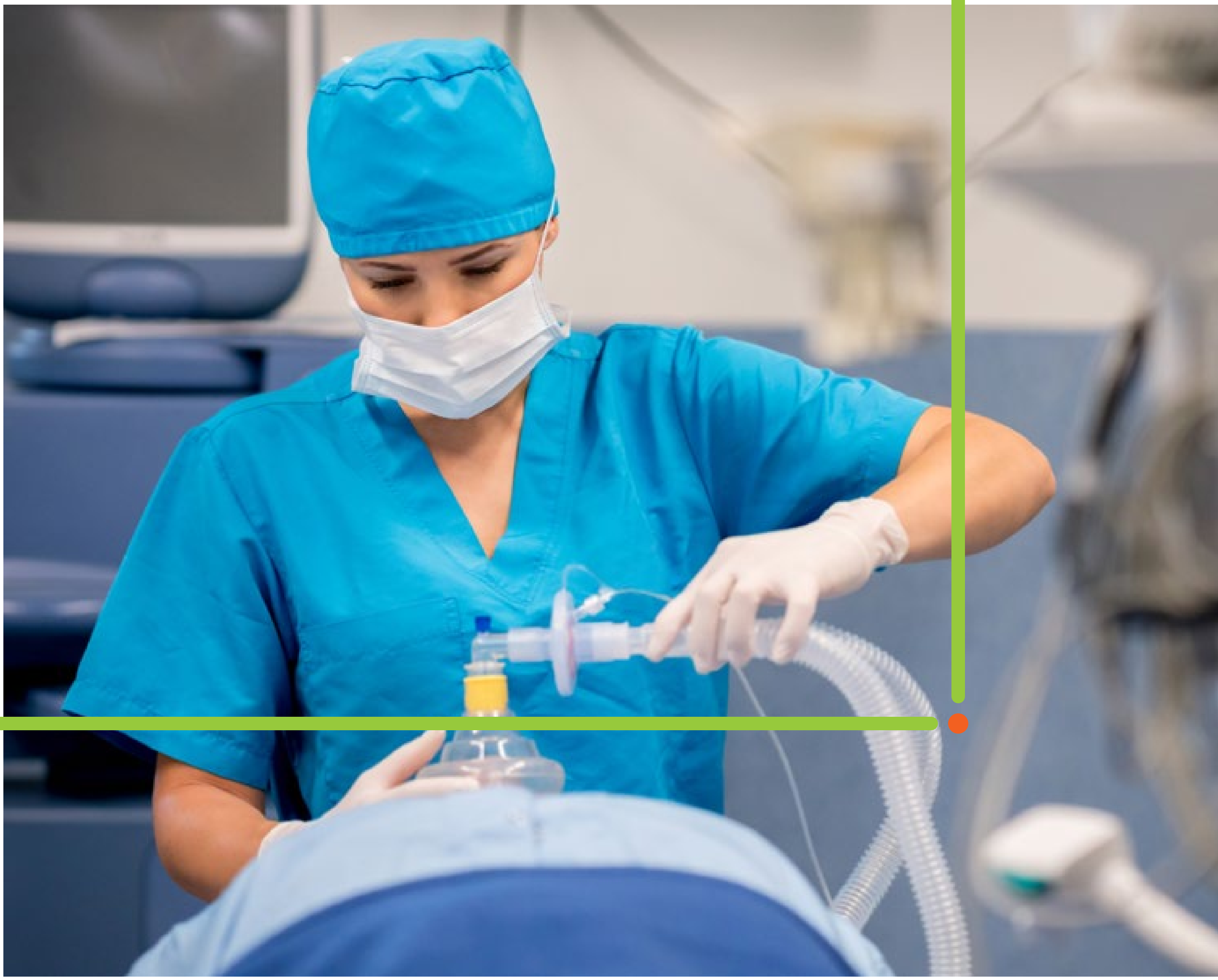
An overview of the general anesthesia gases

Going under without going under

June 2020



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Introduction

Anesthesia gases are a subset of general anesthetics — drugs that induce unconsciousness, analgesia, muscle relaxation and amnesia. They are primarily administered before a surgical procedure in combination with intravenous agents, such as sedatives and muscle relaxants. Effective anesthesia enables the medical team to perform invasive procedures without causing patients pain or emotional trauma.[1,2]

As a cornerstone of perioperative medication, anesthesia gases are universally used by both inpatient and outpatient surgical centers. The market for anesthesia gases is affected by the complex interplay of several factors, including supplier competition, clinical decision-making, and the technological capabilities of vaporizers and anesthesia machines.

This document provides a general clinical primer and market overview of the anesthesia gases, with a focus on sevoflurane and desflurane, the two most commonly used anesthesia gases today.

History of anesthesia gases

Humans have sought anesthetic relief since the earliest known civilizations. Before the mid-19th century, opium poppy, various herbs, alcohol, acupuncture and carotid compression were among the various methods used for analgesia, sedation or both. Because of patient intolerance, surgical procedures were rarely performed. The anesthetic effects of nitrous oxide had been observed since at least 1800 and had been used in dental procedures, but its weak anesthetic effect left much to be desired in the realm of general anesthesia.[3-5]

In 1846, dentist William T.G. Morton's first public and successful demonstration of ether as an anesthetic during surgery launched the modern age of anesthesia. The next year, obstetrician James Young Simpson began popularizing the use of chloroform for surgical and dental procedures. The development of intravenous and local anesthetic agents, as well as advances in anesthetic gas delivery devices and anesthetic monitoring, followed. Although ether and chloroform launched the development of modern anesthesia, they have since waned in popularity. Each one has distinct disadvantages: Chloroform is hepatotoxic and can cause fatal ventricular fibrillation, while ether is highly flammable, has a prolonged induction period, frequently causes postoperative nausea and vomiting, and emits an unpleasant odor.[3-5]

Ether remained the most widely used inhaled general anesthetic until the 1950s, when fluorinated anesthetics were introduced. Fluorination addressed a major problem that had plagued anesthetic gases up to that point: flammability. In particular, halothane (Fluothane), introduced in 1951, gained popularity for its improvements over ether, with its pleasant odor, better potency, low flammability and improved patient tolerance. However, it soon fell out of favor and is no longer available in the U.S. after being associated with hepatic necrosis and failure (known as halothane hepatitis); additionally, of the fluorinated gases, halothane was frequently associated with malignant hyperthermia.[3,5] Methoxyflurane (Penthrane, Penthrox) followed halothane in 1960 but is also no longer marketed due to nephrotoxicity caused by a metabolic byproduct. The search for a fluorinated anesthesia gas with metabolic stability and a favorable toxicity profile continued with enflurane (Ethrane) and its isomer isoflurane (Forane and Terrell). However, enflurane was found to cause cardiovascular depression and lower the seizure threshold; thus, it is no longer marketed. Isoflurane is still used today, although sevoflurane (Ultane) and desflurane (Suprane) are more common. Although sevoflurane was first synthesized in the 1960s, concerns with fluoride release, nephrotoxicity and potentially dangerous interactions with soda lime limited its use; however, these adverse effects have since been found to be rare or avoidable. Desflurane was also developed in the 1960s but was slow to be adopted due to risk of explosions caused by high vapor pressure. The development of the Tec 6 vaporizer has since mitigated this risk.[3,6]

Looking forward

Although several anesthesia gases have been developed and used, only three remain on the U.S. market today: isoflurane, sevoflurane and desflurane. Furthermore, no new anesthesia gases are in the development pipeline. The recent decline in new anesthetic drug development is likely due to several factors[7]:

- A lack of understanding about the complete mechanism of action of general anesthesia.
- A risk-averse pharmaceutical market that can be difficult for a new agent to enter.
- Clinicians that are hesitant to adopt a new, unfamiliar agent.

- Pharmaceutical companies that may find it difficult to justify the cost of research and development for a new anesthesia gas when the market share for the gases is relatively small and prices continue to erode.[7]
- Anesthesia gases being commonly targeted in cost-saving measures as hospitals attempt to cut costs.[8]
- A lack of demand for safer anesthetics because improvements in anesthesia administration and monitoring have improved patient safety without changing the agents themselves. Anesthesia-related morbidity and mortality have declined since the 1960s, as standards and training for anesthesiologists have continued to advance.[7]

Clinical overview

The mechanism of action of the anesthesia gases is not completely understood, but is thought to work through inhibitory actions on excitatory neuronal pathways. Known ion channel targets include neurotransmitter receptors (type A gamma-aminobutyric acid, glycine, nicotinic acetylcholine, serotonin and glutamate receptors) and voltage- and non-voltage–activated calcium, sodium and potassium channels.[9] Halothane, isoflurane, desflurane and sevoflurane are classified as volatile gases, while nitrous oxide is a nonvolatile gas. The volatile gases are liquids at room temperature and thus require administration via a vaporizer, whereas nonvolatile gases are gas at room temperature.[2]

Administration considerations

The three stages of anesthesia are induction, maintenance and recovery. Because needle sticks are problematic in the pediatric population, inhaled anesthetics are preferred, especially for induction.[8]

When inhaled, gas flows from the vaporizer's anesthesia machine to the patient's alveoli; from there, it moves to the arterial blood supplying the brain. Physiologically, the goal of inhaled anesthesia is to develop and maintain an anesthetizing partial pressure of the agent in the brain.[8] The concentration of an inhaled anesthetic that is necessary to provide general anesthesia is referred to as the minimum alveolar concentration (MAC), defined as the percentage of concentration in the alveoli that prevents 50% of patients from responding to surgical stimuli at 1 atmosphere of pressure. MAC is a fixed physical variable of a gas, but the required MAC varies depending on the desired physiological response in the patient (i.e., depth of anesthesia). The higher the MAC, the less potent the gas may be considered.[2,10]

Solubility, defined as the affinity of the gas to absorb into blood or tissue, is an important determinant of onset and recovery. Solubility is quantified by the blood:gas partition coefficient — the ratio of the agent in the blood and gas phases at equilibrium. Isoflurane, which has a relatively high blood:gas partition coefficient (see Table 1), has a high affinity for blood as well as a slower onset and longer duration of action. Conversely, desflurane has the lowest blood:gas partition coefficient of the three gases but also

Table 1. Characteristics of currently available anesthesia gases

	Isoflurane	Desflurane	Sevoflurane
Year of introduction	1981	1992	1995
Year generic(s) available	1993	2019	2002
Labeled indications	Induction and maintenance of general anesthesia	Induction and maintenance of anesthesia for inpatient and outpatient surgery in adults	Induction and maintenance of general anesthesia for inpatient and outpatient surgery in adults and pediatric patients
MAC (%)	1.15	6.0	2.05
Blood:gas partition coefficient (relative solubility)	1.4 (highest)	0.42 (lowest)	0.69 (low)
Pungency	Pungent	Pungent	None
Mean WAC per 100 mL ($) (range)	16 (10-24)	64 (60-67)	64 (48-75)

Data derived from Stachnik and Wolters Kluwer.[9,11]
Abbreviations: MAC = minimum alveolar concentration; WAC = wholesale acquisition cost.

has the fastest onset and recovery, which provides tighter control over anesthesia levels. Sevoflurane has an intermediate recovery time.[8,9]

Pungency is another characteristic that must be considered before administration. Isoflurane and desflurane have pungent odors that can cause respiratory irritation and should be avoided in patients with asthma or active bronchospasm.[2] Furthermore, although they are approved for induction anesthesia, isoflurane and desflurane are not preferred due to the risk of respiratory irritation, especially in children. Sevoflurane is the best choice for induction because it has no pungency.[8]

Adverse events

Historical adverse events of concern with anesthesia gases, including nephrotoxicity and hepatotoxicity, are uncommon with the modern anesthesia gases.[9] Although sevoflurane has not clinically been shown to cause nephrotoxicity, its metabolism by CYP2E1 produces fluoride relatively more quickly and animal studies have shown renal impairment; therefore, the package insert warns against use in patients with renal insufficiency (creatinine > 1.5 mg/dL).[2,12] In general, isoflurane, desflurane and sevoflurane have relatively benign safety profiles. Compared with older agents, they are less likely to cause cardiac arrhythmias, cerebral vasodilation and increased cerebral blood flow. In terms of cardiac effects, desflurane and isoflurane may cause transient increases in heart rate. Respiratory depression occurs with all of the anesthesia gases, and respiratory irritation is most common with desflurane, the most pungent agent.[2,9] Because of these respiratory reactions, desflurane is not recommended for induction of anesthesia in children and is not approved for maintenance of anesthesia in nonintubated children.[13] The anesthesia gases may be associated with postoperative nausea and vomiting. Malignant hyperthermia may occur with modern agents, although not to the extent seen with halothane. Post-anesthesia agitation, characterized by restlessness, combativeness, disorientation, incoherence and unresponsiveness after surgery, has also been observed with desflurane and sevoflurane, especially in children.[9]

Environmental concerns

The modern anesthesia gases are greenhouse gases, with desflurane and nitrous oxide under particular scrutiny because of their contributions to climate change. Because the general anesthesia gases undergo minimal in vivo metabolism, they are vented into the atmosphere intact and take one to 14 years to degrade. Nitrous oxide lasts 114 years in the atmosphere. Global warming potential (GWP100) measures how much a given mass of greenhouse gas contributes to global warming over 100 years compared with the same mass of carbon dioxide (carbon dioxide has a GWP of 1, regardless of time period). Desflurane has the highest GWP100 at 2,540, with the GWP100 of isoflurane and sevoflurane at 510 and 130, respectively.[14]

In addition to GWP, the environmental impact of the gases depends on fresh gas flow rate and potency (i.e., MAC). Higher fresh gas flows increase the amount of gas vented into the atmosphere. Less potent gases have a higher MAC; thus, greater quantities must be administered compared with other gases at similar fresh gas flow rates. In addition to its high GWP, desflurane also has a relatively higher MAC, requiring that three to six times more must be administered compared with sevoflurane. The American Society of Anesthesiologists concludes that contributions to greenhouse gases are lower when desflurane is avoided. Other recommendations to reduce anesthetic waste include using low fresh gas flow rates during the maintenance phase and using systems that prevent gas waste from venting into the atmosphere.[14]

Cost considerations

The cost of anesthesia care can be divided into three main components: direct costs of the products, other materials and labor; indirect costs due to the consequences of anesthesia administration; and intangible costs associated with pain and suffering resulting from anesthesia. Intangible costs may be difficult or even impossible to measure. Most cost-saving efforts target direct and indirect costs, which can be further divided into two categories: fixed costs, which vary based only on the selected gas agent; and variable costs, which can be affected by clinician decision-making.[10,15]

Direct fixed cost components include the acquisition cost and volume of vapor produced per milliliter of liquid, and potency of the gas.[8,10] Duration of action may also be considered an indirect fixed cost component, as shorter anesthesia recovery time has been shown to lead to less time in the post-anesthesia care unit, faster discharge, and lower institutional and labor costs.[16-18] However, shorter recovery time with desflurane or sevoflurane compared to isoflurane has been difficult to demonstrate.[10] Furthermore, demonstrating that a shorter recovery time can result in cost savings may be difficult to accomplish in a real-world setting.

The primary direct variable cost is anesthetic agent waste, which directly correlates with the fresh gas flow rate set by the anesthesiologist. Higher flow rates increase the amount of gas vaporized, decrease rebreathing of exhaled gas and provide greater control over the anesthetic effect, but result in higher costs. Furthermore, higher flow rates result in more waste and gas venting into the atmosphere. Lower flow rates enhance rebreathing of exhaled anesthesia gas, decrease waste and gas venting into the atmosphere, and are less costly. A low flow rate may also conserve a patient's expired heat, but may result in less control over the anesthetic effect.[10]

The cost per MAC hour, a conceptual formula used by clinicians to quantify the costs of anesthesia gas administration, is shown below[10,19]:

$$\text{Cost per MAC hour, \$} = \frac{(\text{MAC, \%})(\text{fresh gas flow rate, L/min})(\text{duration, 60 min})(\text{molecular weight, g})(\text{cost/mL, \$})}{(2{,}412)(\text{density, g/mL})}$$

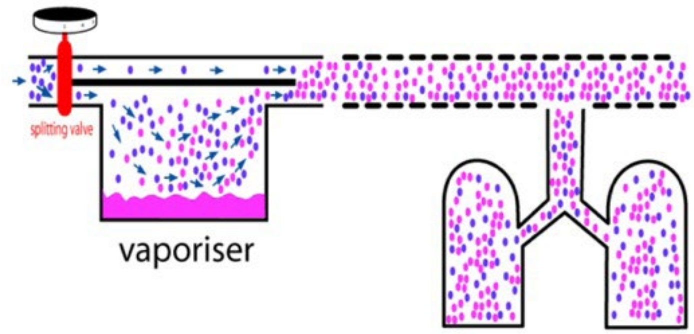
Most components of this formula are fixed except for the fresh gas flow rate, which may vary based on provider preference, current intraoperative conditions and the gas being administered. Considering the relative pricing and MACs of the individual agents (see Table 1), it is evident that desflurane and sevoflurane are far more expensive than isoflurane when flow rates are increased.

Cost considerations associated with vaporizers

An examination of the general anesthesia gases would be incomplete without a discussion of anesthesia machines and vaporizers. Vaporizers convert the liquid anesthesia into the vapors needed for patient administration. Vaporizers work by accurately splitting the incoming gas (oxygen) into two streams (see Figure 1). One of the streams passes straight through the vaporizer into the bypass channel. The other is diverted into the vaporizer chamber, where the gas becomes fully saturated with volatile anesthetic vapor. This gas is then mixed with the gas in the bypass channel before leaving the vaporizer.[20,21]

Vaporizers are gas-specific. For example, a sevoflurane-specific vaporizer is required to administer sevoflurane; using a desflurane-specific vaporizer would not be recommended. Among other agent-specific features, desflurane vaporizers heat the gas for delivery. Older anesthesia machines may feature three vaporizers, but most newer machines have two vaporizers, while compact machines only have one vaporizer. Switching vaporizers on a machine takes caution and effort, although newer machines have safety features such as connectors to help prevent errors.[10]

Figure 1. Flow of gas through vaporizer



Source: How anaesthesia vaporisers work explained simply. How equipment works.com website. https://www.howequipmentworks.com/vaporisers/. Accessed December 18, 2019.

Vaporizers can be provided by an anesthesia gas company, although health care costs may not be apparent in the vaporizer agreement depending on how it is written. For instance, if a health care facility commits to purchasing a minimum quantity of a manufacturer's gas product in exchange for the manufacturer providing the facility with the necessary vaporizers, the facility must also agree to use that manufacturer's gas product in the vaporizer. This type of arrangement can lead to long-term commitments with one anesthesia gas manufacturer. The advantage of acquiring vaporizers in this manner is a deferment of the capital expense of equipment to the gas manufacturer. The manufacturer would also be responsible for any planned services; replacing a damaged vaporizer; and upgrading to newer, more advanced models of vaporizers if needed.

Additionally, the health care facility needs to be aware of any recertification fees or penalties if it terminates its vaporizer agreement early. Because these agreements tie the sources of gases and vaporizers together, health care facilities may have difficulty switching either type of product. This effectively becomes a cost consideration when selecting products, though the opportunity cost may be difficult to quantify.

Vaporizers and anesthesia machines can also be purchased directly from vaporizer and anesthesia machine manufacturers. In recent years an increasing number of hospitals and surgery centers have begun considering this option, although there are potential hidden costs with this method as well. For example, a facility may need to keep backup vaporizers in case one of the vaporizers in the surgery suite becomes inoperable. As mentioned previously, certain vaporizers may need to be fitted to the different kinds of anesthesia machines, which can prevent the facility from switching between gases from different manufacturers. Lastly, service agreements need to be drafted for the upkeep and maintenance of the vaporizer equipment. A well-organized plan is necessary when making a choice between using a gas manufacturer's vaporizer program or purchasing the vaporizer outright. Communication is essential between materials managers, pharmacy and the surgery staff. In addition, a facility may want to work with its legal department and risk management to determine the best method of acquiring vaporizers.

Owning a vaporizer versus using a vaporizer agreement

Table 2 illustrates the potential financial implications of owning a vaporizer versus using a vaporizer agreement. This information is unaudited and does not represent specific products available on the market. Health care staff must consider a number of factors when determining the most appropriate financial course of action. Factors not included in this model — but that must also be considered — include the opportunity cost of committing to a vaporizer agreement and one gas supplier while foregoing other potentially better-priced gases, the cost of upgrading vaporizers every 10 to 15 years once they become obsolete, the cost of expanding a facility (e.g., expanding operating rooms), replacing existing vaporizers, depreciation and labor.

The "Minimum purchase agreement" column shown below lists costs for an institution that participates in a vaporizer agreement involving a minimum purchase requirement of gas in exchange for a vaporizer agreement with a supplier. In this model, the minimum purchase requirement is at least 24 bottles per year at a cost of $100 per bottle. Manufacturer representatives may refer to a vaporizer agreement as a "lease" or "rental" agreement, even though it does not represent a true lease or rental. Rather, the agreement assigns a value to the capital equipment expenditure of the vaporizer. The supplier also pays for the cost of vaporizer repair and recertification, which is recommended at least once every five years. The "Purchased vaporizer" column shows costs for an institution that elects to purchase its own vaporizers.

Table 2 also provides a comparative example of a low- versus high-volume institution. For institutions that purchase low volumes of anesthesia, vaporizer agreements may generally be more cost-effective, as the cost of vaporizers represents a significant portion of the budget.

Table 2. Financial implications of using vaporizer agreements versus owning vaporizers

Fixed costs	Time period	Minimum purchase agreement ($)	Purchased vaporizer ($)
Each vaporizer		0	3,200
Each bottle of anesthesia[a]		100	100
Each vaporizer repair		0	500
Each vaporizer recertification		0	800
Low-volume institution (10 years)			
10 vaporizers	Year 1	0	32,000
Two backup vaporizers	Year 1	0	6,400
50 bottles of anesthesia per year	Years 1-10	50,000	50,000
Vaporizer repair/recertification[b]	Years 5, 10	0	31,200
Total cost		**50,000**	**119,600**
High-volume institution (10 years)			
70 vaporizers	Year 1	0	224,000
Five backup vaporizers	Year 1	0	16,000
3,000 bottles of anesthesia per year	Years 1-10	3,000,000	3,000,000
Vaporizer repair/recertification[b]	Years 5, 10	0	195,000
Total cost		**3,000,000**	**3,435,000**

Data derived from internal Vizient data and Wolters Kluwer.[11]
[a] In this model, the institution is assumed to meet the minimum purchase agreement every year.
[b] Vaporizer maintenance is recommended at least once every five years.

For high-volume institutions, the marginal cost difference between using a vaporizer agreement versus owning a vaporizer becomes relatively smaller, but the maintenance costs still increase overall institutional costs. Having the freedom to purchase lower-cost anesthesia may help to offset the cost of owning vaporizers.

Figure 2 shows the incremental costs over time in both the low- and high-volume examples. With all other factors constant, institutions that participate in a minimum purchase agreement have consistent annual costs. Institutions that purchase their vaporizers may have more cost variation related to vaporizer maintenance, although these costs may be offset through varied purchasing practices (not shown in this model).

Figure 2. Using vaporizer agreements versus owning vaporizers: incremental costs over time

Data derived from internal Vizient data and Wolters Kluwer.[11]

Market overview

Although the anesthesia gases are widely used, there are only a few players in the market. Few generic suppliers have joined the market in recent years and even fewer are expected to join in the future. Barriers to joining the market include complex development and production cycles, the contractual tying of gas to vaporizers at the member level and the lack of economic incentive to join the market. Fortunately, current suppliers have been able to meet demand for the gases, as no known shortages of the gases have occurred in recent years (University of Utah, unpublished data, 2019); however, occasional disruptions at the wholesale level have been reported.

Table 3 gives an overview of the currently available anesthesia gas products. Desflurane was a branded sole-source product until a generic product was released in January 2019. The market for sevoflurane is more diversified, with four main suppliers.

Figure 3 illustrates the mean wholesale acquisition cost per mL of desflurane, sevoflurane and isoflurane between 1999 and 2018, as available. Desflurane and sevoflurane have consistently been more expensive than isoflurane, although the price of sevoflurane began eroding around the time multiple manufacturers entered the market. The price of desflurane has remained stable, a reflection of its sole-source status for several years. However, with generic competition now in the market, prices for desflurane may begin to erode.

Table 3. Current general anesthesia gas products

Generic name	Product name	Size, quantity (number of bottles)	Manufacturer
Desflurane	Desflurane inhalation solution	240 mL (1) 240 mL (6)	Sandoz
	Suprane inhalation solution	240 mL (6)	Baxter
Isoflurane	Forane inhalation solution	100 mL (6) 250 mL (6)	Baxter
	Isoflurane inhalation solution	100 mL (1) 250 mL (1)	Piramal
	Terrell inhalation solution	100 mL (1) 250 mL (1)	Piramal
Sevoflurane	Sevoflurane inhalation solution	250 mL (6) 100 mL (1) 250 mL (1)	Baxter, Piramal, Sandoz
	Ultane inhalation solution	250 mL (1)	AbbVie

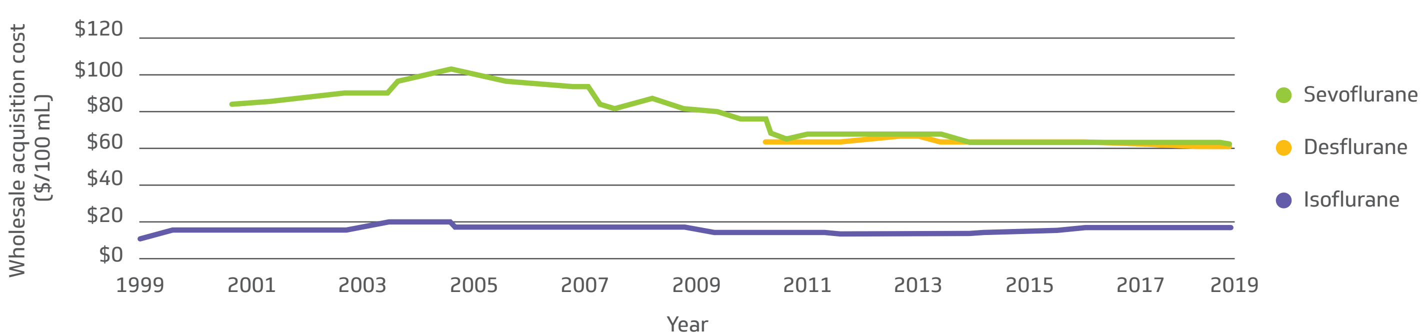
Data derived from Wolters Kluwer[11] and First DataBank.[22]

Real-world utilization

Data on the real-world utilization of isoflurane, desflurane and sevoflurane were extracted from the Resource Manager, a tool within the Vizient® Clinical Data Base (CDB). The CDB includes nearly 500 hospitals' administrative billing data and has patient demographics, diagnoses, procedures and other characteristics related to hospital inpatient and outpatient encounters. Procedural utilization of the general anesthesia gases for 2018 was captured for 53 hospitals in the inpatient setting and 86 hospitals in the outpatient setting. Procedures were further stratified by principal Clinical Classification Software procedure codes, which are clusters of ICD-10 diagnoses separated into broader, more clinically meaningful categories. Of the 224,372 captured procedures, 81% were inpatient and 19% were outpatient.

Of the 172,376 adult inpatient encounters, the most common procedures were spinal fusion (7.22%), hip replacement (4.35%) and fracture treatment of the hip or femur (3.18%). Of the 9,044 pediatric inpatient encounters, the most common procedures were appendectomy (6.82%), fracture treatment of the hip or femur (5.38%) and other fracture treatment (4.57%). Of the 41,739 adult outpatient encounters, the most common procedures were miscellaneous joint procedures (6.56%), cholecystectomy and common duct exploration (5.37%), and miscellaneous muscle and tendon procedures (4.92%). Of the 1,213 pediatric outpatient encounters, the most common procedures were tonsillectomy, adenoidectomy or both (17.39%); myringotomy (15.17%); and other miscellaneous mouth and throat procedures (7.67%).

Figure 3. Average wholesale acquisition cost per 100 mL, 1999-2018



Data derived from Wolters Kluwer.[11]

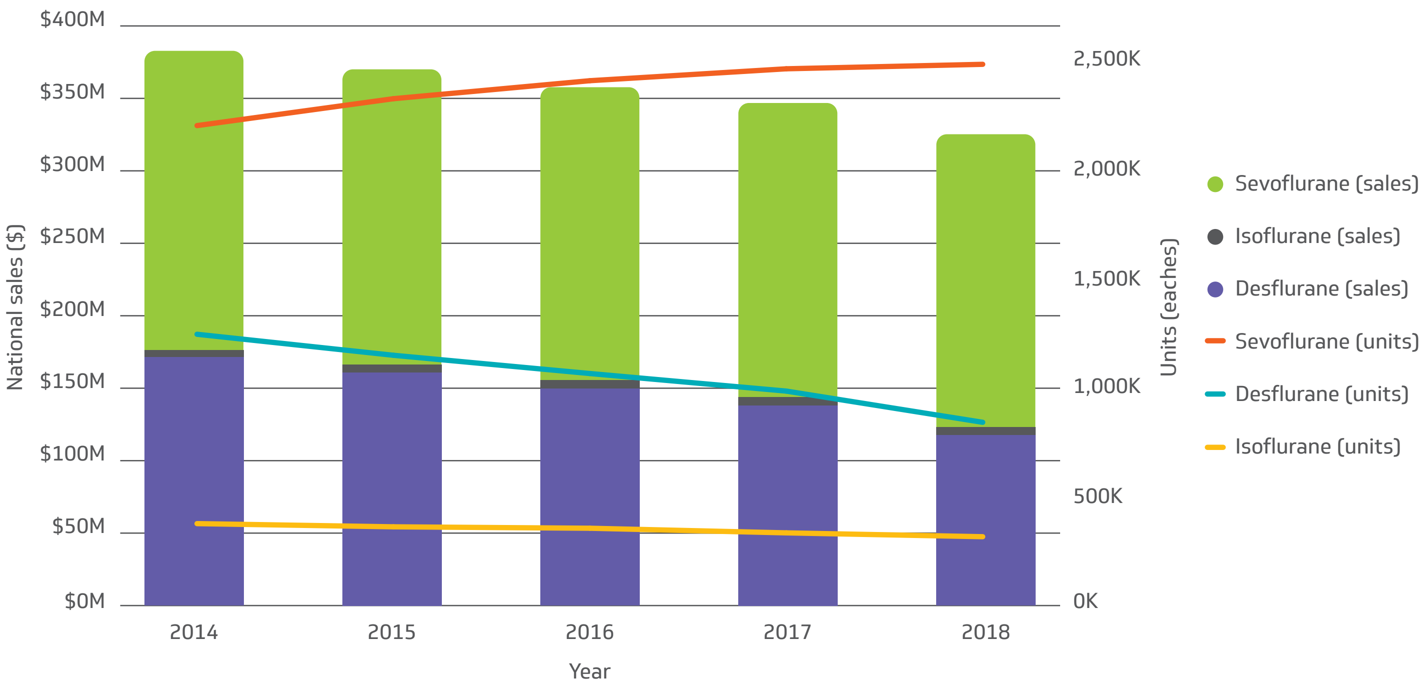
National market

National market data from IQVIA shows that overall spend on the anesthesia gases has been steadily declining (see Figure 4), which may be due to price erosion, effective cost-saving measures and improvements in anesthesia monitoring. Sevoflurane dominates the market with stable sales and units sold. Although prices have remained steady, desflurane sales and units have been declining over time, reflecting lower demand. With a generic product introduction in January 2019, desflurane sales may continue to fall due to price competition.

Vizient member market

The Vizient member market comprises a large portion of the national market but is largely composed of acute care hospitals and is affected by which products are on contract. As with the national market, sevoflurane dominates sales, especially in the pediatric arena.

Figure 4. National market data on the anesthesia gases, 2014-2018



Data derived from IQVIA.[23]

Summary

Although many anesthesia gases have been used throughout history, only three are currently available: isoflurane, desflurane and sevoflurane. No new anesthesia gases are anticipated to enter the market in the near future. Desflurane and sevoflurane dominate the market; they have clinically favorable profiles for anesthesia control but are also more expensive than isoflurane. Although desflurane provides the tightest control over anesthesia levels, it is not preferred for induction and has the most negative environmental impact. Sevoflurane has the most favorable profile for induction anesthesia, particularly in children, and is especially favored in the pediatric market according to spend data from the Children's Hospital Association. Overall, national spend for the anesthesia gases, especially desflurane, has decreased over time. Members planning their anesthesia gases budget will need to consider several factors in addition to clinical preference, including new entrants to the anesthesia gas market, local vaporizer agreements, the hidden costs of purchasing vaporizers and environmental impact. Materials managers, surgery suite personnel, pharmacy, legal and risk management should be involved in creating an implementation plan that accounts for procurement and distribution of the gases themselves as well as vaporizers and other relevant equipment.

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