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Pharmacokinetics of an Implanted Osmotic Pump Delivering Sufentanil for the Treatment of Chronic Pain

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Background: **A matchstick-sized implanted osmotic pump (Chronogesic™) that delivers sufentanil subcutaneously for more than 90 days is being developed to treat chronic pain. This study evaluates pharmacokinetic characteristics related to the absorption of sufentanil using a prototype 60-day system.**

Methods: **Twelve opioid-naive volunteers were given naltrexone to prevent opioid effects. Sufentanil, 60 μg, was infused intravenously over 6 h, then 48 h later, the pump was implanted subcutaneously in the upper arm under local anesthesia. Pumps were removed 9 days later. In six volunteers, fever (1.6–3.3°C) was induced with interleukin-2. Plasma was sampled and population pharmacokinetic modeling was performed to estimate *in vivo* release rate and absorption half-life. Bioavailability was calculated by comparing *in vivo* to *in vitro* release rates. The impact of perturbations in release rate on sufentanil plasma concentration (Cp) was simulated.**

Results: **Fever had no systematic effect on Cp. Release rate estimated *in vivo* was similar to that measured *in vitro*; bioavailability did not differ from 100%. Absorption half-life was 16.2 h. Simulation demonstrated that supplemental release of sufentanil from the implant (as might occur with local heating) increases Cp an average of 2.5–2.8% per hours supplemental dose.**

Conclusions: **An implantable osmotic pump delivered sufentanil *in vivo* at the rate predicted from *in vitro* experiments. The rate at which sufentanil was absorbed from the subcutaneous space (half-life > 16 h) was markedly slower than reported with subcutaneous or intramuscular administration of large volumes of dilute opioids; this slow absorption dampens potential changes in Cp if release rate is perturbed.**

AN osmotically driven implantable pump, Chronogesic™ Sufentanil Pain Therapy System, is being developed by the DURECT Corporation (Cupertino, CA) to deliver sufentanil subcutaneously for the treatment of chronic pain. The matchstick-sized pump (diameter, 4 mm; length, 4.4 cm) consists of a titanium cylinder containing a semipermeable membrane, the osmotic engine (NaCl tablets), a piston to separate the osmotic engine from the drug formulation, and 155 μl of a concentrated solution of sufentanil§ in benzyl alcohol (fig. 1). *In vitro*, the pump delivers sufentanil at a zero-order rate for a period exceeding 3 months, preceded by a brief startup period (fig. 2). Because the *in vivo* performance of this type of osmotic pump mirrors *in vitro* performance,[1] the pump delivers sufentanil at a constant rate to patients for an extended period. The present study examines the pharmacokinetic characteristics of this opioid delivery system, focusing on the bioavailability of sufentanil and the absorption half-life. In addition, because fever would be expected to increase delivery of sufentanil transiently, thereby potentially increasing sufentanil plasma concentration, the study also examines the impact of experimentally induced fever. Finally, because experimental fever failed to produce systematic changes in sufentanil plasma concentration (either because fever produced physiologic changes that altered either distribution or clearance of sufentanil or because the lengthy absorption half-life dampened the increase in sufentanil plasma concentration), simulation was used to estimate the impact of changes in sufentanil release rate that were not accompanied by changes in distribution or elimination.

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Materials and Methods

The study was conducted at Inveresk Research in Edinburgh, Scotland. With local institutional review board approval and informed consent, 12 healthy opioid-naive volunteers, six male and six female, aged 19–38 yr, were enrolled (table 1). To prevent opioid-related effects, all subjects received naltrexone, 50 mg orally, once or twice per day through the period of sufentanil exposure.

The study consisted of three parts. First, all volunteers received a 6-h intravenous infusion of sufentanil citrate, 10 μg/h (total dose = 60 μg) on day 0. In the second part, approximately 48 h after the start of the intravenous infusion, all volunteers were implanted with the Chronogesic™ Sufentanil Pain Therapy System (hereafter called Chronogesic sufentanil). Implants in the present study delivered sufentanil for 60 days, in contrast to the > 90-day delivery profile that will characterize all future systems. The implant was placed subcutaneously in the inner aspect of the upper arm, ap-

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§ The concentration of sufentanil in these implants was 52.3 mg/ml. Different dosage strengths will have different concentrations of sufentanil to accommodate the same volumetric flow rate for all doses.

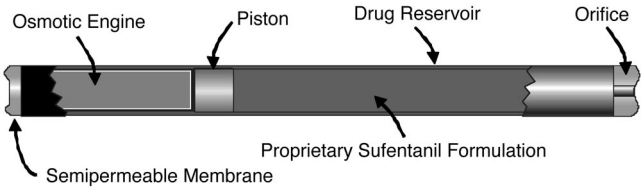

Fig. 1. A cross section of the Chronogesic™ Sufentanil Pain Therapy system is shown. A titanium cylinder, 4 mm in diameter and 4.4 cm in length, is plugged at one end with a semipermeable membrane and at the other with an orifice. A piston separates the "osmotic engine" (which contains a sodium chloride tablet) from the drug reservoir (which contains a concentrated solution of sufentanil). When implanted subcutaneously, the osmotic potential of the salt engine causes tissue water to cross the membrane, increasing the size of the engine, displacing the piston, and forcing sufentanil through the orifice. An excess of sodium chloride in the osmotic engine ensures constant (zero-order) delivery after the initial startup period. Although units in the present study delivered sufentanil for 60 days, future units will deliver sufentanil for more than 90 days.

proximately 10 cm proximal to the antecubital fossa; the procedure was performed under local anesthesia. The implants had a nominal steady-state sufentanil delivery rate of 5 μg/h; this delivery rate was preceded by a startup period. In all subjects, units were removed under local anesthesia at day 11 of the study (day 9 of implant).

One-half of the subjects (three male, three female) underwent the third portion of the study, induction of experimental fever with aldesleukin[2] (interleukin-2, Chiron Corporation, Emeryville, CA) on day 9 of the study (day 7 of implant). The first dose was 50,000 IU/kg, followed at 2-h intervals with two doses of 100,000 IU/kg (total dose of 250,000 IU/kg, except for one female subject who refused the third dose). The purpose of this portion of the study was to determine the magnitude and direction of change in plasma sufentanil concentration (Cp) to be expected with clinical fever. Fever should increase the temperature of the implants, which causes thermal expansion of sufentanil within the reservoir, expelling a predictable temperature-dependent quantity of sufentanil from the implant.‖ Maintaining an increased temperature should increase the steady-state release rate from the implants; the magnitude of this increase is relatively small.** Based on these *in vitro* findings, we expected that fever could increase sufentanil Cp transiently.

Venous plasma samples were obtained throughout all portions of the study. This included eight samples on day 0, three on day 1, eight on day 2, one on day 3, two on each of days 4–10, seven on day 11, two on day 12, and one on each of days 13 and 14 (fig. 3). For subjects given aldesleukin, an additional seven samples were obtained on day 11. Concentration of sufentanil in plasma was determined using an LC-MS-MS technique by MDS Pharma (Sunnyvale, CA) using validated methods. The limit of quantification of the assay is 2.0 pg/ml; coefficient of variation at the limit of quantification is 8.9%.

In the first set of analyses, plasma sufentanil concentrations during the initial 48 h were used to provide initial estimates to characterize the systemic distribution and elimination of sufentanil. In the second set of analyses, plasma sufentanil concentrations during the remainder of the study (as well as those associated with intravenous administration) were used to characterize the release rate of sufentanil from the implanted pump and the rate of absorption from the subcutaneous space, and to quantify the bolus dose of sufentanil associated with thermal expansion of sufentanil during the implant procedure.†† However, Cp values obtained during the period of administration of aldesleukin and the occurrence of experimental fever were excluded from the second analysis.

Although parameter estimates (values for the "typical" individual) and the magnitude of interindividual variability for the systemic pharmacokinetics of sufentanil were fixed in the second analysis, values for each individual were permitted to differ from the population estimates (*i.e.*, *thetas* and the corresponding elements of the OMEGA matrix were fixed to the estimates obtained in the first analysis). *Post hoc* estimates of parameters (NONMEM's estimates for each subject) for the individuals would then reveal whether the additional informa-

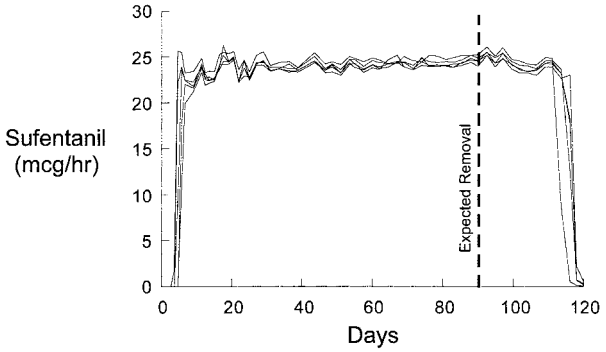

Fig. 2. Release rate of the Chronogesic™ Sufentanil Pain Therapy system is shown; these units are designed to deliver sufentanil at a rate of ~ 25 μg/h for more than 90 days. To estimate the release rate, implants are placed in a physiologic buffer solution at 37°C and samples are obtained at periodic intervals to quantify the sufentanil released. After an initial startup period, sufentanil release is constant until formulation is exhausted from the reservoir. Each line represents the release rate of an individual unit (n = 6). In clinical practice, the implant will be removed or replaced at 90 days, ensuring constant delivery of sufentanil throughout the treatment cycle.

‖ Based on the *in vitro* thermal expansion coefficient of the sufentanil formulation, a typical clinical fever (2.5°C increase in core temperature) should increase a 155-μl volume of sufentanil formulation by 0.3 μl (approximately 6 h dosing). Although the titanium implant also expands with increasing temperature, the magnitude of this expansion is far less than that of the sufentanil formulation.

** Based on theoretical considerations of the flux of water through the semipermeable membrane, an increase in temperature of 2.5°C should increase steady-state release by 4.2%. This small change cannot be detected in *in vitro* experiments.

†† Implants stored at room temperature are abruptly warmed to body temperature at the time of implant. As with fever, this increases the volume of sufentanil, potentially releasing sufentanil from the orifice.

Table 1. Demographic Data (mean ± SD) for 12 Volunteers

Volunteers	No.	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Fat Thickness* (mm)
All	12	28.4 ± 5.9	66.2 ± 13.5	168 ± 8.6	23.3 ± 3.4	21.5 ± 7.4
Male	6	26.2 ± 5.7	73.1 ± 13.9	174 ± 6.3	24.0 ± 3.8	15.5 ± 4.2
Female	6	30.7 ± 5.7	59.3 ± 9.7	162 ± 5.2	22.7 ± 3.0	27.5 ± 4.2

* Caliper measurement of body fat.

BMI = body mass index.

tion obtained from the plasma sufentanil concentration data during the implant phase indicated systematic deviations of the pharmacokinetic parameters estimated from the initial intravenous data. Estimates for residual error between observed and predicted concentrations (elements of the SIGMA matrix) from the first analysis were used as initial estimates in the second analysis but were not fixed; this strategy was adopted because there is no evidence that residual error from the remainder of the experiment (*i.e.*, drug administration with Chronogesic sufentanil) will result in the same magnitude of error (due to model misspecification) as during the initial part of the experiment.

All pharmacokinetic models assumed usual mammillary characteristics, *i.e.*, peripheral compartments are linked by first-order rate constants to the central compartment. Elimination of sufentanil was assumed to occur from the central compartment. For the systemic pharmacokinetics of sufentanil, two-compartment models had the parameters volume of the central and peripheral compartments (V_1 and V_2, respectively), clearance (Cl), and distributional clearance (Cl_{rapid}). Three-compartment models had additional parameters volume of the third compartment (V_3) and slow distributional clearance (Cl_{slow}).

Additional parameters were used to determine the rate at which sufentanil is absorbed from the subcutaneous space, the release rate profile for Chronogesic sufentanil, and the magnitude of the bolus associated with thermal expansion of Chronogesic sufentanil during the implant procedure. These additional parameters were the absorption half-life, equal to $\ln(2)/k_a$ (where k_a is the first-order constant quantifying the rate at which sufentanil is absorbed from the subcutaneous space after its release from the implant), the time and height of the knots of the linear spline used to describe the release rate function (see below), and a parameter to quantify the bolus associated with thermal expansion during the implant procedure. Additional information regarding the NONMEM code and the organization of the data records to reflect dosing from the implant is provided in Web Enhancements A and B (www.anesthesiology.org).

‡‡ With the four-knot model, the time of the typical value of the second knot was constrained to be between 1 and 60 h after implant, that of the third knot between 72 and 150 h. Similar constraints were applied to the model with five knots.

Release rate was described by a series of linear splines (fig. 4). This approach was based on *in vitro* data (fig. 5) indicating that during the first several days after exposure to moisture (as would be the case with subcutaneous implant), release rate is minimal, then increases rapidly to more than 70% of the nominal delivery rate, then increases more slowly to the nominal rate. The first knot (cutpoint) of the spline is at the time of implant and the final knot is at the time of removal. The time of the intermediate knots is estimated (boundary conditions are imposed during the analysis to prevent statistical errors‡‡) and the height (release rate) at each of the knots is estimated.

Interindividual variability was initially permitted for each of the pharmacokinetic parameters. Interindividual variability was typically assumed to be log-normally distributed. For example:

$$Cl_i = Cl_{typical} \cdot \exp(eta(Cl)_i) \quad (1)$$

where Cl_i is the value of Cl for the *i*th individual, $Cl_{typical}$ is the population value determined by NONMEM, and *eta*(Cl) is a normally distributed random variable with mean 0.0 and variance *omega*.[2] A log-normal, rather than a normal, distribution is selected for two reasons. First, pharmacokinetic parameters typically have a skewed distribution that normalizes in the log domain; second, a log-normal distribution ensures that pharmacokinetic parameters estimated in NONMEM's *post hoc* step (in which estimates are obtained for each subject) are nonnegative. If variability for a particular parameter was estimated to be quite small, subsequent models evalu-

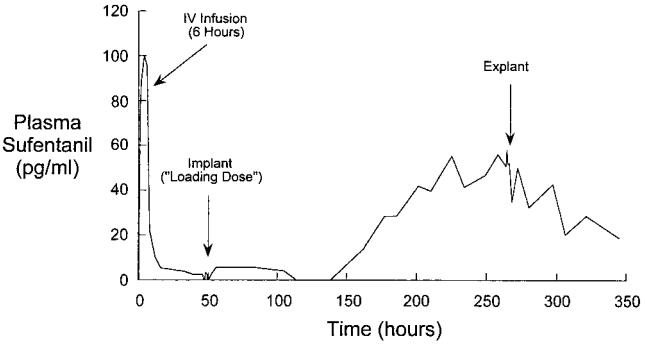

Fig. 3. Sufentanil plasma concentrations for a 94-kg-male volunteer are shown. The intravenous infusion, time of implant, aldesleukin administration, and removal are marked. Values for all subjects are shown in Web Enhancement C.

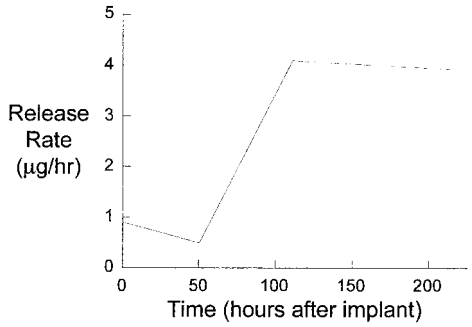

Fig. 4. The *in vivo* release rate profile for the implant system, as estimated in the optimal model, is displayed.

ated whether it was necessary to permit such variability in the model.

Residual error between measured and predicted concentrations of sufentanil was initially modeled as having two components, one proportional to the predicted concentration ("constant coefficient of variation") and one additive. This model was chosen because most assays have a constant coefficient of variation as long as concentrations are significantly larger than the limit of detection of the assay; however, as concentrations approach the limit of detection of the assay, error of the assay increases as a percentage of the predicted concentration. NONMEM assigns the error appropriately to the proportional and additive components. Other error models were evaluated, if appropriate.

The appropriate pharmacokinetic model was selected based on several criteria:

1. The plot of the ratio of observed-to-population predicted values was examined. Systematic deviations from the line of unity suggested model misspecification.

2. The objective function (the objective function, $-2 \cdot$ log likelihood, is equivalent to the residual sum of squares in traditional analyses) was determined for each model. Some comparisons involved two models in which neither model was a smaller version of the other (*e.g.*, comparing weight-normalized and nonweight-normalized models); in this instance, the model with the smaller objective function was accepted. Some comparisons involved a "larger" *versus* "smaller" version of the same model (*e.g.*, 3- *vs.* 2-compartment models). Using the likelihood ratio test, for each additional parameter (*theta*) added to the model, an improvement (decrease) in the objective function of 6.63 units achieves statistical significance with $P < 0.01$. This conservative P value was selected to prevent type I errors when multiple comparisons (*i.e.*, a possible role for many covariates) are performed in an exploratory analysis.

3. *Post hoc* (individual) values for the pharmacokinetic parameters were plotted against covariates; systematic trends were sought and, if appropriate, incorporated into the model.

4. For the analysis of the systemic pharmacokinetics of sufentanil, an additional goal was to minimize the terms quantifying interindividual variability.

Half-lives were determined using standard equations implemented in Excel (Microsoft, Redmond, WA) or S-PLUS (Insightful Corp., Seattle, WA).

In Vitro *Analyses and Estimation of Bioavailability*

The release rate profile determined *in vivo* was compared with the *in vitro* release rate profile. Six implants from the same batch used in volunteers underwent release rate testing. The *in vitro* release rate testing procedure quantifies release of sufentanil over predetermined intervals, typically 24 h. Therefore, *in vitro* testing does not permit precise definition of the time at which release rate changes. Interindividual variability is quantified differently using the *in vitro* and *in vivo* approaches (the *in vivo* approach estimates the time at which release rate changes; the *in vitro* approach permits only day-to-day comparisons). Thus, release rate profiles obtained from *in vitro* testing cannot be compared directly with values obtained in the present analysis. Instead, the typical value (and interindividual variability) for release rate obtained at certain time points in the NONMEM analysis can be compared with the average value (and variability of these values) for *in vitro* release rate at similar time points. The typical values for the times of the predicted knots of the release rate function (the times of predicted change) can be compared with the day-to-day changes in *in vitro* release rate.

If there were systematic deviations of the estimated *in vitro* release rate from the measured *in vivo* release rate, it would suggest that bioavailability differs from 100% and/or *in vivo* release rate differs from the labeled value (which is based on *in vitro* release data). If the estimated time of changes in the *in vivo* release rate is similar to those obtained *in vitro*, it would suggest that *in vivo* performance (particularly startup) is well described by the *in vitro* estimates.

A second approach to evaluate bioavailability is to quantify the cumulative release rate *in vivo* and *in vitro*

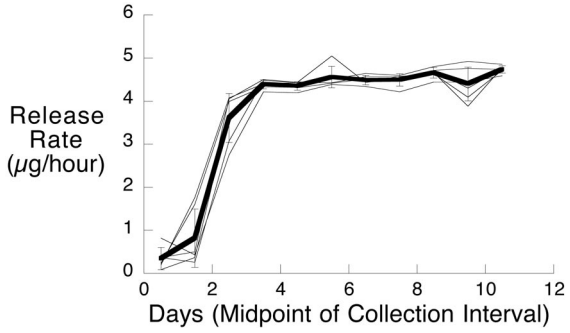

Fig. 5. Sufentanil (μg/h) released during *in vitro* testing is plotted against the midpoint of the collection interval; these units are designed to deliver sufentanil at 5 μg/h. *Thin lines* represent data from each of six individual implant systems. The *thick line* indicates the mean value; *error bars* represent SD.

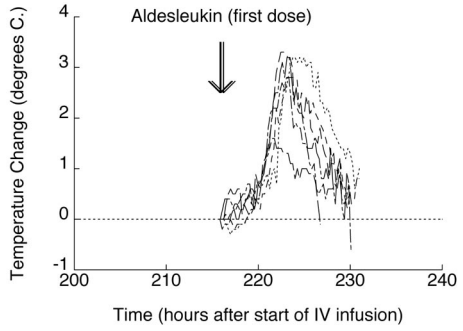

Fig. 6. The change in core body temperature (°C) for six volunteers given aldesleukin is shown. Five volunteers received three doses (total dose: 250,000 IU/kg), the sixth received two doses (total dose: 150,000 IU/kg). Different line styles identify each volunteer.

and compare these values at the end of 9 days of implant (at which time the implants were removed). Values for *in vitro* cumulative release rate for individual implants were obtained; mean and SD of the value at day 9 was determined. Values for *in vivo* release rate for the same 9-day period were determined for each of the 12 volunteers based on the release rate profiles estimated in the analysis. Mean and SD of this cumulative release from each of the *in vivo* and *in vitro* analyses were determined; mean values were compared using the Student *t* test for unpaired data.

Simulation of a Transient Perturbation of Sufentanil Release

Induction of experimental fever was expected to describe the impact of increases in release rate on the plasma sufentanil concentration profile. However, as shown in Results, experimental fever failed to increase plasma sufentanil concentrations systematically, possibly because of other physiologic changes in the distribution or elimination of sufentanil. Thus, evaluation of the impact of an isolated perturbation in sufentanil release rate (*i.e.*, one not associated with other physiologic changes) requires simulation based on the rate at which sufentanil is absorbed from the subcutaneous depot and the systemic pharmacokinetics of sufentanil.

Using NONMEM, sufentanil plasma concentration profiles for 100 male and 100 female subjects were simulated using the pharmacokinetic parameters (*thetas* and *etas*) estimated in the optimal model; residual error was assumed to be zero. Sufentanil release rate was assumed to be 5 μg/h for the entire duration of the implant period, except at day 60 when a subcutaneous bolus dose of 5 μg was administered (*i.e.*, the implant acutely released an additional 1-h dose). Peak plasma concentration during the next 24 h was compared to the steady-state value before the bolus dose and time to peak concentration was determined.

Results

Effects of Induced Fever

Magnitude of increase of core body temperature (mean ± SD) was 2.8 ± 0.6°C (range, 1.6–3.3°C; fig. 6). Induction of experimental fever did not result in systematic increases in plasma sufentanil concentration (fig. 7).

Modeling of the Systemic Pharmacokinetics of Sufentanil

These analyses were based on the plasma concentration data obtained before Chronogesic was implanted (fig. 3 and Web Enhancement C). Initially, two-compartment models in which all of the pharmacokinetic parameters were or were not weight-normalized were tested. The weight-normalized model was preferred over the non–weight-normalized model. Graphic display of goodness of fit from these models suggested that an additional compartment was needed. Next, three-compartment models, both weight-normalized and non–weight-normalized, were tested. Again, the weight-normalized model was preferred over the non–weight-normalized model. For the weight-normalized model, the objective function improved 9.970 units compared to the comparable two-compartment model ($P = 0.007$, based on the addition of two structural parameters).

Graphic display of the relationship between covariates and parameter estimates in the weight-normalized model suggested that weight-normalized V_2 was larger in women than in men. A model that permitted different values for V_2 for men *versus* women improved the objective function by 11.072 units ($P = 0.004$). With this model, four elements of the OMEGA matrix (quantifying interindividual variability) were quite small, suggesting that it was not necessary to allow for interindividual variability for V_2 in male subjects, V_1, V_3, or Cl_{slow}. Therefore, the final model did not permit interindividual variability for these parameters. The objective function for this final model was identical to that for previous model, confirming that terms to quantify interindividual variability were not needed for these parameters.

Based on these analyses, the optimal model for the

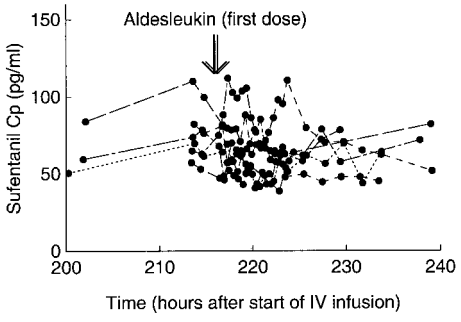

Fig. 7. Sufentanil plasma concentrations in the period of experimental fever in six volunteers given aldesleukin are shown. There was no systematic increase in Cp. Different line styles identify each volunteer.

Table 2. Parameter Estimates Determined in the NONMEM Analysis for the Optimal Model for the Systemic Pharmacokinetics of Sufentanil

	Typical Value	SE	Interindividual Variation* (%)
Cl (mL · kg^{-1} · min^{-1})	15.2	0.619	9.42
V_1 (mL/kg)	174	100	NA
Cl_{rapid} (mL · kg^{-1} · min^{-1})	24.8	6.97	49.4
V_2 (mL/kg)			
Female	2,410	586	78.7
Male	1,090	120	NA
Cl_{slow} (mL · kg^{-1} · min^{-1})	5.05	0.582	NA
V_3 (mL/kg)	4,470	1,390	NA

* Computed as 100% · $\sqrt{omega^2}$, where $omega^2$ = variance(*eta*); 68% of the population lies within this range of the typical value.

NA = not applicable to the optimal model; SE = standard error.

systemic pharmacokinetics of sufentanil is a three-compartment model in which all pharmacokinetic parameters are weight-normalized and V_2 is larger for women than for men (tables 2 and 3). Interindividual variability is necessary for Cl and Cl_{rapid} and for V_2 in women.

Modeling of the Pharmacokinetic Characteristics of Chronogesic

Data for these analyses included all plasma samples except those associated with administration of aldesleukin. The first model tested used a four-knot spline to describe sufentanil release. The quality of the fit of the model to the data was very good, except for the period immediately after the implant. A model using a five-knot spline did not improve the quality of the fit.

With the four-knot spline, variance of interindividual variability for two parameters, Cl_{rapid} and the height of the third knot, was extremely small, suggesting that permitting interindividual variability for these parameters was not necessary. A model that did not permit interindividual variability in these parameters (*i.e.*, one with fewer parameters) yielded the same objective function as the model allowing interindividual variability; the model with fewer parameters is justified statistically. Covariate graphics for this model suggested that absorption half-life increased with increasing body mass index. Therefore, a new model permitted absorption half-life to vary with body mass index:

$$\text{ABSORB} = \text{THETA(x)} * (1 + \text{THETA(y)} * (\text{BMI-23})) * \text{EXP(ETA(z))} \quad (2)$$

Table 3. Derived Parameters for the Optimal Model for the Systemic Pharmacokinetics of Sufentanil

	Derived Value of Subjects	
	Female	Male
$t_{1/2}\pi$ (min)	2.6	2.5
$t_{1/2}\alpha$ (min)	147	69
$t_{1/2}\beta$ (min)	853	833
Vss (mL/kg)	7,054	5,734

Table 4. Parameter Estimates Determined in the NONMEM Analysis for the Optimal Model for the Pharmacokinetics of Chronogesic Sufentanil

	Typical Value	SE	Interindividual Variation* (%)
Absorption half-life (h)	16.2	2.1	27.7
Bolus (μg)	27.5	8.85	47.0
Height			
Knot 1 (μg/h)	0.904	0.551	148
Knot 2 (μg/h)	0.485	0.206	79.9
Knot 3 (μg/h)	4.09	0.480	20.9
Knot 4 (μg/h)	3.92	0.342	14.2
Time			
Knot 2 (h)	50.4	0.134	32.1
Knot 3 (h)	111	7.30	NA

* Computed as 100% · $\sqrt{omega^2}$, where $omega^2$ = variance(*eta*); 68% of the population lies within this range of the typical value.

NA = not applicable to the optimal model; SE = standard error.

where ABSORB is the absorption half-life for an individual, THETA(x) is the typical value of absorption half-life for the population, 23 is approximately the median value for body mass index in this population, and the final term permits interindividual variability in ABSORB. The objective function for this model improved 2.975 units compared to the previous model ($P = 0.08$). Thus, a relationship between body mass index and ABSORB is not justified statistically.

Based on the *in vitro* release rate profile, release rate should be stable or increasing during the final days of the implant period. Previous models that did not constrain the relative heights of the knots and parameter estimates for the previous model indicated a small decrease in release rate (from 4.09 to 3.92 μg/h) during the period starting 111 h after implant until removal. Thus, a model was tested that required the release rate to be stable or increasing between knot 3 and knot 4. The objective function for this model increased 0.126 units compared to the previous model. In that the two models have the same number of parameters, the previous model is preferred.

Post hoc estimates of *etas* for the systemic pharmacokinetic parameters are centered around zero (graphics of observed divided by predicted values are available as Web Enhancements at www.anesthesiology.org). This indicates that the estimates for the typical values for the systemic pharmacokinetics of sufentanil obtained from the initial intravenous dosing, coupled with an absorption half-life, are sufficient to describe the time course of washout of sufentanil after prolonged administration.

Based on these analyses, the optimal pharmacokinetic model for the systemic administration of sufentanil is a three-compartment model in which all structural parameters are weight-normalized and V_2 is larger for women than for men (tables 2 and 3). Interindividual variability is permitted for Cl and Cl_{rapid} and for V_2 in women. The optimal model for the pharmacokinetics of Chronogesic

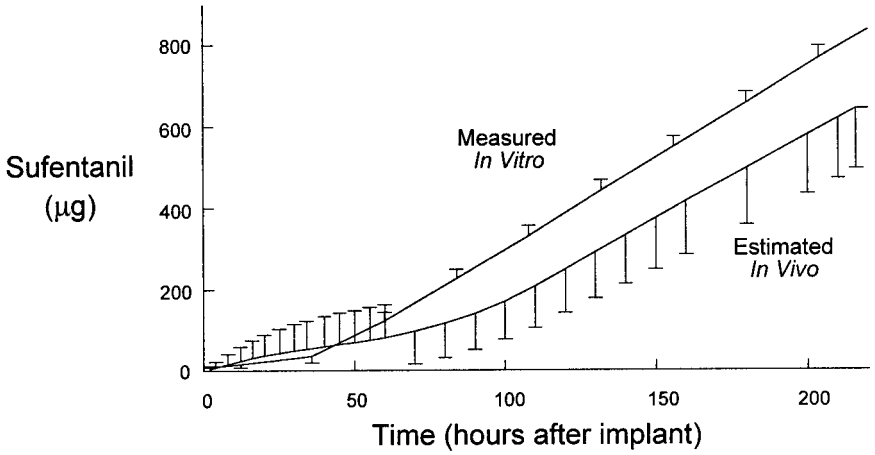

Fig. 8. Cumulative release (μg, mean ± SD) of sufentanil *in vivo* and *in vitro* are shown. The *x* axis is truncated at the time at which the implants are removed (at which time no further release occurs).

sufentanil contains a four-knot release rate model in which there is first-order absorption of sufentanil from the depot (fig. 4, table 4). At the time of implant, a bolus dose§§ (typical value, 27.5 μg, equal to a 5.5-h dose) is released. Between the time of implant and typically 50.4 h later, the release rate is slow and relatively constant (starting at 0.904 μg/h, ending at 0.485 μg/h). Then at 50.4 h, release rate increases in a linear manner to 4.09 μg/h at a typical time of 111 h. There is a slight decrease in release rate (from 4.09 μg/h to 3.92 μg/h; <1% per day) between knot 3 (typical value: 111 h) and knot 4 (approximately 216 h). Graphics displaying the goodness of fit for the optimal model are available in Web Enhancement D.

In Vitro *Analyses and Estimation of Bioavailability*

In vitro, the mean value for sufentanil release rate ranged from ~ 4.4 μg/h at day 5 to ~ 4.7 μg/h at day 9. This can be compared to estimates based on *in vivo* data indicating a release rate of 4.09 μg/h at approximately 4.6 days, decreasing in a linear manner to 3.92 μg/h at the time of removal (approximately 9 days). The range of values estimated *in vivo* overlies the range measured *in vitro*. This suggests that bioavailability of Chronogesic sufentanil is not different from 100%.

The second approach to estimating bioavailability was to compare the cumulative *in vivo* release, including the bolus released at the time of implant, to the cumulative *in vitro* release (fig. 8). After 9 days of implant, cumulative *in vivo* release of sufentanil was 670 ± 112 μg; cumulative *in vitro* release was 768 ± 30 μg. Based on these values, the point estimate for bioavailability is 87%. Values estimated *in vivo* do not differ from those estimated *in vitro*; *i.e.*, bioavailability does not differ statistically from 100%.

§§This bolus dose is specific to the product design used in this study. Design changes eliminate the bolus dose from product to be used in phase 3 clinical studies and beyond.

Timing of Startup

Inflection points in figure 5 indicate that, *in vitro*, release rate from the implant systems increases significantly at approximately day 2 and plateaus at approximately day 4. These values are consistent with the time of knots 2 and 3 in the optimal model, 50.4 and 111 h, respectively. Thus, the timing of the startup release rate profile estimated *in vivo* is consistent with *in vitro* release rate data.

Simulation of a Transient Perturbation of Sufentanil Release

Supplemental release of a 1-h dose during steady-state administration of sufentanil causes a 2.8% increase in women and a 2.5% increase in men (table 5); time to peak Cp averaged 4.4 and 7.1 h, respectively. Based on the mean value and SD, less than 1% of subjects would exhibit an increase in Cp exceeding 5% per hours supplemental dose.

Discussion

The systemic pharmacokinetics of sufentanil are well described by a three-compartment model, as has been reported previously.[3] The disposition function is similar to that reported by Gepts *et al.*[3] in healthy adults. The pharmacokinetic characteristics associated with subcutaneous administration of sufentanil *via* Chronogesic are well described by the proposed model in which there is first-order absorption of sufentanil from the site of ad-

Table 5. Expected Maximal Increase in Sufentanil Plasma Concentration and Time to Maximal Increase Resulting from Bolus Administration of 1-h Dose at a Time When Implant Systems are Delivering at Steady State

	Female	Male
Maximal increase in Cp (%)	2.8 ± 0.9	2.5 ± 0.9
Time to maximal increase in Cp (h)	4.4 ± 0.8	7.1 ± 2.8

Values are mean ± SD.

ministration and the release rate for sufentanil is described by a series of linear splines. The data indicate that release rate peaks at ~ 111 h after implant at a typical value of 4.09 μg/h, followed by a slow decrease to 3.92 μg/h at the time of removal; the magnitude of the decrease is small (approximately 6% over 4.5 days). Another model in which release rate was essentially constant during this period was only slightly inferior to the model selected.

The fit of the model to the plasma concentration data at the time of the implant is not as good as other portions of the model. Most likely this poor fit of the model to the data at the time of the implant represents variability in the release rate profile occurring at that time, not adequately described by a bolus dose immediately at the time of implant, followed by release described by the linear spline. Although the quality of fit of the model to these data are not as good as other portions, there is no evidence of systematic bias.

Bioavailability, assessed by comparing the release rate estimated from *in vivo* data with values obtained *in vitro* using comparable implant systems, appears to not differ from 100%. Bioavailability, assessed by comparing the cumulative release during the entire 9-day implant period with the corresponding values from *in vitro* data, was 87% (not statistically different from 100%). Thus, the labeled dose represents the dose received by the patient.

The absorption half-life for sufentanil from the subcutaneous space is 16.2 h, a value far longer than typically associated with intramuscular or subcutaneous administration of opioids.[4,5] This may result from the markedly smaller volume of administration with Chronogesic sufentanil (~ 2.3 μl/day for the units used in the present study) compared with the typical volume of an intramuscular or subcutaneous injection (*e.g.*, 0.5–1.0 ml or more). A second difference is that Chronogesic sufentanil is formulated as a viscous solution in benzyl alcohol, whereas other opioids given subcutaneously are typically not.

Induction of fever *via* aldesleukin was not associated with a systematic increase in the plasma concentration of sufentanil. In that fever should produce an acute increase in release from the Chronogesic system (because of thermal expansion of the drug formulation), this finding was unexpected. A likely explanation is that fever-induced changes in distribution and/or elimination counterbalance the increase in release rate; in addition, the lengthy half-life with which sufentanil is absorbed from the subcutaneous space dampens any increase in plasma sufentanil concentration. Should other events (*e.g.*, application of a heating pad over the implant system) yield changes in release rate in the absence of the physiologic changes induced by fever, plasma sufentanil concentration might increase. The expected magnitude of increase in plasma sufentanil concentration under these circumstances was estimated based on simulation using the pharmacokinetic parameters estimated in the present study. These simulations indicate that supplemental release of 1-h dose of sufentanil increases Cp only 2.5–2.8% and that fewer than 1% of patients will experience an increase exceeding 5%.

No studies have specifically examined the magnitude of change in opioid Cp (or, more appropriately, concentration in the effect compartment, Ce) that patients who are chronically exposed to opioids can tolerate. However, Bruera *et al.*[6] studied 15 patients with chronic pain who took opioids chronically and who also had sufficient lung disease to cause severe dyspnea at rest and who required chronic administration of supplemental oxygen. At the time that they were scheduled to receive their opioid dose, they were given subcutaneous morphine in a dose equivalent to 2.5 times their regular 4-hourly dose. On the basis of simulations that we performed (not shown), this large dose increases peak Cp and Ce approximately twofold. Despite a marked increase in opioid concentration, there was no change in respiratory rate, a decrease in dyspnea, no decrease in oxygen saturation measured by pulse oximetry, and no increase in end-tidal partial pressure of carbon dioxide. These findings suggest that a doubling of opioid concentration is well tolerated in patients with chronic opioid exposure, even in those patients with compromised ventilatory reserve. *In vitro* experiments demonstrate that the maximal supplemental opioid release associated with a 2.5°C increase in the temperature of implant should not exceed 6-h dose. The simulations indicate that even if fluctuations in release rate caused an acute release of a supplemental 20-h worth of opioid (based on a 100% increase in Cp being well tolerated in these patients and a maximal 5% increase per supplemental hours dose), it is likely that respiratory status of the expected patient population would not be compromised. The lengthy absorption half-life contributes by damping the peak increase in plasma concentration for a given dose.

Several aspects of our study design and analysis warrant comment. First, if we had measured the quantity of sufentanil remaining in the implant at the time of its removal, we could have calculated bioavailability from the area under the sufentanil Cp *versus* time curve during each of the intravenous and implant portions of the study and the doses administered during these portions of the study. However, technical considerations prevented us from sampling the residual sufentanil in these units.

Second, another approach, based on the *in vitro* release rate data, was available for estimating bioavailability. We could have assumed that the mean *in vitro* release rate multiplied times bioavailability represented the mean *in vivo* release rate (interindividual variability could have been modeled appropriately). However, *in vitro* data were obtained at 24-h intervals—applying this

approach would not account properly for a situation in which release rate was essentially zero during the first portion of the day, then increased significantly during another portion of the day. The approach that we used allowed flexibility as to the time at which release rate changed.

There are several limitations to this analysis. First, by design, this was an intermediate–duration trial in volunteers. As a result, implanted pumps were removed before steady-state release conditions were achieved. Therefore, estimates of *in vivo* release rates are based on conditions before steady state is achieved. Second, implanted pumps were removed before the planned clinical removal time. In that duration of drug administration was shorter than will occur in clinical practice, estimates of terminal half-life may underestimate the value observed with chronic administration. Third, the models for release rate that we tested assumed that release rate changed in a linear manner between cutpoints; this necessitated abrupt changes in release rate at the cutpoints. It is likely that the actual release rate changes at the cutpoints in a smoother manner. We could have used a more complex spline model (*e.g.*, curvilinear rather than linear splines) to allow more gradual changes; however, it is unlikely that the available data would support a model with multiple additional parameters. In addition, it is likely that between cutpoints there are periodic fluctuations in release rate. Addition of more parameters may have allowed modeling such perturbations; however, the additional parameters required by such a model would not be justified statistically.

Subjects in the present study were healthy volunteers in whom marked physiologic changes (other than induced fever) were absent. One issue of importance to the safety of the implanted pump regards the potential impact of physiologic changes on its delivery rate. Physical principles suggest that the only physiologic change that would be important is a marked fluctuation in serum osmolarity. Two factors minimize the likelihood of such fluctuations impacting on sufentanil release rate. First, under most physiologic conditions, fluctuation in serum osmolarity is small. Second, the osmotic gradient between the salt engine in the implant and the body is quite large such that even large changes in tissue osmolarity are dwarfed by this gradient.

In summary, *in vivo* performance of the Chronogesic™ Sufentanil Pain Therapy system correlates well with *in vitro* performance. Sufentanil is absorbed slowly from the subcutaneous space (half-life $>$ 16 h), indicating that perturbations in sufentanil delivery (such as those induced by thermal changes) will impact minimally on the plasma concentration of sufentanil.

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