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## Anesthetic Management of the Horse: Inhalation Anesthesia (31-Jan-2003)

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### Introduction

Management of intermediate and long-term (more than 30 - 60 minutes) anesthetic procedures most commonly involves the use of inhalational anesthetic methods in many species. Over the last 40 years, this has become true also for equine anesthesia. The delivery of anesthetic drugs via the lungs offers some advantages - in part caused by the pharmacokinetics of the volatile agents in clinical practice. Among these advantages, the relatively quick and easy adjustment of anesthetic depth ranks high. Rapid changes in anesthetic delivery and tissue concentrations of volatile anesthetics allow for the anesthetist to quickly react to alterations in organ system functions (central nervous, cardiovascular, and respiratory) and thereby control functionality within physiologic limits. This is even more important when taking clinical conditions and diseased patients into consideration. Furthermore, inhalation anesthesia with the modern volatile anesthetics may produce a relatively short recovery period, a factor of growing interest in the literature of equine anesthesia.

Volatile anesthetics are potent drugs with a relatively low margin of safety (therapeutic index: 2 - 4). They must be used carefully as overdosing may result in severe depression of the cardiopulmonary, central nervous, and other system functions and lead to death. In the past, several surveys on morbidity and mortality rates related to anesthesia - even if not specific to horses - suggested that a major percentage of anesthetic deaths were avoidable [1,2]. Fortunately, a newer and equine specific study (CEPEF-1) does not show similar results [3], but unwanted effects - even though quantitatively reduced with halothane, isoflurane, desflurane, and sevoflurane - can still not be excluded. Therefore, understanding of principles and concepts of inhalational anesthesia in general is crucial to the employment of volatile anesthetics. These topics are considered basic to this chapter and are discussed elsewhere [4-12]. The scope of this chapter is, instead, to provide a focused review of selected topics, namely interactions with carbon dioxide absorbers, mechanism of action of inhaled anesthetics, and use of sevoflurane and desflurane in the equine patient.

### Reactions with CO<sub>2</sub>-absorbers

All volatile anesthetics react with the carbon dioxide absorbers currently used or tested. The degree of reaction varies greatly though, and significant amounts of research have been put forth in order to assess and minimize such reactions. Three types of reactions are of possible concern: Firstly, absorption of volatile anesthetics to components of the carbon dioxide absorbers (silica, polyvinylpyrrolidone; Table 3) may occur. This plays a minor role in the decreased anesthetic concentration leaving the CO<sub>2</sub>-absorber. Secondly, volatile agents containing a difluoromethoxy moiety (CHF<sub>2</sub>, Table 1) may react with the absorber to form carbon monoxide (CO) [13]. With classic soda lime (Table 3), the amount of CO produced decreases in the order: desflurane > enflurane > isoflurane [14]. The clinical significance of such carbon monoxide production is probably low in equine anesthesia, given the large volume of the anesthetic circuit and the high fresh gas flow rates that are commonly used. Even though halothane does not present the above mentioned difluoromethoxy component, Dodam et al., [15] found the carbon monoxide concentration in horse circle rebreathing systems to be higher with halothane (highest at 90 min with 54 ± 33 ppm [parts per million]) than with isoflurane (highest at 90 min with 21 ± 18 ppm). However, this group as well concluded that the detected concentrations were of no clinical significance with either agent. Also, trifluoromethane, a breakdown product of desflurane (and isoflurane) may react with carbon dioxide absorbers to form CO [7]. Thirdly, halothane and more vigorously sevoflurane may react with carbon dioxide absorbers and be degraded to haloalkenes. These substances, mainly BCDFE (2-bromo-2-chloro-1,1-difluoroethylene) from halothane and Compound A (FDVE, fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether) from sevoflurane degradation have been demonstrated to exert nephrotoxic effects in rats [16]. Thresholds for nephrotoxicity for compound A in rats are generally accepted to be within clinically relevant concentrations [17-19]. Other than in rats, thresholds for nephrotoxicity due to compound A have been demonstrated only in non-human primates and lay outside the range of clinically produced exposure [20]. Even though such nephrotoxicity has not been shown in other species to date, the potential for it and the lack of exclusion represents a

possible concern and further investigation in different species is required. However, carbon dioxide absorbers break down sevoflurane to Compound A with decreasing quantities: barium-OH lime > sodium-OH lime > KOH-free sodium-OH lime > calcium-OH lime. Both, carbon monoxide and haloalkene exposure is dependent on the presence of strong alkali (monovalent hydroxides: KOH, NaOH) in the CO<sub>2</sub>-absorber, the fresh gas flow as well as the degree of desiccation and the absorbent temperature [13,14,21]. Absorbers not containing strong alkali degrade halothane and sevoflurane to significantly lesser degrees [13,22,23], resulting in significantly lower haloalkane production (about 10% of that of other absorbers). Clinically, it is impossible to detect decreases in absorber humidity and therefore regular exchange of the absorber in the anesthetic circuit is warranted, even when unused. Several attempts have been made to develop methods for absorber cooling in order to decrease degradation of inhalants. Although cooling does effectively reduce the formation of carbon monoxide and haloalkenes in vitro [24,25], and the addition of dead space reduces absorber temperature in vivo [26], none of these methods has found a clinical application.

### **Mechanism of Action**

The mechanism of action of inhaled anesthetics remains undefined. However, a vast number of recent publications highlight the research effort put forth in an attempt to bring light to this particular topic. A review of the current literature is therefore included here.

Actions on Central Nervous System (Macroscopic) - Inhalant anesthetics act differently at different sites of the central nervous system (CNS). The reticular formation plays an important role in regulation of consciousness and motor activity, and therefore this brainstem region has often been proposed as an important part of anesthetic action of inhalant anesthetics. Generally, inhalant anesthetics cause a decrease in brain activity, but such a decrease in tone at the level of the reticular formation as mechanism for general anesthesia, today, is regarded as an oversimplification. In fact, anesthetics can cause decreases, but also increases or no changes in neuronal transmission, depending on the agent and the anatomical location. Furthermore, there is evidence for alterations in neuronal activity of the cerebral cortex and hippocampus [27], as well as the transmission from the thalamus to certain cortical regions under the influence of inhalant anesthetics [28]. Also at the level of the spinal cord, inhalant anesthetics cause changes in excitatory and inhibitory function of neuronal transmission. More precisely, they alter the dorsal horn mediated responses to noxious and non-noxious stimuli, decrease the activity of spinal motor neurons and decrease tonic descending input.

To date, there is no evidence of peripheral receptor depression involved in the action of inhaled anesthetics. Historically, both main effects of general anesthesia, amnesia and immobility, were thought to be caused by the same mechanism - only at different concentrations, ie., amnesia occurring at lower and immobility at higher concentrations of an anesthetic drug. Today, there is evidence that these two main actions are mediated through different sites of action [29-31]: When comparing different anesthetics in their ratio between concentrations needed to produce amnesia and immobility, respectively, they differ markedly among different drugs, suggesting two different mechanisms or sites of action. Such differential activity has been found also in the horse [32]. Furthermore, the existence of so-called non-immobilizing drugs, ie., drugs that produce amnesia, but not immobility, implies that the site that mediates amnesia is not associated with the production of immobility. These non-immobilizers do not even reduce the requirements for conventional anesthetics to produce immobility (definition of MAC, Minimum Alveolar Concentration) [33]. Furthermore, functional separation of the spinal cord from the brain has been found not to decrease the anesthetic partial pressure required for immobility [34], suggesting that immobility is mediated at the level of the spinal cord [29].

Interruption of Neuronal Transmission (Microscopic) - The sensitivity of single neurons to the actions of anesthetics varies. Some are hypersensitive (inhibition of axonal firing at less than 1 MAC), some sensitive (inhibition at 1 MAC), and some are not sensitive. The understanding is further complicated as inhaled anesthetics may alter the neuronal transmission at several different levels. Axonal inhibition may be achieved at near-clinical concentrations, and even an incomplete inhibition of action potentials may result in a decreased neurotransmitter release at the subsequent synapsis. The degree to which inhaled anesthetics alter axonal transmission seems to be dependent on the impulse frequency of the axon (low frequency transmission is blocked, while higher frequencies are not), the fiber diameter (inversely proportional), and the axonal region (branching points > axons). However, synapses are circa 5 times more sensitive to the inhibitory actions of inhaled anesthetics than axons [35]. Such synaptic inhibition can be on the presynaptic site, decreasing the amount of neurotransmitter release or decreasing the rate of re-uptake from the synaptic cleft, or at the postsynaptic site, altering the binding of neurotransmitter or influencing the ionic conductance changes that follow activation of the postsynaptic receptors. Both, pre- and postsynaptic effects have been found and inhalant anesthetics may increase, decrease or not affect presynaptic neurotransmitter release and the postsynaptic response [36]. The variation of effects depends on the single neurotransmitter, the anesthetic drug, and the anatomical location, but no single neurotransmitter concentration seems to allow for an explanation of the anesthetic state.

**Site of Action (Molecular)** - The differential activity of inhalant anesthetics at several macro- and microscopic locations does not preclude a unitary molecular site of action [36]. Historically this has led to the idea of a unitary theory of narcosis [37]. In fact, despite the wide spectrum of substances that cause anesthesia (inert gases, simple organic and inorganic molecules, haloalkenes, ethers, etc.), there are astonishing correlations between physical properties of the various inhalant anesthetics and their anesthetic activity. The best correlation can be found between anesthetic potency and lipid solubility and is termed Meyer-Overton rule after the two independent discoverers (Hans Horst Meyer 1899 in Marburg, Germany and Charles Ernest Overton 1901 in Zurich, Switzerland) [38]. Accordingly, the product of the anesthetizing partial pressure and the olive oil/gas partition coefficient varies only very little over a 100,000 fold range of anesthetizing partial pressures. Thereby, anesthesia is produced when a sufficient number of molecules (independent of their type) occupy the respective hydrophobic regions in the central nervous system. Since the Meyer-Overton postulates, several apparent exceptions to their rule have been found. Enflurane and isoflurane are structural isomers (Table 1), have similar oil / gas partition coefficients (Table 2), and would therefore be expected to show similar anesthetic potency, but the MAC for isoflurane is only about 62% of that for enflurane (in the horse, Table 4). Secondly, complete halogenation of the end-methyl groups on alkanes and ethers results in decreased anesthetic potency and increased convulsant activities of the compound, despite the respective increase in lipid solubility. Thirdly, the higher n-alkanes in a homologous series do not follow the Meyer-Overton rule [36]. Lastly, the lipophilicity of non-immobilizers would indicate that they produce immobility, but they do not [29]. In 1954, LJ Mullins hypothesized on the basis of the Meyer-Overton rule a possible molecular mechanism of anesthesia, the critical volume hypothesis [39]. Thereby, anesthetic molecules would be absorbed into the lipid bilayer of the cell membrane, cause a volume expansion beyond a critical volume, and obstruct ion channels or change electrical conductance of neurons. In fact, a volume expansion of membranes was found later on, as well as a reversal of anesthetic state with increases in hydrostatic pressure [40]. On the other hand, the increases of anesthetic requirements seen with increased temperature (and consequent increase in membrane volume) clearly contrast this hypothesis, as well as the fact that not all lipid soluble agents produce anesthesia and the non-linearity of the pressure reversal curve for some anesthetics. To date, the critical volume hypothesis is regarded as an oversimplification of the anesthetic state [36].

On the basis of the fact that inhalant anesthetics interrupt neuronal transmission and because this transmission occurs as an ion movement at the level of the neuronal membrane, the latter is commonly thought to be the primary site of action. Possible molecular sites of such membrane interference would be in the non-polar interior of the phospholipid bilayer, in hydrophobic pockets in proteins embedded or outside this bilayer, or at the interface between lipophilic sites and intrinsic membrane proteins. Several theories exist regarding changes in the neuronal membrane conformation (alteration in membrane dimension or physical state) as an attempt to explain anesthetic action, but to date most authors agree that ultimately the action of inhalant anesthetics is on neuronal membrane proteins that permit ion fluxes during membrane excitation [29,30,36,37,41-45]. Nevertheless, it remains unknown whether anesthetic molecules act primarily through an indirect alteration in surrounding lipids or via a second messenger system or directly by binding on channel proteins. Possibly, immobility is mediated by the binding to specific channel proteins (GABA<sub>A</sub> [46], glutamate [45], nicotinic acetylcholine [47] receptors), while amnesia may present with a different, unspecific, underlying molecular mechanism [29].

### **Sevoflurane**

**History** - B M Regan while working for Travenol Laboratories synthesized sevoflurane in 1968. His findings, though, were not published until 1971 [48] and apparent toxic effects (which later were found to be consequences of flawed study design) impeded further development of the compound [49]. Because at that time sevoflurane did not seem promising for release into practice, the rights for this compound first went from Baxter-Travenol to Anaquest (Ohmeda / BOC) and then to Maruishi in Japan for human anesthesia. The Japanese company continued research and development and released sevoflurane in 1990 in Japan. Within three years an estimated one million people received sevoflurane. Abbott subsequently obtained the rights to sevoflurane, continued its development, and finally released sevoflurane in the United States in 1994. The first report of sevoflurane use in horses was published in 1994 by Aida et al., in Japan [50].

**Physico-chemical Properties and Recovery Characteristics** - Some physico-chemical properties of sevoflurane are included in Table 1. Sevoflurane is structurally related to isoflurane and enflurane (Table 1) and consequently shares many of the physico-chemical properties with these agents. The vapor pressure of this inhalant permits use of conventional, temperature-compensated vaporizer technology and, in fact, the vaporizers commercially available are similar to the ones for halothane and isoflurane. Sevoflurane is unstable in most carbon dioxide absorbers, resulting in the production of several compounds. The most prominent of these, Compound A, is a haloalkene with potential for nephrotoxicity (see paragraph on carbon dioxide absorbers). Carbon monoxide production from sevoflurane interaction with carbon dioxide absorbers is not significant [51]. The blood/gas partition coefficient, a measurement of solubility in this particular solvent, of sevoflurane (0.69, see Table 2) is significantly lower than that for halothane or isoflurane. Therefore, other conditions being equal, one would expect anesthetic induction, recovery, and intraoperative modulation of anesthetic depths to be notably faster than

with the other mentioned agents. This potential advantage over older compounds has been confirmed in a number of studies indicating a fast and smooth recovery from sevoflurane anesthesia in adult horses and humans [52-58]. In children, however, several reports describe more postanesthetic agitation with sevoflurane than with halothane [59-61], although Read et al., [62] found no difference in induction and recovery characteristics between isoflurane and sevoflurane when used as the sole anesthetic in foals.

Central Nervous effects - Sevoflurane is less potent than halothane or isoflurane, but more potent than desflurane, nitrous oxide or xenon, as reflected by MAC (Table 4). Sevoflurane, like other volatile anesthetics, produces a dose-related, generalized depression of the central nervous system, as reflected by burst suppression on the EEG, but isoelectric patterns seem to require concentrations exceeding 2 MAC (in dogs and rabbits) [11]. Also, the bispectral index (BIS), a numerical value derived from the EEG to assess CNS depression (not fully validated in Veterinary Medicine), seems to correlate well with delivered sevoflurane doses in dogs [63]. As other volatile anesthetics, sevoflurane causes dose-related decreases in cerebral vascular resistance and metabolic rate [64,65]. It may therefore increase cerebral blood flow (to a lesser degree than halothane [66]) and intracranial pressure to a similar degree as isoflurane, even though the latter can be prevented by hypocapnia [67,68]. In fact, cerebral autoregulation is maintained during sevoflurane anesthesia [69]. Sevoflurane is not seizuregenic [49,65].

Cardiovascular Effects - Sevoflurane induces dose-dependent cardiovascular depression to a degree similar to that of isoflurane, except for an inconsistently reported positive chronotropic effect [11,52,54,57,70-75]. Much of this information derives from experiments with other species but in horses too, sevoflurane decreases cardiac output, systemic vascular resistance, arterial blood pressure and mean pulmonary artery pressure [76]. However, these effects are also affected by anesthetic duration, i.e., arterial blood pressure may increase with anesthesia time [77], as has been reported for halothane [78]. Sevoflurane does not cause arrhythmias of the heart as halothane and the arrhythmogenic epinephrine dose in dogs is similar to that for isoflurane [79].

Respiratory Effects - Sevoflurane induces a dose-dependent respiratory depression to a similar degree as isoflurane [6,80]. Both agents, sevoflurane and isoflurane, cause greater increases in PaCO<sub>2</sub>, decreases in pH and ventilatory response to hypercapnia than does halothane in horses [71,81]. Respiratory rate is lower than with halothane, and minute ventilation decreases [50,52,73,74,82].

Biotransformation - Sevoflurane is metabolized to a moderate extent (5%, Table 5). Very little amounts of the drug is probably lost percutaneously, via surgical incisions, in the urine and feces [83], and the remainder of the total administered dose is exhaled unchanged (as for the other volatile agents). Most published data reflect findings from humans or laboratory species. It is unknown whether or not there are substantial differences in volatile drug metabolism in the horse. However, it is known that the anatomical site for sevoflurane metabolism is the endoplasmic reticulum (ER) of hepatocytes [84]. More specifically, as for other volatile anesthetics, the cytochrome P450 enzyme system represents the major metabolic pathway [85,86]. The 2E1-isoform of cytochrome P450 catalyzes sevoflurane oxidative metabolism to inorganic fluoride (F) and hexafluoroisopropanolol (HFIP, which is then glucuronidated and eliminated via the kidney) in a ratio of 1:1 [87,88]. This metabolic reaction is dose-dependent (MAC-hours) [70,89]. Enzyme induction by pretreatment with phenobarbital [90], phenytoin [91], isoniazid [92], and chronic ethanol administration [93] may enhance sevoflurane defluorination.

Hepatic Effects - Little information is available about direct hepatic effects of sevoflurane. However, splanchnic circulation and with it portal and hepatic arterial blood flow suffers only little from a generalized cardiovascular depression that is assumed to be similar to isoflurane [94]. Despite potential hepatotoxicity of HFIP, fulminant hepatic failure or hepatic necrosis have not been reported with the use of sevoflurane, probably because HFIP is glucuronidated so quickly that it cannot exert toxic action [80,95]. However, hepatic dysfunction as measured, increased serum enzyme levels after sevoflurane occasionally has been suspected in human patients [96,97]. Controlled, prospective studies in humans, on the other hand, did not show significant potential of sevoflurane to produce liver dysfunction [98,99], a result confirmed in one study in horses as well [100].

Renal Effects - Two sevoflurane breakdown products are of potential concern because of their nephrotoxicity: Compound A and inorganic fluoride. The first results mainly from sevoflurane reaction with desiccated, warm (> 40°C) carbon dioxide absorbers containing strong alkali (baralyme > sodalyme). It has been demonstrated to cause renal tubular necrosis in Fischer 344 rats when at concentrations exceeding 50 ppm for three hours [19], which has led the US Food and Drug

Administration (FDA) to recommend the use in human patients for not more than 2 MAC-hours of low-flow anesthesia (at 1L/min fresh gas flow, as of December 1997). In the countries of the European Union, there is no restriction regarding the applied fresh gas flows for management of human patients. Concentrations necessary to produce severe renal injury are inversely related to duration of anesthesia in rats [101]. However, several studies by Bito and Ikeda [102-104] using sodium- and barium hydroxide lime have shown no toxic effects attributable to compound A even after prolonged low-flow anesthesia (up to 18.6 MAC-hours) and the highest compound A concentrations measured in these studies were 30 ppm, 46.5 ppm, and 60.78 ppm, respectively. Goeters et al., [105] found compound A concentrations of up to 57 ppm after two hours of minimal-flow anesthesia (0.5 L/min), but no detectable changes in renal or hepatic function. Conversely, Eger et al., [106] found compound A concentrations of up to 56 ppm after 10 MAC-hours of sevoflurane anesthesia at 2 L/min fresh gas flow. In this study, sevoflurane administration was associated with transient injury to the glomerulus (albuminuria), the proximal tubule (glucosuria, increased urinary alpha-GST), and the distal tubule (increased urinary gamma-GST). No clinical studies of humans demonstrate significant changes in BUN, creatinine, or the ability to concentrate urine after sevoflurane anesthesia when compared to other inhalant anesthetics. This is true also for a study in horses [100]. Inorganic fluoride is another metabolic breakdown product from sevoflurane (table 5), and serum fluoride levels are increased after sevoflurane anesthesia in humans [11,86,95], horses [82,100], and other species [18]. Its nephrotoxicity has not been shown, even at elevated serum concentrations. Nephrotoxicity of increased serum fluoride concentrations seems to be related only to methoxyflurane and, to a lesser degree, to enflurane. Kharasch et al., [107] hypothesized this to be related to the relative lack of intrarenal cytochrome P450 2E1 production of fluoride ions with sevoflurane when compared to methoxyflurane and enflurane. Nephrotoxicity from sevoflurane increased serum fluoride levels is therefore probably not a clinical problem.

Effects on Skeletal Muscles - Sevoflurane produces skeletal muscle relaxation that is comparable to that of isoflurane and enhances neuromuscular block to a similar degree as isoflurane [108,109]. Sevoflurane, as other inhalant anesthetics, can trigger malignant hyperthermia in animal [110] and human patients [111].

Other Effects - Sevoflurane decreases capillary filtration coefficients in the microvascular bed, thereby decreasing the extravasation of fluids into the interstitial space in human patients [112].

## **Desflurane**

History - In the 1960's, RC Terrell at Ohio Medical Products (later Anaquest, today Ohmeda/BOC) synthesized some 700 compounds in the search for a better inhalant anesthetic [113]. Enflurane, introduced into clinical practice in 1973 was compound number I-347 in this series. Isoflurane, its stereoisomer, released in 1981 (compound number I-469), as well as desflurane (compound I-653) were also synthesized in that series. The latter was released only in 1992 as it was initially produced with a hazardous method of synthesis involving elemental fluorine. Almost twenty years passed before a less explosive method involving hydrogen fluoride and antimony pentachloride was developed for the synthesis of desflurane [114].

Physico-chemical Properties and Recovery Characteristics - Desflurane's vapor pressure is the highest among the volatile anesthetics in clinical use and close to normal atmospheric pressure (Table 1). In fact, desflurane boils at room temperature (22.8°C) and, hence, confers special technical problems for its vaporization. Currently, the only vaporizer that produces controllable and predictable concentrations of desflurane is electronically controlled and therefore requires electricity. For a detailed technical description the reader is referred to other literature [114,115] or the manufacturers' website (Datex Ohmeda - Product Portfolio - Tec 6 Plus Vaporizer). The blood/gas partition coefficient for desflurane is very close to that of nitrous oxide (Table 2) and consequently modulation of anesthetic depth should be achieved quickly, and recovery from anesthesia fast [6,114]. Clinical data from human patients seem to confirm this contention [116-118], for example Eger et al., [119] found recovery from desflurane anesthesia to proceed nearly twice as fast than with sevoflurane. The few studies published that mention recovery from desflurane show analogous results for equine use [120]. Horses' recovery from desflurane anesthesia is fast (for example 15 min to standing after 100 minutes of anesthesia), and subjectively rated good to excellent [121].

Desflurane is stable in sodium hydroxide lime unless the latter is dry and temperatures high (60°C) [122], when desflurane is broken down to produce significant amounts of CO [51].

Central Nervous Effects - Desflurane is the least potent among the volatile anesthetics in clinical use (Table 4), and only the gaseous anesthetics have higher MAC values. This confers a notable decrease in inspired oxygen concentration, for example: at 2 MAC (a dose commonly used at the beginning of a clinical anesthetic) the delivered concentration of desflurane lies in the range of 16% (for isoflurane circa 2.6%). Consequently, carrier gas (oxygen) concentration cannot be

higher than 84% (97.4% for isoflurane), and inspired oxygen is decreased by 13.4% with respect to isoflurane anesthesia. This may result in a decrease of arterial oxygen partial pressure (PaO<sub>2</sub>) in the range of 54 - 67 mmHg compared to similar isoflurane anesthesia, a dramatic reduction not always tolerable-particularly in equine clinics. The changes in EEG seen with desflurane anesthesia are similar to those found with isoflurane [123] and are probably the ones associated with anesthesia [80]. Electrical silence is not produced until 1.7 MAC is achieved [123]. Seizuregenicity is not reported with desflurane use [6]. Desflurane, as sevoflurane, can decrease cerebral vascular resistance and cerebral metabolic oxygen requirements and increase intracranial pressure in a dose-dependent fashion [11,80,114]. This has led to the recommendation to use desflurane with caution in patients with decreased intracranial compliance [6,7]. Cerebrovascular autoregulation in response to carbon dioxide is well maintained as with isoflurane [124]. Jones et al. reported desflurane to exert good analgesic effects in horses [125].

Cardiovascular Effects - The circulatory effects of desflurane parallel those of isoflurane [72]. Desflurane decreases blood pressure by decreasing systemic vascular resistance, but tend to preserve cardiac output at clinically used doses [126]. It can, however depress myocardial contractility [126,127]. Desflurane consistently causes increases in heart rate more than the other volatile agents [128]. Studies in horses confirm this effect [129-131]. Chronotropic effects are accentuated by sudden changes in anesthetic delivery, such as induction of anesthesia [114]. Such increases in heart rate may well be caused by sympathetic stimulation and are blunted by administration of opioid or alpha-2 agonist drugs [80]. Desflurane does not cause in itself or predisposes the heart to epinephrine-induced arrhythmias [132].

Respiratory Effects - As the other inhaled anesthetics, desflurane causes dose-dependent respiratory depression. The magnitude in horses seems to parallel or exceed that of isoflurane [72,125,129,130], and is expressed in drastic decreases of respiratory rate, but tidal volume decreases as well, once 1.5 - 2 MAC are reached. In humans, desflurane causes airway irritation with resulting coughing, secretions and breath holding [11,133].

Biotransformation - Only very small amounts of desflurane are metabolized (0.02%, Table 5) [134]. Consequently, in humans [134], rats [135], and pigs [136] little or no increases in serum or urine inorganic or organic fluoride levels has been demonstrated and the trifluoroacetate levels found are only 1/5 - 1/10 of those produce by isoflurane metabolism [11].

Hepatic Effects - As predictable by the minimal biodegradation, the sustained cardiac output and the rapid elimination after anesthesia, desflurane affects liver function minimally or not at all [137]. Furthermore, desflurane seems not to worsen pre-existing liver disease [138]. Studies about hepatic blood flow in swine and dogs have not shown significant decreases in total hepatic blood flow (portal and hepatic arterial), and there is evidence of decreases in portal vascular resistance in normotensive and hypotensive pigs under desflurane anesthesia [139,140]. To assess hepatocellular function in desflurane exposed human patients, Schmidt et al., [141], measured the centrilobularly sensitive alpha glutathione S-transferase and found no changes. Conversely, Steffey et al., found mild, transient increases in aspartate aminotransferase and sorbitol dehydrogenase in horses after desflurane anesthesia, but judged these alterations as clinically unremarkable (as for sevoflurane) [100].

Renal Effects - As for hepatic function, desflurane only minimally affects renal function [142]. This has proved true for human patients [137], rats [143], and dogs [144] and the study done by Steffey et al., suggests similar findings in horses [100]. Both, renal function and blood flow seem unaffected. Consequently, even in patients (human) with pre-existing disease, no worsening of renal function could be detected [138].

Effects on Skeletal Muscles - As the other volatile agents, desflurane causes muscle relaxation, enhances action of neuromuscular blocking agents and may trigger malignant hyperthermia [145,146].

**Table 1. Some Physicochemical Properties of Inhalational Anesthetics Used in Veterinary Medicine.**

Property	Halothane	Methoxy-flurane	Isoflurane	Enflurane	Sevoflurane	Desflurane	Nitrous Oxide	Xenon
Formula	$\begin{array}{c} \text{Br} \text{ F} \\   \quad   \\ \text{H}-\text{C}-\text{C}-\text{F} \\   \quad   \\ \text{Cl} \text{ F} \end{array}$	$\begin{array}{c} \text{Cl} \text{ F} \text{ H} \\   \quad   \quad   \\ \text{H}-\text{C}-\text{C}-\text{O}-\text{C}-\text{H} \\   \quad   \quad   \\ \text{Cl} \text{ F} \text{ H} \end{array}$	$\begin{array}{c} \text{F} \text{ Cl} \text{ F} \\   \quad   \quad   \\ \text{F}-\text{C}-\text{C}-\text{O}-\text{C}-\text{H} \\   \quad   \quad   \\ \text{F} \text{ H} \text{ F} \end{array}$	$\begin{array}{c} \text{Cl} \text{ F} \text{ F} \\   \quad   \quad   \\ \text{H}-\text{C}-\text{C}-\text{O}-\text{C}-\text{H} \\   \quad   \quad   \\ \text{F} \text{ F} \text{ F} \end{array}$	$\begin{array}{c} \text{F} \\   \\ \text{H}-\text{C}-\text{H} \\   \quad   \\ \text{F} \text{ O} \text{ F} \\   \quad   \\ \text{F}-\text{C}-\text{C}-\text{C}-\text{F} \\   \quad   \quad   \\ \text{F} \text{ H} \text{ F} \end{array}$	$\begin{array}{c} \text{F} \text{ H} \text{ F} \\   \quad   \quad   \\ \text{F}-\text{C}-\text{C}-\text{O}-\text{C}-\text{H} \\   \quad   \quad   \\ \text{F} \text{ F} \text{ F} \end{array}$	$\begin{array}{c} \text{N} - \text{N} \\ \diagdown \quad / \\ \text{O} \end{array}$	Xe
Substance Type (Derivative)	Alkane	Methyl Ethyl Ether	Methyl Ethyl Ether	Methyl Ethyl Ether	Methyl Isopropyl Ether	Methyl Ethyl Ether	Inorganic Gas	Noble Gas
Odor	Sweet	Pungent, Ethereal	Pungent, Ethereal	Pungent, Ethereal	None-Sweet	Pungent, Ethereal	None-Sweet	None
Molecular Weight (D)	197	165	185	185	200	168	44	130
Boiling Point (°C, 760mmHg)	50.2	105	48.5	56.5	58.5	22.8	-89	-107.1
Vapor Pressure (mmHg, 20°C)	244	23	240	172	170	669	-	-
Stable in Soda Lime (40°C)	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Reactivity with Metal	Yes	Yes	No	No	No	No	No	No
mL vapor / mL liquid (20°C)	227	206.9	194.7	197.5	182.7	209.7	-	-
Preservatives	Thymol	Hydroxy-toluene	No	No	No	No	No	No

Data from: [4-6,49,70,80,113,114,147-151].

**Table 2. Some Partition Coefficients of Inhalational Anesthetics used in Veterinary Medicine**

	Methoxy-flurane	Halothane	Isoflurane	Enflurane	Sevo-flurane	Desflurane	Nitrous Oxide	Xenon
Blood/gas at 20°C	15	2.54	1.46	2	0.69	0.42	0.47	0.18
Brain/gas at 20°C	20	1.9	1.6	2.7	1.7	1.3	0.5	N.D.
Fat/blood at 37°C	61	62	52	36	55	30	2.3	N.D.
Rubber/gas at 37°C	742	190	49	74	29	19	1.2	F.D.
PVC/gas at 37°C	-	223	114	120	68	35	-	F.D.
Polyethylene/gas at 37°C	118	128	58	2	31	16	-	-
Oil/gas at 37°C	970	224	99	98	55	19	104	20

Data from: [5,6,12,49,83,114,148,152,153].

N.D.: not determined

F.D.: free diffusion through this solvent

Table 3. Chemical Composition of some Carbon Dioxide Absorbents									
CO <sub>2</sub> -Absorbent	Ba(OH) <sub>2</sub> (%)	Ca(OH) <sub>2</sub> (%)	KOH (%)	NaOH (%)	CaCl <sub>2</sub> (%)	CaSO <sub>4</sub> (%)	H <sub>2</sub> O (%)	Silica (%)	Polyvinylpyrrolidone (%)
Barium hydroxide lime	16	64	4.6	-	-	-	14 - 18	-	-
Sodium hydroxide lime (classic)	-	80 - 81	2 - 2.6	1.3 - 3	-	-	14 - 18	0.1	-
Sodium hydroxide lime (KOH-free)	-	81.5	0.003 - 0.005	2 - 2.6	-	-	14 - 18	0.1	-
Calcium hydroxide lime	-	75 - 83	-	-	0.7	0.7	14.5	-	0.7

Data from: [13,14,22,23,114,154]

Table 4. MAC (Minimum Alveolar Concentration,%) of Different Inhalant Anesthetics in the Horse.		
	MAC (%)	Reference
Halothane	0.88	[155]
Methoxyflurane	0.28	[9]
Isoflurane	1.31	[155]
Enflurane	2.12	[155]
Sevoflurane	2.31, 2.84	[50,75]
Desflurane	7.6 (at 600 m elevation), 8.06	[120,121]
Nitrous Oxide	205	[156]
Xenon	ND (119, dog; 71, human)	[157,158]

ND: not determined

Table 5. Degree of Metabolism and Principle Metabolites of Inhalational Anesthetics in Humans			
	Degree of Metabolism * (%)	Mechanism of Metabolism	Principal Metabolites
Halothane	20 - 45	Hepatic Cytochrome P450 (2A6, 2E1, [3A4] □)	- Trifluoroacetic acid - Cl - Br - [chlorotrifluoroethane, chlorodifluoroethene, F] □
Methoxyflurane	50 - 75	Hepatic Cytochrome P450 (2E1, 2B4) Renal Cytochrome P450 (2E1, 2A6, 3A, 1A2, 2C, 2D6)	- Methoxydifluoroacetic acid - Dichloroacetic acid - F - Oxalic acid

	Degree of Metabolism * (%)	Mechanism of Metabolism	Principal Metabolites
Isoflurane	0.2	Hepatic Cytochrome P450 (2E1, 3A)	- Trifluoroacetic acid - Trifluoroacetaldehyde - Trifluoroacetylchloride
Enflurane	2 - 8	Hepatic Cytochrome P450 (2E1)	- Difluoromethoxydifluoroacetic acid - Acetylates - F
Sevoflurane	5	Hepatic Cytochrome P450 (2E1)	- Hexafluoroisopropanolol - F
Desflurane	0.02	Hepatic Cytochrome P450 (2E1, 3A)	- Trifluoroacetic acid - F - CO <sub>2</sub> - Water
Nitrous Oxide	0.004	Intestinal bacteria (E.coli)	- N <sub>2</sub> - Inactivated methionine synthase - Reduced cobalamin (Vit. B12)
Xenon	0	-	-

Data from: [5,83-85,95,107,159-161]

\* : Degree of metabolism includes estimates from recovery of metabolites and estimates from recovery of the unchanged drug

□ : Smaller fonts in italics indicate reductive metabolism

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