents include differences in tissue and blood solubility that affect onset and emergence (i.e., offset) times. The agent’s cost and propensity to cause airway irritation and coughing are other factors that inﬂuence selection. Optimizing the choice of drug for the individual patient and his or her disease state is also a consideration. The patient’s ability to tolerate induction using a mask from the anesthesia machine with spontaneous inhaled anesthesia must be considered; this is of particular concern for pediatric patients and patients with marked obesity.

Inhaled anesthetic agents with low solubility in blood and tissues (e.g., desﬂurane and sevoﬂurane) have a rapid onset and offset of effect. The MAC (which can be thought of as a measure of drug potency) of inhaled anesthetic agents varies from 1.15% for isoﬂurane to 6.0% for desflurane (i.e., lower potency than isoﬂurane).4 However, differences in MAC or potency are a minor consideration in anesthesiology care providers’ choice of inhaled anesthetic agent.

Differences in metabolism among the inhaled anesthetic agents may be clinically relevant because the extent and products of metabolism are linked to hepatotoxicity.11 The metabolism of halothane, the ﬁrst ﬂuorinated agent introduced in the 1950s, is high (20–40%). This agent is no longer used in the United States, at least in part because of hepatotoxicity. Metabolism of currently used inhaled anesthetic agents is much lower (up to 5% for sevoﬂurane, 0.2% for isoﬂurane, and 0.02% for desflurane), so hepatotoxicity from inhaled anesthesia is of less concern than in the past when halothane was used.11 Sevoﬂurane is metabolized by cytochrome P450-2E1 to hexaﬂuoroisopropanol, inorganic ﬂuoride, and carbon dioxide. The risk for hepatotoxicity may be lower for sevoﬂurane than for isoﬂurane or desﬂurane. The metabolism of isoﬂurane and desﬂurane is thought to produce reactive intermediate metabolites that could trigger hepatotoxicity, but the sevoﬂurane metabolic pathway does not result in such reactive metabolites.11

### Table 1. Factors That Can Affect the MAC of Inhaled Anesthetic Agents

<table>
<thead>
<tr>
<th>Factors that can increase MAC</th>
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<tbody>
<tr>
<td>Hyperthermia</td>
</tr>
<tr>
<td>Use of monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Use of cocaine or other CNS stimulants</td>
</tr>
<tr>
<td>(acute cocaine intoxication increases MAC)</td>
</tr>
<tr>
<td>Infancy</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Use of opioid analgesics</td>
</tr>
<tr>
<td>Co-administration of i.v. anesthetic agents</td>
</tr>
<tr>
<td>The neonatal period</td>
</tr>
<tr>
<td>Increases in age after age 30</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Acute alcohol ingestion</td>
</tr>
<tr>
<td>Use of lithium</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factors that can decrease MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyrmia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Use of opioid analgesics</td>
</tr>
<tr>
<td>Co-administration of i.v. anesthetic agents</td>
</tr>
<tr>
<td>The neonatal period</td>
</tr>
<tr>
<td>Increases in age after age 30</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Acute alcohol ingestion</td>
</tr>
<tr>
<td>Use of lithium</td>
</tr>
<tr>
<td>Severe hypotension or hypoxia</td>
</tr>
</tbody>
</table>

*MAC = minimum alveolar concentration; CNS = central nervous system.*
**Obesity**

Obesity is defined as a body mass index (BMI) of 30 kg/m$^2$ or higher. A BMI of 25–29.9 kg/m$^2$ is considered overweight. Two thirds of the U.S. adult population—approximately 130 million American adults—are overweight or obese, including one third of the population (roughly 60 million people) who are obese. Extreme (i.e., morbid) obesity, defined as a BMI of 40 kg/m$^2$ or greater, affects nearly 1 in 20 Americans.

Patients who are overweight or obese present challenges to anesthesia care providers and surgeons because of the high prevalence of comorbid conditions (e.g., hypertension) and the physical demands that a high BMI places on limited cardiovascular and other physical reserves. The possibility of pulmonary hypertension with impending right heart failure and systemic hypertension with coronary artery disease must be considered. The increase in tissue volume and metabolism demands an increase in oxygen delivery. Maintaining airway and pharyngeal patency, respiration, and ventilation are of great concern during anesthesia in these patients. Obstructive sleep apnea requiring continuous positive airway pressure or bilevel positive airway pressure is common in extremely obese patients, and postoperative recovery of laryngeal tone and reflexes is always a concern in this patient population.

Deep vein thrombosis and pulmonary embolism are also potential complications requiring prophylaxis during and after surgery in obese patients. The dosing of medications in obese patients can be complex because of the large amount of adipose tissue and the need to make adjustments based on BMI for certain lipid-soluble medications. Dosing algorithms are available for some drugs, but experience to guide dosing of all drugs for patients who are extremely obese is lacking.

The goals of anesthesia in extremely obese patients are to maintain a stable airway and tight cardiovascular and hemodynamic control (i.e., both heart rate and blood pressure) and to ensure a rapid recovery. Prompt restoration of baseline respiratory and mental status, avoidance of hypoxemia and hypercarbia (hypercapnia), and recovery of laryngeal tone and reflexes are sought. Providing pain control and preventing PONV are universal goals of anesthesia.

Bariatric surgery is an increasingly common procedure for patients with extreme obesity or a BMI of 35 kg/m$^2$ or higher with medical complications. Bariatric surgery includes various procedures designed to manage obesity and its complications; all of these procedures reduce the size of the stomach.

The Roux-en-Y gastric bypass procedure is a common, complex, and lengthy procedure that requires two to three hours even for an experienced surgeon. It entails the creation of a small pouch at the upper end of the stomach and connection of the jejunum to the new pouch. After the surgery, food passes directly from the small stomach pouch into the jejunum, bypassing the lower part of the stomach and the duodenum.

The use of laparoscopic procedures instead of open surgical procedures reduces the size of the incision and risk of wound-related complications. However, pneumoperitoneum during the abdominal insufflation used to visualize organs during laparoscopic procedures (i.e., the introduction of air into the peritoneal cavity to facilitate surgery) can cause problems in patients with cardiovascular disease who are undergoing laparoscopic bariatric surgery. The hemodynamic changes that accompany pneumoperitoneum are not well tolerated by these patients, and thus an agent like desflurane is often used to minimize cardiovascular depression.

**Bariatric surgery case**

A 28-year-old woman presents for laparoscopic Roux-en-Y gastric bypass. She is 5’6” tall, weighs 388 lb, and has a BMI of 62 kg/m$^2$. She has hypertension (systolic/diastolic blood pressure 142/90 mm Hg) and a heart rate of 88 beats per minute. Pulse oximetry reveals an oxygen saturation of 94%, which is low, probably because of Pickwickian hypoventilation syndrome. She has no documented obstructive sleep apnea, but her significant other reports that she snores loudly (i.e., this patient probably has undiagnosed obstructive sleep apnea). In the preoperative holding area, she exhibits mild wheezing and a Mallampati class II airway, which may be moderately challenging to the anesthesiologist.

Patients like this undergo the Roux-en-Y gastric bypass procedure to minimize the risk for gastric emptying problems. She is pretreated with a single i.v. 20-mg dose of the histamine H$_2$-receptor antagonist famotidine, a single oral 30-mL dose of an antacid containing citric acid and sodium citrate, albuterol inhalation by nebulizer for her wheezing, and the benzodiazepine midazolam 2 mg i.v. for perioperative anxiety.

In the OR, standard monitors are applied as the patient is placed in a “sniff” position with the head slightly raised and upper body flat, which allows for optimal visualization of the glottic opening for intubation. Positioning extremely obese patients can be critical for ease of induction and intubation. Induction of anesthesia and intubation by direct laryngoscopy are performed in rapid sequence, using fentanyl, lidocaine, propofol, and succinylcholine. Muscle relaxation subsequently is provided using the neuromuscular blocking agent vecuronium.

Inhaled desflurane is used for maintenance of anesthesia because of its low solubility and rapid onset and offset of effect, which are critical for those with large amounts of
adipose tissue; the long duration of surgery anticipated; and the need for rapid emergence from anesthesia and postoperative maintenance of a normal airway. Desflurane has lower solubility in blood and tissues than sevoflurane or isoflurane, so it is usually chosen for patients undergoing bariatric surgery. Desflurane is titrated to maintain blood pressure and other hemodynamic endpoints within the desired range. The patient’s brain function is monitored using a bispectral index or other monitor. Analgesia is provided with hydromorphone and ketorolac.

Although desflurane, sevoflurane, and isoflurane differ in the time to onset of anesthetic effect, these differences are not of critical importance to anesthesia care providers in this situation. The delay in onset associated with use of the highly soluble isoflurane instead of desflurane, for example, is only a matter of minutes. The i.v. induction agents remain in the circulation, and surgical stimulation from an incision will not take place within this brief time frame. Moreover, the anesthesiologist could use a technique referred to as overpressure to compensate for an agent with a slow rate of induction by dialing up the vaporizer to overpressurize the system and deliver 3 MAC, for example. Obviously, this technique must be used with caution to avoid an overdose.

At the end of surgery, the anesthesiologist prepares the patient for smooth emergence from anesthesia. Approximately 20 minutes before the anticipated surgical end time, the patient receives a serotonin 5-HT1 antagonist to prevent PONV, local anesthetic injection at the laparoscopic site, and neostigmine for reversal of the neuromuscular blockade used for muscle relaxation during surgery. The delivery of desflurane is gradually reduced until spontaneous ventilation is observed roughly four to six minutes before completion of the surgical procedure. Thus, the patient opens her eyes and is able to follow commands (e.g., a request for a hand squeeze). She is extubated and transferred to the postanesthesia care unit (PACU), where her recovery continues smoothly without complications.

Although the differences between the three inhaled anesthetic agents in solubility in blood and tissues do not matter much during anesthetic induction or the beginning of maintenance anesthesia, the lower solubility and more rapid offset of anesthesia with desflurane and sevoflurane than with isoflurane make a big difference at the end of surgery. Solubility in fat tissue is particularly important in bariatric surgery cases.

Table 2 lists the blood:gas partition coefficients and tissue:gas partition coefficients for halothane, isoflurane, desflurane, and sevoflurane. These figures are the ratio of the concentration of the anesthetic in blood to the concentration of the anesthetic in the tissue when the anesthetic is in equilibrium. The values for fat tissue are particularly relevant for patients undergoing bariatric surgery. The fat:gas partition coefficient (i.e., solubility in fat) is lowest for desflurane, with a value tenfold lower than that for halothane. This characteristic makes desflurane the agent with the greatest ease of titration at the end of a bariatric surgical procedure so that emergence from anesthesia is controlled and predictable. Experienced anesthesiologists who have worked extensively with isoflurane can achieve the same smooth offset of anesthesia with isoflurane as with less soluble agents, because they are able to anticipate when to begin to gradually decrease the delivery of the agent. However, less-experienced practitioners achieve better results with desflurane and sevoflurane than isoflurane because of greater predictability. If isoflurane is used, the failure to plan far enough in advance and achieve emergence from anesthesia before the end of a surgical case could delay patient transfer from the OR to the PACU and impede efforts to fast-track (i.e., expedite) recovery. In a busy surgery center with five or six cases in each of many ORs each day, the costs of unnecessarily keeping each patient in the OR for an extra 5 to 10 minutes while awaiting emergence from anesthesia for extubation can be additive and substantial.

Significant differences in recovery time between inhaled anesthetic agents have been demonstrated in the clinical setting. In a randomized study of 30 obese patients (BMI > 35 kg/m²) who underwent laparoscopic gastric banding (another bariatric surgical procedure) with sevoflurane or isoflurane for maintenance of anesthesia, the times to extubation, emergence from anesthesia (i.e., eye opening), and response (i.e., ability to follow commands) were significantly shorter after sevoflurane (6 min, 8 min, and 12 min) than isoflurane (10 min, 14 min, and 21 min; p = 0.001, p = 0.03, and p = 0.0005, respectively). The median time to PACU discharge also

Table 2.

| Table 2. Partition Coefficients of Inhaled Anesthetic Agents in Blood and Various Tissues a,b,20
<table>
<thead>
<tr>
<th>Type of Tissue</th>
<th>Halothane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>2.4</td>
<td>1.4</td>
<td>0.45</td>
<td>0.65</td>
</tr>
<tr>
<td>Brain</td>
<td>3.4</td>
<td>2.1</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Muscle</td>
<td>3.8</td>
<td>2.1</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Fat</td>
<td>137</td>
<td>71</td>
<td>15</td>
<td>41</td>
</tr>
</tbody>
</table>

aMeasurements taken at 37°C.
was significantly lower after sevoflurane (15 min) than isoflurane (27 min, \( p = 0.0005 \)).

**Pediatric surgery case**

Pediatric patients generally fear needles. DR is a three-year-old boy who presents for tonsillectomy and adenoidectomy. He recently had an upper respiratory infection and has a residual dry cough, although he is afebrile. DR is anxious about the procedure and hates needles. His older sister has asthma, which is a potential concern because asthma tends to run in families and the associated airway irritability and bronchospasm can present difficulties during inhaled anesthesia.

DR’s parents accompany him to the preoperative holding area where he is given midazolam 8 mg as an oral syrup to facilitate the induction of anesthesia. Sevoflurane is the inhaled anesthetic agent of choice for induction of anesthesia in pediatric patients because it lacks the unpleasant pungent odor of and respiratory irritation from isoflurane and desflurane. Sevoflurane does not have a pungent odor or cause respiratory irritation from isoflurane and desflurane. Sevoflurane is the agent during periods of instability. High flow rates are used initially to establish a steady base of inhalation anesthesia, during which time the anesthesia agent is rapidly absorbed and equilibrated into tissues. Later and near the end of surgery, the isoflurane vaporizer is dialed down and a propofol infusion is initiated for sedation. The propofol is continued with titration during and after MG’s transfer to the ICU so that he remains asleep and comfortable.

**Cardiac surgery case**

The priorities for anesthesia care during cardiac surgery differ from those in most other surgeries because the duration of cardiac surgery is long (usually three to six hours but sometimes even longer). Most patients will be transferred to an intensive care unit (ICU) and remain intubated during and after the transfer until hemodynamic, respiratory, and hemostatic stability are established. Homeostasis must be established before extubation. Most anesthesiologists choose to use isoflurane for maintenance of anesthesia in cardiac surgery patients because rapid emergence from anesthesia at the end of surgery is not traditionally a goal. Moreover, an i.v. sedative infusion is typically titrated during and after transfer to an ICU to ensure that the patient remains comfortable for the initial hours after surgery.

MG is a 73-year-old man who presents for coronary artery bypass graft and aortic valve replacement surgery. In addition to hypertension, left ventricular hypertrophy, and severe three-vessel atherosclerotic coronary artery disease, MG has type 2 diabetes mellitus and moderate renal dysfunction. Early on the morning of surgery, he receives metoprolol and diazepam, and venous and arterial catheters are in place. He is calm and comfortable as he is taken to the OR.

MG undergoes induction of anesthesia over a four-minute period using etomidate, midazolam, and fentanyl, followed by cisatracurium for neuromuscular blockade (i.e., muscle relaxation) and nitroglycerin titrated for blood pressure management. MG receives isoflurane during his six-hour surgery, with active, frequent titration of the anesthetic agent during periods of hemodynamic instability during surgery. The fresh gas flow rate ranges from 1 L/min during periods of stability to 4 L/min during periods of instability. High flow rates are used initially to establish a steady base of inhalation anesthesia, during which time the anesthesia agent is rapidly absorbed and equilibrated into tissues. Later and near the end of surgery, the isoflurane vaporizer is dialed down and a propofol infusion is initiated for sedation. The propofol is continued with titration during and after MG’s transfer to the ICU so that he remains asleep and comfortable.

**Dispelling myths**

Anesthesia care providers are keenly aware of the economic constraints faced by health systems and watch the financial bottom line whenever possible. The consistent use of low fresh gas flow rates (e.g., 1 L/min) is a tempting strategy for minimizing the costs of inhaled anesthesia by reducing waste. However, this strategy is not always feasible because it is necessary to account for the volume of the respiratory circuit and the time from a change in the vaporizer setting to the resulting change in alveolar concentration of the anesthetic gas, which relates to the concentration at the site of action in the brain. The volume of the respiratory circuit is approximately 4–5 L, including 1.0–1.5 L for the circuit hoses and internal piping of anesthesia machines, 1 L for the intergranular spaces in the carbon dioxide absorbent, and 2.0 L for the functional residual lung capacity of the typical 70-kg patient in a supine position. The dynamics of inhaled gases of all types (i.e., regardless of solubility or potency) can be quantified using a time constant (\( \tau \)) that is calculated by dividing the total gas volume (5 L) by the fresh gas flow rate. A period three times the time constant is needed for 95% equilibration of the inhaled anesthesia gas in the alveolar spaces after adjustment of the vaporizer (Table 3). When the fresh gas flow rate is low (e.g., 0.5 L/min or 1 L/min), the
time required for 95% equilibration is long (30 min or 15 min, respectively), which may be acceptable for some patients who are stable and do not require immediate changes in alveolar gas concentrations. However, these equilibration times may be unacceptably long in some clinical scenarios (e.g., surgery with rapid changes in intensity of painful stimulation); then, a higher fresh gas flow rate may be needed to accommodate the need for more rapid equilibration to maintain anesthesia.

The traditional paper anesthesia record does not show the exact minute-to-minute changes in fresh gas flow rates and vaporizer settings needed to titrate inhaled anesthesia and maintain hemodynamic stability, although major changes are documented. The minute-to-minute changes are made intuitively by experienced anesthesiologists to ensure a smooth postoperative recovery. Anesthesiologists weigh the need to minimize anesthesia waste and costs against the need to optimize postoperative recovery.

One of several issues surrounding the use of inhaled anesthetic agents is emergence delirium (i.e., agitation), especially in children. The problem has been attributed to the use of sevoflurane, but it has been reported with all three inhaled anesthesia agents and is not unique to any one agent.24 Emergence delirium may reflect the rapid emergence from anesthesia with new agents and inadequate analgesia in the immediate postoperative period. Patients who experience this problem typically awaken from anesthesia with intense pain, distress, and disorientation. The problem can be ameliorated by providing optimal analgesia. Desflurane may be associated with a higher frequency of coughing and respiratory irritation during emergence than sevoflurane or isoflurane.25

Some anesthesia providers are concerned about the potential for renal injury from sevoflurane because nephrotoxicity from compound A, a degradation product of sevoflurane, is easily demonstrated in animals exposed to high concentrations of sevoflurane and the resultant compound A.11 However, this experience in animals does not translate directly to humans, in part because of species differences in the distal renal tubules.

The possibility of renal toxicity from inorganic fluoride produced during the use of all inhaled fluorinated anesthesia should be considered. However, this must be kept in perspective, because the amount of inorganic fluoride production is not excessive when typical concentrations of anesthesia agents are used for customary periods.41 Concerns about the renal effects of inhaled anesthetic agents are further mitigated by the years of clinical experience with inhaled anesthesia agents that current anesthesia care providers possess.

Finally, all inhaled anesthetics (particularly desflurane) can react with certain carbon dioxide absorbents to form carbon monoxide. This problem is more likely if the absorbent is desiccated than if it is moist.25 Awareness of this potential problem enables anesthesia care providers to take steps to avoid it.

**Conclusion**

In the intense environment of the OR, health care practitioners are accustomed to the rapidly changing status of patients and the need to anticipate and respond to hemodynamic and respiratory changes. Anesthesia care providers continuously adjust inhaled anesthetics to safe and cost-effective levels, considering the characteristics of the available agents, type and duration of surgery, and patient age and comorbid conditions.

References

Clinical and economic considerations in the use of inhaled anesthesia from the perspective of health-system pharmacists and anesthesiologists

Learning objectives
After studying these articles, the reader should be able to

1. Identify and discuss challenges that health-system pharmacists face in managing the use and costs of inhaled anesthetic agents in the operating room.

2. Compare and contrast the characteristics of currently available inhaled anesthetic agents and describe the dynamics of and systems for delivering inhaled anesthesia and the role of inhaled anesthesia in fast-track recovery after surgery.

3. Describe the components of and factors contributing to the costs of inhaled anesthesia, basis for quantifying and comparing these costs, and practical strategies for performing pharmacoeconomic analyses and reducing the costs of inhaled anesthesia.

4. Outline the stages and goals of anesthesia, and explain the nomenclature for and factors that can affect the dosing of inhaled anesthesia and the basis for choices among inhaled anesthetic agents by anesthesiologists.

5. Name a consideration in using inhaled anesthesia in bariatric surgery patients, pediatric patients, and cardiac surgery patients; and dispel myths associated with inhaled anesthesia in these and other patient populations.

Self-assessment questions
For each question there is only one best answer.

1. Which of the following factors poses a challenge to health-system pharmacists in managing the cost of inhaled anesthetic agents?
   a. Lack of control over purchasing of inhaled anesthetic agents by members of the pharmacy department.
   b. Lack of concern among anesthesia care providers about waste of anesthetic agents.
   c. Lack of accountability among anesthesia care providers for the amount of anesthetic agents administered during surgical procedures.
   d. Lack of familiarity with inhaled anesthetic agents among pharmacists.

2. Which of the following characteristics of inhaled anesthetic gases is a measure of the amount of inhaled anesthetic agent necessary for anesthesia?
   a. The minimum alveolar concentration.
   b. The blood:gas partition coefficient.
   c. The tissue:gas partition coefficient.
   d. The volume of vapor per mL of liquid.

3. Which of the following inhaled anesthetic agents is best chosen for use as part of fast-track surgery because of its low solubility in blood and tissues?
   a. Desflurane.
   b. Halothane.
   c. Isoflurane.
   d. Nitrous oxide.

4. Which of the following inhaled anesthetic agents does not have a pungent odor or cause respiratory irritation?
   a. Desflurane only.
   b. Isoflurane only.
   c. Sevoflurane only.
   d. Desflurane and sevoflurane.

5. Which of the following interventions is best used to minimize the amount of inhaled anesthetic agent used for maintenance of anesthesia?
   a. Use of a high flow rate instead of a low flow rate.
   b. Use of a low flow rate instead of a high flow rate.
   c. Use of a moderate flow rate instead of a low flow rate.
   d. Use of an agent with high solubility in blood and tissues and high flow rate.
6. Which of the following inhaled anesthetic agents has the lowest acquisition cost when administered at 1 MAC hour at any fresh gas flow?  
   a. Desflurane.  
   b. Isoflurane.  
   c. Sevoflurane.  
   d. The acquisition cost is comparable for desflurane, isoflurane, and sevoflurane.

7. Compared with a high fresh gas flow rate, the use of a low flow rate for delivery of inhaled anesthetic agent  
   a. Increases rebreathing of exhaled anesthetic gas and provides less control of the level of anesthesia at a lower cost.  
   b. Increases rebreathing of exhaled anesthetic gas and provides greater control of the level of anesthesia at a lower cost.  
   c. Decreases rebreathing of exhaled anesthetic gas and provides less control of the level of anesthesia at a higher cost.  
   d. Decreases rebreathing of exhaled anesthetic gas and provides greater control of the level of anesthesia at a higher cost.

8. Which of the following is the most variable factor in the formula used to estimate the cost per MAC hour of an inhaled anesthetic agent?  
   a. Concentration.  
   b. Cost per mL.  
   c. Fresh gas flow rate.  

9. Which of the following statements about the anesthesia machines and vaporizers used for delivery of the three inhaled anesthetic agents currently available in the United States is correct?  
   a. Older and newer anesthesia machines can accommodate all three inhaled anesthetic agents, and vaporizers are standardized for use with any agent.

b. Only newer anesthesia machines can accommodate all three inhaled anesthetic agents, and vaporizers are standardized for use with any agent.

c. Only newer anesthesia machines can accommodate all three inhaled anesthetic agents, and a different vaporizer is required for each anesthetic agent.

d. Newer anesthesia machines cannot accommodate all three inhaled anesthetic agents, and a different vaporizer is required for each anesthesia agent.

10. Which of the following statements best characterizes the usefulness of anesthesia records for conducting pharmaco-economic analyses of inhaled anesthesia use?  
   a. They are maintained on paper in most institutions and provide information about patterns of use, but not minute-to-minute changes in fresh gas flow rates and vaporizer settings.

b. They are automated in most institutions and provide information about patterns of use, but not minute-to-minute changes in fresh gas flow rates and vaporizer settings.

c. They are maintained on paper in most institutions and provide considerable detail about minute-to-minute changes in fresh gas flow rates and vaporizer settings, but not patterns of use.

b. They are automated in most institutions and provide considerable detail about minute-to-minute changes in fresh gas flow rates and vaporizer settings, but not patterns of use.

11. In which of the following stages of anesthesia are patients particularly vulnerable to problems with laryngospasm, airway obstruction, regurgitation, vomiting, and aspiration during induction of or emergence from anesthesia?  
   a. Stage 1 sensory depression.  
   b. Stage 2 excitement.  
   c. Stage 3 surgical unresponsiveness.  
   d. Stage 4 very deep, possible decompensation.

12. Which of the following goals of anesthesia is the highest priority for anesthesia care providers?  
   a. A rapid onset and offset of anesthetic effect to minimize the costs of anesthesia.

b. Proactive management of postoperative discomfort to maximize patient satisfaction.

c. Safety during the performance of surgery or an invasive procedure.

d. Timely discharge from the hospital or ambulatory surgery center.

13. Which of the following statements about the relationship between age and minimum alveolar concentration (MAC) of inhaled anesthetic agents is correct?  
   a. MAC increases as age increases after infancy.  
   b. MAC decreases as age increases after infancy.  
   c. MAC is unchanged throughout infancy and childhood, but it increases with age beginning in young adulthood.  
   d. MAC is unrelated to age throughout life.

14. Which of the following is the most legitimate consideration for anesthesiologists in selecting an inhaled anesthetic agent?  
   a. Habits established during one’s training.  
   b. Familiarity based on experience during one’s career.  
   c. MAC and potency.  
   d. Solubility in blood and tissues.
15. Which of the following inhaled anesthetic agents is associated with the highest risk for hepatotoxicity?
   a. Desflurane.
   b. Halothane.
   c. Isoflurane.
   d. Sevoflurane.

16. Which of the following is an important consideration in choosing to use desflurane during bariatric surgery in a patient with a large amount of adipose tissue and obstructive sleep apnea?
   a. The lack of a pungent odor and respiratory irritation.
   b. The low solubility in fat and rapid onset of anesthesia.
   c. The high fat:gas partition coefficient and gradual emergence from anesthesia.
   d. The low fat:gas partition coefficient and rapidity of emergence from anesthesia.

17. Which of the following characteristics of most cardiac surgery patients strongly influences decisions about anesthesia?
   a. The long duration of the procedure and need for prolonged sedation.
   b. The fear of needles and preference for anesthesia induction by inhalation.
   c. The lack of experience and clinical data to guide dosing in this patient population.
   d. The concerns about postoperative recovery of laryngeal tone and reflexes.

18. Which of the following statements about the risk for emergence delirium after the use of inhaled anesthetic agents is correct?
   a. The risk is limited to isoflurane in obese patients and probably reflects slow emergence from anesthesia due to high solubility in fat.
   b. The risk is limited to sevoflurane and probably reflects rapid emergence from anesthesia and inadequate analgesia.
   c. This risk is not limited to any one inhaled anesthetic agent and probably reflects rapid emergence from anesthesia and inadequate analgesia.
   d. This risk is not limited to any one inhaled anesthetic agent and probably reflects slow emergence from anesthesia due to slow dialing down of the vaporizer.

19. Which of the following statements best summarizes concerns about the risk for nephrotoxicity from the use of inhaled anesthetic agents?
   a. The risk of nephrotoxicity from compound A is limited to pediatric patients receiving sevoflurane.
   b. The risk of nephrotoxicity from inorganic fluoride is limited to patients receiving desflurane.
   c. The risk of nephrotoxicity from inorganic fluoride is not limited to any one inhaled anesthesia agent, but it appears to be limited to cases in which the carbon dioxide absorbent is moist.
   d. The risk of nephrotoxicity from inorganic fluoride appears minimal when usual amounts of inhaled anesthesia agents are used for customary periods.

20. The use of a low fresh gas flow rate to minimize inhaled anesthesia costs is not always feasible because of
   a. The long time required for equilibration of inhaled anesthetic gases in the alveolar spaces after adjustment of the vaporizer when the fresh gas flow rate is low, regardless of the solubility of the gas in blood and tissues.
   b. The short time required for equilibration of inhaled anesthetic gases in the alveolar spaces after adjustment of the vaporizer when the fresh gas flow rate is low, regardless of the solubility of the gas in blood and tissues.
   c. The long time required for equilibration of inhaled anesthetic gases in the alveolar spaces after adjustment of the vaporizer when the fresh gas flow rate is low and the solubility of the gas in blood and tissues is low.
   d. The long time required for equilibration of inhaled anesthetic gases in the alveolar spaces after adjustment of the vaporizer when the fresh gas flow rate is low and the solubility of the gas in blood and tissues is high.
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