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Computer-controlled Infusion of Alfentanil for Postoperative Analgesia

A Pharmacokinetic and Pharmacodynamic Evaluation

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Background: **Although computer-controlled infusion (CCI) of alfentanil has been shown to be effective intraoperatively, this technique has not been validated for postoperative use. Therefore, the authors examined the efficacy of this technique in providing postoperative pain relief. The study comprised both a validation of published pharmacokinetic data sets and the definition of the minimum effective analgesic concentrations after major orthopedic surgery.**

Methods: **The bias and inaccuracy of the implemented pharmacokinetic data set were examined, in 20 patients who had undergone major orthopedic surgery, by determination of the median performance error (MDPE) and median absolute performance error (MDAPE). The performance of two other published pharmacokinetic data sets was also examined by simulating the plasma concentrations that would have been predicted, had these data sets been implemented. The minimum effective analgesic concentrations (MEAC) were determined at the following time points: at the onset of pain, at 9:00 PM on the day of surgery, and at 9:00 AM and 9:00 PM on the first postoperative day.**

Results: **Measured plasma concentration-time profiles generally were parallel to the target concentration-time profiles. The MDPE and MDAPE obtained were 12% and 28%, respectively. The MEACs ranged from < 1 to 175 ng/ml and showed substantial interindividual variability. The median MEACs at the four study times were 59, 52, 65, and 43 ng/ml. The MEAC at 9:00 PM on the first postoperative day was significantly lower than those at the other study times ($P < 0.05$).**

Conclusion: **Computer-controlled infusion of alfentanil provides adequate postoperative analgesia. The study demonstrated that pharmacokinetic data sets that are useful for intraoperative CCI of alfentanil are equally valid in the postoperative phase. Although required plasma concentrations of alfentanil are reasonably stable in time, interindividual variations are large, necessitating individual titration. (Key words: Analgesia: postoperative. Analgesics: alfentanil. Computer: computer-controlled infusion. Pharmacodynamics: alfentanil; minimum effective analgesic concentration. Pharmacokinetics: alfentanil. Predictions, drug levels: errors.)**

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 27A.

THE degree of postoperative pain varies widely between individuals, and also fluctuates in time. A technique for administering analgesics tailored to the needs of the individual patient should, therefore, provide the best pain relief. At present, patient-controlled analgesia (PCA) with morphine, diamorphine, or meperidine is the only individually tailored technique for postoperative analgesia that is commonly used in clinical practice. The current PCA devices rely on the administration of bolus doses (with or without a baseline infusion), and, consequently, the plasma concentration, the concentration in the central nervous system, and the analgesic effect will vary considerably during the intervals between doses. Theoretically, more stable analgesic effects could be obtained if the plasma opioid concentration would remain constant between patient demands and if the patient could stepwise increase or decrease the opioid concentration to a desired level.

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Computer-controlled infusion (CCI) techniques have been described for intraoperative use.[1] Computer-controlled infusion allows automatic adjustment of the infusion rate to maintain a desired target concentration of the drug, minimizing the fluctuations in plasma concentrations. When opioids are administered using CCI techniques intraoperatively, it would be logical to extend this technique into the postoperative period for postoperative analgesia. Kenny *et al.*†† used a computer-controlled infusion of alfentanil for postoperative pain relief and reported a good overall quality of analgesia after major vascular surgery. However, comprehensive basic information on the relationship between the plasma concentration of alfentanil and the analgesic effect in the postoperative setting is still limited.

The performance of a CCI system depends largely on how well the supplied pharmacokinetic data match the pharmacokinetics of the individual patient.[2] Ideally, the computer should be programmed with individual pharmacokinetic data. However, in practice, individual pharmacokinetic data are seldom available. Pharmacokinetic data, derived from either volunteers or patients during surgery, are not necessarily relevant in the postoperative period when long-term infusions are used and required plasma concentrations are much lower than those required intraoperatively.

In this study, we evaluated the feasibility of a CCI of alfentanil for postoperative pain relief over a 36-h period. In addition, we examined the analgesic concentration-effect relationship for alfentanil in the postoperative period, and determined the effect of time on this relationship. We also prospectively tested the population pharmacokinetic data of Maitre *et al.*[3] in a CCI for postoperative analgesia. In addition, two other sets of pharmacokinetic data, previously reported by Scott *et al.*[4] and Lemmens *et al.*,[5] were evaluated.

Materials and Methods

Subjects

After obtaining approval from the Medical Ethics Committee and informed consent, 25 patients, ASA physical status 1 or 2, aged 21–65 yr, scheduled for orthopedic surgery under general anesthesia lasting longer than 1 h, were studied. Patients with a history of cardiovascular, pulmonary, hepatic, or renal disease or with rheumatoid arthritis were excluded from the study. Also excluded were patients who had taken opioids in the preceding month.

Computer-Controlled Infusion System

A computer-controlled infusion pump was used for the administration of alfentanil. The computer (Atari Portfolio, Okasaki, Japan) was interfaced to a syringe pump (Ohmeda 9000, Strector, U.K.) *via* a serial RS232 communication channel. The software, written in Pascal by one of the authors, was supplied with population pharmacokinetic data reported by Maitre *et al.*[3] The system allowed a theoretical target plasma concentration of alfentanil to be rapidly attained and maintained. To achieve this, the infusion range was changed every 10 s by a computer controlling the infusion pump. The algorithm for the computation of the infusion rate during each 10-s time segment is based on equations described by Hull.[6] Thus, based on the implemented three-compartment pharmacokinetic data, the computer keeps track of the concentrations of alfentanil in each of the three compartments of the model. After calculating the concentrations at any time, the computer calculates the infusion rate that is needed during the next 10 s to reach the new target (central compartment) plasma concentration, or to maintain the unaltered target plasma concentration, after this 10-s period. Subsequently, the concentrations in the compartments are again calculated, a new infusion rate computed, and so on.

If the computed infusion rate exceeds the preset maximum infusion rate of the pump (200 ml/h), the infusion rate is set to the maximum, and this is maintained until the plasma concentration, calculated (predicted) by the computer, matches the target concentration, which, in this case, takes longer than 10 s. This will be the case with a large stepwise increase in the target concentration. The infusion rates, averaged over 1-min intervals, were stored on a 128-Kb Portfolio memory card (Atari, Sunnyvale, CA). If the target concentration was changed, infusion rates were stored every 5 s from immediately before the change until the new predicted concentration was reached. To maximize safety, the maximum infusion rate of the Ohmeda pump was limited to 200 ml/h. Intraoperatively, a solution containing 0.5 mg/ml alfentanil was used. For postoperative use, the solution was diluted to 0.25 mg/

†† Kenny GNC, Davis F, White M: Computerised alfentanil infusion in postoperative analgesia. Proceedings of the 6th International Symposium on Computers in Anaesthesia and Intensive Care, Hamahatsu, Japan, April, 1991, p 178

Table 1. Changes in Target Plasma Concentration (C_T) of Alfentanil Related to Patient Status for the Determination of the Minimum Effective Analgesic Concentration

Patient Status	Change in C_T (ng/ml)
Patient is oriented and indicated a need for additional analgesia	
VAS score ≥4.0	10↑
VAS score <4.0	5↑
Patient indicated no need for additional analgesia	
VAS score ≥2.5	5↓
VAS score <2.5	10↓

ml. The system performance was validated using Euler's method,[7] supplied with the volumes delivered, and recorded by the infusion pump. This validation showed that predicted concentrations (based on actually given volumes by the infusion pump) were, on average, 1% lower than the target concentrations.

Anesthetic Technique

The anesthetic technique was standardized. Premedication was with oral temazepam, 0.3 mg/kg to the nearest 10 mg, 1 h before surgery. On the patient's arrival in the operating room, ECG electrodes were attached and blood pressure was measured. An intravenous cannula was placed in a large forearm vein. Pancuronium, 0.02 mg/kg, was given, and then anesthesia was induced by computer-controlled infusion of alfentanil and 66% nitrous oxide in oxygen. The target plasma concentration for induction was 400 ng/ml, to be achieved in 3 min. When the CCI device predicted that the target plasma concentration for induction was reached and consciousness had not been lost, 0.15–0.3 mg/kg etomidate was given. Succinylcholine, 1 mg/kg, was given to facilitate intubation of the trachea. After induction of anesthesia, a 20-G catheter was introduced into a radial artery for blood pressure monitoring and collection of blood samples. Anesthesia was maintained with 66% nitrous oxide in oxygen, and alfentanil. Pancuronium was given for muscle relaxation. When signs of inadequate anesthesia developed, the target concentration of alfentanil was increased by 20–50 ng/ml. Inadequate anesthesia was defined by the following criteria: (1) increase in systolic blood pressure by more than 15 mmHg above normal for the patient (the normal systolic blood pressure was defined as the mean of three systolic blood pressures measured on the day of admission to the hospital, at the administration of premedication, and just before induction); (2) a heart rate higher than 90 beats/min in the absence of hypovolemia; (3) other autonomic signs, such as sweating, flushing, or epiphora; and (4) somatic responses, such as movements, swallowing, coughing, grimacing, or eye movement.

If a patient did not respond during a 10-min period, the target plasma concentration of alfentanil was decreased by 20 ng/ml. At the end of surgery, the computer-controlled infusion of alfentanil and nitrous oxide were discontinued and residual neuromuscular block was antagonized with 0.5 mg atropine and 1 mg neostigmine. The trachea was extubated after the patient had recovered consciousness and when adequate ventilation had been established (respiration rate > 8 breaths/min, end-tidal CO_2 < 6.5 vol%, and tidal volume > 7 ml/kg). After tracheal extubation, the patient was transported to the recovery room and supplemental oxygen was routinely given. Supplemental oxygen was continued on the ward, if the patient had an Sp_{O_2} < 90% while breathing room air.

Postoperative Management

The patient was instructed to report the onset of pain to one of the investigators. At that moment, the patient's pain was scored using a 10-cm visual analog scale (VAS), and the degree of sedation was scored using a five-point scale: (1) awake, oriented, initiates conversation; (2) sleepy, oriented, initiates conversation; (3) sleepy, oriented, does not initiate conversation; (4) very drowsy, disoriented, does not initiate conversation; and (5) stupor, disoriented, does not initiate conversation.

If the sedation score was ≤ 3, the computer-controlled infusion of alfentanil was restarted with a target concentration equal to the plasma concentration of alfentanil predicted by the computer at that moment. After 15 min, the patient's sedation and pain scores were again assessed, and the plasma concentration was increased or decreased according to criteria described in table 1. These assessments and adjustments were repeated at 15-min intervals until the patient, while oriented, indicated no need for additional analgesia, and had a VAS score < 3. When these criteria were met, the target concentration was maintained at the corresponding level. At 9:00 PM that evening and at 9:00 AM and 9:00 PM on the first postoperative day, this procedure was again started. Again, every 15 min, the target plasma concentration was readjusted until the

Table 2. Pharmacokinetic Data: The Central Volume (V_c) and Rate Constants of the Studied Pharmacokinetic Data Sets

			Lemmens *et al.*[5]		
	Maitre *et al.*[3]	Scott *et al.*[4]	Male	Female ≤50 yr	Female >50 yr
V_c		2.185	4.106	4.174	3.566
Male	0.111 × weight (kg)				
Female	0.111 × 1.15 × weight (kg)				
k12	0.1040	0.656	0.2818	0.3475	0.1810
k21	0.0673	0.214	0.1219	0.1580	0.1580
k13	0.0170	0.113	0.0806	0.1298	0.1352
k31		0.017	0.0150	0.0170	0.0143
≤40 yr	0.0126				
>40 yr	0.0126 − [0.000113 × (age − 40)]				
k10		0.091	0.0679	0.1031	0.0717
≤40 yr	$0.356/V_c$				
>40 yr	$\{0.356 - [0.00269 \times (age - 40)]\}/V_c$				

oriented patient indicated no need for additional analgesia, and had a VAS score < 3; when these criteria were met, the corresponding concentration was again maintained. These adjustments were done to establish the minimum effective analgesic concentration providing adequate analgesia at these four study times (see also the pharmacodynamics section).

At 3:00 AM on the night after surgery, and at 3:00 PM on the first postoperative day, the target plasma concentration of alfentanil was decreased by 5 or 10 ng/ml, if the patient met the criteria for reducing the concentration, as described in table 1. If the patient was oriented and indicated a need for additional analgesia at any time during the study period, the target plasma concentration of alfentanil was increased, as specified in table 1, until an adequate level of analgesia was achieved.

Every 15 min during the period of adjustment of the target plasma concentration, and every 2 h during the remaining observation period, the VAS score, the sedation score, and the vital signs were documented. No VAS scores were obtained when the patient was asleep. Peripheral oxygen saturation (Sp_{O_2}) (Nellcor, Hayward, CA) and heart rate were continuously registered, and a respiration monitor (MR10; Graseby Medical, Watford, UK) constantly recorded the respiration rate. Respiratory depression was defined as a respiration rate < 8 breaths/min, or Sp_{O_2} < 90%, or an arterial Pa_{CO_2} > 7.3 kPa (55 mmHg). Side effects observed during the postoperative period were registered. After the fourth assessment, the study was ended. At the end of the study, patients were asked whether they were satisfied with their postoperative analgesia.

Blood Samples and Alfentanil Assay

Postoperative arterial blood samples (3 ml) for the measurement of the plasma concentration of alfentanil were collected before every change in target plasma concentration of alfentanil and 15 min after the target plasma concentration was achieved. The maximum amount of blood collected was restricted to 125 ml per patient. Plasma was obtained by centrifugation and stored at −20° C until analysis. A capillary gas chromatographic technique[8] was used to determine the plasma concentration of alfentanil. The detection limit was 0.1 ng/ml plasma. The coefficient of variation in the concentration range (> 1 ng/ml) encountered in this study was < 5%.

Data Analysis

Pharmacokinetics and Computer Simulations. The performance of the computer-controlled infusion system, implemented with the population pharmacokinetic data set from Maitre *et al.*[3] (table 2), was assessed by examining the bias and inaccuracy as described by Raemer *et al.*[2] Bias is a measure of a systematic failure to achieve the target plasma concentration. Inaccuracy is a measure of the expected failure to achieve the target plasma concentration. Both bias and inaccuracy are aggregated measures of the performance of the system. For each blood sample, the performance error (PE) was calculated as

$$PE = \frac{(C_p - C_{pred})}{C_{pred}} * 100$$

where C_p = the measured plasma concentration of alfentanil, and C_{pred} = the corresponding predicted

Table 3. Patient Characteristics, Type of Surgery, Duration of Anesthesia, and Onset of Postoperative Pain

Patient No.	Sex	Age (yr)	Weight (kg)	Type of Surgery	Duration of Anesthesia (min)	Intraoperative Alfentanil Consumption ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Onset of Pain (min)	Postoperative Alfentanil Consumption ($\mu g \cdot kg^{-1} \cdot h^{-1}$)
1	M	24	64	Bankart repair shoulder	143	2.3	65	18.6
2	F	22	71	Block resection tumor tibia allograft	165	1.4	45	24.8
3	M	26	87	Putti-Platt shoulder	135	3.3	387	8.5
4	F	28	46	Resection giant cell tumor distal radius	235	2.5	107	11.4
5	M	36	85	Resection osteoid osteoma humerus	133	2.5	115	4.6
6	M	45	78	Acromionplasty	165	2.0	180	14.8
7	M	29	97	Putti-Platt shoulder	172	1.6	121	14.5
8	F	31	57	Resection giant cell tumor femur condyl	141	2.1	223	8.5
9	M	51	69	Reconstruction elbow	118	2.0	250	6.7
10	M	30	90	Putti-Platt shoulder	158	2.5	113	23.9
11	M	24	63	Shelf operation hip	187	1.9	230	1.3
12	M	43	75	Resection allograft humerus	194	1.6	249	6.9
13	M	47	89	Resection malignant giant cell tumor femur and prosthesis	316	1.4	255	10.7
14	M	27	73	Putti-Platt shoulder	170	1.5	153	7.3
15	F	32	65	Resection giant cell tumor fibula	146	2.4	194	12.1
16	F	41	91	Revision total hip	216	1.6	113	18.0
17	F	59	83	Total hip	142	1.6	320	1.7
18	F	26	71	Resection distal clavicle	166	1.9	220	7.0
19	F	34	65	Boneplasty of proximal femur	185	2.4	195	16.3
20	M	21	96	Bankart repair shoulder	178	2.8	116	30.8
Mean	M/F	33.8	75.8		173.3	2.1	183	14.8
(SD)	12/8	(10.3)	(13.4)		(43.0)	(0.52)	(86.5)	(7.6)

plasma concentration. The bias of the system is expressed as the median PE (MDPE) over all blood samples. The system inaccuracy is the median of the absolute values of the individual PEs (MDAPE). Median PE and MDAPE were calculated for each patient from all blood samples collected from that patient. In addition, MDPE and MDAPE were calculated from all blood samples collected from the entire population. Data points with $C_T = 0$ ng/ml and $C_p < 1$ ng/ml, where C_T is the target plasma concentration of alfentanil, were omitted from this analysis.

The performance of two other pharmacokinetic data sets, described by Scott *et al.*[4] and Lemmens *et al.*[5] (table 2), was assessed. Using these pharmacokinetic data sets and the original stored infusion rates, we calculated new predicted plasma concentrations of alfentanil for each patient. Subsequently, the performance of these sets was determined as described above, but with substitution of the newly predicted concentrations for the originally predicted concentrations.

Pharmacodynamics. The minimum effective analgesic concentration (MEAC) was defined as the measured plasma concentration of alfentanil at which the patient was oriented, indicated no need for additional analgesia, and had a VAS score < 3. The MEAC was determined for each patient at the four previously described observation times, *i.e.*, at the onset of pain, at 9:00 PM on the day of surgery, and at 9:00 AM and 9:00 PM on the first postoperative day. Subsequently, the median MEAC at each observation time was determined from the individual MEACs at each time. A sigmoid E_{max} model was used to describe the concentration-effect relationship over all patients, at each aforementioned study time, according to the formula:

$$E = \frac{E_{max} * C_p^{\gamma}}{C_p 50^{\gamma} + C_p^{\gamma}}$$

where E = the effect, defined as the percentage of patients who had a MEAC $\leq C_p$; C_p = the measured plasma concentration of alfentanil; E_{max} = the maximum effect (*i.e.*, 100%); C_p50 = the concentration corresponding with 50% of E_{max} (*i.e.*, 50% of the patients have a MEAC $\leq C_p50$); and γ = a dimensionless parameter indicating the slope of the curve. The model was fitted to the data using unweighted least-squares nonlinear regression. If, at any of the aforementioned times, the target con-

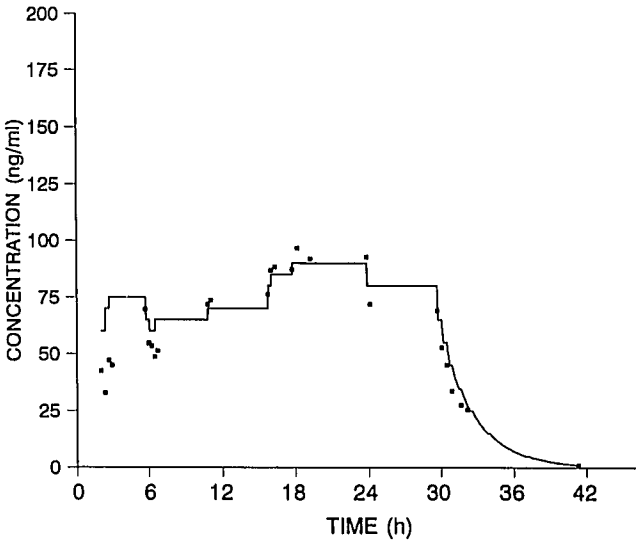

Fig. 1. Measured (squares) and predicted (solid line) plasma concentration of alfentanil for a representative patient. Alfentanil was administered by a CCI system supplied with population pharmacokinetic data, reported by Maitre *et al.*[3]

centration could be lowered to 0 in any of the patients, these patients were omitted from the nonlinear regression at that study time. These patients were considered as no longer requiring alfentanil.

Statistical Analysis

Data were examined for normality using the Shapiro-Wilk test and are presented as mean ± SD, or as median and 95% confidence interval (CI) or range, where appropriate. Adverse reactions are reported as frequency of the occurrence.

The comparative performance of the different pharmacokinetic data sets was examined by the multisample median test, followed by a multisample comparison test,[9] when indicated. The influence of time on the PE was determined by the Spearman rank test. The intra-individual variability (time dependence) of the MEAC of alfentanil was examined by the Friedman test, followed by a Tukey test when indicated.

A value of $P < 0.05$ was regarded as the minimum level of statistical significance.

Results

Twenty-five patients were enrolled in the study. Five patients were excluded from the data analysis for the following reasons. In four patients, the arterial catheter occluded within 24 h from the start of the study. In the other one patient, alfentanil was discontinued on the first postoperative morning because of $Sp_{O_2} < 90\%$. An Sp_{O_2} between 80 and 90% persisted for 4 days after discontinuation of alfentanil administration in this patient.

The demographic data of the 20 remaining patients (12 men and 8 women), details of the type of surgery, the duration of anesthesia, the intraoperative and the postoperative alfentanil consumption, and the time of onset of postoperative pain are presented in table 3. No patient needed naloxone to restore adequate ventilation after the termination of anesthesia. All patients were spontaneously breathing on arrival in the recovery room. Alfentanil infusion was restarted 183 ± 87 min after the end of anesthesia.

Pharmacokinetics

The plasma concentration of alfentanil *versus* time of a representative patient is shown in figure 1. In general, measured plasma concentrations of alfentanil were grossly parallel to the predicted plasma concentrations. Figure 2 shows the relationship between measured and predicted concentration of alfentanil for all blood samples. Figure 3 shows the performance error of all blood samples *versus* time in individual patients, as obtained with the implemented pharmacokinetic data of Maitre *et al.*[3] No systematic over- or undershoot was seen at the start of the pain treatment. Time had no influence on the PE.

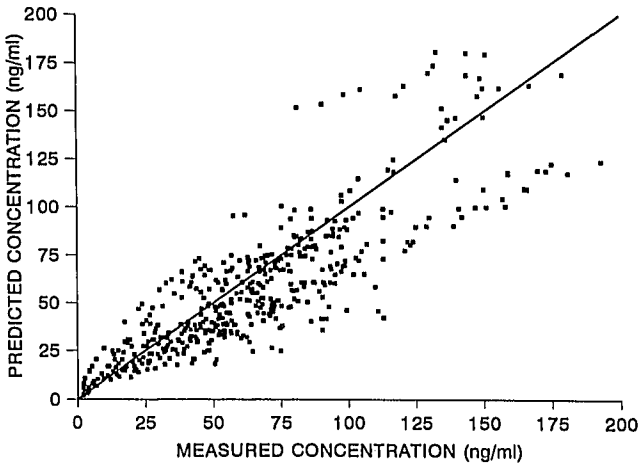

Fig. 2. Plot of the predicted (using the pharmacokinetic data of Maitre *et al.*[3]) plasma concentrations of alfentanil *versus* the measured plasma concentrations of alfentanil and the line of identity (N = 465).

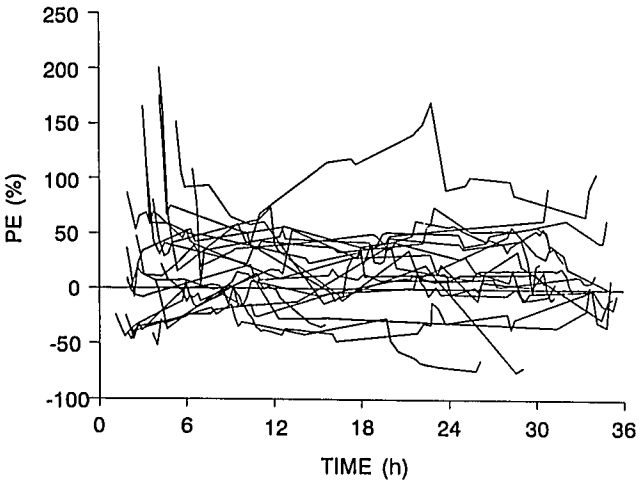

Fig. 3. Performance error (PE) of all blood samples *versus* time (N = 465) for all 20 patients, as obtained with the population pharmacokinetic data of Maitre *et al.*[3]

Median PEs and MDAPEs are presented in table 4. The bias of the system, calculated from all collected blood samples using the population pharmacokinetic data of Maitre *et al.*, was 12% (CI 9–17%) and the inaccuracy was 28% (CI 24–32%) (table 5). The medians, calculated from the MDPE and MDAPE of the individual patients, were 19% (CI 0.5–42%) and 31% (CI 11–45%).

Table 4. Median Performance Error (MDPE) and Median Absolute Performance Error (MDAPE) with Corresponding 95% Confidence Intervals (CI) Reflecting the Performance of the CCI System, Implemented with the Population Pharmacokinetic Data Set as Described by Maitre *et al.*[3] for the Postoperative Administration of Alfentanil

Patient No.	No. of Samples	MDPE (%)	95% CI	MDAPE (%)	95% CI
1	25	7.7	−8.7–13.8	13.8	11.3–24.2
2	17	1.3	−4.9–−9.8	6.1	4.7–10.7
3	13	48.3	36.5–62.8	48.3	36.5–62.8
4	21	−41.9	−64.5–−27.5	41.9	27.5–64.5
5	17	−6.4	−8.7–2.0	8.4	6.4–19.4
6	24	45.1	41.1–57.0	45.1	41.1–57.0
7	28	0.5	−7.0–7.8	9.4	7.0–13.8
8	27	29.4	13.1–40.7	29.4	18.0–40.7
9	19	39.8	13.9–56.5	39.8	13.9–56.5
10	27	42.4	36.7–50.1	42.4	36.7–50.1
11	14	0.5	−28.2–12.9	14.4	5.7–28.2
12	23	94.2	97.9–115.1	94.2	67.9–115.1
13	25	7.8	2.3–16.7	12.7	3.7–17.1
14	25	29.6	16.2–36.6	29.6	16.2–36.6
15	23	36.6	24.8–46.3	36.6	24.8–46.3
16	28	6.7	2.4–9.3	7.3	6.2–9.4
17	12	59.3	−14.1–3.4	68.0	21.8–93.4
18	31	−31.9	−37.0–−27.4	31.9	27.4–37.0
19	31	48.7	42.2–55.4	48.7	42.2–55.4
20	35	−11.1	−16.1–−6.1	11.1	6.5–18.6

Table 5. Median Performance Error (MDPE) and Median Absolute Performance Error (MDAPE) and Corresponding 95% Confidence Intervals (CI) for Three Pharmacokinetic Data Sets

Pharmacokinetic Data Set	No. of Patients	N*	MDPE (%)	95% CI	MDAPE (%)	95% CI
Maitre *et al.*[3]	20	465	12	9–17	28	24–32
Scott *et al.*[4]	20	465	−35	−38–−32	36	32–38
Lemmens *et al.*[5]	20	465	11	8–15	26	23–28

* Total number of blood samples, from which MDPE and MDAPE were calculated.

Table 6. The Minimum Effective Analgesic Concentration of Alfentanil in All Individual Patients at the Four Observation Times

Patient No.	$MEAC_1$ (ng/ml)	$MEAC_2$ (ng/ml)	$MEAC_3$ (ng/ml)	$MEAC_4$ (ng/ml)
1	43	47	64	60
2	87	94	94	68
3	—	52	73	93
4	62	42	4	<1
5	69	5	<1	<1
6	98	94	71	71
7	45	51	97	<1
8	36	32	33	11
9	59	44	51	10
10	159	175	166	52
11	26	3	<1	<1
12	46	69	60	37
13	83	60	66	49
14	38	37	30	<1
15	54	53	72	63
16	113	82	85	68
17	48	22	14	<1
18	46	19	27	16
19	91	80	79	122
20	105	121	140	98
Median	59	52	65	43†
Range	26–159	3–175	<1–166	<1–122
Median*	59	52	69	61‡
Range*	26–159	3–175	4–166	10–122

$MEAC_1$ = at the onset of pain; $MEAC_2$ = at 9 PM on the day of surgery; $MEAC_3$ = at 9 AM on the first postoperative day; $MEAC_4$ = at 9 PM on the first postoperative day; — = onset of pain in patient 3 was not until the second study time.

* Patients with MEAC <1 ng/ml were excluded (corresponding target concentrations were zero).

† $MEAC_4 < MEAC_1, MEAC_2, MEAC_3$, $P < 0.05$.

‡ $MEAC_4 < MEAC_1, MEAC_3$, $P < 0.05$.

The bias and inaccuracy obtained after computer simulation with the other pharmacokinetic data sets are shown in table 5. The bias, obtained with the pharmacokinetic data of Maitre *et al.*[3] (12%) and Lemmens *et al.*[5] (11%), was significantly smaller than that obtained with the data of Scott *et al.*[4] (−35%) ($P < 0.001$).

Pharmacodynamics

The minimum effective analgesic concentrations of alfentanil at the four observation times are shown in table 6. The intersubject variability was substantial, as shown by the range at the different observation times. For the 19 patients who had a MEAC assessed at all four study times, the MEAC at 9:00 PM on the first postoperative day was significantly lower than the MEAC at the 3 other study times. The target plasma concentration could be decreased to zero in two patients at the third (first postoperative day, 9:00 AM) and six patients at the fourth (first postoperative day, 9:00 PM) observation time. In these patients, the computer-controlled infusion of alfentanil was maintained until the predicted alfentanil concentration was < 1 ng/ml. Corresponding measured plasma concentrations also were

Table 7. C_p50 (ng/ml), γ, and Standard Error Obtained by Fitting a Sigmoid E_{max} Function to the Percentage of Patients with a MEAC ≤ C_p *Versus* C_p*

	C_p50 (ng/ml)	SE (ng/ml)	γ	SE
$MEAC_1$	58.3	1.0	3.3	0.4
$MEAC_2$	48.8	1.1	2.6	0.2
$MEAC_3$	60.4	2.4	2.7	0.3
$MEAC_4$	54.6	2.4	3.3	0.6

$MEAC_1$ = at the onset of pain; $MEAC_2$ = at 9 PM on the day of surgery; $MEAC_3$ = at 9 AM on the first postoperative day; $MEAC_4$ = at 9 PM on the first postoperative day.

* Also see figure 4.

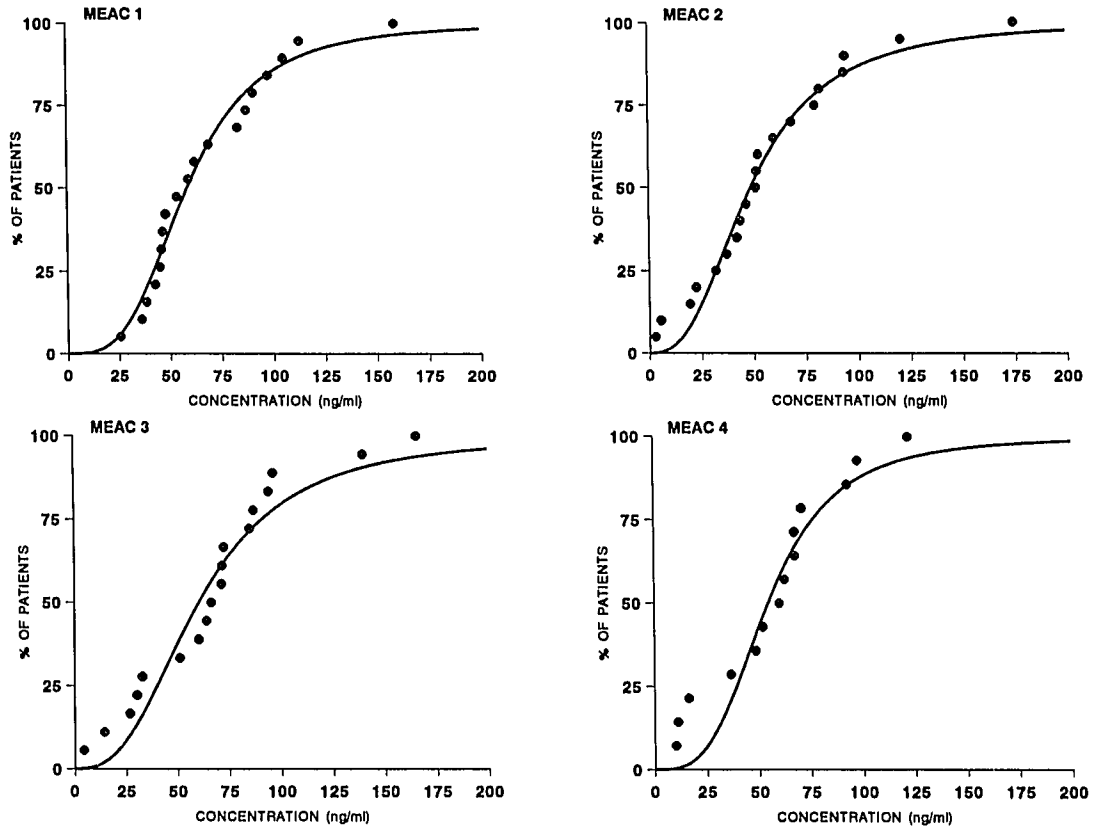

Fig. 4. Relationship between the plasma concentration of alfentanil and the percentage of patients having a MEAC ≤ C_p (points) at the four observation times. Cumulative concentration-effect curves (solid lines) were obtained by fitting a sigmoid Emax model. (MEACs are reported in table 6, C_p50 and γ are described in table 7.)

< 1 ng/ml. If patients who no longer required alfentanil (C_T = 0) were excluded, there was still a statistical significant effect of time on MEAC: MEACs at 9:00 PM on the first postoperative day were significantly lower than the MEACs obtained at the first and the third assessment. The cumulative alfentanil plasma concentration-effect curves for each observation time, based on the data given in table 6, are shown in figure 4. The calculated C_p50 values and slopes of the curves are presented in table 7.

Adverse Effects

Respiration rate and postoperative Sp_{O_2} were always within the clinically acceptable range, except for one patient, who was excluded from the data analysis. Hypotension, defined as a decrease in blood pressure of more than 15% from preoperative control values, did not occur. Side effects that occurred during the treatment period were nausea, vomiting, urinary retention, and itching. Nausea and vomiting occurred in 18 patients. For 12 patients, an antiemetic was indicated and given. Nine patients, seven men and two women, had urinary retention that required catheterization of the urinary bladder. Mild itching was reported in one patient, but no therapy was indicated. Despite these side effects, all patients were satisfied with this method of providing analgesia.

Discussion

Although alfentanil is widely used intraoperatively, there have been relatively few studies investigating its efficacy as a postoperative analgesic. Andrews *et al.*[10] used a postoperative infusion of 20 $\mu g \cdot kg^{-1} \cdot h^{-1}$ alfentanil for 1 h in patients after body surface surgery. They reported adequate analgesia, but described depression of CO_2 responsiveness to 50% of its preoperative value with only moderate effects on the respiratory minute volume and Pa_{CO_2}.

Compared with constant-rate infusions, a major advantage of the administration of alfentanil by CCI is that the plasma concentration can be more easily adjusted to the needs of the patient and maintained at a stable level. The pharmacologic properties of alfentanil[11] make it the most suitable of the currently available opioids for use in a CCI system. Its onset of action is very rapid, because it equilibrates rapidly between blood and brain.[4] In addition, fast distribution and elimination allow rapid changes to the desired target plasma concentrations, even after prolonged infusions. Subsequently, the rapid brain-blood equilibration will also result in correspondingly rapid changes of effects, when either an increase or decrease in analgesic effect or fewer opioid side effects are indicated.

From a pharmacokinetic point of view, the optimal lockout time or the optimal background infusion varies in time during the therapy. With conventional PCA, it is impossible to implement these pharmacokinetic principles. Theoretically, low or no background infusion and long lockout times can lead to ineffective analgesic concentrations at the start of therapy. On the contrary, a short lockout time or a high background infusion can result in overdosing the patient at a later stage. With computer-controlled infusions, the pharmacokinetic principles can be used to obtain the optimal plasma concentrations according to the patient's need at any time.

Compared with PCA administration, a CCI device theoretically has the advantage that more stable analgesic effects can be obtained. Like a conventional PCA system, the CCI system can be made patient controlled. For example, if the patient required more effective analgesia, he could increase the target concentration by pushing a button. In addition, the target concentration may be decreased in the absence of any demands for a preset time period (*e.g.*, 1 h). In this study, we intentionally abstained from the patient-control option, because this would result in less consistent MEAC determinations (see pharmacodynamics section).

Pharmacokinetics

Hill *et al.*[12,13] investigated a CCI system with morphine or alfentanil in patients suffering from oral mucositis pain after bone marrow transplantation, and reported excellent pain relief, with only minor side effects. In their study, the CCI system was programmed with pharmacokinetic data of the individual patients, which had been previously determined. However, in general, individually predetermined pharmacokinetic data are not available. Therefore, the application of a relevant and valid pharmacokinetic data set in a CCI system is important.

The current study demonstrates that administration of alfentanil can be achieved with an acceptable bias when the system is supplied with appropriate pharmacokinetic data. The bias using the pharmacokinetic data sets described by Maitre *et al.*[3] (12%) and Lemmens *et al.*[5] (11%) were small enough to warrant application in the CCI system. However, the bias obtained

with the pharmacokinetic data set described by Scott *et al.*[4] was unacceptably large (−35%).

In an intraoperative study, designed to verify their original data, Maitre *et al.*[14] reported a bias of −8%. In contrast, Raemer *et al.*[2] found a considerable bias of 53% when prospectively testing the data of Maitre *et al.*,[3] but reported only a 1% bias associated with the data of Scott *et al.*[4] They concluded that Scott's pharmacokinetic data set was more appropriate for use in a CCI system than that of Maitre. We have no explanation for the discrepancies encountered in evaluations of the performance of different pharmacokinetic data sets implemented in a CCI. Methodologic differences in the various study designs and large population variability have both been suggested as contributing factors.[2]

Even after implementation of population pharmacokinetic data, the performance of the system in individual patients still shows a large variability, reflecting the existing interindividual variability in the pharmacokinetics of alfentanil. It would be expected that the performance of a CCI system will be much improved when the system is supplied with the patient's individual pharmacokinetic data. Hill *et al.*[15] tested the performance of a CCI system using alfentanil, supplied with individual pharmacokinetic data, for the relief of experimental pain in healthy male volunteers. The mean bias was small, and varied from −8% (SD 23%), at a target concentration of 20 ng/ml, to 13% (SD 25%), at a target concentration of 80 ng/ml. The corresponding mean absolute prediction errors varied from 20% (SD 15%) to 23% (SD 15%), respectively. Thus, although both MDPE and MDAPE are smaller when the CCI system is provided with individual pharmacokinetic data, the gain compared with implementation of appropriate population pharmacokinetic data may be minimal. We feel that a MDPE of less than 15% and a MDAPE of less than 30% are acceptable for postoperative patient care, provided that the predicted concentration parallels the measured plasma concentration and the PE is approximately constant over the period of infusion. In this study, we clearly demonstrated that time did not influence the PE.

The performance error, as used in this and other studies,[2,16–18] is a measure of how well the measured concentration compares with the predicted concentration. A performance error of, for example, −50% (measured concentration 50% of predicted) is as good or as bad as a performance error of + 50% (measured concentration 150% of predicted), and twice as bad as a performance error of 25%. However, the clinical consequence of a −50% (a twofold) error in terms of the resulting error in effect will generally differ from that of a performance error of + 50% (a 1.5-fold error), because the concentration-effect relationship is likely to be nonlinear (logarithmic or sigmoid shaped). However, the error in the effect with a −50% performance error is not necessarily greater than that with a + 50% error. For example, if we assume either a logarithmic or a sigmoid-shaped concentration-effect relationship, and the predicted concentration is the minimum effective analgesic concentration (the threshold), a −50% performance error may decrease the effect below threshold, *i.e.*, the change in effect will be 100% and the patient has a need for additional analgesia. In the same situation, a + 50% performance error may increase the intensity of effect by much more than 100% if the concentration-effect relationship is steep and the patient will be sedated or respiratory depressed. In other words, the percentage of change in effect with a given performance error is dependent on the concentration-effect relationship and on the effect corresponding with the target. Therefore, it is not possible to judge the implications of a given performance error in terms of the change in effect, unless the concentration-effect relationship is known, which is not the case for an individual patient.

The only goal of the calculation of performance errors in this study was to derive measures that would allow us to judge the applicability of three pharmacokinetic data sets in a computer-controlled infusion of alfentanil for postoperative analgesia. The message from this study is that the data sets of both Maitre *et al.*[3] and Lemmens *et al.*[5] are useful in that the bias and inaccuracy resulting from implementation of these data sets are within reasonable limits. Nevertheless, considering the variability in MEAC, as shown in table 6, and the above-mentioned consequences of an either positive or negative performance error, one should never fail to titrate a computer-controlled infusion to the patient's needs.

Pharmacodynamics

The intraoperative pharmacodynamics of alfentanil have been extensively studied. Alfentanil plasma concentration *versus* effect curves for intubation, skin incision, skin closure, and spontaneous ventilation have been described by Ausems *et al.*[19] and Lemmens *et al.*[20] However, information on the intraoperative pharmacodynamics of alfentanil cannot be extrapolated to the postoperative patient.

We designed our study to reduce the extraneous influences on the pharmacodynamics of alfentanil to a minimum. Only patients undergoing major orthopedic surgery were studied, and alfentanil was the only opioid used intra- and postoperatively. Because the investigators were not blinded to the target concentration, precisely and rigidly defined criteria were used to control the administration of alfentanil to minimize the influence of investigator bias on the results. Our definition of the MEAC is based on three features: (1) the patient had to be oriented; (2) the quality of analgesia had to be adequate without the need for additional analgesia, and (3) VAS score had to be < 3. These criteria gave both the patient and the investigator explicitly defined guidelines to work with.

A pharmacologic endpoint based on a subjective parameter, such as the patient's need for additional analgesia, can be criticized. Nonetheless, we feel that this is a better criterion to work with than the VAS score alone. The answer to the question of the adequacy of analgesia can only be either affirmative or negative, and, therefore, is the basis for the direction of the change in target concentration. Until there is an objective, valid measurement for the intensity of pain, the patient is, and can be, the only one to declare how effective he considers the treatment.

We found that MEAC varied considerably between patients (from < 1 to 175 ng/ml), and was significantly lower at 9:00 PM on the first postoperative day. The variability is consistent with that reported in other studies. Owen *et al.*[21] tested a PCA system using alfentanil after upper abdominal surgery. They were unable to identify an optimal bolus dose and infusion rate. The concentration of alfentanil just before the patients made demands, *i.e.*, the maximum concentration still associated with pain (MCP), ranged from 21 to 101 ng/ml. In another study,[22] in which they investigated the effect of supplementing PCA alfentanil with a background infusion, Owen *et al.* reported a MCP 4–8 h postoperatively of 58 ng/ml for the PCA only group and 80 ng/ml in the PCA + infusion group. Of the 40 patients studied, 13 patients were withdrawn because of inadequate analgesia or respiratory depression. In a study using PCA alfentanil, supplemented by a low-dose fixed-rate infusion of alfentanil, for patients recovering from major abdominal or orthopedic surgery, Lehmann *et al.*[23] reported a MCP range from 0.6 to 99 ng/ml. Camu *et al.*[24] compared the efficacy of intravenous and epidural infusions of alfentanil in patients after abdominal hysterectomy. After the intravenous infusion was stopped, 20 h postoperatively, the mean MCP was 46 ng/ml.

The validity of the MCP/MEAC concept in PCA has been challenged by Owen *et al.*[22,25] It is known that patients usually prefer PCA for postoperative analgesia, despite sometimes suboptimal pain relief. By being in control of pain relief, the patients seek diminution in pain and are often satisfied if they only perceive less pain after a demand. The values for MCP determined in a PCA setting may, therefore, underestimate the actual MCP/MEAC values. In our study, using a continuous computer-controlled infusion, an effective plasma concentration of alfentanil was maintained, and, accordingly, the MEAC in each individual patient was defined more accurately.

All previous studies, as well as our study, have shown a large variability in MCP or MEAC. A factor that contributes to this variability is that the severity of postoperative pain is variable in intensity and duration. In this study, 6 out of 20 patients no longer required alfentanil at 9:00 PM on the first postoperative day; their target concentration could be lowered to 0 ng/ml. For the patients requiring analgesia, the MEAC remained virtually constant until 9:00 AM on the first postoperative day. Twelve hours later, the MEAC was significantly lower. Owen *et al.*[21] reported the mean MCP for alfentanil after upper abdominal surgery as 58 ± 25 ng/ml on the day of surgery and 37 ± 24 ng/ml on the first postoperative day. However, they studied their patients for only 24 h, and included all patients in their calculation of MCP. By excluding the patients having a C_T = 0 ng/ml at the different time points, the median MEACs so obtained give the clinician a guideline for the effective concentration of alfentanil at that time for the patients still needing analgesia.

Adverse Effects

The safety of a computer-controlled infusion in the postoperative setting still has to be investigated. We did not encounter any respiratory depression in our 20 patients, in contrast to the experience of others, using PCA alfentanil[21] or constant-rate infusions of alfentanil.[10,24,26] Sedation did not occur in our patients. There was a high incidence of nausea and vomiting (18/20), and 12 of 20 patients needed antiemetic therapy. This incidence is higher than that reported in most studies in patients given opioids for postoperative analgesia, which varies from 0–60%.[23–25] We did not give prophylactic antiemetics. Antiemetics were only

given when a patient vomited or complained of substantial nausea.

Urinary retention occurred in 45% of our patients. A high incidence has been reported earlier[27] in patients undergoing joint replacement surgery. In that study, the postoperative use of opioids did not correlate with the occurrence of urinary retention.

Conclusions

This study demonstrated the feasibility of computer-controlled administration of alfentanil in providing postoperative analgesia. Implementation of population pharmacokinetic data resulted in an acceptable bias and inaccuracy of the CCI system. The minimum effective analgesic concentration of alfentanil providing adequate analgesia varies widely between patients, and generally decreases during the first postoperative day. The wide variability in pharmacodynamics can be overcome by tailoring the target plasma concentration to the individual patient's needs. We believe that a computer-controlled infusion of alfentanil has potential for providing effective postoperative analgesia.

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