Special Article

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Controversies with new inhaled anesthetics

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Kinetic profiles of many new anesthetic drugs permit a more rapid and precise adjustment of effect, including a more rapid recovery of normal function. Sevoflurane and desflurane fit this mold. These newest inhaled anesthetics differ kinetically from isoflurane and halothane because of their lower solubility in blood (table I)[1-4], a feature produced by halogenation solely with fluorine [CHF_2-O-CHF-CF_3 (desflurane); CH_2F-OCH-$(CF_3)_2$ (sevoflurane)]. Tissue/gas partition coefficients approximately double from desflurane to sevoflurane to isoflurane to halothane (table I).

Comparison of the properties of isoflurane and desflurane illustrates the effect of substitution of fluorine for chlorine. Desflurane differs from isoflurane (CHF_2-O-CHCI-CF_3) only by a fluorine for chlorine substitution. This substitution increases vapor pressure at room temperature (240 mm Hg for isoflurane and 670 mm Hg for desflurane) and decreases potency (MAC for sevoflurane in middle-aged patients is 2%; for desflurane it is 6%, five times the value of 1.15% for isoflurane). MAC-Awake (the concentration permitting voluntary response to command in 50% of patients) is a third of MAC for desflurane and sevoflurane[5,6], as well as for isoflurane[7]. This finding is important because MAC-Awake may indicate the concentration providing amnesia in most patients. Such data suggest that desflurane and sevoflurane are potent amnesic drugs.

The lower solubility of desflurane and sevoflurane indicates a more rapid rate of rise of the alveolar concentration towards the concentration inspired. Several results confirm this prediction (figure 1)[8,9]. In the case of sevoflurane, the rapidity of change correctly implies a rapidity of induction of anesthesia. Sevoflurane has replaced halothane for induction of anesthesia in children in many practices. However, despite its lower solubility and an absence of pungency, sevoflurane is not readily distinguished from halothane in rapidity of induct[illegible]. In contrast to sevoflurane, the pungency of desflurane results in respiratory tract irritation and coughing, breathholding and laryngospasm, particularly at concentrations exceeding 6%. These responses limit desflurane's usefulness as an induction agent, and desflurane is not recommended for this purpose, especially in children.

Once induction is complete, the effect of pungency on clinical practice appears to be minor or non-existent. During maintenance, the concentration of desflurane or sevoflurane can be rapidly adjusted to meet changing clinical needs. Furthermore, the difference between the inspired and alveolar concentrations is relatively small, and the inspired concen-

Table 1. Human blood/gas and tissue/gas partition coefficients (mean ± SD)[1-4]

Tissue	Desflurane	Sevoflurane	Isoflurane	Halothane
Blood	0.42 ± 0.02	0.69 ± 0.05	1.46 ± 0.09	2.54 ± 0.18
Brain	0.54 ± 0.02	1.2 ± 0.1	2.1 ± 0.1	4.8 ± 0.4
Heart	0.54 ± 0.07	1.2 ± 0.1	2.2 ± 0.3	4.6 ± 0.8
Liver	0.55 ± 0.06	1.2 ± 0.2	2.3 ± 0.3	5.1 ± 0.7
Kidney	0.40 ± 0.05	0.78 ± 0.12	1.4 ± 0.2	2.8 ± 0.5
Muscle	0.94 ± 0.35	2.4 ± 1.0	4.4 ± 2.0	9.5 ± 4.6
Fat	12 ± 2	34 ± 6	64 ± 12	136 ± 33

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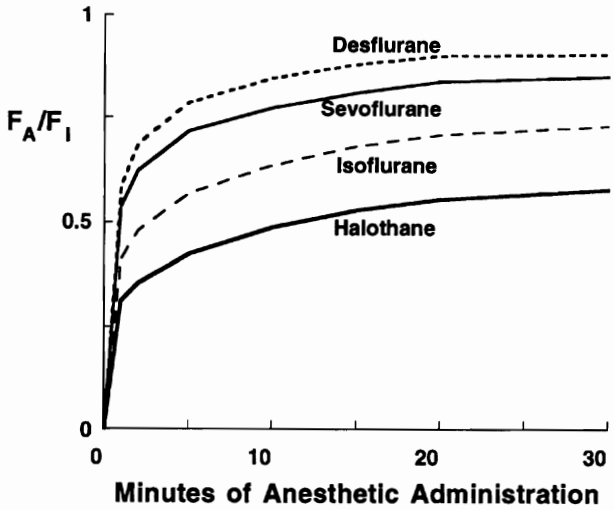

Figure 1. The alveolar concentration (FA) rises to the inspired concentration (FI) at a rate inversely related to the solubility of the anesthetic in blood[8,9] except that the rate of rise in the case of nitrous oxide also is accelerated by the concentration effect. Reproduced with permission from Eger[11].

tration may be used as a surrogate of the alveolar concentration. In turn, given a modest inflow rate (1 L/min or greater), the difference between the concentration delivered from the vaporizer and that in inspired gas becomes small (presently, however, sevoflurane is not recommended for use at flow rates less than 2 L/min). Thus, the alveolar concentration and the level of anesthesia may be controlled and known if one uses an accurately calibrated vaporizer and a modest inflow rate. For more soluble anesthetics, the difference between the concentration delivered and that in the alveoli may be considerable.

As would be predicted from their low solubilities, elimination of anesthetic from the body and recovery from anesthesia during the first 10-20 min after anesthesia is faster with sevoflurane and desflurane than with isoflurane[11-13]. Immediate and longer-term recovery from desflurane is more rapid than recovery from sevoflurane (figure 2)[14]. Regarding stay in the recovery room, a short duration of anesthesia appears to produce limited differences from agents such as isoflurane in long-term recovery[15], but the results of at least three studies suggest a more rapid release after anesthesia with desflurane[16-18]. In contrast, studies to date appear not to show a difference in time to discharge after anesthesia with sevoflurane vs. Isoflurane[19].

To make use of the potential for an earlier release from the recovery room may require the development of new guidelines for the dismissal of patients.

One element of rapid recovery may be less desirable. Children anesthetized with desflurane or sevoflurane for maintenance of anesthesia may awaken with more excitation than with older, more soluble anesthetics. This does not appear to be a problem with adults.

Many other pharmacological characteristics of desflurane and sevoflurane resemble those familiars to the practitioner who administers agents such as isoflurane or halothane. All depress respiration, raising $PaCO_2$ and decreasing the ventilatory response to imposed increases in $PaCO_2$. Like isoflurane, desflurane irritates the respiratory tract (desflurane more than isoflurane), whereas sevoflurane (like halothane) does not. Both compounds can relax bronchial musculature.

Several cardiovascular effects of desflurane and sevoflurane parallel those of isoflurane and halothane. All decrease blood pressure, but not necessarily by the same mechanism. Desflurane, sevoflurane and isoflurane tend to sustain cardiac output, at least in part decreasing blood pressure by decreasing systemic vascular resistance. In contrast, halothane decreases pressure by decreasing cardiac output without affecting systemic vascular resistance. All four agents depress myocardial contractility, halothane the most. Neither agent appears to increase the incidence of untoward outcomes in patients at risk of coronary artery disease[21-23].

Under steady-state conditions in unstimulated adults, sevoflurane and desflurane have similarly minimal effects on heart rate and produce similar

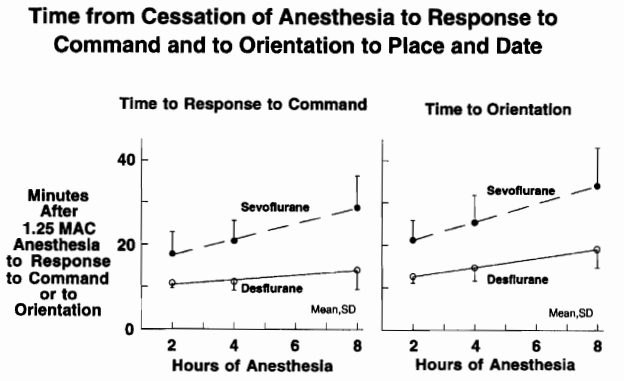

Figure 2. Volunteers anesthetized with desflurane for 2, 4, or 8 hr respond to command sooner and are oriented sooner than the same volunteers after anesthesia with 1.25 MAC sevoflurane[14,20]. Reproduced with permission.

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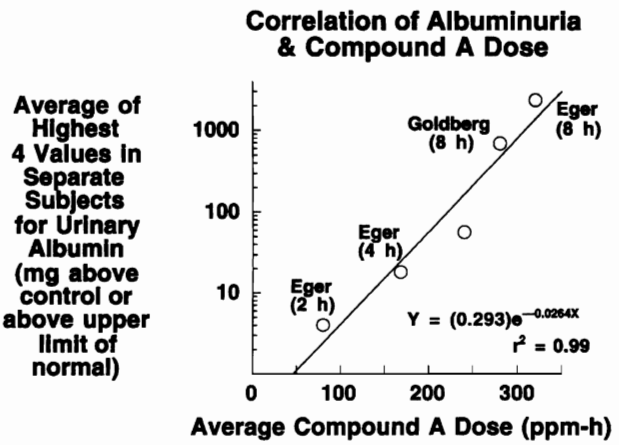

Figure 3. The four highest values for urinary albumin from four separate subjects studied by various investigators for various durations of sevoflurane anesthesia correlate directly with the dose of compound A (ppm-h).

decreases in blood pressure. In addition, desflurane (and to a lesser extent, isoflurane) can transiently (3-6 min) increase both pulse rate and blood pressure when the inspired concentration is rapidly increased above MAC[24-25]. Fentanyl administration may attenuate these transient increases in heart rate and blood pressure[26]. Second and third increases in desflurane concentrations produce only muted increases in rate and pressure (i.e., the response to desflurane rapidly adapts)[27]. In contrast to the capacity of desflurane to increase heart rate and blood pressure, sevoflurane does not increase heart rate or blood pressure when the concentration is acutely increased above 1 MAC.

Ethers such as desflurane, isoflurane, and sevoflurane do not increase sensitivity to the arrhythmogenic effects of exogenously - administered epinephrine whereas the alkane halothane predisposes to arrhythmias[23]. Coronary steal does not appear to occur with either sevoflurane or desflurane although one report suggests that steal is possible with desflurane and isoflurane[29]. This report also suggested that desflurane might have a counterbalancing effect of dilating larger coronary vessels. In at-risk patients, an increase in heart rate and blood pressure may be associated with an increase in myocardial ischemia during induction of anesthesia with desflurane (or any agent)[21]. In the absence of heart rate and pressure increases, no increase in the incidence of ischemia has been reported[22-30]. Desflurane has been used in several hundred patients with coronary artery disease without increasing the incidence of untoward outcomes (e.g., myocardial infarction or death), compared to the incidence with other approaches to anesthesia[21,22,30]. Cardiovascular responses in at-risk patients given sevoflurane appears to be similar to such responses in patients anesthetized with isoflurane[31].

Both desflurane and sevoflurane depress the electroencephalogram in a dose-related manner, neither causing convulsive activity. Both decrease cerebrovascular resistance and can increase intracranial pressure, and do so in a dose-related manner. These effects resemble those of isoflurane.

Both desflurane and sevoflurane cause muscle relaxation sufficient to permit endotracheal intubation or the conduct of intraabdominal procedures. Both enhance the action of muscle relaxants, a desirable effect because the elimination of the inhaled agents should remove the enhancement and thereby assist in the recovery from paralysis, an effect documented with desflurane[32].

Desflurane and sevoflurane differ in their resistance to biodegradation. Desflurane resists biodegradation. Degradation is too small to measure accurately. Approximately 0.02% of the desflurane taken up during its administration can be recovered as urinary metabolites[33]. The metabolism of sevoflurane is approximately 100 times greater[9], slightly exceeding that of enflurane. Inorganic fluoride and trifluoroacetate result from the metabolism of desflurane. Inorganic fluoride and hexafluoroisopropanol result from the metabolism of sevoflurane.

Biodegradation of anesthetics is of concern because of the known connection between degradation and toxicity for several older anesthetics such as chloroform, methoxyflurane, halothane, and possibly enflurane. By this reasoning, desflurane should be minimally toxic, and results from studies in animals and 20 million humans bear out this prediction. Because of its metabolism, sevoflurane is less above suspicion. However, extensive studies in animals and humans reveal minimal evidence of toxicity. Sevoflurane also has been used in 20 million patients with few reports of clinically significant renal injury.

One report found that renal function can be transiently impaired after prolonged sevoflurane anesthesia[34], and on the basis of this and other reports. Mazze and Jamison recommended that sevoflurane not be used in patients with impaired renal function[35]. Goldberg et al. found increases in creatinine and BUN in a few patients anesthetized for longer (approximately 3 hr) intraabdominal procedures with sevoflurane, particularly in association

with higher concentrations of inorganic fluoride[36]. Although comparable patients in this study given isoflurane did not have increases in creatinine or BUN, the results for sevoflurane may be confounded by factors such as the site of surgery and dehydration.

The strength of the carbon-fluorine bond increases physical stability, a fortunate effect because alkali (e.g., soda lime or Baralyme®) degrade sevoflurane, especially at the increased temperatures found in the carbon dioxide absorber needed for closed circuit anesthesia. Were the stability less, sevoflurane might not be clinically useful. In contrast, desflurane resists degradation by standard absorbents (those containing a normal compliment of water) and does so more than its chlorinated analog, isoflurane. Sevoflurane breaks down to a lethal product [CFH_2-O-C(=CF_2)(CF_3), also known as compound A] that in clinical practice[37,38] appears in concentrations associated with injury in rats[37,39,40]. These products raised a concern that through its degradation to compound A, sevoflurane may injure human kidneys[41]. In volunteers, anesthesia with 1.25 MAC sevoflurane for 8 hours can produce average compound A concentrations of 42 ppm and associated transient renal damage as revealed by increases in urinary albumin, glucose and the tubular enzyme a-GST[42]. The same volunteers show no significant abnormalities in these variables when given desflurane for comparable periods and concentrations. More recently we demonstrated that a 4-hr anesthetic with sevoflurane at 1.25 MAC can cause renal injury in volunteers[43]. In contrast, Bito et al.[44] and Kharasch et al.[45] found no difference in the injurious effects of sevoflurane vs. isoflurane in patients. These apparently discrepant findings can be reconciled by the concept of a threshold; our data were obtained at doses of compound A (ppm-hr) that exceeded 150 ppm-hr, whereas Bito et al. applied a dose of 122 ppm-hr and Kharasch et al., a dose of 79 ppm-hr. The implications to clinical practice remain to be determined, but there can be no doubt that sevoflurane, probably through degradation to compound A, can cause dose-related renal injury (figure 3). Recognition of this possibility led to the present package labeling for sevoflurane that warns against its use at fresh gas flow rates of less than 2 L/min. Compound A also is genotoxic[46].

Desiccated absorbents can break down desflurane, enflurane and isoflurane to produce carbon monoxide[47]. Although, sevoflurane degradation produces compound A, it does not produce carbon monoxide. The degradation of desflurane, enflurane and isoflurane to carbon monoxide can be prevented by avoiding the use of desiccated absorbents. Prospective clinical studies of carbon monoxide production do not reveal production with desflurane[48], or with isoflurane or enflurane[49].

There have been reports of hepatic injury after anesthesia with sevoflurane, without establishment of a causal relationship[50-54]. A recent study in children suggested that transient increases in alanine aminotransferase (ALT) can follow sevoflurane anesthesia[55]. Transient mild hepatic injury followed sevoflurane anesthesia in the volunteer study noted above[42], and also appears to have occurred in the patients given sevoflurane in the study by Kharasch et al.[45]. One case of severe hepatic injury has been reported after anesthesia with desflurane[56].

In summary, both desflurane and sevoflurane offer advantages over other modern inhaled anesthetics. Both agents provide a greater precision of control over anesthetic administration, and both permit a significantly more rapid recovery from anesthesia, with desflurane allowing a more rapid recovery than sevoflurane. An absence of pungency recommends the use of sevoflurane for a rapid induction of anesthesia by inhalation, whereas desflurane has a pungency that hinders induction by inhalation, particularly at concentrations exceeding 1 MAC. Both agents little affect heart rate at light levels of anesthesia or at steady- state, but when desflurane concentrations initially are acutely increased above MAC, heart rate and blood pressure transiently increase. Sevoflurane does not produce this effect. Desflurane strongly resists biodegradation and degradation by standard carbon dioxide absorbents, whereas sevoflurane is vulnerable to degradation and thereby may produce renal injury, especially in association with prolonged anesthesia at lower inflow rates. Finally, these new anesthetics can provide anesthesia in the absence of nitrous oxide without compromising recovery from anesthesia.

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