Pharmacokinetics of inhaled anaesthetics in a clinical setting: description of a novel method based on routine monitoring data†

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Pharmacokinetic parameters of inhaled anaesthetics have previously been assessed experimentally in healthy volunteers. In contrast, we developed a method to estimate pharmacokinetic parameters under clinical conditions. We obtained data from the continuous routine monitoring of fractional concentration and ventilation during anaesthesia with desflurane, isoflurane and sevoflurane. By simulation studies, we assessed the effects of several sources of variation, including the noise of measurement, the second gas effect and rounding errors or a limited number of displayed digits. Stable fits to a two-compartment model were obtained for both real and simulated data sets in all cases. The most stable parameter was the intercompartmental clearance, and the most sensitive parameter was the volume of distribution. The bias in pharmacokinetic parameters caused by adding errors to measured concentrations was similar for the different compounds. We conclude that the model allows the estimation of an alternative set of pharmacokinetic parameters that can reliably describe the behaviour of volatile anaesthetics under clinical conditions, and allow comparison between agents.

The pharmacokinetics of inhaled anaesthetics has been assessed in experimental settings in healthy volunteers. Previous studies obtained classical wash-in and wash-out curves from step changes of the inspired partial pressure of the anaesthetic.1–3 These curves are easily analysed, even with graphical methods, to give different time constants representing different virtual volumes of distribution. Blood or expired vapour partial pressures in these studies were determined by gas chromatography. Samples from the blood or the expired gas were taken first at frequent intervals (1–3 min), and subsequently less frequently. During wash-out, samples were drawn for up to several days after drug administration, allowing the construction of pharmacokinetic models with up to four or five compartments.1–3

These experimental conditions are not easily transferred to clinical anaesthesia, when volatile anaesthetic partial pressure is increased or decreased in relation to the surgical stimulus. The variable inspired and end-tidal partial pressure of the compound under investigation makes pharmacokinetic variables difficult to assess. As pharmacokinetic parameters vary between subjects, an adequate number of subjects must be investigated in order to obtain reliable mean values. For the comparison of different compounds, intraindividual variation must also be considered. One of the merits of a purely experimental approach, with simultaneous administration of several anaesthetics, is that intraindividual variability is minimized. However, for ethical and cost reasons, only a few subjects were tested in such studies.2,3

In the present investigation, we examined an alternative approach. In current anaesthetic workstations, ventilatory variables as well as the inspired and end-tidal anaesthetic concentrations are measured continuously and recorded frequently. Therefore, from a formal point of view, the input function ($x_i(t)$) and the system response (output function, $x_o(t)$) of the pharmacokinetic system under investi-

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gation is recorded almost continuously, so that we can determine the characteristics of the transfer system. Figure 1 illustrates the formal description of the transfer system. As a function vs time it is described by pharmacokinetic parameters. Pharmacokinetic methods can be used to describe the transfer function and to determine the implicit differential equations.

We set out to develop and describe a method that can derive pharmacokinetic parameters for inhaled anaesthetics from routine data in patients, and to assess the stability of the parameter estimates obtained. We used clinical data for the entire period of anaesthesia from intubation to extubation to establish a two-compartment model and to estimate pharmacokinetic parameters. We found distinct differences between desflurane, isoflurane and sevoflurane other than differences that could be attributed to their physicochemical properties.4–7

Methods

Acquisition of experimental data

Data from low-flow anaesthesia in 48 patients receiving desflurane, isoflurane or sevoflurane (16 patients for each anaesthetic) were used. Mean duration of anaesthesia was 111 (SD 44) min for desflurane, 148 (41) min for isoflurane and 115 (57) min for sevoflurane. Details of anaesthesia are described in the accompanying paper.4 The concentrations of these compounds and the ventilation data provided by the monitoring system of the Ohmeda Modulus CD/CV were recorded at 20-s intervals using the integrated floppy disk drive. Alveolar ventilation (V_{alv}) was estimated from the inspiratory measured tidal volume (V_i) less a dead space of 2.0 ml per kg body weight, corresponding to 25% of the set tidal volume.8

After calibration, the accuracy of the internal gas analyser of the Ohmeda Modulus CD/CV was assessed using mixtures of calibration vapour and ambient air. In the range from 0 to 1.1 vol% isoflurane the variation was less than ±0.5 of the least significant digit. The accuracy was the same after 6 h of continuous working and after 1 week.

A modified Ohmeda Miniasbsorber System circle system was used which did not influence the measured inspiratory concentration.9 The accuracy of the turbine volumeter was measured by ventilating an adiabatic test lung. Variation was less than ±5% throughout the operating range.

Estimation of parameters

Based on the direct relationship between the volume of a gas and its molar mass, pharmacokinetic parameters were derived from the inspired and end-expired vapour concentration vs time and alveolar ventilation using a two-compartment model. The central compartment includes the lung and very rapidly equilibrating tissues (not anatomically defined); the peripheral compartment is the rest of the body. The data were also assessed using a corresponding three-compartment model, but this gave stable results in only 50% of data sets and is therefore not described further.

The following pharmacokinetic parameters were derived from inspired and end-expired concentration values and alveolar ventilation: volume of distribution in the central compartment, V_1; intercompartmental clearance, CL_{12}; measuring transport into the periphery; and microconstant, k_{21}, for transit from the periphery. To this end, a two-compartment model was applied to describe changes of expired concentrations (equation 1) and concentration in the peripheral compartment (equation 2) for inhaled anaesthetics with time:

\[
\frac{d}{dt} V_1 F_1 = -k_{12} F_1 V_1 + k_{21} F_2 V_2 - V_{alv} F_1 + V_{alv} F_1 \tag{1}
\]

\[
\frac{d}{dt} V_2 F_2 = k_{12} F_1 V_1 - k_{21} F_2 V_2 \tag{2}
\]

V_1 and V_2 denote the central and peripheral volume of distribution respectively, k_{12} and k_{21} the microconstants, F_1 and F_2 the fraction of anaesthetic vapour in the central and peripheral compartments respectively, and V_{alv} the alveolar ventilation. Because the system assumes that the central volume of distribution is well stirred, F_1 is assumed to equal the fraction of anaesthetic in the end-expired gas, F_{E'}; Thus, F_{E'} is used subsequently in place of F_1. In addition, the uptake of volatile anaesthetic U(t) can be expressed as

\[
U(t) = V_{alv}(F_1 - F_{E'}) \tag{3}
\]

The following equation was used for the calculation of intercompartmental transport clearance CL_{12}:

\[
CL_{12} = k_{12} V_1 = k_{21} V_2 \tag{4}
\]

Based upon this definition, equations (1) and (2) become

\[
\frac{d}{dt} V_1 F_1 = -CL_{12} F_{E'} + CL_{12} F_2 + U(t) \tag{5}
\]

\[
\frac{d}{dt} V_2 F_2 = -CL_{12} F_{E'} - CL_{12} F_2 \tag{6}
\]

Solving for F_{E'} and F_2 yields

\[
\frac{d}{dt} F_{E'} = \frac{CL_{12}}{V_1} F_{E'} + \frac{CL_{12}}{V_1} F_2 + \frac{U(t)}{V_1} \tag{7}
\]

\[
\frac{d}{dt} F_2 = \frac{CL_{12}}{V_2} F_{E'} - \frac{CL_{12}}{V_2} F_2 \tag{8}
\]

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The microconstant $k_{21}$ can be interpreted as the inverse of the transit time in the periphery. Subsequently, we used $V_1$, $CL_{12}$ and $k_{21}$ to characterize the two-compartment model.

The solution of the differential equation can be obtained by solving the two-compartment model with zero order absorption for each sampling interval after algebraic manipulation of the uptake term. The differential equations were solved explicitly for each sampling interval to obtain the calculated expired fractional concentration, $F_E^{\text{calc}}$. $F_E^{\text{calc}}$ was then fitted to the observed values by the least squares method based on the simplex algorithm. An additive error model was assumed because the rounding errors of the recorded concentrations are absolute errors.

**Simulation studies**

We assessed the robustness of the parameter estimates. These estimates may be influenced by factors such as measurement noise, changes in carbon dioxide, oxygen and water concentrations in the measured volumes, the second gas effect, rounding errors of the measurement device, and a limited number of displayed digits. In the pharmacokinetic system, measurement noise is present in the input and output variables. Because of subsequent calculation of end-expired concentrations, the second gas effect, mimicking an increase in ventilation, may be important at the start of anaesthesia. It can be simulated by an artificial increase in uptake. The loss of precision as a result of rounding errors by the measurement device may be assessed by normally distributed random replications.

Thus, the effect of the presumed confounding factors can be assessed from the dependence of the curve fit on random and/or systematic error of the input signal, on the sampling rate and on random error of the output signal.

In the following simulation studies using published routines, we made worst-case assumptions about the magnitude of the error that could confound the estimation of the pharmacokinetic parameters.

**Study A: random error of the input signal**

To consider this uncertainty in the uptake $U(t)$, the input variables $F_1$ and $V_{div}$ were disturbed simultaneously by independent log-normally distributed random noise. A standard deviation of $\sigma=0.1$ was used to simulate arbitrary non-specific noise causing 10% variation in both input variables, and $\sigma=0.025$ was applied to assess the 2.5% increase in variation expected by the round-off error at a concentration of 1–10 vol% when two digits were available.

**Study B: systematic bias combined with round-off error of the input signal**

For the initial 10 min the uptake was increased by a factor of 1.2 to simulate an initial second gas effect. For the round-off error of the uptake, $\sigma=0.025$ was assumed, as in study A.

**Study C: decreased sampling rate**

The sampling rate was diminished by factors of 2, 3 and 4 to determine its influence.

**Study D: random error of the output signal**

The sampled expiratory concentrations were distorted by log-normally distributed random noise ($\sigma=0.1$).

In all cases, simulation was based on the 16 measured time courses of desflurane, isoflurane and sevoflurane anaesthesia. When random errors were applied (in studies A, B and D), 20 data sets were generated based on each of the measured time courses. From these simulated data sets, pharmacokinetic parameters were estimated as described above. The mean difference between the model parameters determined from the measured time courses and those determined from the perturbed time courses was defined as bias. The mean coefficient of variation of the parameters estimated from artificially perturbed time courses was defined as scatter.

**Results**

**Goodness of fit**

Stable fits were achieved with the two-compartment model described for both real and simulated data sets in all cases. The average (SD) of the root mean square errors for $F_{E,\text{calc}}$ were 0.16 (0.04) (max. 0.21) vol% for desflurane, 0.05 (0.01) (max. 0.07) vol% for isoflurane and 0.05 (0.01) (max. 0.08) vol% for sevoflurane in real data sets, while measured expiratory concentrations reached 9.5 vol% for desflurane, 1.5 vol% for isoflurane and 3.4 vol% for sevoflurane.

In no case did the individual plots of residuals vs time and estimated vs measured concentration show that the model was incorrect. To illustrate the goodness of fit for each of the volatile anaesthetics, the residuals of the data sets with the highest mean square errors are shown in Figure 2.

The results from the original data sets are reported in the accompanying paper.

**Robustness of parameter estimates**

The bias and scatter for the parameters $V_C$, $CL_{12}$ and $k_{21}$ are shown in Tables 1, 2 and 3 respectively. The scatter reflects the introduced error in all cases. The most stable parameter was the intercompartmental clearance. The volume of distribution was more dependent on the magnitude of error than the remaining parameters. The data with 20% initial systematic error, simulating a second gas effect, gave the largest bias; visual examination of the residual plots shows a slightly impaired fit for the first 10 min. The effect of variation in the input value was considerably more pronounced than that of the output value. A reduction of the sampling rate to 1/4 changed the estimated volume of distribution by up to 43% (mean), whereas the other parameters were not changed by more than 15% (mean). The impact of the error introduced in the parameter estimates was similar for the different inhaled anaesthetics, although isoflurane, the compound with the largest time constants,
was somewhat less affected than the other compounds. An individual time profile with a steep concentration change for sevoflurane, including the fitted curve obtained with perturbation, is shown in Figure 3.

### Discussion

This method for the determination of the pharmacokinetics of volatile anaesthetics using routine clinical data should have advantages compared with experimental measurements.1–3 These include the number of patients that may be investigated, the frequency of sampling, the fact that it is non-invasive and that it takes into account possible feedback of physiological effects of the individual agent on its own pharmacokinetic properties, and the lower cost of measurement. However, these advantages may be unimportant if the estimation of parameters by this method is subject to important bias. Therefore, we required a model with the following properties:

- The model should be as simple as possible since otherwise parameter estimation might become unstable;
- The model should incorporate transport to a peripheral compartment;
- The method should not be affected by systematic and random errors.

In this study, we applied the least squares method using the end-expired fractional concentration as the dependent variable. This is because standard maximum likelihood methods comprising the statistical error of the dose administered would yield a large covariance matrix, which cannot be inverted by standard methods within a reasonable computing time. The maximum likelihood procedure is based on the parameterised distribution of the observed values and selects those parameters with the largest likelihood for the observed values. If these are uncorrelated and normally distributed, the maximum likelihood approach coincides with the least squares method.15

Quality of fit can be quantified using the root mean square error. As its values were small compared with the measured concentrations, estimated values for $F_E$ in general described the measured data very precisely. In addition, the root mean square errors of the data sets with the poorest fit exceeded the mean values by not more than 1.6-fold, showing that the model used was satisfactory in all cases. Even for these data sets, the residuals vs time plots do not suggest misspecification of the model (Fig. 2). The observation that the root mean square errors were within the magnitude of rounding errors suggests that improving the fit by the use of more complex models is not generally feasible. This is supported by the finding that stable estimates of pharmacokinetic parameters for a three-compartment model could not be obtained in 50% of the data sets.
and that multicompartment models such as those derived experimentally1–3 were not appropriate. It therefore appears that during clinical anaesthesia under the conditions examined here, slow transport processes to a third compartment are of minor importance, and to a fourth or fifth compartment are not relevant to the concentration in the central compartment.

The random error used in the simulation studies to disturb input and output variables represents the round-off error and the uncertainty of the measurement. The round-off

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<th>Modification of data sets</th>
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<th>Isoflurane</th>
<th>Sevoflurane</th>
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<td>Scatter ‡</td>
<td>Bias †</td>
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error accounts for not more than 2.5% when both digits are available and the fractional concentration is in the range of 1–10 vol% (for 1.0 vol%, maximal round-off error is 0.05 = 5%, and minimal round-off error is zero, giving a mean error of 2.5%). Since the accuracy of the measurement was better than the round-off error, it is supposed that the overall random error is closer to 2.5 than to 10%. Other sources of error include the effects on inspired and expired measurements of volumes and concentrations of inhaled agents caused by changes in carbon dioxide, oxygen and water concentrations. No corrections were made for water vapour and respiratory quotient; however, they are included, at least in part, in the procedure used to estimate alveolar dead space. The error caused by these factors was less than 5%, taking the compliance of the system and condensation of water in the expiratory limb into account. For a simulated 2.5% error in the input variables, the bias of all pharmacokinetic parameters was negligible (Tables 1–3). A presumed 10% error (well above true error of measurement) caused important changes, mainly for the volume of distribution, only when applied to the input variables. In summary, it appears that the expected sources of inaccuracy have no major impact on the results.

The second gas effect caused by nitrous oxide ventilation was presumably overestimated in early studies. When applying the square root law for nitrous oxide postulated by Severinghaus, the mean excess ventilation is estimated as 630 ml within the first 10 min of anaesthesia. Although the true second gas effect is expected to be considerably lower, it is less than our assumption of an initial systematic error of 20%. Therefore, we expect that the bias in the central volume of distribution introduced by a possible second gas effect is less than 40% and has little effect on the other parameters.

Contamination of $F_E$ by $F_I$ from parallel dead space was not taken into account by our model. We expect that this contamination is negligible, as we applied concentration changes in a low-flow circle system, and these changes are slower than those that occur with step-like changes in a non-rebreathing system.

Because of the continuous and variable input of drug into the system, a high sampling rate is essential for the correct description of the dose. The observation that the calculated volume of distribution was affected only if the sampling rate was reduced by more than a factor of two may be explained by the velocity of transport processes described by the microconstants (Table 3), which were slower than changes in inspiratory concentrations.

Despite the different physicochemical properties of the inhaled anaesthetics, the simulated effects of the confounding factors were similar for isoflurane, desflurane and sevoflurane. Therefore, it appears that comparisons between the pharmacokinetics of these substances based on the method described are valid even if the true errors are at the upper limit of those described above.

Our procedure provides an alternative set of pharmacokinetic parameters that can describe the behaviour of volatile anaesthetics under clinical conditions. Because of the simplicity of the methods used, it appears possible to conduct online estimations of individual pharmacokinetic parameters during anaesthesia. These estimates may serve to predict the individual behaviour of patients, such as forecasting the duration of coasting to a given end-tidal concentration, and thus to improve patient control.

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