Pharmacokinetic Model-driven Infusion of Fentanyl: Assessment of Accuracy

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Computer-assisted continuous infusion (CACI) is a pharmacokinetic model-driven infusion device that enables physicians to administer intravenous (iv) drugs in a quantitative fashion, specifying a theoretical blood or plasma concentration. This study evaluated the accuracy of CACI administration of fentanyl using a newly developed CACI device programmed with a well-known set of pharmacokinetic parameters for fentanyl. Patients received diazepam 1 or 2 h before surgery. Anesthesia was induced by a combination of 70% N2O and fentanyl administered by CACI to a predicted concentration of 15–25 ng·ml⁻¹. After neuromuscular blockade and tracheal intubation, the desired plasma fentanyl concentration (setpoint) entered into CACI was 3–6 ng·ml⁻¹, and then the setpoint fentanyl concentration was titrated according to strict criteria of adequate or inadequate anesthesia. Plasma samples for subsequent assay of fentanyl concentration then were taken at predefined stimuli, when inadequate anesthesia occurred, or 5 min before an anticipated decrease in the fentanyl setpoint. The predictive accuracy of CACI was assessed by calculating for each patient the tenth, 50th, and 90th percentile of the performance error and absolute performance error from each measured and predicted plasma sample pair. Cumulative probability functions for each of these were then plotted. Precision was defined as the dispersion of the tenth to 90th percentile of the median percent performance error for the population and was found to be −31–26%. The median population performance error was −4%, and the median population absolute performance error was 21%. It was concluded that a CACI device using a single set of pharmacokinetic parameters can provide sufficient accuracy within a relatively homogeneous patient population to allow fentanyl to be administered to a concentration (rather than dose) that provides the desired therapeutic effect. (Key words: Anesthetics, intravenous; fentanyl. Anesthetic techniques: continuous infusion, intravenous. Equipment: computers. Pharmacokinetics: models.)

INTRAVENOUS ANESTHETICS can be administered either as a single large bolus, by intermittent boluses, or as a continuous infusion. Recent studies have indicated that bolus administration of an intravenous (iv) anesthetic, when compared to continuous infusion, results in variable anesthetic depth with more frequent periods of poor hemodynamic control, slower recovery from anesthesia, and a larger total amount of drug used.1–4 Thus, when using an iv drug for the maintenance of anesthesia, continuous infusion is preferable.

Common techniques for the continuous infusion of iv drugs do not provide a means for delivering the agent to a known or predicted concentration. Recently, computerized pharmacokinetic model-driven administration of iv drugs using computer-assisted continuous infusion (CACI) devices has been developed that enable clinicians to administer iv anesthetics to predicted plasma or blood drug concentrations.1,2,9–10 This is desirable because dynamic effect is better related to drug concentration than to drug dosage.11 However, before widespread use of CACI devices, it is important to establish their accuracy and efficacy.

In this study, we evaluated the accuracy of pharmacokinetic model-driven infusion of fentanyl using a CACI device developed by us. Plasma fentanyl concentrations measured (when combined with 70% N2O) during anesthesia for general surgery are also presented.

Methods

The study was approved by the Duke University Medical Center Institutional Review Board for human investigation. All patients provided written, informed consent to participate in the study. Patients between the ages of 18 and 55 yr, with ASA physical status 1 or 2, and within ±20% of ideal body weight presenting for lower limb or lower abdominal surgery were included. Patients requiring a rapid sequence induction and tracheal intubation, those receiving chronically administered opioids or antidepressant therapy, or patients with a history of alcohol or drug abuse were excluded. Patients orally received 10 mg diazepam 1 or 2 h before induction of anesthesia.

COMPUTER-ASSISTED CONTINUOUS INFUSION DEVICE

The pharmacokinetic model-driven CACI device constructed for use in this study consisted of a microcomputer (Datavue, Model 25, Norcross, GA) interfaced to a digitally controllable drug infusion pump (Abbott Labora-
tories, Lifecare Model 4, Abbott Park, IL) and computer software written by us.

To use the device, a burette was filled with fentanyl (50 μg·ml⁻¹), and the pump and iv tubing were primed with infusate. The anesthesiologist used the computer keyboard to specify the patient’s weight (kg) and the desired plasma fentanyl concentration (setpoint), which was entered in units of ng·ml⁻¹. At 9-s intervals, a real-time simulation of a pharmacokinetic model for fentanyl predicted the current plasma drug concentration. At these same intervals, the setpoint and the predicted concentration were acted on by the infusion algorithm to determine the optimal drug infusion rate required to achieve or maintain the setpoint by the end of the next 9-s interval. Every 9 s, the computer also interrogated the infusion pump to obtain information about the volume of drug infused and about the error status of the pump. The infusion rate used by the pump was communicated to the host computer electronically and entered into the pharmacokinetic simulation so that the next prediction could be computed. During a significant error condition, such as occlusion of the iv cannula, the pump automatically reverted to an infusion rate of 0 ml·h⁻¹, but since this information was transmitted to the host computer, which also alerted the user of the specific error condition, the infusion algorithm automatically compensated for the period of interrupted drug delivery once the problem was corrected. The software program allowed the anesthesiologist to adjust the setpoint as frequently as needed.

The drug infusion algorithm has been described in detail elsewhere.¹² The pharmacokinetic simulation was implemented using difference equations that formed a discrete approximation to the linear differential equations describing the three-compartment open pharmacokinetic model with drug administration into, and drug elimination from, the central compartment. The values of the model parameters, the central compartment volume (V₁), and the rate constant values (k₁₂, k₂₁, k₁₃, k₃₁, and k₁₀) were taken from the data of McClain and Hug.¹³ The values used were V₁ = 0.356 l·kg⁻¹; k₁₂ = 0.185 min⁻¹; k₂₁ = 0.103 min⁻¹; k₁₃ = 0.141 min⁻¹; k₃₁ = 0.020 min⁻¹; and k₁₀ = 0.041 min⁻¹.

ANESTHESIA

Before induction of anesthesia, 50% N₂O in oxygen was administered to the patient via a tight-fitting face mask. One minute thereafter, the N₂O concentration was increased to 70% and was maintained at 70% until the conclusion of surgery. After 3 min of N₂O administration, fentanyl was infused by means of CACI.

The setpoint fentanyl concentration for induction of anesthesia was 15 ng·ml⁻¹ and increased incrementally up to 25 ng·ml⁻¹ to obtain loss of consciousness. Once loss of eyelash reflex had occurred, 0.04 mg/kg vecuronium was administered. At the same time, the setpoint for fentanyl was decreased to 6–10 ng·ml⁻¹ for tracheal intubation. After loss of response to neuromuscular stimulation, the trachea was intubated and the setpoint was again decreased to 3–6 ng·ml⁻¹ for skin incision. The setpoint for intubation and incision was determined by the concentration required to induce anesthesia (i.e., the higher the concentration required to obtain unconsciousness, the higher the setpoint for intubation and skin incision). Thereafter, the fentanyl setpoint was altered according to strict criteria used to define adequate/inadequate anesthesia. Anesthesia was considered inadequate when either a somatic, hemodynamic, or autonomic response to surgery occurred. A hemodynamic response was defined as a 15% increase in systolic blood pressure or heart rate above baseline. Baseline values were calculated from the mean of three readings that were taken the night before surgery, the morning of surgery, and just before induction of anesthesia. A somatic response was defined as any purposeful movement by the patient, and an autonomic response was defined as any sign of increased autonomic activity, such as diaphoresis or lacrimation. If a response occurred, the fentanyl setpoint could be increased every 2–4 min in 0.5–1.0-ng·ml⁻¹ steps (depending on the magnitude of the response) until the response was ablated. Every 15–20 min, if anesthesia had been adequate, the fentanyl setpoint was decreased by 0.2–0.5 ng·ml⁻¹. Thus, the infusion rate was adjusted so that the plasma fentanyl concentration was maintained at that level consistent with light to moderate surgical anesthesia.

Neuromuscular blockade was maintained with small iv doses of vecuronium so that at least two twitches of a train-of-four were maintained. Blood pressure and heart rate, which were measured with a noninvasive blood pressure monitor, were obtained and recorded every minute for the first 10 min following induction of anesthesia and every 3 min thereafter.

Fentanyl was infused into a peripheral vein. Venous blood samples were taken from an iv catheter in the antecubital vein of the contralateral arm. These blood samples were taken 5 min before any decrease in the fentanyl setpoint, whenever the patient demonstrated a response to inadequate anesthesia, and at predetermined stimuli occurring during anesthesia. These stimuli were skin incision, spontaneous ventilation, response to simple command, and orientation. Additional blood samples were taken when patients responded to bone, nonbone (superficial), or intraabdominal stimuli and when they did not respond to these stimuli. These blood samples were collected into heparinized evacuated glass tubes and immediately placed on ice. They were subsequently centrifuged, and the plasma was stored at −70°C. The fentanyl con-
Concentration in these samples was later measured by radioimmunoassay. Sensitivity of the assay was 0.1 ng·ml⁻¹, and the coefficient of variation ranged between 5 and 9% at concentrations of 0.1 and 8.0 ng·ml⁻¹, respectively. Samples taken within 10 min of the initiation of fentanyl administration or within 5 min of any increase in the fentanyl setpoint were excluded from subsequent analysis due to transient arteriovenous gradients in the fentanyl concentrations that have been demonstrated for other highly lipid soluble drugs.¹⁴

At skin closure, neuromuscular blockade was antagonized pharmacologically if indicated by the patient’s train-of-four response to peripheral nerve stimulation. At the completion of surgery, N₂₀ was discontinued and 100% oxygen was administered. The time from the discontinuation of N₂₀ to spontaneous ventilation (respiratory rate greater than 8 breaths per min and PEₜCO₂ < 50 mmHg), and orientation to place, person, and recall of date of birth were recorded. If spontaneous ventilation occurred before the discontinuation of N₂₀, the time to spontaneous ventilation was recorded as zero. If spontaneous ventilation was inadequate 10 min after N₂₀ was discontinued, then naloxone was administered iv (40-μg doses) until adequate spontaneous ventilation was present. The incidence of nausea or vomiting and analgesic requirements in the first postoperative hour were noted.

The total dose of fentanyl administered by CACI up to the time of loss of the eyelash reflex and the total amount of fentanyl administered by CACI for the entire duration of anesthesia were recorded. An average infusion rate for each patient was calculated by subtracting the dose given up to the time of loss of eyelash reflex from the total amount of fentanyl given and dividing this result by the duration of anesthesia. The average of these was computed for the 24 patients. It is emphasized that the fentanyl infusion rates actually used by CACI during the surgical procedure were calculated every 9 s and varied according to the kinetic model, the duration of the infusion, the desired plasma fentanyl concentration, and other factors.

**Statistical Analysis**

The accuracy of CACI fentanyl administration was assessed by comparing the predicted and measured plasma fentanyl concentrations. The percent performance error, which was determined by the formula:

\[
\%PE = \frac{\text{measured} - \text{predicted}}{\text{predicted}} \times 100
\]

and percent absolute performance error (absolute value of the performance error) were calculated for each plasma sample. For these two variables, the 10th, 50th (median), and 90th percentiles were calculated for each patient. The percent performance error is the normalized residual describing the difference between measured and predicted plasma drug concentrations. Performance error is an overall reflection of the relationship between a measured and a predicted plasma drug concentration regardless of the sources of the error (e.g., pharmacokinetic variability, assay error, infusion device inaccuracy). A negative performance error occurs when CACI overpredicts the measured plasma fentanyl concentration (i.e., CACI has underdosed relative to the plasma drug concentration that it is predicting). The reverse applies to a positive performance error. The median absolute performance error is not influenced by the positive or negative sign of the performance errors and thus represents the typical magnitude of the performance error.¹⁵

To evaluate accuracy within the population, cumulative probability functions were plotted from the tenth, 50th, and 90th percentiles of the performance error and the absolute performance error from each patient. A measure of precision was defined as the dispersion of the tenth to 90th percentile of the median performance error in the population. The hypothesis that the median percent performance error of the population differed from zero was tested using the Wilcoxon signed rank test. To evaluate whether time affected accuracy, the performance error (measured − predicted) and absolute value of the performance error at an early (skin incision) and late (skin closure) period of the infusion were compared (using a paired t test).

All hemodynamic data are expressed as a percentage change from their baseline value. A frequency histogram was constructed for each patient, and the group percentiles were calculated and graphed. Unless stated otherwise, data are reported as mean ± SD.

**Results**

**Demographics**

Fifteen male and nine female patients participated in the study. The average age was 36 yr (range, 19–50 yr). The patients weighed 79 ± 18 kg (range, 45–114 kg). All patients underwent either major orthopedic (n = 22) or gynecologic (n = 2) procedures with a duration of 4.3 ± 2 h (range, 1.3–9.5 h).

**Accuracy and Precision of the Device**

To assess the predictive accuracy of CACI fentanyl administration, 16 ± six plasma samples (range, 6–27) were taken from each patient for a total of 391 samples. The measured versus predicted values for all samples are plotted in figure 1, which shows that the measured plasma fentanyl value was within ±30% of that predicted in 87% of the 391 samples. The tenth, 50th, and 90th percentiles
of the percent performance error and percent absolute performance error for each individual patient are plotted in figures 2 and 3, respectively. The cumulative probability functions for the 10th, 50th, and 90th percentiles of the percent performance error are plotted in figure 4. The group median percent performance error was −4%, and the median percent absolute performance error was 21% (table 1). The median percent population performance error did not differ significantly from zero ($P > 0.25$). The precision was found to be −31–26% (tenth to 90th dispersion of median performance error).

To demonstrate the ability of the CACI device to make proportional changes as the setpoint was altered, the measured and predicted fentanyl concentrations over the time course of the anesthetic for four representative patients are given in figure 5. The performance error and absolute performance error of an early sample (skin incision) in each individual compared to the same measures of a late sample (skin closure) were not significantly different ($P > 0.2$). Seventeen simultaneous steady-state arterial and venous samples were obtained from three patients requiring placement of a radial artery catheter for hemodynamic monitoring. Under these conditions, venous fentanyl concentrations were generally slightly less than arterial fentanyl concentrations (fig. 6). The correlation coefficient between venous versus arterial samples was 0.958 ($P < 0.0001$). The percent error (100[arterial − venous]/arterial) was 4.8 ± 12.5%.

**Anesthesia**

Anesthesia was induced in all patients at or below a fentanyl setpoint of 25 ng·ml$^{-1}$. The mean fentanyl induction dose was 12.3 ± 3.2 μg·kg$^{-1}$ (range, 8–23 μg·kg$^{-1}$). The infusion rate following induction, although varied throughout the procedure, averaged 0.056 ± 0.027 μg·kg$^{-1}$·min$^{-1}$.

Patients responded to skin incision when the measured plasma fentanyl concentration was between 2.2 and 3.7 ng·ml$^{-1}$. All patients in whom the plasma fentanyl concentration was greater than 3.7 ng·ml$^{-1}$ ($n = 5$) did not respond to skin incision. The measured plasma fentanyl concentrations required to maintain anesthesia during surgery varied between 1 and 9 ng·ml$^{-1}$ (superficial surgery, 1.5–8 ng·ml$^{-1}$). When surgery was completed, spontaneous ventilation occurred in 14 patients in whom the plasma fentanyl concentration was greater than 2 ng·ml$^{-1}$. Two patients with measured fentanyl concentrations of 2.5 and 6.2 ng·ml$^{-1}$ required naloxone to...
restore adequate spontaneous ventilation after the completion of surgery. All patients in whom the plasma fentanyl concentration was less than 2 ng·mL⁻¹ at the end of surgery (n = 7) breathed spontaneously without the requirement for naloxone. In 1 additional patient, a blood sample could not be obtained at the time of spontaneous ventilation. Within each patient and within the population, there was a large overlap in the plasma fentanyl concentrations measured at the time of a response or no response to the surgical stimulus.

The mean arterial blood pressure in each patient was maintained within ±15% of baseline for 60% (median) of observations. The heart rate tended to slow following fentanyl administration and therefore was within ±15% of baseline in only 29% (median) of observations (fig. 7). After discontinuation of N2O, adequate spontaneous ventilation was rapidly established (1.5 ± 1.7 min; range, 0–6 min), and this was soon followed by awakening and orientation (5.3 ± 3.7 min; range, 2–18 min). Seven patients experienced nausea or vomiting, and 19 patients required no analgesics within the first postoperative hour.

Discussion

CADI is a pharmacokinetic model-driven infusion device that uses pharmacokinetic parameters to provide a simple means to administer IV drugs according to concentration rather than dose. Administration of an IV agent to a predicted concentration is similar to the manner in which potent inhalation agents are presently given. We evaluated the accuracy of our CADI device to deliver fentanyl when using the pharmacokinetic parameters published by McClain and Hug.¹³

THE DEVICE

Pharmacokinetic models provide a mathematical description of drug disposition within the body. The model parameters (e.g., volume of distribution, clearance, microconstants, etc.) can be exploited to derive the infusion profile necessary to obtain physician-specified plasma drug concentrations.

Kruger-Thieme¹⁵ described the derivation of an infusion regimen to quickly achieve and maintain a constant plasma concentration of an intravenously administered drug whose kinetics are described by a multicompartment model. Implementation of such an infusion scheme requires the use of microprocessor technology to perform the many mathematical calculations and to control the infusion device. Schwilden et al.⁵,¹⁶ were the first to demonstrate clinical application of computer-controlled infusions based on pharmacokinetic models. Subsequently, many other authors using slightly different approaches have developed similar CADI devices that use pharma-
Table 1. Accuracy of CACI Fentanyl Delivery

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<tr>
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<th>Performance Error (%) (percentile)</th>
<th>Absolute Performance Error (percentile)</th>
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<tr>
<td></td>
<td>10</td>
<td>50</td>
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<td>Median 80% dispersion</td>
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<td>-55-12</td>
<td>-31-26</td>
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Data shown are for the patient population studied, using pharmacokinetic parameters published by McClain and Hug.\textsuperscript{13}

Pharmacokinetics to calculate infusion regimens to obtain and vary the plasma or blood concentration of drugs administered intravenously.\textsuperscript{17}

The ability of a CACI device to achieve the desired concentration is dependent both on the hardware and software used. Hardware problems, such as inaccurate volumetric flow rates, should be eliminated before implementation. Software can contribute to measured-to-predicted inaccuracies through errors in the infusion algorithm or pharmacokinetic simulation or by using pharmacokinetic parameters that are inappropriate for the subject receiving the infusion. Algorithmic errors can be revealed and corrected by computer modeling.\textsuperscript{8} The pharmacokinetic parameters used are generally taken from the published literature. These parameters differ according to observer\textsuperscript{18} and methodology, and from patient to patient. Thus, the pharmacokinetic values used for each drug are likely to be the major source for performance error. When using a single set of pharmacokinetic parameters for a group of patients, it is essential to use the set of values that "best" describes that population. Evaluation of the accuracy of CACI is therefore a measure of how well the pharmacokinetic parameters describe the population for which they are used.

Previous studies evaluating the accuracy of CACI devices have reported the mean and standard deviation of the performance error as a measure of the bias and precision, respectively.\textsuperscript{5,10} The average absolute performance error has been reported as a measure of accuracy. These assume that the values are normally distributed both within a patient and within the population. Neither the performance error nor the absolute performance error can be assumed to be normally distributed. A skewed distribution in which there are a few extreme values can cause the arithmetic mean to be displaced from the "center" of the distribution. The methods used in this article

![Figure 5](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931346/f5.jpg)
make no assumptions about the form of the distribution of errors. The median better estimates the center of the distribution.

The median population performance error in the 24 patients included in this study was −4% and was not significantly different from zero. This implies that the CACI device did not consistently over or under predict the measured concentration (i.e., the device had a nonsignificant bias). A measure of the variability of the performance error (precision) is also needed to describe the accuracy of the system. Using the cumulative probability function of the median performance error (fig. 4), the precision (tenth to 90th dispersion of the median population performance error) for the population was −31–26%. This implies that in 80% of patients, the median performance error was less than ±30%. This is consistent with the observation (fig. 1) that 67% of all predictions were within ±30% of the measured concentration. In clinical practice, the absolute accuracy may be less important than the ability to accurately make proportional changes in the plasma concentration. Figure 5 demonstrates the accuracy with which proportional changes in the plasma drug concentration could be made. That CACI was able to make proportional changes is further supported by the generally small range of the absolute performance error within each patient (fig. 3). The median 90th percentile of the absolute performance error was 43%, indicating that 50% of the patients had less than 43% absolute error 90% of the time.

As perfect accuracy of pharmacokinetic model-driven infusion systems is unlikely, it is important to establish what degree of accuracy is both acceptable for clinical use and possible to obtain. Schuttler et al.20 suggested that the performance of a CACI system is acceptable when the mean variation of measured concentration around the predicted values is approximately 20–30% and when the maximal variation does not exceed 50–60%. In our study, 67% of the measured values were within ±30% of those predicted. In addition, the median percent performance error and the median percent absolute performance error were within the required 20–30%. Only 20 (5%) of 911 samples exceeded ±60% of predicted. Shafer et al.,21 after retrospectively recalculating a best-fit three-compartment model in a population receiving fentanyl via a pharmacokinetic model-driven infusion system, were able to obtain a mean performance error of −1% and a mean absolute performance error of 32%. In several studies assessing the accuracy of pharmacokinetic infusion devices with alfentanil (using pharmacokinetics determined by Schuttler and Stoeckel22), a nonsignificant performance error and approximately 30% mean absolute performance error were found.5,20 When pharmacokinetic parameters were calculated for individual volunteers and then these individualized pharmacokinetic parameters were used in a CACI device to administer alfentanil to the individual, the result was a nonsignificant bias and an overall mean absolute performance error of 20.5%.23,24 Thus, even when the individual's own pharmacokinetic parameters are used to program the CACI device, the resultant accuracy is similar to that which has been achieved when a single set of pharmacokinetic parameters has been used for a population of patients, including our study with fentanyl. Therefore, it would appear for fen-
tanyl that a nonsignificant median performance error with a 30% median absolute performance error is close to the "best" accuracy that can be obtained when using a single set of pharmacokinetics to describe the population. With our CACI device, the pharmacokinetic parameters for fentanyl published by McClain and Hug 15 provided this degree of accuracy in the general surgical population.

In studies where Schuttler's accuracy criteria have been met, CACI devices have provided very acceptable clinical anesthesia when the infusion has been carefully titrated to pharmacodynamic response. 1,5,20,24 In our study, we were able to obtain good hemodynamic control with rapid awakening. It therefore appears that when a CACI device provides a plasma drug concentration within approximately ±30% of the predicted concentration, the device provides a simple means (albeit with sophisticated technology) of titrating the chosen iv agent to obtain excellent anesthesia. To further improve the accuracy of CACI, the use of population-specific kinetics 26 or, for individuals, the use of Bayesian forecasting from a single early sample have been suggested. 26 When the iv agent is titrated with a CACI device that has achieved "best" accuracy, very satisfactory anesthesia is obtained. Therefore, it does not necessarily follow that any further improvement in accuracy will provide a better clinical outcome. This is analogous to the practice of administering an inhalational agent without an end-tidal drug concentration value.

ANESTHESIA

White et al. 5 reported the fentanyl concentration required during superficial surgery (in combination with 66% N2O) as 1–4 ng ⋅ ml–1. This is lower than the concentrations (1.5–8 ng ⋅ ml–1) required in this study for nonnose (superficial) stimuli. In the study by White and co-workers, several concomitant drugs (thiopental and droperidol) were administered with fentanyl. It is likely that these decreased the requirements of fentanyl to provide adequate anesthesia. In patients undergoing lower abdominal procedures, plasma fentanyl concentrations of 5–10 ng ⋅ ml–1 were found to provide adequate anesthesia. 27 Plasma fentanyl concentrations above 2 ng ⋅ ml–1 produce both a substantial increase in PETCO2 and a significant decrease in the slope of the CO2 response curve. 13,28 The plasma fentanyl concentrations measured by us during and after anesthesia are thus in general agreement with previous studies. The plasma concentration range of fentanyl required to provide adequate anesthesia for a given stimulus was large within the patient population studied. Therefore, to provide an appropriate plasma concentration for anesthesia with fentanyl/N2O, it is essential that fentanyl is continuously titrated to individual requirements. Within a patient, the concentration–effect curve for opioids for analgesia is very steep (i.e., only small increases in concentration are needed to go from an inadequate effect to an adequate effect). 20,30

In this regard, CACI provides a major advantage over manual methods of iv drug administration because small increments in plasma concentration are rapidly and easily achieved with CACI. To increase the plasma concentration in a manual scheme requires both adjustment in infusion rate and additional bolus doses that are difficult to calculate accurately because they vary according to the desired increase in concentration and the duration of the infusion.

There is a need to establish the C50 (plasma concentration at which there is a 50% chance of a somatic, hemodynamic, or autonomic response to a predefined surgical stimulus) for fentanyl so that the potency of fentanyl relative to other drugs (e.g., alfentanil) can be estimated, thus enabling comparative studies to be done. Our study design was similar to that with which Ausems et al. 29 defined the C50 for alfentanil for a variety of stimuli during surgery. However, we do not feel that it would be appropriate to subject our measured plasma fentanyl concentrations for response/no response to statistical analysis similar to that used by Ausems et al. First, in the studies by Ausems et al., relatively large fluctuations in the plasma concentration of alfentanil were made; therefore, a large number of response/no response samples could be obtained within each patient. In our study, the plasma fentanyl concentrations did not fluctuate between high and low concentrations but instead were titrated within a much narrower band. Therefore, the concentrations at which there was always a "response" and always a "no response" were not obtained. Another reason for not using our data to define a C50 for fentanyl is the difference in pharmacodynamic effect between fentanyl and alfentanil. The plasma concentration of alfentanil and changes in EEG spectral edge (a measure of central narcotic effect) closely parallel each other. However, there is a considerable delay (hysteresis) between declining plasma fentanyl concentrations and changes in EEG spectral edge frequency. 11 Thus, the plasma fentanyl concentration may only reflect brain concentration while a steady-state plasma concentration is maintained (i.e., changes in brain fentanyl concentration do not parallel rapid fluctuations in plasma fentanyl concentrations). A better model for defining the C50 for fentanyl may be that of obtaining a steady-state plasma concentration before the predefined stimulus. 31

In summary, using a CACI device to titrate a continuous infusion of fentanyl to specified plasma concentrations, we were able to obtain satisfactory anesthesia. Using a single set of pharmacokinetic coefficients for fentanyl, our CACI device provided acceptable accuracy within a general surgical population. Thus, the efficacy of CACI infusion of fentanyl during anesthesia should be compared to other modes of fentanyl administration.
References


