The Clinical Use of Desflurane

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(Submitted October 25, 1993; accepted December 13, 1993)

Desflurane, a newly introduced potent, inhaled anesthetic, differs from its predecessors in having a lower solubility in blood and tissues. The lower solubility imparts a greater control to the maintenance of anesthesia and a more rapid elimination and recovery from anesthesia. In other respects, the pharmacological properties of desflurane resemble those of its sister anesthetic, isoflurane, currently the most widely-used potent anesthetic in this and other countries. The qualitative exceptions to this resemblance are that desflurane is more pungent and produces a greater increase in heart rate, particularly at deeper levels of anesthesia.

The drugs developed for anesthetic purposes in the past decade have focused on the perceived need for a greater control over the anesthetic state, including a need to provide a more rapid recovery from anesthesia. Thus, midazolam has replaced diazepam, propofol is used instead of thiopental, and atracurium and vecuronium have displaced pancuronium. On the horizon beyond these advances are injected drugs with even shorter durations of action, affording even greater control over the anesthetic state. The delivery of inhaled anesthetics may similarly change. Desflurane, recently introduced to clinical practice in the United States, provides a greater control over the maintenance of anesthesia, and a more rapid recovery from anesthesia than previously available inhaled anesthetics.

The mechanisms supplying greater control and more rapid recovery differ among the classes of anesthetic drugs. To achieve these ends, injected drugs depend on a more rapid rate of metabolism, a more limited volume of distribution, and/or a more rapid redistribution. Modern inhaled anesthetics rely on the last two of these means, and both result from lower blood/gas and tissue/blood partition coefficients. Inhaled anesthetic differ from injected agents in the obvious routes of injection and elimination, routes that confir special advantages to the inhaled approach to anesthesia, perhaps particularly to the newer, less soluble inhaled anesthetics. First, elimination via the lungs is always assured and subject to but minimal variation for a given agent. Second, the lungs provide a window to the effective partial pressures imposed on the patient: we can know with precision these partial pressures, either with devices that measure anesthetic concentrations or, in the case of less soluble agents, by the concentration produced by the vaporizer.

Molecular structure and physical characteristics

A lower solubility in blood and tissues is accomplished by halogenation solely with fluorine [1]. Indeed, desflurane is distinguished from its predecessor, isoflurane, by the substitution of a single fluorine for a chlorine on the α-ethyl moiety (Table 1). Before discussing solubility and its impact on kinetics, we will consider the impact of fluorination vs. chlorination on some other physical properties. Fluorination changes boiling point,

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cAbbreviations used: MAC, minimum alveolar concentration required for non-responsiveness to skin incision.
vapor pressure, and stability. The boiling point of desflurane (22.8°C) is much lower than that of isoflurane at 48.5°C. Because the boiling point of desflurane is close to room temperature, conventional plenum (tec-type) vaporizers cannot be used for this agent, and a new vaporizer technology has been developed to permit the administration of desflurane in a manner similar to that familiar to anesthetists using anesthetics such as isoflurane. Thus, the concentration of desflurane delivered from the vaporizer is close to that indicated on the dial, regardless of room temperature or the background gas flow rate, but the manner in which this is accomplished differs from that used for isoflurane.

Fluorination also increases the stability of the molecule, increasing its resistance both to biodegradation (to be considered later) and to breakdown by alkali, such as soda lime or Baralyme. Desflurane is not measurably broken down by soda lime at temperatures of 40° - 60°C, and at 80°C, it is but slightly degraded [2]. In contrast, isoflurane is measurably broken down at 60°C, and, at 80°C, the breakdown equals 12%/hr (Figure 1) [2]. Some anesthetics (e.g., sevoflurane) are broken down at far greater rates. Resistance to breakdown may be desirable for two reasons. First, if the breakdown is sufficient, it may be difficult to administer an adequate level of anesthesia using a low-flow (rebreathing) system. Second, the breakdown products may be toxic, as is the case with the products resulting from the degradation of halothane or sevoflurane [3]. The issue with such products is whether in clinical practice the concentrations produced approach or are far distant from those that can cause injury [4].

Potency

Fluorination also affects potency. Desflurane is one-fifth as potent as is isoflurane (respective MAC values for patients aged 30–60 years are 6.0% and 1.15%) [5, 6]. Although desflurane is less potent than its sister compound, its MAC still permits the administration of high concentrations of oxygen, even in the presence of nitrous oxide.

The MAC of desflurane is affected by the same factors that affect the MAC of other potent anesthetics. MAC is decreased by increasing age (except for a slight increase from the newborn to a few months of life), by decreasing body temperature, and by the administration of other depressant drugs such as nitrous oxide, fentanyl, and midazolam [7].

MAC-awake is the concentration at which 50% of patients or volunteers respond

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| Name                        | Desflurane | Sevoflurane | Isoflurane | Halothane |
|-----------------------------|------------|-------------|------------|-----------|
| Structure                   | CHF₂OCHFCF₃| CH₃FOCH(CF₃)₂| CHF₂OCHCICF₃| CF₂CHClBr |
| Gram Molecular Weight       | 168        | 200         | 184.5      | 197       |
| Specific Gravity (g/mL)     | 1.47       | 1.50        | 1.50       | 1.86      |
| Vapor Pressure (20°C) (mm Hg)| 669        | 160         | 240        | 244       |
| Blood/Gas Part Coef.        | 0.45       | 0.65        | 1.4        | 2.5       |
| MAC (30–60 years)           | 6.0        | 2.0%        | 1.15%      | 0.75%     |
appropriately to command, and for desflurane equals about 2.5% in subjects aged 20–30 years [8]. This is approximately one-third the value for MAC for this age group. MAC-awake is important for two reasons. First, patients will not awaken after cessation of anesthetic administration until the cerebral partial pressure decreases below that equivalent to MAC-awake. Thus, the lower the ratio of MAC-awake to MAC, the longer will be the time to recovery. Second, our studies suggest that MAC-awake is also the concentration (really, a partial pressure because the concentration for both MAC and MAC-awake are defined as a percentage of one atmosphere) that abolishes memory [9]. Thus, desflurane appears to be a potent amnestic anesthetic, one that is twice as potent in this regard as nitrous oxide.

**Uptake and distribution: implications for induction and maintenance of anesthesia and for recovery from anesthesia**

The solubility of desflurane in blood is one-third that of isoflurane (blood/gas partition coefficients, respectively, 0.45 and 1.4), and the value for isoflurane is lower than that for halothane (2.5). Desflurane also has lower lean tissue/blood partition coefficients than either isoflurane or halothane [7]. As a consequence, the rate of rise of the alveolar concentration towards the concentration inspired is more rapid for desflurane than for isoflurane which, in turn, has a more rapid rate of rise than found with halothane (Figure 2) [10, 11]. One might be tempted to predict from this that a patient given the an inspired concentration twice that of the MAC of desflurane would go to sleep more rapidly than if given twice the MAC of halothane. This ignores another factor that influences the induction of anesthesia. Desflurane has a pungency that can cause breathholding, secretions, coughing, and laryngospasm, particularly at inspired concentrations exceeding 6–7%, whereas halothane has little or no pungency and does not evoke such respiratory respons-
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Figure 2. The alveolar anesthetic (FA) rate of rise toward the inspired concentration (FI) is largely determined by the solubility of the anesthetic, being more rapid with less soluble agents such as nitrous oxide and desflurane than with a more soluble agent such as isoflurane. (Modified from the data of Yasuda et al. [10])

In adults, these irritant effects of desflurane do not produce respiratory responses sufficient to lead to oxyhemoglobin desaturation. However, in children, desaturation can occur and desflurane is not recommended for induction of anesthesia in children.

Maintenance of anesthesia requires a control over the alveolar concentration, a capacity to sustain a given level of anesthesia and to rapidly increase or decrease that level in response to changing surgical or patient needs. One measure of the control that can be applied is the difference between the concentration of anesthetic delivered from the vaporizer and the concentration it sustains in the alveoli. The smaller this difference, the greater the control. Several factors affect this difference, including the degree of equilibration of tissues with anesthetic, but among the most important is solubility. Thus, the ratio of the delivered concentration (FD) to the alveolar concentration that might be desired (FA) will be considerably lower (the two values will be closer together) for desflurane than for isoflurane or halothane (Figure 3) [7]. The smaller ratio for desflurane has several implications. One implication is the greater control defined above; a second is that the anesthetist can better rely on the vaporizer setting to indicate the alveolar concentration obtained in the patient, and a third is related to anesthetic cost, a point we will return to later.

As would be predicted from its lower solubility, the elimination of desflurane is more
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Figure 3. The data gathered by Yasuda et al. in volunteers may be used to predict the concentration that must be delivered ($F_D$) from a vaporizer to sustain a constant alveolar concentration ($F_A$). The ratio of the two is inversely proportional to the uptake of the anesthetic. Thus, the difference is greater early in anesthesia and smaller with less soluble anesthetics. At the end of an hour of anesthesia, $F_D$ must be only 10% greater than $F_A$, whereas for isoflurane, a 60% difference is found. The smaller difference for desflurane implies a greater, more predictable control over the level of anesthesia. A smaller difference also decreases cost. (Adapted from Eger [7])

rapid than the elimination of isoflurane or halothane (Figure 4) [10, 11]. These results would suggest that awakening should be quicker with desflurane, and data from studies in animals and humans confirm this suggestion. Patients given desflurane respond to commands about twice as rapidly as patients given isoflurane. This may add to the safety of anesthesia in that a responsive patient may better support the airway. In addition to a more rapid immediate recovery from anesthesia, longer-term recovery is more rapid (Figure 5) [12, 13]. Results for both subjective and objective measures of recovery suggest that patients given desflurane return to normal approximately twice as rapidly as patients given isoflurane. There may also be less shivering and delirium in patients given desflurane, perhaps because they pass through the stages of disinhibition more rapidly [13]. These results suggest that patients given desflurane may be ready for discharge from the post-anesthesia care unit sooner than patients given isoflurane. Although a few studies support this view, others do not, and more definitive studies are needed to determine whether this aspect of desflurane can lead to an earlier discharge, and potentially a lower post-anesthesia care unit cost.

Respiratory effects

Apart from its greater pungency, the respiratory effects of desflurane are similar to
Figure 4. Solubility influences the rate of anesthetic elimination: a lower solubility accelerates elimination. Thus, for desflurane the rate of decrease of the alveolar concentration of anesthetic ($F_A$) from the last alveolar anesthetic concentration obtained during anesthesia ($F_{AO}$) easily outstrips the rate of decrease found with isoflurane. (Adapted from Yasuda et al. [10])

those seen with isoflurane. Both compounds cause a dose-related increase in arterial pCO$_2$ and a decrease in the ventilatory response to imposed increases in pCO$_2$ [14]. Desflurane has been used without difficulty in patients with a history of asthma [7], but studies of desflurane's effect on bronchomotor tone remain to be done.

Circulatory effects

Desflurane and isoflurane similarly affect the circulation, differences between the two being quantitative rather than qualitative. Neither anesthetic predisposes the heart to the arrhythmogenic effect of epinephrine. Both decrease blood pressure by decreasing systemic vascular resistance [15, 16]. Both tend to sustain cardiac output, at least in part by providing sympathetic stimulation. Desflurane produces greater sympathetic stimulation, and this stimulation becomes manifest at concentrations greater than 1 MAC [17]. The result of stimulation may be both a greater tendency to sustain cardiac output and blood pressure, and a greater effect on heart rate. Thus, at concentrations above 1 MAC (but not below 1 MAC), steady-state concentrations of desflurane produce a dose-related increase in heart rate [15]. In addition, again at concentrations exceeding 1 MAC, abrupt increases in the imposed concentration of desflurane can cause transient (2–4 min) increases in heart rate and blood pressure$^d$. Such effects may underlie the transient

$^d$ Weiskoph and Eger, unpublished data.
Figure 5. Recovery of coordination and cognitive function may occur more rapidly after anesthesia with desflurane than after anesthesia with a more soluble anesthetic such as isoflurane. Specifically, results for the digit symbol substitution test (a measure of cognition or judgment) return to normal at about twice the speed with desflurane. (Adapted from Tsai et al. [13])

ischemia seen by Helman et al. in 14% of their patients during induction of anesthesia for coronary artery bypass procedures [18]. Such ischemia has not been seen by other investigators anesthetizing similar patients with desflurane but differing in their approach by the use of opioids as a major part of the induction process [19–21] (Helman et al. [18] did not use opioids). The use of opioids may attenuate or abolish the sympathetic effects of desflurane. Finally, desflurane does not appear to directly dilate coronary blood vessels and does not produce coronary steal in a conventional canine model which can be used to reveal steal by coronary vasodilators such as adenosine [22].

**Neuromuscular effects**

Desflurane produces a dose-related impairment of myoneural transmission and can be used to supply relaxation sufficient for any procedure [23]. Laryngoscopy can be accomplished using the relaxation provided by desflurane. Like isoflurane, desflurane enhances the effect of muscle relaxants. This confers a theoretical safety to the use of relaxants in that when desflurane is eliminated the enhancing effect also is eliminated.

**Effects on the central nervous system**

The electroencephalogram under anesthesia with desflurane resembles that found during anesthesia with isoflurane [24]. Both agents cause an increase in low voltage-fast wave activity at low (sub-MAC) concentrations that changes to higher voltage-slow wave activity at anesthetizing levels with the appearance of burst suppression. At deep levels of
anesthesia (> 1.5 MAC) the burst suppression may become continuous (isoelectric EEG). Desflurane does not produce convulsive activity at any partial pressure or at any level of pCO₂.

Desflurane can cause cerebral vascular dilation, and cerebral blood flow increases if blood pressure is sustained (e.g., by vasopressors) [25]. Cerebral responsiveness to changes in pCO₂ are maintained, even at anesthetizing concentrations of desflurane [26]. At concentrations up to about three-quarters of MAC, desflurane has little effect on intracranial pressure, even in patients with intracranial space-occupying lesions [7]. Higher concentrations can increase intracranial pressures in such patients.

**Malignant hyperthermia**

No cases of malignant hyperthermia have been reported in humans. However, in a swine model, desflurane can trigger malignant hyperthermia [27].

**Metabolism and toxicity**

The substitution of fluorine for chlorine enhances the resistance of desflurane to biodegradation. In patients given 3.1 MAC-hrs of anesthesia, or volunteers given 7.4 MAC-hrs, no measurable increase in serum inorganic fluoride is found [28]. Similarly, urinary inorganic fluoride or organic fluoride changes little or none at all. Measurement of blood and urine does reveal trace amounts of trifluoroacetate after anesthesia with desflurane, but the amounts produced appear to be approximately one-tenth that produced after anesthesia with isoflurane. Metabolism appears to remove 0.02% of the desflurane that is taken up. The metabolism of isoflurane, heretofor the least metabolized of the modern inhaled anesthetics, is ten times greater.

The minimal metabolism of desflurane suggests that it should have little or no toxicity. Results of studies in patients and volunteers support this prediction [7]. No nephrotoxicity or hepatotoxicity have been reported. Studies in animals subjected to prolonged anesthesia and/or deep levels of anesthesia, or anesthesia with concurrent stresses such as enzyme induction and hypoxia, or anesthesia with desflurane repeated several times a week over eight weeks, do not reveal evidence of nephrotoxicity or hepatotoxicity.

The data from studies in humans cover a limited number of subjects. Because the metabolism of desflurane produces trifluoroacetate, and because trifluoroacetate is implicated in the hepatotoxicity of halothane via an allergic phenomenon, it is possible to imagine that desflurane could produce hepatic injury in a rare patient by a similar mechanism. However, this possibility would appear to be vanishingly small. Isoflurane is metabolized to an identical end-product but, if hepatic injury results from isoflurane's metabolism, the incidence appears to be a minute fraction of that which occurs with halothane. Given that isoflurane's metabolism is ten times that of desflurane, the risk with desflurane must be still less or nonexistent.

**Summary**

The modern inhaled anesthetics constituted a remarkable advance over the smelly, sometimes toxic, sometimes flammable compounds available to me in my residency. We have yet to find the ideal inhaled anesthetic. The pungency of desflurane and the capacity of desflurane to increase heart rate are not what we would wish in the ideal agent. However, in terms of solubility and control over the maintenance of anesthesia and recovery from anesthesia, in terms of resistance to biodegradation, desflurane comes close to the ideal.

**ACKNOWLEDGEMENT:** Source of funding for this review was from Ohmeda.
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