

New drugs in companion animal anesthesia

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KEY POINTS

- Many anesthetics have recently been added to the veterinary armamentarium.
- Most new 'veterinary' drugs were actually developed for use in humans and may be less useful in animals.
- New anesthetics have different properties from previous drugs but may be no safer.
- 'New' agents are less safe when anesthetists are unfamiliar with their use.
- Propofol has some advantages over thiopentone in veterinary anesthesia.
- Isoflurane has some advantages over halothane but is not universally superior.

INTRODUCTION

The search for 'better' drugs is prompted by the tenet that there are no safe anesthetics or safe anesthetic techniques and by increasing medico-legal pressures. There is also the expectation of a lay population for more complicated operations to be performed on higher-risk subjects. Greater demands on surgical facilities favor the development of short-acting drugs without residual effects. Anesthesiologists themselves are interested in drugs that have different pharmacokinetics, are more potent or effective, have less toxicity, or simply create a new effect.

New drugs and safety

Anesthetic risk depends as much on the anesthetist's familiarity with an agent as it does on the drug's theoretical lethality (i.e., therapeutic index), and the assumption that new anesthetics are inevitably safer is misconceived. Indeed, the reverse is often true:

new, allegedly 'safer' anesthetics may provide a temptation to anesthetize cases that would previously have been regarded as unacceptable risks. Under these circumstances, the use of unfamiliar drugs – which are unlikely to be safer – in susceptible subjects may have dire consequences. Thus it has been a long-held axiom that, when confronted with high-risk cases, anesthetists should use drugs with which they are accustomed and not unfamiliar compounds that may, in theory, be more suitable. Given the inherent danger of anesthetics, the promotional material that accompanies the launch of new products, and the apocryphal information that develops thereafter, critical examination is warranted.

Problems with data extrapolation

The validity of pharmacological data from laboratory animals or humans may be limited in companion animals where drugs have different pharmacodynamic and pharmacokinetic characteristics. Different pathophysiological processes may also invalidate data from other species. For example, chronic liver disease in humans often refers to cirrhosis, while 'heart' disease usually implies coronary arteriosclerosis. As these conditions are rare in animals, a drug's benefits in human hepatic or cardiac disease may be less obvious in companion animals with liver or heart conditions. Similarly, the extrapolation of data for subpopulations (i.e., neonates, geriatrics, the obese, and the pregnant) may be inappropriate.

Limitations of experimental studies

Experimental data from laboratory cats or dogs are of limited value because these subjects lack the diversity in age, breed, size, and health encountered in general practice. The physiological effects of anesthetics are markedly different when examined under laboratory versus clinical conditions. In the former, the drug is used alone, at controlled doses, under controlled conditions of ventilation; surgery may be limited to superficial vascular cannulation. This contrasts with clinical conditions in which the drug is given at varying doses, along with other agents, to animals undergoing operations of varying severity.

Limitations of clinical studies

New anesthetics available to medical practice prompt many studies in which they are compared with previous drugs in various patient subpopulations. Similar comparisons are rarely made in veterinary anesthesia, making it difficult to refute claims that new drugs are superior to their predecessors. This problem is compounded by neophilia – an obsession with the new – and may account for discrepancies between the number of enthusiastic reports describing drug effects and the number of drugs actually used, and by the observation that new drugs usually perform better in the hands of investigators than with those who read a preliminary report (1).

Advantages of one anesthetic over another can be identified only when *all* important variables are monitored. Meaningful comparison is difficult in veterinary practice because the level of physiological



Table 1
Benzodiazepines: developments in anesthesia

<i>Previous drugs</i>	<i>Limitations</i>	<i>Developments</i>	<i>Advantages</i>	<i>Relevance in veterinary anesthesia</i>
Diazepam	Pain on IV and IM injection Thrombophlebitis Erratic absorption after IM administration Slow, unpredictable onset after IV injection	Midazolam Flumazenil	Water-soluble Nonirritant Rapid onset Short-acting Benzodiazepine antagonist	Slight. Use of benzodiazepines limited in animals, reflecting unpredictability and ineffectiveness as sedatives and anesthetics IV diazepam infrequently painful in dogs Slight. Low use of benzodiazepines in animals limits potential of antagonists

Table 2
Opioid agonist drugs: developments in anesthesia*

<i>Previous drugs</i>	<i>Limitations</i>	<i>Developments</i>	<i>Advantages</i>	<i>Relevance in veterinary anesthesia</i>
Morphine For perioperative analgesia and long-term relief of intractable pain	Respiratory depression Nausea Euphoria Dysphoria Addiction Tolerance Constipation	Buprenorphine Butorphanol	Fewer side-effects, less respiratory depression	High. Immunity from controlled drug legislation. However, less effective analgesia than morphine; 'ceiling effect' – lowering respiratory depression limits analgesia, and there is less euphoric effect. Animals seldom undergo analgesic therapy for periods likely to cause addiction or tolerance. Concern with morphine's sideeffects results mainly from descriptions of overdose; suitable doses (which depend on species, degree of pain present, route of administration) provide analgesia with minimal sideeffects
Fentanyl For intraoperative analgesia	Intermediate duration Accumulation Sideeffects Low potency	Sufentanil Lofentanil Alfentanil Remifentanil Rapifentanil Mirfentanil	Produce anesthesia in conjunction with N ₂ O. Obviate need for inhalation anesthetics	Slight. Fentanyl, alfentanil, and sufentanil used with propofol or midazolam for induction and maintenance of anesthesia in dogs. Popularity as a component of total intravenous anesthesia may be limited; severe respiratory depression mandates use of positive-pressure ventilation

*New drugs are given in different ways – e.g., PCA (patient-controlled analgesia) and computer-assisted continuous infusion; by different routes – e.g., neuraxial, transdermal, intranasal, and transmucosal; in combination with other analgesics

(balanced analgesia); and in anticipation of, rather than in response to, pain (preemptive analgesia). Older opioids are also being used in new ways.

Table 3
Local anesthetics: developments in anesthesia*

<i>Previous drugs</i>	<i>Limitations</i>	<i>Developments</i>	<i>Advantages</i>	<i>Relevance in veterinary anesthesia</i>
Lignocaine	Few Intermediate duration of action	Prilocaine Mepivacaine	Lower toxicity	Slight. Lignocaine is usually satisfactory except for prolonged activity
Bupivacaine	Slow onset Long duration of action Cardiomyotoxicity	Ropivacaine	Greater analgesia Less arrhythmogenic	Slight. Bupivacaine is preferred for prolonged block – e.g., intercostal or interpleural block following thoracotomy, or extradural analgesia after pelvic surgery

*Local anesthetic development has been fuelled by attempts to: (a) overcome the disadvantages of available drugs (related to *in vitro* stability, fetal, and spinal toxicity);

(b) create a range of drugs providing a spectrum of onset and duration of action times.

Table 4
α₂-agonists: developments in anesthesia*

<i>Previous drugs</i>	<i>Limitations</i>	<i>Developments</i>	<i>Advantages</i>	<i>Relevance in veterinary anesthesia</i>
Clonidine	Minimal sedation Hypotension	Dexmedetomidine	Potential role in premedication, for TIVA, hemodynamic control (induced hypotension), postoperative analgesia, as an adjunct agent for regional anesthesia and analgesia	Slight. Effective veterinary α ₂ -agonists (xylazine, detomidine, romifidine, and medetomidine) already exist. Problems of adverse cardiopulmonary effects (bradycardia, hypertension, hypotension, and cardiac arrhythmias) unaddressed
Yohimbine	Nonselectivity	Atipamezole	Specific α ₂ -antagonist	High. Accounts for popularity of medetomidine

*The technique of extradural and intrathecal α₂-agonist injection (which exerts marked antinociceptive effect) is being evaluated in many species.

Table 5
Nonsteroidal antiinflammatory drugs: developments in anesthesia

<i>Previous drugs</i>	<i>Limitations</i>	<i>Developments</i>	<i>Advantages</i>	<i>Relevance in veterinary anesthesia</i>
Aspirin	Toxicity, unavailability of IV formulations	Ketorolac	Comparable analgesia to opioids claimed in certain circumstances	None. Causes sideeffects linked with COX-1 inhibition**
Paracetamol (BP)*		Diclofenac		
Phenylbutazone	Low potency	Carprofen	Reduced toxicity	High. Selective (COX-2) inhibitors prevent proliferation of inflammatory mediators that 'sensitize' nociceptors to pain with lower risk of toxicity
		Ketoprofen	Potent analgesia	
		Tolfenamic acid		
		Meloxicam		

*Acetaminophen (USP).

**Toxic effects arise from indiscriminate cyclooxygenase 1 (COX-1) inhibition. (COX-1 catalyses the generation of homeostatic prostaglandins controlling gastric mucus

production, renal blood flow preservation, and thrombocyte function). Toxicity includes renal papillary necrosis, gastrointestinal disturbances (gastric ulceration), platelet dysfunction (prolonged clotting), and blood dyscrasias.

Table 6
Cardiac drugs: developments in anesthesia

<i>Previous drugs</i>	<i>Limitations</i>	<i>Developments</i>	<i>Advantages</i>	<i>Relevance in veterinary anesthesia</i>
Aminophylline	Nonselectivity Ineffectiveness	Amrinone Milrinone Propentophylline	Increases cardiac output without changing heart rate. Lowers pulmonary and SVR (Systemic Vascular Resistance). Improves myocardial and cerebral blood flow	High. Widespread cardiovascular effects of phosphodiesterase III inhibitors preclude simple discussion. Any improvement in vital organ perfusion probably lowers risk of anesthesia in older animals. Propentophylline causes cerebrovasodilatation; cardiovascular effects are modest
None		Enalapril Benaxapril	An alternative method of afterload reduction with few side-effects	High. Angiotensin-converting enzyme (ACE) inhibitors widely prescribed in dogs for management of congestive cardiac failure
None		Adenosine	Marked antiarrhythmic properties against paroxysmal supraventricular tachycardia	High. This endogenous purine nucleoside is effective, albeit very short-acting in dogs. Infusion by central venous catheter is required
Propranolol	β_2 -agonism Intrinsic sympathetic activity	Esmolol	Selective β_1 -antagonism, rapid onset and ultrashort duration of action	Low. General satisfaction with propranolol
Dopamine	Ineffective in prolonged 'shock'	Dopexamine	Lowers systemic vascular resistance, increases renal and hepatic flow, and increases cardiac output	Low. General satisfaction with dopamine and/or dobutamine

monitoring is low. Comparison is further bedevilled by different criteria used to define 'good anesthesia'. Without physiological monitoring, anesthetics can be compared only in terms of operating conditions, rate and quality of recovery, and morbidity and mortality. These are barely acceptable criteria in healthy cases and are unacceptable in diseased animals when risk of complications is higher.

NEW DEVELOPMENTS IN MEDICAL AND VETERINARY ANESTHESIA

Most developments in benzodiazepines, opioid agonists, injectable and inhalational anesthetics, neuromuscular blocking agents, local anesthetics, nonsteroidal antiinflammatory drugs, and cardiovascular support drugs have been engendered by the needs of human patients, and not by the shortcomings of available veterinary products. The α_2 -agonists are an exception. Consequently, many 'developments' in human preparations do not represent improvements in veterinary anesthesia.

Indeed, many are less useful than the drugs they supersede. This is illustrated for various drug classes in **Tables 1–6**.

INTRAVENOUS INDUCTION AGENTS

New intravenous anesthetics are sought because of the limitations of available drugs (**Table 7**) and the increasing popularity of total intravenous anesthesia (TIVA) and 'same-day' surgery. Development has involved benzodiazepines, steroids, carboxylated imidazoles, eugenols, cyclohexanones, barbiturates, and phenols. Many regard propofol as the acme of development, although 5- β -pregnanolone (a steroid anesthetic) may challenge its primacy. No intravenous agents, including propofol, rapidly achieve unconsciousness without producing significant cardiopulmonary changes or disturbing sideeffects. Consequently, many anesthetists favor combinations of sedative-hypnotic and analgesic drugs with similar pharmacokinetic profiles (e.g., etomidate and alfentanil) to induce

anesthesia. Some veterinary anesthetists prefer cyclohexanone/benzodiazepine combinations, while others still regard thiopentone as the gold standard.

THIOPENTONE VERSUS PROPOFOL IN COMPANION ANIMAL ANESTHESIA

Formulation

Thiopentone's chemical stability and solubility in aqueous solutions is limited (shelflife is about 24–48 hours), so preparations contain sodium carbonate, which is irritant. Extravascular injections may cause tissue damage, although intravenous injection is not painful. Propofol is virtually insoluble in water and requires dissolution in an egg-phosphatidyl-soya bean oil emulsion. This contains no bacteriostat, and opened ampules must be discarded. Despite nonirritancy, propofol occasionally elicits signs of discomfort during intravenous injection. The clinical relevance of these differences are detailed in **Table 8**.



Table 7

Comparison of thiopentone and propofol with characteristics of an ideal intravenous anesthetic

<i>Properties</i>		<i>Thiopentone</i>	<i>Propofol</i>	
Physical	Water-soluble	+	--	
	Nonirritant (extravascular)	--	+	
	No pain on injection	+	-	
	Stable in aqueous solution	+/-	--	
	Long shelflife	+/-	-	
Pharmacodynamic	Smooth onset; no hiccoughing, excitement, movement	+	-	
	Rapid onset; effects in one arm-brain circulation time	+++	+++	
	No adverse cardiopulmonary effects	--	--	
	Analgesia	-	+/-	
	Amnesia	+	+	
	Muscle relaxation	+/-	+/-	
	Repeatable, dose-dependent signs of anesthesia	+	+	
	Smooth, excitation-free recovery	+/-	+/-	
	Safe for use in common pathophysiological states	+	+	
	No histamine release	+	-	
	No idiosyncratic reactions	+/-	-	
	Safe in malignant hyperthermia-susceptible subjects	+	+	
	Capable of antagonism	-	-	
	Pharmacokinetic	Very short-acting	+	+
		Rapid redistribution	++	++
Rapid hepatic or extrahepatic metabolism		-	++	
Metabolism to inactive metabolites		-	+	
Rapid renal clearance		-	+	
Miscellaneous	Noncumulative with repeated doses or infusion	-	++	
	Low cost	+	-	
	Nonteratogenic Noncarcinogenic	+	+	

+, ++, +++ Ever more closely meets ideal criterion.

-, --, --- Does not meet ideal criterion.

Table 8

Suggested clinical advantages of propofol over thiopentone

- When risk of extravascular injection exists and normal precautionary measures* are impractical
- For total intravenous anesthesia produced by multiple injections or infusion
- When precise control of reflex depression is needed – e.g., during laryngeal reflex examination
- For short procedures with rapid 'hangover'-free recoveries – e.g., pharyngeal foreign body removal**
- When sustained, effective airway reflexes are required following endotracheal extubation**
- In greyhounds and whippets (preanesthetic medication with acepromazine is recommended)
- When postinduction tachycardia is undesirable
- Last case on the surgical list (if suitable) – an opportunity to use opened ampules

*Risk of extravascular injection reduced by adequate physical and/or chemical restraint followed by insertion of intravenous catheter. Problems of extravascular injection are diminished by using dilute (e.g., 1.25% thiopentone solutions). **When perioperative opioid analgesia is not required.

Pharmacokinetics

Differences in the rates of hepatic and extrahepatic metabolism and fat solubility confer propofol with noncumulative pharmacokinetic properties. The recovery of partial consciousness after single doses of propofol and thiopentone are similar,

although *full* recovery is more rapid and 'hangover' less marked with propofol. Differences in recovery characteristics are most striking when multiple injections, or infusions of each drug, are compared but are less obvious when inhalational anesthesia follows induction. In humans,

differences in the return of psychomotor or cognitive function between thiopentone or propofol are eliminated by 35 or more minutes of halothane-N₂O anesthesia (2). Under some circumstances propofol appears to be accumulative in dogs, with infusion resulting in prolonged recovery (3).

Rapid recoveries are not always desirable. When postoperative analgesia is imperfect, rapid recoveries allow the sudden appreciation of discomfort and may cause restlessness and excitement. Adequate preemptive analgesia using opioid drugs will limit this but also prolong recovery, so negating propofol's principal feature. Thiopentone is no better in these circumstances because subanesthetic levels increase sensitivity to painful stimuli (produce hyperalgesia). Propofol's rapid plasma clearance also contributes to a turbulent transition from intravenous into inhalational anesthesia. This occurs in part because the drug depresses breathing. This can be prevented by periodic lung inflation with anesthetic gas.

Sight-hounds

Recovery from thiopentone anesthesia in greyhounds and whippets is undesirably long and reflects prolonged elevation of plasma drug levels. This probably occurs because hepatic enzymes responsible for thiopentone degradation are more readily saturated in greyhounds than mixed-breed dogs (4). Propofol clearance in Greyhounds is also less than half that of mixed-breed dogs (5), but this does not detract from the drug's usefulness in this breed. There is little evidence that an absence of body fat accounts for prolonged recovery after single thiopentone injections, so either agent is suitable in very thin animals.

Cesarean operation

Single injections of the minimal effective dose used to induce anesthesia in females undergoing Cesarean operation should ensure that neonates are conscious on delivery, irrespective of the drug used. First-pass metabolism in the fetal liver, tissue binding, and the diluting effect of right-to-left shunts within the fetal circulation ensure that maternal drug concentrations do not reach the fetal brain. This may explain why four surveys have failed to establish differences in infant neurobehavioral scores after use of either thiopentone or propofol (6). There appears to be no evidence that the viability of whelps delivered by Cesarean operation is greater when propofol is used.

Liver disease

The hepatic metabolism of propofol



Figure 1 Intraoperative photograph of high-risk patient with portosystemic shunt.

(and its subsequent plasma clearance) is slower in cats than dogs, so recoveries take longer. This raises the question of drug choice in animals with diminished hepatic function (i.e., neonates and animals with advanced liver disease). In these, limited liver function may reduce the disparity between hepatic clearance rates, causing recovery times to become similar. This is supported by data from human studies that show that the benefits of propofol over thiopentone during recovery are minimal in the very young but increase with age (7). The recovery rate of animals with advanced liver disease is unlikely to be influenced by the induction agent, providing single, minimum effective doses are given, and that anesthesia is maintained using inhalation agents.

Quality of anesthesia

Thiopentone causes hyperalgesia and 'hangover' after recovery, but not the bizarre neurological reactions occasionally seen with propofol. One study reported muscle twitching, opisthotonus, limb hyperextension, panting, accessory respiratory muscle (brachiocephalicus) contractions, tongue retraction severe enough to complicate induction to anesthesia, endotracheal intubation, and surgery itself (8). Similar complications follow continuous propofol infusion (9). While propofol shows both proconvulsant and anticonvulsant activity, the Committee



Figure 2
Lateral contrast radiograph of a dog with a diaphragmatic rupture.

Table 9
Comparison of halothane and isoflurane with characteristics of an ideal inhalation anesthetic

Properties		Halothane	Isoflurane
Physical	Noninflammable	+	+
	Nonexplosive	+	+
	Stable in air, to UV light exposure	-	++
	Compatible with soda-lime and Baralyme	+	+
	Compatible with breathing system material	+	+
Pharmacodynamic	Potent (low minimal anesthetic concentration)	++	+
	Analgesia	+	++
	Muscle relaxation	+	++
	Minimal airway irritation	++	+
	Pleasant odor at clinical concentrations	+	+/-
	Perceptible odor at low concentrations	+	+
	Minimal adverse cardiopulmonary effects	-	-
	Nonarrhythmogenic	-	+/-
	No CNS stimulation	+	+
	No toxic metabolites	+/-	+
	No organ toxicity	+	+/-
	Smooth, excitation-free recovery	+	+/-
	Safe for use in common pathophysiological states	+	+
Safe in malignant hyperthermia-susceptible animals	-	+	
Pharmacokinetic	Short-acting – i.e., low blood-gas and tissue-gas solubility	+	++
	No hepatic or extrahepatic metabolism	-	+
	Miscellaneous		
Miscellaneous	Low cost	+	-
	Nonteratogenic	-	-
	Noncarcinogenic	+	+

+, ++, +++ Ever more closely meets ideal criterion.
-, --, --- Does not meet ideal criterion.

on Safety of Medicines (1989) has recommended care with its use in epileptic patients (10).

'High-risk' cases

There is little evidence to support the belief that propofol is safer than thiopentone in 'high-risk' cases. Both drugs cause equally severe cardiopulmonary depression, although the processes are different and, with propofol, inconsistent. Thiopentone causes hypotension through myocardial depression, increased venous capacitance, and reduced systemic vascular resistance (SVR). Propofol also causes hypotension (usually by lowering SVR);

heart rate and stroke volume are normally unchanged, but, occasionally, cardiac output rises. This inconsistency makes it difficult to predict responses in animals with poorly characterized cardiovascular disease. Both drugs cause apnea during induction to anesthesia, which in humans is more severe after propofol. This is normally inconsequential providing that the trachea is intubated and the lungs are periodically inflated with oxygen-rich gas. The respiratory depressant effects of propofol justify tracheal intubation and oxygen-enrichment of inspired gas during TIVA.

INHALATION ANESTHETIC AGENTS

Developments in inhaled anesthetics have involved production of more stable molecules with minimal solubility in body tissues (Table 9). Stability confers resistance to biotransformation, lower flammability, and robust storage characteristics, while low solubility allows better control over drug tensions in the brain. Isoflurane superseded halothane in medical practice during the 1980s but has been replaced by desflurane and sevoflurane. Desflurane is impotent (minimal anesthetic concentration [MAC] in dogs, 7.2 %; in cats, 9.8%) but insoluble



Table 10
Suggested clinical advantages of isoflurane over halothane

- Operations requiring rapid recovery
- Isoflurane is preferred (normally in conjunction with N₂O) in:
 - small, hypothermia-prone animals*
 - short-duration operations that do not warrant perioperative opioid analgesia
- Prolonged operations in obese animals**
- When intracranial pressure is unstable** – e.g., head trauma, postresuscitative management
- Cardiac disease, in which cardiac output maintenance and systemic vascular resistance reduction are desirable
- Cardiac arrhythmias, when a further lowering of heart rate is undesirable
- When cerebral oxygen delivery may be curtailed – e.g., intracranial surgery
- When plasma catecholamine levels cannot be stabilized – e.g., pheochromocytoma
- Abnormal myocardial sensitivity to catecholamines – e.g., hyperthyroidism, hypothermia
- Cases susceptible to malignant hyperthermia

*Care is required in cases susceptible to respiratory depression in which endotracheal intubation may be impossible.

**Positive-pressure ventilation is highly recommended.



Figure 3 *Gastric dilation-volvulus – these cases can have marked metabolic and circulatory derangements, and anesthesia needs to be undertaken with care.*

(blood-gas solubility, 0.4), so recovery is extremely rapid (MAC reflects inhaled drug potency, with low values indicating high potency; low blood-gas solubility coefficients indicate insolubility in blood). Unfortunately, it boils at 23.5°C – almost room temperature – so a fundamentally different vaporizer is needed (e.g., the desflurane Tec 6). Sevoflurane is more potent (MAC in dogs, 2.1%; in cats, 2.58%) but less soluble in blood (blood-gas solubility coefficient, 0.6). Its disadvantages include chemical instability in soda-lime and fluoride release from biotransformation.

The high cost of these new agents will ensure limited popularity in veterinary practice for some time, restricting options to isoflurane and halothane. Isoflurane has clear advantages over halothane in companion animal anesthesia, the speed of recovery after prolonged administration being the most important. However, this

occasionally impressive feature has prompted much unfounded acclaim, as well as an unfair condemnation of halothane. Attempts to limit isoflurane consumption (and cost) using 'low-flow' or 'closed' rebreathing systems obviate the use of nitrous oxide and incur other risks and problems. These specialized techniques must be fully understood if cost-cutting strategies are to be employed safely.

HALOTHANE VERSUS ISOFLURANE IN COMPANION ANIMAL ANESTHESIA

Formulation

Halothane has a fruity-smelling vapor but because it is unstable in UV light is stored in amber bottles containing thymol 0.01% w/w. Isoflurane has a pungent ethereal odor but contains no preservatives. This pungency may account for greater resistance to mask induction with isoflurane seen in human infants and many animals – except birds. The accumulation of thymol may adversely affect the operation of halothane vaporizers.

Pharmacokinetics

Isoflurane has a lower blood-gas solubility coefficient than halothane (1.4 versus 2.3), which means that induction to, and recovery from, isoflurane anesthesia is more rapid, while the response to altered inspired concentration is brisker. However, this predicted behavior depends on other variables that affect drug pharmacokinetics, particularly cardiac output and alveolar ventilation. The effect of halothane versus isoflurane on these variables reduces the advantage of isoflurane's low solubility. For example, in human neonates a greater

incidence of breath-holding, laryngospasm, struggling, and sinus tachycardia means that induction with isoflurane takes considerably longer than halothane (11). Nevertheless, low blood-gas and blood-fat solubility make isoflurane the preferred agent for certain operations (**Table 10**).

Anesthetic properties

Halothane is a more potent anesthetic than isoflurane (MAC values in dogs, 0.86% and 1.3% respectively; in cats, 0.82% and 1.61%), so lower inspired concentrations are required to achieve a given 'depth' of anesthesia. However, adrenergic responses persist with halothane, suggesting that it is a weaker analgesic. Isoflurane produces more muscle relaxation than halothane. This provides better surgical conditions on the one hand but causes greater respiratory depression on the other. Isoflurane also potentiates nondepolarizing neuromuscular blocking agents to a greater extent. Halothane is a more potent 'trigger' of malignant hyperthermia than isoflurane, although the condition is rare in dogs.

Cardiovascular effects

The term 'cardiovascular stability' is often applied to isoflurane's circulatory effects, but the term is ill-defined, so the claim cannot easily be refuted. Information on the 'cardiac safety' of inhaled anesthetics does not help because these vary according to species. For example, the 'cardiac anesthetic index' gives values of 5.7 and 3.0 for isoflurane and halothane respectively, making isoflurane 'safer' in laboratory rats (12). In contrast, the predicted concentration (in relation to potency) needed to eliminate blood pressure in dogs is higher for halothane, which suggests it is safer (13). These facts are not contradictory – they simply illustrate the complexity of anesthetic action upon cardiovascular function.

Equipotent doses of halothane and isoflurane cause similar degrees of hypotension. With halothane, this results from lowered cardiac output rather than changes in SVR. With isoflurane, cardiac output remains constant or rises, so hypotension is caused by a lowered SVR. In humans, this is associated with a fourfold increase in skeletal muscle and cutaneous blood flow; this increases the delivery of neuromuscular blocking agents and their antagonists, wastes perfusion relative to whole body oxygen needs, and predisposes to hypothermia. A feature of inhalation anesthesia is the return of depressed haemodynamic variables to baseline; cardiac output and heart rate rise substantially after 5 hours of halothane.



Figure 4 Road accident trauma case – these cases can have marked cardiovascular and respiratory compromise, and thus decompensate suddenly upon stress or anesthesia.

This effect is minimal with isoflurane (making 'cardiovascular stability' in this context an undesirable feature).

Claims that isoflurane is better for animals with cardiac disease are in some circumstances untrue. First, the term 'cardiac disease' is too vague to be meaningful. Secondly, anesthetics affect different facets of cardiac function (e.g., ventricular contractility, conductivity, pacemaker excitability, coronary blood flow, afterload, and preload) in different ways, but no one drug demonstrates universal superiority. Thirdly, apparently beneficial features often prove to be undesirable. For example, isoflurane's more potent coronary vasodilator effects would appear advantageous. However, this property causes the diversion of blood supplying damaged myocardium (containing maximally dilated vessels) to healthy muscle and aggravates ischemia. Even the preservation of cardiac output is not always desirable because this may jeopardize myocardial oxygen balance in some diseases. In pigs, myocardial oxygen consumption and efficiency of use are optimum during halothane, not isoflurane, anesthesia (14).

Dogs anesthetized with isoflurane require more adrenaline to promote ventricular arrhythmias compared with those given halothane (15, 16), which suggests that isoflurane should be used when ventricular arrhythmias are likely. However, one study found a *similar* incidence of ventricular arrhythmias in unhealthy dogs given halothane or isoflurane, and a *higher* incidence with isoflurane in healthy animals (17). These conflicting facts show that the arrhythmogenicity of inhaled anesthetics depends on factors in addition to myocardial 'sensitization'. In maintaining cardiac output and myocardial work, isoflurane is more likely to promote arrhythmias linked with myocardial hypoxia. Furthermore, ventricular arrhythmia in

companion animals is readily suppressed by *increasing* inspired halothane concentration (18), presumably because many arrhythmias arise from inadequate anesthesia.

Ultimately, well-managed anesthesia is not characterized by high plasma catecholamine levels (except in uncontrolled pheochromocytoma), so priority should be placed on minimizing plasma catecholamine levels (avoiding hypoxemia, hypercapnia, hypotension, hypoglycemia, etc.) and suppressing other arrhythmogenic influences. The choice of anesthetic is then of secondary importance.

Respiratory effects

Postinduction apnea and respiratory depression are greater with isoflurane than halothane (17), and the ratio of apneustic to anesthetic dose is lower in both dogs and cats (19). Surgical stimulation elevates minute ventilation, but CO₂ does not fall accordingly because metabolic CO₂ production also rises. This does not preclude the use of isoflurane in cases susceptible to respiratory depression but indicates that the need for ventilatory support is greater.

Hepatic metabolism and toxicity

Isoflurane undergoes less degradation than halothane (0.17% versus 12–25%), mainly because low blood solubility ensures inspired drug is exhaled before exposure to hepatic metabolic pathways. These differences have minimal pharmacokinetic effect and do not influence the inhaled concentration needed for anesthesia. The significance of metabolic degradation is that it may generate reactive intermediate molecules that initiate events leading to tissue destruction – for example, centrilobular necrosis in halothane-associated hepatitis (HAH). That isoflurane undergoes less degradation than halothane supports claims for its greater safety in terms of liver, renal, and fetal toxicity.

However, such claims ignore three points relevant to veterinary anesthesia. First, while inhalational agents are toxic in several ways – acute, gross overdose, adverse reactions (e.g., malignant hyperthermia and HAH) and possibly chronic environmental exposure – halothane's metabolic intermediates have been incriminated only in HAH. Secondly, HAH is very rare in animals. The literature contains only three reports of a condition resembling HAH in animals; one involves a dog (20), the second an alpaca (21), and the third a goat (22). Thirdly, inhalation anesthetics are rarely hepatotoxic per se, with factors like repeated anesthetics,



Figure 5 Postoperative portosystemic shunt attenuation. These cases need constant careful monitoring for a considerable time postoperatively.

microsomal enzyme induction, concurrent drug therapy, hepatocellular hypoxia, genetic predisposition, age, sex, and degree of obesity being identified in most cases. Failure to eliminate predisposing factors has thrown doubt over alleged cases of HAH in animals – except for the alpaca (23).

The occupational exposure standards based on time-weighted averages for halothane (10 ppm) and isoflurane (50 ppm) represent one-fifth of the lowest concentration known not to cause adverse effects in experimental animals and, as such, are the *only* data available upon which human exposure recommendations can be based. However, because the data were taken from unrelated studies, it cannot be inferred that isoflurane is five times safer than halothane.

Although there are no differences in signs of postanesthetic hepatocellular integrity between humans given isoflurane or halothane (24), isoflurane may be more useful in animals with liver disease. This is because it depresses hepatic blood flow less and maintains hepatic venous oxygen saturation better, not because it undergoes less metabolism. The absence of hepatic function has minimal effects on recovery from inhaled anesthetics because any drug not metabolized is exhaled.

Cesarean operation

It is difficult to recommend one inhaled anesthetic in preference to another for Cesarean operation. All inhalation anesthetics produce similar reductions in uterine blood flow and contractility, while the benefits of isoflurane versus halothane on neonatal recovery are difficult to predict. Low blood solubility should allow rapid recovery; however, it also promotes rapid saturation of maternal and fetal blood, which would contribute to higher fetal tissue levels at the time of delivery. These opposing influences are probably of similar importance; at least one study found no



differences in any important physiological variables – maternal and neonatal – between isoflurane or halothane recipients; maternal recovery time was not recorded (25).

Renal disease

There is little to choose between inhaled anesthetics in animals with renal disease. Any drug will aggravate renal disease if it adversely alters renal blood flow, glomerular filtration rate, intrarenal blood distribution, and ADH secretion, or by yielding nephrotoxic metabolites such as fluoride. Nephrotoxicity is most likely with methoxyflurane, enflurane, and (possibly) sevoflurane, when renal perfusion is inadequate and when cyclooxygenase 1 (COX-1) inhibitors (e.g., flunixin) are given. There are reports of renal failure following

flunixin administration to halothane- and methoxyflurane-anesthetised dogs. However, nephrotoxicity directly attributable to halothane, isoflurane, or their metabolites has not been reported in dogs. In any case, the canine kidney is resistant to high plasma fluoride levels.

CNS effects

Comparisons between the electroencephalographic effects of isoflurane and halothane indicate that isoflurane is probably more suitable in operations when cerebral oxygen delivery may be curtailed. Isoflurane is also less likely to raise intracranial pressure (26). However, these benefits will be negated if hypercapnia, caused by respiratory depression, is not remedied using positive-pressure ventilation.

CONCLUSION

The desire for increased safety during anesthesia provides a constant motive for new drug development. In veterinary anesthesia, however, a reduction in risk would probably be achieved more readily if greater emphasis were placed on preoperative risk assessment and intraoperative monitoring rather than the use of 'better' drugs. New drugs are always welcome but, like anything new and potentially dangerous, must be used with care until their true behavior and worth become established.

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