Sevoflurane use in Veterans Affairs medical centers: Utility, safety, and cost-effectiveness

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It has long been realized that the Veterans Affairs (VA) patient has a high incidence of multiorgan system diseases, especially diseases of the pulmonary and cardiovascular systems. The typical Birmingham VA Medical Center patient presenting for surgery is male, with a national mean age of 60 years. More than one half of these patients have a significant history of current or prior tobacco abuse, and many have cardiovascular impairments. When sevoflurane became available, a careful review of the characteristics of the drug, as well as cost comparisons of inhaled agents, was done by our department of anesthesia. Sevoflurane appears to be an ideal inhaled anesthetic for the veteran patient population. If used appropriately, sevoflurane can be administered safely at a cost comparable to desflurane.

Key words: Cost comparisons of inhaled agents, desflurane, inhaled anesthetics, sevoflurane, Veterans Affairs patients.

Introduction

Sevoflurane is a clear, colorless, stable liquid that is used as an inhaled anesthetic to induce and maintain general anesthesia. Sevoflurane is characterized by a lack of respiratory irritation, and it has rapid and extensive pulmonary elimination that minimizes the amount of anesthetic available for metabolism. Changes in the depth of anesthesia rapidly follow changes in the inspired sevoflurane concentration, so extubation time, the time until recovery of cognitive functions and motor coordination, and the time until patient eligibility for discharge from the postanesthesia care unit may be significantly shortened. A summary of the characteristics of sevoflurane and current cost analysis with comparisons of other inhaled agents follows.

Respiratory response to sevoflurane

While researching journal articles, abstracts, and textbooks for this article, it was decided to include Veterans Affairs (VA) statistical data regarding the incidence of pulmonary and cardiovascular disease among the veteran patient population. After numerous attempts, this effort was abandoned because no centralized computer data existed that contained the information we desired. The following data were derived from our preanesthetic summaries.

During a typical month, our department provided anesthetic care to 211 patients for elective surgeries. Of the 211 patients, 74 (35%) had documented chronic obstructive pulmonary disease or emphysema, pulmonary fibrosis, or reactive airway disease, and were receiving medical treatment for these conditions. The most prevalent causative factor was a continuing or prior history of smoking. Another 54 (25.6%) of those patients are currently smoking but are not receiving medical treatment for pulmonary complications due to tobacco
use. Thus, more than 50% of our patients have irritable or impaired airways, whether they are receiving active treatment or not.

Sevoflurane is relatively nonirritating to the respiratory tract, does not induce secretions, and seems to be effective in reversing bronchospasm. A unique feature of sevoflurane is the acceptability for an inhaled induction of anesthesia by mask, because it is nonpungent; it is less irritating than desflurane, enflurane, isoflurane and even halothane. Previous investigators have reported that halothane caused less airway irritation than isoflurane. Sevoflurane should then be considered to be superior to isoflurane, desflurane, and enflurane for mask induction. With its lack of irritability, it may represent an excellent agent for the typical VA patient population because, by our observations and survey, more than 50% have some degree of pulmonary compromise or airway irritability.

Cardiovascular and neurocirculatory response to sevoflurane

The VA patient population has a high incidence of cardiovascular impairment. Sevoflurane has not been associated with coronary flow redistribution, commonly known as coronary steal. Sevoflurane has been associated with stable and with even lower heart rates compared with isoflurane. Desflurane and, to a lesser extent, isoflurane have been associated with periods of tachycardia when first administered into the inspired gas after intravenous induction of anesthesia and after increasing the inspired concentration during steady state periods of anesthesia. Neurocirculatory excitation (increases in heart rate and sympathetic nerve activity, central venous pressure, and in plasma norepinephrine), generally seen with desflurane, did not occur with sevoflurane. The interaction of sevoflurane with epinephrine seems to be equivalent to that seen with isoflurane. These data suggest that untoward cardiovascular events, such as tachycardia and hypertension, are less likely than with isoflurane and, particularly desflurane.

Response of elderly and VA patients to sevoflurane

Elderly patients were randomized to receive sevoflurane or isoflurane for maintenance of anesthesia during operations lasting 2 to 3 hours. Sevoflurane has been found as efficacious as isoflurane for the maintenance of anesthesia in the elderly. Efficacy parameters included time to recovery events, postanesthesia nausea and vomiting, and plasma fluoride concentrations. Sevoflurane was favored for Modified Aldrete Scores for consciousness and circulation. Postanesthesia nausea and vomiting was significantly higher in the isoflurane group (17%) compared with the sevoflurane group (3%). Higher plasma fluoride concentrations were noted in the sevoflurane group, without adverse effects on renal function. One patient (sevoflurane exposed) had a fluoride concentration of more than 50 micromolar (μmol/L) without evidence of renal impairment.

In a comparative study of patients older than 65 years conducted at the Miami, Florida VA, sevoflurane was associated with a more rapid emergence than isoflurane. While systolic blood pressures were found to be equivalent in both groups, heart rates were lower with sevoflurane. Fluoride concentrations (measured at various intervals for 1 week) were always higher with sevoflurane than with isoflurane during and after anesthesia, but levels approached normality at 1 week. There was no evidence of renal damage. Laboratory values (hematology, electrolytes, and hepatic and renal function tests) were equivalent in both groups. Cognitive function (time to eye opening, response to commands, orientation to name and birthday) was recovered almost twice as fast in the sevoflurane group.

Fluoride ion and base stability of sevoflurane

Concerns regarding possible nephrotoxicity from fluoride ion formation during biotransformation and toxicity from degradation in the presence of alkaline carbon dioxide absorbents were the primary reasons for the slow introduction of sevoflurane in the United States. During and after the administration of sevoflurane, the plasma fluoride ion level increases, but no studies to date have demonstrated significant postanesthesia renal dysfunction or renal impairment.

A long-held theory of clinical anesthesia is the concept that plasma fluoride ion levels of greater than 50 μmol/L lead to subclinical nephrotoxicity and that levels greater than 90 μmol/L lead to clinically apparent high-output renal failure. It is by no means certain that the "nephrotoxic threshold" concentration of serum inorganic fluoride is 50 μmol/L for anesthetics other than methoxyflurane. Peak levels of plasma inorganic fluoride that exceed 50 μmol/L have been observed in patients given isoflurane for prolonged periods during surgery who did not sustain overt renal damage. Studies in volunteers and patients have shown plasma fluoride levels exceeding 50 μmol/L in 7% of those who received sevoflurane exposure, yet this does not seem to result in clinical or subclinical nephrotoxicity. This is probably attributable to...
the low tissue solubility of sevoflurane and to its relatively low rate of metabolism by renal cytochrome P-450. When anesthesia with sevoflurane is discontinued, high levels of inorganic fluoride are maintained for only a few hours, in contrast to methoxyflurane, after which high levels may persist for days.8,10

Another concern is Compound A, a vinyl ether produced by the breakdown of sevoflurane in soda lime and baralyme. Compound A causes nephrotic effects in rats at inhaled concentrations between 50 and 100 ppm.3 When compound A was administered to Wistar rats for 3 hours at concentrations exceeding 50 ppm, histologic evidence of corticomedullary renal tubular necrosis was exhibited 1 day after exposure.8 These histopathologic renal changes ranged from relatively minor to moderate, and changes observed after 4 days were markedly less severe than the changes observed after 1 day. Severe nephrotoxicity was not found.8

In a recently published study, Compound A was administered to Fisher rats for 3 hours at concentrations ranging from 0 to 200 ppm.11 The rats were pretreated with varying doses (0-1,000 mg/kg) of acetaminophen to predispose to renal and hepatic injury. Renal cortical and hepatic injury were observed in rodents that received large doses (500-1,000 mg/kg) of acetaminophen and Compound A.11 Given the large doses of acetaminophen required to provoke renal or hepatic injury when Compound A was administered, the clinical relevance of these findings is unclear.11 Studies of toxic effects in rodents have raised the possibility that nephrotoxicity may occur; however, it is difficult to assess the significance of the measured concentrations of Compound A because a threshold for human toxicity has not been established.9 As a point of interest, halothane is base unstable, and in the presence of soda lime it is broken down to a vinyl compound (difluoromonomochloroethylene, or Compound BCDFE) that is more toxic to animals than is Compound A.3,8 Yet decades of clinical use of halothane, including the use of low-flow and closed-system techniques, have not demonstrated nephrotoxicity.3

During prolonged anesthesia with sevoflurane at low flow rates (<700 mL/min) in humans, Compound A concentrations were maximal at 7.6 ppm using soda lime as the carbon dioxide absorbent. Another study using low flow rates (total flow 500-700 mL/min) demonstrated Compound A levels no higher than 16 ppm using soda lime. No evidence of renal (or hepatic) toxicity effects were observed.5 Baralyme causes more production of Compound A than does soda lime. Compound A levels are inversely correlated with the fresh gas flow rate, so lower fresh gas flow rates result in a greater production of Compound A. With a fresh gas flow of 2 L/min or more, concentrations of Compound A measured in the anesthesia circuit when sevoflurane is used clinically are not known to be deleterious to humans.12 Because of limited clinical experience with sevoflurane in low flow systems, the drug's manufacturer (Abbott Laboratories, North Chicago, Illinois) does not recommend fresh gas flow rates below 2 L/min in a circle absorber system.12

Metabolism of sevoflurane

The rapid and extensive pulmonary elimination of sevoflurane minimizes the amount of anesthetic available for metabolism, with less than 5% undergoing metabolic degradation.10 Sevoflurane is metabolized in the liver, predominately by cytochrome P-450 2E1, to hexafluoroisopropanol (HFIP) with release of inorganic fluoride and carbon dioxide. Once formed, HFIP is rapidly conjugated with glucuronic acid and eliminated as a urinary metabolite.10 Methoxyflurane undergoes metabolism in the liver and the kidney, whereas sevoflurane metabolism is limited primarily to the liver, with minimal amounts of renal metabolism.8,10 No renal dysfunction or toxicity, measured by serum urea nitrogen and creatinine, creatinine, or urine osmolality, has been observed. After sevoflurane and enflurane anesthetics, measured urinary excretion of N-acetyl-B-glucosaminidase (NAG), a renal enzyme that can indicate renal tubular injury, was found to be increased at 7 days with enflurane but not with sevoflurane. Based on this evidence, it was concluded that renal tubular damage after sevoflurane was less than with enflurane.8,10

Hepatic/renal effects of sevoflurane

Much has been learned from halothane about the hepatotoxicity of inhalation anesthetics. Although the rare phenomenon of hepatic toxicity is real, the mechanisms of hepatic injury have taken years to elucidate because of the scarcity of cases.23 The mechanism currently favored is hepatic biotransformation of the anesthetic with the production of reactive metabolites and the binding of these products to liver macromolecules, which then elicits an immune response in a small number of individuals.13 In susceptible individuals, neoantigens stimulate formation of antibodies that mediate hepatic destruction when subsequently exposed to halothane.10 Sevoflurane seems to have an extremely low potential to initiate such a cascade. The metabolic product of sevoflurane (HFIP) has
much less protein binding capacity and does not accumulate, but is quickly conjugated with glucuronic acid and is rapidly excreted in the urine.\textsuperscript{13}

Indocyanine green (ICG) clearance and portal blood flow in rats were evaluated during sevoflurane anesthesia. The clearance of ICG was less altered with sevoflurane than with halothane. The clearance of ICG did not differ between sevoflurane and isoflurane, suggesting that hepatic metabolic function was well preserved.\textsuperscript{13}

Three cases of unexplained postoperative hepatic injury in patients anesthetized with sevoflurane have been reported in the Japanese literature. Because postoperative hepatic injury has many possible causes, it is far too early to conclude that sevoflurane was causative.\textsuperscript{8,10} Even if it could be concluded that these cases of postoperative hepatic damage were sevoflurane induced, the incidence would be minuscule, since by 1995, more than 2 million sevoflurane anesthetics have been administered in Japan. A multicenter study compared the safety of sevoflurane and isoflurane in patients with mild to moderate hepatic impairment. Neither drug adversely affected hepatic function.\textsuperscript{12}

More than 3,000 administrations of sevoflurane have been done during clinical trials in the United States and Europe. Evidence demonstrating that sevoflurane has hepatotoxic effects is essentially nonexistent.\textsuperscript{12,13}

Potential renal toxicity of sevoflurane is of concern because the metabolic liberation of inorganic fluoride occurs with its use.\textsuperscript{8,9} In healthy volunteers, renal concentrating function and urinary excretion of NAG were examined after prolonged sevoflurane anesthesia. None of the volunteers receiving sevoflurane exhibited impaired renal concentrating function, and urinary NAG excretion (measured at 1, 2, and 5 days) was unchanged from preanesthetic values.\textsuperscript{8} Previous studies for renal toxicity from inorganic fluoride or Compound A have not resulted in significant postanesthesia renal dysfunction or evidence of injury.\textsuperscript{8,10}

In a study by Eger et al to determine renal damage due to Compound A, sevoflurane was administered in a steady state end-tidal concentration of 1.25 minimum alveolar concentration (MAC) with a 2 L/min fresh gas flow (FGF) to healthy volunteers for an 8-hour period.\textsuperscript{14} The subjects were tested for markers of renal injury (urinary albumin, glucose, $\alpha$-glutathione-S-transferase (GST), $\pi$-GST, serum creatinine, and blood urea nitrogen) before and up to 7 days after anesthesia. Compound A concentrations were measured, and the average inspired concentration of Compound A was 41 ppm plus or minus 3 ppm. Sevoflurane was associated with transient injury to the proximal and distal tubules and dysfunction of several parts of the human nephron.\textsuperscript{13} For the 10 volunteers given sevoflurane, effects ranged from no significant injury to transient nephrotic-range proteinuria.\textsuperscript{14} In almost all cases, elevated levels of renal injury-sensitive enzymes returned to normal within 5 to 7 days.

“A multicenter study recently duplicated the protocol used by Eger et al, where sevoflurane was administered to normal volunteers at 1.25 MAC at 2 L/min for 8 hours. In contrast to Eger’s study, this blinded study revealed no abnormalities in renal function, assessed by BUN, creatinine, and urinary excretion of glucose, protein, $\alpha$GST or $\pi$GST (FDA data on file).” (Personal communication with Evan D. Kharasch, MD, PhD, associate professor of Anesthesiology and Medicinal Chemistry (adjunct), Department of Anesthesiology, University of Washington, Seattle, Washington, on March 17, 1997.)

In a soon to be published paper, a multicenter randomized investigation was done to investigate, using sensitive markers of renal tubular injury, the renal effects of sevoflurane during low flow anesthesia (1 L/min).\textsuperscript{15} Of the 73 patients investigated, (all with normal preoperative renal function), 36 received sevoflurane and 37 isoflurane for an average time period of 3.8 hours. Conditions were chosen to maximize Compound A exposure. There were no significant differences between sevoflurane or the isoflurane groups in postoperative standard renal function tests or urinary excretion of sensitive markers of renal tubular toxicity. There was no significant correlation between Compound A exposure and urine excretion of protein, glucose, NAG, $\alpha$GST, or $\pi$GST in the sevoflurane patients. These results suggest that moderate duration low flow sevoflurane anesthesia was as safe as low flow isoflurane.\textsuperscript{15}

Sevoflurane was evaluated in renally impaired patients with baseline serum creatinine equal to or greater than 1.5 mg/dL. Comparisons were made between patients who received enflurane, isoflurane, and sevoflurane. Postanesthesia creatinine levels increased in 7% of patients who received sevoflurane, 8% of patients who received isoflurane, and 10% of patients who received enflurane.\textsuperscript{9,12} Because of the small numbers of patients with renal insufficiency studied, the safety of sevoflurane administration in this class of patients has not been fully established. Therefore, Abbott Laboratories advises that sevoflurane should be used with caution in patients with renal insufficiency.\textsuperscript{12}

**Cost comparison of inhaled anesthetics**

The Veterans Health Administration (VHA)
has developed and is implementing a new approach to the healthcare of veterans. Managed care within integrated delivery systems will become the most common mode of healthcare delivery in the United States. The VHA had and will continue to uphold its long tradition of putting the patient's welfare first. However, the VHA has an obligation to ensure that taxpayer monies are well spent and that it is getting the best possible healthcare return on its resources. There is now an emphasis on reducing operating costs by increasing outpatient care, which includes ambulatory surgical facilities that compare with those of private hospitals. Individual departments are encouraged to reduce costs by reviewing products and obtaining competitive bids from various companies. With cost reductions in mind, why then would we request an agent that, on first glance, seems to be more expensive?

In a recent cost analysis, the comparable maintenance drug cost was similar for isoflurane, desflurane, and sevoflurane for surgeries lasting up to 1 hour. In addition, the drug costs of anesthesia were dwarfed by labor costs; total anesthetic drug cost continues to be a very small component in the overall surgical costs.

Several factors may be responsible for comparable costs between these inhaled anesthetics. Although the MAC for sevoflurane and desflurane is greater than that for isoflurane, the low solubility of the new anesthetics reduces anesthetic consumption such that cost does not increase to the degree that might be assumed based on potency alone. For example, the rate at which the ratio of delivered anesthetic concentration and the alveolar concentration approach a value of 1.0 is fourfold more rapid with sevoflurane than isoflurane for a given FGF of 2 L/min. To attempt to achieve greater depth rapidly with isoflurane, the FGF must be increased or the delivered concentration must be greatly increased; both of these actions increase anesthetic use and cost. This is the reason cost cannot be estimated for a new anesthetic agent solely on a dollar amount per bottle.

Cost comparison of various inhaled anesthetics is complicated because multiple factors are involved. Important factors that help dictate the cost include the following:

1. Patient-specific uptake and distribution of inhaled anesthetics, which is highly contingent on solubility of the inhaled anesthetics.
2. The MAC values of the inhaled anesthetic.
3. The cost per milliliter of liquid anesthetic.
4. The number of milliliters of anesthetic vapor generated by one milliliter of anesthetic liquid.
5. The duration of the case.

6. The FGF rate (Table I).

To compare costs of three inhaled anesthetics, we developed a simple model based solely on vaporizer dial settings, and we disregarded patient-specific uptake and distribution. The anesthetic cost for any inhaled anesthetic at specific dial settings, FGF rates, and time periods can be calculated using the milliliters of vapor per milliliter liquid equation, the volumes percent equation, and the cost per milliliter of liquid anesthetic.

### Table I

<table>
<thead>
<tr>
<th>Inhaled Anesthetic</th>
<th>Liquid per Bottle</th>
<th>VA Cost per Milliliter Liquid</th>
<th>Milliliter Vapor per 1 mL Liquid</th>
<th>MAC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane</td>
<td>100 mL</td>
<td>$20.76</td>
<td>200 mL</td>
<td>1.15</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>250 mL</td>
<td>$134.23</td>
<td>184 mL</td>
<td>2.00</td>
</tr>
<tr>
<td>Desflurane</td>
<td>240 mL</td>
<td>$52.83</td>
<td>215 mL</td>
<td>6.00</td>
</tr>
<tr>
<td>VA = Veterans Affairs</td>
<td></td>
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<tr>
<td>MAC = Minimum alveolar concentration</td>
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</table>

*Milliliters vapor at 37°C/mL liquid = Specific gravity \times 22,400 \times (273 + °C) 
Molecular weight \times (273)

Table II shows the cost per hour to flow 2 L/min through vaporizers with the following dial settings: 1.15% isoflurane, 2.0% sevoflurane, and 6.0% desflurane. Although desflurane is accepted and widely used within the VA hospital system, Table II shows that sevoflurane is slightly less expensive. Desflurane requires an expensive, electrically heated, pressurized vaporizer, whereas sevoflurane uses a relatively inexpensive variable-bypass vaporizer for delivery. Now, however, vaporizer cost is not a factor when comparing costs of inhaled anesthetics because both Abbott Laboratories and

### Table II

<table>
<thead>
<tr>
<th>Inhaled Anesthetic</th>
<th>Vaporizer Dial Setting</th>
<th>Milliliters Vapor Entrained during 1 Minute</th>
<th>Milliliters Vapor Entrained during 1 Hour</th>
<th>Milliliters Anesthetic Used During 1 Hour</th>
<th>Cost per Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane</td>
<td>1.15</td>
<td>23.2 mL</td>
<td>1,392 mL</td>
<td>7 mL</td>
<td>$1.47</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>2.00</td>
<td>40.8 mL</td>
<td>2,448 mL</td>
<td>13.3 mL</td>
<td>$7.14</td>
</tr>
<tr>
<td>Desflurane</td>
<td>6.00</td>
<td>128 mL</td>
<td>7,680 mL</td>
<td>35.7 mL</td>
<td>$7.85</td>
</tr>
</tbody>
</table>

*Volume\% = \frac{\text{Vapor flow rate}}{\text{Fresh gas flow rate} + \text{vapor flow rate}} \times 100%
Ohmeda (Madison, Wisconsin) provide complimentary vaporizers for use with the drugs.

One of the anesthetic methods we currently use with desflurane that has proven beneficial to the patient and is economical is the "sandwich technique." After the intravenous induction, desflurane is used to quickly anesthetize the patient, then we change to isoflurane for maintenance of the inhalation anesthetic because many of our inhalation cases exceed 2 to 3 hours. Approximately 20 minutes before the conclusion of the case, we change back to desflurane. The patient has received the benefits of both agents, promptly awakens, and we have used our resources prudently.

We recommend the use of the "sevoflurane sandwich" for long cases to provide our patients with the positive benefits of sevoflurane and to contain costs. By using sevoflurane as depicted in Figure 1, the anesthesia provider could certainly minimize costs while gaining positive benefits such as its lack of respiratory irritation, early extubation, and rapid recovery of cognitive and motor functions.

Summary

Higher anesthetic drug costs should be acceptable if they are offset by better patient outcome and by reduction of overall hospital costs. The following objective evidence supports the use of sevoflurane for the VA patient population:

- Has a nonpungent odor, is nonirritating to the respiratory tract, and is effective in reversing bronchospasm.
- Can be used as an induction agent.
- Provides a more stable heart rate than desflurane or isoflurane.
- VA neurocirculatory study concludes sevoflurane more stable than desflurane and isoflurane.
- Is as safe and efficacious as isoflurane and has a lower incidence of postanesthesia nausea and vomiting in the elderly.
- More rapid emergence and recovery than isoflurane for patients aged 65 years or older.
- Hepatic and renal safety.
- Less expensive than desflurane, as suggested by the proposed model.
- Delivered by a simple variable-bypass vaporizer that has a long record of safety.

REFERENCES

AUTHORS

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ACKNOWLEDGMENTS

The authors would like to thank George R. Wells III, DMD, MD, for his assistance and encouragement, and they are also grateful to Tonya Mitchell for her invaluable clerical assistance.