Isoflurane as an inhalational anesthetic agent in clinical practice

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Abstract

Isoflurane is the most recently available inhalational anesthetic agent on the market today. Although there have been few clinical trials comparing its use to halothane and methoxyflurane, the pharmacology of the agent suggests certain situations in which it may be the preferable agent. These include avian anesthesia, geriatric patients, patients with cardiovascular disease or hepatic disease, critically ill and unstable patients, cases such as brachiocephalics where upper airway obstruction is a concern during recovery, patients where increases in intracranial pressure should be avoided, and cesarean section. In addition, the rapid recoveries seen with isoflurane may be an advantage for outpatient surgeries.

Résumé

L'isoflurane comme agent anesthésique volatile en pratique clinique

L'isoflurane est l'agent anesthésique volatile le plus récemment disponible sur le marché. Bien qu'il existe peu d'essais cliniques comparant l'emploi de l'isoflurane à celui de l'halothane ou du méthoxyflurane, les propriétés pharmacologiques de cet agent suggèrent que son emploi serait préférable dans les situations suivantes : lors d'anesthésie chez les oiseaux, chez les patients gériatriques, chez les patients atteints de maladie cardiovasculaire ou hépatique, chez les patients dont la condition est critique et instable, chez les animaux brachycéphaliques susceptibles d'obstruction respiratoire supérieure lors du réveil, chez les animaux dont l'augmentation de la pression intracrânienne est à éviter et enfin, lors de césarienne. De plus, le réveil rapide associé à l'emploi de l'isoflurane peut présenter des avantages pour les chirurgies effectuées chez les patients externes.

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Introduction

Since the 1960's, halothane and methoxyflurane have been widely used as inhalational anesthetic agents in veterinary practice in Canada. Isoflurane, an inhalational agent widely used in human medicine, is currently licensed for use in horses and dogs in Canada. The recent licensing for use in dogs has created a greater awareness of and interest in isoflurane among Canadian veterinarians.

Chemical and physical properties

Isoflurane is a highly stable, non-explosive, potent, and non-flammable volatile anesthetic. It is not affected by light, requires no chemical stabilizers, and does not react with soda lime, metals or rubber. Its use is compatible with nitrous oxide and all currently used injectable preanesthetic and anesthetic drugs.

Isoflurane is a halogenated ether and thus is chemically and structurally similar to methoxyflurane. However, its physical characteristics are more closely related to those of halothane.

The vapor pressure of halothane and isoflurane are almost identical (244.1 mm Hg and 239.5 mm Hg at 20°C respectively), while that of methoxyflurane is much lower (22.8 mm Hg at 20°C). This means that isoflurane and halothane will evaporate to nearly identical vapor concentrations, which are much higher than that of methoxyflurane. This has several clinical implications. The high vapor concentration means that anesthetizing concentrations can be rapidly attained, thereby decreasing the time for anesthetic inductions. This contributes to isoflurane's suitability for mask inductions. However this also means that potentially fatal concentrations can be rapidly attained. Thus, as with halothane, a precision vaporizer must be used to safely administer the drug. It has been shown experimentally that it is possible to use new or recently factory-serviced vaporizers designed and calibrated for halothane administration to deliver isoflurane at clinically acceptable, predictable, and relatively consistent concentrations over a wide range of commonly encountered conditions (1). However, frequently changing anesthetic agents in a vaporizer cannot be recommended, and the potential danger which could arise from confusion over which agent was being administered makes this an unacceptable practice in my opinion.

Solubility of an anesthetic gas in a solvent such as blood or fat is represented by a partition coefficient. This is the ratio between the number of molecules of the gas existing in two phases at equilibrium. Normally

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Table 1. Solvent/gas partition coefficients at 37°C

Solvent:	Isoflurane	Halothane	Methoxy-flurane
Blood	1.4	2.3	12.0
Brain	2.6	6.7	24.2
Liver	3.5	6.0	22.8
Kidney	1.8	3.7	11.2
Muscle	5.2	8.0	16.1
Fat (tissue)	60.0	138.0	635.0
Conductive rubber[a]	62.0	120.0	630.0

[a]Rubber/gas partition coefficient at room temperature

the ratios are standardized at 37°C, with the tissue concentration in the numerator and the gas phase in the denominator (e.g. blood/gas, fat/gas). The larger the partition coefficient, the greater the solubility of the gas in the tissue. Isoflurane has the lowest partition coefficients of all of the commonly used inhalational anesthetic agents (Table 1).

Pharmacokinetics

The clinical importance of partition coefficients lies in their influence on speed of induction and recovery from anesthesia with a given anesthetic agent. If factors such as concentration of the inhaled anesthetic, minute ventilation, pulmonary blood flow and tissue perfusion remain constant, then speed of induction can be related directly to the partition coefficients of the gas being used. An inhalational anesthetic agent with low partition coefficients will quickly saturate the blood and tissues giving rapid induction and recovery times. Conversely, large partition coefficients imply that the anesthetic will be slow to saturate blood and tissues and induction and recovery times will be slow. Thus *isoflurane provides the most rapid induction and recovery times of the volatile anesthetic agents in common use*. This also provides the agent with the most rapid response to decreasing or increasing the inspired concentration during maintenance, allowing for rapid alterations in anesthetic depth as required.

Mask inductions with this agent in dogs and cats take about the same length of time as with halothane. This may be due to the inability to obtain equipotent inhaled concentrations during a mask induction since vaporizers for both agents commonly have a maximum output of 5%. It has been reported that the mild pungency of isoflurane could delay induction by causing struggling and breath-holding. In my experience, this has not occurred when the inspired concentration is gradually increased to the required induction concentration. It has been suggested that the rate of uptake of isoflurane is more rapid than halothane from the alveolar space to the blood but not from the blood to the brain (2). This could also contribute to similar induction times for the two agents.

Recoveries, on the other hand, are more rapid following isoflurane anesthesia than following halothane. This difference is important, since injury to the recovering animal or attendant can occur during extubation if the level of anesthesia lightens more quickly than expected and the animal resists.

The low fat/gas partition coefficient also results in a small reservoir of anesthetic remaining in the fat at the end of anesthesia. This contributes to the very low percentage of metabolism of the total drug administered during an anesthetic procedure.

Anesthetic potency (MAC)

The minimum alveolar concentration (MAC) of an inhalational anesthetic agent is the index most commonly used for comparison of the potency of inhaled anesthetics. It is defined as the minimum alveolar concentration required to prevent purposeful movement in response to a standardized painful stimulus in 50% of a population (3). For inhalational anesthetics, MAC is the standard of equipotency of anesthetic dose. Once the MAC value for an agent is known, clinical usage of the drug becomes easier to understand. Generally an alveolar concentration of 1.2 to 1.4 MAC is required to maintain adequate surgical anesthesia.

Isoflurane is the least potent of the three inhalational anesthetics being discussed (see Table 2). The MAC value for isoflurane is 1.5 to 2.0 times that of halothane, depending on species.

In the dog for example, the MAC of halothane is 0.87%. In clinical practice, this translates to mask inductions using a vaporizer setting of 3–4% and maintenance with a vaporizer setting of 1–2% depending on age and health of the patient, anesthetic circuit and carrier gas flow rates being used, preanesthetic and induction agents, and amount of pain involved with the surgical procedure. The MAC for isoflurane in the dog is 1.28%. If isoflurane is used, mask inductions require a vaporizer setting of 3.5–5.0% and maintenance requires a vaporizer setting of 1.5–2.5% using oxygen flow rates similar to those used with halothane. Typical oxygen flow rates using a semi-closed circle system are 50–100 mL/kg/min for induction and 20–30 mL/kg/min for maintenance.

These are guidelines only and all anesthetic agents should be administered to effect depending on the response of the individual animal. Critically ill animals, geriatric or hypothermic patients, as well as heavily premedicated animals, may require vaporizer settings as low as 0.5–1.0% for isoflurane.

When using isoflurane, it is important to remember that induction will be at least as rapid as with halothane, and reduction of the vaporizer setting to maintance levels will often the necessary within 3–5 minutes to avoid overdosage.

Pulmonary system

Isoflurane is nonirritating to the respiratory tract and does not increase secretions. This agent also causes bronchodilation which may be beneficial in patients with asthma or chronic obstructive pulmonary disease.

As with all potent inhalational anesthetic agents, isoflurane produces dose-dependent depression in ventilation. In the dog, this is due to a decreased respiratory rate (4), which can be marked during the period of surgical preparation. The rate and depth of respiration usually increases with the onset of surgical stimulation. In the horse, although respiratory rate is significantly slower during isoflurane anesthesia than it is

with halothane, arterial oxygen and carbon dioxide concentrations are not significantly or clinically different (5).

Cardiovascular system

There are several features which distinguish isoflurane from the other potent inhalational agents. *Isoflurane sensitizes the heart to epinephrine to a lesser degree than does halothane (6), and has antifibrillatory effects in canine atrial tissue (7).* Decreased frequency or complete resolution of intraoperative ventricular arrhythmias have been reported in cats and dogs intraoperatively following the change of inhalational agent from halothane to isoflurane (8). Fewer cardiac arrhythmias have also been reported in Pekin ducks anesthetized with isoflurane as compared to halothane (9). It must be emphasized, however, that this is no substitute for accurate diagnosis and management of intraoperative arrhythmias.

In the dog, the cardiovascular effects of isoflurane do not differ significantly between spontaneous and controlled ventilation. (4) Between 1.0 and 2.0 MAC, cardiac output is maintained. This is due to a slight increase in heart rate which compensates for a slight decrease in stroke volume. However, there is a significant decrease in mean arterial pressure (MAP) due to decreased total pripheral resistance. The MAP also decreases in the cat although heart rate remains unchanged.

In the horse, cardiovascular effects include dose-dependent decreases in mean arterial pressure, cardiac output, and stroke volume. These effects are not significantly different from cardiovascular effects caused by halothane, except for reduced depression of cardiac output and stroke volume with isoflurane during controlled ventilation (5).

It is important to remember that isoflurane does cause a decrease in blood pressure that is comparable to the other agents in most if not all species at equipotent doses (5,6). In small animals this is due to vasodilation, whereas it is due to a combination of myocardial depression and vasodilation in horses. Careful monitoring and adjustment of anesthetic depth to suit the requirements of the individual patient is required.

The margin of safety (ratio of lethal dose of anesthetic to anesthetizing dose) is greater with isoflurane than for other commonly used inhalational anesthetics. The ratio in rats is 5.7 for isoflurane, 3.7 for methoxyflurane and 3.0 for halothane (10). While this difference does exist, all agents can be fatal unless monitored carefully and administered to effect. There have been no clinical trials in any species to determine if there are differences in morbidity and mortality when anesthesia is maintained by the various agents.

Central nervous system

Isoflurane is a central nervous system depressant. It does not cause muscle twitching or seizure-like activity on the EEG. It is a more potent analgesic agent than halothane, but recovery from anesthesia is so rapid that postoperative pain and restlessness may be observed during the recovery period. Opioid analgesics with sedative properties are helpful in these situations.

Table 2. Minimum alveolar concentration (MAC) values of the modern inhalant anesthetics

	MAC (%)			
Anesthetic	Dog	Cat	Horse	Sandhill crane
Methoxyflurane	0.23	0.27	0.23	—
Halothane	0.87	0.82	0.88	—
Isoflurane	1.28	1.68	1.31	1.34

Intramuscular morphine sulfate administered 15 minutes before the end of anesthesia or as required postoperatively is effective. Dosages of 0.1–0.2 mg/kg IM in dogs and 0.01–0.05 mg/kg IM in cats are generally adequate. Analgesics are usually required following orthopedic and other painful surgical procedures.

Studies on the cerebrovascular effects of isoflurane are conflicting and not yet conclusive.

Liver

Isoflurane has not been reported to produce hepatic injury clinically or experimentally. This may in part be due to the fact that isoflurane undergoes minimal metabolism (see below). In addition, the hepatic circulation appears to be better maintained during isoflurane anesthesia. Thus in animals with hepatic dysfunction, isoflurane may be a preferable agent, although this has not been verified.

Kidneys

All inhalational anesthestics will decrease renal blood flow, glomerular filtration rate, and urine flow. This depression is temporary and dose dependent.

Isoflurane is an ether derivative, as is methoxyflurane. However it undergoes minimal metabolism (see below) and has not been reported to cause nephrotoxicity in man or animals. While the use of isoflurane may be preferable to methoxyflurane in animals with renal disease, it does not appear to provide any advantages over halothane in similar circumstances.

Metabolism and toxicity

Less than 0.2% of the isoflurane inhaled over the course of an anesthetic procedure is metabolized, compared to up to 20% of halothane and up to 50% of methoxyflurane. This contributes to its apparent lack of toxicity, but by no means precludes the need for adequate scavenging of waste anesthetic gases.

Isoflurane does not appear to have any mutagenic, carcinogenic or adverse reproductive effects.

Special considerations in horses

Equine anesthesia provides unique requirements and challenges in the perioperative period. Intraoperative hypotension, hypoventilation and hypoxemia are common occurrences. There is a need for rapid, smooth recoveries with minimal excitement. In addition, the animal must have good coordination before attempting to stand. Myopathies and neuropathies are serious complications which can occur in the postoperative period.

In the horse, halothane and isoflurane produce similar circulatory and pulmonary effects during spontaneous and controlled ventilation except for reduced depression of cardiac output and stroke volume with isoflurane during controlled ventilation (5). Cardiovascular depression is most severe during controlled ventilation with both agents. Although the spontaneous respiratory rate is significantly lower during isoflurane anesthesia (average 5.5/min vs 10.8/min for halothane) arterial carbon dioxide and oxygen tension values are similar.

A study of "recovery quality" in ponies after various inhalational agents (11) found the time to sternal recumbency was 18.5 minutes after two hours of isoflurane anesthesia and 30 minutes after two hours of halothane anesthesia. Time to standing was 36.6 minutes for isoflurane and 42.2 minutes for halothane. *Ponies anesthetized with isoflurane had very quiet and prolonged sternal recumbency with excellent coordination upon standing.* The primary difficulties observed in the animals after maintenance with halothane were shivering and incoordination upon standing.

There have been no publications comparing rates of postoperative myopathy and neuropathy following halothane or isoflurane anesthesia. However, several authors have studied the two agents in horses, and have reported irreversible muscle damage during the recovery period following both agents when hypotension, or extensive periods of recumbency on unpadded surfaces were present (12,13). This is in spite of the fact that microcirculation in the uppermost muscle masses in isoflurane anesthetized horses is significantly higher than in the halothane group (12). A similar comparison in dependent muscles has not been published.

One study using a small sample size of 38 horses compared halothane and isoflurane during emergency colic surgery (14). Cardiopulmonary responses were generally comparable. Recovery times to standing were significantly shorter with isoflurane (52 min vs. 68 min for halothane) but recoveries were uneventful with both agents.

Avian anesthesia

Isoflurane has been used to anesthetize a wide range of species of birds. Inductions are very rapid (5 min or less) due to the low solubility of the agent and the anatomy of the avian respiratory system. Induction can be done in a box with a 5-6 L flow of oxygen and a 4-5% vaporizer setting, or with a face mask with vaporizer settings of 3-4% and a reduced oxygen flow. Using a Bain circuit for maintenance with a mask or after intubation, vaporizer settings of 1-2% are usually adequate.

Isoflurane may reduce the risk of arrhythmia development and cardiovascular collapse among psittacines during anesthesia when compared to halothane.

Recovery is often very rapid with a time to extubation of 2-3 min. and time to standing of 5-10 min. after the end of anesthesia. *It is considered by some to be the agent of choice for avian anesthesia.*

Clinical hints

There are a number of points which may facilitate the introduction of this agent into a practice. If halothane is currently in use, the transition should not be difficult. Induction times, specifically mask inductions, do not seem noticeably different with the two agents. However, recovery times are definitely more rapid, and it is important to be prepared for extubation within five minutes of turning off the vaporizer. If you are presently using methoxyflurane, the differences will be more noticeable and special attention should be paid to monitoring anesthetized animals until you have used the agent a number of times. Due to the low tissue solubility and high vapor pressure compared to methoxyflurane, it would be easy to overdose the animal in the induction period.

Animals which may appear adequately anesthetized during surgical preparation may respond to the start of surgery to a greater extent than with other agents. Although this can be surprising, anesthetic plane can be rapidly increased.

Recovery from the drug is rapid and so complete that postoperative analgesics should be used following painful surgeries. Without this, animals can become very excited and distressed in the recovery period. As mentioned previously, morphine works well in these situations. CVJ

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