

Pharmacokinetics and Pharmacodynamics of Inhaled versus Intravenous Morphine in Healthy Volunteers

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Background: A new pulmonary drug delivery system produces aerosols from disposable packets of medication. This study compared the pharmacokinetics and pharmacodynamics of morphine delivered by an AERx prototype with intravenous morphine.

Methods: Fifteen healthy volunteers were enrolled. Two sub-

This article is featured in "This Month in Anesthesiology."
Please see this issue of ANESTHESIOLOGY, page 5A.

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Received from the Department of Anesthesia and Critical Care, Massachusetts General Hospital, Boston, Massachusetts; and Harvard Medical School, Boston, Massachusetts. Submitted for publication November 25, 1998. Accepted for publication March 15, 2000. Supported in part by a grant from Aradigm Corporation, Hayward, California. Presented in part at the annual meetings of the American Society of Anesthesiologists, San Francisco, California, October 18-22, 1997, and Orlando, Florida, October 17-21, 1998.

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jects were administered four inhalations of 2.2 mg morphine each at 1-min intervals or 4.4 mg over 3 min by intravenous infusion. Thirteen subjects were given twice the above doses *i.e.*, eight inhalations or 8.8 mg intravenously over 7 min. Arterial blood sampling was performed every minute during administration and at 2, 5, 7, 10, 15, 20, 45, 60, 90, 120, 150, 180, and 240 min after administration. The effect of morphine was assessed by measuring pupil diameter and ventilatory response to a hypercapnic challenge. Pharmacokinetic and pharmacodynamic analyses were performed simultaneously using mixed effect models.

Results: The pharmacokinetic data after intravenous administration were described by a three-exponent decay model preceded by a lag time. The pharmacokinetic model for administration by inhalation consisted of the three-exponent intravenous pharmacokinetic model preceded by a two-exponent absorption model. The authors found that, with administration by inhalation, the total bioavailability was 59%, of which 43% was absorbed almost instantaneously and 57% was absorbed with a half-life of 18 min. The median times to the half-maximal miotic effects of morphine were 10 and 5.5 min after inhalation and intravenous administration, respectively ($P < 0.01$). The pharmacodynamic parameter k_{e0} was approximately 0.003 min^{-1} .

Conclusions: The onset and duration of the effects of morphine are similar after intravenous administration or inhalation *via* this new pulmonary drug delivery system. Morphine bioavailability after such administration is 59% of the dose loaded into the dosage form. (Key words: Drug aerosol; pulmonary drug absorption; pulmonary drug delivery.)

WHEN medications are aerosolized, distribution to the smaller airways in which absorption takes place is largely dependent on the droplet size, inspiratory flow rate, and inspired volume. Larger droplets collide with the walls of the oropharynx and larger airways, and the medication contained within them is therefore minimally available for rapid absorption. The AERx Pulmonary Drug Delivery System (AERx system; Aradigm Corp., Hayward, CA) uses disposable medication forms and produces a fine monodisperse aerosol by extruding the prepackaged solution through hundreds of laser-micromachined holes in the single-use container. If the subject's inspiratory flow profile is within specified flow-volume parameters, medication is

aerosolized during a single breath. The resulting aerosol has a mass median aerodynamic diameter of approximately 2 μm (geometric SD = 1.4) (data on file, Aradigm Corp., Hayward, CA).¹

A previous pharmacokinetic analysis of morphine delivered by the AERx system has been reported.² This study compared 4.4 mg morphine (four inhalations of 1.1 mg each administered over 2.1 min) with 2 mg and 4 mg morphine administered intravenously over 3 min. The mean value for bioavailability was 95% (95% confidence interval, 82–107%), with a range of 56–135%.

This study was designed to compare the pharmacokinetics and pharmacodynamics of morphine delivered by this system with those of morphine delivered intravenously. We chose the effects of morphine on pupil size³ and ventilatory drive⁴ as sensitive measures of central opioid action.

Methods

The study was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital. Fifteen healthy volunteers gave written, informed consent. Exclusion criteria included pregnancy; body weight not within 15% of the ideal weight, as specified in the Metropolitan Life tables;^{4A} history of drug, alcohol, or tobacco abuse; glaucoma or pupil abnormalities; and use of medications, within 30 days, that induce microsomal enzymes, use of any other prescription medication within 14 days, or use of any over-the-counter medication within 3 days. Thirteen subjects were administered morphine on 2 days separated by at least 1 week. The drug was administered once by inhalation (eight inhalations of 2.2 mg each given at 1-min intervals) and once by intravenous infusion (8.8 mg over 7 min). The remaining two subjects were given half these doses, that is, either four inhalations of 2.2 mg each given at 1-min intervals or 4.4 mg over 3 min by intravenous infusion. The dosing regimens were designed so that the rate of drug administration was similar for both routes. The intravenous doses were chosen on the basis of *in vitro* data that suggested that approximately 50% of the loaded dose exits the AERx device as a respirable aerosol.¹

Description of the AERx Device

The AERx system used in this study was a research prototype that has been described in detail.¹ It uses single-use dosage forms of 45 μl of a solution of 50 mg/ml morphine sulfate (*i.e.*, 2.2 mg/dosage form). A respirable

aerosol is created by using a mechanical piston to compress the dosage form, thereby extruding the liquid formulation through a single-use nozzle that consists of an array of precisely machined holes. The aerosol bolus is mixed with warmed inhaled air, which promotes controlled evaporation and optimizes aerosol particle size.

During each inhalation, the AERx device monitors the subject's inhaled flow rate and volume. Delivery of medication occurs only if the flow rate is between 65–80 l/min and the inhaled volume is between 0.25–0.5 l. Subjects are trained to inhale properly by viewing colored lights on the AERx device. When the inhaled flow rate is within the aforementioned limits, a steady green light is seen. When the flow rate exceeds 80 l/min, a flickering red light is seen. No light is seen if the flow rate is below the optimal range. Using dosage forms that contain sterile water, all subjects were trained in less than 5 min to inhale in the optimal manner.

Measurements

Arterial blood sampling was performed every minute during drug administration and at 2, 5, 7, 10, 15, 20, 45, 60, 90, 120, 150, 180, and 240 min after drug administration. Blood samples were added to tubes containing EDTA and centrifuged, and the plasma was stored at -20°C until assay. Each sample was analyzed for morphine by use of liquid chromatography–mass spectrometry. The morphine assay had a sensitivity of 0.5 ng/ml and a coefficient of variation less than 5%.

Pupil diameters were measured at frequent intervals after drug administration with use of a commercially available pupillometer, with a resolution of 0.1 mm (Fairville Medical Optics, Amersham, UK). Ambient room light during pupil measurements was 20 lux and was kept constant for each measurement in each individual. Ventilatory drive was measured at 10, 20, 45, 60, 90, 120, 150, 180, and 240 min after drug administration and was determined by measuring minute ventilation before and after a steady state challenge with 7.5% carbon dioxide, as previously described.⁴ Pupil size was not measured during carbon dioxide administration.

Pharmacokinetic Model after Intravenous Morphine Administration

Pharmacokinetic data were analyzed using the program NONMEM (The Regents of the University of California, San Francisco, CA). The concentration of morphine in the central compartment was described by a three-exponent decay with a lag time

$$\text{Conc} = (Ae^{-\alpha(t-\delta)} + Be^{-\beta(t-\delta)} + Ce^{-\gamma(t-\delta)}) \times U(t-\delta)$$

The parameters (A, B, C, α , β , γ , and δ) were estimated from the data with use of first-order conditional estimation and η - ε interaction. The unit-step function, $u(t-\delta)$, was defined to be 0 for times $t < \delta$ and 1 for times $t \geq \delta$. An additive error was chosen for the intraindividual variance on a log transformation of the data.⁵ Log-normal interindividual variances were attributed to each parameter of the exponential decay when such an addition caused a significant improvement in the objective function.⁶ Bayesian estimates were obtained for each individual's parameters.

Pharmacokinetic Model after Inhaled Morphine Administration

Absorption models traditionally are formed by appending a model that describes uptake from absorption to the pharmacokinetic model found by intravenous administration. For intramuscular, subcutaneous, and sublingual administration, this works well because the drug is eventually absorbed by the veins, becoming input to the simpler model. In the case of pulmonary delivery, however, the absorbed drug bypasses the veins, the right side of the heart, and much of the lung, and so nowhere along its initial path may be considered as input to the simpler model. We addressed this issue by including a lag time in the intravenous pharmacokinetic model to account for the delay from administration to first appearance of the drug at the sample site. We assumed that most of this delay occurred in the high-compliance, low-velocity, systemic vein side of the lung so that, consequently, the multicompartmental model, excluding the lag time, adequately describes the distribution of drug administered into pulmonary capillaries and veins. No variability was ascribed to the lag time. Into the central compartment of the three-compartment systemic model we added one- and two-compartment absorption models to describe the uptake of aerosolized drug (fig. 1). Mathematically, this is equivalent to convolution of the Bayesian estimates found herein (without the lag time) with a function of the form

$$\text{Uptake}(t) = F_0(F_1k_a e^{-k_a t} + (1 - F_1)k_b e^{-k_b t})$$

where F_0 represents the bioavailability of the inhaled drug, F_1 represents the fraction absorbed at rate k_a , and $(1 - F_1)$ represents the fraction absorbed at rate k_b . These inhalation data were similarly fit with first-order conditional estimation, η - ε interaction, intraindividual addi-

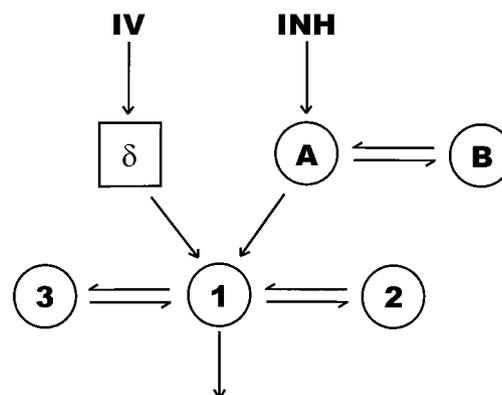


Fig. 1. The kinetic models for intravenous (IV) and inhalation (INH) administration of morphine. The intravenous model contains a lag time, indicated by δ , to account for the delay from administration to first appearance of the drug at the sample site. The inhalation model contains a two-compartment absorption model to describe the uptake of aerosolized drug, in which these two compartments are indicated by A and B. In both models, the drug is then deposited into the central compartment (1) of a standard three-compartment systemic model containing two peripheral compartments (2 and 3).

tive error on a log transformation of the data, and log-normal interindividual variances. The goodness-of-fit was assessed by calculating the median weighted residual (MWR), with the weighted residuals defined as

$$\text{WR} = \frac{\text{measured} - \text{predicted}}{\text{predicted}}$$

and the median absolute weighted residual (MAWR) of the Bayesian estimates.

The dose for the inhalation route was taken to be the nominal dose loaded into the disposable dosage form. At the time of this study, *in vitro* data suggested that approximately 50% of the loaded dose could be expected to reach the subject's lungs.

Pharmacodynamic Model

Ventilatory depression data could not be sampled at sufficiently frequent intervals to estimate drug onset, so pharmacodynamic analysis was restricted to pupillary effects. The concentration of morphine in the effect site was assumed to result from the convolution of the Bayesian plasma concentration-*versus*-time curves with a function of the form

$$y(t) = k_{e0} e^{-k_{e0} t}$$

The resulting effect-site concentration was linked to

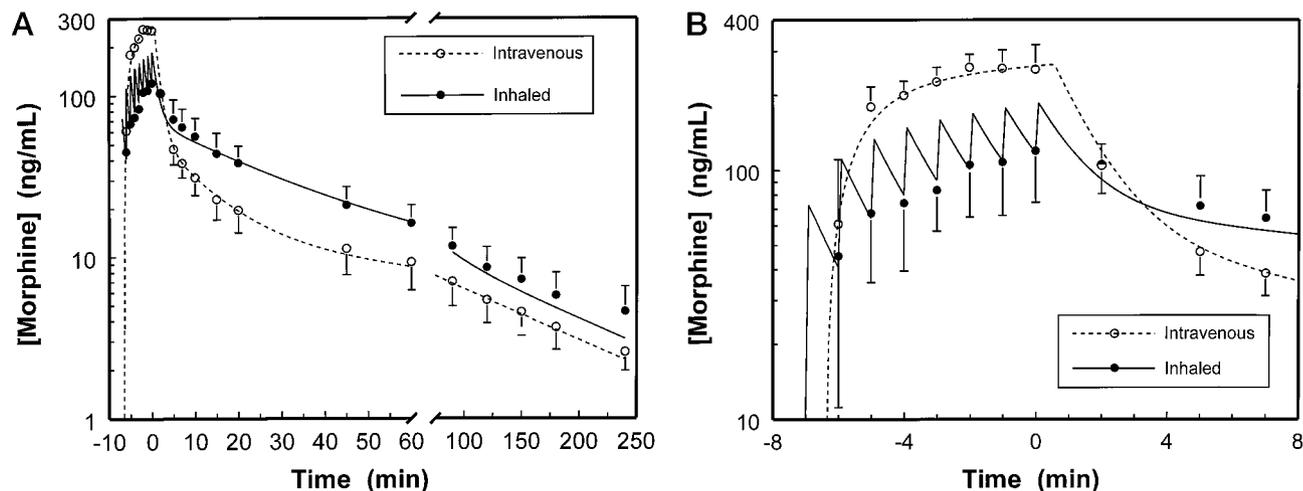


Fig. 2. (A) The arterial plasma concentrations of morphine after inhalation (solid circles and line) and intravenous (open circles and dashed line) administration in the subjects administered the higher dose. The lines represent the best fit derived from the pharmacokinetic model. Each point is the mean \pm SD. Error bars are omitted from the earlier time points for clarity and are shown for these time points in B. (B) The time course of A is expanded to show in detail the absorption and early distribution phases of morphine disposition after inhalation (solid circles and line) and intravenous (open circles and dashed line) administration in the subjects administered the higher dose. The lines represent the best fit derived from the pharmacokinetic model. Each point is the mean \pm SD.

the effect (pupil size) by the two different pharmacodynamic models. The equation for the linear model was

$$\text{Pupil diameter} = E_0 - \text{slope} \times C$$

where E_0 is the resting pupil diameter and C is the effect-site morphine concentration. The equation for the E_{\max} model was

$$\text{Pupil diameter} = E_0 \left(1 - F_{\max} \left(\frac{C^\lambda}{C^\lambda + EC_{50}^\lambda} \right) \right)$$

where E_0 is the resting pupil diameter, F_{\max} is the maximum fractional decrease in pupil size, C is the effect-site morphine concentration, EC_{50} is the effect-site morphine concentration producing the half-maximal decrease in pupil size, and λ is the slope of the sigmoid relation. The pharmacodynamic data from both intravenous and inhaled administration were fit with NONMEM using first-order conditional estimation, η - ϵ interaction, intraindividual additive error on the data, and log-normal interindividual variances on k_{e0} , E_0 , F_{\max} , and EC_{50} . No intraindividual variance was ascribed to λ .

Results

The protocol originally specified that half the subjects would receive the lower dose of morphine (4.4 mg intravenously and 8.8 mg *via* inhalation) and half would

receive the higher dose (8.8 mg intravenously and 17.6 mg *via* inhalation). After two subjects (patients 1 and 2) were administered the lower dose, it was clear that the magnitude of the ventilatory depressant effect was small and therefore, the remaining 13 subjects (patients 4-16) were administered the higher dose of morphine. Data are omitted for subject 3 who did not complete the protocol. Subject 6 had such dark irides that the pupillometer was unable to determine the pupil diameter. Data are therefore reported for 15 subjects, 10 of whom were men. Mean age was 35 yr (range, 22-45 yr) and mean weight was 74 kg (range, 52-90 kg).

The plasma concentrations of morphine (for the higher dose) after inhaled and intravenous administration are depicted in figure 2. Zero-time represents the time of the final inhalation of morphine or the time of the end of the intravenous infusion. The peak arterial morphine concentrations (95% confidence interval) were 120 ng/ml (99-157 ng/ml) after 17.6 mg inhaled and 286 ng/ml (263-309 ng/ml) after 8.8 mg intravenous.

Table 1 displays the parameters of the intravenous kinetic model. Interindividual variability was ascribed to parameters A, C, α , and β ; adding interindividual variability to parameters B and γ did not significantly improve the fit. The addition of the lag time caused a significant improvement in the fit, as evidenced by a

PHARMACOKINETIC-PHARMOCODYNAMIC STUDY OF INHALED *VERSUS* INTRAVENOUS MORPHINE**Table 1. Pharmacokinetic Parameters**

A (ng/ml)	B (ng/ml)	C (ng/ml)	α (min ⁻¹)	β (min ⁻¹)	γ (min ⁻¹)	δ (s)
130 (15.5)	6.6 (1.0)	1.5 (0.12)	0.78 (0.10)	0.086 (0.012)	0.0072 (0.00032)	35 (7.8)

The parameters are derived from a mixed-effects model fit of the pharmacokinetic data to the model: $\text{conc} = (Ae^{-\alpha(t-\delta)} + Be^{-\beta(t-\delta)} + Ce^{-\gamma(t-\delta)}) \times u(t-\delta)$ where $u(t-\delta)$ is defined to be 0 for times $t < \delta$ and 1 for times $t \geq \delta$. The coefficients A, B, and C are normalized to a dose of 1 mg. Values in parentheses represent the standard error of the parameter estimates. These parameters may be used to predict plasma concentrations that result from the administration of doses other than 1 mg by multiplying the administered dose by the coefficients for the specific model.

decrease in the objective function of 60 points. The lag time was approximately 35 s.

Table 2 shows the parameters for the lung absorption model. A two-exponent absorption model was found to fit significantly better than a monoexponential model. From these parameters we deduced that the total bioavailability was 59%, of which 43% was absorbed almost instantaneously ($k_a = 2.2 \times 10^7$) and 57% was absorbed with a half-life of approximately 20 min ($k_b = 0.039$).

By WR and absolute WR, the intravenous and inhalational models exhibited very good fits, with less than 1% bias (WR) and less than 8% inaccuracy (absolute WR; table 3). It appears from figure 2A that the inhalation model underpredicts the latest data point and consequently may not be adequate to estimate accurately the concentrations after 4 h.

Pupil size was measured frequently; therefore, data were obtained as the effect was increasing and decreasing. Ventilatory drive could not be measured at such frequent intervals; therefore, most measurements were made after the steeply increasing portion of the concentration-*versus*-time curve and after the effect had reached a plateau. The effect of morphine on ventilatory drive as a function of time is shown in figure 3. Because frequent sampling could not be performed, the rate of the decrease in ventilatory drive could not be used to assess the onset of the opioid effect. Ventilatory drive, as measured by carbon dioxide responsiveness, was de-

pressed approximately 30% after both methods of administration, and minimal recovery was seen during the 4-h measurement period for most subjects. Morphine administered intravenously (8.8 mg) and by inhalation (17.6 mg) produced approximately the same maximum degree of ventilatory depression. This finding is consistent with the bioavailability value of 59%.

Table 4 lists the pharmacodynamic parameters. The k_{e0} value for miosis is approximately 0.003 min⁻¹. The typical pupil size was 6.1 mm at baseline and constricted to approximately half its size. Individual Bayesian fits of the pupil data are presented in figure 4. The median times to the half-maximal effect were 10 and 5.5 min after inhalation and intravenous administration, respectively ($P < 0.01$, Student *t* test for paired data). The maximum decrease in pupil size was approximately the same after intravenous or inhalation administration. This finding was consistent with the bioavailability value of 59%. Subject 8 showed little pupillary effect after inhaled morphine but a very large effect when the drug was administered intravenously. These data were consistent with the low value for bioavailability in this subject (14%, data not shown). Subject 15 had a very small pupillary response to morphine administered by either route. This subject's data were not used in comparing the onset times.

Discussion

This was the first trial of the AERx system with morphine in which effects of the drug, in addition to blood

Table 2. Parameters of the Inhalation Model

k_a (min ⁻¹)	F_0	k_b (min ⁻¹)	F_1
2.2×10^7 (0.8×10^7)	0.59 (0.06)	0.039 (0.0035)	0.43 (0.03)

The inhalational model consisted of convolving the Bayesian estimates found in table 1 (without the lag time) with the function:

$$\text{uptake}(t) = F_0(F_1 k_a e^{-k_a t} + (1 - F_1) k_b e^{-k_b t})$$

where F_0 represents the bioavailability of the inhaled drug, F_1 represents the fraction absorbed at rate k_a , and $(1 - F_1)$ represents the fraction absorbed at rate k_b . Values in parentheses represent the standard error. The total bioavailability is 59%. Forty-three percent of this is absorbed instantaneously ($k_a = 2.2 \times 10^7$) and 57% is absorbed with a half-life of 18 min ($k_b = 0.039$).

Table 3. Goodness of Fit of the Models

Method of Administration	Weighted Residuals	Absolute Weighted Residuals
Intravenous	-0.9	6.0
Inhalation	0.1	7.9

Values for the weighted residuals (WR) and the average weighted residuals (AWR) indicated good fits for both the intravenous and the inhalation models. There was less than 1% bias (WR) and less than 8% inaccuracy (AWR).

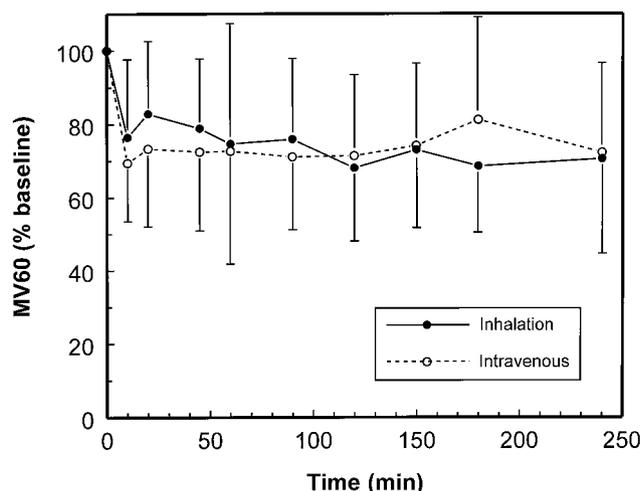


Fig. 3. The pooled data of the ventilatory depressant effects of morphine as a function of time. Ventilatory drive is expressed as the minute ventilation achieved at an end-tidal carbon dioxide concentration of 60 mmHg, determined by interpolation from the carbon dioxide response curve (MV60). The closed circles and solid lines depict the effect after inhalation administration; the open circles and dashed lines show the effect after intravenous administration. Each point is the mean \pm SD.

concentrations, were measured. Our results suggest that both the onset and the duration of the miotic effect of morphine after inhalation are similar to those after intravenous administration. Further studies are necessary in patients with pain, acute and chronic, to determine the optimum regimens with use of the AERx system. Assuming that the time course of the analgesic effect parallels that of the miotic effect, an observation that has been shown previously,⁷ the AERx system may be useful for providing rapid-onset, patient-controlled analgesia, without necessitating the presence of an intravenous catheter. The safety of this new practice will need to be established for inpatients and outpatients. *In vitro* data suggested that approximately 50% of morphine contained in the dosage form would be delivered at the

outlet of the AERx system. The bioavailability of 59% indicates that more than 50% must have been delivered to the patient. Pulmonary absorption must also have been very efficient. Roughly, 75% of orally-administered morphine undergoes first-pass metabolism, and, therefore, any swallowed drug would contribute significantly less to measured bioavailability.

The inclusion of a lag time in the model after intravenous administration of morphine is not a novel approach.⁸ This parameter accounts for the delay that must intuitively occur as the drug travels within the vasculature from the vein into which it was injected, through the right heart and lung, and then through the left heart to the artery from which the blood sample was obtained. We found this value to be 35 s, and inclusion of the lag time in the model significantly improved the quality of the kinetic fits.

Most previous studies that used simultaneous pharmacokinetic-pharmacodynamic analyses of opioids in humans relied on an electroencephalographic parameter as the dynamic measurement. The advantages of this method are that electroencephalography may be continuously recorded and that the calculated pharmacodynamic parameters can be used to predict drug effect fairly accurately. This method has been successfully applied to fentanyl,⁹ alfentanil,¹⁰ sufentanil,¹¹ and remifentanyl.¹² A significant disadvantage of this method is that a measurable effect usually necessitates doses that produce apnea or muscle rigidity.

We used opioid-induced ventilatory depression as the pharmacodynamic effect in simultaneous pharmacokinetic-pharmacodynamic studies of remifentanyl.^{4,13} The advantages of this method are the clinical relevance of the measurement and the finding that the depression of carbon dioxide responsiveness occurs at doses that permit adequate ventilation. The major disadvantage of the steady state method we used was that the determination

Table 4. Pharmacodynamic Parameters

Model	k_{e0} (min^{-1})	E_0 (mm)	Slope ($\text{mm} \cdot \text{ml}^{-1} \cdot \text{ng}^{-1}$)		
Linear	0.0033 (0.0004)	6.0 (0.2)	0.23 (0.03)		
Model	k_{e0} (min^{-1})	E_0 (mm)	F_{max}	EC_{50} (ng/ml)	λ
E_{max}	0.003 (0.0005)	6.1 (0.2)	0.46 (0.06)	4.8 (1.1)	2.1 (0.3)

The parameters are derived from a mixed-effect-model analysis of the PD data with a single-compartment effect site. The pupil diameter was related to the morphine effect-site concentration according to two different models, a linear model and an E_{max} model (see text for equations used for linear and E_{max} models). The values in parentheses represent the standard errors.

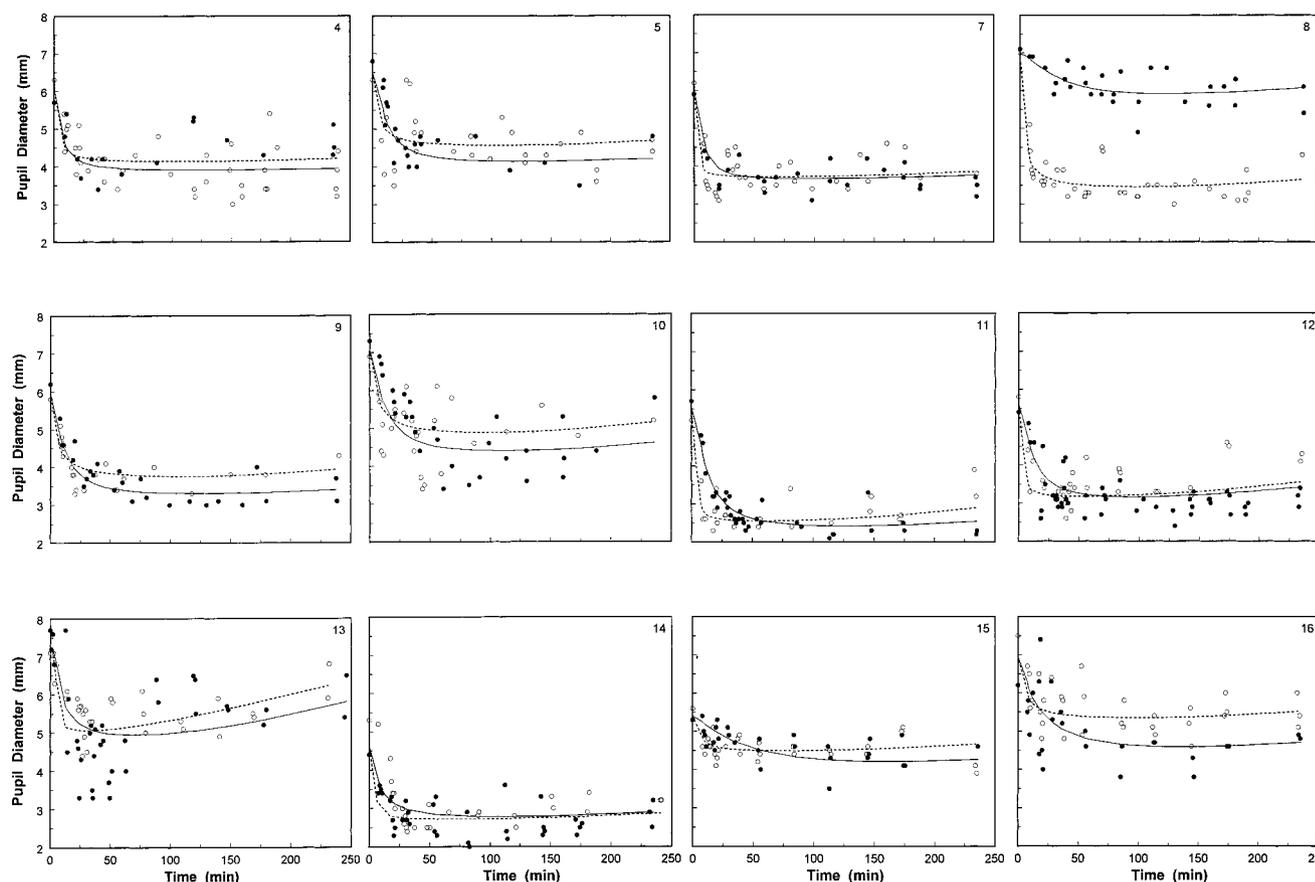
PHARMACOKINETIC-PHARMOCODYNAMIC STUDY OF INHALED *VERSUS* INTRAVENOUS MORPHINE

Fig. 4. Change of pupil size *versus* time for individual subjects administered the high dose of morphine. Subject numbers are in the upper right corner of each panel. The closed circles and solid lines depict the effect after inhalation administration; the open circles and dashed lines show the effect after intravenous administration. The lines represent the best fit derived from the E_{\max} pharmacodynamic model.

of ventilatory drive takes several minutes and is therefore not appropriately applied in situations in which the drug concentration may change rapidly. The respiratory data did not characterize the onset and offset of ventilatory depression; therefore, we did not use these data to estimate k_{e0} for this effect.

Other investigators have used pupillometry to assess opioid-induced miosis as the pharmacodynamic effect in a simultaneous pharmacokinetic-pharmacodynamic analysis.^{14,15} Miosis is thought to be caused by a direct opioid effect on μ receptors in the autonomic nucleus of the oculomotor nerve. The advantages of this method are that repeated measurements may be made rapidly (up to approximately every 15 s), so that the determination of the effect is nearly continuous and an easily measured effect occurs at very low doses of opioids.³ The ED₅₀ for morphine-induced miosis is approximately

11 mg intravenously (unpublished data, 1998), and the doses used in this study were in the linear portion of the dose-response curve.

We successfully used pupillometry to observe the onset of the miotic effect of morphine and to calculate the relevant pharmacodynamic parameters (table 4). In the dog, morphine also enters the central nervous system slowly after intravenous administration; therefore, cerebrospinal fluid concentrations do not peak until approximately 30 min after injection. The ventilatory depressant effect, as indicated by increasing values for end-tidal carbon dioxide, peaks later, approximately 1 h after administration.¹⁶

The pharmacodynamic parameters in table 4 show that a large dose of morphine that produces the maximal miotic effect would decrease pupil size from an average baseline size of 6.1 (using our standardized lighting con-

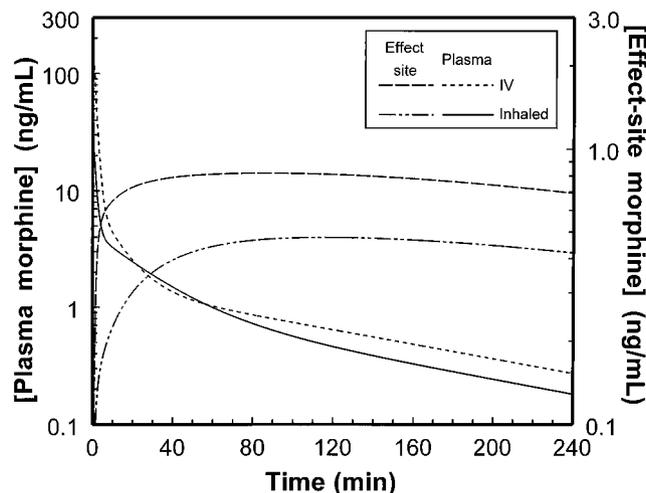


Fig. 5. Predicted arterial and effect-site concentrations after administration of 1 mg morphine by either the intravenous or the inhalation route. The curves depicting the arterial plasma concentrations use the kinetic parameters from table 1. The curves depicting the effect-site concentrations are obtained by convolution of the arterial plasma concentration curves, with a curve of the form $y = k_{e0}e^{-k_{e0}t}$ using the E_{max} pharmacodynamic parameters from table 4. The model predicts that similar effect-site concentrations would be achieved after administration of 1.0 and 1.7 mg morphine intravenously and *via* the AERx device, respectively.

ditions) to 3.3 mm. Based on our previous studies³ in which the miotic effects of relatively larger doses of fentanyl and alfentanil were measured, and our unpublished data that use larger doses of morphine, constriction of the pupil to approximately 2 mm should be expected. To ascertain the effects of this apparently low estimate of F_{max} , we performed the pharmacodynamic calculations, assuming 2 mm for the value of the maximally constricted pupil. During these conditions, the resulting value for k_{e0} was unchanged, and the value for EC_{50} increased to 7.7 ng/ml. The current data do not provide a good estimate for F_{max} because we did not administer morphine doses that approach the asymptotic portion of the dose-response curve. This limitation is unlikely to have adversely affected our ability to measure reliably the value for k_{e0} .

The miotic effect of morphine has an onset, after either intravenous injection or inhalation, with a half-life of approximately 5–10 min and a peak of approximately 1.5–2 h after administration (figs. 4 and 5). Figure 5 shows the results of a simultaneous pharmacokinetic-pharmacodynamic analysis of arterial morphine concentrations and pupillary effects. Because morphine was administered in this study as a series of inhalations and the onset times depicted in figure 4 are clearly related to

the timing of morphine administration by either route, we chose to compare the effects of a single inhalation with a single intravenous bolus. Figure 5 shows the predicted plasma and effect-site concentrations after intravenous and inhaled administration of 1 mg morphine. The peak concentrations in both the plasma and the effect site are lower after inhalation, reflecting less than 100% bioavailability based on the loaded dose. The model predicts that similar effect-site concentrations would be achieved after the administration of 1.0 and 1.7 mg morphine intravenously and *via* the AERx device, respectively. Although the time to the peak effect was longer after inhalation administration (table 5), the times to 25% of the peak effect were similar (1.2 and 2.0 min after 1 mg intravenous administration and by inhalation, respectively). The model predicts that 43% of bioavailable morphine (*i.e.*, 25% of the dose loaded into the dosage form) enters the central circulation almost instantaneously, and 57% of bioavailable morphine (*i.e.*, 34% of the dose loaded into the dosage form) enters the central circulation with a half-life of 18 min. Future studies in humans with pain will be necessary to assess the onset time of meaningful analgesia after morphine administration by the AERx device. The similar times to 25% of the peak effect-site values suggest that morphine administration *via* AERx will provide analgesia within minutes of administration.

We found that inhaled and intravenous morphine produce similar intensity and duration of ventilatory effect when the doses are adjusted for bioavailability. This suggests that the normal guidelines for dosing of intravenous morphine may be applicable to administration by inhalation. This is reassuring because the ultimate goal of this research is to develop a noninvasive method of patient-controlled morphine analgesia, with onset, intensity, and duration similar to the those of the intravenous route. When inhaled morphine is tested for this indication, it will probably be appropriate to evaluate the same

Table 5. Modeled Onset Times for Intravenous and Inhaled Morphine

	Intravenous	Inhaled
C_{max} after a 1-mg dose (ng/ml)	0.82	0.48
Time to C_{max} (min)	86	116
Time to 50% C_{max} (min)	2.3	11.5
Time to 25% C_{max} (min)	1.2	2.0

Using the data from figure 5, the times to the maximum morphine effect-site concentrations (C_{max}), and various fractional values of C_{max} , were determined after intravenous or inhalation administration of 1 mg morphine. The lower value for C_{max} after inhalation reflects the 59% bioavailability of this method of administration. Although the time to the peak effect is longer after inhalation, the times to 25% of the peak effect are similar.

lockout time (e.g., 6 min) for patient-controlled analgesia delivered by intravenous or inhaled routes. The amount of each dose will need to be individualized for each patient.

Morphine-6-glucuronide (M-6-G) is an active metabolite of morphine,¹⁷ but we chose not to include it in our pharmacodynamic model. Recent work by Lötsch *et al.*^{18,19} has shown that M-6-G does not contribute to the short-term effects of morphine. Although M-6-G is potent, studies show that M-6-G crosses the blood-brain barrier slowly, accounting for its lack of short-term effects. Simulation studies have shown that the slow, plasma-effect-site equilibration results in insignificant clinical effect during short-term administration; however, M-6-G may contribute significantly to the analgesic properties of morphine with long-term administration.²⁰ Based on the results of Lötsch *et al.*,¹⁸⁻²⁰ M-6-G did not contribute to the opioid effects reported in this study. For this reason, we did not include M-6-G in our pharmacodynamic model.

The time courses we observed in the plasma and the effect site are a function of the time over which the medication was administered. The prototype of the AERx system used in this study permitted 1 inhalation/min because the morphine dosage forms were single units and had to be loaded and unloaded into the device individually. The AERx system being developed uses a cassette of dosage forms, and up to 4 inhalations/min may be administered. Ultimately, when morphine is given *via* the newer device, the onset of the effect after multiple doses is likely to be significantly faster than we observed.

The data in figure 5 show that the effect-site concentration is more than 90% of its peak value for 181 and 172 min after intravenous and inhalation administration, respectively. This suggests that the duration of opioid effect will probably be similar with either route of administration.

There is one previous pharmacokinetic study of morphine administered by the AERx system, which also compared morphine administered intravenously and *via* the AERx device.² Ward *et al.*,² determined values for the two, faster half-lives of morphine, $t_{1/2\alpha}$ and $t_{1/2\beta}$, which were essentially the same as ours; however, their value for the terminal half-life, $t_{1/2\gamma}$, was approximately twice the value reported herein (197 *vs.* 96 min). Furthermore, Ward *et al.*,² estimated the bioavailability of morphine administered by the AERx device to be 95%, in comparison with our value of 59%. The discrepancies between the studies may be a result of differences in doses and sampling times: Ward *et al.*,² studied 2 and

4 mg intravenous doses and an inhaled dose of 4.4 mg, and they sampled for 360 min after drug administration. We used 8.8 mg intravenously and 17.6 mg inhaled, and we sampled for only 240 min. It must be emphasized that both of these studies were designed primarily to measure drug onset. Ideally, longer sampling times should be used to estimate the terminal half-life, $t_{1/2\gamma}$. A subsequent study of morphine administered by a newer prototype of the AERx system (unpublished) determined the bioavailability of morphine to be 75%, a value much closer to that reported in the current study (unpublished data on file, Aradigm, Inc., Hayward, CA, 1999).

In summary, our pharmacokinetic-pharmacodynamic analysis confirmed that morphine administered by either the inhalation or the intravenous route has a rapid onset but necessitates several hours to come to full equilibration with effect sites in the central nervous system. We have demonstrated that morphine administered by inhalation using this prototype of the AERx technology efficiently delivers the drug, with a bioavailability of 59%. In conjunction with the *in vitro* data,¹ we can conclude that almost all the morphine delivered to the patient by the AERx device is absorbed by the respiratory tract. In healthy volunteers, the initial onset phase and duration of the pupillary and respiratory effects of morphine are not different between the two routes of administration.

The authors thank Dennis M. Fisher, M.D., Departments of Anesthesia and Pediatrics, University of California at San Francisco, for helpful discussions regarding the pharmacokinetic-pharmacodynamic analyses; J. Steven Jenkins, Ph.D., Jet Propulsion Laboratory, Pasadena, California, for assistance with the software we used to perform the ventilatory depression measurements; Daria Stypinski, MDS Harris Laboratories, Lincoln, Nebraska, for the analyses of morphine and its metabolites; and José M. Rodriguez-Paz, M.D., Department of Anesthesia and Critical Care, Boston, Massachusetts, Lori A. Maarschalk, R.N., and Donna M. Polasik, R.N.C., Aradigm Corporation, Hayward, California, for assistance in performing the pharmacokinetic-pharmacodynamic measurements.

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