AN EVALUATION OF THE ACCURACY OF PHARMACOKINETIC DATA FOR THE COMPUTER ASSISTED INFUSION OF ALFENTANIL

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In recent years, pharmacokinetic and pharmacodynamic research has developed new concepts which are applicable to the i.v. administration of anaesthetic drugs: for example, the rates of distribution and elimination in the body have been quantitated. Moreover, new i.v. anaesthetics with desirable pharmacokinetic profiles (for example, rapid elimination from the body) have been introduced. Numerous studies have defined the relationships between plasma concentrations and the therapeutic and adverse effects of i.v. anaesthetic drugs such that it is now possible to estimate the range of plasma concentrations that results in desirable drug effects (therapeutic window) for several anaesthetic drugs. In addition, knowledge is accumulating about factors (intensity of surgical stimulation, drug interactions) which may change the therapeutic window of a drug. Finally, the concept of a continuous infusion of the anaesthetic(s) to maintain the therapeutic plasma concentration(s) has been introduced.

Alfentanil is an example of a relevant drug. It has desirable pharmacokinetic and pharmacodynamic properties (Stanski and Hug, 1982): a short terminal elimination half-life, a rapid onset of action as a result of rapid blood:brain equilibration (Scott and Stanski, 1984), and a definable therapeutic window that varies with the intensity of surgical stimulation (Ausems and Hug, 1983). The continuous infusion of alfentanil (to supple-

SUMMARY

The accuracy of using average alfentanil pharmacokinetic data in a computer assisted infusion pump (TIAC) to predict alfentanil plasma concentrations was tested in 35 patients (divided into three groups) receiving alfentanil and nitrous oxide in oxygen anaesthesia for lower and upper abdominal surgery. By frequently measuring the arterial plasma concentration, it was possible to determine the average prediction error for individual patients and for groups of patients. For the groups, there were no significant systematic over- or underpredictions of the alfentanil plasma concentrations (bias). However, there existed a moderate degree of variability (imprecision) within the groups, caused by deviations of measured and predicted plasma concentrations in the individual patients within each group. As a result, prediction errors of 22.2–32.5% can be expected with the average pharmacokinetic data used in this study to drive TIAC. It was concluded that, as a result of the moderate degree of imprecision, it is unwise to rely totally on the absolute values of alfentanil plasma concentrations predicted by a computer-regulated infusion pump such as TIAC. However, such devices can be used to attain rapidly a relatively stable plasma concentration that can be adjusted (titrated) to the requirements of an individual patient during anaesthesia.
TIAC (Titration of Intravenous Agents by Computer) Janssen Scientific Instruments, Janssen Pharmaceutica, Belgium). The anaesthetist is required to provide the computer (Hewlett-Packard 86) with the appropriate pharmacokinetic data for the specific drug in the patient population. The computer then drives a calibrated infusion pump to administer the drug. The device can be used in either of two ways:

1. The infusion pump is controlled by the user, who can give defined bolus doses or infusion rates, or both, to the patient. In this case, the computer continuously calculates the theoretical consequences of the dosing scheme in terms of plasma concentrations predicted by a two-compartment pharmacokinetic model and the pharmacokinetic data provided by the user of the drug. In this situation, TIAC provides only a prediction of the plasma concentration over time and the amount of drug in the peripheral compartment.

2. The user defines a certain plasma concentration (or a certain amount of drug in the peripheral compartment) and the computer uses the pharmacokinetic model and data to calculate the amount of drug and the rate of infusion that the pump must deliver. To achieve the chosen plasma concentration, the computer uses a BET infusion scheme consisting of an initial bolus \((B)\) for filling up the initial volume of distribution, the maintenance infusion rate required to replace drug that has been eliminated \((E)\) and an exponentially declining infusion rate compensating for the transfer \((T)\) of drug into the peripheral compartment (Schwilden, 1981). In this way the computer calculates (every 15 s) the amount of drug needed to achieve and maintain the chosen plasma concentration and adjusts the infusion rate accordingly. During anaesthesia the chosen plasma concentration may be changed by the user.

### Table I. Alfentanil pharmacokinetic data used in TIAC.

Pharmacokinetic data of alfentanil determined in a group of seven female patients (ASA physical status 1 or 2) scheduled for minor gynaecological surgery (Schütter and Stoeckel, 1982)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{P(0)} = A.e^{-\alpha t} + B.e^{-\beta t})</td>
<td></td>
</tr>
<tr>
<td>(A = 0.44) mg litre(^{-1})</td>
<td>(\alpha = 0.18) min(^{-1})</td>
</tr>
<tr>
<td>(B = 0.132) mg litre(^{-1})</td>
<td>(\beta = 0.01) min(^{-1})</td>
</tr>
<tr>
<td>I.v. bolus dose = 5 mg</td>
<td></td>
</tr>
<tr>
<td>Distribution half-life = 4.3 min</td>
<td></td>
</tr>
<tr>
<td>Elimination half-life = 70 min</td>
<td></td>
</tr>
<tr>
<td>Clearance = 336.2 ml min(^{-1})</td>
<td></td>
</tr>
<tr>
<td>Initial distribution volume = 10.2 litre</td>
<td></td>
</tr>
<tr>
<td>Steady state distribution volume = 33.3 litre</td>
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</table>

As a part of the evaluation of such computer-controlled devices, it is important to know the relationship between the computer predictions of drug concentrations and the concentrations that are actually produced in plasma. The purpose of this study was to examine the accuracy of using previously reported alfentanil pharmacokinetic data (table I) (Schütter and Stoeckel, 1982) in the TIAC device to predict the plasma concentrations of alfentanil in patients having lower and upper abdominal surgical procedures.

### Patients and Methods

Three groups of patients were studied.

**Lower abdominal group.** Ten female patients, ASA physical status 1, aged 25–49 yr, scheduled for lower abdominal gynaecological surgery.

**Upper abdominal group.** Ten patients (4 female), ASA physical status 1, aged 23–54 yr, scheduled for upper abdominal surgery.

**Interactive group.** Fifteen female patients, ASA physical status 1, aged 20–50 yr, scheduled for gynaecological surgery (11 lower abdominal, four major vaginal surgery).

The patients in the first two groups were participating in clinical studies examining the pharmacokinetics and dynamics of alfentanil. In these groups the alfentanil was administered by a calibrated infusion pump (WTI, SP1002): bolus injections were administered via a syringe with the anaesthetist defining the bolus doses and rates of infusion. TIAC was used retrospectively to predict the alfentanil plasma concentrations that would be expected from the dosing scheme utilized for each patient. In the interactive group the TIAC was used prospectively to control the rate of the alfentanil infusion. All patients in each group consented to the procedure as approved by the Medical Ethics Committee of the University of Leiden.

In the lower and upper abdominal groups, anaesthesia was first induced with a bolus injection of alfentanil 150 \(\mu\)g kg\(^{-1}\) and subsequently maintained with 66% nitrous oxide in oxygen and a continuous infusion of alfentanil. During the maintenance of anaesthesia for the surgical procedure, bolus doses of alfentanil were administered and the alfentanil infusion rate was changed as indicated by the responses of the patients to surgical stimuli (Ausems, Hug and de Lange, 1983).

In the interactive group, the anaesthetist...
prospectively chose the desired alfentanil plasma concentration, whereupon the TIAC computed and administered the amount of alfentanil needed, based upon the alfentanil pharmacokinetic data described by Schüttler and Stoeckel (1982) (table I). Control measurements were made while the patient breathed oxygen, then anaesthesia was induced with alfentanil administered by TIAC and 66% nitrous oxide in oxygen. Ventilation was controlled as the patient’s spontaneous effort was depressed. The chosen alfentanil plasma concentration for the induction of anaesthesia was 400 ng ml⁻¹. Thereafter the chosen plasma concentration of alfentanil was changed as indicated by the same clinical signs of adequate or inadequate anaesthesia used in the lower and upper abdominal groups (Ausems, Hug and de Lange, 1983). If the patient demonstrated clinical signs of inadequate anaesthesia, the alfentanil concentration was increased by 50 or 100 ng ml⁻¹ from the initial value. If the patient did not respond at a given alfentanil concentration, the desired concentration was decreased by 50 or 100 ng ml⁻¹. All patients were premedicated with diazepam 10 mg orally 2 h before and atropine 0.5 mg i.m. 30 min before the induction of anaesthesia.

In all patients arterial blood samples were taken to determine the concentration of alfentanil in plasma. In the lower and upper abdominal groups samples were taken before and 2, 5 and 10 min after the alfentanil induction and every 10 min thereafter until the first sign of inadequate anaesthesia. Additional blood samples were obtained at the time of such signs and 2, 5 and 15 min after any supplementary bolus dose and then every 15 min until the next sign of inadequate anaesthesia appeared. In the interactive group, samples were obtained 5 min after a stable plasma concentration of the desired value was predicted by TIAC and every 10–20 min if this desired plasma concentration was not changed. A sample was also taken just before making any change in the desired plasma concentration.

Blood was collected in heparin-rinsed syringes, transferred to dry heparinized tubes and chilled in ice until centrifugation. Plasma was separated from blood and stored at −20 °C until assayed. Alfentanil plasma concentrations were determined by a radioimmunoassay or gas chromatography (Michiels, Hendriks and Heykants, 1983).

**Data analysis**

Linear regression was used to display the relationship between the measured and predicted alfentanil plasma concentrations for each patient in all groups. Although the regression analysis gives a good visual impression of the data in different groups of patients, it is not the optimal statistical approach to quantitate the accuracy of the population pharmacokinetic data used in TIAC (Sheiner and Beal, 1981). Therefore, the following was determined for each measured blood sample:

\[
\text{prediction error (ng ml}^{-1}\text{)} = C_P(\text{measured}) - C_P(\text{predicted})
\]

\[
\text{prediction error (\%)} = \frac{C_P(\text{measured}) - C_P(\text{predicted})}{C_P(\text{measured})} \times 100\%
\]

where \(C_P\) was the concentration of alfentanil in plasma. The prediction error (\%) scaled the prediction error (ng ml⁻¹) to the measured alfentanil value, since the alfentanil plasma concentrations changed within an individual patient during the course of anaesthesia and the concentrations differed between patients.

For each patient, it was possible to derive two measures that characterized the accuracy of the pharmacokinetic data used to programme TIAC, namely bias and precision (Colton, 1974). Bias is the mean prediction error and is an estimate of the systematic over- or underprediction of the alfentanil plasma concentration; it was calculated as follows:

\[
\text{Bias} = \frac{\Sigma \text{prediction error (ng ml}^{-1}\text{ or \%))}}{\text{number of measurements per patient}}
\]

The standard deviation of the bias is an estimation of the spread of the prediction error and can be used as a measure of precision. The bias and precision, calculated for each patient, do not provide direct information on the typical size of the prediction error if there are both over- (positive) and under- (negative) predictions in an individual patient. Therefore, we also calculated for each patient the mean absolute prediction error as follows:

\[
\text{mean absolute prediction error} = \frac{\Sigma |\text{prediction error (ng ml}^{-1}\text{ or \%)}|}{\text{number of measurements per patient}}
\]

In contrast to the mean prediction error, the mean absolute prediction error is not influenced by the positive or negative sign of the prediction.
errors and gives direct information on the typical size of the prediction error in individual patients and groups of patients.

The bias, 95% confidence bounds of the bias, the precision and the mean absolute prediction error were calculated for each patient. By examining the degree of bias and 95% confidence bounds of the bias it was possible to determine if an individual patient had a statistically significant degree of bias (P < 0.05). The individual estimates of mean prediction error and mean absolute prediction error were then averaged to obtain the group performance. One-way analysis of variance (P < 0.05) was used to determine if a significant difference existed between the group means: if so, multiple two-tailed unpaired t tests with the Bonferroni correction (P < 0.05) were performed to examine individual group differences.

RESULTS

The three groups of patients were comparable in age, weight and ASA physical status (table II). In the lower abdominal and interactive groups the average alfentanil plasma concentrations required to block the patient’s responses to surgical stimulation were approximately the same. The average alfentanil plasma concentration was significantly higher in the upper abdominal group (table II). This difference represented the higher alfentanil plasma concentrations needed to block patient’s responses to the stimuli of upper abdominal surgery.

Figure 1 shows the predicted and measured alfentanil plasma concentrations for two patients in the interactive group. One graph is from a typical patient (left panel, maximal difference between measured and predicted plasma concentration 30–40 ng ml⁻¹) and the other is from the most extreme patient (right panel, difference between measured and predicted plasma concentration 100–200 ng ml⁻¹). In regard to the latter patient, it should be noted that the pattern of measured concentrations over time paralleled the predicted pattern, but the actual concentrations were approximately 150 ng ml⁻¹ lower than predicted. These systematically smaller than predicted concentrations could reflect a pharmacokinetic difference (for example, this patient’s clearance of alfentanil may have been twice that of the average data used to programme TIAC). However, this pharmacokinetic difference did not impede the anaesthetist’s ability to increase or decrease the alfentanil concentration as required to maintain a satisfactory anaesthetic state.

To visualize the relationship between measured and predicted alfentanil plasma concentrations for all patients, we regressed, for each patient, the

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**Table II. Patient characteristics (mean±SD).** *Significantly different (P < 0.05) from all other groups*

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Average alfentanil plasma concn (ng ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower abdominal</td>
<td>10</td>
<td>37±9</td>
<td>66±16</td>
<td>305±61</td>
</tr>
<tr>
<td>Upper abdominal</td>
<td>10</td>
<td>44±12</td>
<td>72±12</td>
<td>427±129*</td>
</tr>
<tr>
<td>Interactive</td>
<td>15</td>
<td>36±8</td>
<td>63±11</td>
<td>276±87</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Measured arterial plasma concentrations of alfentanil (*) and the predicted plasma concentrations (——) in a representative patient (left panel) and the most extreme patient (right panel); both patients from the interactive group. Note that the pattern of predicted and measured concentrations over time are similar in the right panel, but that the actual values are 100–200 ng ml⁻¹ lower than predicted. See text for discussion.
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![Graphs showing regression analysis of predicted and measured alfentanil plasma concentrations for different groups.](image)

**Fig. 2.** Regression analysis of the predicted alfentanil plasma concentrations on the measured alfentanil plasma concentrations. Left panel: the regression lines (solid lines) for each patient of the upper abdominal group. Right panel: typical fit in one patient of the lower abdominal group (dots are data points). The interrupted line is the line of identity (measured concentration = predicted concentration).

**Fig. 3.** Regression analysis of the predicted alfentanil plasma concentrations on the measured alfentanil plasma concentrations. Left panel: the regression lines (solid lines) for each patient of the lower abdominal group. Right panel: the regression lines for each patient of the interactive group. The interrupted line is the line of identity (measured concentration = predicted concentration).

predicted plasma concentrations on the measured plasma concentrations. Figure 2 (right panel) shows a typical fit in one patient in the lower abdominal group. In figure 3 the regression lines for each patient in the lower abdominal (left panel) and interactive group (right panel) are shown. Although individual patients deviated from the line of identity, there did not appear to be a systematic over- or underprediction of the alfentanil plasma concentrations in the overall groups. Both groups showed approximately the same degree of variability. For example a predicted value of 300 ng ml⁻¹ could result in a measured value of approximately 200 or 400 ng ml⁻¹ in the most extreme patients in these groups, but on an average it was 300 ng ml⁻¹. Figure 2 (left panel) shows the regression lines for the upper abdominal group. In this group the alfentanil plasma concentrations needed to suppress patient’s responses during the intra-abdominal part of the operation were higher than those in the two groups which involved only lower abdominal surgery.
Again, there appeared to be no systematic over- or underprediction. However, there were larger individual deviations from the line of identity. For example, a predicted concentration of 400 ng ml\(^{-1}\) could result in a measured concentration of 200–600 ng ml\(^{-1}\) in the most extreme patients of the upper abdominal group (fig. 2, left panel).

Table III shows the degree of bias in the individual patients. All patients had some degree of bias. In only six of the 35 patients was this bias not significant (that is, the 95% confidence bounds included zero). The bias estimates showed that there were patients with systematic overprediction as well as patients with systematic underprediction of the alfentanil plasma concentration within each group.

Table IV shows the degree of bias in the three groups of patients. In all groups there was a slight tendency to overpredict the alfentanil plasma concentrations by 12–19 ng ml\(^{-1}\) or 5–18%. However, the bias in these groups was not significant, since the 95% confidence bounds included zero. Also, there was no significant difference in the estimates of bias between the three groups.

In addition, we calculated the mean absolute prediction error (in ng ml\(^{-1}\), and as a percentage of the measured alfentanil plasma concentration)
TABLE IV. Accuracy of the predicted alfentanil plasma concentrations in groups of patients. ns = No significant bias since the 95% confidence bounds of the bias include zero. There were no significant differences between groups (one way analysis of variance)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Prediction error (Mean (bias) ± SD (precision))</th>
<th>Absolute prediction error (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower abdominal</td>
<td>10</td>
<td>-12 ± 63 ns -5.1 ± 20.27 ns</td>
<td>69 ± 24 22.2 ± 6.60</td>
</tr>
<tr>
<td>Upper abdominal</td>
<td>10</td>
<td>-19 ± 136 ns -14.7 ± 37.83 ns</td>
<td>119 ± 65 32.5 ± 23.70</td>
</tr>
<tr>
<td>Interactive</td>
<td>15</td>
<td>-14 ± 74 ns -17.6 ± 33.81 ns</td>
<td>70 ± 33 32.1 ± 21.70</td>
</tr>
</tbody>
</table>

which gave an estimate of the magnitude of the difference between predicted and measured plasma concentrations. Table III shows the mean absolute prediction errors for each patient. Notice that the absolute values of the mean prediction error and the mean absolute prediction error were the same in patients that consistently had only overpredictions or only underpredictions during the course of anaesthesia. In those patients (and groups of patients) that had overpredictions as well as underpredictions during anaesthesia, the mean absolute prediction error gave a more direct estimate of the typical size of the prediction error than did the mean prediction error ± SD. Table IV shows the mean absolute prediction error in the three groups. When calculated in ng ml⁻¹, the mean absolute prediction error was approximately the same in the interactive and lower abdominal group (±70 ng ml⁻¹). In the upper abdominal group it was greater (±120 ng ml⁻¹), but the differences between it and the interactive and lower abdominal groups were not significant. There was, also, no significant difference between the groups, when the mean absolute prediction error was calculated as a percentage of the measured alfentanil plasma concentration.

DISCUSSION

With inhalation anaesthetic agents it is possible to deliver a precise inspired concentration of drug, which rapidly equilibrates with the alveolar gases and reaches the blood stream for delivery to the brain: one continuously infuses the inhalation anaesthetic to the body via the lungs, resulting in relatively stable brain concentrations which can be changed in a controlled manner by changing the inspired concentration. With i.v. anaesthetic agents, it is not possible to obtain the same degree of control. With intermittent i.v. injections, the blood and brain concentrations frequently overshoot the therapeutic requirement initially, then decay to subtherapeutic concentrations in a variable period of time. These fluctuations in blood and brain concentrations can be obviated by infusing the i.v. drug continuously.

Two problems arise when using an infusion technique to administer an i.v. anaesthetic. First, it is desirable to achieve a stable blood concentration rapidly (with a constant rate infusion it takes more than four elimination half-times of the drug to approach a steady state). Second, it is desirable to be able to change from one stable blood concentration to another in a rapid and controlled manner. The changing of the desired drug concentrations according to the patient's individual needs (for example, for different intensities of surgical stimulation) will prevent the unnecessary accumulation of the i.v. anaesthetic that results from using a single stable concentration which is sufficiently high to block all of the patient's responses to the most intense surgical stimuli. With accumulation comes prolonged recovery from the effects of the drug.

Wagner (1974) has described the popular approach of a rapid then slower infusion to attain steady-state blood concentrations. This concept does result in some degree of overshoot of the desired blood concentration and does not immediately achieve the steady state concentration. Kruger-Theimer (1968) proposed the administration of a bolus loading dose followed by an exponentially declining infusion to increase rapidly and maintain the blood concentrations of a drug with multicompartment behaviour. Schwilden (1981) favoured the approach of Kruger-Theimer and developed the equations for an open, two-compartment pharmacokinetic model that are necessary to increase rapidly and then maintain constant blood concentrations. These equations have been implemented in the computer-driven infusion device, TIAC, that was evaluated in this
study. A device like TIAC makes it possible to administer the exponentially-declining infusion rate necessary to achieve a certain stable plasma concentration rapidly, and can also do the continuous calculations needed to change the chosen plasma concentration as quickly as possible. Schwilden and colleagues have used the TIAC to deliver etomidate and alfentanil for short surgical procedures (Schützl, Schwilden and Stoeckel, 1983). In their study, they achieved a mean measured etomidate plasma concentration of 0.29 μg ml\(^{-1}\) with a desired predicted value of 0.3 μg ml\(^{-1}\) and a mean measured alfentanil plasma concentration of 0.45 μg ml\(^{-1}\) with the predicted value at 0.40 μg ml\(^{-1}\).

Before the evaluation of the clinical utility of a computer-driven infusion device such as TIAC, we evaluated its accuracy in predicting and in producing alfentanil plasma concentrations in a general surgical patient population. Our study involved the calibration of pharmacokinetic data and a pharmacokinetic model that governed a computer-driven infusion pump administering drug to a biological system—the surgical patient. The visual distillations of our study are given in figures 2 and 3. The regression lines for the three groups of patients are distributed evenly around the line of identity. The number of patients having their alfentanil plasma concentrations overpredicted was equal to the number with underpredictions. The slopes of the regression lines are close to a value of 1. A moderate degree of variability is also obvious in these figures. The statistical quantitation of the data is presented in tables III and IV. A statistically significant bias was present in most patients in the three groups (table III). However, when the individual estimates of bias in each group were pooled (table IV), there was no statistically significant bias in the three groups of patients. The mean prediction error was remarkably small: \(-12\) to \(-19\) ng ml\(^{-1}\) or \(-5.1\%\) to \(-17.6\%\).

Evaluating the statistical estimates of precision is more difficult. In table III one sees that the degree of precision (standard deviation of the prediction error) was extremely variable between patients. In table IV the degree of precision for each group is much larger than the mean degree of bias in that group, reflecting moderate variability in the patient population. The absolute prediction error values in table IV indicate that, in the best case (lower abdominal), the mean absolute prediction error was 68.6 ng ml\(^{-1}\), whereas in the worst case (upper abdominal) the mean absolute prediction error was 119.3 ng ml\(^{-1}\). Expressing these values as percentages eliminates the fact that the alfentanil plasma concentrations were higher in the upper abdominal group than in the other two groups. The absolute prediction error ranged from 22.2% to 32.5%.

In the three groups of patients studied, the alfentanil pharmacokinetic data generated by Schützl and Stoeckel (1982) (table I) did not result in a systematic over- or underprediction of alfentanil plasma concentrations; that is, there was no bias. Systematic over- or underprediction would be evidence that the pharmacokinetic data were not representative of the patient population. Schützl and Stoeckel generated their alfentanil pharmacokinetic data from a small (n = 7) group of healthy female patients undergoing a short surgical procedure. Their pharmacokinetic data appear to be applicable to our patients, who were more varied in age and weight and had longer surgical procedures. Many factors might explain the moderate degree of variability found between the measured and predicted alfentanil plasma concentrations. Factors such as age, weight, gender, smoking, concurrent medication, or disease could cause variability in alfentanil pharmacokinetics. The pharmacokinetic data used in the current study did not adjust for any of these factors. Systematic pharmacokinetic research will be needed to determine if these factors are significant and if adjusting for them decreases the variability between individuals. The degree of variability found in our study was comparable to that found by other investigators reporting on large population studies of the pharmacokinetics of other drugs (Sheiner, Rosenberg and Marathe, 1977). When the technology of measuring alfentanil plasma concentrations during anaesthesia becomes available, it will then be possible to adjust the pharmacokinetic data used in an infusion device like TIAC to each individual patient during anaesthesia, thereby minimizing the influence of the between-patient variability in pharmacokinetics on the accuracy of the predicted plasma concentrations.

Does the moderate degree of between-patient variability limit the clinical utility of a device like TIAC? It is unwise to rely totally on any device as a means of predicting alfentanil plasma concentrations from rates of administration defined by the anaesthetist. Individual patients may deviate from the average pharmacokinetic behaviour, and there is the potential for substantial
errors. A TIAC-like device can, however, be used to obtain relatively stable alfentanil plasma concentrations rapidly and then adjust these concentrations in a regular and controlled manner depending upon the clinical responses. If the clinical signs indicate inadequate anaesthesia, it is obvious that the alfentanil plasma concentrations need to be increased. A computer-regulated infusion device like TIAC allows one to make these incremental steps in a defined manner. Less obvious, but equally important, is the decreasing of the alfentanil plasma concentrations if there are no signs of inadequate anaesthesia. The latter is necessary in order to approach the minimal plasma concentration needed to block the individual patient’s responses to surgical stimuli and, thereby, prevent any unnecessary accumulation of alfentanil—which will prolong the recovery time. Devices such as TIAC allow this titration of i.v. anaesthetic administration in a way that is analogous to the current use of a precision vaporizer for an inhalation anaesthetic.

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REFERENCES