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Inhaled Anesthetics in Horses

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Within six months after William T. G. Morton's seminal demonstration in 1846 that diethyl ether could be used to produce "insensibility" during surgery in people, veterinarians were actively experimenting with inhaled anesthesia in animals. Initial anecdotes regarding anesthesia in horses suggested that "a common soap-dish, filled with ether, and held to the animal's nose, was all that was required, and that the sensation was so delightful that it was eagerly inhaled, and that when sufficiently affected, the animal quietly laid down and submitted to whatever was requisite to be done." However, scientific study quickly revealed a very different story; inhaled anesthetics were associated with violent and traumatic anesthetic inductions and recoveries as well as a high incidence of cardiovascular and respiratory system depression or arrest.¹ Today, inhaled agents comprise a very useful class of anesthetic drugs, but equid size, behavior, and physiology continue to contribute significant risks and challenges to inhalation anesthesia in horses relative to other species.²

Inhaled Anesthetic Agents

Historically, a diverse array of volatile hydrocarbons have been used to produce general anesthesia in horses, including alkanes, alkenes, and ethers. Due to concerns about flammability, metabolic byproducts, toxicity, and/or arrhythmogenic side-effects from older agents, modern inhalation anesthetic practice in North America now principally utilizes three halogenated ether anesthetic derivatives: isoflurane, sevoflurane, and to a lesser degree desflurane (Figure 1).

There are several commonalities to all three modern agents (Table 1). All are clear, colorless, and liquid (desflurane scarcely so) at a room temperature of 20°C with a sweet-to-mildly pungent odor that is somewhat reminiscent of ether. Agents are also sufficiently halogenated such that flammability is restricted to a concentration range that is approximately 3-to-6 times the minimum alveolar concentration (MAC, a measure of the anesthetic EC₅₀); hence, they are non-flammable under clinical conditions. Administration in horses typically utilizes an agent-specific, out-of-circuit vaporizer that achieves desired drug concentrations through dilution of a saturated anesthetic vapor within a carrier gas

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comprised of oxygen or a mixture of air-oxygen or helium-oxygen. Anesthetic gas mixtures are delivered via a common gas outlet to a standard large animal (>150 kg horses) or small animal (<150 kg horses) circle breathing circuit, and excess volume is relieved through an adjustable pressure limiting valve. To minimize personnel exposure in the operating room, waste anesthetic gases are scavenged using an activated charcoal canister or exhausted to the outside environment where they may act (albeit trivially) as greenhouse gases and contribute to global warming.³

Isoflurane (Aerrane[®], Attane[®], Forane[®], Isoflo[®])

Isoflurane is the most widely used volatile inhaled anesthetic in equine anesthesia, in part because it is also the least expensive. Isoflurane is the most potent of the three agents, as evidenced by the lowest MAC value of 1.3%, but its greater blood solubility both delays anesthetic equilibration between the alveoli and CNS and delays anesthetic elimination during recovery. The vapor pressure-temperature relationship for isoflurane is almost co-linear with that for halothane; therefore although use of isoflurane-specific vaporizers is recommended, isoflurane can be safely used in clean, empty, and functional halothane vaporizers.⁴

Sevoflurane (Sevoflo[®], Ultane[®])

Sevoflurane is approximately half as potent as isoflurane and correspondingly has a MAC value that is about twice that for isoflurane. Its substantially lower blood solubility predicts faster elimination kinetics compared to isoflurane, although faster anesthetic recovery from sevoflurane may not always be realized in horses due to greater respiratory depression that delays drug washout.⁵

Approximately 2–5% of sevoflurane undergoes hepatic metabolism, far greater than its comparatives, to hexafluoroisopropanol and free fluoride ions; the latter is a potential nephrotoxin. Sevoflurane reacts with certain carbon dioxide absorbents—either with the monovalent bases sodium hydroxide or potassium hydroxide found in “classic” soda lime formulations or with barium hydroxide found in Baralyme—to form a second nephrotoxin, Compound A. Evidence of possible mild renal injury from sevoflurane in horses has only been documented during very prolonged (>10 hours) low-flow techniques,⁶ yet a potential nephrotoxic effect in horses cannot be excluded. Nonetheless, this potential risk can be easily reduced by avoiding carbon dioxide absorbents that contain more reactive bases—NaOH, KOH, Ba(OH)₂—or by using higher fresh gas flows to decrease Compound A concentrations within the circuit.

Sevoflurane also reacts with Lewis acids—such as metal surfaces in anesthetic vaporizers that may contain metal oxides—to produce hydrofluoric acid that can corrode the vaporizer filling port and etch the vaporizer sight glass. A small amount of water (>150ppm) is added as a preservative to some formulations to quench this reaction.⁷ The vapor pressure-temperature relationship for sevoflurane is almost co-linear with that for enflurane; therefore although use of sevoflurane-specific vaporizers is recommended, sevoflurane can be safely used in clean, empty, and functional enflurane vaporizers.

Desflurane (Suprane[®])

Desflurane is the least potent of the three modern volatile anesthetics and has a MAC value that is about 6 times higher than that of isoflurane. Desflurane is also the least soluble agent in blood; consequently horses rapidly awake even following a relatively long four hour maintenance period.⁸ Taken in combination with low lipid (oil) solubility, there is diminished total tissue capacitance for desflurane. Hence, total body drug uptake as ratio of drug potency (MAC) is less for desflurane compared to equipotent doses of either

sevoflurane or isoflurane, and these differences are magnified further over time.⁹ From a pharmacokinetic standpoint, desflurane could be the ideal inhalation anesthetic to facilitate rapid recoveries in large horses after long surgical procedures.

Desflurane (and, to a far lesser degree, isoflurane) can degrade in desiccated soda lime containing monovalent bases (NaOH or KOH) to produce carbon monoxide. In practice, it is unknown whether this poses any real risks to desflurane-anesthetized horses connected to a breathing circuit with low fresh gas flows and dry “classic” soda lime. Partial hydration of the absorbent (as little as 4.8% water in soda lime or 9.7% water in Baralyme) is sufficient to prevent carbon monoxide production.¹⁰ With a horse attached to an anesthetic circle system, large amounts of water condensation from expired gas may be more than adequate to ensure hydration of the CO₂ absorbent.

The boiling point of desflurane is only slightly above room temperature, and so it is not possible to achieve thermocompensation using a flow-over-the-wick variable bypass vaporizer, such as with the Tec 3, Tec 4, Tec 5, and Tec 7 isoflurane or sevoflurane vaporizers. Instead an electronic vaporizer (Tec 6 or Tec 6 Plus) is used to heat desflurane above its boiling point, and the resulting desflurane gas is injected through a variable resistor to achieve a precise and temperature-compensated anesthetic concentration.¹¹ Desflurane must only be used in desflurane-specific vaporizers; misfiling desflurane into conventional vaporizers intended for other agents will produce a lethal anesthetic concentration.¹²

Pharmacokinetics

Pharmacokinetics describe the rates of drug delivery to the anesthetic circuit, pulmonary washin and uptake by the horse, distribution to active sites and other tissues, and metabolism and pulmonary washout. In short, pharmacokinetics describe what the animal does to the drug.

Drug Delivery to the Anesthetic Circuit

An adequate inspired anesthetic concentration requires an adequate circuit anesthetic concentration. Using a semi-closed circle breathing system with an out-of-circuit vaporizer, the rate of anesthetic concentration change in the circuit is a function of the anesthetic concentration and flow rate in the common gas outlet entering the circuit and the rate of anesthetic uptake from the circuit by the patient and anesthetic dissolution or destruction within the anesthetic circuit itself. Setting aside drug uptake and distribution, the anesthetic concentration of an unprimed circuit as a function of time, $C(t)$, during washin is described by the relationship: $C(t) = C_v(1 - e^{-t/\tau})$, where C_v is the vaporizer concentration, t is the washin time, and τ is the time constant.¹³ The time constant is defined as the time required for the circuit concentration to change by about 63.2% of the difference between the starting concentration and the common gas outlet concentration. For example, when a sevoflurane vaporizer is turned to 3% in a circuit initially containing no anesthetic, the sevoflurane concentration after 1 time constant is $0.63 \times (3\% - 0\%)$ and equals 1.90% (Table 2). The duration of the time constant reflects the speed with which the circuit anesthetic

concentrations can be changed; it is calculated as follows: $\tau = \frac{\text{circuit volume}}{\text{fresh gas flowrate}}$.

The volume contained in a large animal breathing circuit is about 50 L, about 7 times larger than a small animal circle system.¹⁴ Large circuit volumes increase τ and buffer against and delay changes to the circuit anesthetic concentration (Table 2). From a practical standpoint, this means that a large animal circuit utilizing control settings typical of a small animal circuit will not achieve sufficient anesthetic concentrations for sometimes an hour or longer (Table 2). Two solutions—often in combination—are used with large animal circuits to

address this problem. First, higher fresh gas flows decrease τ and hasten the rate of rise in the circuit anesthetic concentration. Second, the vaporizer is set far higher than the actual targeted circuit anesthetic concentration, a technique called “overpressuring”, so that this concentration target is reached in fewer time constants (Table 2). An unavoidable consequence of overpressuring is that the concentration of anesthetic indicated by the vaporizer dial may bear little resemblance to (and thus cannot be used to approximate) the concentration of anesthetic within the breathing circuit.

Pulmonary Washin and Uptake

Volatile anesthetics are delivered to the alveoli via the inspired breath. Factors that increase alveolar minute ventilation (such as controlled ventilation) or increase the inspired anesthetic partial pressure (by increasing circuit anesthetic concentration) will increase the alveolar anesthetic partial pressure and the alveolar-to-venous gradient that drives drug diffusion into the blood.

Anesthetic uptake from the lung (U_L) is described by the equation: $U_L = \lambda_{B:G} \cdot Q \cdot \frac{P_A - P_V}{P_B}$, where P_A and P_V are the anesthetic partial pressures in the alveoli and blood, respectively, P_B is barometric pressure (equal to 760 mmHg at sea level), Q is cardiac output, and $\lambda_{B:G}$ is the anesthetic blood:gas partition coefficient.¹⁵ The Ostwald partition coefficient is a distribution constant that describes the ratio of gas molecules between a solvent and gas phase (or between two solvents) at a defined temperature at equilibrium (Figure 2). When $\lambda_{B:G}=1$, equal volumes of blood and gas will contain the same number of anesthetic molecules. Higher $\lambda_{B:G}$ values indicate greater blood solubility; hence many more anesthetic molecules can move into the blood phase without causing as much of an increase in anesthetic concentration (or partial pressure) in the gas phase. Since anesthetics diffuse according to their gas phase partial pressure gradients (not according to liquid phase concentrations), highly blood soluble agents maintain a high alveolar-to-venous partial pressure gradient ($P_A - P_V$) that promotes greater drug uptake. Likewise, greater cardiac output (Q) increases the volume of the blood into which anesthetic can diffuse, resulting in greater drug uptake.

Ventilation-perfusion (V/Q) mismatch and physiologic right-to-left shunts commonly occur in recumbent anesthetized horses, resulting in an increased alveolar-to-arterial oxygen gradient that reflects impaired pulmonary gas exchange function. As with oxygen, physiologic pulmonary shunts also impede anesthetic uptake and cause an alveolar-to-arterial anesthetic gradient; this effect is greater at the beginning of anesthesia (when uptake is normally high) and greater with poorly soluble agents (due to limited capacity of high V/Q lung regions to make up for poor uptake from low V/Q lung regions).^{16,17} Since modern inhaled agents all have relatively low blood solubility, venous admixture in horses at the beginning of anesthesia likely results in an as yet undefined anesthetic gradient in which the alveolar (or end-tidal) anesthetic partial pressure overestimates the arterial and CNS anesthetic partial pressures.

Anesthetic Distribution

Though perhaps counterintuitive, faster anesthetic uptake does not translate into faster anesthetic onset. The vessel rich group (VRG) of tissues that receive high mass-specific blood flow include sites within the central nervous system (CNS) responsible for anesthetic actions.¹⁸ As a result, the partial pressure of anesthetic within the VRG is in delayed equilibrium with the partial pressure of anesthetic in the alveoli. Factors that promote increased anesthetic uptake from the alveoli, namely high cardiac output and high $\lambda_{B:G}$,

oppose the rate of partial pressure increase of anesthetic in the alveoli, and thus delay the partial pressure increase in the CNS.

Volatile anesthetics are taken up by all body tissues at rates proportional to the arterial-to-tissue partial pressure gradient, tissue specific blood flow, and blood:tissue partition coefficient. Equilibration between the alveolar and VRG partial pressures is rapid with modern agents. However, tissues with poor blood flow, such as adipose, may take up drug throughout anesthesia without ever achieving equilibrium with the VRG or alveolar partial pressures. Since these agents are all far more soluble in lipid than in water (Table 1, $\lambda_{\text{oil:gas}} \gg \lambda_{\text{saline:gas}}$), adipose acts as a tremendous anesthetic reservoir. Restated, adipose has a high capacity to dissolve anesthetic while maintaining a high anesthetic partial pressure gradient that promotes further uptake and inter-tissue diffusion away from areas with lower partition coefficients (such as from the heart to the pericardial fat or from the intestine to the omental fat).¹⁹ The amount of anesthetic contained in the adipose reservoir will increase with obesity, anesthetic duration, and agents with a high $\lambda_{\text{oil:gas}}$. These same factors, in turn, will prolong anesthetic washout and recovery time.

Anesthetic Washout and Recovery

Recovery occurs when anesthetic within active sites in the CNS is either eliminated or redistributed to other tissues. Although modern volatile anesthetics are subject to hepatic metabolism to varying extents, this is a comparatively minor route of elimination (even for sevoflurane). The minimum alveolar concentration at which (human) patients awake from anesthesia (MAC-awake or MAC_{AW}) occurs at about 35% of MAC for isoflurane, sevoflurane, or desflurane.²⁰ Thus, even as horses are able to sense and react to their environment, a substantial amount of anesthetic remains and can affect neurologic and motor function during recovery.⁵

The percent clearance (%CI) of an inhaled anesthetic can be expressed as follows:

$\%CI = \frac{V_A}{(\lambda_{B:G} \times Q) + V_A}$, where $\lambda_{B:G}$ is the anesthetic blood gas partition coefficient, Q is cardiac output, and V_A is alveolar minute ventilation.¹⁹ Consequently, washout is hastened by increasing minute ventilation (such as with an oxygen demand valve) in the apneic or hypoventilating horse, although hyperventilation should be avoided since the resulting cerebral vasoconstriction and reduced cerebral blood flow would be counterproductive to anesthetic washout from the CNS. The second method to increase pulmonary clearance is to use anesthetic agents that are more insoluble in blood (such as desflurane versus isoflurane). Additionally, for the three contemporary haloethers, the agents that are less soluble in blood are also less soluble in oil (fat). This means that anesthetic washout and recovery from desflurane will be less affected by obesity or anesthetic time (context sensitivity) compared to isoflurane since adipose capacitance, inter-tissue redistribution, and recirculation is also less.

Pharmacodynamics

Pharmacodynamics address mechanisms of drug action, potency, and biologic effects—both desirable and adverse. In short, pharmacodynamics describe what the drug does to the animal.

Mechanisms of Action

How inhaled anesthetics act to produce anesthesia is presently a mystery.²¹ This drug class has unusual pharmacologic properties. First, inhaled agents can reversibly immobilize not just humans and horses, but all vertebrate and invertebrate animals in which they have yet

been studied. In fact, efficacy is not limited to the animal kingdom, as inhaled anesthetics can even prevent movement in protozoa²² and plants (those with touch-sensitive contractile leaves).²³ Second, most drugs require a specific shape, size, and/or polarity in order to interact with specific cell ligands and produce a pharmacologic effect. Yet there is no conserved structural motif among inhaled anesthetics, which include compounds as diverse as single atoms (xenon),²⁴ short and long chain alcohols,^{25,26} and endogenous byproducts of metabolism (CO₂,²⁷ ammonia,²⁸ and ketones²⁹), in addition to the contemporary and historical conventional agents.

Molecular Sites of Action

Around the turn of the 20th century, Meyer and Overton empirically related increasing oil:gas partition coefficients ($\lambda_{\text{oil:gas}}$) to increasing anesthetic potency (Figure 3). They hypothesized that anesthetics acted in the “fatty substances” in nerve cells: the lipid membrane.³⁰ This was an appealing hypothesis in part because it provided a unitary mechanism that could explain both the diversity in species affected by anesthetics and the diversity of drugs that could produce it. But was it correct? Volatile anesthetics dissolve in lipid bilayers and increase the “fluidity” or disorder in cell membrane, by which it was postulated anesthesia might ensue.³¹ However, temperature effects on lipid membrane fluidity far exceed those produced by dissolution of inhaled agents, and temperature effects on MAC completely contradict those predicted by a membrane fluidity mechanism of action. Increasing body temperature increases membrane fluidity and anesthetic requirement, whereas decreasing body temperature decreases membrane fluidity and MAC.^{26,32} Moreover, some extremely hydrophobic compounds that should exhibit anesthetic potency based on their lipid solubility are actually unable to produce immobility, and are appropriately named “nonimmobilizers.”²¹

These observations do not necessarily exclude a lipid site of anesthetic action. It is possible that distribution within the lipid bilayer is different between compounds that are very hydrophobic and ones that are less so.³³ Anesthetics with greater aqueous affinity concentrate closer to the membrane lipid-water interface and might alter the bilayer pressure profile that proteins must act against as they undergo conformational changes during cell excitation.³⁴ However, the most compelling argument against a lipid molecular mechanism of anesthetic action is that a lipid membrane need not be present to observe anesthetic-like effects. General anesthetics can inhibit enzyme activity of a purified protein, firefly luciferase, in concentrations that parallel *in vivo* anesthetic potency.³⁵ This suggests that proteins, not lipids, are the molecular targets for anesthetic action.

Anesthetics affect the function of many ion channels and receptors that in turn modulate neuronal excitability. In general, volatile anesthetics potentiate inhibitory cell targets such as γ -aminobutyric acid type A (GABA_A) receptors, glycine receptors, and two-pore domain potassium channels; and these same agents also inhibit excitatory cell targets such as N-methyl-D-aspartate (NMDA) receptors, α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, nicotinic receptors, and voltage-gated sodium channels.^{21,25} In many of these proteins, specific mutations at putative anesthetic binding sites alter anesthetic effects on receptor kinetics or ion conductance, and can sometimes render the receptor insensitive to one or more anesthetics altogether. And yet this evidence for specific protein-receptor ligand interactions is inconsistent with the ability for so many chemically unrelated substances to modulate so many phylogenetically unrelated proteins. It is also unclear why the type of pharmacologic effect on a receptor or channel—either potentiation or inhibition—should vary depending on whether the receptor or channel itself is inhibitory or excitatory. How does the anesthetic “know” whether the receptor is inhibitory or excitatory? Finally, the creation of several mutant anesthetic-resistant receptor knock-in or knock-out mice models has so far failed to produce animals resistant to the immobilizing effects of

anesthetics. Perhaps the critical receptor target responsible for inhaled anesthetic actions has yet to be discovered. Or perhaps anesthetic effects on cell receptors are mediated through non-specific anesthetic-protein interactions.

Anatomic Sites of Action

The inhaled agents cause immobility and amnesia, but these distinct endpoints are achieved via actions at different CNS sites. In an experimental goat model in which the cerebral circulation was isolated from the rest of the body, selective brain isoflurane administration more than doubled the anesthetic requirement for immobility compared to whole-body isoflurane administration. This demonstrated that the spinal cord, and not the brain, is principally responsible for preventing movement during surgery with inhaled anesthetics.³⁶ Within the spinal cord, immobility is most likely produced by depression of locomotor neuronal networks located in the ventral horn.³⁷ At sub-anesthetic concentrations, depression of premotor neurons in the spinal cord reduces proprioception,³⁸ and may underlie the incoordination and ataxia commonly observed during inhaled anesthetic recoveries in horses.

In contrast, amnestic effects of inhaled anesthetics are produced by actions within the brain, most probably within the amygdala and hippocampus.³⁹ Lesions created within the amygdala of rats can block amnestic actions of sevoflurane.⁴⁰ On electroencephalography, hippocampal-dependent θ -rhythm frequency slows in proportion to the amnestic effects observed with subanesthetic concentrations of isoflurane in rats.⁴¹ Furthermore, mutant mice lacking the gene encoding either the α_4 or β_3 subunits of GABA_A receptors are resistant to isoflurane depression of hippocampus-dependent learning and memory,^{42,43} and antagonism of α_5 subunit-containing GABA_A receptors restores hippocampal-dependent memory during sevoflurane administration.⁴⁴ Clearly the mechanisms of inhaled anesthetic action responsible for amnesia are different from those responsible for immobility.

Theory: “Willie Sutton Hypothesis”

An infamous bank thief who repeatedly escaped from prisons only to be recaptured each time after committing new heists, Willie Sutton was asked by a newspaper reporter why he still kept robbing banks. His (apocryphal) reply: “Because that’s where the money is.”⁴⁵

Inhaled anesthetics have a large steady-state volume of distribution⁵ and can modulate multiple cell targets to reduce cell excitability throughout the body. Glycine receptors⁴⁶, NMDA receptors⁴⁷, and potassium channels⁴⁸ likely contribute to immobility for the reason that these anesthetic-sensitive receptors are highly expressed within the spinal cord, the anatomical site responsible for immobility. GABA_A receptors likely contribute to amnesia because these anesthetic-sensitive receptors are highly expressed within the amygdala and hippocampus, the sites of memory formation.⁴² Analogous to Willie Sutton, inhalants are agents of opportunity. Anesthetics cause immobility and amnesia by modulating multiple anesthetic-sensitive receptors at these sites, simply put, because that’s where the receptors are.

The ability to modulate multiple receptors and multiple control points within a single receptor may explain how anesthetics that differ in potency or action among receptor types usually exhibit apparently additive—rather than predicted synergistic—effects in combination.^{49,50} Drugs that act principally through a single receptor should be reversible when an antagonist of that receptor is administered, and the antagonist should cause a dose-dependent increase in the anesthetic median effective dose. Although propofol and isoflurane both modulate GABA_A receptors, only propofol exhibits dose-dependent reversal by GABA_A receptor antagonists.⁵¹ Thus GABA_A receptors might contribute to immobility

from isoflurane, but they do not act alone to cause immobility from isoflurane. Finally, the contribution of one receptor type to anesthesia can depend upon the magnitude of contributions from other anesthetic-sensitive receptors. When either GABA_A or glycine receptors are inhibited within the spinal cord, isoflurane or sevoflurane must inhibit more NMDA receptors in order to produce immobility.^{52,53} The sum of inhibition at multiple excitatory targets plus potentiation at multiple inhibitory targets depresses CNS function, and is most probably responsible for what we observe as general anesthesia.

Anesthetic Endpoints and Potency

At a minimum, general anesthesia consists of immobility and amnesia,⁵⁴ but may also include muscle relaxation, autonomic quiescence, analgesia, and unconsciousness. Inhaled agents achieve most of these endpoints, but not at the same anesthetic concentration.

Inhaled anesthetics produce immobility at one minimum alveolar concentration (MAC), which is defined as the mean of the highest end-tidal anesthetic concentration that allows movement and the lowest end-tidal anesthetic that prevents movement in response to a painful stimulus.⁵⁵ Essentially, MAC represents a median effective concentration (EC₅₀) for inhaled agents. MAC is increased by hyperthermia, hyponatremia, and CNS stimulants such as ephedrine. Anesthetic MAC is decreased by hypothermia, hyponatremia, severe hypercapnea or hypoxemia or hypotension, hepatic or renal failure, sepsis, senescence, pregnancy, and by many sedatives and other anesthetics. In contrast to MAC-sparing effects in humans and many animals, opioids have little or no effect on inhaled anesthetic potency in horses at clinically-relevant doses,^{56,57} although opioids at very high doses may actually increase MAC.⁵⁸

The median anesthetic concentration (in humans) at which wakefulness occurs, defined as voluntary responsiveness to commands, occurs around 0.4 times MAC and is defined as MAC-awake.^{59,60} Amnesia occurs at even lower anesthetic concentrations—about 0.3 times MAC.^{61,62} Hence, even though movement may inadvertently occur at a sub-MAC anesthetic plane, horses should not form memories of surgical events so long as the inhalant concentrations are above 0.4-to-0.5 times MAC.

Inhalants also cause dose-dependent muscle relaxation, although profound relaxation using a non-balanced technique requires deep anesthetic planes at which cardiorespiratory side-effects are similarly profound. Though inhalants inhibit nicotinic cholinergic receptors and intracellular calcium release, skeletal muscle relaxation is primarily mediated via spinal actions rather than via direct actions on the muscle itself.⁶³

Autonomic responses to surgical stimuli are manifested clinically by hypertension, tachycardia, and/or tachypnea. This is because peri-MAC anesthetic doses that cause depression of ventral horn spinal neurons and which prevent movement do not affect afferent nerve conduction or dorsal horn input.^{64,65} As with profound muscle relaxation, deep anesthetic planes with inhalants alone produce autonomic quiescence but at severe cost to cardiorespiratory function.

To the extent that they interfere with the motivational-affective dimension of pain,⁶⁶ inhaled anesthetics prevent horses from experiencing pain at concentrations above MAC. Additionally, anesthetic concentrations between 0.8-to-1.0 times MAC decrease (but do not ablate) wind-up and central sensitization and so may help prevent heightened post-operative pain sensitivity; however, higher concentrations of contemporary ether anesthetics offer no further benefit in this regard.^{67,68} Inhaled anesthetic concentrations between 0.4-to-0.8 times MAC decrease withdrawal responses to noxious stimuli, but lower concentrations actually cause hyperalgesia with a peak effect at 0.1 times MAC.^{69,70} This is the result of potent

nicotinic cholinergic receptor inhibition by modern inhaled agents.⁷¹ For horses recovering from anesthesia, low end-tidal inhalant concentrations could enhance post-operative pain and could contribute to poor recovery quality.

It is difficult to define at what anesthetic concentration unconsciousness occurs, in part, because unconsciousness itself is difficult to define. Intuitively, it must occur somewhere over the wide concentration range between MAC-awake and depths that produce an isoelectric EEG.⁷² However, the extent to which a horse experiences consciousness, the types and number of sensory-neural inputs responsible for consciousness, and the perception of consciousness are all undoubtedly different from that of the human experience, such as defined by Descartes: *Cogito ergo sum* (I think, therefore I am). Finally, it may not be possible to definitively test for the presence or absence of consciousness when administering drugs that act via the central nervous system to produce immobility and amnesia.⁵⁴ The study of inhaled agents and consciousness thus remains as much the domain of philosophers as it does anesthesiologists.

Anesthetic Side-Effects

Respiratory

All agents cause dose-dependent hypoventilation. As a species, horses are much more sensitive to the respiratory-depressant effects of volatile anesthetics than are dogs, cats, or humans. Lightly-anesthetized horses at concentrations around MAC commonly have arterial CO₂ tensions >65 mmHg and may require ventilatory support. Isoflurane doses ranging between 1-to-2 times MAC linearly decrease respiratory rate,⁷³ but sevoflurane and desflurane concentrations above 1.5 times MAC may be associated with a high incidence of apnea due to greater respiratory depression.^{74,75} Tidal volume also decreases with dose, and this response is most steep above 1.5 times MAC. Temporal increases in respiratory depression during the first 2 hours of anesthesia parallels reductions in respiratory rate.⁷⁶

As compared to isoflurane, greater respiratory depression from sevoflurane delays anesthetic washout, despite a much lower sevoflurane blood:gas partition coefficient.⁷⁷ In this manner, sevoflurane pharmacodynamics can adversely modify its own pharmacokinetics.⁵

Cardiovascular

All agents cause dose-dependent hypotension (Figure 4). Although the modern ether-type anesthetics are potent vasodilators, reductions in blood pressure above 1 MAC are largely due to dose-dependent decreases in stroke volume and cardiac output.^{73–75} When ventilated to maintain isocapnea, cardiac output is much better preserved between 1.0-to-1.5 times MAC with desflurane and sevoflurane than with isoflurane. However, at concentrations above 1.5 times MAC, cardiac output is significantly higher with desflurane than with either isoflurane or sevoflurane.^{73–75} Desflurane is associated with increased sympathetic tone, particularly following large concentration changes,⁷⁸ which might mask some of the hypotension observed with other agents. During the first 2 hours of anesthesia, at least with isoflurane in horses, there are also time-dependent increases in stroke volume, cardiac output, and blood pressure that may be the result of endogenous β -adrenergic receptor activation.⁷⁹

When anesthesia is induced and maintained using only an inhaled anesthetic, mean blood pressure is often 70 mmHg at light to moderate anesthetic planes (Figure 4). However, when combined with sedative-hypnotics such as α_2 -agonists or acepromazine, hypotension is likely.^{80,81} Since induction and maintenance with an inhalant alone is uncommon (and often impractical) and because horses require higher tissue perfusion pressures for adequate blood flow to dependent muscle having high intracompartmental pressure, a positive

inotrope is often necessary to support a mean arterial pressure above 70 mmHg under clinical conditions.⁸²

Central Nervous System

The brain, cerebrospinal fluid, and cerebral blood volume are contained within the rigid calvarium, and since horses have very high intracranial elastance, even a small uncompensated increase in volume of any of these components causes a large increase in intracranial pressure.⁸³ The difference between mean arterial pressure and intracranial pressure is the cerebral perfusion pressure—the driving pressure for blood flow into the brain. If increased intracranial pressure is not accompanied by similar increases in mean arterial pressure, the cerebral perfusion pressure will decrease, possibly putting the patient at risk for cerebral ischemia.

Intracranial pressure in awake horses remains constant irrespective of head position,⁸⁴ but cerebral vasodilation during inhalant anesthesia causes large increases in intracranial pressure—sometimes similar in magnitude to values seen in severe head trauma patients—that is exacerbated by dorsal recumbency, head-down positioning, hypercapnea during spontaneous ventilation, and anesthetic time during controlled ventilation.^{18,85–87} In many species, inhaled anesthetics interfere with compensatory vasomotor responses to changes in cerebral perfusion pressure, resulting in either uncontrolled excess or inadequate tissue perfusion. Surprisingly, over a wide range of perfusion pressures, isoflurane-anesthetized horses maintain regional cerebral blood flow relatively constant, albeit at a low flow that may still place animals at risk for tissue hypoxia.⁸⁸ Blood flow to the thoracolumbar spinal cord is particularly low, and further reduction may predispose to post-anesthetic myelomalacia in horses.⁸⁹

Visceral Organs

Aside from the formation of potentially nephrotoxic metabolites discussed previously (*vide supra* Sevoflurane), undesirable effects on visceral organs principally arise from decreased cardiac output and blood flow redistribution to other parts of the animal. Without inotropic support, for example, isoflurane in ponies dose-dependently reduces renal perfusion, to the point that blood flow is less than half of awake values at 1.5 times MAC. Blood flow to the small intestine and colon is halved by only 1.1 times MAC isoflurane compared to awake measurements, but higher anesthetic concentrations do not further reduce flow.⁹⁰ What effect such reductions might have in bowel that is already compromised, as in the equine intestinal colic patient, remains unknown. Although hepatic arterial flow is unaffected, dose-dependent reductions in intestinal perfusion by modern ether-type anesthetics causes similar reductions in portal venous and total hepatic blood flow.⁹¹ As a result, inhaled anesthetics can decrease hepatic clearance of many drugs, including other anesthetics.

Conclusion

Inhaled anesthetics provide an effective means to produce immobility, amnesia, and muscle relaxation in horses undergoing surgical and diagnostic procedures. They offer many advantages, including favorable washout kinetics, elimination that is not dependent upon hepatic or renal function, and the ability to indirectly monitor real-time effect-site concentrations by measuring alveolar (end-tidal) anesthetic gas concentrations. At the same time, these agents present several potential challenges in horses, including profound cardiovascular and respiratory depression and the requirement of large-volume anesthetic delivery circuits that slow anesthetic uptake and delay changes to anesthetic inspired concentrations and depth.,

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Synopsis

Inhaled agents represent an important and useful class of drugs for equine anesthesia. This article reviews the ether-type anesthetics in contemporary use, their uptake and elimination, their mechanisms of action, and their desirable and undesirable effects in horses.

Key Points

- The median effective concentration (EC_{50}) for inhaled anesthetics is commonly expressed as the minimum alveolar concentration (MAC).
- Volatile anesthetics with lower blood:gas partition coefficients—such as desflurane—equilibrate partial pressures between the alveoli and CNS more quickly (resulting in a faster drug onset) than anesthetics with higher blood:gas partition coefficients—such as isoflurane.
- Inhaled anesthetics primarily act within the spinal cord (ventral horn) to produce immobility and within the brain (hippocampus and amygdala) to produce amnesia.
- Inhaled agents likely mediate CNS depression through inhibition of multiple excitatory cell receptors and potentiation of multiple inhibitory cell receptors.
- Different anesthetic endpoints (immobility, amnesia, muscle relaxation, autonomic quiescence, analgesia/hyperalgesia) occur at different anesthetic concentrations (MAC multiples).
- All volatile anesthetics cause dose-dependent respiratory depression (hypoventilation) and dose-dependent cardiovascular depression (hypotension).

Diethyl Ether

Isoflurane

Sevoflurane

Desflurane

Figure 1.
Chemical structures of diethyl ether and modern haloether anesthetics.

Figure 2.

Diagram showing the distribution of isoflurane (I) versus desflurane (D) between equal volumes of blood and gas phases within a closed container. Each container has the same number of anesthetic molecules, but there are more isoflurane molecules in the blood than the gas phase compared to desflurane because isoflurane has a higher Ostwald blood:gas partition coefficient ($\lambda_{B:G}$). Restated, isoflurane is more soluble in blood than desflurane.

Figure 3.

Log-log plot of the anesthetic minimum alveolar concentration (MAC) in horses versus the Ostwald oil:gas partition coefficient ($\lambda_{oil:gas}$) at 37°C for six agents.^{15,74,75,77,94,95} The Meyer-Overton hypothesis states that as lipid solubility increases (as reflected by an increased $\lambda_{oil:ga}$), the anesthetic potency also increases (as reflected by a decreased MAC).

Figure 4.

Graph of direct mean arterial blood pressure as a function of anesthetic dose expressed as multiples of minimum alveolar concentration (MAC) for isoflurane, sevoflurane, and desflurane. ENREF 73⁷³⁻⁷⁵

Table 1

Summary of physical, chemical, and pharmacologic properties of contemporary inhaled ether anesthetics in horses.

Property	Isoflurane	Sevoflurane	Desflurane
Molecular Weight (amu)	184.49	200.05	168.04
Specific Gravity (g/mL, 20°C) ⁹²	1.5019	1.5203	1.4651
Vapor Pressure (mmHg, 20°C)	240	160	664
Boiling Point (°C)	48.5	58.5	23.5
Preservative	none	H ₂ O ⁷	none
Stability in CO ₂ Absorbents ⁹³ (breakdown product)	Excellent (carbon monoxide)	Good (compound A)	Excellent (carbon monoxide)
Partition Coefficients (λ) ⁷⁷			
• $\lambda_{\text{oil:gas}}$	98.9	51.3	19.2
• $\lambda_{\text{saline:gas}}$	0.517	0.329	0.287
• $\lambda_{\text{blood:gas}}$	1.13	0.648	0.537
MAC (% atm)	1.31% ⁹⁴	2.84% ⁷⁴	8.06% ⁷⁵

The effect of circuit size, fresh gas flow rate, and vaporizer dial setting on the circuit time constant (τ) and the rate of rise of sevoflurane in an unprimed anesthetic circle breathing system connected to a 150kg foal with a functional residual capacity (FRC) of 6 L. The time constant is defined as the total volume (circuit + FRC) divided by the fresh gas flow rate. The number of time constants ($\# \times \tau$) and the time in minutes to reach a circuit sevoflurane concentration equal to MAC (2.84%) are calculated. For this example, patient anesthetic uptake is not considered. The time to reach a desired anesthetic concentration can be hastened by decreasing circuit volume (using the smallest circuit and breathing bag or ventilator bellows that accommodates the horse's vital capacity), increasing the fresh gas flow rate, and increasing the vaporizer dial setting. Note that the vaporizer dial setting differs greatly from the circuit anesthetic concentration prior to the third time constant.

Table 2

Circuit Volume	7 L	7 L	7 L	7 L	50 L	50 L	50 L	50 L
Circuit + FRC	13 L	13 L	13 L	13 L	56 L	56 L	56 L	56 L
Fresh Gas Flow	2 L/min	2 L/min	6 L/min	6 L/min	2 L/min	2 L/min	6 L/min	6 L/min
Vaporizer Setting	3%	6%	3%	6%	3%	6%	3%	6%
Time Constant (τ)	6.5 min	6.5 min	1.2 min	1.2 min	28 min	28 min	9.3 min	9.3 min
$0 \times \tau$	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %	0.00 %
$1 \times \tau$	1.90 %	3.79 %	1.90 %	3.79 %	1.90 %	3.79 %	1.90 %	3.79 %
$2 \times \tau$	2.59 %	5.19 %	2.59 %	5.19 %	2.59 %	5.19 %	2.59 %	5.19 %
$3 \times \tau$	2.85 %	5.70 %	2.85 %	5.70 %	2.85 %	5.70 %	2.85 %	5.70 %
$4 \times \tau$	2.95 %	5.89 %	2.95 %	5.89 %	2.95 %	5.89 %	2.95 %	5.89 %
$\# \times \tau$ @ 2.84% Sevo	$2.9 \times \tau$	$0.6 \times \tau$	$2.9 \times \tau$	$0.6 \times \tau$	$2.9 \times \tau$	$0.6 \times \tau$	$2.9 \times \tau$	$0.6 \times \tau$
Time to 2.84% Sevo	19 min	4 min	3 min	1 min	82 min	18 min	27 min	6 min