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The Prospective Use of Population Pharmacokinetics in a Computer-Driven Infusion System for Alfentanil

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Maitre *et al.* recently evaluated the accuracy of a set of previously determined population pharmacokinetic parameters for the opioid alfentanil using data from an earlier study in which the drug had been administered using a computer-controlled infusion pump (CCIP). The present study evaluated the accuracy of these same parameters in a CCIP prospectively in two groups of clinically dissimilar patients: 29 healthy female day surgery patients and 11 relatively older and less healthy male inpatients. In addition, another set of pharmacokinetic parameters, previously determined by Scott *et al.* in the CCIP in 11 male inpatients was also evaluated. The bias and inaccuracy were assessed by the median performance error (MDPE) and the median absolute performance error (MDAPE) in which the performance error was determined as the difference between measured and target serum concentration as a fraction of the target serum concentration. Unlike Maitre *et al.*, the current study found a consistent bias in both populations. The MDPE was +53% and the MDAPE was 53%, with no difference between patient groups. In the 11 patients studied using the Scott *et al.* pharmacokinetic parameters, the MDPE was +1% and the MDAPE was 17%. The parameters of Scott *et al.* were further tested by simulating the serum concentrations that would have been achieved had they been used in the CCIP in the first 40 patients; results indicated MDPE of +2% and an MDAPE of 18%. Therefore, reasonably reliable and accurate target serum concentrations of alfentanil can be achieved using the pharmacokinetic parameters of Scott *et al.* in a CCIP. Furthermore, these pharmacokinetic parameters are more suitable for use in a CCIP than are the population pharmacokinetic parameters of Maitre *et al.* (Key words: Analgesics: alfentanil. Anesthetic, intravenous: alfentanil. Anesthetic techniques: computer-assisted intravenous infusion. Pharmacokinetics: alfentanil. Predictions, drug levels: errors.)

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ALFENTANIL is a synthetic opioid with a rapid onset and relatively short duration. These characteristics enable the anesthesiologist to adjust the level of opioid analgesia to match the changing surgical stimulus. To facilitate this titration, several computer-controlled infusion pumps (CCIP) based on pharmacokinetic models of alfentanil have been developed.[1–3] The CCIP allows the anesthesiologist to specify a "target" alfentanil serum concentration (C_T). The infusion pump then administers the appropriate alfentanil dose according to a pharmacokinetic model. The performance of a pharmacokinetic model-based administration system is dependent on the parameter values of the model, the interindividual variability of those parameters, and the error from improper specification of the model. Ausems *et al.*,[4] using pharmacokinetic parameters from Schuttler and Stoeckel,[5] tested a CCIP in a group of female patients undergoing gynecologic surgery and reported no systematic bias and a moderate degree of interindividual variability. Maitre *et al.*[6] performed a population analysis of alfentanil pharmacokinetics with NONMEM, a statistical nonlinear regression program, using data from four published studies. Table 1 shows the optimal pharmacokinetic parameters determined in the NONMEM analysis relative to gender, age, and weight. Recently, Maitre *et al.*[7] applied the population pharmacokinetic parameter values to the infusion regimen reported by Ausems *et al.*[8] They found a slight tendency for the population parameters to underpredict the measured arterial blood concentrations and moderate interindividual variability. Encouraged by these results, we sought to test the population pharmacokinetic parameter values of Maitre *et al.*[6] prospectively in a CCIP system.

Materials and Methods

SUBJECTS

Two groups of patients were selected for this study. Group 1 consisted of 29 female patients at the day surgery clinic of Brigham and Women's Hospital undergoing laparoscopic surgery with expected durations of less than 1 h. Group 2 consisted of 22 male patients at Palo Alto Veteran's Administration Hospital undergoing a variety of surgical procedures with expected durations greater

TABLE 1. Pharmacokinetic Parameters

Clearance (l/min)	
Age < 40 yr	0.356
Age > 40 yr	0.356 − [0.00269 × (age − 40)]
V1 (l)	
Men	0.111 × weight (kg)
Women	0.111 × 1.15 × weight (kg)
Rate constants (1/min)	
k12	0.104
k21	0.673
k13	0.017
k31	
Age < 40 yr	0.0126
Age > 40 yr	0.0126 − [0.000113 × (age − 40)]

Reprinted from Maitre *et al.*[6]

than 1 h. All patients gave written informed consent as approved by the review board of the respective institutions. The median age in group 1 was 34 yr (range 24–45 yr), and the median body weight was 59 kg (range 43–93 kg). The median age in group 2 was 64 yr (range 29–76 yr) and the median body weight was 85 kg (range 69–101 kg).

Group 1 patients received midazolam 1–2 mg intravenously (iv) to facilitate insertion of the radial arterial cannula for blood sampling. Alfentanil was administered by CCIP to achieve a constant C_T of 100 ng/ml for 10 min. Three minutes after the infusion was begun, induction of anesthesia was accomplished with thiopental (3–4 mg/kg) and succinylcholine (1.5 mg/kg). Anesthesia was maintained with 70% N_2O, 30% O_2, the alfentanil infusion, and succinylcholine or atracurium infusion. Isoflurane was added for mean blood pressure greater than 95 mmHg. After 10 min the target serum concentration of alfentanil was increased to 200 ng/ml for 8–12 min until the surgery was completed. The alfentanil was then discontinued (*i.e.*, C_T set to zero). Arterial blood samples were taken just prior to and 1, 3, and 6 min after each change of alfentanil level. A total of 12 samples per patient were obtained.

Group 2 patients received no preanesthetic medication. Following insertion of the radial artery cannula for blood sampling the patients breathed 100% O_2 and a small dose of muscle relaxant (*e.g.*, vecuronium 0.01 mg/kg) was administered. Sequential alfentanil concentrations of 400, 550, and 700 ng/ml were targeted for 5-min periods while the patients lungs were ventilated with 70% N_2O and 30% O_2. The balance of the muscle relaxant (0.1 mg/kg) was administered 60 s after beginning the alfentanil infusion. Following tracheal intubation C_T was decreased and subsequently titrated to the patient's level of responsiveness. Isoflurane was added in approximately one-third of cases when increasing concentrations of alfentanil were ineffective in controlling hypertension or tachycardia during surgical stimulation. About 45 min before the anticipated end of surgery, C_T was decreased to 200 ng/ml, then discontinued approximately 20 min prior to the end of surgery. Arterial blood was sampled 5–10 times at each alfentanil concentration plateau and then less frequently during the balance of the anesthetic and subsequent recovery. A total of 14–24 samples per patient were obtained.

The CCIP administered alfentanil to group 1 and the first 11 patients of group 2 (group 2A) using the Maitre *et al.*[6] pharmacokinetic parameters, which were adjusted for patient gender, weight, and age. The results from groups 1 and 2A were then analyzed. It was observed that the pharmacokinetics previously reported by Scott *et al.*[9] (table 2) appeared to more accurately predict the observed serum alfentanil concentrations in these 40 patients than did the Maitre *et al.*[6] pharmacokinetic parameters. To prospectively verify this observation, the CCIP was programmed to administer alfentanil to the next 11 patients in group 2 (group 2B) using the Scott *et al.*[9] pharmacokinetic parameters.

SAMPLE PREPARATION AND ASSAY

All blood samples were immediately centrifuged, frozen, and stored at −20° C for later analysis. Serum alfentanil concentrations were determined using the radioimmunoassay (RIA) technique described by Michiels *et al.*[10] and modified by Schüttler and White.[11] Antisera and ^3H tracer were obtained from commercially available RIA kits (Janssen Pharmaceutica, New Brunswick, New Jersey). The specificity of alfentanil, relative to cross-reactive metabolites in humans, has been established by comparing the RIA to a specific gas chromatographic (GC) assay.[12] A chemical quench curve was routinely used on all samples. The lower limit of quantification of the alfentanil assay is 40 ng/ml and the coefficient of variation between paired aliquots is <5%.[13]

INSTRUMENTATION

A CCIP system was developed for this study to deliver alfentanil according to a pharmacokinetic model. The software was written in Better Basic (Summit Software, Norwood, Massachusetts) by one of the authors (D.B.R.)

TABLE 2. Pharmacokinetic Parameters

Clearance (l/min)	0.199
V1 (l)	2.185
Rate constants (1/min)	
k12	0.656
k21	0.214
k13	0.113
k31	0.017

Reprinted from Scott *et al.*[9]

and interfaced to a customized syringe pump (C. R. Bard, Medsystems Div., N. Reading, Massachusetts) *via* a serial communication channel. The pharmacokinetic model equations[14] are solved using the Euler integration technique[15] with an iteration rate of one per second. The infusion regimen is saved on a magnetic disk to allow further analysis of the system performance using other sets of pharmacokinetic parameters. The syringe pump delivers alfentanil at a maximum rate of 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Data Analysis

The accuracy with which a pharmacokinetic model-based delivery system can achieve target serum concentrations can be assessed by examining the bias and inaccuracy. Bias is an indication of a systematic failure to achieve the target serum concentration. Inaccuracy is a measure of the expected failure to achieve C_T. In previous studies the term "precision" has been used in a similar sense to the term "inaccuracy" used here.[16] However, the term precision is inappropriate because it usually refers to the ability of a system to produce a result that is within a narrow bound. Accuracy usually refers to the ability of a system to produce a result close to the truth. For example, if one were in the unenviable position of William Tell's son with an apple on his head, one would wish the archer to be accurate rather than precise. If William were to put three arrows through the fifth intercostal space he would be precise but inaccurate!

Both bias and inaccuracy are aggregate measures of the performance error at each blood sample point. For a given measurement of serum concentration, the performance error (PE, as a percentage) is expressed as follows:

$$PE = [(C_M - C_T)/C_T] \times 100$$

where C_M is the measured serum concentration of alfentanil. This definition differs from that used in previous studies where the performance error has been expressed as the difference between measured and predicted serum concentration as a fraction of the measured concentration.[4,7,14]

The bias of the system is expressed as the median performance error for all blood samples (MDPE). The system inaccuracy is the median absolute value of the performance errors computed by the formula:

$$MDAPE = \text{median } |PE|$$

The MDPE and MDAPE measures of bias and inaccuracy are different from those in earlier publications.[4,7,16] In previous literature the bias was expressed as the group mean performance error and the inaccuracy (precision) was expressed as the group mean of the absolute values of the performance errors. We have chosen measures based on the median for three reasons. First, we have attempted to be consistent with the origin of the pharmacokinetic parameters used in the study. The pharmacokinetic parameters were determined using an iteratively reweighted least squares method (IRLS), which minimizes the mean squared error between predicted and measured concentrations. It would then be appropriate to use measures of performance that are based on the mean squared error to evaluate systems developed using IRLS. One of the authors (J.R.V.) has shown that the MDPE and MDAPE measures tend to track the mean squared error, whereas the mean PE and mean absolute value of PE do not. Thus, MDPE and MDAPE more fairly measure the performance of the system. Second, it is clear from a plot of the frequency of PE *versus* PE that the PE are not normally distributed. Therefore, it is misleading to cite the

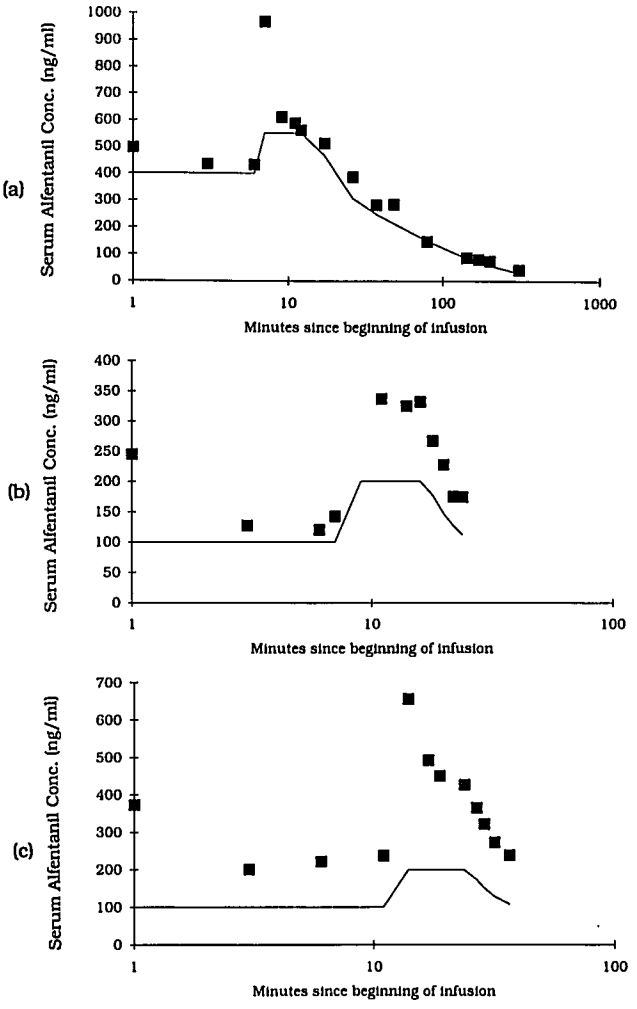

FIG. 1. Measured (*solid squares*) and target (*solid line*) serum concentrations of alfentanil *versus* time, for representative patients when the drug was administered by CCIP: (*A*) best performance. (*B*) representative performance, (*C*) worst performance. Alfentanil was administered with CCIP using Maitre *et al.*[6] pharmacokinetic parameters.

mean and variance as a measure of the expectation of the system performance. Third, the MDAPE can easily and usefully be interpreted: the measured serum concentration will be less than the MDAPE of the targeted concentration exactly one-half of the time.

Results

The alfentanil serum concentration *versus* time for three representative patients are shown in figure 1. Figure 1*A* shows the patient from group 2 in which C_M most closely agrees with C_T throughout the anesthetic course. More typically, figure 1*B* shows a patient from group 2 in which the C_M greatly exceeds C_T following changes in C_T but shows the ability to maintain a constant serum concentration during plateau periods. Figure 1*C* shows the patient from group 1 in which C_M least closely follows C_T throughout the anesthetic course.

Both the bias and inaccuracy for the system using the Maitre *et al.*[6] pharmacokinetic parameters were 53%, as shown in figure 2 where PE for each patient is plotted *versus* time. Also indicated are the 90th and 10th percentiles of the PE: +143% and +11%, respectively.

No substantive difference in system performance between the two patient groups is noted. The bias and inaccuracy for the group 1 patients are both 52% and for the group 2A patients are 54% and 55%, respectively.

We used the infusion regimens from the group 1 and 2A patients to predict the system performance if the Scott *et al.*[9] rather than the Maitre *et al.*[6] pharmacokinetic parameters had been used in the CCIP. The predicted serum concentrations were determined by numerical convolution of the three-compartment system equations having the Scott *et al.*[9] parameters with infusion regimens stored

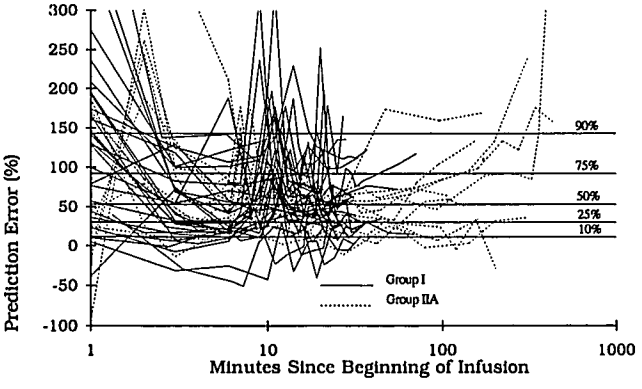

FIG. 2. Prediction error (difference between measured and target serum concentration as a fraction of target serum concentration) in percent *versus* time. Alfentanil was administered with CCIP using Maitre *et al.*[6] pharmacokinetic parameters. Solid lines represent 29 healthy female day surgery patients (group 1). Dotted lines represent 11 relatively less healthy male inpatients (group 2A). The 10th, 25th, 50th (median), 75th, and 90th percentiles of the prediction errors are shown.

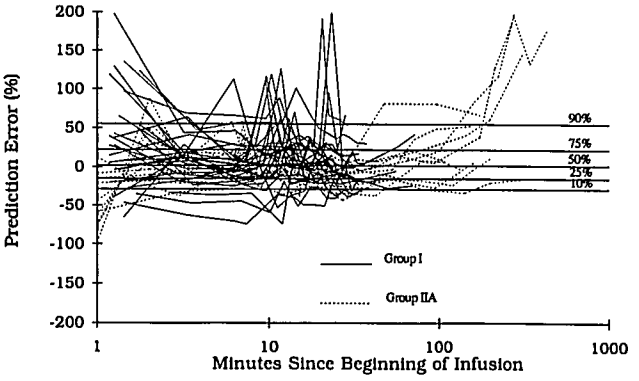

FIG. 3. Prediction error (difference between measured and target serum concentration as a fraction of target serum concentration) in percent *versus* time. The target serum concentrations were simulated as if the CCIP used Scott *et al.*[9] pharmacokinetic parameters. The infusion regimen used was that saved from the previous experiment in which Maitre *et al.*[6] pharmacokinetics were in the CCIP (see fig. 3). Solid lines represent 29 healthy female day surgery patients (group 1). Dotted lines represent 11 relatively less healthy male inpatients (group 2A). The 10th, 25th, 50th (median), 75th, and 90th percentiles of the prediction errors suggest improved performance when Scott *et al.*[9] pharmacokinetic parameters are used.

by the computer. The PE for each patient *versus* time are shown in figure 3 and demonstrate the vastly improved performance we would have observed if the CCIP had used these parameter values. The improvement is especially pronounced in the group 1 patients at points immediately following changes in C_T at around 10 min. Some residual error remains at these times and at times greater than 100 min.

Figure 4 shows C_M and C_T *versus* time from group 2B in which C_M and C_T agree most closely, representatively, and least closely. A substantial improvement in performance when using the Scott *et al.*[9] pharmacokinetic is demonstrated even in the worst case.

The PE for the patients in group 2B are shown in figure 5. The improved performance achieved by using the Scott *et al.*[9] pharmacokinetic parameters in the CCIP is demonstrated by a bias and inaccuracy of +1% and 17%, respectively.

The bias, inaccuracy, and the 10th, 25th, 75th, and 90th percentiles for all of the various pharmacokinetic parameters and for the three patient groups are summarized in table 3.

Discussion

We have demonstrated that a CCIP can be used to achieve C_T of alfentanil that compare rather closely to the actual serum concentration when the appropriate pharmacokinetic parameters are used. This prospective study suggests that the Scott *et al.*[9] alfentanil pharmacokinetic parameters are appropriate for use in a CCIP. With

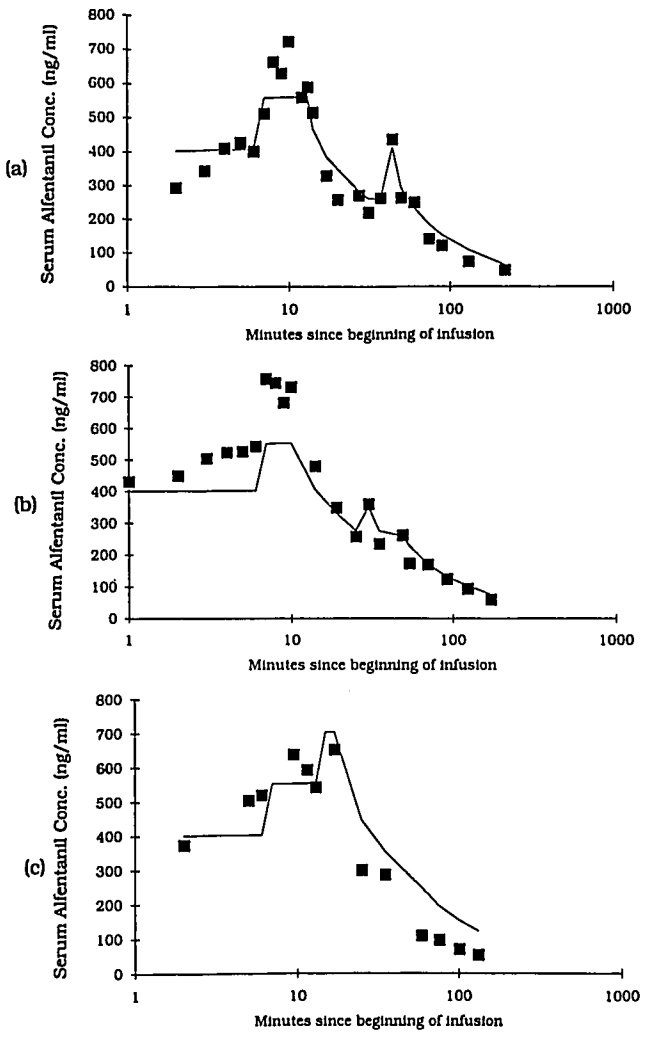

FIG. 4. Measured (*solid squares*) and target (*solid line*) serum concentrations of alfentanil *versus* time, for representative patients when the drug was administered by CCIP: (*A*) best performance, (*B*) representative performance, (*C*) worst performance. Alfentanil was administered with CCIP using Scott *et al.*[9] pharmacokinetic parameters.

these parameters 80% of the time the actual serum concentration will be within a range between 29% below C_T and 38% above C_T. The suitability of the Scott *et al.*[9] parameters for use in a CCIP is further validated by the fact that the reanalysis of the group 1 and 2A patients using the Scott *et al.*[9] pharmacokinetics substantially improved the apparent performance.

It appears that the Maitre *et al.*[6] population-based pharmacokinetic parameters are not appropriate for use in a CCIP because of a bias of approximately 50%. The inaccuracy is especially great at times immediately following a change in C_T.

For a CCIP to be useful, it must be able to maintain fairly stable serum concentrations that are reasonably close to the C_T. The ability of our CCIP to hold a constant serum concentration is clearly shown in figures 1 and 4. This fact is obscured by somewhat larger inaccuracy reported in our two groups of patients than that stated in other studies. A major component of inaccuracy in our data is the large positive performance errors seen immediately following changes of the target level.

CCIP have been shown to achieve serum and plasma alfentanil concentrations that are moderately close to C_T. Ausems *et al.*[4] in a prospective study, demonstrated a relatively small average bias of −17.6%. Similarly, Maitre *et al.*[7] found a relatively small average bias of −7.9% in their retrospective analysis of population pharmacokinetic parameters applied to the data from the Ausems *et al.*[4] earlier study. These results imply that alfentanil administered to a given patient with a CCIP system using population pharmacokinetic parameters would result in serum concentrations close to C_T on average. In addition, the precision of 32.1% reported by Ausems *et al.*[4] and 22.3% reported by Maitre *et al.*[7] suggest that the size of the typical miss is relatively small.

Unlike these previous studies, we have demonstrated consistent biases of 52% and 54% in two clinically dissimilar groups of patients using the Maitre *et al.*[6] population-based pharmacokinetic parameters. In both groups 1 and 2A, 94% of the C_M exceeded the corresponding C_T.

The Maitre *et al.*[6] pharmacokinetic parameters were derived using data from several previous studies and analyzed using NONMEM, the most sophisticated statistical nonlinear regression analysis available. Maitre *et al.*[6] then prospectively tested their pharmacokinetic parameters using data previously gathered by Ausems *et al.*[4] with good results. Why, then, did the Maitre *et al.*[6] pharmacokinetic

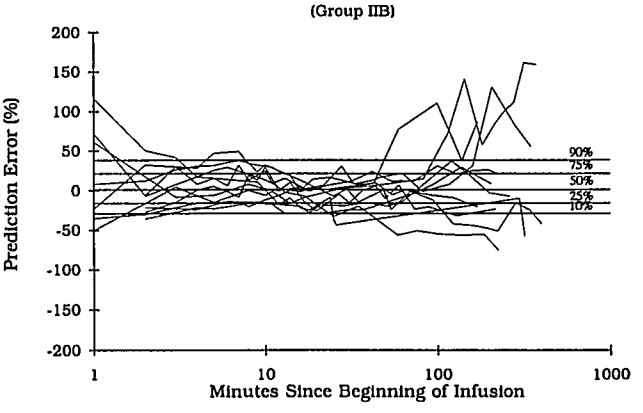

FIG. 5. Prediction error (difference between measured and target serum concentration as a fraction of target serum concentration) in percent *versus* time. Alfentanil was administered with CCIP using Scott *et al.*[9] pharmacokinetic parameters. Eleven male inpatients (group 2B) are represented. The 10th, 25th, 50th (median), 75th, and 90th percentiles of the prediction errors are shown.

TABLE 3. CCIP Performance with 2 Sets of Pharmacokinetic Parameters

Pharmacokinetic Parameter Set	Group	No. of Patients	MDAPE* (%)	Percentiles for Prediction Errors (%)				
				10th	25th	50th†	75th	90th
Maitre *et al.*[6]	1	29	52	9	27	52	94	138
Maitre *et al.*[6]	2A	11	55	11	32	54	89	158
Maitre *et al.*[6]	1 and 2A	40	53	11	30	53	92	143
Scott *et al.*[9]	2B	11	17	−29	−16	1	21	38
Maitre *et al.*[6] patients analyzed using Scott *et al.*[9] kinetics	1 and 2B	40	18	−29	−15	2	22	55

* Median Absolute Prediction Error is a measure of inaccuracy.

† The 50th percentile (median prediction error) is a measure of bias.

parameters perform so poorly in this large, truly prospective study, whereas those of Scott *et al.*[9] derived from fewer patients with less sophisticated analysis, perform well?

We examined five possible explanations for the poorer performance of the Maitre *et al.*[6] pharmacokinetics in this study. First, the assay could have been systematically different. If so, improved performance using the Scott *et al.*[9] pharmacokinetics would be expected because the samples in their study were assayed in the same laboratory. To validate the assay, samples from a previous study were exchanged with multiple laboratories and the results compared. A subset of samples from the current study were assayed by GC as well, and the results compared closely to the RIA results.‡‡ We also compared whether the alfentanil concentration differed between plasma and serum. We partitioned several of the arterial samples from two studies into both serum and plasma aliquots. In none of these exercises were any systematic analytical errors found.

Second, the computerized infusion system could have been inaccurate. The mathematical algorithm used in the software was verified against three independently derived techniques. The accuracy of the software driven syringe pump was evaluated gravimetrically and was found to be accurate within 1% throughout the operating range of the device.

Third, the patient populations could have been pharmacokinetically different than the populations studied by Maitre *et al.*[6] or Ausems *et al.*[4] However, we studied two different patient populations: healthy young female day surgery patients and relatively older and less healthy male inpatients. The consistently poor CCIP performance using the Maitre *et al.*[6] pharmacokinetics and the apparently good CCIP performance using the Scott *et al.*[9] pharmacokinetics in both populations suggest that patient selection was not responsible for the differences in performance we observed.

Fourth, the data analysis method used in our study (*i.e.*, expressing PE as a function of C_T) could have led to an exaggerated difference compared with earlier studies. However, we have reanalyzed the Maitre *et al.*[7] results with the Ausems *et al.*[8] data, using our measure of performance, MDAPE and MDPE. The MDAPE from Maitre *et al.*[6] "prospective" study is 27% and the MDPE is 16%. Thus, their conclusions remain the same, and this can only partially explain the different results we report here.

Fifth, the frequent collection of arterial blood samples in our study may not reflect the procedure used in the studies upon which the population pharmacokinetic parameters were obtained. Venous samples were used in two of the four studies from which Maitre *et al.*[6] obtained data for their population pharmacokinetic analysis. We

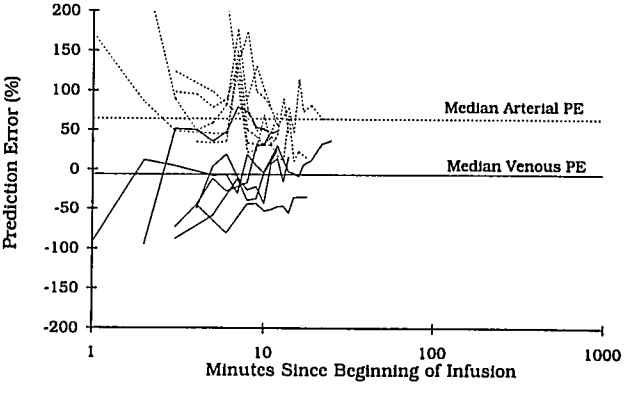

FIG. 6. Prediction error (difference between measured and target serum concentration as a fraction of target serum concentration) in percent *versus* time. Radial artery (*dotted lines*) and antecubital vein (*solid lines*) alfentanil serum concentrations sampled simultaneously in six male inpatients were used as the measured values. Alfentanil was administered with CCIP using Maitre *et al.*[6] pharmacokinetic parameters. The median arterial and median venous prediction errors demonstrate better performance of Maitre *et al.*[6] pharmacokinetic parameters when venous samples are used.

‡‡ Bjorkman S, Aziz N, Stein DA: Determination of alfentanil in serum by radioimmunoassay or capillary column gas-liquid chromatography: A comparison of two assays. Acta Pharm Nordica 1:211–220, 1989.

measured simultaneous antecubital venous blood samples from the first six patients in group 2A. As shown in figure 6, the MDPE of −6% for the venous samples was much less than the MDPE of 64% for the arterial samples. This would suggest that the Maitre *et al.*[6] population pharmacokinetic parameters were more consistent with venous levels than arterial in our population. However, the Ausems *et al.*[4] data, analyzed "prospectively" by Maitre *et al.*,[6] used arterial samples. Thus, site of sampling cannot entirely explain why the CCIP, using the Maitre *et al.*[6] pharmacokinetic parameters, performed so poorly.

In the four studies from which Maitre *et al.*[6] obtained data for their population pharmacokinetic analysis, alfentanil was administered as a single bolus in less than 30 s. In the Scott *et al.*[9] study, alfentanil was administered over 4–6 min. Also, blood sampling was conducted well into the postoperative period in the studies included by Maitre *et al.*[6] It may be that these differences in study design cause the substantial differences in pharmacokinetic parameters estimated by the two sets of authors. In that our study design was more similar to that of Scott *et al.*[9] with respect to an infusion and restriction to the operative period may partially explain the improved CCIP performance using the Scott *et al.*[9] parameters.

We are left without a complete explanation for the differences in performance of the CCIP using the Maitre *et al.*[6] pharmacokinetics observed in the present study and performance reported by Maitre *et al.*[7] in their "prospective" study of the Ausems *et al.*[8] data. It would appear that the Scott *et al.*[9] parameters, for whatever reason, more accurately describe the actual pharmacokinetics in the patient's studied than do the parameters of Maitre *et al.*[6]

Although the Scott *et al.*[9] pharmacokinetic parameters appear to match our patient populations fairly well, examination of figures 4 and 5 suggests areas for improvement. There is a tendency toward overshoot when the target concentration is increased, both in group 2B and in the reanalysis of groups 1 and 2A. There is also a tendency toward elevated levels during the elimination phase. It appears that fitting the data collected in this study to determine new alfentanil pharmacokinetic parameters may result in a better model on which to base a CCIP system. To test this hypothesis, a prospective study using the new pharmacokinetic parameters will be required.

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