

## SEVOFLURANE, DESFLURANE, AND XENON NEW INHALED ANESTHETICS IN VETERINARY MEDICINE

### SEVOFLURANO, DESFLURANO E XENÔNIO NOVOS ANESTÉSICOS INALATÓRIOS EM MEDICINA VETERINÁRIA

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#### - REVIEW -

#### SUMMARY

*Inhalation anesthesia is widely used in veterinary medicine. New inhalation anesthetics that present less untoward effects, are more potent and produce a safe and easily changeable anesthetic plane are desirable over the older agents presently available. In this review some of the physical and chemical aspects of inhalation anesthesia is revisited. Because the agents used in inhalation anesthesia are gases or vapors, the physics of vaporization, delivery and administration of these agents should be understood. The two new inhalation anesthetics sevoflurane and desflurane, and the new anesthetic gas xenon have been used in human beings for some time. In veterinary medicine there is a lack of investigation and reports that assure the safety and clinical aspects of using them in animals. The information available on the use of these new agents in animals is revised in this article.*

**Key words:** *inhalation anesthesia, sevoflurane, desflurane, and xenon.*

#### RESUMO

*A anestesia inalatória é amplamente utilizada em Medicina Veterinária. Novos anestésicos inalatórios que apresentem menos efeitos indesejáveis, que sejam mais potentes e que favoreçam a rápida modificação do plano anestésico com ampla margem de segurança, são desejáveis sobre os fármacos mais antigos disponíveis atualmente. Neste artigo de revisão, os aspectos físicos e químicos da anestesia inalatória foram revistos. Como, em geral, os fármacos anestésicos inalatórios são gases ou vapores, os aspectos físicos da volatilização desses anestésicos, assim como os de sua administração devem ser entendidos. Os dois novos anestésicos inalatórios sevoflurano e desflurano e o novo gás anestésico xenônio têm sido usados em seres humanos já há algum tempo. Em medicina veterinária, ainda existe a necessidade de mais investigação e literatura publicada com*

*relação ao uso clínico e a segurança do uso desses novos fármacos em animais. A literatura disponível sobre o uso desses anestésicos em animais está revisada neste artigo.*

**Palavras-chave:** *anestesia inalatória, sevoflurano, desflurano, xenônio.*

#### INTRODUCTION

Inhalation anesthetics are used widely for the anesthetic management of animals. They are unique among the anesthetic drugs because they are administered, and in large part removed from the body, via the lungs. Their popularity arises in part because their pharmacokinetic characteristics favor predictable and rapid adjustment of anesthetic depth. In addition, a special apparatus is necessary to deliver the inhaled agents. This apparatus includes an oxygen source, and a patient breathing circuit that in turn usually includes an endotracheal tube or a mask, a means of eliminating carbon dioxide, and a compliant gas reservoir. Measurement of inhalation anesthetic concentration enhances the precision and safety of anesthetic management beyond the extent commonly possible with injectable anesthetic agents. Over the nearly 150 years that inhalation anesthesia has been used in clinical practice, less than 20 agents have actually been introduced and approved for general use with patients (Table 1). Less than 10 of these have had any history of

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widespread clinical use in veterinary medicine, and only 5 are of current clinical importance (STEFFEY, 1996). The search for even more pharmacologically perfect inhaled anesthetics did not end with the introduction and widespread use of isoflurane. The exclusion of all halogens except fluorine results in nonflammable liquids that are poorly lipid soluble and extremely resistant to metabolism. Desflurane and sevoflurane (Table 1) are inhalation anesthetics with very low solubility in blood which would facilitate the rapid induction of anesthesia, permit precise control of anesthetic concentrations during maintenance of anesthesia, and favor prompt recovery at the end of anesthesia independent of the duration of administration (STOELTING, 1999).

Table 1 – Inhalation anesthetic agents (Year available for clinical use).

Agents in clinical use	New Agents	Agents of historical interest
Halothane (1956)	Desflurane (1992)	Chloroform (1847)
Isoflurane (1981)	Sevoflurane (1994)	Cyclopropane (1925)
Enflurane (1973)	Xenon (1997)	Diethyl ether (1846)
Methoxyflurane (1960)		Fluroxene (1951)
Nitrous Oxide (1844)		Trichlorethylene (1930)

## PHYSIOCHEMICAL CHARACTERISTICS OF INHALATION ANESTHETICS

The chemical structure of inhalation anesthetic agents and their physical properties are important determinants of their actions and safety of administration. All contemporary inhalation anesthetics are organic compounds except nitrous oxide and xenon (inorganic anesthetic gases). Agents of current interest are classified as aliphatic hydrocarbons (straight or branch chained) or ethers (two organic radicals attached to an atom of oxygen =ROR=). Inhalation anesthetics must be transferred under control from a container to sites of action in the central nervous system. The agent is diluted to an appropriate amount (concentration) and supplied to the respiratory system in a gas/vapor mixture that contains enough O<sub>2</sub> to support life. The chain of events that ensues is influenced by many physical and chemical characteristics that can be quantitatively described (STEFFEY, 1996).

## ABSORPTION AND ELIMINATION OF INHALANT ANESTHETICS

The greater the inhaled concentration (V%), the greater the alveolar anesthetic tension, and therefore the partial pressure (mm Hg) gradient for each vapor or gas, will be (Dalton's law). Consequently,

the greater the inhaled concentration, the more rapidly the inhalant anesthetic will diffuse across the alveoli. Rate of diffusion is directly proportional to the pressure differences at the oral cavity and the alveoli (Fick's law). Rate of diffusion is inversely proportional to molecular size (Graham's law). The upper limit of the inspired concentration of an inhalant agent is determined by the vapor pressure (mm Hg) of that agent, which in turn depends on temperature. The anesthetic delivery system is a major factor in determining the inspired anesthetic concentration. Characteristics of the breathing circuit that are important are volume of the system, amount of rubber or plastic components, amount of fresh gas inflow into the circuit, vaporizer position relative to the circuit (STEFFEY, 1996, STOELTING, 1999).

Minute ventilation directly affects movement of the anesthetic vapor into the alveoli. Increased rate and depth of ventilation will increase the delivery of the anesthetic mixture to the alveoli. Inhalation of volatile anesthetics does not alter the carbon dioxide and water tension in the alveoli, but the volatile anesthetics will displace N<sub>2</sub> and O<sub>2</sub> in the alveoli. The alveolar tension or partial pressure of an inhalant anesthetic will vary with up take by blood and tissues, warming effect of cool gases within the alveoli, and presence of other gases or vapors. Factors that increase the alveolar partial pressure (mm Hg) of an inhalation anesthetic are increased vaporization (V%), increased fresh gas flow (ℓ/min), decreased volume of patient's breathing circuit (ℓ), increased alveolar ventilation (ml/kg/min), decreased dead space (ℓ), decreased blood/gas solubility, decreased cardiac output (ℓ/min), and decreased alveolar-venous anesthetic gradient (STEFFEY, 1996).

Diffusion of an anesthetic gas into the blood is directly proportional to the size of the alveolar surface exposed to the gas. Diffusion is indirectly proportional to the thickness of the alveolar membrane. Diffusion is a physical process determined by solubility coefficient of the gases, molecular weight, pressures gradient from the alveolus and plasma. The partition coefficient (Solubility) is the ratio between the number of the molecules of an anesthetic gas existing in two phases (solvent/gas). It indicates the solubility of an anesthetic gas in a particular tissue, blood or inert material. An inhalant anesthetic with a low numeric partition coefficient will quickly saturate the blood and tissues; thus the induction and recovery times will be rapid. An inhalant anesthetic with a high numeric partition coef-

ficient will be slow to saturate blood and tissues; thus the induction and recovery times will be slow (Table 2) (STOELTING, 1999).

Pulmonary blood flow, the amount of blood flowing through the lungs, will help determine the amount of anesthetic gas uptake from the alveoli. The more blood is exposed to the anesthetic, the more molecules will move into the blood (STEFFEY, 1996).

The amount of anesthetic gas passing into the tissues (tissue absorption) depends on the degree of perfusion of the tissue, and the solubility of the anesthetic gas (solubility coefficient = partition coefficient) in the tissue. Highly perfused tissues receive and absorb the majority of the anesthetic gas taken up from the alveoli. Approximately 75% of the cardiac output perfuses the brain, heart, lungs, liver, kidneys, intestines, and the endocrine glands (6-10% of the body mass). These tissues are the first to reach equilibrium during uptake of an anesthetic gas and the first to de-saturate. Approximately 20% of the cardiac output perfuses the muscles and skin (50% of the body mass). These tissues are the next to reach equilibrium. Approximately 5% of the cardiac output perfuses the adipose tissue (20% of the body mass). Adipose tissue reaches equilibrium slowly (STEFFEY, 1996).

Lipid-rich cells (brain) take up more of an anesthetic gas than do lipid-poor cells. Anesthetic uptake by the brain is directly proportional to the amount of perfusion of the brain cells. Anesthetic uptake of the brain depends on cerebral blood flow, blood-brain barrier, and lipid content of the brain. Anesthetic uptake is the product of three factors: solubility (blood/gas =  $S$ ), cardiac output (CO), and the difference in the anesthetic partial pressure between the alveolus ( $P_A$ ) and venous blood ( $P_V$ ) returning to the lungs. Note that if any of these three factors equals zero, there is no further uptake of anesthetic by blood.  $Uptake = S \times CO \times (P_A -$

$P_V/P_{bar})$   $P_{bar}$  = barometric pressure in mm Hg (STEFFEY, 1996, STOELTING, 1999).

Inhalation anesthetics are not chemically inert. They undergo varying degrees of metabolism (Table 2) primarily in the liver, but also to lesser degree in the lung, kidney, and intestinal tract. The importance of this is twofold. First, in a very limited way with older anesthetics, metabolism may facilitate anesthetic recovery. Second, and more important is the potential for acute and chronic toxicity by intermediary or end-metabolites on kidneys, liver, and reproductive organs (COLLINS 1996, STOELTING 1999).

Anesthetic potency (Potency =  $1 /$  Minimum Alveolar Concentration, or MAC) of an inhaled anesthetic is inversely related to MAC. MAC is defined as the minimum alveolar concentration of an inhalation anesthetic at one atmosphere (760mm Hg) that produces immobility in 50% of subjects exposed to a supramaximal noxious stimulus (EGER II *et al.*, 1988, STEFFEY, 1996).

## DESFLURANE

Desflurane is a fluorinated methyl ethyl ether that differs from isoflurane only by substitution of a fluorine atom for the chlorine atom found on the alpha-ethyl component isoflurane. Fluorination rather than chlorination increases vapor pressure, decreases intermolecular attraction, enhances molecular stability, and decreases potency. The vapor pressure of desflurane exceeds that of isoflurane by a factor of three such that desflurane would boil at normal operating room temperatures. A new vaporizer technology addresses this property, producing a regulated concentration by converting desflurane to a gas (heated and pressurized vaporizer that requires electrical power), which is then blended with diluent fresh gas flow. The only evidence of metabolism of

Table 2 – Physical and chemical properties of inhalation anesthetics.

Anesthetic	(%) Metabolism	Solubility (blood) (37°C)	MAC Ovine	MAC Canine	MAC Feline	MAC Equine	MAC Swine
Methoxyflurane	50	15.00	0.26	0.23	0.23	0.28	0.25
Halothane	20 – 25	2.54	0.97	0.83	0.82	0.89	0.9
Sevoflurane	3.0	0.68	3.3	2.36	2.58	2.31	2.66
Enflurane	2.4	2.00	2.2	2.37	2.20	2.12	2.2
Isoflurane	0.17	1.46	1.58	1.30	1.63	1.31	1.45
Desflurane	0.02	0.42	9.5	7.20	9.79	7.6	8.28-10
Xenon	< 0.004	0.14	N/A	N/A	N/A	N/A	N/A
Nitrous Oxide	0.004	0.47	204	204	150-200	>200	>200

N/A – Not available.

MAC – Minimum alveolar concentration.

desflurane is the presence of measurable concentrations of serum and urinary trifluoroacetate that are one-fifth to one-tenth those produced by the metabolism of isoflurane. The potency of desflurane as reflected by MAC is about fivefold less than isoflurane (Table 2).

Unlike halothane and sevoflurane, desflurane is pungent, making it unlikely that inhalation induction of anesthesia will be feasible or pleasant for the patient. The pungency of desflurane produces airway irritation and an appreciable incidence of salivation, breath holding, coughing, or laryngospasm when >6% inspired desflurane is administered to an awake patient. Carbon monoxide results from degradation of desflurane by the strong base present in carbon dioxide absorbers. Desflurane produces the highest carbon monoxide concentrations, followed by enflurane and isoflurane, whereas amounts produced from halothane and sevoflurane are trivial (Table 2).

Solubility characteristics (blood:gas partition coefficient 0.45) and potency (MAC 6-10%) permit rapid achievement of an alveolar partial pressure necessary for anesthesia followed by prompt awakening when desflurane is discontinued (STOELTING, 1999).

## DESFLURANE IN VETERINARY SPECIES

### Ovine

Desflurane MAC in adult sheep is 9.5% (hemostat application to the coronary band for 60s). Doses above 1.5 MAC cause significant hypotension. Heart rate is not altered increasing desflurane concentration. Mask induction with 18% desflurane is rapid and smooth with recumbency occurring in less than 5 minutes, although in human beings desflurane irritates the laryngeal mucosa and cough and laryngospasm could occur (TINKER, 1992). Regurgitation, struggling or excess salivation does not occur. After discontinuing anesthesia, time to stand is within 5 minutes when desflurane is used alone (LUKASIK *et al.*, 1998b).

### Equine

Desflurane MAC in adult horses is 7.6% (noxious electrical stimulation of oral mucous membrane for 60s). Induction with 18% desflurane with a face mask produces recumbency in 6 minutes. After 100 minutes of anesthesia with 1 MA, time required for sternal recumbency is 6.6 minutes and time to standing is 14.3 minutes. Recovery is uneventful when desflurane is used without other anesthetic drugs (TENDILLO *et al.*, 1997). After induction

with xylazine (1.1mg/kg IV) and ketamine (2.2mg/kg IV) the MAC of desflurane in adult Welsh ponies is 7.0% (electrical stimulus 50 Volts, 5 Hz for 60s applied to the buccal mucosa). Mean time for ponies to stand after cessation of desflurane is 13.3 minutes (0.2mg/kg IV xylazine administered at the end of the anesthetic period). Minimum ataxia is observed (CLARKE *et al.*, 1996b). Desflurane doses above 1.5 MAC after anesthetic induction with 1.1mg/kg IV xylazine and 2.2mg/kg IV ketamine, produces significant hypotension due to myocardium depression (CLARKE *et al.*, 1996c). For castration, surgical anesthesia can be maintained at delivered concentration of 7.9V% desflurane, after premedication with 1.1mg/kg IV xylazine or 0.03mg/kg IM acepromazine and induction with 2.2mg/kg IV ketamine (JONES *et al.*, 1995).

### Canine

The MAC of desflurane for adult Beagles is 10.3V% (supramaximal electrical stimulus) after induction with desflurane 18V% with a facial mask (HAMMOND *et al.*, 1994). There are reports suggesting that MAC for adult Beagles is 7.2V% (tail clamp) after induction with desflurane 20V% (DOOLERY *et al.*, 1988). When 1:1 N<sub>2</sub>O and O<sub>2</sub> is used as carrier gas, the desflurane MAC for adult Beagles is 7.99V% (supramaximal electrical stimulus). Induction with facial mask is rapid (3-6 minutes). Periods of excitement, episodes of second degree AV-block and multifocal ventricular ectopic depolarization are the most common side effects after mask induction. Doses of desflurane of up to 1.5 MAC produce significant decrease in cardiac output and significant increase in systemic vascular resistance. Arterial blood pressures do not change significantly (CLARKE *et al.*, 1996a).

### Feline

In cats induced in a 20% plexiglass chamber with 18V% desflurane, mean time from the start of anesthetic induction until the cat is removed from the chamber is 3.5 minutes, and 6.2 minutes from the start of induction until intubation. The MAC of desflurane in adult cats is 9.79V% (tail clamp). Time to sternal recumbency in cats anesthetized with desflurane alone is less than 4 minutes (McMURPHY & HODGSON, 1995). Desflurane at 1.7 MAC significantly decreases systolic and mean arterial blood pressures. Hypercapnia caused by 1.7 MAC of desflurane significantly increases pulmonary artery pressures. Cardiac index and stroke volumes are not different between 1.3 and 1.7 MAC of desflurane (McMURPHY & HODGSON, 1996).

### Swine

The MAC value for desflurane in pigs is 8.28V% (tail clamp) and 10V% (coronary band clamp). Cardiovascular effects are similar to those of isoflurane. Increasing desflurane concentrations progressively decrease mean blood pressure, stroke volume, and cardiac output. It is a dose-related respiratory depressant comparable to halothane (STEFFEY, 1992).

### SEVOFLURANE

Sevoflurane is a fluorinated methyl isopropyl ether. The vapor pressure of sevoflurane (170 mm Hg) is similar to Enflurane (172 mmHg), permitting delivery of this anesthetic via a conventional unheated vaporizer. The blood:gas partition coefficient of sevoflurane (0.69) resembles that of desflurane (0.42), ensuring prompt induction of anesthesia and recovery after discontinuation of the anesthetic. Sevoflurane is nonpungent, has minimal odor, produces bronchodilatation similar in degree to isoflurane, and causes the least degree of airway irritation among currently available volatile anesthetics. For these reasons, sevoflurane, like halothane, is acceptable for inhalation induction of anesthesia.

Sevoflurane may be 100-fold more vulnerable to metabolism than desflurane. The resulting metabolites include inorganic fluoride (plasma concentrations exceed those that occur after enflurane) and hexafluoroisopropanol. The chemical structure of sevoflurane is such that it cannot undergo metabolism to an acyl halide. Sevoflurane metabolism does not result in the formation of trifluoroacetylated liver proteins and therefore cannot stimulate the formation of antitri-fluoroacetylated protein antibodies. In this regard, sevoflurane differs from halothane, enflurane, isoflurane, and desflurane, all of which are metabolized to reactive acyl halide intermediates with the potential to produce hepatotoxicity as well as cross-sensitivity between drugs. Sevoflurane does not form carbon monoxide on exposure to carbon dioxide absorbents. In contrast to other volatile anesthetics, sevoflurane breaks down in the presence of the strong bases present in carbon dioxide absorbents to form compounds that are toxic in animals (compounds A, B, C, D, and E). The principal degradation product is fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl-ether (compound A). Compound A is a dose-dependent nephrotoxin in rats, causing renal proximal tubular injury. Although this finding is a concern, the levels of these compounds that occur during administration of sevoflurane to patients are far below speculated toxic levels, even when total gas flows are 1 liter/minute (STOELTING, 1999).

Sevoflurane does not appear to increase the arrhythmogenicity of the heart to exogenous epinephrine. Cardiopulmonary depression is dose-related and similar to other inhalation anesthetics. Sevoflurane at 2.5 MAC does not cause electroencephalographic or gross motor evidence of seizure activity in dogs (STEFFEY, 1992).

### SEVOFLURANE IN VETERINARY SPECIES

#### Ovine

In adult sheep induced with sevoflurane 8V% via face mask in 10ℓ/min of O<sub>2</sub>, tracheal intubation is possible after 8 minutes. Sevoflurane MAC is 3.3V% (hemostat application to the coronary band for 60s). After discontinuing sevoflurane anesthesia recovery occurs in less than 7 minutes. Increasing sevoflurane doses from 1.0 to 1.5 to 2.0 MAC, produces significant decrease in mean arterial blood pressure (LUKASIK *et al.*, 1998a).

#### Equine

The MAC of sevoflurane in adult horses is 2.31V% (stimulation of upper oral mucosa with electrical currents of 50Volts, 5 Hz for 60s). Inhalation induction of anesthesia with sevoflurane at 8V% in 10ℓ/minute O<sub>2</sub> flow in horses produces central nervous system excitation, beginning at 2.7 minutes (head movement). At 5.7 minutes slight transient excitation occurs. Recumbency is obtained after 20 minutes. Recovery from anesthesia without sedation occurs in 10 minutes (AIDA *et al.*, 1994). After sedation with 1.1mg/kg IV xylazine, induction of anesthesia with 0.03mg/kg IV diazepam and 2.2mg/kg IV ketamine, and maintenance of anesthesia with sevoflurane at 1.2 MAC for 90 minutes, time to stand is 13.9 minutes and usually the horses show some degree of ataxia (MATHEWS *et al.*, 1998). Respiratory rate is depressed significantly from baseline at 1.0, 1.5, and 2.0 sevoflurane MAC. Respiratory acidosis is produced at 1.0, 1.5, and 2.0 sevoflurane MAC in spontaneously breathing adult horses. Cardiac output, stroke volume, and arterial blood pressures are significantly decreased at 1.0, 1.5, and 2.0 sevoflurane MAC in adult horses (AIDA *et al.*, 1996).

#### Canine

Sevoflurane MAC in adult Beagles is 2.36V% (tail clamp). Increasing vaporizer setting concentrations in stepwise from 0.5 to 2.0 MAC of sevoflurane produces a time to intubation of 5.7 minutes. After 30 minutes of sevoflurane anesthesia, recovery time to standing is 10.4 minutes (JOHNSON

*et al.*, 1998). Sevoflurane anesthesia at 1.5 and 2.0 MAC produce significant increase in heart rate and decrease in systemic cardiovascular resistance, stroke volume and arterial blood pressures. Cardiac index remains constant due to increase in heart rate. At 2.0 MAC of sevoflurane, respiratory depression occurs (decrease in respiratory rate and unchanged tidal volume), resulting in respiratory acidosis (MUTOH *et al.*, 1997, PADDLEFORD, 1999).

### Feline

The MAC of sevoflurane in adult cats is 2.58V% (tail clamp). Sevoflurane decreases respiratory rate at 2.0 MAC, hypercapnia and respiratory acidosis occur. Hypotension occurs at 2.0 MAC (HIKASA *et al.*, 1997).

### XENON

Xenon is an inert gas with many of the characteristics considered important for an ideal inhaled anesthetic. Its MAC is 71% in humans, suggesting that this gas is more potent than nitrous oxide (MAC 104%). It is nonexplosive, nonpungent and odorless, and extremely unreactive and produces only minimal cardiac depression. Unlike other inhalation anesthetics, it is not harmful to the environment because it is prepared by fractional distillation of the atmospheric air. Nitrous Oxide is less potent in animals than in human beings. The MAC for nitrous oxide in animals is close to 200%, leading low decrease in inhalation anesthetic MAC. Because xenon is almost twice as potent than nitrous oxide in human beings, it is fair to speculate that xenon could be used in animals in the same manner that it is in man (i.e. to decrease inhalant MAC and provide intra-operative analgesia). Higher potency of an anesthetic gas could permit a decrease in the inhalant MAC. Production cost is a concern but this disadvantage may be offset to some degree by using low fresh gas flow rates and development of a xenon-recycling system. Xenon has a blood:gas partition coefficient of 0.14%, which is lower than that of other clinically useful anesthetics and even lower than that of nitrous oxide (0.46), sevoflurane (0.69), and desflurane (0.42). Emergence from xenon anesthesia is two to three times faster than that from equal-MAC nitrous oxide plus isoflurane or sevoflurane. A risk of recall would seem to be present but has not been observed in small numbers of patients (STOELTING, 1999).

### CONCLUSIONS

The new inhalation anesthetic drugs will show in the future their usefulness in veterinary

medicine. So far, the number of experimental studies has been small enough that no specific recommendation is achieved. Desflurane has a very low solubility, which may allow faster induction and recovery times, as well as may permit a rapid change in the anesthetic plane when an anesthetic emergency presents or there is an autonomic or central response to a noxious stimulation. In small animals the use of desflurane could become a reality if the costs issues are solved. In horses, a too fast recovery may create a scenario where potential risk for the patient and personal involved presents. Sevoflurane is already in clinical use in small and large animals with some advantages and disadvantages, although without definite advantage over isoflurane. Xenon is still ongoing pre-clinical evaluation in human beings and the production costs are prohibitive for animal use; however, research and animal studies are likely to be done veterinary species such as dogs and cats, and laboratory species such as rats and mice.

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