

## Theoretical context-sensitive elimination times for inhalation anaesthetics

G. Lockwood\*

Centre for Perioperative Medicine and Critical Care Research, Hammersmith Hospital, Duane Road,  
London W12 0HS, UK

\*E-mail: g.lockwood@imperial.ac.uk

**Background.** Context-sensitive times to 50%, 80%, and 90% elimination from the brain have been calculated for volatile anaesthetics. This does not represent complete recovery because there are important residual effects even at 90% elimination, and the effect of anaesthetic metabolism on the rate of elimination has not been considered.

**Methods.** A physiologically based model of anaesthetic uptake and distribution was elaborated to include anaesthetic metabolism and fluoride kinetics. It was validated by comparing its predictions with real data, then experiments were undertaken to calculate the partial pressure of anaesthetic in the brain after the administration of 1 MAC of halothane, enflurane, isoflurane, sevoflurane or desflurane, or 50% of inspired nitrous oxide or xenon, for up to 6 h.

**Results.** The model generated data that were compatible with many published measurements of anaesthetic kinetics and fluoride production. Metabolism had a negligible effect on kinetics. After 4 h of anaesthesia, the model predicted body content to be 28 g nitrous oxide, 26 g desflurane, 14 g sevoflurane, or 15 g isoflurane, and 99.9% brain elimination times were then 9 h for nitrous oxide, 33 h for desflurane, 52 h for sevoflurane, and 71 h for isoflurane. At this stage of elimination, the whole body still retained between 4% and 13% of the absorbed dose. Differences between sevoflurane and desflurane were obvious only during the final stages of elimination (>99% from the vessel-rich group).

**Conclusions.** Large amounts of anaesthetics are absorbed during anaesthesia and significant amounts remain in the body for days after apparent recovery.

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In 1997, Bailey published his investigations in context-sensitive half-times and other decrement times of inhaled anaesthetics.<sup>1</sup> He pointed out that a time to half the final end-tidal concentration was not clinically useful and so he calculated times for the partial pressures of desflurane, sevoflurane, isoflurane, and enflurane in the vessel-rich group to reduce to 20% and 10% of their value at the end of administration. Even a reduction to 10% of a clinical concentration is unlikely to represent full recovery—indeed, the patients may still be at risk from an obtunded hypoxic ventilatory drive<sup>2</sup>—and kinetics may be affected by metabolism, which Bailey did not consider. This paper considers more complete recovery for a wider range of anaesthetics and the effect of metabolism.

When compartmental models are fitted to experimental data, the size and perfusion of the reconstructed, virtual

compartments are physiologically implausible.<sup>3</sup> Such a model may be useful to interpolate between measured data points, but its application outside the generally small number of original experimental subjects would be questionable. The alternative approach adopted here is to build model using standard reference values for compartment size and blood flow and then validate its predictions with the measured data.

This study was staged as follows: a pharmacokinetic model that is physiologically plausible was adopted; where values for the parameters of the Michaelis–Menten kinetics of anaesthetic metabolism were available they were included in the model; because values for these parameters are not available for most anaesthetics, a model of inorganic fluoride kinetics was developed and values of unknown metabolic parameters were chosen to give a

good fit of computed fluoride concentrations to published measurements of serum fluoride concentrations; the kinetics of the complete model were compared with the published data to provide confidence in it; finally, context-sensitive decrement times were investigated.

## Methods

A physiologically based mamillary four compartmental model of the body was used. There is no unarguable set of compartment sizes, perfusions, or anaesthetic solubilities; Tables 1 and 2 show the values used for the present study. Compartments are based on Fiserova-Bergerova's review,<sup>4</sup> but modified by partitioning the fat compartment into better and less well-perfused components; solubilities are taken from Zhou and Liu.<sup>5</sup> The computer model assumed continuous (i.e. non-tidal) ventilation and did not include a time lag for circulation, making it unrealistic for investigations of a few minutes but simpler and much faster for longer simulations. Dead-space ventilation was assumed to be 35% of the minute ventilation, and end-expired gas was assumed to be a mixture of 90% alveolar gas and 10% inspired gas: this mixture was used for comparison with earlier publications of 'alveolar' gas samples, except when explicitly stated otherwise. The rate of change of anaesthetic alveolar concentration was calculated from the difference between the rate at which anaesthetics entered (from inspired gas and mixed venous blood) and left (in expired gas and pulmonary capillary blood) the alveoli. A right-to-left shunt equal to 10% of the cardiac output (6 litre min<sup>-1</sup>) was assumed when calculating arterial anaesthetic partial pressures. Each compartment was

assumed to follow perfusion-limited kinetics, so that the partial pressure of anaesthetic in the venous blood was in equilibrium with that in the compartment. The perfusion of each compartment was constant, an unrealistic point but sound data upon which to base changes in compartmental perfusion during anaesthesia are lacking. Similarly, minute ventilation was constant at 7.5 litre min<sup>-1</sup> throughout. Anaesthetic partial pressure in mixed venous blood was calculated by a weighted average of the compartmental perfusions. All the differential equations were solved simultaneously using a fourth-order Runge–Kutta numerical routine. The output from this generic algorithm is determined by the derivatives of the variables and their calculation is described in the Appendix.

Fluoride kinetics were modelled to enable anaesthetic metabolism to be deduced from serum fluoride measurements. The model assumed that the fluoride produced by anaesthetic metabolism in the body was immediately diluted in a volume of extracellular fluid (ECF; thus giving a serum concentration) and removed from the circulation by elimination through the kidneys and uptake into two compartments that were unrelated to the compartments used for modelling anaesthetic kinetics. The values of the parameters defining the fluoride model were based on a study of the kinetics of an i.v. bolus of radioactive fluoride.<sup>6</sup> Data were extracted from their graphs and other published results using Data Thief III v.1.5 ([www.datathief.org](http://www.datathief.org)). Effective glomerular filtration rate and the characteristics of two compartments were adjusted iteratively to obtain the best fit for their serum concentration and urine content measurements. Non-radioisotope studies always have non-zero baseline fluoride serum and urine concentrations. The model was adapted to this by the constant addition of fluoride to the body throughout the model study at a rate equal to the baseline urinary excretion (deduced from the measured baseline serum concentration).

The liver compartment was taken to be the site of metabolism. Inhibition of metabolism by clinical concentrations of anaesthetics was not included in the model. There is a choice of clinically or laboratory derived values of  $K_m$  and  $V_{max}$  for halothane, and both possibilities were explored. Cahalan and co-workers calculated  $V_{max}$  to be 6.5 mg min<sup>-1</sup> and  $K_m$  0.029% from an *in vivo* study;<sup>7</sup> a later *in vitro* study identified two oxidative pathways with

**Table 1** Values used for compartment sizes and perfusion (70 kg subject, cardiac output 6000 ml min<sup>-1</sup>), based on reference values given by Fiserova-Bergerova<sup>4</sup>

	Mass (% body)	Perfusion (ml min <sup>-1</sup> 100 g <sup>-1</sup> )	Perfusion (% cardiac output)
Vessel-rich	8	47	44
Liver	6	37	26
Muscle	44	4.7	24
Fat 1	9	3.8	4
Fat 2	9	1.0	1
Vessel-poor	24	0.4	1

**Table 2** Blood:gas and tissue:gas solubility coefficients used by the model, based on values given by Zhou and Liu<sup>5</sup>

	Halothane	Enflurane	Isoflurane	Sevoflurane	Desflurane	Nitrous oxide	Xenon
Blood	2.44	1.99	1.34	0.69	0.58	0.47	0.14
Vessel-rich	3.5	2.3	2.1	1.1	0.6	0.45	0.15
Liver	5.2	3.03	2.97	1.43	0.8	0.45	0.15
Muscle	3.76	2.47	2.09	1.08	0.62	0.40	0.15
Fat	137.1	95.3	70.5	40.6	15.3	1.1	1.3
Vessel-poor	3.8	2.5	2.1	1.3	0.8	0.44	0.15

$V_{\max}$  1.8 mg min<sup>-1</sup>,  $K_m$  0.04% and  $V_{\max}$  1.32 mg min<sup>-1</sup>,  $K_m$  1%<sup>8</sup> (these  $V_{\max}$  values have been scaled up from rates per unit of liver protein to rates per 70 kg human).<sup>9</sup> Values of  $K_m$  and  $V_{\max}$  for sevoflurane and enflurane metabolism were obtained by assuming that one mole of fluoride is produced for each mole of anaesthetic metabolized (which may over-estimate, but never underestimate, the extent of anaesthetic biodegradation) and selecting values providing a good fit for clinical fluoride measurements.  $V_{\max}$  and  $K_m$  for isoflurane were set at 0.05 mg min<sup>-1</sup> and 0.03% (too small to affect kinetics) and the metabolism of the other anaesthetics was ignored.

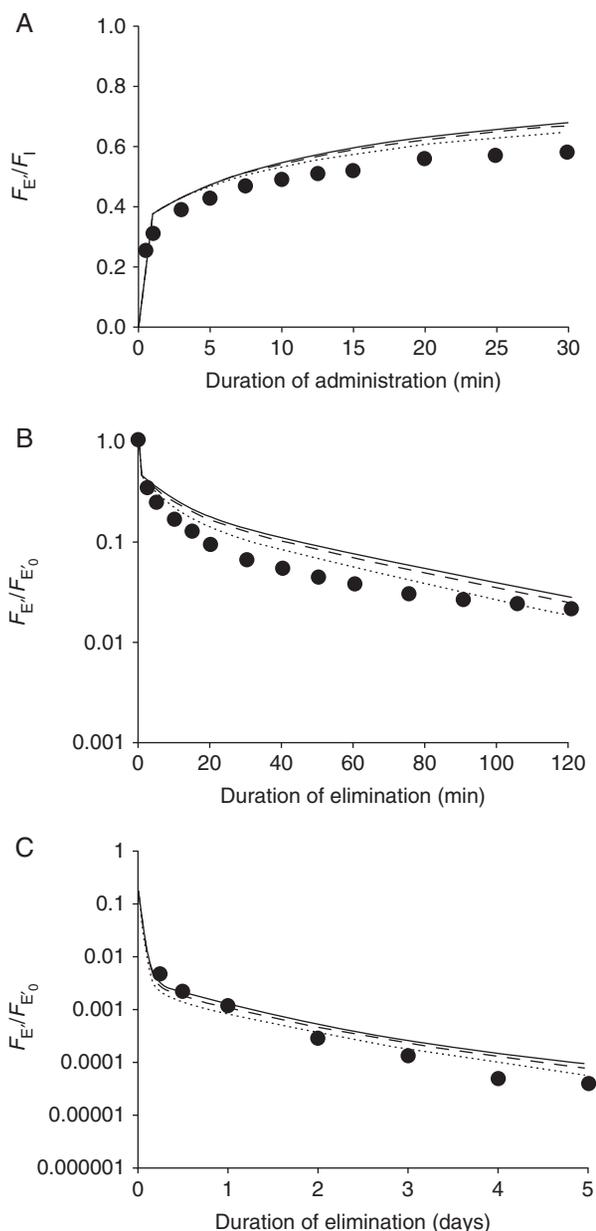
The model was then validated by reproducing experiments of brief wash-in and 5-day washout for enflurane (using model values of alveolar gas for wash-in and early washout data in recognition of the particular gas-sampling technique used in that study),<sup>10</sup> for sevoflurane,<sup>11</sup> and again for nitrous oxide, isoflurane, halothane, and desflurane.<sup>3</sup> It was required both that the predicted values lay within the 95% confidence intervals of the experimental data (where given), and that the shape of the curves representing model and experimental data were similar.

The times to 10%, 1%, and 0.1% anaesthetic partial pressure decrement in the vessel-rich group were calculated after simulated administration of 1 MAC end-expired halothane, enflurane, isoflurane, sevoflurane, desflurane (using the values recommended by Mapleson),<sup>12</sup> and of 50% inspired nitrous oxide and 50% xenon. The anaesthetics were modelled individually to exclude second gas effects.

## Results

The values shown in Table 3 gave an excellent fit for data of fluoride elimination from blood and its appearance in urine with the exception of their result at 2.5 min, which is an outlying value resulting from the bolus injection and not relevant to the present context.

The effect of varying values for the Michaelis–Menten parameters on the kinetics of halothane were marked with the best fit to experimental data using values obtained *in vivo* (Fig. 1). The choices of  $V_{\max}$  and  $K_m$  for enflurane shown in Table 4 gave acceptable fit to fluoride data from four sources.<sup>13–16</sup> It was not possible to find a single pair of values for sevoflurane that satisfied data from the several sources available,<sup>17–21</sup> but the different values of  $V_{\max}$  and  $K_m$  resulted in insignificant differences in pharmacokinetics. The values derived from the results of



**Fig 1** Comparison of the model with real measurements<sup>3</sup> of brief wash-in and extended washout of halothane (closed circles). The continuous line shows model results when no allowance is made for metabolism. The dotted line shows predicted results when the Michaelis–Menten parameters  $V_{\max}$  and  $K_m$  are set to 6.5 mg min<sup>-1</sup> and 0.029%, respectively, as derived from an *in vivo* study.<sup>7</sup> The dashed line shows predicted results using values derived by an *in vitro* study (two enzymes with  $K_m$  and  $V_{\max}$  1.8 mg min<sup>-1</sup> and 0.04%, and 1.3 mg min<sup>-1</sup> and 1%<sup>8</sup>). In plot (A), end-expired concentrations are shown as a fraction of the inspired concentration; in plots (B, C) as a fraction of the end-expired concentration at the end of administration.

**Table 3** Parameters for the fluoride model. GFR, glomerular filtration rate

Immediate volume of distribution (litre)	8
Effective GFR (ml min <sup>-1</sup> )	60
Compartment 1 volume (litre)	5
Equilibration halftime (min)	10
Compartment 2 volume (litre)	38
Equilibration halftime (min)	189

Nishiyama and Hanaoka<sup>21</sup> were used in subsequent modelling (Table 4).

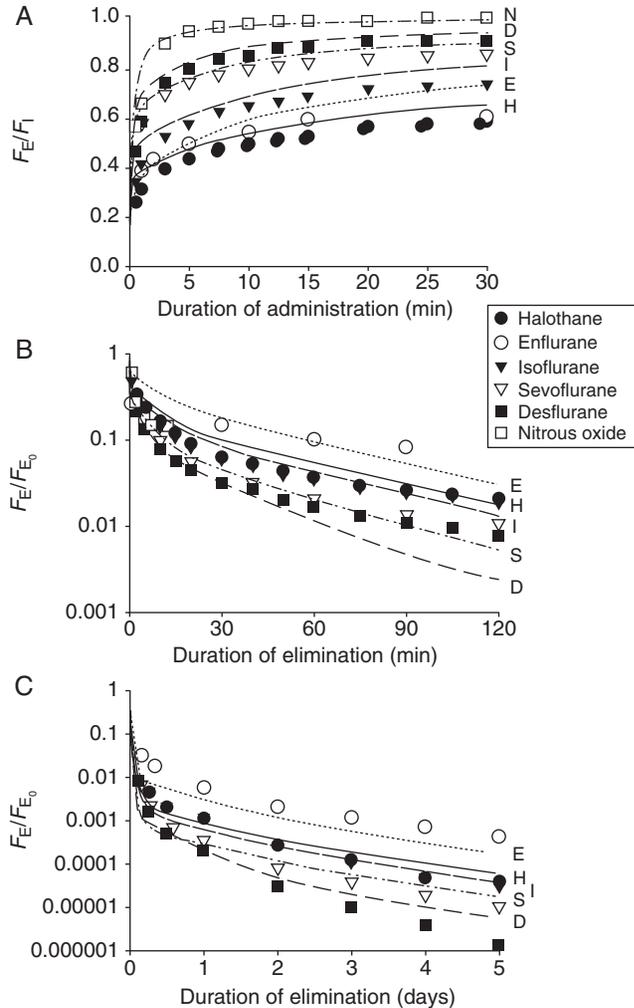
The modelling of kinetics is compared with data from Eger's group in Figure 2, showing an acceptable match for all the agents they studied<sup>3 10 11</sup> (there are no good data against which to compare computed xenon concentrations).

**Table 4** Values adopted for the model of metabolism

	$V_{max}$ (mg min <sup>-1</sup> )	$K_m$ (%)
Halothane	6.5	0.029
Enflurane	0.6	0.1
Isoflurane	0.05	0.03
Sevoflurane	1.2	0.15

**Table 5** Anaesthetic absorbed at the end of administration (g)

	30 min	1 h	2 h	3 h	4 h	6 h
Halothane	7.7	11.0	15.1	18.2	21.2	26.6
Enflurane	10.1	14.0	18.9	22.9	26.6	33.5
Isoflurane	5.7	8.0	10.8	12.9	14.7	18.2
Sevoflurane	5.4	7.6	10.3	12.4	14.3	17.8
Desflurane	9.9	13.6	18.3	22.2	25.7	31.9
Nitrous oxide	14.9	19.6	23.7	26.0	27.5	29.5
Xenon	15.6	21.5	28.2	33.1	37.1	43.1



**Fig 2** Comparison of the model (continuous lines, identity indicated by letter at extreme right: Halothane, Enflurane, Isoflurane, Sevoflurane, Desflurane, and Nitrous oxide) with real measurements of brief wash-in and extended washout (symbols).<sup>3 10 11</sup> In plot (A), end-expired concentrations are shown as a fraction of the inspired concentration; in plots (B, C) as a fraction of the end-expired concentration at the end of administration. Anaesthetics were administered for 30 min except for nitrous oxide (3.5 h) and enflurane (2 h).

Predicted uptake and metabolism are shown in Tables 5 and 6. In all the experiments the model predicted that less than 0.05% of the administered dose would remain in the tissues after 28 days.

Context-sensitive decrement times for vessel-rich tissues are shown in Figure 3. The order in which anaesthetics are 90% eliminated from the vessel-rich group matches their

**Table 6** Calculated metabolism after 28 days (per cent of the dose absorbed at the end of administration)

	30 min	1 h	2 h	3 h	4 h	6 h
Halothane	17	18	20	22	23	24
Enflurane	1.1	1.2	1.4	1.5	1.6	1.7
Isoflurane	0.2	0.2	0.3	0.3	0.3	0.4
Sevoflurane	1.9	2.2	2.6	3.0	3.3	3.7

blood:gas solubility. The order for later elimination suggests that a greater blood:fat solubility coefficient accelerates elimination to intermediate partial pressures, but slows down terminal elimination. Thus, the older anaesthetic agents (halothane, enflurane, and isoflurane) have a markedly slower 90% elimination time than sevoflurane or desflurane, but when the 99.9% elimination times are compared the differences between the older agents and sevoflurane is much less marked. Similarly, late elimination of xenon lags behind nitrous oxide, but both the gases exhibit much smaller context-sensitive elimination effects than the volatile agents.

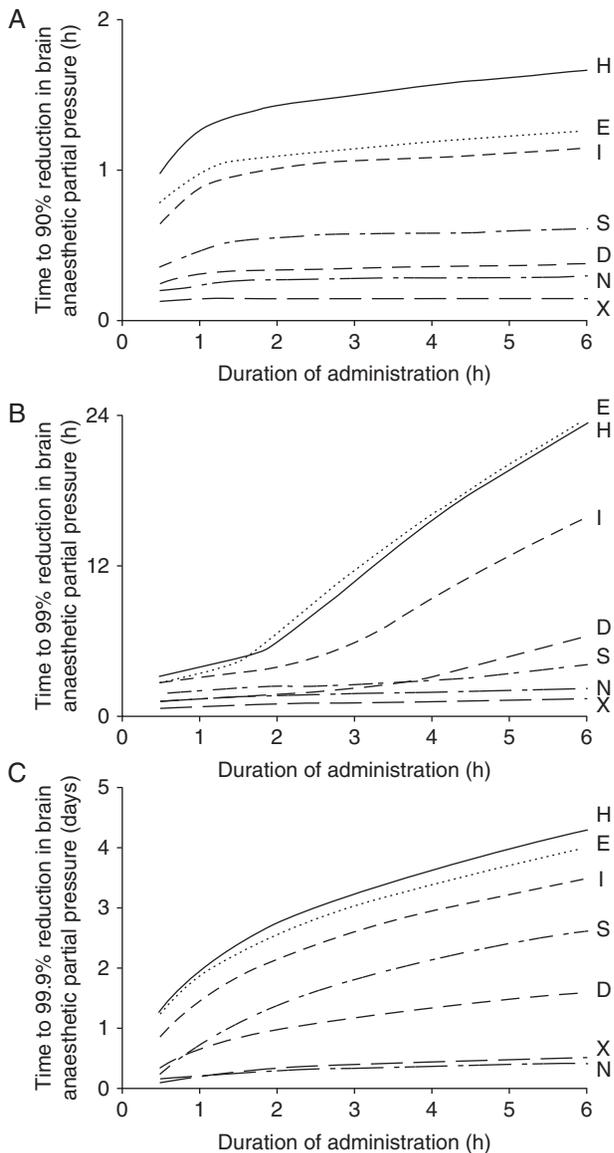
## Discussion

These simulations predict that significant amounts of volatile anaesthetics remain in the body several days after routine anaesthesia, delaying late elimination even from vessel-rich tissues.

### Limitations of the model

The results of this work are not facts but predictions obtained by extrapolating our current knowledge base. Extrapolation is a risky business, at best producing hypotheses for real-world investigation. This point is so important that it is worth listing a few of the potential pitfalls. The first of these must be the admission that all complex computer program contain errors, although the only ones discovered recently in the software used for this study have made no difference to its conclusions.

The insistence on physiologically plausible compartments implies a belief that a perfusion-limited model does indeed faithfully represent the human body. Unfortunately, when arbitrary best-fit pharmacokinetic models are interpreted in terms of real, perfusion-limited tissue



**Fig 3** The time for anaesthetic partial pressure in the brain to reduce to 10% (A), 1% (B), and 0.1% (C) of the value at the start of elimination as a function of the duration of administration. Letters identify the lines: Halothane, Enflurane, Isoflurane, Sevoflurane, Desflurane, Nitrous oxide, and Xenon. Note the markedly different scales on the vertical axes of the three plots.

compartments the results are not realistic (e.g. the volumes of all body compartments total only 25 litre for halothane, increasing to 40 litre for the desflurane model).<sup>3</sup> There are many possible explanations for this failure. For example, the underlying perfusion-limited model may be false, the values of the perfusion and solubility parameters may be wrong, the relationship assumed between anaesthetic partial pressures in end-expired gas samples and arterial blood may not hold at the very low concentrations present days after anaesthesia. In the modelling itself, the solution space for the parameters may be relatively flat, so that the fit obtained by a large deviation

in the best parameter values may only be a little worse than the best fit. It is also true that parameters derived by fitting a model to pooled data can be very different from the average of model parameters fitted to individual results. Regardless of the reason for the implausible physical interpretation of the best pharmacokinetic fit to data, the approach adopted here has been to assume normal values for the size and perfusion of tissues included in the model compartments.

The selection of tissue solubility coefficients is rather arbitrary given the choice available from previously published work. It might also be reasonable to increase the solubility of one of the fat compartments on the grounds that peripheral fat—one interpretation of the fat compartment with less perfusion—is likely to be a few degrees cooler, but plausible alternative choices for the solubility coefficients have modest effects on the simulations and do not alter the comparative conclusions.

The clinical studies selected for model validation were chosen because their experimental design allowed replication on a computer and the data reported were suitable for comparison. No single study provides all the necessary information, therefore there is no single population that the program can claim to represent. The best that can be hoped is that the model has produced data that would be unremarkable had they been measured in a patient, and that comparisons between anaesthetic agents will be qualitatively correct. The most extensive elimination data available come from Eger's group,<sup>3 10 11</sup> although, in common with most such investigations, the number of experimental subjects in each report is only in single figures and the variation in data is incompletely reported. Comparison is reassuring, for the model was designed from first principles with only the selection of values for halothane and sevoflurane metabolism based on their work. On the other hand, comparison of the current model with data from Shiraishi and Ikeda,<sup>19</sup> who measured alveolar concentrations, uptake, and estimated metabolism of enflurane, halothane, isoflurane, and sevoflurane, is disappointing (see Supplementary material). The main differences are (i) the measurements of end-expired concentration plateau after 20 min, but the model predicts a continued, slow increase; (ii) the model overestimates the uptake of isoflurane at 1 h by 50% (the estimates for the other agents are within 5%); (iii) the model overestimates the rate of elimination compared with measurements made over the first hour (i.e. the shape of the curves differ); and (iv) the model underestimates the serum fluoride during the first day after anaesthesia. Although the model can be fitted more exactly to the serum fluoride measurements without stretching credulity too far, the changes to the compartments necessary to fit the uptake data render the model unrealistic. This is not a reason to reject the model because the comparison has simply highlighted differences between the experimental results of different research groups, but it emphasizes that model predictions should be applied to the real world with caution.

### Metabolism

Working backwards from serum fluoride measurements is not an ideal way to estimate anaesthetic metabolism. Shiraishi and Ikeda<sup>19</sup> estimated metabolism by measuring uptake and the mass of fluoride excreted in urine. They used a simple model of fluoride kinetics, which assumed that half of all inorganic fluoride formed was taken up by bone and obtained values similar to those reported. The model of fluoride kinetics used in this work is more sophisticated but not necessarily better in practice: fluoride kinetics have been based on a 4-h data collection, so a third, slow compartment may have been missed. Even the adoption of a compartment with a 3 h halftime from just 4 h of measurement, while being the best fit to the data, is open to scepticism. The derived compartments may have no obvious physical analogue but at least the value for 'glomerular filtration' is close to expectations, given that fluoride is known to be re-absorbed in the tubules.<sup>22</sup> However, reduced glomerular filtration during anaesthesia will result in greater blood fluoride concentrations so the method used here would over-estimate the degree of metabolism; such an effect has been demonstrated with enflurane. The assumption that subjects with greater baseline serum fluoride have greater intake throughout the study period is untested and may be incorrect. There is evidence for the assumption that one mole of fluoride is produced per mole of anaesthetic metabolized for enflurane<sup>14</sup> and sevoflurane.<sup>19</sup>

There seems to be at least two populations of sevoflurane metabolizers: Kharasch and co-workers reported serum fluoride concentration increasing for some hours after discontinuation of sevoflurane,<sup>18</sup> but most other studies have reported a reduction in serum fluoride concentration in the first hour after anaesthesia.<sup>17 20 21</sup> It was therefore inevitable that a single pair of values for  $V_{\max}$  and  $K_m$  would not be found to satisfy all published reports. Whichever derived pair of values is chosen there is little effect on sevoflurane kinetics, although the total proportion metabolized may increase to 6.4%. In fact, metabolism affected the pharmacokinetics only of halothane, and that effect was modest. The metabolism of isoflurane is too slow to be estimated in this way, and the values used in the programme were chosen to show a small amount of fluoride production without affecting kinetics. Metabolism of desflurane was ignored because it is not associated with a significant increase in serum fluoride concentration.

### The vessel-rich group and the brain

This study has followed the design used originally by Bailey,<sup>1</sup> reporting anaesthetic elimination from the vessel-rich compartment as an index of elimination from the brain even though we know that it is not a homogeneous compartment and, within the brain, grey and white matter have differing perfusions and anaesthetic solubilities. The consequences of these differences will be greatest during

the first few minutes of elimination at which changes in cardiac output and ventilation are likely to have more effect. In clinical practice, the effects of supplemental drugs are marked at this time so that inferences about anaesthetic effects on the brain will be less relevant.

In most models of anaesthetic uptake and distribution, the liver is included in the vessel-rich group. Such a model, with a single, large vessel-rich group in which metabolism takes place would introduce two errors. First, the large volume would lessen the reduction in anaesthetic concentration caused by metabolism and so maintain the rate of metabolism. Secondly, any reduction in the concentration of anaesthetic in the vessel-rich group owing to metabolism would artificially reduce the anaesthetic partial pressures in the model brain. To avoid this error, two well-perfused, lean compartments were included in the model to separate the representation of the brain and the liver.

### Anaesthetic uptake

There are two points worth emphasis regarding anaesthetic uptake. The first is the huge dose administered. This fact is well established experimentally but mostly ignored because it cannot be easily measured clinically and it is an inevitable consequence of achieving the desired therapeutic concentration. However, we administer no other drugs in such quantities and it brings to light the potential importance of anaesthetic metabolism. The exact fraction metabolized is meaningless without knowledge of the quantity involved. The second point is that terms such as '90% elimination' are misleading. When the end-expired concentration has reduced to 10% of the concentration at the end of administration, about 85% of the xenon taken up remains in the body, that is 90% concentration elimination occurs at 14% mass elimination. At '99% elimination' about 35% remains in the body and 9% remains at '99.9% elimination'. The values for all the agents are shown in Table 7; the effect of the duration of administration is not great.

### Conclusions

Given the similarity in design between Bailey's original study of context-sensitive elimination times and the current

**Table 7** Mass of anaesthetic remaining in the body after 3 h of administration, expressed as per cent of the dose absorbed, at different stages of elimination, where elimination refers to reduction in brain anaesthetic partial pressure

	90% elimination	99% elimination	99.9% elimination
Halothane (%)	57	35	7
Enflurane (%)	64	36	7
Isoflurane (%)	61	41	8
Sevoflurane (%)	66	46	13
Desflurane (%)	73	50	10
Nitrous oxide (%)	61	21	4
Xenon (%)	78	45	11

model, it is no surprise that, where they overlap (90% elimination), the results are in broad agreement. The only exception is his prediction that the elimination of sevoflurane is markedly delayed after 100 min of administration. The model used here shows little difference between the elimination of sevoflurane and desflurane until it is 99.9% complete. This work emphasizes the very large doses of volatile anaesthetics routinely administered, their very slow terminal elimination from the vessel-rich group and their even slower elimination from the whole body.

### Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

### Acknowledgement

This work was inspired by Dr David White, who guided the development of the software until his death in 2008. I also wish to acknowledge the support of the UK NIHR Biomedical Research Centre Scheme.

### Conflict of interest

None declared.

### Appendix

For Runge–Kutta integration of differential equations, the derivatives of the variables must be calculable from their current values. The equations used are presented below in a way that is intuitive. However, this sometimes results in implicit equations that require rearrangement before they can be solved. The program is written in Pascal using the adaptive stepwise control given in ‘Numerical Recipes’.<sup>23</sup>

The subject of the model is 70 kg, has a cardiac output of 6 litre min<sup>-1</sup> that is not depressed by anaesthesia, a constant and continuous (in contrast to the more accurate tidal) minute ventilation of 7.5 litre min<sup>-1</sup> and a functional residual capacity of 2 litre. A right-to-left shunt equal to 10% of the cardiac output is assumed. The compartments are characterized by the values shown in Tables 1 and 2.

The following symbols are used:

$\lambda_{BG}, \lambda_{TG}$	blood:gas and tissue:gas partition coefficients.
$C_{comp}$	anaesthetic content in a body compartment.
$C_F, C_F(i)$	fluoride content in the whole body and in the <i>i</i> th fluoride compartment ( <i>i</i> =1 or 2).
[F]	concentration of fluoride in serum.
FRC	functional residual capacity, taken to be 2 litre.

$P_I, P_A, P_a, P_{\bar{V}}, P_{comp}$	partial pressure in inspired gas, alveolar gas, arterial blood, mixed venous blood, and a body compartment.
$\dot{Q}, \dot{Q}_{comp}$	cardiac output, flow through a body compartment.
$t_{1/2}(i)$	halftime of fluoride equilibration with the <i>i</i> th fluoride compartment ( <i>i</i> =1 or 2).
$\dot{V}_{A,insp}, \dot{V}_{A,exp}$	alveolar ventilation, inspired and expired.
$V_{comp}$	volume of body compartment.
$V_d(i)$	volume of the <i>i</i> th fluoride compartment ( <i>i</i> =1 or 2).
$V_{ECF}$	extracellular volume for fluoride distribution.

The rate of change of alveolar partial pressure for each gas is given by the difference between the rate at which volume enters and leaves the alveoli, divided by the functional residual capacity. The rate of volume entry is the product of the inspired alveolar ventilation, taken to be 65% of the minute ventilation, and the fraction of anaesthetic in the inspired gas. The rate of loss from the alveoli is the sum of that lost in expired alveolar ventilation and the difference in content between pulmonary arterial and mixed venous blood (this term will be negative during elimination)

$$\frac{dP_A}{dt} = \frac{\dot{V}_{A,insp} \times P_I - (\dot{V}_{A,exp} \times P_A + 0.9\dot{Q} \times \lambda_{BG} (P_A - P_{\bar{V}}))}{FRC}$$

The expired alveolar ventilation is derived from the inspired alveolar ventilation by subtracting the total of the rates of uptake for all anaesthetics in use (the respiratory quotient is taken to be 1.0).

For each compartment, the rate of change of anaesthetic content (i.e. the rate of uptake) is determined by classical perfusion-limited kinetics:

$$\frac{dC_{comp}}{dt} = \dot{Q}_{comp} \times \lambda_{BG} \times (P_a - P_{comp})$$

$$P_{comp} = \frac{C_{comp}}{V_{comp} \times \lambda_{TG}}$$

The arterial partial pressure is derived from the alveolar partial pressure and the mixed venous partial pressure, weighted by the pulmonary flow and the right-to-left shunt, respectively.

$$\frac{dP_a}{dt} = 0.9 \frac{dP_A}{dt} + 0.1 \frac{dP_{\bar{V}}}{dt}$$

The mixed venous partial pressure is the flow-weighted

mean of the compartment partial pressures.

$$\frac{dP_{\bar{V}}}{dt} = \frac{\sum \dot{Q}_{\text{comp}} \times P_{\text{comp}}}{\dot{Q}},$$

where the sum is taken over all body compartments.

For the compartment in which metabolism occurs, the rate of metabolism is given by Michaelis–Menten kinetics, allowing one or two enzyme systems.

$$\text{Rate of metabolism} = \left( \frac{V_{\text{max},1}}{P_{\text{comp}} + K_{m,1}} + \frac{V_{\text{max},2}}{P_{\text{comp}} + K_{m,2}} \right) \times P_{\text{comp}}$$

The rate of change of anaesthetic content and partial pressure are decremented appropriately and the rate of fluoride production is determined stoichiometrically (one mole of fluoride per mole of anaesthetic metabolized for the halogenated ethers, otherwise none). The rate of fluoride production is augmented by an amount equal to the rate of fluoride excretion, which would occur at the chosen baseline blood concentration. The rate of urinary excretion of fluoride is the product of the glomerular filtration rate and the blood fluoride concentration and this is subtracted from the rate of fluoride production to give the change of total body fluoride content.

Fluoride is distributed into two compartments:

$$\frac{dC_F(i)}{dt} = \frac{0.693 \times ([F] \times V_d(i) - C_F(i))}{1_{1/2}(i)}, \quad i=1, 2$$

$$\frac{d[F]}{dt} = \frac{dC_F/dt - \sum dC_F(i)/dt}{V_{\text{ECF}}}$$

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