Br. J. Anaesth. (1986), 58, 563–571

CONTROL OF END-TIDAL HALOTHANE CONCENTRATION

Part B: Verification in Dogs

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SUMMARY

Conventional anaesthetic techniques do not allow for the automatic control of end-tidal halothane concentration and, therefore, brain concentration cannot be predicted. In this study, eight dogs were ventilated with halothane in oxygen using a new closed-loop anaesthetic breathing system which provided a constant end-tidal concentration. During the first 60 min the end-tidal concentration was maintained at 0.87 vol% (1 MAC). Then followed 60 min of halothane wash-out and a further 120-min period of halothane at 1.74 vol% (2 MAC). Halothane concentrations were measured in the inspired and expired air, and in the arterial, cerebral venous and mixed venous blood. Haemodynamic and respiratory variables were measured. The system reached 95% of the target end-tidal concentration within 6 min without over-shooting. After 2 h of wash-in, significant gradients still persisted between end-tidal, arterial and cerebral venous blood concentrations. Measured uptake differed from theoretically calculated uptake by 18.3–57.6%, depending on the model used. Measured arterial and cerebral venous concentrations differed from theoretically calculated values by 7% and 17.5%, respectively. It was shown that the required end-tidal concentrations can be obtained rapidly and accurately, and that brain tissue concentrations can be predicted within certain limits.

Currently, volatile anaesthetic agents are administered according to their clinical effects as judged by changes in haemodynamic, respiratory or cerebral indices. Dosing is generally based on empiricism, which may work well in the hands of the experienced anaesthetist, while the trainee will encounter difficulties. Theoretically, knowledge of the expired concentration should permit prediction of the patient's reaction to surgical stimulation. Eger, Saidman and Brandstater (1965) developed the concept of minimum alveolar concentration (MAC) and De Jong and Eger (1975) quantitatively established the relationship between the log of the end-tidal concentration to the probit of the motor response. Roizen, Horrigan and Frazer (1981) established a similar correlation between the end-tidal concentration and the baro-adrenergic reaction of the patient. Further correlations have been established between end-tidal and cerebral (EEG) depression (Tinker, Sharbrough and Michenfelder, 1977), and readiness for intubation (Yakaitis, Blitt and Anguilo, 1977). Thus it appears that volatile agents should be delivered so as to achieve a precise end-tidal concentration.

The aim of this study was to test a new anaesthetic breathing system which controls precisely the end-tidal concentration. Arterial, cerebral venous and mixed venous concentrations were measured during the uptake of a volatile anaesthetic. The results were compared with mathematical models to predict brain and end-tidal concentrations.

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MATERIALS AND METHODS

The closed-loop breathing system with feedback control of the delivery of the anaesthetic is described in the preceding paper (Westenskow et al., 1986). In short, the system includes a 2-litre water-sealed bellow, a circulating pump and a soda-lime canister. Feedback controllers maintain

end-tidal halothane concentration and system volume at the desired level by regulating halothane and oxygen inflow to the system. As leakage from the system is negligible, oxygen and halothane uptake by the subject equal the oxygen and halothane supplied to the system.

Eight mongrel dogs (31–46 kg) were premedicated with fentanyl 40 μg kg^{-1} and droperidol 2 mg kg^{-1} i.m. 1 h before instrumentation. Anaesthesia was induced with pentobarbitone 12 mg kg^{-1} i.v. and the trachea intubated. The dogs were then placed on the operating table in the supine position and the lungs ventilated with 100% oxygen at 12 b.p.m. with a tidal volume sufficient to keep the arterial carbon dioxide at 5.0 kPa (38 mm Hg). To provide basal anaesthesia during the surgical preparation and subsequent experimental period, a bolus of droperidol 30 mg and fentanyl 600 μg was given followed by a continuous infusion of fentanyl 15 μg kg^{-1} h^{-1} and pancuronium 60 μg kg^{-1} h^{-1}. Sodium chloride 0.9% was infused at 2 ml kg^{-1} h^{-1} and temperature was maintained at 37 °C. Haemodynamic monitoring consisted of ECG, arterial, central venous, pulmonary artery and pulmonary capillary wedge pressures via a catheter in the femoral artery, and a thermistor-tipped flow-directed catheter inserted via the internal jugular vein. Cardiac output was measured in triplicate using an Edwards 520A cardiac output computer with 5 ml iced injectate.

The halothane concentrations in arterial, cerebral venous and mixed venous samples were determined using a head space gas chromatography method (Zbinden et al., 1985). The blood/gas partition coefficient was measured in each dog. The retroglenoid vein was isolated and all branches ligated except that from the brain. A 1-mm diameter Teflon catheter was advanced so that the catheter tip was located intracranially.

Fifteen minutes after completion of the surgical preparation, a complete set of measurements was obtained to establish baseline values: arterial pressure, heart rate, cardiac output, pulmonary capillary wedge pressure, oxygen uptake, and inspired, end-tidal, arterial, cerebral venous and mixed venous halothane concentrations. Halothane was then given to a feedback controlled end-tidal concentration of 0.87 vol% (1 MAC for dogs (Steffey and Howland, 1977)). Measurements were repeated 1, 2, 3, 6, 9, 20, 40 and 57 min after starting the halothane. After 60 min, halothane was removed by introducing a 1.0-litre activated charcoal absorber to the breathing system. Wash-out continued for 60 min. During this period, the same indices were measured at 61, 62, 63, 66, 69, 80, 100 and 117 min. Then the charcoal filter was removed, and in the next 2-h period the end-tidal concentration of halothane was increased to, and maintained at, 1.74 vol% (2 MAC). Measurements were taken 121, 122, 123, 126, 129, 140, 160, 180, 200 and 220 min after starting the halothane.

Inspired, end-tidal, arterial, cerebral venous and mixed venous concentrations were compared with those predicted by the kinetic model of Zwart, Smith and Beneken (1972), scaling the tissue volumes, blood volumes and functional residual capacity by 35.2/75.0 to correct approximately for weight differences between the original model (in man) and the mean weight of the dogs. The average halothane uptake measured in this study formed the input to the model. We used a blood/gas partition coefficient of 3.41, a mean arterial pressure of 88 mm Hg, a barometric pressure of 740 mm Hg, a breathing system volume of 2.5 litre, an initial cardiac output of 2.4 litre min^{-1}, an alveolar ventilation of 1.4 litre min^{-1}, and a physiological deadspace of 30% of alveolar ventilation.

Halothane uptake was also compared with the uptake model of Lowe and Ernst (1981). The following symbols are used:

t = time in minutes after start of wash-in
$\dot{Q}$ = measured cardiac output (dl min^{-1})
Ca = measured arterial blood concentration (vol%)
λ = measured blood/gas partition coefficient
W = measured body weight (kg)
$\dot{V}O_2$ = measured oxygen uptake (ml min^{-1})
$\dot{V}hal$ = calculated uptake of halothane (ml of liquid min^{-1})
/240 = used to convert ml of vapour into ml of liquid.

Three methods were used to calculate uptake. In Method A the following equation was used:

$$\dot{V}hal = \dot{Q} \cdot Ca \cdot t^{-0.5}/240. \quad (1)$$

This method used both the measured cardiac output ($\dot{Q}$) and the measured arterial blood concentration (Ca). In Method B the following equation was used:

$$\dot{V}hal = 2 \cdot W^{0.75} \cdot 3.4 \cdot 0.87 \cdot t^{-0.5}/240. \quad (2)$$

This method used body weight to predict cardiac output (Brody, 1945), a mean alveolar concen-

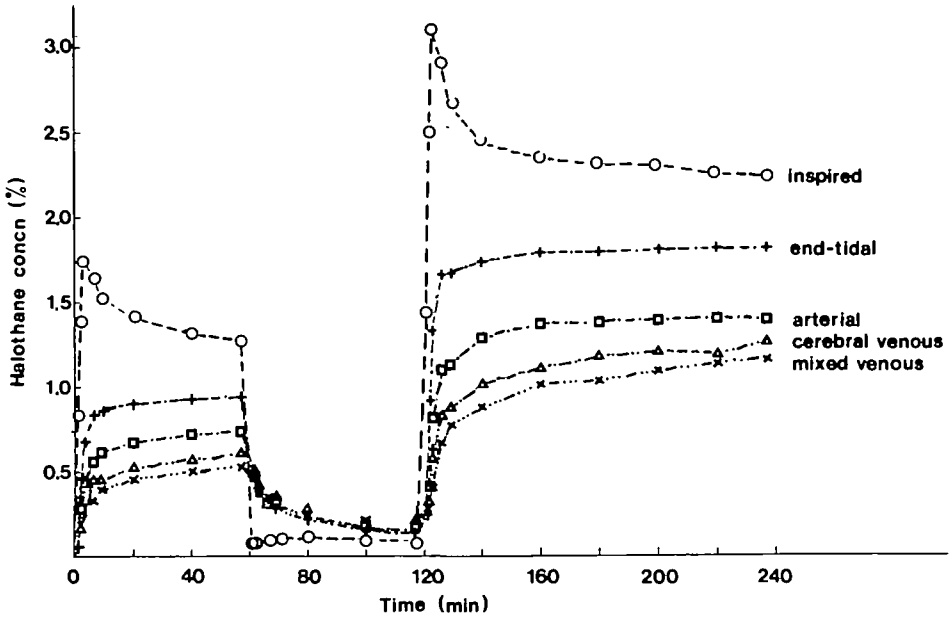

FIG. 1. Measured concentrations (means of eight dogs) of various body compartments are compared during the 1 MAC period, the wash-out period and the 2 MAC period. Blood concentrations were divided by the blood/gas partition coefficient for comparison with the concentration of the gas phase.

tration of 0.87 vol% and a blood/gas partition coefficient of 3.4 to predict arterial concentration. Method C was obtained using the following equation:

$$\dot{V}\text{hal} = \dot{V}o_2/5 \cdot 0.87 \cdot 3.4 \cdot t^{-0.5}/240. \quad (3)$$

This method used measured oxygen uptake to predict cardiac output, a mean alveolar concentration of 0.87 vol% and blood/gas partition coefficient of 3.4 to predict arterial concentration.

RESULTS

Figure 1 shows the halothane concentrations in the inspired and end-tidal gas, and in the arterial, cerebral venous and mixed venous blood during wash-in with 0.87 vol% (1 MAC) end-tidal concentration, during wash-out and during wash-in at 2 MAC end-tidal concentration. Within 6 min, 96% of the desired end-tidal halothane concentration was reached during the 1 MAC induction and 95% within the first 6 min of 2 MAC induction. After 20 min, the coefficient of variation of the end-tidal concentration was 6.3% at 1 MAC and 3.8% at 2 MAC. The end-tidal concentration increased from 1.65 vol% at 126 min to 1.79 vol% at 237 min as the result of an offset error in the feedback system (Westenskow et al., 1986). The end-tidal concentration averaged 74% of the inspired concentration after 57 min of wash-in at 1 MAC and 77% after 60 min of wash-in at 2 MAC. After the first 57 min of wash-in at 1 MAC, the arterial concentration was 78%, the cerebral venous was 64% and the mixed venous 56% of the end-tidal concentration. After 60 (120) min at 2 MAC, the arterial concentration was 77% (77%), the cerebral venous 65% (70%) and the mixed venous was 57% (64%) of the end-tidal concentration. The correlation coefficient between $(CA_{hal} - Ca_{hal})$ and $(CI_{hal} - CA_{hal})$ was 0.64 with a slope of 0.165 during the 1 MAC period (where CA_{hal} = end-tidal concentration, Ca_{hal} = arterial concentration, CI_{hal} = inhaled concentration). After inserting the charcoal absorber to the closed-loop, the inspired concentration decreased to 0.08 ± 0.01 vol% within 1 min. The end-tidal concentration decreased exponentially to 0.15 ± 0.05 vol% after 57 min. The end-tidal, arterial, cerebral venous and mixed venous concentrations decreased concomitantly.

Figure 2 compares measured concentrations in five compartments with the simulated data from the model of Zwart, Smith and Beneken (1972). The fit between measured and simulated end-tidal

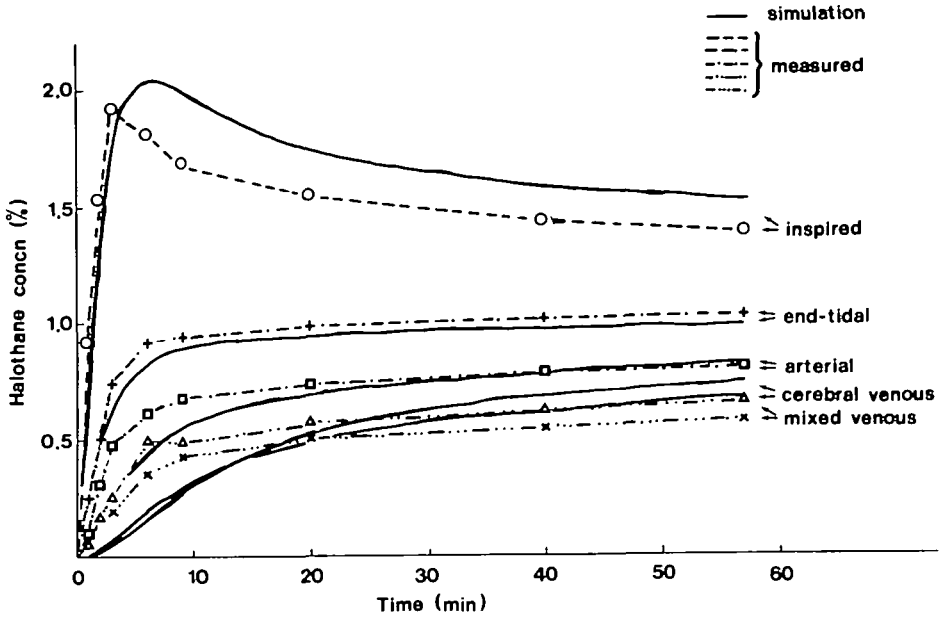

FIG. 2. Measured concentrations (means of eight dogs) of various body compartments during the 1 MAC period in comparison to theoretical values according to the model of Zwart, Smith and Beneken (1972).

concentration was good. The fit for the arterial, cerebral venous and mixed venous blood concentrations was not as good. During the first minutes, the measured concentrations increased more rapidly than the simulated.

The average rate of halothane uptake during the 1 MAC period was:

$$\dot{V}\ (\text{ml liquid min}^{-1}\ \text{kg}^{-1}) = 10.1e^{-0.56t} + 1.14e^{-0.038t} + 1.1.$$

For the 2 MAC period:

$$\dot{V}\ (\text{ml liquid min}^{-1}\ \text{kg}^{-1}) = 25.4e^{-0.77t} + 3.0e^{-0.033t} + 1.3.$$

Figure 3 compares the 1 MAC measured uptake curve with the three curves (A, B, C) calculated from equations (1), (2) and (3), which are based on Lowe and Ernst (1981).

Table I compares the areas under the experimental to the areas under the calculated values for concentration and uptake. The best fit between measured and predicted uptake was obtained when all measurable values were used (fig. 3, Curve A). The total area under the curves was almost identical, although the shapes of the curves were different, with the theoretical curve increasing

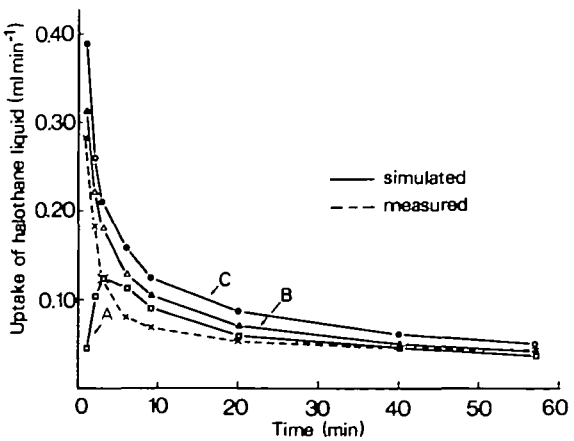

FIG. 3. Measured whole body halothane uptake and simulated uptake using the Lowe and Ernst (1981) model. In the Lowe model A measured cardiac output and measured arterial halothane concentration were used. In Lowe model B, body weight was used to predict cardiac output at a mean alveolar halothane concentration of 0.87 vol% and a blood/gas partition coefficient of 3.4 was used. Model C is the same as model B, but measured oxygen consumption was used to predict cardiac output.

first before declining exponentially. Using body weight to predict cardiac output and a mean alveolar concentration and blood/gas partition

TABLE I. *Comparison between measured and calculated values. Zwart's model is used to predict concentration in various compartments. Lowe's model is used to predict the whole-body uptake. In the Lowe model A, measured cardiac output and measured arterial halothane concentration were used. In Lowe model B, body weight was used to predict cardiac output at a mean alveolar halothane concentration of 0.87 vol% and a blood/gas partition coefficient of 3.4 was used. Model C was the same as model B, but measured oxygen consumption was used to predict cardiac output. The areas between the curves (ABC) divided by the area under the calculated curve (AUC_{calc}) are given as well as the area under the measured curve (AUC_{meas}) divided by the area under the calculated curve*

	$\frac{ABC}{AUC_{calc}} \cdot 100$ (%)	$\frac{AUC_{meas}}{AUC_{calc}} \cdot 100$ (%)
Inspired concentration	10.6	91.1
End-tidal concentration	5.3	108.8
Arterial concentration	7.0	108.5
Cerebral concentration	17.5	103.4
Venous concentration	14.9	100.0
Uptake according to Lowe A	18.3	99.1
Uptake according to Lowe B	24.8	80.1
Uptake according to Lowe C	57.6	63.5

TABLE II. *Haemodynamic variables and oxygen uptake. t = Time (min) after start of wash-in. All values are expressed as mean ± standard deviation*

	Arterial pressure (mm Hg)	Heart rate (beat min^{-1})	$\dot{Q}$ (litre min^{-1} kg^{-1})	$\dot{V}_{O_2}$ (ml min^{-1} kg^{-1})
Control	88.35 ± 35	116 ± 21	0.113 ± 0.032	5.70 ± 1.05
1 MAC (t = 57)	74 ± 19	102 ± 24	0.088 ± 0.021	5.07 ± 0.88
Washout (t = 117)	96 ± 17	125 ± 26	0.129 ± 0.030	4.99 ± 1.77
2 MAC (t = 180)	52 ± 16	115 ± 21	0.075 ± 0.020	4.75 ± 0.94
2 MAC (t = 240)	50 ± 16	114 ± 13	0.076 ± 0.023	4.78 ± 0.87

coefficient, resulted in a considerable overestimate of the uptake (fig. 3, Curve B). Using measured oxygen uptake resulted in an even greater overestimate (fig. 3, Curve C).

Haemodynamic indices, halothane uptake and oxygen uptake are displayed in table II. Arterial pressure, heart rate, cardiac output and oxygen uptake at each period were compared with the control value at the beginning of the experiment. The haemodynamic depression was no more severe immediately after induction (6 min) at both 1 MAC and 2 MAC than at the end of the period, despite high inspiratory concentrations. Thus haemodynamic indices remained stable after the beginning of the wash-in period. The cumulative halothane uptake averaged 3.8 ± 0.5 ml during the 1 MAC period and 9.3 ± 0.9 ml of liquid halothane during the 2 MAC period (this includes the system uptake of approximately 0.48 ml). The average halothane blood-gas solubility was 3.41 ± 0.11. Throughout all procedures, Pa_{CO_2} and Pa_{O_2} averaged 5.6 ± 0.1 kPa (42 ± 0.9 mm Hg) and 55.2 ± 2 kPa (414 ± 14 mm Hg), respectively. The end-tidal P_{CO_2} averaged 35 ± 0.8 mm Hg, the temperature 37.1 ± 0.8 °C.

DISCUSSION

This study describes the successful application of an automatic system which controlled the end-tidal halothane concentration. It was shown that a target end-tidal concentration could be obtained rapidly without overshoot. Furthermore, stable anaesthesia was obtained for several hours as judged by the absence of significant haemodynamic variability. Future clinical application may show that the controller is not optimized for patients: even if body weight or more sophisticated measurements (body surface, etc.) are used to preset the gains, large inter-individual and intra-individual variability in the uptake characteristics may make it necessary to use a self-adaptive controller, that is, one which tunes itself according to the patient's response.

Tatnall, Morris and West (1981) used the difference between the measured inspiratory and expiratory concentration to set the constants of their feedback system. In a study with 80 patients, Morris, Tatnall and Montgomery (1983) evaluated the system and found it able to accommodate individual patient response, to change the alveolar concentration of the anaesthetic in 1–2 min and to be resistant to measurement disturbances (diathermy). The controller needed approximately 10 min for initial identification. Thus it was not self-adaptive during the critical period of induction of anaesthesia, nor did it change its characteristics in subsequent periods. Furthermore, it was used in a completely open system. Recent work by Smith and colleagues (1984) has shown that feedback control systems are capable of assuming certain of the anaesthetist's tasks. It was also shown that control systems often performed better than the experienced anaesthetist.

Successful end-tidal control does not necessarily result in precise control of arterial or brain concentrations. During the time of observation (2 h) we observed persistent end-tidal to arterial, and arterial to cerebral venous, gradients. These gradients diminished very slowly over time. To predict the concentrations in gas, tissue and blood compartments, theoretical models for the uptake and distribution of volatile anaesthetics have been developed. Most of these models are based on the work of Kety (1951) on the uptake of inert gases. Mapleson (1962, 1963) described a kinetic model for halothane which he based on data for tissue volumes, blood flows and tissue/gas partition coefficients obtained from several investigators. He could only partially verify this model experimentally and found it limited by the assumption of a uniform blood flow per unit tissue volume. In 1973, Mapleson evaluated a new model, which considered circulation time as well. This resulted in more accurate concentration curves for the first minutes of induction of anaesthesia. The more recent models (Ashman, Blesser and Epstein, 1970; Zwart, Smith and Beneken, 1972; Fukui and Smith, 1981a, b) consider the impact of the anaesthetic concentration on haemodynamics and respiration. Fukui and Smith's (1981a) 18-compartment model, the most sophisticated, considers respiration as cyclic, and incorporates a loop between baroreceptors and heart rate which is affected by the halothane concentration. This model has not been tested experimentally and, furthermore, does not include the anaesthetic delivery system.

Uptake models usually make the following unverified assumptions:

(1) No metabolism occurs. However, up to 20% of halothane taken up by the body seems to be metabolized (Rehder et al., 1967; Sawyer et al., 1971).

(2) No diffusion exists between tissues or through the skin. The contrary was first suggested by Perl and co-workers (1965) and later verified for the skin (Stoelting and Eger, 1969a) and for the tissues (kidney and perirenal fat tissue) (Allott, Steward and Mapleson, 1976). Allott, Steward and Mapleson (1976) found that the area under the calculated arterial concentration curve was 7.4% higher than the area under the measured arterial curve, confirming an earlier and similar study by Cowles, Borgstedt and Gillies (1972).

(3) Halothane concentration does not affect organ function. Either heart or brain tissue anaesthetic concentration controls the contractility of the myocardium. Other factors also influence organ function: Munson and Bowers (1967) have shown theoretically two antagonistic effects of hyperventilation on the rate of cerebral anaesthetic uptake—hyperventilation increased the increase in alveolar concentration while hypocarbia decreased cerebral perfusion and uptake. Analogous results have been found during recovery (Stoelting and Eger, 1969b).

(4) Ventilation and circulation are continuous cyclic processes.

(5) Gas can diffuse freely through the surface of the walls of the capillaries, thus the concentration of the agent in the venous blood equals the concentration dissolved in the tissue.

(6) The concentration of the agent in the arterial blood equals alveolar concentration.

(7) The Ostwald tissue/gas and blood/gas partition coefficients are independent of concentration and remain constant.

(8) The circulation time from lungs to tissues is insignificant.

(9) Blood flow to the compartments is constant and not dependent on the anaesthetic concentration.

(10) Data for organ weights and blood flows are well defined. However, these vary considerably from author to author (Cowles, Bergstedt and Gillies, 1971; Smith and Smith, 1972; Mapleson, 1973).

(11) The anaesthetic system delivers well-defined concentrations. In none of the models is the anaesthetic breathing system included. In semiclosed systems inspired or end-tidal concentrations are not well defined.

In this study, the Zwart, Smith and Beneken model (1972) was used. It is not as complicated as the more recent Fukui and Smith model (1981a) and yet it considers the impact of anaesthetics on cardiac output and organ conductance using the quantitative data provided by Smith and Smith (1972). We were well aware that its constants originate from measurements in man and not in dogs. We did not verify all the detailed data of the model (blood flow to the brain, halothane solubility in the organs, etc.). To tune our halothane feedback system, the model was modified by the serial addition of compartments for the real and virtual volume of the anaesthetic breathing system plus the addition of delay times between these compartments. Our measured data of uptake and concentration were compared with this modified model by using the area between the theoretical and measured curves and dividing it by the total area under the theoretical curve. This resulted in an agreement of 10.6% for the inspired and of 5.3% for the end-tidal concentration. These figures could be improved considerably by decreasing cardiac output and increasing pulmonary shunt in the model. However, this manipulation led to a smaller theoretical uptake from the alveolar gas space, which in turn caused a greater deviation between theoretical and measured curves for arterial, cerebral venous and mixed venous blood concentrations.

The arterial concentration was still only 78% of the end-tidal after the first 57 min of the 1 MAC wash-in. Eger and Bahlman (1971) tried to predict arterial concentration by using the difference between inspired and end-tidal anaesthetic concentration. In human healthy volunteers, they found that the end-tidal–arterial concentration difference was always 17% of the inspired–end-tidal concentration difference. However, the correlation coefficient was only 0.60 and it was not stated over which period these measurements were performed. Applying this method to our results gave a value of 16% during the 1 MAC period and a correlation coefficient of 0.64. During the 2 MAC period, there was no correlation. We concluded that this method of predicting arterial concentration from end-tidal concentration was not valid.

The arterial to end-tidal concentration difference may be predicted by modelling. The Zwart, Smith and Beneken (1972) model allowed prediction of the arterial concentration with 7% accuracy. According to other authors, the end-tidal–arterial gradient depends mainly on the right-to-left shunt (Eger, 1964; Stoelting, 1972; Stoelting and Longnecker, 1972), but during anaesthesia for dogs this shunt is approximately only 11.2% (Pavlin et al., 1980), which is too low to explain the measured arterial–end-tidal difference. Deadspace ventilation may also contribute. Pang and colleagues (1980) found that the persistence of an end-tidal–arterial gradient resulted mainly from a continuous transfer of halothane to the blood. The transfer takes place to replenish losses attributable to metabolism, diffusion through the skin and prolonged absorption by adipose tissue.

Zwart, Smith and Beneken (1972) predicted a rapid equilibration between arterial blood and anaesthetic concentration in the brain. However, in our dog study the cerebral venous concentration was about 10% lower than the arterial even after 2 h. This can be explained by the admixture of blood from slower compartments suggested by Allott, Steward and Mapleson (1976), but a persistent gradient of the magnitude we found, could only be simulated in the model by allowing an arbitrary 8% admixture from fatty tissue to the cerebral venous blood.

Models are not only helpful in the prediction of cerebral tissue concentration from end-tidal concentration, but can also improve dosage of volatile anaesthetics. Cowles, Borgstedt and Gillies (1972) found a mean difference of 11.4% between actual and theoretical uptake for four agents. Lowe and Ernst (1981) applied another model and found that the uptake of any anaesthetic gas was proportional to the alveolar gas concentration and cardiac output, and inversely proportional to the square root of time. This model was mathematically simpler than other models and could be used easily to calculate dosage during closed-loop clinical anaesthesia. When inserting all measurable variables (blood-halothane concentration, cardiac output) to the Lowe and Ernst (1981) equation, the total area below the theoretical curve was almost equal to that below the measured uptake curve, although the shape of the curve was different as the arterial concentration increased only slowly, thereby delaying organ tissue uptake. In clinical practice, the blood-halothane concen-

tration and cardiac output are usually not continuously available. Lowe and Ernst (1981) suggest calculating cardiac output using either oxygen consumption, which can be measured easily when using a closed-loop system, or body weight and calculating arterial concentration using alveolar concentration and the blood/gas partition coefficient. However, when we inserted the measured oxygen uptake values, together with a presumed alveolar concentration and blood/gas partition coefficient, to their equation, the uptake was overestimated by 57.6%. When body weight was used, it was overestimated by 24.8%. Thus basing dosage on oxygen uptake or body weight may result in overdosage, but if the initial peak increase had been used in place of the constant arterial concentration, there would have been a better fit. The Lowe and Ernst method only gives a rough estimate of the whole body uptake of volatile anaesthetics.

The results of the present study suggest that control of the end-tidal anaesthetic concentration together with the application of a multicompartment uptake model allows for prediction of the brain tissue anaesthetic concentration. This mode of anaesthetic delivery may provide better operating conditions because of an established correlation between brain tisue concentration and the motor response (Wolfson et al., 1972). Halothane anaesthesia delivered according to clinical signs is reliable only after extensive clinical training. According to Cullen and co-workers (1972), the only clinical sign related to anaesthetic depth during spontaneous ventilation is respiration, and during controlled ventilation, arterial presure—but only during the initial stage of anaesthesia.

The next step will certainly be to include the model in the breathing system. A recent sophisticated study (Chilcoat, Lunn and Mapleson, 1984) was the first one to use a "feed forward loop" to control brain concentration with Mapleson's Model P (Mapleson, 1973). However, it is based on on-line measurements of cardiac output and arterial halothane which are difficult to perform in clinical practice. Furthermore, it used an open anaesthetic breathing system and did not verify brain tissue concentration.

The variable which is on-line, which can be measured non-invasively and which is the closest alternative to brain concentration is the end-tidal concentration. Future anaesthesia systems will, therefore, most probably control brain concentration by adjusting end-tidal concentration according to a model which is included in the anaesthetic breathing system.

ACKNOWLEDGEMENTS

We thank Barbara Funk for her very careful gas chromatographic analysis of blood-halothane concentrations and Sarah Nevill for editing and typing the manuscript.

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