

## Bayesian Forecasting Improves the Prediction of Intraoperative Plasma Concentrations of Alfentanil

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To achieve therapeutic plasma concentrations of the opioid alfentanil, one must administer the drug as a variable rate continuous infusion. For most patients, using population pharmacokinetic parameters of alfentanil for dosing regimen allows accurate prediction of the plasma concentration of the drug over time. However, for some patients, using such parameters results in systematic over- or underprediction of the concentration. Retrospectively studying a data set (dosage history and measured concentrations) for 34 patients, the authors examined how Bayesian forecasting could improve the precision of prediction. For each patient, a Bayesian regression was performed to estimate "individualized" pharmacokinetic parameters, using population pharmacokinetic values for alfentanil and the measurement of alfentanil in one or more plasma samples from each patient. These individualized parameters were then used to predict the subsequent plasma concentrations of alfentanil over time. By comparing the value of each measured point with its corresponding predicted value, the authors calculated the prediction error as a percentage of the measured value. The precision of the prediction was assessed by the percent mean absolute prediction error. After Bayesian forecasting using a single point sampled at 80 min after start of anesthesia, the average precision of the prediction was  $13.8 \pm 6.1\%$  (SD). Using no Bayesian forecasting and only population values of the pharmacokinetic parameters for the prediction of the concentration, the precision was  $24.3 \pm 16.9\%$ . The improvement in precision brought by Bayesian forecasting was especially noticeable for those patients whose prediction of alfentanil was poor using population pharmacokinetic values (*i.e.*, "outlier" patients). These results suggest that Bayesian forecasting may facilitate optimal ad-

ministration of alfentanil during long procedures and that a rapid assay should be developed to measure plasma concentrations of alfentanil intraoperatively. (Key words: Analgesics: alfentanil. Anesthetics, intravenous: alfentanil. Pharmacokinetics: alfentanil; population. Predictions, drug concentration: Bayesian forecasting; error; precision.)

THE PHARMACOKINETIC and pharmacodynamic characteristics of newer intravenous anesthetics such as alfentanil allow one to administer high doses of the drug in order to achieve a profound analgesic state, and yet have a rapid recovery after the infusion is discontinued.<sup>1</sup> However, while insufficient anesthesia may be detected by clinical signs, overdosing cannot be recognized as easily and may result in delayed recovery and respiratory depression. Progress in both clinical pharmacology concepts, analytical chemistry and computer technology, may enable us to improve the administration of intravenous anesthesia and avoid overdosing. Pharmacostatistical techniques can determine pharmacokinetic characteristics of drugs in the population of interest, and can identify factors that explain the pharmacokinetic and pharmacodynamic variability.<sup>2</sup> Innovative drug delivery devices such as computer-driven infusion pumps<sup>3,4</sup> use pharmacokinetic models to choose the rate of drug administration and, in this way, achieve rapidly and maintain target plasma concentrations of the drug of interest. Finally, the use of rapid drug assays and statistical forecasting techniques individualize the pharmacokinetic profile of a drug and thus enable one to predict more accurately the relationship of dose and plasma concentration over time in an individual patient.<sup>5,6</sup> In the future, all of the above advances should make intravenous anesthesia a more predictable and easier to control process.

Many of the above concepts have been applied to the opioid alfentanil. The range of plasma concentrations of alfentanil required for different phases of anesthesia and different types of surgical stimuli have been defined.<sup>1,7</sup> Furthermore, a population pharmacokinetic analysis has characterized the disposition of alfentanil in surgical patients.<sup>2</sup> Using these population pharmacokinetic parameters, one can accurately predict the plasma concentration of alfentanil over time in most surgical patients.<sup>8</sup> Studies have also found that a computer-controlled pump can deliver drug so as to rapidly achieve and maintain a specific target plasma concentration,<sup>3</sup> and that a computer-driven infusion provides more stable hemodynamics during anesthesia than does intermittent bolus administration of the drug.<sup>9</sup>

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However, the pharmacokinetics of alfentanil vary greatly among individual surgical patients.<sup>2</sup> This variability is a clear limitation to the accurate prediction of the relationship between dose, plasma concentration, and anesthetic response.<sup>8</sup> Such variability also contributes to inadequate or excessive dosage in some patients. The logical way to improve one's ability to predict this relationship is to obtain more information about the pharmacokinetic behavior of the drug in question in the particular patient of interest. This information requires intraoperative measurement of the plasma concentration of alfentanil and the use of a mathematical technique to extract the essential pharmacokinetic information from the measurement. Although a rapid assay is not yet available for alfentanil, the technology does exist for other drugs<sup>10</sup> and could be applied to alfentanil. Use of a statistical technique called Bayesian forecasting<sup>‡</sup> and intraoperative measurement of a single plasma concentration of alfentanil in a patient allows one to improve the estimates of the pharmacokinetic parameters of the drug for that particular individual. Bayesian forecasting was first proposed by L. B. Sheiner for pharmacokinetic predictions of digoxin<sup>11</sup> and has been used by other authors to individualize the dosing strategy for drugs having a narrow therapeutic window (*i.e.*, lidocaine,<sup>12,13</sup> theophylline,<sup>14</sup> gentamicin,<sup>15</sup> and phenytoin<sup>16</sup>). This technique needs the following information: 1) the measured concentration of the drug in the patient of interest; 2) the variance of the assay error; 3) the population pharmacokinetic parameters for that drug; and 4) the interindividual variability in pharmacokinetic parameters. Using these components, the Bayesian statistical procedure produces a set of estimated values for pharmacokinetic parameters that has the greatest likelihood of being true for that individual patient. This data set permits forecasting (prediction) of the future plasma concentration *versus* time profile.

Our present study investigates whether intraoperative measurement of plasma concentrations of alfentanil would improve the ability to predict (forecast) future plasma concentrations of the drug. This study also examines how often and when plasma concentrations of alfentanil should be measured in order to optimize Bayesian forecasting of intraoperative plasma concentration of alfentanil.

### Materials and Methods

#### ALFENTANIL DOSE AND PLASMA CONCENTRATION DATA

We retrospectively analyzed the dose and plasma concentration data described by Ausems *et al.*<sup>1</sup> to evaluate

the ability of Bayesian forecasting to predict the plasma concentrations of alfentanil. Data for 34 surgical patients (29 women and five men, ASA Physical Status I or II) of 37 patients undergoing intra-abdominal or superficial surgical procedures lasting 2–4 h were available for our study. Patients had been given a bolus dose (150  $\mu\text{g}/\text{kg}$ ) of alfentanil for induction of anesthesia and then a variable-rate infusion (25–150  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) of alfentanil with 66% nitrous oxide in oxygen for maintenance of anesthesia. Alfentanil was administered with a conventional infusion pump. Additional boluses were given during surgery according to clinical needs, sometimes concomitantly with changes in the infusion rate. Further information about the data can be found in the original article by Ausems *et al.*<sup>1</sup> The data set used in this study consisted of the exact dosing regimen for each patient, the time each dose was given (time 0 = start of the first bolus dose for induction of anesthesia), the values for 20–50 measurements of the plasma concentration of alfentanil per patient, as well as the exact time at which each blood sample was drawn.

#### BAYESIAN PROCEDURE AND DATA ANALYSIS

The theoretical basis of Bayesian forecasting has been discussed in detail by Sheiner *et al.*<sup>11</sup> An overview of the procedure is provided in the appendix. In essence, the Bayesian approach attempts to balance *a priori* information regarding statistical distribution of pharmacokinetic parameters of a drug (obtained from a study of the drug in a population of patients) against the observation of one or more measured plasma concentrations of the drug in the patient of interest. The method involves the use of nonlinear regression for which purpose the computer program NONMEM<sup>§</sup> was used. Other Bayesian forecasting programs have been developed to operate efficiently on small eight-bit personal microcomputers.<sup>18</sup> The pharmacokinetic model used in the present study was an open three-compartment mammillary model implemented using a previously described iterative method<sup>8</sup> that efficiently handles the complexity of the administration scheme.

Figure 1 shows the general procedure used in this study. From the original data set for each patient (open and solid dots), we chose one to three points (circled solid dot) as representing an intraoperatively measured concentration of alfentanil. For each patient, we then performed a Bayesian regression on these measurements of alfentanil to obtain *individualized* estimates of two pharmacokinetic parameters: elimination clearance and initial volume of

‡ Named after Bayes, who developed conditional probability theory in the 17th century.

§ Beal SL, Sheiner LB. NONMEM Users Guide, Part II, page 9. Division of Clinical Pharmacology, University of California, San Francisco, 1980

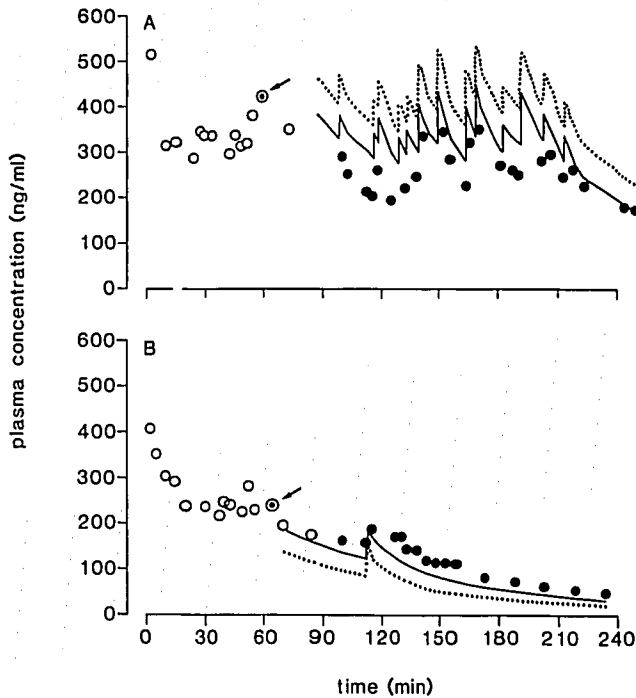


FIG. 1. The plasma concentration of alfentanil over time (open and solid dots) measured in two representative patients A and B. A Bayesian regression was performed on an intraoperative measurement of the plasma concentration of alfentanil at 60 min (circled solid dot) and provided estimates of the pharmacokinetic parameters of the drug in that particular patient. These estimates were then used to predict (calculate) the plasma concentration of alfentanil over time after the 90th minute (solid line). For comparison purposes, the dotted line shows predictions made without the Bayesian procedure (no concentration measured) using mean population pharmacokinetic parameter values only.

distribution. The values for the remaining pharmacokinetic parameters (distribution clearances and volumes of compartments 2 and 3) were not estimated during this procedure, and were assumed equal to population values. The reason for choosing elimination clearance and initial volume of distribution as the only parameters to be estimated is discussed below. For every concentration measured after 90 min (solid dots), the value of the corresponding predicted concentration (solid line) was calculated using the set of individualized pharmacokinetic parameters. The prediction error (PE) was calculated for each prediction and was expressed as a percentage of the measured concentration:

$$PE = \left( \frac{C_{PP} - C_{PM}}{C_{PM}} \right) \cdot 100,$$

where  $C_{PM}$  is the actual measured plasma concentration of alfentanil and  $C_{PP}$  is the calculated value (prediction) of the plasma concentration. The absolute values of all the prediction errors for points after 90 min for each

patient were averaged to obtain the "average absolute prediction error for the individual." By further calculating the mean of the 34 "average absolute prediction errors for the individual," one obtains an estimate of the mean absolute prediction error ( $\pm$ SD) of the group of patients. This mean absolute prediction error is a measure of the precision with which Bayesian forecasting predicts the concentration time course of alfentanil in a typical patient.

The precision of the predictions obtained using intraoperative measurements and Bayesian forecasting was compared with the precision obtained without Bayesian forecasting (*i.e.*, the predictions were based solely on population parameter estimates and no intraoperative measurements of plasma concentration of alfentanil were performed). For that purpose, the above procedure was repeated but without the Bayesian regression step. The predictions (fig. 1, patients A and B, dotted line) were based only on population pharmacokinetic parameters.<sup>2</sup> The overall precision of the prediction obtained using intraoperative measurement of plasma concentration and Bayesian forecasting can then be compared with the precision obtained using only population pharmacokinetic parameters and no intraoperative measurement.

Several additional questions were asked in order to optimize the Bayesian forecasting procedure. First, what is the ideal time to obtain the measurement of plasma concentration of alfentanil for the best prediction of future plasma concentrations of the drug? To answer this question, we varied the time of intraoperative measurement of alfentanil. The prediction procedure described earlier was repeated eight times, simulating sampling of one single blood sample at 10, 20, 30, 40, 50, 60, 70, or 80 min, respectively, after the start of anesthesia. We calculated the overall mean absolute prediction error for each of these times.

The second question was: does using more than one plasma concentration measurement for the Bayesian regression improve the estimation of the *individualized* pharmacokinetic parameters and the subsequent quality of the prediction? To answer the second question, we performed four additional simulations. We compared the mean absolute prediction error resulting from using one measurement of plasma concentration of alfentanil at 60 min with that obtained using two measurements (at 5 and 60 min, or at 30 and 60 min, or at 50 and 60 min) or three measurements (at 5, 30, and 60 min).

The third question was: what is the best blood sampling strategy to predict when the infusion of alfentanil needs to be stopped in order to extubate the trachea at a given time? Ausems *et al.*<sup>1</sup> showed that plasma concentrations of alfentanil below 200 ng/ml at the end of surgery permit uneventful tracheal extubation without respiratory depression. Therefore, if one knows the pharmacokinetic parameters of a drug in an individual patient, one can

calculate the time at which infusion of alfentanil should be stopped to obtain this target concentration at the end of surgery. A question closely related to this issue is: at what time should the concentration of alfentanil be measured to most closely approach this ideal clinical result? Because our data were analyzed retrospectively, it was not possible to modify the administration scheme. Rather, we examined the ability to predict the exact concentration of alfentanil at the time the nitrous oxide was discontinued (*i.e.*, at the end of surgery). We therefore examined the precision of the prediction of this particular point, first without Bayesian forecasting (using only population pharmacokinetic parameters), and then with Bayesian forecasting using a single measurement of the plasma concentration of alfentanil at 30 or 60 min after start of anesthesia, or at 90, 60, or 30 min before the end of surgery. The precision of the prediction was evaluated as above, except that only one point per patient (the measured plasma concentration at the time of discontinuation of nitrous oxide) was used in the calculation of precision.

As a last step, we repeated the Bayesian forecasting procedure but estimated four pharmacokinetic parameters (elimination clearance, initial volume of distribution, and, additionally, the micro rate constants  $k_{13}$  and  $k_{31}$ ). Our goal was to determine whether estimation of additional parameters would increase the precision of the prediction.

**Results**

Figure 1 shows the measured and predicted values for the plasma concentrations of alfentanil over time for two representative patients (in A, the prediction using population parameters was representative of a "poor" prediction, and, in B, it was representative of a "good" prediction, but these were not the worst and best predictions). The solid dots represent the measured concentrations of alfentanil. The dotted line represents the predicted concentration time course of alfentanil obtained when no alfentanil concentration measurement was used (no Bayesian procedure) and only population pharmacokinetic parameters were used for the prediction. The solid line represents the predicted concentration time course of alfentanil when one uses *individualized* parameters obtained by Bayesian regression on a single measurement at 60 min (circled solid dot). For both patients, the prediction after Bayesian forecasting was more accurate than the prediction without Bayesian forecasting. The improvement was greater, however, for patient A. For this patient, prediction was particularly poor when population pharmacokinetic parameters were used (*i.e.*, the pharmacokinetic parameters of alfentanil in this patient differ markedly from the population mean values).

Table 1 shows the individual and overall values for the

TABLE 1. Individual and Overall Values for the Mean Absolute Prediction Error (in Percent of Error), When Using Only Population Pharmacokinetic Parameters (No Bayesian Feedback) for the Prediction of the Concentration Time Course, or Bayesian Feedback on One Single Concentration Sampled at 20 or 60 Min

Patient	No Bayesian Feedback	Feedback at	
		20 min	60 min
1	10.0	6.4	9.5
2	10.7	27.0	9.8
3	29.9	13.9	13.7
4	16.9	9.2	15.2
5	51.5	46.0	21.5
6	46.8	27.4	30.2
7	18.5	13.1	16.1
8	13.7	13.7	28.3
9	10.8	26.9	14.6
10	44.6	31.0	13.0
11	11.0	8.1	32.6
12	16.5	10.3	14.9
13	28.5	6.6	13.3
14	22.1	15.6	9.4
15	27.5	20.8	24.7
16	53.2	46.6	25.0
17	23.6	8.6	18.6
18	28.5	18.7	12.6
19	3.6	4.8	11.1
20	7.9	11.8	26.1
21	6.0	8.0	20.2
22	49.7	27.9	24.7
23	10.2	9.0	10.0
24	41.4	8.6	20.0
25	22.6	55.9	42.3
26	13.2	43.6	13.1
27	12.0	43.9	13.6
28	29.9	6.4	11.7
29	13.0	46.7	25.8
30	80.3	55.4	12.6
31	13.0	24.5	13.3
32	10.7	25.7	6.5
33	22.6	12.8	12.4
34	27.3	11.9	15.5
Mean	24.3	22.0	17.7
SD	16.9	15.3	7.8

mean absolute prediction error (in percent of error), when using only population pharmacokinetic parameters for the prediction of the concentration time course (No Bayesian Feedback), or Bayesian feedback using one single concentration sampled at 20 or 60 min. It can be seen that Bayesian feedback did not improve the precision in all patients—it did even worse for some individuals—but, overall, the prediction was more precise (smaller value for the mean absolute prediction error) and more uniform across individuals (smaller standard deviation) after Bayesian feedback using one single concentration sampled at 60 min, than without Bayesian forecasting. Of importance is that the prediction for all patients having a poor prediction using population parameters (No Bayesian Feedback, patients 5, 6, 10, 16, 22, 24, and 30) was improved after Bayesian feedback (60 min).

Figure 2 provides the values ( $\pm$ SD) for the mean ab-

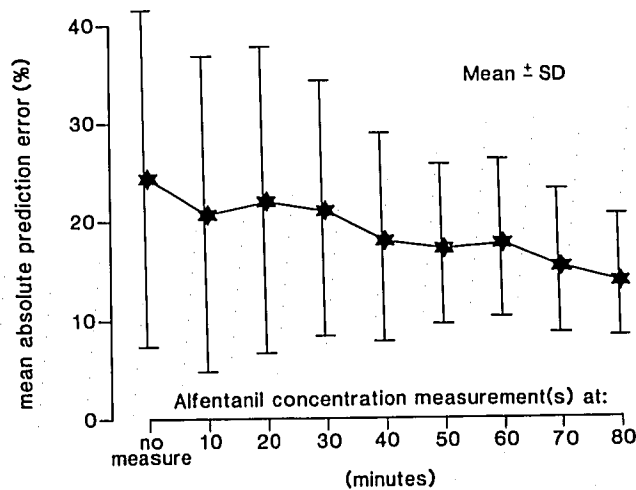


FIG. 2. Standard deviation and average value of the mean absolute prediction error without Bayesian procedure ("no measure") and with Bayesian parameter estimation based on a single measurement of the plasma concentration of alfentanil at various times. The decrease in the standard deviation for the last four sampling times (50–80 min) indicates that the predictions of alfentanil concentrations for those patients whose alfentanil concentrations were predicted poorly with population pharmacokinetic parameters markedly improved after Bayesian forecasting based on a single measurement of alfentanil concentration.

solute prediction error in the group of 34 patients during surgery, using either no measurement of drug concentration (population parameters) or *individualized* parameters obtained after Bayesian regression was performed on a single measurement at 10, 20, 30, 40, 50, 60, 70, or 80 min, respectively. Early sampling after initiating alfentanil does not appear to provide useful information. However, measurement of the plasma concentration of alfentanil 50–80 min after commencing alfentanil improved the precision of the subsequent prediction. The

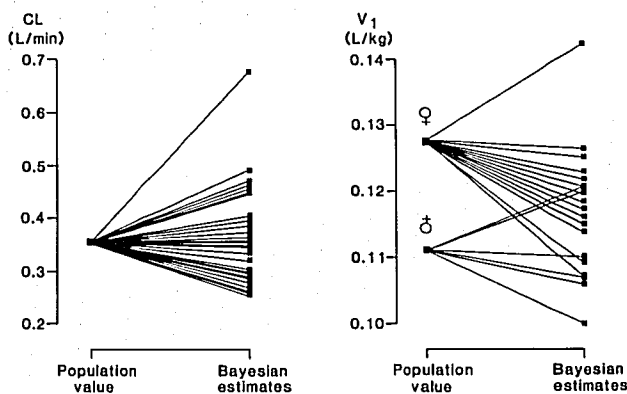


FIG. 3. Population values<sup>2</sup> for elimination clearance (CL) and the initial volume of distribution ( $V_1$ ) for alfentanil were compared with the individual Bayesian estimation values obtained from a single measurement of the plasma concentration of alfentanil at 60 min.

reduction of the mean absolute prediction error (stars) indicates that, on average, the prediction is better with Bayesian forecasting than without. More important, however, is the fact that the standard deviation of the mean absolute prediction error becomes much smaller. This indicates that the prediction is much better especially for the "outlier" patients (*e.g.*, patient A in fig. 1).

Figure 3 shows the difference between the population values and the individualized values for elimination clearance and the initial volume of distribution ( $V_1$ ) of alfentanil, estimated with Bayesian regression after a single measurement of the plasma concentration of alfentanil at 60 min. Note that population values for  $V_1$  have been shown to be different for males and females.<sup>2</sup>

Figure 4 shows the mean absolute prediction error for the concentration at the time of discontinuation of nitrous oxide and end of surgery. The prediction for this particular point in time could be improved only by measuring the plasma concentration of alfentanil 30–60 min before the end of surgery.

Figure 5 demonstrates that the intraoperative measurement of more than one concentration of alfentanil for the Bayesian procedure does not improve the predictions of subsequent alfentanil concentrations.

Finally, the results (not reported) obtained after estimating four pharmacokinetic parameters with Bayesian forecasting were almost identical to those obtained with estimating only two parameters. The computational effort required, however, was about twice as great.

## Discussion

Precise drug dosage to achieve therapeutic drug concentrations and avoid both toxic or ineffective concentrations is a common therapeutic goal. Drugs like digoxin, lidocaine, theophylline, gentamicin, and phenytoin have a narrow therapeutic window where efficacy is close to toxic concentrations. Also, toxicity can be difficult to diagnose. Bayesian forecasting is the current method of choice to optimize individual dosing of these drugs.<sup>11–16</sup> Although the pharmacokinetic characteristics of alfentanil in surgical patients have been well documented,<sup>2</sup> differences among individuals can produce inadequate plasma concentrations of the drug in some patients in spite of "normal" dosage.

The present study demonstrates that Bayesian forecasting can be successfully applied to alfentanil. Keeping in mind that our results are based on retrospective data, the following conclusion can be drawn: the precision with which one can predict the plasma concentration of alfentanil over time is substantially better when using Bayesian forecasting than when using only population pharmacokinetic parameters. In this study, two or more measurements of alfentanil concentration did not produce a more

precise prediction than that following a single measurement, and our results tend to show that one measurement of alfentanil concentration may be adequate in predicting future concentrations of alfentanil during surgery. The best prediction was obtained when the plasma concentration of alfentanil was measured after 60 min of infusion. Measuring the concentration of alfentanil before 45 min produced results that were not much better than when alfentanil was not measured at all. A possible explanation for this result is the changing nature of the pharmacokinetics, evident in some patients, *i.e.*, the pharmacokinetics changed during the different phases of anesthesia, possibly as a result of changing hemodynamic status. Aulsems *et al.*<sup>1</sup> have emphasized the presence of hemodynamic stability during alfentanil-nitrous oxide anesthesia; however, hemodynamic changes due to minor peripheral cooling during surgery or to fluctuations in the intensity of the nociceptive stimuli may be reflected by changes in the distribution of blood flow to different parts of the body, without affecting gross measures such as heart rate or blood pressure. If a fluctuating pharmacokinetic state were the case, a Bayesian forecast would be expected to produce precise predictions only for the period immediately after the measurement used for feedback. As time progresses, pharmacokinetic parameters may change, and the quality of the prediction, based on "old" pharmacokinetic parameters, will decrease. This reasoning suggests that additional measurement of alfentanil concentration may be necessary if changes in the patient's physiologic state (*e.g.*, hypovolemia, hypothermia, hyperdynamic state, shock) are noticed during anesthesia. A similar explanation may account for the observation that Bayesian forecasting based on measurement of the plasma concentration of alfentanil 60 min after induction of anesthesia does not lead to precise predictions of alfentanil concentrations at the time the nitrous oxide is discontinued, whereas measurements at 60–30 min before the end of surgery does.

Estimating only two pharmacokinetic parameters (elimination clearance and the initial volume of distribution) during the Bayesian procedure allowed an adequate prediction of subsequent alfentanil plasma concentrations. Estimating more than two pharmacokinetic parameters did not lead to better results. This observation agrees with our previous study,<sup>2</sup> in which we showed that the variability between patients in the pharmacokinetic parameters of alfentanil can be reasonably well described by only the *interindividual* variations in clearance and initial distribution volume. This previous finding was the rationale for initially choosing clearance and initial volume of distribution as the primary parameters to be estimated by the Bayesian procedure.

Rapid intraoperative assay for alfentanil does not exist to date. However, the methodology already exists for

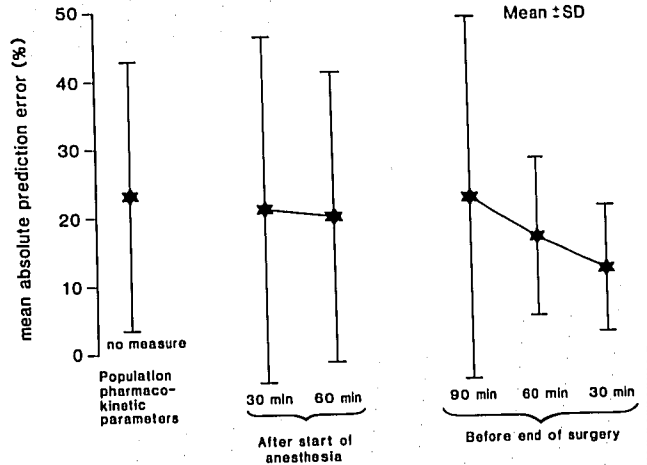


FIG. 4. Mean absolute prediction error for the concentration at the time of discontinuation of nitrous oxide, when the prediction is performed without Bayesian procedure ("no measure") or after Bayesian parameter estimation based on a single measurement of the plasma concentration of alfentanil at 30 or 60 min after the start of anesthesia, or at 90, 60, or 30 min before the end of surgery. Only Bayesian forecasting based on measurements of plasma concentration of alfentanil 60 or 30 min before the end of surgery appears to be useful for an individual dosing of the drug near the end of the surgery, in order to ensure that the plasma concentration of alfentanil is low enough for tracheal extubation without the use of an opioid antagonist.<sup>1</sup>

other drugs. It is possible, for example, to measure plasma concentration of theophylline with a "strip" (dry chemistry strip assay) in less than 2 min.<sup>17</sup> While we have applied the intraoperative measurement of alfentanil to Bayesian parameter estimation and to prediction of future concentrations, intraoperative measurement of plasma concentration of alfentanil could be used empirically by the anes-

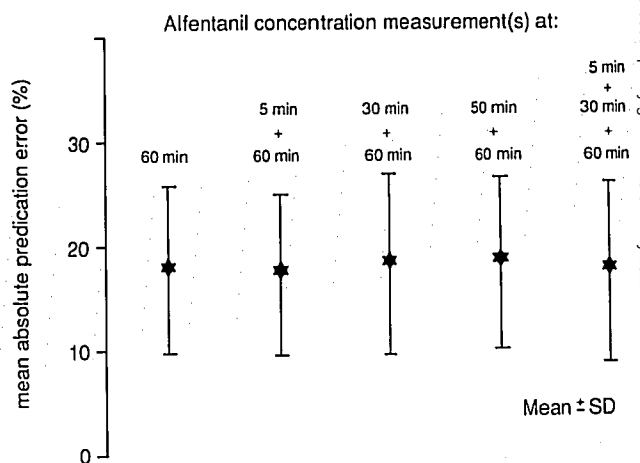


FIG. 5. Mean absolute prediction error after Bayesian parameter estimation based on a single measurement of the plasma concentration of alfentanil or on two or three measurements. Increasing the number of measurements does not lead to more precise prediction of the concentration of the drug over time.

thesiologist to assess the adequacy of the dosing regimen. An appropriate clinical analogy is the measurement of the arterial  $P_{CO_2}$  to assist in the setting of ventilation. Optimal drug dosing with a measured drug concentration is more complex, however, than setting the ventilation using a measure of the  $P_{CO_2}$ . For example, if a measured concentration for a drug is greater than expected, the reason can be either a smaller initial volume of distribution ( $V_1$ ), or a smaller clearance, or both. This is important to discriminate: if the cause of this increased concentration is only  $V_1$ , it will be increased only transiently and keeping the same infusion rate should result in future true concentration close to the target concentration. On the other hand, if the reason for this increased value is a smaller clearance, keeping the same infusion rate will result in overdosing. The Bayesian forecasting program can, to some degree, find which parameter is more likely to be responsible for the difference observed between measured and predicted concentration, whereas our intuition cannot. In this setting, a Bayesian forecasting system, as described in the present paper, may prove more efficient.

The present study is a simulation based on retrospective data. The concept presented may be perceived by many as too complex, and anesthesiologists may question the usefulness and applicability of our suggestions. Has Bayesian forecasting a future in the real life of a busy operating room? We believe so. Optimally, the Bayesian forecasting concept should be implemented in the emerging computerized pump technology for drug delivery. Computer driven infusion pumps implementing Bayesian forecasting coupled with an intraoperative assay could improve both the popularity and accuracy of intravenous anesthesia by improving predictability.

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### Appendix

The Bayesian procedure takes into account the known statistical distribution of the pharmacokinetic parameters in the population (called "prior distribution") and one or more measurements of a drug's concentration in the plasma of a particular patient. It then estimates optimal individual pharmacokinetic parameters for that patient by calculating the mode of the posterior distribution of the pharmacokinetic parameters (*i.e.*, a new point estimate taking into account the measured value(s) of the plasma concentration and the *a priori* information on the pharmacokinetic parameters).

In our work, the Bayesian estimates of the individual pharmacokinetic parameters are those values that maximize the function:

$$g(\theta) = - \underbrace{\frac{1}{2} \left[ \sum_{i=1}^n \left( \frac{\ln C_i - \ln f_i(\theta)}{\sigma_i} \right)^2 \right]}_{\text{part 1}} + \underbrace{\sum_{k=1}^m \left( \frac{\ln \bar{\theta}_k - \ln \theta_k}{\sigma_{\theta_k}} \right)^2}_{\text{part 2}}$$

where  $\theta$  is the vector of the pharmacokinetic parameters to be estimated;  $f_i$  is the function describing the relationship between dose, time, kinetic parameters, and predicted concentration;  $C_i$  is the  $i$ th measured concentration;  $\theta_k$  (where  $k = 1$  to  $m$ ) are the

individual pharmacokinetic parameters to be estimated;  $\bar{\theta}_k$  are the corresponding population mean parameter values.  $\sigma_{n_k}$  and  $\sigma_r$  are (approximately) the coefficient of variation of the pharmacokinetic parameters in the patient population (*interindividual* variability) and the coefficient of variation of the residual *intra*-individual error (error in the assay, error in recording the time of blood sampling, and other factors accounting for the *intra*-individual variability), respectively.

The above equation calculates a value for the number  $g(\theta)$  as a function of the  $\theta_k$ s, of the predicted and measured concentration, and of the value of the population pharmacokinetic parameters. The value of  $g(\theta)$  is used by the regression program as a measure of the "goodness" of the parameters. The regression program iterates, continuously changing and improving the values of the  $\theta_k$ s until the value of  $g(\theta)$  does not increase any more, which means that the "ideal" values for the  $\theta_k$  have been found.

The function  $g(\theta)$  has the property that when no measurement of drug concentration is available, part 1 of the equation disappears, and the objective function  $g(\theta)$  is maximized ( $=0$ ) when  $\theta_k$  equal the population values  $\bar{\theta}_k$ . On the other hand, when many measurements of drug concentration are available, part 1 of the equation becomes predominant, part 2 becomes negligible, and the estimates of  $\theta$  approach the least square estimates. However, when only a few measurements are available, both terms are important, and the estimates of  $\theta$  take into account both the information about  $\theta$  in the measured concentration(s) and the information about  $\theta$  in the population distribution. The coefficients of variation determine the relative weight attached to each type of information: the importance of the "error" (numerator) in portion 1 or 2 decreases as the value of the respective coefficients of variations increases. The values of  $\sigma_{n_k}$  and  $\sigma_r$  were determined in a previous study.<sup>2</sup>