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Solubility of Haloether Anesthetics in Human and Animal Blood

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Abstract

Background—Anesthetic blood solubility predicts pharmacokinetics for inhaled agents and is essential for determination of blood anesthetic concentrations from end-tidal gas concentrations using Henry's Law. Though used to model anesthetic effects in humans, there are limited interspecies solubility comparisons that include modern haloethers. This study aimed to measure hematocrit-adjusted blood:gas anesthetic partition coefficients ($\lambda_{B:G}$) for desflurane, sevoflurane, isoflurane, and methoxyflurane in humans and animals.

Methods—Whole blood was collected from 20 rats, 8 horses, and 4 each of cats, cattle, humans, dogs, goats, pigs, rabbits, and sheep. Plasma or cell volume was removed to adjust all samples to a packed cell volume of 40%. A single agent calibration gas headspace was added to blood in a glass syringe and was mixed and equilibrated at 37°C for 2 hours. Agent concentrations in the calibration gas and syringe headspace were measured using gas chromatography. Anesthetic solubility in saline, citrate-phosphate-dextrose-adenine, and olive oil were similarly measured.

Results—Except for goats, all animal species had at least one $\lambda_{B:G}$ measurement that differed significantly from humans. For each agent, $\lambda_{B:G}$ positively correlated with serum triglyceride concentrations, but this only explained 25% of interspecies variability. Desflurane was significantly less soluble in blood than sevoflurane in some species (e.g., humans) but not in others (e.g., rabbits).

Conclusions—Anesthetic partition coefficients differ significantly between humans and most animals for haloether anesthetics. Because of their similar $\lambda_{B:G}$ values, goats may be a better animal model for inhaled anesthetic pharmacokinetics in people.

Introduction

The partition coefficient (partition ratio, λ) describes the molar distribution ratio of a compound at equilibrium between two immiscible fluids.[1] For volatile and gaseous

anesthetics, λ can be expressed as the concentration in saline or organic phase (such as blood, oil, or tissue) versus the gas phase at body temperature and 1 atmosphere pressure.

Accurate anesthetic partition coefficient measurements are important for several reasons. Agent concentrations can be measured easily and quickly from end-tidal gas samples. Under ideal gas conditions[2] and for a constant activity coefficient, Henry's Law states that the ratio of anesthetic vapor concentration within a liquid to the anesthetic vapor partial pressure is constant.[3,4] Since vapor concentration in the gas phase equals the vapor partial pressure divided by barometric pressure, the vapor concentration ratio between liquid and gas phases is also constant. Accurate Ostwald partition coefficients at body temperature are thus essential to correct calculations of blood and tissue anesthetic concentrations at equilibrium from measurements of end-tidal anesthetic gas concentrations.

Accurate solubility measurements allow for prediction of anesthetic potency. Conventional anesthetics generally obey the Meyer-Overton hypothesis; the anesthetic EC_{50} or minimum alveolar concentration (MAC) correlates inversely with the oil:gas partition coefficient $(\lambda)_{O:G}$.[5] Among conventional and experimental anesthetics with greater range of water solubilities, the Meyer-Overton Constant—defined as $MAC \times \lambda_{O:G}$—correlates inversely with the saline:gas partition coefficient $(\lambda)_{S:G}$.[6] In addition to pharmacodynamics, partition coefficients are important to modeling inhaled anesthetic pharmacokinetics. Uptake from the lung into blood and from the blood into tissues is directly proportional to the anesthetic blood:gas partition coefficient $\lambda_{B:G}$. Agents with a high $\lambda_{B:G}$ exhibit a slow rate-of-rise of the alveolar anesthetic partial pressure, resulting in a slow rate-of-rise in anesthetic partial pressure in the central nervous system and slow onset kinetics. During recovery, anesthetics with a high $\lambda_{B:G}$ or $\lambda_{O:G}$ will exhibit slow elimination kinetics because arterial-to-alveolar partial pressure diffusion gradients are lower for a given blood anesthetic concentration and because greater anesthetic solubility will increase the total quantity of anesthetic dissolved in tissues.[7]

The λ varies with temperature,[8-11] hematocrit,[12,13] plasma protein,[13,14] osmolarity,[15] and lipid concentration.[13,14,16,17] However, $\lambda_{B:G}$ may vary between species as well. Although anesthetic partition coefficients have been measured in several species, it is difficult to know to what extent different values in animals and humans are due to methodology versus actual solubility differences. Furthermore, data for contemporary agents is entirely lacking in some animal species of veterinary and research importance.

The aims of this study were to validate a chromatography method by comparing measurements of $\lambda_{S:G}$ and $\lambda_{O:G}$ for desflurane, isoflurane, methoxyflurane, and sevoflurane to previously published values and then to use this same method and equipment to determine $\lambda_{B:G}$ of these anesthetics for humans, cats, cattle, dogs, goats, horses, pigs, rabbits, rats, and sheep.

Materials and Methods

Blood Collection and Preparation

A 120mL sample of human blood was drawn aseptically and with the written, informed consent from 4 healthy, awake, adult volunteers with the approval of the Institutional Review Board at the University of California, Davis, CA, USA. Samples were stored in separate sterile bags (Teruflex, Terumo Corporation, Tokyo, Japan) with 1 volume of citrate-phosphate-dextrose-adenine (CPDA-1) per 9 volumes of blood (13 mL CPDA-1 per 120 mL of blood). Animal phlebotomies were performed with the approval of the Institutional Animal Care and Use Committee at the University of California, Davis, CA, USA. Samples comprising <20% of estimated blood volumes were aseptically collected

without sedation in 4 cattle, 4 dogs, 4 goats, 8 horses, and 4 sheep and stored in separate sterile 10% CPDA-1 bags as described previously for human blood. Four cats and 4 pigs were anesthetized with ketamine (10 mg/kg intramuscularly) and midazolam (0.5 mg/kg intramuscularly) for aseptic collection of <20% of estimated blood volumes into separate CPDA-1 bags; all animals subsequently recovered uneventfully. In 4 rabbits and 20 rats anesthetized with ketamine (40 mg/kg and 100mg/kg, respectively, intraperitoneally) and midazolam (2 mg/kg and 5 mg/kg, respectively, intraperitoneally), a midline laparotomy was performed to expose and catheterize the abdominal aorta through which blood was collected into CPDA-1 bags until animals were exsanguinated. Because of their small size, blood from 5 rats was pooled into each collection bag to yield 4 separate and independent samples containing approximately 50mL of blood each.

Packed cell volumes (%) were measured in centrifuged microhematocrit tubes, and plasma protein (g/dL) was estimated using a hand-held refractometer (Model 10423, Leica Microsystems Inc., Buffalo Grove, IL). Hematocrit modestly affects anesthetic solubility.[12] Intra- and inter-species hemoglobin variability could thus increase solubility measurement variability; it could make it more difficult to determine whether solubility differences were due to particular blood protein and/or lipid compositions or simply due to hemoglobin concentration differences between species. Thus, packed cell volumes in all samples were adjusted to 36 to 42% by either withdrawing plasma or blood cells from bags. Potassium, sodium, and glucose were measured in whole blood using an automated analyzer (ABL800 FLEX, Radiometer America, Westlake, OH) and the sum of the glucose concentration plus two times the cation concentrations in mmol/L was used to estimate plasma osmolarity. To measure triglyceride concentrations, 40μL of a saturated $CaCl_2$ solution plus 40μL of a saturated $MgCl_2$ solution were added to a 1 mL aliquot of blood from the CPDA-1 bag which was subsequently centrifuged. The plasma was removed and analyzed using an automated colorimetric assay (Cobas C501, Roche Diagnostics, Indianapolis, IN). The accuracy of colorimetric triglyceride measurements from anticoagulated blood was validated using paired blood samples from horses and cattle with or without CPDA-1; differences between measurements were all within 10% of each other.

Ostwald Partition Coefficient Measurements

Solubility of desflurane (Suprane, Baxter, Deerfield, IL), sevoflurane (SevoFlo, Abbot Laboratories, Abbot Park, IL), isoflurane (Attane, Piramal Critical Care, Boise, ID), and methoxyflurane (Penthrox, Medical Developments International, Springvale, VIC, Australia) were measured in 0.9% NaCl (USP, Baxter), olive oil (Bertoli Extra Light, Unilever, Englewood Cliffs, NJ), CPDA-1 (Terumo Corporation, Tokyo, Japan). Blood solubility was measured within 1 week of collection, and saline anesthetic solubility was simultaneously re-measured with the same agent as a process validation control. All studies were conducted in Davis, CA which is located approximately 16m above sea level.

Three drops of pure silicone oil (Fluke, American Fork, UT) were used to coat the plungers of non-interchangeable, graduated 100mL glass syringes and were shown in a pilot study not to affect anesthetic solubility measurements in saline. The syringe chamber was sealed with a nylon stopcock, 10 to 40 mL of liquid (saline, oil, CPDA-1, or blood) was added, and the syringes were incubated in a temperature-calibrated oven at 37°C for 30min. The precise volume of liquid in the syringe was measured using calibrated scales and previously-determined densities for each study liquid.

A 20 to 40 mL volume of either a desflurane (1.080%), sevoflurane (2.610%), isoflurane (1.207%), or methoxyflurane (0.288%) calibration gas standard was anaerobically added using gravimetrically-calibrated glass syringes to each liquid-containing 100 mL syringe, thus creating a headspace with a precisely known volume. To minimize the effects of tiny

measurement error on calculations of partition coefficients, a higher ratio of liquid volume (V_L) to gas volume (V_G) in the syringe was used for the less soluble agents desflurane and sevoflurane. Conversely, a lower V_L:V_G ratio in the syringe was used for the more soluble agents isoflurane and methoxyflurane.

After addition of the gas headspace, syringes were incubated in an oven for 2 hours at 37°C and vigorously shaken every 15 min during the first hour. Anesthetic concentrations were measured using gas chromatography by direct headspace injection from a 0.25mL sample loop onto a packed 183cm, 0.32cm 10% SF-96 column with a flame ionization detector (Clarus 500, Perkin Elmer, Waltham, MA). Chromatograph temperature and gas flow protocols, along with retention times for each agent, are listed in Table 1. The detector signal was integrated over time using commercial software (TotalChrom, Perkin Elmer). Proportionality between the area under the curve and anesthetic concentration was verified using gas standards that encompassed the range of study measurements.

Liquid:gas partition coefficients ($\lambda_{L:G}$) were calculated using Equation 1, where C_0 and C_G are the respective concentrations (or areas under the chromatogram curves) of the calibration gas and the post-equilibration headspace gas, and V_L and V_G are the respective volumes of liquid and gas in the syringe. Derivation of a similar relationship used to determine halothane $\lambda_{L:G}$ via this headspace equilibration method has been published.[18]

$$\lambda_{L:G} = \frac{V_G \times (C_0 - C_G)}{V_L \times C_G}$$

Equation 1

Statistical Analysis

Measurements were described using mean±SD. Anesthetic solubility comparisons between agents and species were made using a two-way ANOVA with Holm-Sidák[19] corrections for multiple two-tailed comparisons between agents within a species and for multiple two-tailed comparisons between humans and animals for each agent (v.11, SPSS, Chicago, IL). Pearson product-moments were used to assess correlation between solubility measurements for each agent and plasma osmolarity and serum triglycerides. A $P<0.05$ defined statistical significance.

Results

Measured blood parameters are presented in Table 2, and solubilities for each of the haloethers are summarized in Table 3. The saline- and oil-gas partition coefficients were similar among all agents except methoxyflurane for which values in the present study were 5-8% lower for saline and 35-39% lower for oil. A log-log regression of human MAC for each agent[20-23] versus $\lambda_{O:G}$ values in Table 3 yielded a line described by the equation: $\log(MAC) = 1.043 \cdot \log(\lambda_{O:G}) + 2.113$, with $R^2=1.000$.

Anesthetic solubility in blood differed significantly by agent and by species (Table 3). In comparison to human blood, all anesthetics tended to be more soluble in blood from dogs, rats, and rabbits and less soluble in blood from cattle. Horse blood exhibited a mixed pattern, with greater desflurane solubility but less isoflurane solubility compared to human blood. Only goat blood approximated human $\lambda_{B:G}$ for all of the anesthetics.

The rank order for increasing liquid phase solubility was: saline ≈ CPDA-1 < blood < oil. For most species, the order of increasing $\lambda_{B:G}$ was desflurane < sevoflurane < isoflurane < methoxyflurane. However, in rabbit blood, sevoflurane was actually slightly less soluble than desflurane, although this difference was not statistically significant.

Packed cell volumes and plasma osmolarities were similar between samples, but plasma protein and triglycerides varied considerably (Table 2). Solubility for each agent positively correlated with triglyceride concentrations, but this only explained approximately 25% of the variability in $\lambda_{B:G}$ values (Table 4). Desflurane solubility also negatively correlated with plasma albumin concentration, but no statistically significant protein effects were detected for the other agents.

Discussion

Haloether anesthetic $\lambda_{B:G}$ were measured in humans and 9 animal species of research and veterinary importance using identical equipment and methodology. The consistency between partition coefficient measurements in saline, oil, and human blood measured in the present study and in published literature for contemporary agents served to validate these methods.

Although no longer widely used, methoxyflurane was included in this study as an example of a more soluble chlorofluoroether for which interspecies λ differences might be magnified. The methoxyflurane $\lambda_{O:G}$ measured here (Table 3) was considerably lower than in previous studies.[24,25] This method used for measurement could simply be less accurate for vapors and media with high solubility, as evidenced by the large standard deviations in the methoxyflurane-oil measurement. However, it could also be due to technical limitations of previous methods. For instance, solubility measurements utilizing infrared spectrometry lack precision required to quantify large changes in methoxyflurane headspace concentration caused by its very high $\lambda_{O:G}$;[25] and even with modern analyzers, anesthetic measurement accuracy can vary considerably.[26] Prior chromatographic methods with longer retention times[1,27] than in the protocol here (Table 1) increase peak asymmetry and alter the relationship between peak height and the area under the chromatogram curve, thereby introducing a small error.[28] The present study also benefited from computerized unattenuated signal integration, high digital sampling rates and high detector sensitivity, all of which increase measurement accuracy but were not as readily available during the times in which previous studies were performed.[28] Consequently, the Meyer-Overton log-log correlation between $\lambda_{O:G}$ and anesthetic MAC in humans was slightly stronger using data from the present study, as evidenced by an R^2 of 1.000 versus 0.946 from a prior analysis.[29]

One limitation of the present study was the use of blood diluted in CPDA-1, which mimics banked but not fresh blood. Yu and coworkers[30] found that the $\lambda_{B:G}$ of desflurane, isoflurane and halothane were between 12 and 13% lower in banked blood than in fresh. Comparisons between these results and our data are somewhat difficult because the prior study did not state how long blood was stored or whether results were controlled for hematocrit which would otherwise be decreased from hemodilution. Since the anesthetics are less soluble in anticoagulant than in whole blood (Table 3), the addition of 1:9 CPDA-1:blood should reduce $\lambda_{B:G}$ by 3.6 to 6.0%. However, since all blood samples contained the same volume fraction of anticoagulant, the relative results from inter-agent and species comparisons should remain unaffected.

Anesthetic $\lambda_{B:G}$ varies for many anesthetics between humans and animals as well as between different animal species. However, one exception is the goat for which $\lambda_{B:G}$ was similar to humans for all agents in our study. For a given alveolar ventilation, cardiac output, and anesthetic partial pressure gradient, the rate of anesthetic uptake and elimination is determined by the agent $\lambda_{B:G}$.[7] Hence, goats may serve as the most suitable animal model for extrapolation of inhaled anesthetic pharmacokinetic data to humans.

The agents desflurane and sevoflurane had statistically indistinguishable $\lambda_{B:G}$ values in some animal species (Table 3). Although sample sizes in this study were relatively small,

the measurement variability was likewise small. Even controlling for multiple comparisons, it was possible to detect statistically significant differences as low as 7% between means. Furthermore, in contrast to humans, the $\lambda_{B:G}$ in rabbits was actually greater for desflurane than for sevoflurane; this finding cannot be simply attributed to inadequate statistical power. When delivered at equal partial pressures, sevoflurane equilibration between the alveolar and central nervous system partial pressures may actually be slightly faster than for desflurane in rabbits. Yet since it is much less potent than sevoflurane as an anesthetic,[31,32] desflurane is typically administered at much higher concentrations, and these higher partial pressure gradients may still permit faster wash-in and washout kinetics.[7] A similar effect has been demonstrated for desflurane and nitrous oxide in humans. Despite having approximately equal $\lambda_{B:G}$ values, nitrous oxide has a much higher MAC than desflurane and is delivered at much higher concentrations, resulting in a faster rate of rise of the alveolar concentration for nitrous oxide than for desflurane.[33]

Although serum osmolality can affect $\lambda_{B:G}$,[15] the range of values in this study were limited and not correlated with solubility. Hematocrit was adjusted for all species to approximately 40%, since changes in red blood cell content could affect inhalants blood solubility.[12,13] Hence $\lambda_{B:G}$ differences cannot be due to hemoglobin quantity in this study. Red blood cells from rats and humans have different affinity for volatile organic compounds—such as toluene, chloroform and n-hexane—as well as for blood components—such as plasma proteins and hemoglobin.[34] Therefore, differences in both the blood protein concentration and the species-specific protein structure could explain differences in inhalant anesthetic $\lambda_{B:G}$. Four plausible explanations for $\lambda_{B:G}$ variability remain: species differences in hemoglobin-anesthetic binding, species differences in cell membrane anesthetic solubility, species differences in plasma protein quantity and/or anesthetic binding, and species differences in plasma lipid quantity and/or solvent properties.

Red blood cells are an important, and perhaps the major, carrier of inhalant anesthetics in blood.[13,34] Two major red blood cells components that can be responsible for $\lambda_{B:G}$ variation within species are hemoglobin and lipids. Species differences in hemoglobin-oxygen binding affinity are well established,[35,36] and are in part the result of differences in hemoglobin molecular structure.[37,38] For example, bovine hemoglobin has a lower affinity for oxygen compared to human hemoglobin because of substitution of alanine by lysine in the N-terminal that increases hydrophilicity.[36] Substitution of histidine at position 2 with methionine in bovine hemoglobin β-chains increase affinity for oxygen even in the absence of 2,3-diphosphoglycerate by creating a hydrophobic pocket.[36] Volatile and gaseous anesthetics can also bind to hydrophobic sites of proteins,[39] such as occurs for xenon in equine hemoglobin.[40] Currently unknown hemoglobin variations may be present in other species as well, and create variability in the number and/or size of hydrophobic and amphipathic pockets suitable for anesthetic binding. Further study of species-specific hemoglobin ultrastructure may be useful to potentially explain the $\lambda_{B:G}$ variability.

Red blood cell membrane lipids vary quantitatively and qualitatively.[41] Mammalian red blood cell membranes have higher concentrations of phospolipids and neutral lipids than gangliosides or glycolipids, although total lipid composition differs among species.[41] If the four haloethers used in this study follow the same pattern as xenon, which had different solubility for gangliosides, phospolipids and neutral lipids,[42] variation in $\lambda_{B:G}$ among species might be due to different lipid solvent properties of red blood cell membranes.

Albumin is the most abundant protein in mammals, and its sequence homology among humans, cows, sheep, rats, horses, dogs and rabbits is greater than 70%. However, because of albumin's importance in binding lipophilic molecules, any nonconservative structural changes could confer differences in drug binding properties.[43] In the presence of normal

concentrations of serum constituents, albumin transports three times more halothane than triglycerides,[44] and it is an important determinant of anesthetic solubility.[45] Albumin has two major drug binding sites (I and II) and these can vary among species; dog albumin has the same site II as humans, but rabbits and rats have the same site I.[43] Interestingly, inhalant anesthetics can bind to albumin in other hydrophobic pockets, and binding affinity and capacity may be affected by the number and size of these pockets. Bovine albumin has 3-5 fold more affinity than human albumin for halothane as a result of a leucine residue at the position 135 (one of the putative albumin binding sites) instead of a tryptophan, suggesting a role for aromatic amino acids in inhaled anesthetic binding.[46,47] Even within a given albumin species, affinity can differ between structural isomers, such as between isoflurane and enflurane,[48] and so relative affinities and effects on interspecies $\lambda_{B:G}$ are not generalizable across all haloethers.

Plasma triglycerides showed a positive correlation with the $\lambda_{B:G}$ of all studied agents. The species with lower plasmatic triglycerides tended to have lower $\lambda_{B:G}$; this finding is consistent with intraspecies triglyceride solubility effects,[14,17,18] but only accounts for 25% of measured interspecies variability. The remaining variability in these data is probably explained by the effects of red blood cells and plasma proteins on the anesthetic solubility in blood.

In summary, Ostwald blood:gas partition coefficients for desflurane, sevoflurane, isoflurane, and methoxyflurane are different between humans and most animals. Use of species non-specific $\lambda_{B:G}$ values in pharmacokinetic models or in calculations of blood anesthetic concentrations from headspace or alveolar gas can introduce significant error.

Acknowledgments

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MS #201111045 Final box summary

What we already know about this topic

- Accurate volatile anesthetic blood-gas partition coefficients are needed to calculate blood concentrations from end-tidal concentrations measured at equilibrium.

- The numerous factors that affect blood-gas partition coefficients could include species.

What this article tells us that is new

- Many blood-gas partition coefficients for desflurane, sevoflurane, isoflurane, and methoxyflurane measured in the blood of nine common species differed from those measured in human blood.

- These differences could be due to species-related differences in both triglyceride concentration and binding to hemoglobin, plasma protein, and red cell membranes.

Summary Statement: Blood solubility for desflurane, sevoflurane, isoflurane, and methoxyflurane differs significantly between humans and most animals. Unlike in humans, desflurane blood solubility is not statistically different from sevoflurane blood solubility for some animal species.

Table 1

Gas chromatography protocols and retention times (RT) for methoxyflurane (MOF), isoflurane (ISO), sevoflurane (SEVO), and desflurane (DES).

	MOF	ISO	SEVO	DES
Temp (°C)				
Oven	120	100	100	100
Detector	125	150	150	150
Flow (ml/min)				
Air	350	350	350	350
H_2	35	35	35	35
He	60	20	20	20
RT (min)	1.08	1.32	1.23	1.16

Table 2

Species demographic data and corresponding measurements of packed cell volume (PCV), plasma osmolarity, and serum triglycerides (mean±SD) in blood collected into citrate-phosphate-dextrose-adenine bags.

Sample	Age (years)	Breed or Strain (N)	Sex (N)	Weight (kg)	PCV (%)	Protein (mg/dL)	Osmolarity (mOsm/L)	Triglycerides (mg/dL)
Cat	4.3 ± 0.8	Domestic Short Hair (4)	M(4)	6.5 ± 0.9	39.5 ± 2.7	6.5 ± 0.3	352 ± 9	242 ± 83
Cow	1.5 –2.0	Angus (4)	F(4)	567 ± 38	37.0 ± 0.8	6.9 ± 0.2	335 ± 3	31 ± 3
Dog	4.2 ± 1.0	Labrador (2) Pitbull Terrier (1) Doberman Pinscher (1)	F(2) M(2)	34.1 ± 3.7	41.5 ±1.3	5.9 ± 0.3	345 ± 3	83 ± 19
Goat	1.0 ± 0.0	Saanen (2) La Mancha (1) Alpine (1)	F(4)	60 ± 3	40.3 ± 1.7	6.2 ± 0.2	341 ± 3	41 ± 6
Horse	15.3 ± 2.4	Quarter Horse (3) Thoroughbred (2) Sella Français (1) American Paint Horse (1) Holsteiner (1)	F(3) M(5)	587 ± 32	38.9 ± 2.2	6.1 ± 0.3	323 ± 5	34 ± 9
Human	33.8 ± 5.0		F(2) M(2)	69 ± 29	39.0 ± 1.2	7.0 ± 0.4	328 ± 3	98 ± 35
Pig	0.3 ± 0.0	Yorkshire (4)	M(3) F(1)	44 ±4	37.5 ± 1.7	5.3 ± 0.2	330 ± 3	69 ± 38
Rabbit	0.9 ± 0.0	New Zealand White (4)	M(4)	3.6 ± 0.4	39.5 ± 1.7	5.4 ± 0.2	324 ± 5	150 ± 80
Rat	1.0 ± 0.3	Brown Norway (20)	F(20)	0.37 ± 0.13	38.9 ± 2.3	6.0 ± 0.2	338 ± 13	164 ± 87
Sheep	0.3 ± 0.0	Suffolk (4)	F(4)	52 ±1	36.0 ± 0.0	5.9 ± 0.3	354 ± 10	23 ± 3

Table 3

The partition coefficients ($\lambda_{S:G}$, $\lambda_{O:G}$, and $\lambda_{B:G}$) for desflurane, sevoflurane, isoflurane and methoxyflurane (mean±SD) measured at 37°C.

	Desflurane	Sevoflurane	Isoflurane	Methoxyflurane
Human	0.498 ± 0.012	0.639 ± 0.011	1.32 ± 0.04	14.3 ± 0.4
	[0.424 - 0.522][8,30,49,50]	[0.60 - 0.686][8,51,52]	[1.25 - 1.46][10,12,50,53]	[13.0 - 16.0][9,10,25,54]
Horse	0.537 ± 0.018 *	0.648 ± 0.051	1.13 ± 0.06 *	13.0 ± 1.3
	-	[0.47][55]	[0.92][55]	-
Cattle	0.442 ± 0.032	0.521 ± 0.016 *	1.22 ± 0.03	11.3 ± 0.7 *
	-	-	-	-
Sheep	0.496 ± 0.056 S	0.557 ± 0.027 *	1.34 ± 0.09	13.2 ± 0.9
	-	-	[1.41][56]	[14.2][56]
Goat	0.520 ± 0.017 S	0.564 ± 0.042	1.37 ± 0.06	13.0 ± 0.7
	-	-	-	-
Pig	0.502 ± 0.054 S	0.521 ± 0.050	1.07 ± 0.05 *	11.1 ± 0.5 *
	[0.35# - 0.40][57,58]	[0.45# - 0.48][57,58]	[0.94#][58]	-
Dog	0.631 ± 0.015 *	0.664 ± 0.013	1.40 ± 0.16	26.1 ± 4.0 *
	-	-	[1.30][59]	-
Cat	0.583 ± 0.012 *S	0.593 ± 0.034	1.40 ± 0.08	26.4 ± 1.3 *
	-	-	-	-
Rat	0.611 ± 0.027 *	0.744 ± 0.019 *	1.41 ± 0.09	17.7 ± 1.9
	[0.79][60]	[0.75 - 0.81][60-62]	[1.56 - 3.05][60,63,64]	[25.02][64]
Rabbit	0.721 ± 0.052 *S	0.691 ± 0.030	1.37 ± 0.09	25.0 ± 2.7 *
	-	-	[1.59][3]	-
Saline	0.287 ± 0.003 *	0.329 ± 0.007 *	0.517 ± 0.014 *	4.01 ± 0.17 *
	[0.225 - 0.282][30,49,65]	[0.30 - 0.37][52,62,65]	[0.529 - 0.63][15,24,30,63,65]	[4.2 - 4.33][9,15,24]
CPDA-1	0.290 ± 0.017 *S	0.315 ± 0.006 *	0.536 ± 0.060 *	3.05 ± 0.02 *
	-	-	-	-
Olive oil	19.2 ± 0.4 *	51.3 ± 1.5 *	98.9 ± 3.1 *	611 ± 77 *
	[17.9 - 18.7][29,49]	[47.2 - 53.4][29,51,52]	[88.2 - 97.8][29,53,66]	[825 - 850][24,25]

* CPDA-1 is the citrate-phosphate-dextrose-adenine anticoagulant solution. Partition coefficient values for an agent that are statistically different from measurements in human blood are denoted by an asterisk.

S Within a species, λ was statistically different between agents, except between desflurane and sevoflurane where denoted by an s superscript.

Published measurements at 37°C for each species are included for comparison; values denoted by a number sign were measured at 38-38.5°C

Table 4

Pearson correlations between $\lambda_{B:G}$ of desflurane, sevoflurane, isoflurane and methoxyflurane with plasma osmolarity, triglycerides, and total protein.

Agent	Osmolarity	Triglycerides	Protein
Desflurane	−0.26	0.50[*]	−0.50[*]
Sevoflurane	−0.26	0.47[*]	−0.18
Isoflurane	0.36	0.54[*]	0.15
Methoxyflurane	0.32	0.48[*]	−0.10

[*] $P < 0.05$