Pharmacokinetics of inhaled anaesthetics in a clinical setting: comparison of desflurane, isoflurane and sevoflurane†

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The pharmacokinetic characteristics of desflurane, isoflurane and sevoflurane (16 patients for each anaesthetic) were estimated from measurements of inspired and end-expired agent concentrations and ventilation, obtained during routine anaesthesia in patients undergoing maxillofacial surgery (mean age 38 yr, duration of anaesthesia approximately 2 h). A two-compartment model described the data adequately. Although isoflurane and sevoflurane have almost the same tissue/blood partition coefficients, significant differences between substances were observed for the peripheral volume of distribution (medians and ranges: desflurane, 612 (343–1850) ml vapour kg⁻¹; isoflurane, 4112 (1472–9396) ml vapour kg⁻¹; sevoflurane, 1634 (762–8843) ml vapour kg⁻¹) and the transport clearance from the central to the peripheral compartment (desflurane, 7.0 (4.4–11.1) ml vapour kg⁻¹ min⁻¹; isoflurane, 30.7 (15.9–38.7) ml vapour kg⁻¹ min⁻¹; sevoflurane, 13.0 (9.8–22.4) ml vapour kg⁻¹ min⁻¹). Thus, during clinical anaesthesia the important characteristics of the compounds could be obtained and compared between substances from simple data.

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The ability to adjust inhalational anaesthesia is determined by the pharmacokinetic features of the anaesthetic agent, such as volumes of distribution and time constants. These variables depend on the physicochemical properties of the compounds and on cardiac output and the distribution of blood flow. Published pharmacokinetic data for inhalation agents have been obtained under controlled experimental conditions in healthy volunteers.1–4

To reduce individual variation in pharmacokinetic behaviour and allow comparisons between substances, Carpenter and colleagues5 5 gave a mixture of potent inhalational anaesthetics (methoxyflurane, halothane, enflurane, isoflurane; totalling 1.1 MAC) in addition to an intravenous anaesthetic. Thus, the pharmacokinetic behaviour of these four compounds, each by itself in subanaesthetic concentration, was measured simultaneously. The number of subjects needed in this design of study is small, and the design has gained wide acceptance. With this method, desflurane was compared with halothane and isoflurane6 in eight healthy volunteers, and sevoflurane with isoflurane in seven.7

In contrast to this procedure, inhalational anaesthesia in patients is carried out with a single volatile anaesthetic. Different inhalational anaesthetics, however, have different effects, such as changes in cardiac output and regional blood flow.8 9 These concentration-dependent effects10 11 may influence the uptake and distribution of the agent. Such effects were suggested in the first published volunteer study of the wash-in pharmacokinetics of desflurane.1 Simultaneous administration of several volatile anaesthetics prevents measurement of the specific effects of each agent,5 12 and extrapolation from such studies to clinical anaesthesia is questionable.

Additional differences between experimental and clinical anaesthesia are that in clinical practice the inhalational anaesthetic is washed into the patient’s breathing system gradually, its concentration has to be adjusted to the stimulus during surgery, and the concentrations used are greater than those used experimentally.

We set out to estimate and compare the pharmacokinetic parameters of the inhalational agents desflurane, isoflurane and sevoflurane during clinical anaesthesia, using a novel method.13

†This article is accompanied by Editorial I.
Methods

We used data from low-flow anaesthesia from 48 patients undergoing maxillofacial surgery. Patients were matched with respect to ASA classification, age, body weight and procedures with small blood loss. Anaesthesia was with desflurane, isoflurane or sevoflurane (16 patients for each anaesthetic) in a nitrous oxide/oxygen mixture (N₂O >50 vol%/O₂ >30 vol%). After a standard induction with pancuronium bromide 1 mg, sufentanil 0.015–0.02 mg, thiopental 300–500 mg and succinylcholine 60–100 mg, the patient’s trachea was intubated. Controlled ventilation was then established and the volatile anaesthetic was given with nitrous oxide. Tidal volume (Vₜ) was set to 8 ml per kg body weight (bw), and normocapnia or mild hypcapnia was achieved by adjusting the respiratory rate (RR), usually between 10 and 12 breaths min⁻¹. Alveolar tidal volume (Vₐₜ) was calculated as the measured tidal volume (Vₜ) corrected for dead space.¹³⁻¹⁴

The initial fresh gas flow (FGF) was set to 2 litres min⁻¹ and was reduced to approximately 1 litre min⁻¹ within the first 10 min. The initial vapouriser setting was 2–2.5 vol% for isoflurane and sevoflurane and 8–12 vol% for desflurane. After approximately 10 min, an end-tidal concentration of 1.3 MAC for the respective inhalational anaesthetic in nitrous oxide was achieved. During the subsequent course of anaesthesia, fresh gas flow was further reduced and the concentrations of the volatile anaesthetic were adjusted to the requirements of the surgery. (Sevoflurane is approved by German authorities for use without fresh gas flow restrictions.) Towards the end of surgery, the fresh gas concentration was usually reduced in a coasting phase, and subsequently the volatile anaesthetic and nitrous oxide were washed out with a high fresh gas flow of pure oxygen.

Uptake was calculated as the difference between F₁ and Fₑ times alveolar ventilation (Vₑₐₜab • RR). The dose administered was calculated as the area under the uptake curve during the initiation and maintenance of anaesthesia; the dose eliminated at extubation was calculated as the negative area under the uptake curve during the washout period. From these data the dose fraction remaining in the body at extubation was calculated.

The individual concentration–time curves and the uptake were fitted to a two-compartment model as described.¹³ The target variables were the volume of distribution for the central compartment (V₁), the transport clearance from the central to the peripheral compartment (Cl₁₂) and the microconstant for distribution from peripheral to central compartment (k₂₁). Based on end-expired concentrations and on the uptake, the parameters were adjusted in an additive variance model so that the calculated end-tidal concentration would correspond as closely as possible to the measured concentration (least-squares method).¹³ From these estimates of the target pharmacokinetic parameters, the microconstant for distribution from central to peripheral (k₁₂ = Cl₁₂ • V₁⁻¹), the volume of distribution of the peripheral compartment (V₂ = Cl₁₂ • k₂₁⁻¹) and the steady-state volume (Vₛₛ = V₁ + V₂) were calculated.

The variables were characterized by their medians and ranges. To check whether baseline characteristics between treatment groups were similar, a comparison of physical characteristics of the patients and of the duration of anaesthesia was carried out using multiple analysis of variance (MANOVA). An exploratory comparison of the pharmacokinetic variables for desflurane, isoflurane and sevoflurane was calculated using the Mann–Whitney U test and 95% confidence intervals based on the Hodges–Lehmann estimator¹⁵ (BIAS software).¹⁶ Using the logarithmically transformed values of the parameters the Hodges–Lehmann estimator companies two random samples by calculating the median ratio of all combinations. If the resulting 95% confidence interval includes unity, then no statistical difference between the samples exists. If 1.0 is encountered outside this interval, a difference is confirmed applying a significance level of P<0.05.

Additionally, analysis of covariance (ANCOVA) was used to check whether gender (nominal covariate), age, body mass index and/or the duration of anaesthesia (continuous covariates) had an influence on the target pharmacokinetic variables V₁, Cl₁₂ and k₂₁ in the whole data set (n = 48). As the inhalational anaesthetics were expected to differ in pharmacokinetic properties, the agent was included in the model as a nominal covariate. Assuming a factorial model, logarithmically transformed values for pharmacokinetic parameters were used in the ANCOVA. Interactions between covariates supposed to affect pharmacokinetics were not taken into account, since a sample of 48 was not large enough to reliably test 10 two-fold and a number of higher interactions between covariates in addition to their main effect. The main question was whether the covariates had an effect on the pharmacokinetic parameters, and there was no a priori evidence that interactions between covariates are important. The calculations were carried out using SPSS 7.5, module General Multivariate (SPSS Inc., Chicago, IL, USA).

Results

Table 1 gives the characteristics of the patients and the duration of anaesthesia in the patients. There were no statistically significant differences between the groups

Table 1 Characteristics of the patients and duration of anaesthesia in the three groups. Age is median (range), all other values are mean (SD). There were no statistically significant differences between the three groups.

<table>
<thead>
<tr>
<th></th>
<th>Desflurane</th>
<th>Isoflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>16 (12:4)</td>
<td>16 (15:1)</td>
<td>16 (12:4)</td>
</tr>
<tr>
<td>Age (yr) (males:females)</td>
<td>33 (29–69)</td>
<td>32 (21–73)</td>
<td>36 (21–61)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>73 (10)</td>
<td>70 (8)</td>
<td>70 (11)</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>175 (7)</td>
<td>176 (8)</td>
<td>173 (10)</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>23.7 (2.1)</td>
<td>22.3 (2.9)</td>
<td>23.7 (2.1)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>111 (44)</td>
<td>148 (41)</td>
<td>115 (57)</td>
</tr>
</tbody>
</table>


Clinical pharmacokinetics of inhaled anaesthetics

Fig 1 Concentration–time plots ($F_I$, $F_E$) and uptake during 3 h of inhalation anaesthesia with desflurane in a representative individual. The uptake (shaded area) depends on the difference $F_I - F_E$ and alveolar ventilation. Uptake during absorption ($F_I > F_E$) corresponds to the dose administered and uptake during elimination ($F_I < F_E$) to the dose eliminated. Initially, there were two rapid concentration changes. The second was carried out at 1 litre min$^{-1}$ fresh gas flow (FGF), setting the vaporiser to 18. In steady-state uptake, absorption was in the same range as that during anaesthesia with isoflurane in Figure 2, but showed a slight decrease with time. In comparison with the isoflurane and sevoflurane anaesthesia shown in Figures 2 and 3 respectively, the long coasting period (vaporiser set to 0) (between 130 and 175 min) and the larger negative component of the uptake curve are noteworthy. Elimination occurred even during coasting. The wash-out period at 3 L FGF until extubation took 12 min.

Fig 2 Concentration–time plots ($F_I$, $F_E$) and uptake measured at the tube-connector during approximately 3 h of inhalation anaesthesia with isoflurane in a representative individual. The uptake (shaded area) during absorption ($F_I > F_E$) corresponds to the dose administered and uptake during elimination to the dose eliminated via the lungs. After the initial 30 min, the uptake remained largely constant. The coasting phase under minimal flow conditions (130–145 min) was markedly shorter than in Figure 1, and during coasting $F_I$ was still greater or equal to $F_E$, indicating that distribution from the central into the peripheral compartment caused a faster $F_E$ decrease than anaesthetic elimination from the circle under minimal flow conditions. The wash-out phase at 3 L FGF until extubation was >30 min, and was longer than for desflurane and sevoflurane anaesthesia in Figures 1 and 3 respectively. (MANOVA), but the mean duration of anaesthesia in patients receiving isoflurane was approximately 30% longer than that for the other anaesthetics.

Figures 1, 2 and 3 represent typical examples of time courses for the inspiratory and end-tidal concentrations and the resulting uptake or elimination during anaesthesia with desflurane (Fig. 1), isoflurane (Fig. 2) and sevoflurane (Fig. 3). Saturation occurred most rapidly with desflurane, shown by the small difference between $F_I$ and $F_E$. The greater elimination of the compound is shown by the greater proportion of the negative area between the uptake curve and the abscissa. Sevoflurane had an intermediate position between desflurane and isoflurane. The gradient between $F_I$ and $F_E$ declined faster for sevoflurane than for isoflurane but most rapidly with desflurane. The absolute uptake was smallest with sevoflurane, but in proportion to $F_E$, this was about twice as great as the uptake of desflurane.

Table 2 shows the values for the administered, eliminated and residual doses as calculated from the uptake. Although the inspired concentration was much greater for desflurane than for isoflurane, the median of the administered dose was only 50% greater. Compared with the administered dose, the median quantity exhaled via the lungs by the time of extubation was 24% for desflurane and about 10% for isoflurane and sevoflurane.

The pharmacokinetic features of the three compounds
could be described adequately in all patients using a two-compartment model,\(^1\) which is therefore used in all further consideration of the compounds. Since only 50\% of the profiles permitted an adequate fit to a three-compartment model, the latter was discarded for this evaluation. The estimates of pharmacokinetic parameters are shown in Table 3. For comparison between the compounds, Table 4 gives the ratios of the respective parameters between the agents and 95\% confidence intervals calculated using the Hodges-Lehmann estimator. Significant differences are marked with an asterisk.

The microconstants \(k_{12}\), describing distribution from the central (1) into the peripheral (2) compartment, and \(k_{21}\), describing the redistribution and the corresponding transport clearance \((Cl_{12})\), show that isoflurane and sevoflurane are distributed into the peripheral compartment faster than desflurane. For desflurane the equilibrium constant \(k_{12}/k_{21}\) showed a more pronounced balance towards redistribution than for the other compounds. The ratios differed from those of \(k_{12}\), as the equilibrium constant is influenced by \(k_{21}\). The microconstants obtained for sevoflurane and isoflurane did not differ.

Using ANCOVA, the covariates tested explained jointly 77\%, 87\% and 50\% of the overall variability for \(V_1\), \(Cl_{12}\), and \(k_{21}\) respectively. Whereas the only significant influence on \(k_{21}\) was exerted by duration of anaesthesia, \(Cl_{12}\) and, to a lesser extent, \(V_1\) depended primarily on the volatile anaesthetic agent used (Table 5). Duration of anaesthesia as well as patient age had also a significant effect on \(V_1\).

Comparisons between compounds for pharmacokinetic parameters depending largely upon tissue/blood partition coefficients, i.e. \(V_1\) and \(Cl_{12}\), are shown together with ratios for published partition coefficients\(^{17}\) in Table 6. The marked difference in pharmacokinetic characteristics of the compounds exceeded those in the respective tissue/blood partition coefficients.

**Discussion**

The determination of the pharmacokinetic profiles of inhalational anaesthetics using respiratory gas analysis is an established method.\(^4\)\(^-\)\(^\)\(^7\)\(^\)\(^8\) The analytical procedures for volatile anaesthetics described in the literature depend primarily on gas chromatography assays, which permit the determination of concentrations over several orders of magnitude. This high sensitivity is required particularly for the determination of minute concentrations several days after exposure.

In this study, we used those data which are now routinely available from anaesthetic workstations. As described in the accompanying paper,\(^1\) the data gathered during routine monitoring, i.e. \(F_i\), \(F_{E}'\) and ventilatory parameters, are sufficient to provide reliable estimates of the pharmacokinetic parameters. This allowed the compounds to be characterised under clinical conditions. Although the estimates were derived from and therefore are valid for the duration of anaesthesia, it remains to be investigated to what extent they also apply to the time after extubation, and how long anaesthesia must be maintained until the

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**Table 2** Medians and ranges of the directly calculated parameters. *The dose remaining in the body at extubation for desflurane was significantly different \((P<0.05)\) from that for isoflurane and sevoflurane, which did not differ from each other.

<table>
<thead>
<tr>
<th></th>
<th>Desflurane</th>
<th>Isoflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose administered</td>
<td>1757 (717–3086) 1143 (82–1189) 649 (282–1786)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose eliminated</td>
<td>367 (174–819) 102 (36–593) 62 (25–286)</td>
<td>76 (55–88) 90* (81–95) 91* (80–97)</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 3** Concentration–time curves \((F_i, F_{E}')\) and uptake measured at the tube-connector during 3 h of inhalation anaesthesia with sevoflurane in a representative individual. The uptake (shaded area) during absorption \((F_i>F_{E}')\) corresponds to the dose administered, and the uptake during elimination \((F_i<F_{E}')\) to the dose eliminated via the lungs. Absolute uptake during steady state was lowest with sevoflurane, but in relation to the end-tidal concentration it was twice as high as that of desflurane. Coasting was shorter than with desflurane (Fig. 1) while uptake was zero, indicating that distribution into the peripheral compartment was as fast as anaesthetic elimination from the circle under minimal flow conditions. The duration of the wash-out phase at 3 L FGF until extubation was similar to that with desflurane anaesthesia in Figure 1.

**Table 4** Comparison between compounds for pharmacokinetic parameters. Differences are marked with an asterisk.

<table>
<thead>
<tr>
<th></th>
<th>Desflurane</th>
<th>Isoflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose not yet eliminated</td>
<td>76 (55–88) 90* (81–95) 91* (80–97)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 5** Dose and pharmacokinetic parameters depending largely upon tissue/blood partition coefficients, i.e. \(V_1\) and \(Cl_{12}\), are shown together with ratios for published partition coefficients\(^{17}\) in Table 6. The marked difference in pharmacokinetic characteristics of the compounds exceeded those in the respective tissue/blood partition coefficients.

**Table 6** Differences in pharmacokinetic characteristics of the compounds exceeded those in the respective tissue/blood partition coefficients.
It may be that

\[ k_{12} \text{ (min}^{-1}) \]

\[ 0.078 \text{ (0.029–0.186)} \]

\[ k_{21} \text{ (min}^{-1}) \]

\[ 0.011 \text{ (0.003–0.022)} \]

\[ k_{12}k_{21} \]

\[ 9.3 \text{ (4.6–27.5)} \]

\[ C_{l12} \text{ (ml}^{-1} \text{ kg}^{-1} \text{ min}^{-1}) \]

\[ 7.0 \text{ (4.4–11.1)} \]

\[ V_1 \text{ (ml}^{-1} \text{ kg}^{-1} \text{ min}^{-1}) \]

\[ 75 \text{ (49–140)} \]

\[ V_2 \text{ (ml}^{-1} \text{ kg}^{-1} \text{ min}^{-1}) \]

\[ 612 \text{ (343–1850)} \]

\[ V_{sa} \text{ (ml}^{-1} \text{ kg}^{-1} \text{ min}^{-1}) \]

\[ 698 \text{ (408–1917)} \]

Table 3 Absolute values for the estimated pharmacokinetic variables and extrapolated parameters. Values are median (range). \( k_{12} \) = microconstant from transport from central to peripheral compartment; \( k_{21} \) = microconstant from transport to central compartment; \( C_{l12} \) = transport clearance from central to peripheral compartment; \( V_1 \) = volume of distribution of the central compartment; \( V_2 \) = volume of distribution of the peripheral compartment; \( V_{sa} \) = total volume of distribution during steady state. \( V_1 \), \( V_2 \) and \( V_{sa} \) are given as milliliters of inhaled anesthetic in relation to body weight. Group differences are given in Table 4 as the ratios for the parameters

Table 4 Comparison of the pharmacokinetic parameters between anaesthetics. The ratios isoflurane/desflurane, sevoflurane/desflurane, isoflurane/sevoflurane and their 95% confidence intervals (CI) were calculated using the Hodges–Lehmann estimator. *Significant group differences at \( P<0.05 \). For explanation of pharmacokinetic parameters, see legend to Table 3

Table 5 Results of ANCOVA for the effect of independent variables on pharmacokinetic parameters. Estimates obtained for logarithmic pharmacokinetic parameters were transformed to factors describing the difference in pharmacokinetics attributable to those variables. For instance, desflurane had a 0.551-fold lower \( V_1 \) than isoflurane, and \( V_1 \) increased 1.181-fold with every hour of duration of anaesthesia. *Significant (\( P<0.05 \)) contribution of the influencing variable to overall variation. For abbreviations, see legend to Table 3

Table 6 To relate estimated pharmacokinetic parameters to physicochemical characteristics, the ratios between substances for the tissue/gas and tissue/blood partition coefficients were calculated from published data.17 Values for \( V_1 \) and \( C_{l12} \) obtained in this study, depending largely upon tissue/blood partition coefficients, are included to facilitate comparison. All estimated ratios for pharmacokinetic parameters (see also Table 4) differ from those expected from the differences in physicochemical properties. For pharmacokinetic parameters, see legend to Table 3

clinical pharmacokinetics of inhaled anaesthetics
desflurane. High uptake and high clearance into the periphery become important in the control of ‘Low and Minimal Flow’ anaesthesia, in which, compared with high-flow applications, the capacity for agent delivery is close to the uptake by the patient (determined by the concentration range of the vaporiser and fresh gas flow: 1 litre min\(^{-1}\) in low-flow and 0.5 litre min\(^{-1}\) in minimal-flow applications). Because of limited agent delivery in these circumstances, rapid distribution to the periphery considerably reduces the velocity of the concentration changes in the central compartment and makes it difficult to increase the depth of anaesthesia by increasing anaesthetic concentrations. In recovery, our data indicate that, during the wash-out period until extubation, pulmonary elimination of isoflurane and sevoflurane is less than that of desflurane (Table 2).

The observation time between intubation and extubation was insufficient to give a valid fit to a model with more than two compartments in 50% of the cases. In none of the patients could more than three compartments be fitted reliably.\(^4\) However, a fourth and even a fifth compartment have been described in other studies\(^5\) with measurements for 5–9 days after experimental anaesthesia. Over this timespan, ventilation has been assumed to correspond to that seen in normal activity of the persons under investigation. How complex a model is needed to ‘correctly’ describe the pharmacokinetics of an inhalational anaesthetic and how realistic are the underlying assumptions?\(^19\)\(^20\) This depends on the context of the question which is to be addressed by means of the model. Hypotheses about the proportion of a compound remaining in the body and possible subsequent metabolism may require complex multicompartment models. A precise allocation of several hypothetical peripheral compartments to anatomical defined tissues, however, is hardly feasible. In contrast, to describe the pharmacokinetics of inhaled anaesthetic agents during clinical anaesthesia in order to compare agents in clinical practice or to improve patient control, our simplified model appears sufficient.\(^13\)

The tables show marked variation in the pharmacokinetic parameters. To reduce this variation, the concept of simultaneous administration of potent inhalation anaesthetics was developed.\(^4\)\(^5\) Using this method, the haemodynamic conditions and regional blood flow are identical for all compounds.\(^5\) Any specific effects of the substances on these factors, which may in certain cases affect the kinetics and clinical features quite considerably, remain undetected by this method.\(^12\) The possibility that two simultaneously administered inhalation anaesthetics could mutually influence their solubility appears negligible,\(^21\) yet interactions with the metabolism of other substances and their plasma protein binding have been described \textit{in vitro},\(^22\)\(^23\)\(^24\) and specific plasma protein binding has been described at least for halothane.\(^25\) Metabolic interactions between inhalational anaesthetics were demonstrated in animals after sequential administration,\(^26\)\(^27\) but could not be confirmed in man during simultaneous administration.\(^28\) Even so, substance-specific effects of the higher clinical doses on the micro- and macrocirculation suggest that pharmacokinetic data from this type of volunteer experiment may differ from those obtained clinically.

Comparison of the volumes of distribution from our data with those from Yasuda and colleagues,\(^6\)\(^7\) derived from the simultaneous application of inhaled anaesthetics, is possible only to a limited extent as the models applied in the studies are different. Yasuda and colleagues\(^6\)\(^7\) found for halothane, isoflurane, desflurane and sevoflurane almost equal tissue blood flows and tissue volumes, indicating that the size of the virtual volumes of distribution varies according to the partition coefficients. This pattern of distribution relates to a time point when all redistribution processes were in steady state or when the compounds under investigation were distributed and redistributed under almost identical conditions.

For the time between intubation and extubation, our data suggest that the observed differences between the volumes of distribution are not fully explained by differences in the partition coefficients of the compounds (Table 6). The peripheral volume of distribution for isoflurane is more than 6 times and that of sevoflurane more than 2 times greater than that of desflurane (Table 4). There is no tissue for which a difference in partition coefficient of that magnitude has been described. Therefore, differences in blood flow distribution must be considered. For isoflurane, it appears that during anaesthesia a pronounced redistribution of blood flow occurs into organs with large storage capacity. For sevoflurane this effect seems to be less pronounced. This assumption is supported by the data for the transport clearance \(Cl_{12}\), the most stable parameter,\(^13\) which is more than 4 times greater for isoflurane and about 2 times greater for sevoflurane than for desflurane, yet it should be only 1.5-fold greater if only the tissue/blood partition coefficients are considered (Table 6). Unexpectedly large peripheral volumes of distribution, which correspond to considerable uptake, have indeed been described for isoflurane during clinical anaesthesia.\(^4\) The finding that isoflurane, even at concentrations around 1 MAC in oxygen, markedly increased the blood flow into muscle tissue in humans\(^29\) and in animal experiments might serve as an explanation.\(^10\) Thus, the pharmacokinetic parameters of our simple two-compartment model could provide a better description of intraoperative processes than the differences in tissue solubility\(^30\) between desflurane and isoflurane.

Because of a slower distribution into a smaller \(V_2\) for desflurane compared with isoflurane or sevoflurane, distribution processes should contribute only slightly to the decrease in concentration in the central compartment after 2 h of anaesthesia with desflurane. However, recent reports on anaesthetic uptake at constant end-tidal concentrations in closed systems describe, after an initial wash-in, a constant rather than a declining uptake of desflurane and isoflurane\(^31\)\(^32\) in the first hour of anaesthesia. These results are said to be in contrast\(^32\) to the square root of time model of anaesthetic uptake of Lowe and Ernst\(^13\) and the
predictions derived from multicompartment models. The two-compartment model, however, was reliably fitted to the measured parameters. Although the model implies decay of uptake, it seems to be almost constant after several minutes (Figs 1 and 2), at constant end-tidal concentrations. With respect to the time constant of distribution, the changes are too small to show a distinct decrease. Thus, uptake appears to be constant, although a biexponential fit for uptake is appropriate.

In conclusion, data from clinical anaesthesia records allow important features of desflurane, isoflurane and sevoflurane to be derived and compared between agents without additional sampling from the patient. The results support clinical observations and data derived from other settings showing that distribution into peripheral compartments is most pronounced for isoflurane and least pronounced for desflurane.

References

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