ANAESTHETIC UPTAKE AND ELIMINATION: IS THERE A DIFFERENCE BETWEEN HALOTHANE AND ISOFLURANE IN THE DOG?

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Volatile anaesthetics are characterized by well defined relationships between their partial pressures in brain tissue and anaesthetic effect [1], and by a narrow therapeutic range [2, 3]. The ultimate goal of inhalation anaesthesia should be to obtain, rapidly and safely, an adequate partial pressure of the volatile anaesthetic in the brain. Isoflurane, because of its reportedly lower partition coefficients (blood/gas and tissue/blood), is considered to have a more rapid pharmacokinetic profile than halothane [4]. Although brain tissue partial pressure cannot be measured directly in patients, the end-tidal partial pressure can be monitored continuously [5] and should be indirectly related to the brain tissue partial pressure. In this study, a feedback system [6] was used to adjust automatically the flow of the anaesthetic agent into a closed breathing system, thereby maintaining the end-tidal partial pressure constant at the desired value. Using this system the uptake and elimination of halothane and isoflurane have been studied by following their partial pressures in arterial, cerebrovenous and mixed venous blood.

MATERIALS AND METHODS

Twelve mongrel dogs (24-39 kg) were premedicated with fentanyl 40 μg kg⁻¹ and droperidol 2 mg kg⁻¹ i.m. 1 h before placement of instrumentation. Anaesthesia was induced with pentobarbitone 12-15 mg kg⁻¹ i.v. and the trachea intubated. The dogs were placed supine and the lungs ventilated with 100% oxygen at 12 b.p.m. Tidal volume was adjusted to maintain arterial carbon dioxide (P_{a\text{CO}_2}) at 5.3 kPa. To provide basal anaesthesia during the preparation, droperidol 30 mg and fentanyl 600 μg were given initially and followed
by a continuous infusion of fentanyl 15 µg kg⁻¹ h⁻¹. Pancuronium 60 µg kg⁻¹ h⁻¹ was also given. Fluid volume was maintained with an infusion of physiological saline 2 ml kg⁻¹ h⁻¹. The dogs were heparinized with heparin 500 iu kg⁻¹. Temperature was maintained at 37 °C using a heated, thermostatically controlled, operating table. Haemodynamic monitoring consisted of ECG, arterial pressure (via a femoral artery catheter), central venous and pulmonary artery and pulmonary capillary wedge pressures (using a thermistor-tipped Swan-Ganz catheter inserted to the internal jugular vein). Iced injectate (5 ml) was used to measure cardiac output in triplicate with an Edwards 520 cardiac output computer. The retroglenoid vein was isolated, all branches were ligated except the one coming from the brain and a 1-mm diameter catheter was advanced into the sagittal sinus for sampling cerebrovenous blood. Correct placement of the catheter was verified by using contrast medium injected to the catheter.

The partial pressure of the volatile anaesthetics in arterial, cerebrovenous and mixed venous samples was determined using a head-space gas chromatographic (GC) method [7]. A tonometer was used to create blood with a well-defined partial pressure of the volatile anaesthetic for each dog before and after the experiment. Thus for each dog an average individual standard curve was obtained from these two curves relating GC counts to partial pressure. During the study, the GC counts were determined in the blood samples and the partial pressure was read from the average standard curve. A Beckman LB-2 infra-red analyser, the accuracy of which had been verified previously [8] was used for determination of the partial pressure in the inspired and expired gas as well as at the outlet of the tonometer. The partial pressure in the gas phase could then be directly compared with the partial pressure in the blood phase. The blood/gas partition coefficient was determined for each dog (table I).

Following surgical preparation and after baseline haemodynamic measurements, six dogs received halothane at an end-tidal partial pressure of halothane 6.44 mm Hg (1 MAC for dogs; 0.87 vol% at 740 mm Hg barometric pressure) and another six dogs were given isoflurane 9.47 mm Hg (1 MAC for dogs; 1.28 vol% at 740 mm Hg barometric pressure) [9]. A feedback controlled anaesthesia delivery system, developed in our laboratory [6], was able to achieve the desired end-tidal partial pressure within less than 3 min within a range of 0.70 ± 0.14 vol% for halothane and 1.2 ± 0.1 vol% for isoflurane without overshooting, and to maintain it during the subsequent uptake period. Measurements of anaesthetic partial pressures, and haemodynamic and respiratory variables were performed. After 160 min of uptake, the anaesthetic was removed from the circuit by switching a 1.0-litre activated charcoal absorber into the breathing circuit. Elimination continued for a further 60 min, and the standard measurements were performed at 161, 162, 163, 166, 169, 180, 200 and 217 min.

To compare the two agents, the arterial, cerebrovenous and mixed venous partial pressures were expressed as fractional percentages of the end-tidal partial pressure values during the uptake phase and, for the elimination phase, of
the value of the end-tidal partial pressure at the start of elimination. In the calculations, the incomplete removal of the anaesthetic by the charcoal was accounted for by subtracting the inspired partial pressure from the arterial, cerebrovenous and mixed venous partial pressure during the elimination phase and the mean inspired partial pressure of the elimination phase from the end-tidal partial pressure value at the start of the elimination (figs 1, 2).

RESULTS

In both groups of dogs, 95% of the desired end-tidal partial pressure (1 MAC) was obtained in less than 3 min and remained constant for 160 min. The inspired partial pressure, as adjusted by the feedback-control system, was significantly higher in the halothane group than in the isoflurane group. The partial pressures of halothane and isoflurane in the arterial, cerebrovenous and mixed venous blood increased at equal rates (fig. 1). The arterial partial pressures of halothane and isoflurane remained significantly lower than the end-tidal partial pressures, and the cerebrovenous partial pressures remained lower than the arterial partial pressures. In two dogs of each group, a second uptake period was started at 220 min to determine if the arterial to cerebrovenous gradient persisted. Approximately 5 h after the start of the second uptake period, the gradient between the arterial and cerebrovenous blood approached zero for both agents.

On discontinuation of the anaesthetic, the inspired concentration decreased immediately to an average value of 0.09 vol% halothane and 0.02 vol% isoflurane. When the slight difference in inspired concentration was accounted for, the partial pressure of halothane in the arterial, cerebrovenous and mixed venous blood decreased at a rate equal to that of isoflurane (fig. 2). The

| Table II. Comparison of haemodynamic variables (mean ± SEM) measured during halothane (H) and isoflurane (I) anaesthesia, during 160 min of uptake and during 60 min of elimination |
|-----------------|-----------------|-----------------|
|                | Heart rate      | Arterial pressure | Cardiac output |
|                | (beat min⁻¹)    | (mm Hg)          | (litre min⁻¹)  |
|                | H    | I    | H    | I    | H    | I    |
| Uptake         | 86 ± 4 | 94 ± 4 | 74 ± 3 | 73 ± 2 | 3.9 ± 0.2 | 3.4 ± 0.2 |
| Elimination    | 94 ± 6 | 90 ± 6 | 67 ± 5 | 59 ± 4 | 2.7 ± 0.3 | 2.5 ± 0.3 |
differences between cerebrovenous, arterial and end-tidal partial pressures were smaller during elimination than during uptake for both agents.

Table II compares heart rate, arterial pressure and cardiac output for each period. A Mann–Whitney test with a significance level of 0.05 was used to compare haemodynamic indices between the halothane and the isoflurane groups. Significant differences ($P < 0.05$) between halothane and isoflurane could not be found for any variable.

The values of additional indices (table I) were determined at the beginning and end (220 min) of each investigation.

**DISCUSSION**

The uptake and elimination of halothane by the lung have been compared [10] with those of isoflurane by determining the $FE:FI$ ratio during, and after, the simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane and nitrous oxide. The uptake of isoflurane was slightly more rapid than that of halothane, but was still considerably slower than that of nitrous oxide. The rates of elimination of halothane and isoflurane were virtually the same, that for halothane being slightly more rapid during the last phase of the elimination from the slow compartment. These results are surprising, as it would be expected that isoflurane would have faster kinetics as a result of its lower blood/gas solubility coefficient. The uptake and elimination to and from the organs seem to be important additive factors. Furthermore, if the uptake and elimination of an agent is rapid between lung and blood (because of its low blood/gas partition coefficient), this does not necessarily mean a rapid transfer between blood and brain tissue. Tissue uptake of volatile anaesthetics is determined by the perfusion of the tissue and the tissue/blood partition coefficient of the anaesthetic [4]. The brain/blood partition coefficient has recently been reported to be $1.74 \pm 0.05$ for isoflurane and $2.03 \pm 0.04$ for halothane in a group of young adults (20–50 yr) [12]. In previous investigations in man a greater difference has been reported (2.57 for halothane [4] and 2.00 for isoflurane [13]). Thus the difference in the blood/gas partition coefficient between halothane and isoflurane is much larger than that of the brain/blood partition coefficient. Enflurane, as another example, has a considerably lower brain/blood partition coefficient than isoflurane (for middle-aged adults it is $1.28 \pm 0.05$ for enflurane and $1.65 \pm 0.06$ for isoflurane), although its blood/gas partition coefficient is higher than that of isoflurane (1.91 for enflurane and 1.37 for isoflurane) [12]. Therefore, it is not possible to draw conclusions about the brain/blood partition coefficient from knowledge of the blood/gas partition coefficient. This explains why the pulmonary uptake and elimination of isoflurane may be faster than that of halothane and why neither the brain nor the whole body uptake and elimination of isoflurane are faster than those of halothane.

In this study, the rate of uptake from the arterial blood to brain tissue was found to be similar for halothane and isoflurane. The rates of elimination from the brain to the blood, and from the blood to the lungs, were also found to be similar for both agents. The unexpectedly slow elimination of isoflurane from the brain compared with that of halothane cannot be explained solely by the relatively high brain/blood solubility coefficient isoflurane. Halothane is metabolized to a considerable extent [14] and this contributes significantly to the whole body elimination of halothane and thus to the rapid decrease of halothane in the arterial blood reaching the brain.

Elimination from brain tissue is also dependent on cerebral blood flow; the higher the blood flow, the more rapid the elimination. Investigations by Theye and Michenfelder [15] Cucchiara, Theye and Michenfelder [16] have compared CBF in dogs under both halothane and isoflurane anaesthesia. CBF was increased by 43 % and 33 %, by 1.13 MAC halothane and 1.09 MAC isoflurane, respectively. Stullken and colleagues [17], however, found almost identical CBF values in dogs for 1 MAC halothane, enflurane or isoflurane, provided arterial pressure was kept constant. We did not measure CBF, but arterial pressure and cardiac output were similar in both of our groups, thus suggesting nearly identical cerebral blood flows in both groups. In man, Murphy, Kennell and Johnstone [18] demonstrated a greater cerebral vasodilator effect of halothane—which would
point to even more rapid kinetics for halothane in man.

Direct tissue determination of the anaesthetic concentration has been performed by Cohen, Chow and Mathers [19] using $^{14}\text{C}$-labelled halothane and an autoradiographic in vitro technique to study the distribution of halothane in the brain of dogs. The uptake varied considerably between different anatomical areas of the brain tissue as a result of differences in lipid content, blood flow and other unknown factors. Recently, nuclear magnetic resonance has been introduced to measure anaesthetic concentration in tissue and in vivo. Wyrwicz and co-workers [20, 21] observed an exceptionally slow elimination rate for both halothane and isoflurane. However, it was not stated whether the obtained signal originated from pure brain tissue or if other compartments, such as orbital fat—which might explain the slow kinetics—were also included.

In this study, another in vivo method of determining the brain anaesthetic concentration was used. It measures the concentration in cerebrovenous blood assuming equilibrium between brain tissue and capillary blood. This assumption is based on the theories of Zuntz [22] and Von Schrötter [23] for inert gas kinetics in the body. According to these theories, diffusion is not a limiting factor in the equilibrium process and all blood which flows through a tissue compartment partakes in this process [24]. In other words, the anaesthetic partial pressure in the cerebrovenous blood should be equal to the brain tissue pressure after the initial uptake period.

It is important to determine partial pressure—not content—of the volatile anaesthetic in the blood as the blood/gas partition coefficient may vary considerably within and between individuals, depending mainly on the lipid content in their blood [25]. Our gas chromatography method [7] compensates for interindividual and, to some extent, for intrindividual variability in the blood/gas partition coefficient by obtaining standard curves both before and after each investigation in each dog.

According to known data for cerebral perfusion rate and tissue/blood partition coefficients, equilibrium between cerebrovenous and arterial anaesthetic partial pressures should occur after about 15–20 min [4, 13]. However, in our study, even after 160 min of uptake, the cerebrovenous partial pressures for both agents were 9% lower than the arterial, and the gradient disappeared only after 5 h. During elimination, the cerebrovenous partial pressure was only slightly greater than the arterial. This difference between uptake and elimination can be explained by the fact that the desired end-tidal, or arterial, partial pressure can be achieved rapidly by unlimited increases in the inspired partial pressure during uptake. A similar process is not possible during elimination as the inspired concentration can only be reduced to zero at most. Consequently, the end-tidal or arterial partial pressure reaches the desired value (zero) more slowly, and an arterial–cerebrovenous pressure gradient cannot be built up to the same extent as during uptake.

A persisting arterial–cerebrovenous gradient could also be explained by a difference of the blood/gas partition coefficient in arterial blood compared with that in the venous blood, as a result of different partial pressures of various gases. The arterial–venous gradients of the oxygen and carbon dioxide partial pressures may affect the gas chromatographic analytical method, although we think we have ruled out these factors [7]. Another reason for a gradient could be diffusion from the brain to an adjacent slow compartment—as has been shown for the kidney [26], but not for the brain. Venous admixture from a slow compartment could also explain the gradient. Cerebral drainage in the dog is different from that in man, but the technique used in this study to collect true cerebrovenous blood from dogs has been used previously by Allott, Steward and Mapleson [26]. Rapela and Green [27] have described cerebrovenous sampling from the sagittal sinus as safe from venous admixture except for irrelevant admixture from the diploë. In this study, correct placement of the catheter in the sagittal sinus was ensured after extensive anatomical studies and using angiography. We found that slight venous admixture may occur from the periorbital area, which is comparable to the human circulation. The observed persistence of a small gradient, however, can only partly be explained by venous admixture from slow compartments. The size of such a compartment can be calculated assuming a cerebral perfusion of 0.5 litre min$^{-1}$/kg of tissue [26], a brain weight of 0.28% of total body mass $= 0.078$ kg [28], and an average body weight of 28.2 kg in the halothane group; a total cerebral blood flow of 0.039 litre min$^{-1}$ results. After 160 min the arterial–cerebrovenous gradient was 9% of the arterial partial pressure, which might be attributed to an ad-
mixture of 0.0035 litre min\(^{-1}\) blood of zero partial pressure (in reality, saturation of fat tissue is about 4% at that time, which is negligible). Assuming 0.025 litre min\(^{-1}\)/kg of fat tissue perfusion, this would correspond to the drainage from 0.14 kg of fat tissue, which is about a volume of 150 ml of fat tissue, a compartment which is almost twice as big as that of the average dog brain. Permanent binding to structures within the brain tissue might be another reason for the persistence of the gradient.

Performance studies in animals and patients are but an indirect, although clinically relevant, technique with which to compare the speed of uptake and elimination of volatile agents. Isoflurane has been found to be faster than [29–31], equal to [32] or slower than [33, 34] halothane. A multitude of factors may affect the results of such studies: (1) In a rebreathing system, the inspired concentration may be unpredictable as a result of absorption of the volatile agent to components of the breathing system [13, 35]. (2) Pulmonary uptake and elimination may vary, depending upon ventilation and perfusion [4]. (3) Because of concentration-dependent metabolism, different results may be obtained depending on whether trace concentrations of anaesthetic concentrations are used [11, 25, 36, 37]. (4) Metabolic products from halothane, such as bromide, may be pharmacodynamically active [38, 39]. (5) Brain tissue uptake and elimination depend on the brain tissue/blood partition coefficient and CBF, as already mentioned.

In summary, when the pharmacokinetics of halothane is compared with that of isoflurane, the low blood/gas partition coefficient of isoflurane points to a more rapid pulmonary uptake of isoflurane in comparison with that of halothane. If, however, the inspired concentration of halothane is augmented sufficiently relative to that of isoflurane, this difference can be overcome. The speed of uptake and elimination to and from the brain is the same for both agents. Furthermore, total body elimination is equally fast for isoflurane and halothane. Other factors, such as metabolism and the individual organ tissue/blood partition coefficient, are as important as the blood/gas partition coefficient. This explains the rapid kinetics of halothane despite its high blood/gas partition coefficient, the importance of which has often been overstressed.

**References**


**Acknowledgements**

We thank Sarah Nevill and Joan Etlinger for their editorial assistance with the preparation of the manuscript, Barbara Funk for her accurate gas chromatography analysis of the anaesthetic concentration in the blood, Joanne Gale for her careful preparation of the animals and Dr M. Wall for his expert statistical advice.


