New Inhaled Anesthetics

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History

This review of new inhaled anesthetics describes the properties of two anesthetics discovered and laid aside 15–25 yr ago. Desflurane was prepared in the 1960s as 1 of more than 700 compounds synthesized in the search for a better inhaled anesthetic.1 Although this work led to the development and release of enflurane (compound I-347) and isoflurane (compound I-469), desflurane (compound I-653) languished for 2 decades because of difficulties and danger in its production2 and a lower potency than that of apparently similar compounds. Sevoflurane was synthesized in the 1970s,3 but had a delayed development for somewhat different reasons. An expensive synthesis and apparently toxic effects4 (later discovered to be a consequence of a flawed experimental design) led to its temporary abandonment.

Both anesthetics now find a place in clinical practice. By the end of 1993, more than 1,000,000 patients had received sevoflurane in Japan, where it is approved for clinical use, and approximately the same number of patients had received desflurane in North America and Europe. Desflurane is now approved for clinical use in the United States, United Kingdom, France, and Sweden.

Both agents fit the mold of several other new anesthetic agents and adjuvants. Both offer a significantly greater precision of control over maintenance of anesthesia and a potential for a more rapid recovery from anesthesia than offered by other potent inhaled anesthetics. Their kinetics parallel those of nitrous oxide and both may be used in lieu of nitrous oxide without an appreciable kinetic disadvantage.

Molecular Structure and Solubility

Solubility in Blood and Tissue

The desirable kinetics of desflurane and sevoflurane result from the exclusion of chlorine (and bromine) in the halogenation required to provide nonflammability. Desflurane (CF3H-O-CF2-CF3) differs from isoflurane (CF2H-O-CCl2-CF3) solely in the substitution of a fluorine for a chlorine atom on the α-ethyl carbon. Sevoflurane (CFH2-O-CH[CF3]2) has no similar commercial chlorinated analog but, like desflurane, is halogenated solely with fluorine. The substitution of flu-
orine for chlorine produces a blood solubility one-half to one-third that found for isoflurane (table 1), approaching (sevoflurane)\(^3\) to equaling (desflurane)\(^7\) the solubility of nitrous oxide.\(^8\) Unlike the result for most other inhaled anesthetics,\(^9\) the solubility of sevoflurane does not change materially with the age of the patient.\(^9\) In addition to a lower solubility in blood, desflurane also is less soluble in tissues (a lower tissue-blood partition coefficient) than halothane, isoflurane, or sevoflurane.\(^10\)\(^11\) Lower tissue solubility should promote a more rapid equilibration. Low blood and tissue solubilities indicate (1) more rapid increase in alveolar anesthetic concentration during induction of anesthesia; (2) more rapid decrease in alveolar concentration during elimination; (3) more rapid equilibration between tissues and blood for desflurane (but not sevoflurane); and (4) more precise control of alveolar anesthetic concentration during maintenance of anesthesia. As described in the succeeding sections, results of several studies support these conclusions.

**Solubility in Plastics and Rubber**

Desflurane and sevoflurane have lower solubilities in rubber and plastics than more potent agents such as isoflurane and halothane.\(^12\) Consequently, the anesthetic circuit extracts less agent during anesthetic administration and contributes less agent to rebreathed gases during elimination. However, neither effect materially alters the course of anesthesia, even for the more soluble agents.

**Induction of Anesthesia**

The rate of increase in alveolar anesthetic concentration (\(F_A\)) toward the concentration inspired (\(F_i\)) during induction relates inversely to solubility of the potent agent in blood (fig. 1).\(^13\)\(^14\) Thus, sevoflurane and desflurane have a rapid increase in \(F_A/F_i\). Only nitrous oxide concentration increases more rapidly, doing so because of the concentration effect.\(^15\)

A more rapid increase in \(F_A/F_i\) suggests the potential for a more rapid induction of anesthesia. However, the pungency of an agent can limit the rate of induction, and the pungency of desflurane exceeds that of other currently used agents. The resulting airway irritation produces an appreciable incidence of salivation, breathholding, coughing, or laryngospasm during induction of anesthesia when desflurane \(F_i\) exceed 6%. These responses do not appear to affect the incidence of hypoxemia in adults, but do result in an increase in

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**Table 1.**

<table>
<thead>
<tr>
<th></th>
<th>Partition Coefficients</th>
<th>Vapor Pressure* at 20°C (mmHg)</th>
<th>MAC in 30–60-year-old patients (%)</th>
<th>% Anesthetic Taken up and Recovered as Anesthetic Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood/Gas</td>
<td>Brain/Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.45</td>
<td>1.3</td>
<td>669</td>
<td>6.0</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.65</td>
<td>1.7</td>
<td>170</td>
<td>2.0</td>
</tr>
<tr>
<td>(N_2O)</td>
<td>0.47</td>
<td>1.1</td>
<td>—</td>
<td>105</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.4</td>
<td>1.6</td>
<td>240</td>
<td>1.15</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.8</td>
<td>1.3</td>
<td>172</td>
<td>2.0</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.4</td>
<td>1.9</td>
<td>244</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Values are from manufacturers.
children,16 and an inhalation induction with desflurane is not recommended in pediatric practice. Despite the limitation imposed by pungency, preliminary reports suggest that induction of anesthesia in adults can be obtained in less than 1 min by application of a "vital capacity rapid inhalation induction,"17,18 albeit at the expense of an incidence of coughing approaching 100%.

In contrast, the pungency of sevoflurane (if present at all) parallels that of halothane, which, combined with beneficial kinetics, makes sevoflurane useful for induction of anesthesia in both children and adults.19–23 Sevoflurane has replaced halothane in many pediatric practices in Japan.24 Compared with pungent agents, sevoflurane produces a more rapid induction of anesthesia,25 accomplished in 2 min (and in a still shorter time when given with nitrous oxide) using a "vital capacity breath technique."24,25 With both desflurane and sevoflurane, the use of intravenous agents for induction of anesthesia diminishes or eliminates pungency as an important issue.

Maintenace of Anesthesia
The difference between the concentration of anesthetic delivered (F_D) from a vaporizer and the F_A may be used to define the degree of control of the anesthetic level obtained with an inhaled agent during maintenance of anesthesia.2 A ratio of F_D/F_A that approaches 1.0 indicates precise control, and deviations from 1.0 less control. Differences in anesthetic uptake and in rebreathing determine the proximity of F_D/F_A to 1.0: The lower the uptake and rebreathing (i.e., a higher inflow rate; a greater fresh gas flow) the closer the value to 1.0. Thus, isoflurane's higher solubility produces a higher ratio than found with sevoflurane or desflurane (fig. 2). For all three agents, an increase in inflow rate decreases the ratio. At any specified fresh gas flow, the differences between F_D and F_A for sevoflurane exceed that for desflurane by a factor of five, and exceeds that for sevoflurane by a factor of four.2

The lower value of F_D/F_A for sevoflurane and desflurane means that at a modest inflow rate (2 L/min or greater), after the initial 5–10-min period of washin and uptake, the F_D approximates—and may be used to estimate—the concentration in the alveoli. For example, at 30 min after the initiation of anesthetic administration at an inflow rate of 2 L/min, F_D/F_A equals 1.18 for desflurane and 1.26 for sevoflurane.2 In contrast, with isoflurane, F_D/F_A equals 1.75 at 30 min after initiation of anesthetic administration, i.e., the F_D does not approximate that in the alveoli.

The use of an agent-specific analyzer (if available) facilitates a precision over the control of maintenance of anesthesia, regardless of solubility. To achieve a higher concentration quickly requires only a relatively greater increase ("overpressure") in F_D with a more soluble anesthetic. However, the greater the difference between F_D and F_A, the greater the potential for an overshoot, for deviations from a targeted anesthetic concentration. Variations in uptake (and hence in the F_D/F_A ratio) consequence to changes in surgical stimulation cannot be anticipated precisely, and such changes can further confound the precision over the control of anesthetic level. In addition, although considerable room exists for increasing F_D relative to F_A, the converse does not apply, i.e., one cannot provide an anesthetic partial pressure of less than zero; F_A can be increased quickly by an appropriate increase in F_D (overpressure), but may not be similarly reduced, particularly with a more soluble anesthetic.

Elimination of Anesthetic
The lower solubilities of desflurane and sevoflurane permit a more rapid decrease in F_A than that obtained
with more soluble agents such as isoflurane and halothane (fig. 3).\textsuperscript{13,14} With discontinuation of anesthetic administration, the $F_I$s of desflurane and sevoflurane decrease from the last alveolar concentration during administration twice as fast as the $F_I$s of halothane or isoflurane. Over time, the difference between desflurane (but not sevoflurane) and halothane or isoflurane increases because of the lower tissue solubility of desflurane: e.g., a 20-fold difference exists after 5 days.

The lower brain–blood partition coefficient of desflurane also indicates a more rapid elimination from the brain. In rabbits anesthetized for 90 min, cessation of anesthetic administration produces decreases in cerebral desflurane concentrations to one-half to one-third those found after the same duration of anesthesia with isoflurane or halothane.\textsuperscript{26} Similarly, cerebral sevoflurane concentrations in rats decrease twice as fast as cerebral concentrations of halothane.\textsuperscript{27}

**Rate of Recovery**

The more rapid elimination of desflurane and sevoflurane produces a more rapid return to normal coordination and judgment. After 2 h of exposure to desflurane at 0.4, 0.8, 1.2, or 1.6 minimum alveolar concentration (MAC), rats trained to walk on a rod rotating at 8 cyc/min could resume this activity twice as quickly as rats exposed to sevoflurane (fig. 4).\textsuperscript{28} Similarly, rats given sevoflurane regained motor coordination in one-half the time of rats given isoflurane.

Humans exhibit a qualitatively similar response. Adult patients or volunteers given sevoflurane or desflurane respond appropriately to commands ("open your eyes," "squeeze my hand," "state your date of birth") twice as quickly as patients given isoflurane or enflurane, usually within 5–10 min.\textsuperscript{22,29–33} This more rapid awakening may be associated with a more rapid return of the capacity to sustain an open airway or maintain ventilation despite a partial obstruction. For example, 20 min after discontinuing administration of sevoflurane, the ventilatory response to imposed increases in carbon dioxide may be normal, compared with a depressed response after halothane.\textsuperscript{34}

Although two reports suggest that increasing the duration of desflurane anesthesia does not increase time to awakening\textsuperscript{29,35} this differs from results of studies in animals.\textsuperscript{28} In animals, the time to recovery of motor function correlates directly with concentration and duration of anesthesia. In humans, the concentrations of agent at the end of anesthesia may differ according to the length of the procedure.

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![Graph showing the rate of recovery for different anesthetics](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931306/)
Recovery of cognition and motor coordination takes a longer period of time than recovery of response to command. Recovery of cognition and motor coordination are important because, with other factors, they may define a patient's readiness to leave the recovery room and assume greater responsibility for self care. Again, recovery occurs more rapidly with desflurane than with isoflurane (sevoflurane remains to be studied). Subjective measures, such as sense of energy, coordination, drowsiness, and confusion, also return to normal (or toward normal) sooner with desflurane than with isoflurane. In addition, patients given desflurane have higher Aldrete Recovery scores than those given isoflurane, and thus may be ready sooner for discharge from the postanesthesia care unit. Patients given desflurane also have less delirium (0% vs. 44% with isoflurane) and shivering (12.5% vs. 56%). It is curious that children anesthetized with sevoflurane tend (P < 0.1) to awaken with greater restlessness and agitation than those anesthetized with halothane, perhaps because of the earlier perception of pain. A similar result may be seen with desflurane.

Few studies actually document a more rapid release from the postanesthesia care unit for patients anesthetized with desflurane or sevoflurane. One or more factors may explain this finding: (1) no real difference may exist between the recovery from anesthesia with desflurane or sevoflurane and recovery from anesthesia with more soluble compounds; (2) confounding factors related to surgery (e.g., pain, blood loss) or administration of other drugs (e.g., nausea associated with administration of narcotics) may obscure differences; or (3) the application of recovery protocols that do not allow for an earlier readiness to leave the postanesthesia care unit (e.g., a rule or mindset that no departure can occur sooner than 1 h after arrival in the postanesthesia care unit or after medication with an opioid) may preclude the manifestation of a difference. Realization of potential economic benefits from an earlier discharge awaits the definition of the importance of these variables.

**Other Consequences of Molecular Structure**

**Vapor Pressure**

The use of fluorination rather than chlorination increases vapor pressure (*i.e.*, decreases intermolecular attraction). Thus desflurane's vapor pressure exceeds isoflurane's by a factor of three (table 1). Because the vapor pressure of desflurane exceeds 1 atm at 22.8°C (the boiling point), the vaporizer technology designed for delivery of enfurane, halothane, and isoflurane cannot be applied to desflurane in a "hot" operating room the desflurane would boil, producing a nonregulatable concentration of 100%. A new vaporizer technology addresses this property, producing a regulated concentration by converting desflurane to a gas (by heating), then blending this gas with diluent fresh gas flow. The new vaporizer resembles older vaporizers: a dial indicates concentration in the output, and concentration output is minimally affected by fresh gas flow, the composition of the background gases, or ambient temperature. The new vaporizer is modestly larger and requires electrical power. Unlike desflurane, the vapor pressure of sevoflurane permits the use of conventional vaporizer technology.

**Potency and Minimum Alveolar Concentration**

Fluorination produces less potent compounds than does chlorination, which, in turn, provides less potent compounds than does bromination. For example, in humans, MAC for desflurane is 5.2-fold greater than MAC for isoflurane (table 1). All modern anesthetics are more potent than nitrous oxide. As for other inhaled anesthetics, various factors influence the MAC of desflurane and sevoflurane. Except for a modest increase from birth, peaking at less than 0.5 yr of age, aging decreases MAC for both desflurane and sevoflurane. Depressants such as nitrous oxide, fentanyl, and midazolam decrease MAC. A 10°C decrease in body temperature decreases the MAC of desflurane by about 50%. MAC values for desflurane and sevoflurane in various animals parallel those for humans.

The alveolar anesthetic concentration abolishing appropriate responses to command defines "MAC awake." For desflurane, this equals 2.4%, for sevoflurane, 0.61%. Both values are one-third the MAC value for that age group and decrease with increasing age in proportion to the decrease in MAC itself. Dwyer et al. found a similar ratio for MAC awake to MAC for isoflurane, but a ratio of nearly two thirds for nitrous oxide. The importance of MAC awake lies in its association with amnesia. For both isoflurane and nitrous oxide, MAC awake equals a concentration that suppresses awareness and the capacity to learn new information. The initial trials of desflurane yielded similar but less objective results (*i.e.*, no volunteer remembered the application of tetanic electrical stimu-
ulation of the ulnar nerve at concentrations exceeding MAC awake.\textsuperscript{63} If MAC awake does indicate the concentration producing unawarness, then desflurane and sevoflurane are potent amnestic agents with a potency (defined as a MAC fraction) twice that of nitrous oxide.

**Stability In Vitro**

Fluorination enhances molecular stability. Both desflurane and sevoflurane resist degradation by strong acids. Desflurane also resists degradation by bases, being more resistant than its chlorinated analog, isoflurane. In contrast, soda lime or Baralyme materially degrade sevoflurane, and do so in a temperature-dependent manner (fig. 5).\textsuperscript{65-72} Although the breakdown of sevoflurane can slightly increase the anesthetic dose requirement, the increase is too small to be economically important or to affect the course of anesthesia.\textsuperscript{69} However, the breakdown product (an olefin, \text{C}F_2-O-C[CF_2][CF_3], also called compound A) warrants concern because it is lethal in rodents at a concentration of 400 ppm.\textsuperscript{67} In low-flow (750-ml/min) circuit administration, concentrations of the olefin reach average values of 8 ppm (soda lime) or 20 ppm (Baralyme) with a report of one value of 61 ppm.\textsuperscript{65} One study suggested average values of 10-25 ppm when a closed circuit is used,\textsuperscript{72} and another study (this one with five 20-30-kg greyhounds as the test subjects) gave average peak values of 90 ± 19 ppm.\textsuperscript{75} In contrast, the use of 5-1/min flows of fresh gas produced average peak concentrations of 7.6 ± 1.0 ppm.\textsuperscript{76} Although these are less than lethal concentrations, and no reports suggest harm or hazard resulting from such low concentrations, Mazze has indicated that the closeness to lethal concentration remains a concern.\textsuperscript{77} The concern may be increased by the finding in our laboratory that the olefin given to rats for 3 h produces very small but measurable renal tubular necrosis at concentrations of 50 ppm.\textsuperscript{78,79}

Various factors will affect the concentration of olefin achieved in clinical practice. As suggested in the preceding paragraph, higher concentrations of olefin might be achieved by the use of low inflow rates.\textsuperscript{74} Low inflow rates increase rebreathing, which in turn decreases the loss of olefin through the overflow. Increased rebreathing also would increase the rate of conversion of sevoflurane to olefin by increasing the temperature in the carbon dioxide absorbent.\textsuperscript{69} Similarly, conditions requiring a greater absorption of carbon dioxide (hyperthermia or increased patient size) should increase olefin production. Should soda lime or Baralyme become dry, they may have a greater capacity to degrade sevoflur-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig5}
\caption{The rate of degradation of anesthetics by 100 g moist soda lime in a sealed 580-ml flask is a function of temperature and the resistance of the anesthetic to degradation. Sevoflurane is the least resistant to degradation and desflurane the most.\textsuperscript{72,73}}
\end{figure}

**Stability In Vivo**

The greater strength of the carbon–fluorine bond renders desflurane (and probably sevoflurane) less vulnerable to biodegradation than its chlorinated analog, isoflurane. Inhalation of desflurane produces little or no increase in serum or urinary inorganic fluoride concentrations in rats treated with phenobarbital or ethanol to induce hepatic enzymes.\textsuperscript{80} Organic fluoride concentrations in urine also change little from preexposure values. In contrast, isoflurane produces small but significant increases in both serum and urinary inorganic fluoride concentrations.\textsuperscript{81} Enflurane produces still greater increases,\textsuperscript{82} and halothane and methoxyflurane produce large increases,\textsuperscript{83,84} particularly in urinary organic concentrations. Pigs given 5.4 MAC-h of desflurane had a small (17%) but significant increase in serum fluoride immediately after anesthesia.\textsuperscript{85} Studies in humans provide similar results. Neither inorganic fluoride in serum or urine nor urinary organic fluoride concentrations increase significantly in volunteers given 0.7 MAC-h of desflurane.\textsuperscript{86} Results are identical in patients given 3.1 MAC-h.\textsuperscript{87} Indeed, 7.4 MAC-h of desflurane in volunteers fail to increase...
serum or urinary inorganic fluoride. The only evidence of metabolism of sevoflurane is a finding of measurable concentrations of serum and urinary trifluoroacetate apparently one-fifth to one-tenth those produced by metabolism of isoflurane. Kinetic studies in volunteers indicate that all the desflurane taken up during administration can be recovered during elimination.

Sevoflurane may be 100-fold more vulnerable to metabolism than desflurane. Results of numerous studies suggest that the liver degrades sevoflurane to organic and inorganic fluoride in animals and humans. Cytochrome P450 2E1 appears to be the specific P450 isoform responsible for the degradation of sevoflurane and other anesthetics such as isoflurane, methoxyflurane and, perhaps, desflurane. In this study, cytochrome P450 2E1 produced defluorination of methoxyflurane > sevoflurane > enfurane > isoflurane > desflurane > zero. Fluoride formation from desflurane exceeded zero but was less than the limit of quantitation. Enzyme induction with ethanol or phenobarbital increased production of inorganic fluoride, with only one study failing to confirm the increase associated with phenobarbital pretreatment. The increases in sevoflurane metabolism correlate with an increase in microsomal P450 content. Similarly, duration of anesthesia and, probably, anesthetic concentration increase the amount of degradation byproducts.

Although in vivo degradation of sevoflurane to inorganic fluoride is less than that of methoxyflurane, rat hepatic microsomes in vitro defluorinate the molecules at essentially the same rate. These results are surprising (and contrast with results from P450 from human liver), considering that each molecule of methoxyflurane yields two fluoride atoms, whereas degradation of sevoflurane yields only one (the fluorine atom on the methyl group). The difference between in vivo and in vitro results may be due to a difference in kinetics. The much more rapid elimination of sevoflurane in vivo means that much less is available for metabolism during recovery from anesthesia. However, this would not explain differences in fluoride concentrations during anesthetic administration.

The results of an initial study of kinetics in human volunteers suggested that most of the sevoflurane taken up did not appear during elimination, a result consistent with considerable biodegradation. However, a subsequent and more detailed study gave data consistent with recovery of all sevoflurane taken up. As defined by recovery of urinary metabolites, about 3% of the sevoflurane taken up is metabolized.

Serum fluoride concentrations do not decrease immediately after cessation of sevoflurane administration, despite the rapid decrease in the concentration of the parent compound. Based on the large volume of distribution of such fluoride, Fujii et al. speculated that the fluoride produced intracellularly from degradation of sevoflurane was trapped because of its high degree of ionization. However, this hypothesis implies an extraordinarily high hepatic concentration of fluoride ion, one that might reach toxic proportions. An alternative explanation is that metabolism of sevoflurane follows zero-order kinetics at concentrations of greater than 0.02–0.05 MAC. That is, a constant level of metabolism might be expected to persist for a few hours despite the rapid decrease in sevoflurane concentration. Such zero-order kinetics have been found with halothane and enfurane.

Although metabolism produces inorganic fluoride from both desflurane and sevoflurane, the organic fluoride byproducts differ. Like isoflurane, desflurane degrades to trifluoroacetate, differing only in the extent of degradation: the production of trifluoroacetate from isoflurane is five to ten times greater than production from desflurane. Hepatic degradation of sevoflurane produces hexafluoroisopropanol, which is excreted, at least in part, as the glucuronide conjugate. The peak excretion of hexafluoroisopropanol glucuronide occurs in the 12 h after anesthesia with an excretion half-life of 55 h.

Effects on Vital Systems

Introduction

For the most part, the effects of desflurane and sevoflurane on various vital systems parallel those of agents like isoflurane and halothane. These agents depress most systems in a dose-related manner.

Respiration

Desflurane and sevoflurane depress ventilation, producing profound decreases in ventilation leading to apnea between 1.5 and 2.0 MAC. Both agents increase arterial carbon dioxide tension and decrease the ventilatory response to imposed increases in carbon dioxide. In cats anesthetized with ketamine, 0.1 and 0.5 MAC sevoflurane depressed the ventilatory response to hypoxia by an amount indistinguishable from the...
depression produced by halothane.\textsuperscript{105} The ventilatory depression associated with sevoflurane may result from a combination of central depression of medullary respiratory neurons,\textsuperscript{106} and depression of diaphragmatic function\textsuperscript{107} and contractility.\textsuperscript{108} Comparable data are not yet available for desflurane.

Like other potent inhaled agents, sevoflurane may relax bronchial smooth muscle constricted by histamine or acetylcholine, perhaps slightly less effectively than halothane.\textsuperscript{109} Similarly, a given concentration of sevoflurane is less potent than the same concentration of halothane, isoflurane or enfurane in antagonizing carbachol-induced increases in canine tracheal smooth muscle contraction.\textsuperscript{110} However, the difference among the anesthetics becomes trivial when considered at comparable MAC multiples. Comparable data are not available for desflurane, but in the initial clinical trials, 74 patients with a history of asthma were anesthetized with desflurane without evidence of bronchospasm.\textsuperscript{†} Similarly, sevoflurane has been used safely in patients with asthma.\textsuperscript{111}

\textit{Circulation}

The circulatory effects of these two new anesthetics parallel many of the characteristics of previous agents: desflurane most closely resembles isoflurane, whereas sevoflurane has characteristics of both isoflurane and halothane. Desflurane and sevoflurane decrease blood pressure in a dose-related manner,\textsuperscript{20,112–116} both apparently in part, by decreasing total peripheral resistance. Both agents also tend to preserve cardiac output\textsuperscript{112,114–116} at clinically useful concentrations; however, they can depress myocardial contractility,\textsuperscript{115–115,117–120} and excessive levels of anesthesia produce cardiovascular collapse.\textsuperscript{121} In dogs, desflurane and isoflurane produce comparable depression of contractility.\textsuperscript{122} The depression of contractility produced by sevoflurane may be due to a block of calcium influx.\textsuperscript{123}

Results from animal studies suggest that desflurane consistently increases heart rate,\textsuperscript{124–127} whereas sevoflurane provides relatively stable heart rate.\textsuperscript{118,119,128,129} Parallel findings exist for humans who at concentrations exceeding 1 MAC may incur an increase with desflurane\textsuperscript{115,114} but not sevoflurane.\textsuperscript{20,115} The stability of heart rate with sevoflurane is desirable because it neither increases myocardial oxygen consumption nor decreases the time available for myocardial perfusion. The increase with desflurane has two components: (1) an effect of dose and (2) an effect of change in the concentration of desflurane. At MAC or lesser concentrations, desflurane has little effect on heart rate,\textsuperscript{112–114} but deeper levels increase rate in proportion to the partial pressure of desflurane.\textsuperscript{114}

Induction of anesthesia with desflurane may be associated with transient increases in heart rate and blood pressure.\textsuperscript{16,130} Similarly, Ebert and Muzi reported that a transient increase in heart rate (and blood pressure) also may accompany a 0.5-MAC increase in the \(F_0\) of desflurane from a vaporizer when that concentration exceeds 1.0 MAC.\textsuperscript{131} They compared these changes with those seen with the same increases in the \(F_0\) of isoflurane, finding that the changes with desflurane were much greater; indeed, Ebert and Muzi found no increase in blood pressure with isoflurane. The cardiovascular changes seen with desflurane also could be correlated with increased sympathetic nerve traffic (measured concurrently).

The comparative aspects (\textit{i.e.}, those pertaining to desflurane relative to isoflurane) of the Ebert and Muzi report are flawed. The investigation was conducted in small groups (\(n = 7\) per group) of subjects who received only one anesthetic (thereby hindering the power of comparison between anesthetics). Assignment was neither random nor prospective. However, these are minor factors compared to the failure to control the \(F_0\) of anesthetic. The investigators increased the \(F_0\) (vaporizer concentration) rather than the \(F_0\) in a square-wave manner. The result must be an increasing \(F_0\) for both anesthetics, but one in which the increase is both more rapid and greater for the less soluble agent, desflurane. Such a differential compromises any comparison between the anesthetics.

When the \(F_0\) is controlled, the difference between the responses to desflurane versus isoflurane decreases.\textsuperscript{132} A rapid increase in the \(F_0\) of desflurane or isoflurane from 0.6 to 1.6 MAC in paralyzed, normocapnic volunteers, increases mean arterial blood pressure half as much with isoflurane as with desflurane. Heart rate increase with isoflurane is three-fourths that with desflurane. Both changes are transient, are essentially complete in 2–4 min, and are associated with increased plasma catecholamines. The transient increase in plasma epinephrine is far greater with desflurane than with isoflurane. Ebert and Muzi's suggestion\textsuperscript{131} that these transient effects of desflurane at concentrations greater than MAC “contraindicate”

\footnote{\textsuperscript{†} Ohmeda: Unpublished data, on file.}

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the use of desflurane in patients with coronary artery disease is not supported by direct evidence in such patients (see below).

Both desflurane and sevoflurane are ethers and, therefore, should not predispose to ventricular arrhythmias nor sensitize the heart to the arrhythmogenic effects of epinephrine (e.g., for an example of the difference between ethers and alkanes see Johnston et al.\textsuperscript{133}). Results from various studies support these predictions. The dose of epinephrine producing ventricular ectopy with either agent does not differ from that producing ectopy with isoflurane or enfurane.\textsuperscript{134–136} Sevoflurane has been used in the anesthetic management of patients undergoing a resection of a pheochromocytoma.\textsuperscript{137}

Administration of either agent can alter tissue blood flow and resistance to blood flow. Their effect on coronary arterial blood flow is small, with evidence of a decrease in coronary vascular resistance with both.\textsuperscript{117,118,124,126,129,130} Both agents tend to preserve splanchnic, including renal, blood flow.\textsuperscript{61,126,129} Hepatic blood flow tends to decrease at deeper levels of anesthesia as a consequence of a decrease in portal venous (but not hepatic arterial) blood flow.\textsuperscript{125,128} Both anesthetics also decrease cerebrovascular resistance, with any increase in cerebral blood flow at least partially determined by their concurrent effects on arterial blood pressure.\textsuperscript{61,129,139,140} Desflurane (and probably sevoflurane) decreases temperature regulation, and can cause cutaneous vasodilation.\textsuperscript{112} Desflurane has little effect on muscle blood flow but decreases resistance to flow,\textsuperscript{114} whereas sevoflurane appears to increase flow while decreasing resistance to flow.\textsuperscript{120}

Because these new anesthetics can decrease coronary arterial vascular resistance, they may be able to cause "coronary steal" (the diversion of blood from a myocardial bed with limited or inadequate perfusion to a bed with a more adequate perfusion, especially one that has a remaining element of autoregulation). This possibility remains to be investigated with sevoflurane. In normal dogs, desflurane and isoflurane do not decrease coronary arterial blood flow, even at deep levels of anesthesia, whereas deep levels of halothane decrease perfusion; none of these anesthetics alter the relationship between endocardial and epicardial perfusion.\textsuperscript{120} In a model that revealed "coronary steal" with a known coronary arterial vasodilator (adenosine), desflurane did not alter the pattern of myocardial blood flow distribution.\textsuperscript{141}

No reports document the use of sevoflurane in patients having known coronary artery disease, although a case report describes a patient with a 25% occlusion of the right coronary artery who apparently experienced unexplained "coronary artery spasm" during anesthesia with sevoflurane.\textsuperscript{142} Results from several studies of desflurane in patients with known coronary artery disease indicate that desflurane does not alter the risk of untoward postoperative outcomes compared with other inhaled or intravenous (opioid) anesthetics.\textsuperscript{143–146} However, one study found a 14% incidence of myocardial ischemia (detected with continuous electrocardiographic or echocardiographic measurements) during induction of anesthesia with thiopental and desflurane in 100 patients in patients scheduled for coronary artery bypass grafting compared with no ischemia in 100 similar patients in whom anesthesia was induced with sufentanil.\textsuperscript{144} Once induction was complete, the difference in the incidence of ischemia disappeared. Conversely, before cardiopulmonary bypass, the severity of ischemia (assessed as a function of the area under the curve for ST deviation) was greater in the patients given sufentanil. The difference in the incidence of ischemia during induction may have resulted from the avoidance of opioid administration when desflurane was used. The incidence of postoperative cardiac death or myocardial infarction was identical for the two groups.

Central Nervous System

The effects of sevoflurane and desflurane on the central nervous system do not differentiate these agents from other commonly used inhaled anesthetics. As noted above, both anesthetics can decrease cerebral vascular resistance and cerebral metabolic rate.\textsuperscript{\textsuperscript{140,147–149}} Both can increase intracranial pressure and do so in a dose-related manner. In hypoxic and humans with intracranial masses, desflurane concentrations of 0.8 MAC or less do not appear to increase intracranial pressure.\textsuperscript{150} whereas 1.1 MAC increases pressure by 7 mmHg.\textsuperscript{151} In rabbits maintained normotensive with administration of angiotensin, administration of 0.5–1.0 MAC increases intracranial pressure to the same extent with sevoflurane and isoflurane.\textsuperscript{148} In dogs allowed to become hypertensive with increasing concentrations of anesthetic, administration of sevoflurane does not increase intracranial pressure.\textsuperscript{152} Similar results may be found with desflurane.\textsuperscript{146}

Cerebral

\textsuperscript{+}Ebrahim Z: Unpublished data.

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autoregulation is maintained during anesthesia with sevoflurane.\textsuperscript{153} Cerebrovascular responses to increases in carbon dioxide are present during anesthesia with either desflurane\textsuperscript{139} or sevoflurane.\textsuperscript{153}

Desflurane and sevoflurane cause similar dose-related changes in the electroencephalogram (EEG) that parallel those found with isoflurane. With desflurane, the EEG of humans progresses from an initial increase in frequency and lowering of voltage at sub-MAC concentrations to increased voltage at anesthetizing concentrations.\textsuperscript{154} Deeper levels produce decreasing voltage and increasing periods of electrical silence (burst suppression), with an isoelectric EEG at 1.5–2.0 MAC. The addition of nitrous oxide to a given level of anesthesia with desflurane causes little or no change in the EEG.\textsuperscript{154} In dogs or rabbits, sevoflurane causes burst suppression at MAC and higher, but an isoelectric EEG appears to require concentrations exceeding 2 MAC.\textsuperscript{148,149} Neither agent causes convulsive activity, either at deep levels of anesthesia or in the presence of hypoxia and auditory stimulation.\textsuperscript{149,154,155} A single report suggested that induction of anesthesia with sevoflurane could be associated with "seizure-like movements" that might reflect either seizure activity or myoclonus.\textsuperscript{156} Consistent with this finding, 9 of 50 children developed transient muscle rigidity during induction of anesthesia with sevoflurane, compared with 0 of 50 with halothane.\textsuperscript{21} In humans, a rapid induction of anesthesia produces "a peculiar pattern of high voltage, rhythmic slow waves," similar to the pattern produced by other anesthetics that activate reticular neurons.\textsuperscript{157} Sevoflurane can suppress convulsive activity induced with lidocaine.\textsuperscript{158}

Increasing concentrations of desflurane (from 0.5 to >1.5 MAC) increasingly depress somatosensory-evoked potentials in patients.\textsuperscript{159} Similarly, we found that sub-MAC concentrations of desflurane suppress intermediate-latency auditory-evoked responses in volunteers.\textsuperscript{5}

Results from a study of the application of deep levels of anesthesia with desflurane in dogs suggested the development of tolerance to this anesthetic.\textsuperscript{140} Results from studies in swine and humans do not support such an interpretation.\textsuperscript{154,160}

\textbf{Muscle}

Like other modern inhaled anesthetics, sevoflurane and desflurane provide sufficient muscle relaxation for most procedures (e.g., for intubation of the trachea).\textsuperscript{112,161} One report indicates that sevoflurane can dramatically affect neuromuscular transmission in a patient with myasthenia gravis.\textsuperscript{162} Both anesthetics enhance the action of muscle relaxants.\textsuperscript{161,163} As would be expected of anesthetics that enhance the effect of muscle relaxants, relative to neuroleptanalgesia, sevoflurane and enflurane (but surprisingly, not isoflurane or halothane) can delay recovery from a fixed dose of vecuronium.\textsuperscript{164}

Both anesthetics can trigger malignant hyperthermia in experimental models.\textsuperscript{165–167} Desflurane is a weaker trigger of malignant hyperthermia than halothane, but is comparable to isoflurane in its triggering capacity.\textsuperscript{168} At least three patients given sevoflurane have developed malignant hyperthermia.\textsuperscript{169,170} No reports have yet associated desflurane and malignant hyperthermia in humans.

\textbf{Liver and Kidney}

The minimal degradation of desflurane both in vitro and in vivo predicts a lack of toxic effects. The experience to date confirms this prediction. Neither the initial\textsuperscript{86} nor subsequent trials in volunteers given deep levels of anesthesia\textsuperscript{171} indicated the presence of hepatorenal toxicity. Administration of desflurane does not appear to worsen chronic hepatic or renal disease.\textsuperscript{172} The initial trials in patients lend further support to the prediction.\textsuperscript{5} Studies in animals extend these observations by providing evidence of desflurane's innocuousness when administered concurrently with various stresses. For example, hepatic enzyme induction with phenobarbital in rats made hypoxic while simultaneously anesthetized with desflurane does not increase the risk of tissue injury.\textsuperscript{173} Repeated\textsuperscript{24} or prolonged anesthesia\textsuperscript{175} also does not appear to increase the risk of tissue injury.

Similarly, despite its far greater vulnerability to degradation in vitro and in vivo, most current evidence indicates that sevoflurane or its degradation products, including inorganic fluoride, does not produce hepatic or renal injury. The one report of massive hepatorenal injury with administration of sevoflurane to rats\textsuperscript{1} may be discounted as the result of a failure to control body temperature adequately. Indeed, previous studies by the same group\textsuperscript{89,99} and subsequent studies by other investigators,\textsuperscript{176,177} detected no evidence of injury in either normal or enzyme-induced rats anesthetized with sevoflurane. In the study by Strum \textit{et al.},\textsuperscript{176} the stresses included the superimposition of hypoxia. More im-

\textsuperscript{§} Hart P, Gonsowski T: Unpublished data.
importantly, only two cases of hepatic injury attributable to sevoflurane (and none for renal injury) have been reported from Japan, where more than 1,000,000 patients now have been anesthetized with this agent.\textsuperscript{178,179} Studies specifically focused on tissue toxicity have failed to reveal injury, despite prolonged anesthesia with associated concentrations of inorganic fluoride much greater than 40 μM.\textsuperscript{92,94,95,160,180} One caution, however, comes from the finding (noted earlier) that the degradation of sevoflurane by soda lime or Baralyme produces a toxic olefin and that the concentration threshold for nephrotoxicity in rats\textsuperscript{78,79} is within the range of concentrations that may be found in clinical practice.\textsuperscript{65}

Desflurane\textsuperscript{f} and sevoflurane\textsuperscript{g} also do not appear to cause mutagenic changes.\textsuperscript{181} Specifically, neither anesthetic reveals mutagenicity in the Ames or several other tests including the sister chromatid exchange test, the human lymphocyte metaphase test, or the mouse micronucleus test. Surprisingly, although the olefin produced from the degradation of sevoflurane by soda lime might be expected to be an alkylating agent (and thus a mutagen), tests of this degradation product do not reveal mutagenicity.\textsuperscript{57}

As noted earlier, neither anesthetic produces untoward changes in hepatic blood flow. In dogs, desflurane slightly decreases portal blood flow but does not alter hepatic arterial blood flow.\textsuperscript{126} Results from a separate study in dogs suggested an increase in hepatic blood flow in association with a decrease in hepatic vascular resistance.\textsuperscript{120} Sevoflurane also has little effect on hepatic arterial blood flow in dogs.\textsuperscript{128,182} In rats, sevoflurane decreases portal venous and hepatic arterial blood flow when ventilation is controlled,\textsuperscript{129} but maintains portal flow while increasing hepatic arterial flow during spontaneous ventilation.\textsuperscript{61} Hepatic oxygenation appears to be unperturbed.

Little is known about the capacity of these new anesthetics to affect the metabolism of drugs administered concurrently. It appears that both can slightly enhance the metabolism of diazepam by hepatic slices when the surrounding medium contains albumin.\textsuperscript{183}

Sevoflurane given to ventilated rats does not change renal blood flow at anesthetic levels producing a mean arterial blood pressure of 70 mmHg but decreases flow when pressure is lowered to 50 mmHg.\textsuperscript{129} In spontaneously breathing rats, 1 MAC sevoflurane also does not change renal blood flow.\textsuperscript{61} Similarly, no change in renal blood flow (measured with a Doppler flow probe) occurs in dogs given desflurane, even at 2 MAC.\textsuperscript{126} Using a microsphere technique, one study in dogs found a 10% decrease in renal cortical flow that was unrelated to concentration.\textsuperscript{120}

Cost

In an editorial, Saidman emphasized the importance of deciding whether desflurane (and he might as easily have written sevoflurane) provides a cost–benefit ratio that recommends its acceptance over the excellent agents that preceded it.\textsuperscript{184} Saidman recognized the potential benefits of desflurane but argued that these must be sufficient to merit any increased costs that might be associated with its adoption in practice.

Three factors may influence the cost of an inhaled anesthetic.\textsuperscript{185} First is the price determined by the manufacturer. Because this is subject to change, it is not considered here. Second are factors inherent to the anesthetic, such as potency and solubility. Some of these are considered above; an additional one is discussed here. Third is the manner in which the anesthetic is applied, particularly the flow rate. This is of particular importance because the decision of the anesthetist then is a major determinant of cost. As the following discussion illustrates, that decision may be influenced by the characteristics of the anesthetic, particularly its solubility.

Among factors inherent to the anesthetic that affect cost is the amount of vapor produced from 1 ml liquid anesthetic. The amount of vapor produced is a function of the specific gravities and molecular weights of desflurane (1.467 g/ml and 168 g, respectively), isoflurane (1.50 g/ml and 184.5 g), and sevoflurane (1.505 g/ml and 200 g). These values indicate that 1 ml liquid desflurane will make 7% more vapor than 1 ml isoflurane. However, 1 ml liquid sevoflurane will make 7% less vapor than 1 ml isoflurane.

Consider now the factors controlled by the anesthetist that influence cost and how these in turn may be dictated by the pharmacology of the anesthetic, namely potency and solubility. Saidman\textsuperscript{184} noted that "because desflurane is only one fifth as potent as isoflurane, a large(r) liquid volume must be vaporized to produce an equal level of anesthesia. This increased cost of desflurane anesthesia can be reduced somewhat by utilization of low flows (or even closed-circuit techniques)." This comment must be joined to another

\textsuperscript{f} Maruishi: Unpublished data, on file.

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reality. Potency as defined by MAC (the “one fifth” cited above) does not, alone, determine the consumption of anesthetic. The $F_D$ must account for the difference between the $F_i$ and the concentration that must be sustained in the alveoli (e.g., MAC). This difference is considerably greater for isoflurane than for desflurane or sevoflurane because of the greater solubility of isoflurane (see fig. 2). In addition, if lower inflow rates are used (e.g., 2 l/min), the $F_D$ also must compensate for the rebreathed gases that are depleted of anesthetic. Because their lower solubility results in less depletion of desflurane or sevoflurane, less compensation is required. Thus, for a 1-h operation and a 2-l/min inflow rate, the amount of desflurane that must be delivered (i.e., consumed) to sustain MAC is only slightly more than three-fold the amount of isoflurane—not the five-fold difference suggested by the ratio of MAC values. Similarly, although the MAC of sevoflurane is 74% greater than the MAC of isoflurane, the amount of sevoflurane that must be delivered to sustain MAC is only 30% greater.

A further consideration affecting cost is the inflow rate required to maintain sufficient control over the precision with which anesthesia is delivered. The smaller the difference among $F_D$, $F_i$, and $F_a$, the lower the inflow rate can be without loss of control. Thus desflurane and sevoflurane may be used at lower inflow rates than isoflurane. As Saidman noted, the clinician who chooses to use lower inflow rates with the less soluble anesthetics will greatly lower cost. A further savings may accrue to the use of these new agents if they provide a more rapid recovery, permitting more economical use of recovery facilities. Some evidence suggests that this may be the case but considerably more information will be required to determine whether a more rapid recovery does result in a savings. These observations ignore the capital costs involved in the adoption of a new anesthetic. Capital costs include the expense of new vaporizers and the cost of converting or purchasing instruments to analyze the new anesthetics.

Summary

Desflurane and sevoflurane provide one clear advantage over other currently available potent inhaled anesthetics. Their lower solubilities permit a more precise control over the delivery of anesthesia and a more rapid recovery from anesthesia. Most of their other properties reflect similar properties of their predecessors—with a few exceptions. Indeed, at concentrations of 1 MAC or less, the pharmacologic properties of these two agents differ little if at all. However, in contrast to desflurane, at concentrations exceeding 1 MAC sevoflurane has little or no respiratory irritant properties and may be used to rapidly induce anesthesia. Neither anesthetic seems to materially affect heart rate at concentrations lower than MAC, but at higher concentrations desflurane, but not sevoflurane, may increase heart rate. Desflurane strongly resists biodegradation and degradation by soda lime, whereas sevoflurane is vulnerable to degradation and the degradation by soda lime or Baralyme produces a toxic product. Thus, neither of these new anesthetics can be said to be ideal, but each may be a step in that direction.

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