Pharmacokinetic-pharmacodynamic relationships of methadone infusions in patients with cancer pain

To determine the relationship between changes in plasma methadone concentration and pharmacodynamic effects, plasma methadone profiles and pharmacodynamics (analgesia and sedation) were measured during and after the continuous infusion of methadone for 180 to 270 minutes in 15 patients with pain caused by cancer. An increase in plasma methadone concentration resulted in a rapid increase in pain relief or sedation. The estimates of values of 50% of maximum effect ($C_{ss}50$) for pain relief and sedation obtained with a pharmacokinetic-pharmacodynamic model varied tenfold to twentyfold among patients; the mean $C_{ss}50$ value for pain relief (0.359 ± 0.158 [SD] μg/ml) was virtually the same as the mean $C_{ss}50$ value for sedation (0.336 ± 0.205 [SD] μg/ml). Similarly, the mean γ (slope function) for pain relief (4.4 ± 3.8 [SD]) and sedation (5.8 ± 5.4 [SD]) did not differ. Examination of hysteresis plots of data obtained during the infusion and for 4 to 5 hours after cessation of the infusion revealed a very rapid equilibration between plasma methadone values and the sites mediating pain relief. There was no indication of the development of tolerance to the pharmacodynamic effects of methadone during the study. This report describes a method for quantitating the pharmacokinetic-pharmacodynamic relationships of the desirable and undesirable effects of opioid analgesics. (CLIN PHARMACOL THER 1990;47:565-77.)

Charles E. Inturrisi, PhD, Russell K. Portenoy, MD, Mitchell B. Max, MD,[a] Wayne A. Colburn, PhD, and Kathleen M. Foley, MD
New York, N.Y., and Ann Arbor, Mich.

A major goal of current pain research is the development of scientifically based guidelines for the selection and use of opioid analgesic agents in a manner that will enhance analgesia relative to side effects such as sedation, nausea, and respiratory depression.[1] Progress in attaining this goal requires a variety of innovative approaches, including those that elucidate the relationship between the disposition of clinically used opioids and their effects. It is of particular importance to be able to characterize the relationship between changes in biofluid opioid concentration and certain of the desirable and undesirable pharmacodynamic effects of these drugs in patients with pain.[2-6]

Methadone is a synthetic opioid analgesic agent that is nearly equipotent with morphine when both are evaluated after intramuscular administration to patients with cancer.[7] Methadone is biotransformed through *N*-demethylation reactions to apparently inactive metabolites.[8] Pharmacokinetic studies in normal individuals, patients with pain, and patients receiving methadone maintenance indicate that methadone has an elimination half-life ($t_{1/2}$) that varies from 4 to 130 hours.[3,9-11]

In a previous study[3] we defined the pharmacokinetics of methadone after a single intravenous bolus dose and demonstrated that concurrently collected pharmacokinetic and pharmacodynamic data could be analyzed by use of a pharmacokinetic-pharmacodynamic model. This model yields parameter estimates that quantitatively characterize the relationship between changes in plasma methadone concentration and measures of analgesia. The approach used in this previous study was limited, however, by the uncertainty inherent in the selection of a safe and appropriate intravenous bolus

From the Pain Research Program of the Department of Neurology, Memorial Sloan-Kettering Cancer Center, the Departments of Neurology and Pharmacology, Cornell University Medical College, New York, and Pharmacokinetics/Drug Metabolism Department, Warner-Lambert/Parke-Davis, Ann Arbor.
Supported in part by Grant CA-32897 from the National Cancer Institute and Grant JFRA-244 from the American Cancer Society.
Received for publication July 21, 1989; accepted Jan. 23, 1990.
Reprint requests: Charles E. Inturrisi, PhD, Department of Pharmacology, Cornell University Medical College, 1300 York Ave., New York, NY 10021.
[a]Present address: NIDR/NIH Pain Research Facility, Bethesda, MD 20892.
13/1/19652

Table I. Clinical characteristics of patients with cancer receiving an intravenous infusion of methadone

Pt. No.	*Sex*	*Age (yr)*	*Weight (kg)*	*Diagnosis*	*Opioid dosage*	*Previous opioid experience**
1	Male	31	89	Rectal adenocarcinoma	Hydromorphone, 32 mg orally every 3 hr	683
2	Female	65	60	Metastatic cervical carcinoma	Levorphanol, 18 mg orally every 4 hr, plus oxycodone, 5 mg orally every 4 hr	560
3	Male	40	54	Diffuse histiocytic lymphoma	Levorphanol, 8 mg orally every 12 hr	80
4	Male	62	66	Lung adenocarcinoma	Hydromorphone, 24 mg orally every 6 hr	256
5	Female	32	48	Sarcoma	Hydromorphone, 28 mg orally every 4 hr	448
6	Female	52	47	Lung squamous cell carcinoma	Hydromorphone, 52 mg orally every 2½ hr	1387
7	Female	54	53	Breast carcinoma	Hydromorphone, 4 mg orally every 3½ hr	75
8	Male	74	62	Rectal adenocarcinoma	Meperidine, 200 mg orally every 8 hr	40
9	Male	48	56	Melanoma	Hydromorphone, 16 mg orally every 3 hr	341
10	Male	25	72	Testicular teratoma	Hydromorphone, 50 mg orally every 3 hr, plus hydromorphone, 4 mg intravenously every 12 hr	1174
11	Male	70	57	Lymphoma	Hydromorphone, 4 mg orally every 3 hr	85
12	Male	71	74	Lung adenocarcinoma	Levorphanol, 24 mg orally every 3 hr	960
13	Male	24	55	Colon adenocarcinoma	Hydromorphone, 10 mg intravenously every 3½ hr, plus hydromorphone intravenously every 24 hr	1027
14	Male	27	92	Osteogenic sarcoma	Morphine, 130 mg orally every 3½ hr	303
15	Male	47	66	Colon adenocarcinoma	Hydromorphone, 36 mg orally every 3 hr, plus hydromorphone, intravenously every 24 hr	808
Mean ± SD		48 ± 18	63 ± 14			549 ± 439

*Expressed as intramuscular morphine milligram equivalents received for the 48 hours before the study.

test dose given the variability observed in pharmacokinetic parameters and other factors (e.g., degree of opioid tolerance and reaction to pain) that determine pharmacodynamic sensitivity to an opioid. Furthermore, the rapidly changing plasma concentrations characteristic of the distribution phase seen after an intravenous bolus of an opioid can produce relatively large errors in estimates of the relationship between changes in plasma opioid concentration and effects, thereby limiting the precision of the pharmacodynamic parameter estimates obtained under these conditions. Finally, there are other considerations that dictate that the general utility of pharmacokinetic-pharmacodynamic models should not be inferred from a single mode of drug administration.[12]

To obviate these problems, we undertook clinical studies in which blood samples and subjective responses were collected concurrently during and after a continuous intravenous administration of methadone. This method allowed plasma methadone levels to be increased and maintained as dictated by the response of each patient.

METHODS

Patient selection. The clinical characteristics of the study patients are given in Table I. Informed consent for the study was granted by 11 men and 4 women ranging in age from 24 to 74 years (mean age, 48 years). All patients were referred to the Pain Service of the Memorial Sloan–Kettering Cancer Center (New York, N.Y.) for evaluation of chronic cancer-related pain. Each had a clearly defined pain syndrome and had reported moderate to severe pain for at least 6 months. Each patient had been receiving opioid analgesic agents other than methadone and, based on duration of treatment and current dosage, was presumed to have some degree of opioid tolerance. All patients had normal hepatic and renal function and were not receiving chemotherapy at the time of the study.

Study design. The plasma methadone concentration-effect relationships were characterized during a continuous intravenous infusion of methadone hydrochloride (IMED No. 960 infusion pump, IMED Corp., San Diego, Calif.). The infusion was initiated if the patient reported pain of moderate to severe intensity and had not received an analgesic agent for at least 3 hours. Because the patients differed in their previous opioid experiences (Table I), and presumably in their degrees of opioid tolerance, the principle of dosing to effect was applied to evaluate opioid responsiveness. The infusion began with a loading dose of 20 or 25 mg/hr, during which pharmacodynamic effects were monitored under single-blind conditions at 15-minute intervals. This infusion rate was continued until a desired criterion level of analgesic effect was achieved. The criterion level was set conservatively at 50% of maximum pain relief for the initial four patients and then raised to 75% for the remainder of the study. When the criterion was reached for two consecutive 15-minute intervals, the loading infusion was decreased by 50%. Assessments continued at 15-minute intervals, and additional 50% decrements in the infusion rate were implemented each time the patient reported 75% of maximum pain relief or greater. In doing so, an effort was made to approach and maintain a plasma methadone concentration associated with analgesia. The magnitude of this decrement was estimated by use of the method of separate exponentials[13] and pharmacokinetic parameters obtained from a previous study wherein an intravenous bolus of methadone was given to patients with chronic pain.[3] The infusions were continued for 180 to 270 minutes, after which pharmacokinetics and pharmacodynamics continued to be assessed repetitively for 4 to 5 hours.

Nurse observers assessed measures of opioid effect and collected venous blood samples (3 ml) into a heparinized syringe before and at 15-minute intervals during the infusion. After cessation of the infusion, observations were recorded and samples were collected at 2, 5, 10, 15, 30, 60, 90, 120, 180, 240, and 300 minutes. At each observation time the patient was requested to report the intensity of pain and sedation and the degree of pain relief (after the infusion began) on visual analog scales (VAS).[14] Each observation time also included categorical measures of pain intensity and pain relief[14] and a report of volunteered or observed side effects. Pharmacodynamic observations were continued as indicated above unless the patient requested remedication with the current analgesic agent (Table I). Pharmacokinetic samples were collected for the duration of the study, after which plasma was separated from blood cells and plasma samples were frozen at −20° C until they were analyzed.

Analytic methods. Plasma methadone concentrations were determined by the radioimmunoassay (RIA) method of Ling et al.[15] The lower limit of sensitivity was 0.003 μg/ml and the interassay coefficient of variation was 9.5%. Neither the metabolites of methadone nor commonly used analgesics, including those opioids the study patients had been receiving (Table I), interfered with the methadone RIA.

Pharmacokinetic-pharmacodynamic analysis. A compartmental model approach was used to characterize the pharmacokinetics and pharmacodynamics of methadone. The pharmacokinetic-pharmacodynamic model, proposed by Sheiner et al.,[16] postulates a hypothetical effect compartment, the dynamics of which are adjusted to reflect the temporal dynamics of the drug effect. The plasma methadone concentration–time profile was modeled by use of a two-compartment model with zero-order input (Appendix, equation 1). The hypothetical effect compartment is modeled as an additional exponential function (Appendix, equation 2). For the pharmacokinetic-pharmacodynamic model, the central compartment drives the effect compartment and the rate constant for drug removal from the effect compartment (k_{e0}) will characterize the temporal aspects of equilibration between the drug concentration in plasma (C) and the effect site. Therefore k_{e0} is a model parameter that will characterize the degree of hysteresis (i.e., any delay between measured plasma drug concentration and the observed effect).[12,16,17]

The data of each patient were fit with a pharmacokinetic-pharmacodynamic model that assumes instantaneous equilibration of the effect site with plasma methadone concentrations (Appendix, equation 1) and the more complex model that includes a k_{e0} term that causes a temporal relationship between plasma

Table II. Methadone infusions: individual predrug (baseline) values for pain intensity (VAS) and sedation intensity (VAS) and peak effect values for pain intensity (VAS), pain relief (VAS), and sedation intensity (VAS)

	Pain intensity (VAS)		*Pain relief (VAS)*	*Sedation intensity (VAS)*	
Pt. No.	*Predrug*	*Peak effect*	*(Peak effect)*	*Predrug*	*Peak effect*
1	1.00	0.25	0.71	0.05	1.00
2	0.90	0.20	0.75	0.00	0.38
3	0.47	0.65*	0.18*	0.00	1.00
4	0.50	0.20	0.78	0.49	0.50*
5	0.91	0.02	0.95	0.20	1.00
6	0.77	0.22	0.78	0.00	0.83
7	0.54	0.08	0.74	0.14	0.71
8	0.78	0.41	0.47	0.11	0.70
9	0.72	0.09	0.93	0.57	0.92
10	0.85	0.35	0.70	0.00	1.00
11	0.74	0.02	0.99	0.08	0.93
12	1.00	0.07	0.90	0.00	0.25
13	0.83	0.34	0.78	0.19	0.23*
14	0.84	0.32	0.69	0.24	0.64
15	0.53	0.06	0.94	0.07	0.59
Mean ± SD	0.76 ± 0.18	0.22 ± 0.17	0.75 ± 0.21	0.14 ± 0.18	0.71 ± 0.27

For the VAS scales, 0.00 = least possible pain, no relief of pain, or alert, and 1.00 = worst possible pain, complete relief of pain, or very sleepy.
*Insufficient or no data for pharmacokinetic-pharmacodynamic model.

methadone concentration and the effect site (Appendix, equation 2). Computationally, Appendix equation 1 was achieved by setting k_{e0} equivalent to infinity (numerically = 100). The sigmoid E_{max} model was selected for simplicity and the fact that analgesic and sedative effects of opioids such as methadone are mediated by specific drug-receptor interactions (Appendix, equation 3). This model predicts a maximal effect when drug concentration is above a specified value, as well as no effect when no drug is present. The theoretical aspects of effect compartment models are discussed by Sheiner et al.,[16] Colburn,[12] and Holford and Sheiner.[17] This model may be oversimplified in that there may be a baseline effect before administration of the test opioid.[18] Nevertheless, this model was selected in the context of the current study design and limited baseline response measures.

For the pharmacokinetic-pharmacodynamic analysis, each patient's pain relief (VAS) scores were expressed as the fraction from 0 to 1.0 of the maximum effect obtainable by dividing the value indicated by the patient on the 100 mm scale reading by 100. The predrug sedation (VAS) score in millimeters (Table II) was subtracted from each subsequent observation and this value was divided by the value obtained when the baseline score was subtracted from 100 mm to yield a sedation intensity difference (VAS) score expressed as the fraction of maximum effect. The pharmacokinetic-pharmacodynamic parameters were obtained by use of the iterative weighted, nonlinear least-squares regression program, NONLIN 84.[19]

RESULTS

All patients reported moderate to severe pain at the start of the study. The mean preinfusion pain intensity (VAS) score was 76 mm (± 18 SD) where the maximum possible score is 100 mm (Table II) and 2.7 (±0.5 SD) on the pain intensity categorical scale where 3.0 is the maximum possible score (not shown). The pain sites included the leg (four patients), arm (three patients), back (two patients), flank (two patients), and sacrum, chest, abdomen, and back (one patient each). The pain was continuous in 13 patients and intermittent (induced by movement) in two patients. In six patients a component of the pain appeared to be attributable to nerve injury.

Decreases in pain intensity (peak effect) were correlated closely with increases in pain relief scores (Table II). The peak effect for decreased pain intensity (VAS) and increased pain relief (VAS) occurred at the same time for each patient except for patients 2 and 8. Thirteen of the 15 patients achieved pain relief of 50% or greater at least once during the study (Table II). One of the two patients who failed to achieve 50% or greater

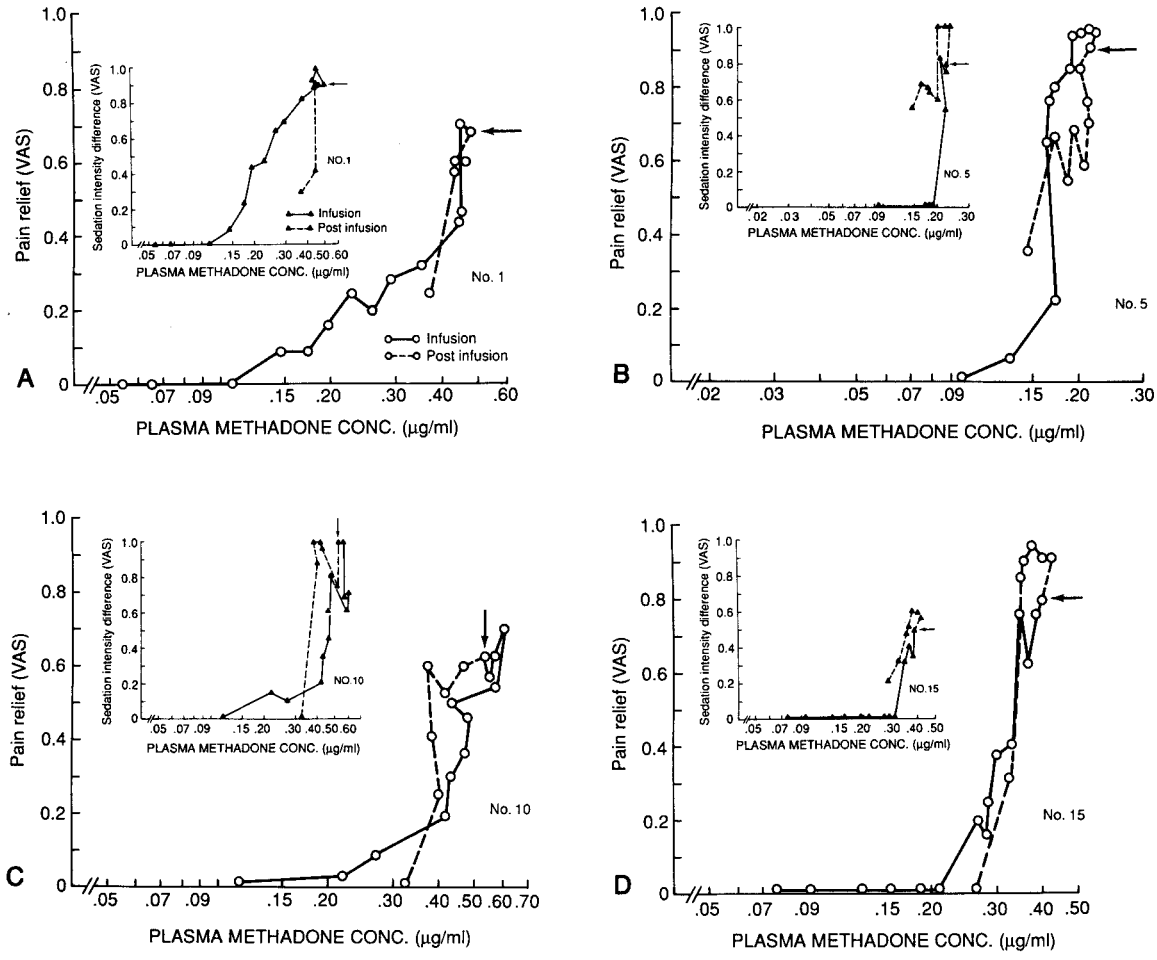

Fig. 1. Plasma methadone concentration–effect curves for study patient 1 **(A)**, patient 5 **(B)**, patient 10 **(C)**, and patient 15 **(D)**. The *solid line* indicates data obtained during the infusion; the *arrow* indicates that the infusion was discontinued, and the *broken line* indicates data collected during the postinfusion phase. The pain relief (VAS) *(open circles)* data for patients 1 and 5 were fit with a pharmacokinetic-pharmacodynamic model without a k_{e0} term (Appendix, equation 1), whereas the pain relief (VAS) *(open circles)* data for patients 10 and 15 required the pharmacokinetic-pharmacodynamic model that included a k_{e0} term (Appendix, equation 2). *Inserts* show the concurrently determined sedation intensity difference data for each patient. (See Table III for pharmacodynamic parameter estimates for these patients.)

pain relief (patient 8) had movement-induced pain in the back, whereas the other patient (patient 3) reported an increase in pain during the infusion (Table II). No reason could be discovered for the failure of this patient to achieve analgesia. No association was observed between a neuropathic component to the pain and the ability of a methadone infusion to provide 50% or greater pain relief. Thirteen of the 15 patients reported an increase in the sedation intensity (VAS) scale, although only 11 patients verbally reported sleepy-drowsy as a side effect to the nurse observer. Fourteen of the patients also reported at least one side effect, with sleepy-drowsy the most common (11 patients). The other adverse effects were also typical of the opioids,[1] and none was of sufficient severity that either the patient, nurse observer, or physician found it necessary to discontinue the study.

Fig. 1 presents examples of the data obtained from four of the study patients. The main panel for each patient shows that analgesia as measured by pain relief

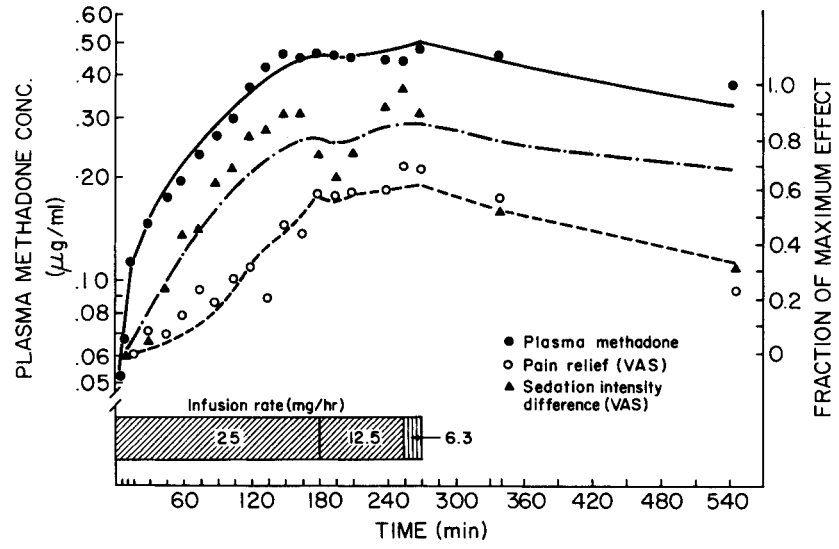

Fig. 2. Plasma concentration–time profiles and concurrent pharmacodynamic effect–time profiles during and after an intravenous infusion of methadone hydrochloride was discontinued (at 270 minutes) in patient 1. *Solid circles* are the observed plasma methadone concentrations; *solid triangles* are the sedation intensity difference (VAS) scores; *open circles* are the pain relief (VAS) scores. *Lines* represent the theoretic lines obtained by fitted data with the pharmacokinetic-pharmacodynamic model (Appendix, equation 1).

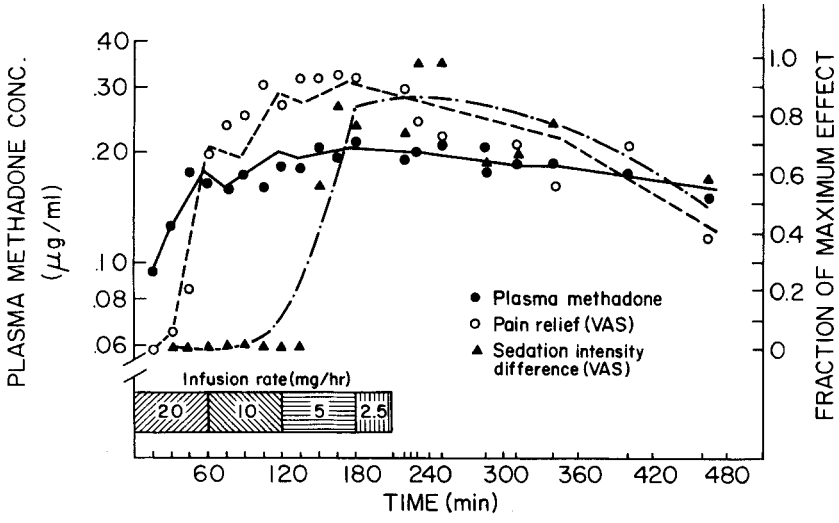

Fig. 3. Plasma concentration–time profiles and concurrent pharmacodynamic effect–time profiles during and after an intravenous infusion of methadone hydrochloride was discontinued (at 210 minutes) in patient 5. *Solid circles* are the observed plasma methadone concentrations; *solid triangles* are the sedation intensity difference (VAS) scores; *open circles* are the pain relief (VAS) scores. *Lines* represent the theoretic lines obtained by fitted data with the pharmacokinetic-pharmacodynamic model (Appendix, equation 1).

Table III. Methadone infusions: pharmacodynamic parameter estimates for pain relief (VAS) and sedation intensity difference (VAS)

	$C_{ss}50$ (μg/ml)		γ		k_{e0}	
Pt. No.	*Pain relief*	*Sedation*	*Pain relief*	*Sedation*	*Pain relief*	*Sedation*
1	0.419	0.265	3.8	2.8	—*	—
2	0.433	0.632	1.5	3.9	0.042	—
3	None†	0.135	None	7.6	None	0.009
4	0.432	None	0.5	None	0.014	None
5	0.167	0.172	11.5	16.8	—	0.019
6	0.234	0.207	2.0	1.1	—	—
7	0.391	0.292	2.9	17.9	0.046	0.007
8	0.572	0.601	1.7	1.2	—	—
9	0.233	0.180	5.7	1.4	—	—
10	0.517	0.382	5.0	5.9	0.148	0.025
11	0.053	0.049	11.4	4.6	—	—
12	0.248	0.717	3.3	3.8	0.021	0.239
13	0.412	None	2.4	None	0.210	None
14	0.604	0.370	0.8	3.4	—	—
15	0.315	0.369	9.5	4.8	0.051	0.019
Mean ± SD	0.359 ± 0.158	0.336 ± 0.205	4.4 ± 3.8	5.8 ± 5.4		

*Data fit to pharmacokinetic-pharmacodynamic model without k_{e0} (Appendix, equation 1).
†No effect data.

(VAS) increased as the plasma methadone concentration increased during the infusion. During the postinfusion phase, the analgesic effect decreased as plasma methadone concentration declined. No evidence for counterclockwise hysteresis was seen with the analgesic data for patients 1 or 5 (i.e., the concentration-effect relationship remained nearly the same after the infusion was discontinued as it was during the infusion). These patient data can be fit with the pharmacokinetic-pharmacodynamic model that does not include a k_{e0} term (Appendix, equation 1). In contrast, the analgesic data for patients 10 and 15 show some evidence of a lag, and these data are best fit with a pharmacokinetic-pharmacodynamic model that includes a k_{e0} term (Appendix, equation 2). The inserts in each panel show the concurrently determined sedation effect. Like analgesia, the sedation effect increases and decreases as a function of increasing plasma methadone concentrations. The sedation data for patient 1 did not show a counterclockwise hysteresis, whereas the sedation data for patients 5, 10, and 15 did require the pharmacokinetic-pharmacodynamic model with the k_{e0} term to accommodate a lag (Fig. 1).

Figs. 2 and 3 show examples (patients 1 and 5) of the observed concentration-time profiles, the concurrent pharmacodynamic time-effect profile for analgesia (pain relief VAS) and sedation (VAS), and the theoretic curves generated from computer-estimated parameters.

The pharmacokinetic parameter estimates obtained from data such as that illustrated in Figs. 2 and 3 include a mean $t_{1/2\alpha}$ of 11.6 ± 10.4 (SD) minutes, a mean $t_{1/2\beta}$ of 15.4 ± 10.6 (SD) hours, and a harmonic mean clearance of 110 ml/min.

Figs. 2 and 3 illustrate a parallel increase in the plasma methadone concentration and analgesia (pain relief, VAS) during the infusion. For most patients, including patient 1 (Fig. 2), analgesia and sedation scores rose together as plasma methadone levels rose; in some patients, including patient 5 (Fig. 2), sedation scores lagged behind the rising plasma levels. When the initial infusion rate was decremented, plasma methadone concentrations remained fairly constant, as did corresponding pain relief and sedation scores (Figs. 1 and 2). As expected from such a low-clearance drug, only a small decline in plasma methadone concentration occurred in the period immediately after discontinuation of the infusion. During this immediate postinfusion phase, the analgesic and sedative effects observed during the infusion declined (Fig. 1).

Table III presents the pharmacodynamic parameter estimates obtained from the data set of each patient. One patient reported sedation without measurable pain relief and two patients had pain relief without sedation. The remaining 12 patients reported both pain relief and sedation (Figs. 1, 2, and 3). The values for 50% of maximum effect ($C_{ss}50$) for pain relief varied 10-fold

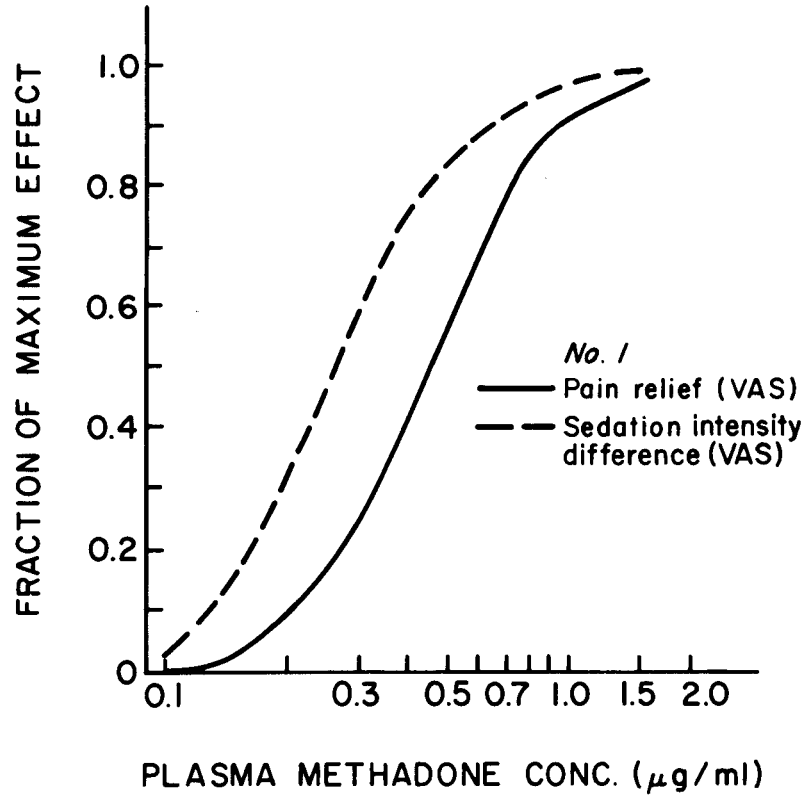

Fig. 4. Simulated plasma methadone concentration–effect curves for pain relief (VAS) and sedation intensity difference (VAS) for patient 1. The *curves* were generated by use of the sigmoid E_{max} equation (Appendix, equation 3); the pharmacodynamic constants for this patient are given in Table III.

(from 0.053 to 0.604 μg/ml), whereas $C_{SS}50$ estimates for sedation varied 15-fold (from 0.049 to 0.717 μg/ml). The mean concentrations for $C_{SS}50$ for pain relief (0.359 ± 0.158 μg/ml [SD]) and sedation (0.336 ± 0.205 μg/ml [SD]) were not significantly different. Also, the mean values for γ, the slope function (4.4 ± 3.8 [SD] for pain relief and 5.8 ± 5.4 [SD] for sedation), were not significantly different.

For a majority of patients the pain relief and sedation data did not require a pharmacokinetic-pharmacodynamic model that included a lag. The analysis of the data sets of these patients with a k_{e0} equivalent to infinity yielded virtually the same parameter estimates for $C_{SS}50$ and γ (Table III) as the pharmacokinetic-pharmacodynamic model that included a finite k_{e0} parameter. The remaining patients' data sets required estimation of k_{e0} and these values are given in Table III.

Figs. 4 and 5 show examples (patients 1 and 5) of simulated plasma methadone concentration–effect curves generated from the pharmacodynamic parameters obtained from the pharmacokinetic-pharmacodynamic model (Table III). For patient 1 (Fig. 2), an increase in the plasma methadone concentration above 0.1 μg/ml is accompanied by a parallel increase in analgesia and sedation, with the curve for sedation to the left of that for pain relief. Fig. 5 shows that the concentration-effect curves for patient 5 are virtually superimposable (Fig. 1).

DISCUSSION

The pharmacokinetic parameter estimates we obtained are consistent with those of previous studies of methadone pharmacokinetics in patients with cancer and chronic pain.[3] They describe methadone as a drug with rapid and extensive distribution and a slow rate of elimination. As we and others have reported previously,[3,10] the interindividual variation in terminal elimination $t_{1/2}$ values and clearance was large (approximately 20-fold). Methadone can be classified as a low hepatic-extraction drug, and the sources of interindividual variation, which include pH-dependent renal elimination, plasma protein binding, and hepatic extraction, are discussed elsewhere.[3,8,10]

In addition to pharmacokinetic factors, a variety of psychological factors (e.g., expectation, suggestion, and mood) can modify analgesic effectiveness by altering the reaction to pain. In this and in previous studies we have shown that, under our study conditions, changes in plasma methadone or morphine concentrations are correlated directly with changes in pain, pain relief, or sedation measured by use of VAS or categorical scales.[2,3] Thus pharmacokinetic factors appear to be the predominant determinant of the intensity of opioid effects in these studies (Figs. 1, 2, and 3).

In attempting to define the contribution of pharmacokinetic factors to the analgesic and sedative effects of methadone, a more precise definition of the relationship between a change in measurable drug concentration in plasma or blood can be achieved by linking the observed pharmacokinetics and pharmacodynamics. In this way the concentration-time profile predicted by a pharmacokinetic model can be related to the drug concentration at the effect site that is not directly measurable. To accomplish this objective, we have analyzed our infusion data using a combined pharmacokinetic-pharmacodynamic model applied previously by us to describe the pharmacokinetic-pharmacodynamic relationships of methadone after an intravenous bolus[3] and by others to compare the electroencephalographic effects of the opioids fentanyl and alfentanil[20] in patients undergoing surgery. One form of the pharmacokinetic-pharmacodynamic model[12,16] estimates a time-dependent lag of effect behind a change in plasma drug concentration (hysteresis). After intravenous bolus administration of methadone, we found a short lag time (expressed as $t_{1/2}$ k_{e0}) of 3.6 minutes.[3] Therefore we conclude that plasma methadone concentrations during and after constant-rate infusion rapidly equilibrate with central nervous system opioid receptors with little measurable lag and therefore most patients do not require a pharmacokinetic-pharmacodynamic model that includes the k_{e0} parameter. These differences between the previous bolus study and the current infusion study support the premise that observed effects are a function of drug input rate. These observations are also consistent with the high brain-to-plasma-partition coefficient calculated for methadone from animal studies.[21] The rapid equilibration of methadone suggests that efficient response control can be achieved with a methadone infusion because changes in analgesia or sedation in the therapeutic range closely parallel changes in methadone plasma concentration.

The pharmacodynamic estimates provided by the model include $C_{ss}50$, which reflects the intrinsic sensitivity of the patient to the drug effect, and γ.

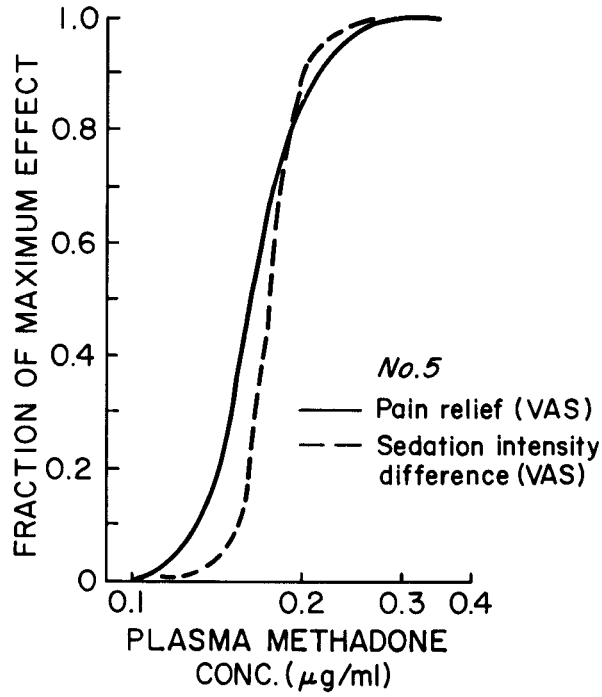

Fig. 5. Simulated plasma methadone concentration–effect curves for pain relief (VAS) and sedation intensity difference (VAS) for patient 5. The *curves* were generated by use of the sigmoid E_{max} equation (Appendix, equation 3); the pharmacodynamic constants for this patient are given in Table III.

From these parameters a complete concentration-effect curve can be generated from experimentally determined data that may be much more limited. Within the limitations discussed below, this analysis provides a powerful method for obtaining quantitative data and increasing our understanding of pharmacokinetic-pharmacodynamic relationships.

The intrinsic sensitivity, as estimated by $C_{ss}50$, was measurable for pain relief in all but one patient and for sedation in all but two patients (Table III). The most notable finding in the present study with respect to these parameters was the large interindividual variation for both pain relief and sedation $C_{ss}50$ values and the close correspondence between these two effects. The individual $C_{ss}50$ values for pain relief and sedation were similar for 8 of the 12 patients who reported data for both effects concurrently. These studies were designed to adjust drug delivery and plasma methadone concentrations to patient reports of pain relief rather than titrated to a given intensity of sedation. Thus the pharmacodynamic parameters obtained for sedation might be considered to be less precise. Nevertheless, there appears to be a close correspondence between the $C_{ss}50$ values for pain relief and sedation, and the mean values

for these two effects are indistinguishable (Table III). These pharmacodynamic results are consistent with those of our previous study, which found a nearly 30-fold variation in $C_{ss}50$ for analgesia and a mean $C_{ss}50$ of 0.290 μg/ml for methadone in patients with pain.[3] As in the previous study, no correlation was found between previous opioid experience and $C_{ss}50$ for pain relief or sedation. This lack of correlation may reflect the relatively small number of study patients or the different degrees of cross-tolerance to methadone resulting from the different opioids the patients were receiving before the study (Table I).

As with the $C_{ss}50$ values, the mean estimates for γ were similar: 4.4 for pain relief and 5.8 for sedation (Table III). A γ value of 4 predicts that the intensity of the analgesic effect will change from a value of 0.1 (10% of maximum) to 0.9 (90% of maximum) in response to a threefold increase in plasma methadone concentrations. Thus, our data demonstrate a steep concentration-effect relationship for both pain relief and sedation in most patients administered methadone for pain. Steep concentration-effect relationships have also been reported for the analgesic effects of meperidine[4] and the electroencephalographic effects of fentanyl and alfentanil.[20,22]

As illustrated in Fig. 5 and Table III, nearly superimposable concentration-effect curves for pain relief and sedation were commonly observed. This result suggests, but does not prove, that the same or similar effect sites (i.e., opioid receptors) may mediate both the pain relief and sedation produced by methadone. The current pharmacological classification of opioid receptors is based on the studies of Martin et al.[23] in dogs that have undergone spinal transections. The μ receptor is thought to mediate supraspinal analgesia, whereas the κ receptor mediates both spinal analgesia and sedation.[24] Morphine and methadone are considered to have agonist actions at μ and, to a lesser degree, κ receptors.[24,25] However, without the use of specific opioid antagonists, an approach not acceptable in tolerant patients with pain, it is not possible to characterize the receptor sites mediating pain relief or sedation in these patients. However, pharmacokinetic-pharmacodynamic modeling may provide an indirect method of evaluating these issues in patients with pain as a result of cancer.

The sedative effects of an opioid such as methadone are commonly seen in patients with pain and in normal subjects, and these sedative effects can limit the use of opioids in the management of acute and chronic pain.[1,26] Our studies present a quantitative demonstration of a concentration-effect relationship of the analgesic and sedative effects of methadone. Furthermore, concentration-effect relationships such as those illustrated in Figs. 1 and 4 suggest that at least some patients are relatively more sensitive to the sedative than to the analgesic effects. However, it is important to recognize that the acceptability of sedation as a side effect of analgesia varies widely, with some patients willing to accept a high degree of sedation to obtain pain relief whereas others report that any degree of sedation interferes with their ability to function and therefore is unacceptable.[1,26] Clinical experience suggests that, in patients in whom the sedative effect is limiting, switching to another opioid may provide adequate analgesia with less sedation.[1] The pharmacokinetic-pharmacodynamic approach we have used in this study could be used to evaluate quantitatively the analgesic and sedative effects of commonly used analgesic agents in the same patients and thereby provide a pharmacological basis for this clinical impression.

The collection of pharmacokinetic and pharmacodynamic data during both the infusion and the washout provides the opportunity to determine whether measurable tolerance occurred during the infusion. Simulations with the pharmacokinetic-pharmacodynamic model indicate that an increase in the $C_{ss}50$ (i.e., tolerance) during the infusion will result in a clockwise hysteresis when effect is plotted as a function of plasma methadone concentration during the infusion and washout (Inturrisi CE, et al. September 1988. Unpublished data.). Concentration-effect plots show little evidence of this type of hysteresis for the analgesic or sedative effects for most patients. However, some indication of clockwise hysteresis is seen with sedation for patient 1 and with pain relief for patient 5 (Fig. 1). If the concentration-effect relationship of methadone was associated with a significant degree of lag (counterclockwise hysteresis), the development of some degree of tolerance could be manifest as a shift from counterclockwise to a lesser or nonmeasurable hysteresis. However, the pharmacokinetic-pharmacodynamic relationships we have observed after either intravenous bolus[3] or infusion do not demonstrate this type of hysteresis. Although tolerance may occur rapidly in animals exposed to high doses of opioids,[27] the rate and degree of tolerance in patients with pain who are receiving opioids can be quite variable.[28] Our findings suggest that test infusions of opioids may be used safely to efficiently evaluate the utility of methadone for a particular patient without the fear of developing clinically significant tolerance during the test procedures.

Furthermore, we have found that a patient who participated in the intravenous bolus study on two occasions separated by 2½ months and continued with a stable dosage of opioid during this period demonstrated no change in the estimate of $C_{ss}50$ for analgesia.[3] These observations suggest that the pharmacokinetic-pharmacodynamic model may be useful in quantitating the development of tolerance after intervals of conventional opioid treatment.

Both the utility and validity of the pharmacokinetic and pharmacodynamic parameter estimates obtained in pharmacokinetic-pharmacodynamic studies require that the methods used for both the pharmacokinetic and pharmacodynamic measures be specific and sensitive and, more important, predictive of alternate drug delivery rates or regimens. This is accomplished more easily with the analytic methods used for the pharmacokinetic observations than for the methods used to obtain pharmacodynamic observations, for which indirect or subjective indexes of effect are often employed. Thus it is important to consider how the pharmacodynamic data were collected and what assumptions influence their interpretation. It is well recognized that the analgesic activity of drugs in patients with pain as a result of disease or trauma must rely on subjective reports rather than so-called objective indexes of pain.[14,29] Measurements of subjective responses, such as pain and pain relief, are subject to both pharmacokinetic and psychological variables. Pharmacokinetic variation is evaluated directly in the design of the pharmacokinetic-pharmacodynamic studies, whereas psychological variation is not assessed directly. A method has been developed for the clinical evaluation of analgesic drugs that involves the use of categorical (descriptor) and VAS scales.[14,29] Although the ordinal values of the categorical scales may not be related linearly, they have generally been treated as equally spaced ordinal data by investigators in the field.[14] Regression of ordinal and VAS measures of changes in pain and pain relief after the administration of analgesic drugs demonstrates extremely high correlations.[14] In general, VAS scales have been found to be reliable indexes, acceptable to the patients, and more sensitive to changes than categorical scales.[14] Both categorical and VAS scales have been validated empirically in studies estimating relative analgesic potency.[7,14,29] In our infusion studies we have not attempted to employ more than one analgesic drug in the same study and therefore we have not obtained direct relative estimates of analgesic response. Furthermore, Wallenstein[14] has shown that the pain descriptors that have a power function relationship to the intensity of the stimulus in experimental pain bear a similar relationship to the VAS scales used in the assignment of clinical pain, where the intensity of the stimulus cannot be measured directly. These observations serve as an indirect validation of the scales used in this study. We have assumed that each patient is capable of a maximum pain relief or sedation response equal to 1.0, although only a few patients actually achieved this level of effect (Table III). Indeed, our decremented infusion schedule is designed to limit data collection above 75% (0.75) of maximum pain relief (VAS), because further increases in plasma drug levels once the maximum effect (1.0) has been achieved greatly increase the risk of adverse effects without a gain in information about pharmacokinetic-pharmacodynamic relationships. Not attaining a maximal effect can cause some imprecision in our estimate of fractional effect, as well as other pharmacodynamic parameter values. However, adequate characterization of the 0.00 to 0.75 portion of the effect curve (Table II) should improve our ability to estimate these parameter values precisely.

The presence of endogenous analgesic agents and previous exogenously administered analgesic agents may influence the intensity of pain at the start of the infusion.[18] The initial pain intensity may in turn influence both the plasma drug concentration required to achieve a given fraction of maximum effect and the rate at which that level of effect is achieved. Therefore the pharmacodynamic parameters we obtained, $C_{ss}50$ and γ, cannot be considered absolute constants but rather as apparent parameters that reflect the initial or baseline conditions. In our studies each patient reported moderate to severe pain before the infusion was initiated, and it is assumed that our pharmacodynamic parameter estimates reflect this initial condition.

In this study we demonstrated that data obtained during an intravenous infusion of an opioid to patients with clinical pain can be analyzed with a pharmacokinetic-pharmacodynamic model. We do not yet know the extent to which the individual pharmacodynamic parameter estimates can be used to predict therapeutic success in the routine clinical management of cancer pain with methadone. However, this approach has increased our understanding of pharmacokinetic-pharmacodynamic relationships, a first step toward the development of pharmacologically based guidelines for the use of opioids in the management of cancer pain.

We thank R. Houde and S. Wallenstein for their helpful discussions and insightful comments.

APPENDIX

A pharmacokinetic model for an intravenous infusion. The time course of drug concentration in the sampled central (plasma) compartment (C) using a two-compartment model with zero-order input is given by:

$$C = \frac{k_0}{V_C}\left[\frac{(k_{21} - \alpha)}{\alpha(\beta - \alpha)}(1 - e^{-\alpha T})\, e^{-\alpha t'} + \frac{(k_{21} - \beta)}{\beta(\alpha - \beta)}(1 - e^{-\beta T})\, e^{-\beta t'}\right] \quad (1)$$

in which k_0 is infusion rate, V_C is volume of central (plasma) compartment, k_{21} is the transfer rate constant from shallow peripheral to central compartment, α is the fastest hybrid rate constant, β is the slowest hybrid rate constant, T is the time that infusion stops, and t' is the time after infusion stops.

Equation 1 multiplied by V_C yields the hypothetical amount of drug in the effect compartment (Ae) when equilibrium is instantaneous. In contrast, when equilibrium is not instantaneous, Ae is defined as:

$$Ae = k_0 k_{e0}\left[\frac{(k_{21} - \alpha)}{\alpha(\beta - \alpha)(k_{e0} - \alpha)}(1 - e^{-\alpha T})\, e^{-\alpha t'} + \frac{(k_{21} - \beta)}{\beta(\alpha - \beta)(k_{e0} - \beta)}(1 - e^{-\beta T'})\, e^{-\beta t'} + \frac{(k_{21} - k_{e0})}{k_{e0}(\alpha - k_{e0})(\beta - k_{e0})}(1 - e^{-k_{e0} T})\, e^{-k_{e0} t'}\right] \quad (2)$$

in which k_{e0} is the elimination rate constant from the hypothetical effect compartment.

Equations 1 and 2 can be used to calculate concentrations or amounts during a decrementing infusion rate (see Methods section and Figs. 2 and 3) by use of the superposition principle.[30]

Transformation of Ae to fractional pharmacologic effect (FR) is accomplished with the following equation:

$$FR = \frac{C^\gamma}{C_{ss}50^\gamma + C^\gamma} \text{ or } \frac{(Ae/V_C)^\gamma}{C_{ss}50^\gamma + (Ae/V_C)^\gamma} \quad (3)$$

in which γ is the power factor for the Hill equation, which determines the sigmoidicity of the concentration-effect curve and $C_{ss}50$ is the steady-state concentration of drug in the driving pharmacokinetic compartment when the observed effect is 50% of the maximum.

References

1. Foley KM, Inturrisi CE. Analgesic drug therapy in cancer pain: principles and practice. Med Clin North Am 1987;71:207-32.
2. Inturrisi CE, Colburn WA. Application of pharmacokinetic-pharmacodynamic modeling to analgesia. In: Foley KM, Inturrisi CE, eds. Advances in pain research and therapy, vol 8. New York: Raven Press, 1986:439-50.
3. Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM. Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. CLIN PHARMACOL THER 1987;41:392-401.
4. Austin KL, Stapleton JV, Mather LE. Relationship between blood meperidine concentrations and analgesic response: a preliminary report. Anesthesiology 1980;53:460-6.
5. Gourlay GK, Willis RJ, Wilson PR. Postoperative pain control with methadone: influence of supplementary methadone doses and blood concentration-response relationships. Anesthesiology 1984;61:19-26.
6. Gourlay GK, Wilson PR, Glynn CJ. Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology 1982;57:458-67.
7. Beaver WT, Wallenstein SL, Houde RW, Rogers A. A clinical comparison of the analgesic effects of methadone and morphine administered intramuscularly, and of orally and parenterally administered methadone. CLIN PHARMACOL THER 1967;8:415-26.
8. Inturrisi CE. Disposition of narcotics and narcotic antagonists. Ann NY Acad Sci 1976;281:273-88.
9. Nilsson MI, Meresaar U, Anggard E. Clinical pharmacokinetics of methadone. Acta Anaesthesiol Scand Suppl 1982;74:66-9.
10. Plummer JL, Gourlay GK, Cherry DA, Cousins MJ. Estimation of methadone clearance: application in the management of cancer pain. Pain 1988;33:313-22.
11. Inturrisi CE, Verebely K. Disposition of methadone in man after a single oral dose. CLIN PHARMACOL THER 1972;13:923-30.
12. Colburn WA. Simultaneous pharmacokinetic and pharmacodynamic modeling. J Pharmacokinet Biopharm 1981;9:367-88.
13. Shand DG, Desjardins RE, Bjornsson TD, Hammill SC, Pritchett ELC. The method of separate exponentials: a simple aid to devising intravenous drug-loading regimens. CLIN PHARMACOL THER 1981;29:542-7.
14. Wallenstein SL. Scaling clinical pain and pain relief. In: Bromm B, ed. Pain measurement in man: neurophysiological correlates of pain. New York: Elsevier Science Publishers, 1984:389-96.
15. Ling GSF, Umans JG, Inturrisi CE. Methadone: radioimmunoassay and pharmacokinetics in the rat. J Pharmacol Exp Ther 1981;217:147-51.
16. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to *d*-tubocurarine. CLIN PHARMACOL THER 1979;25:358-71.
17. Holford NHG, Sheiner LB. Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokinet 1981;6:429-53.
18. Colburn WA, Gibson DM. Endogenous agonists and

pharmacokinetic/pharmacodynamic modeling of baseline effects in pharmacokinetics and pharmacodynamics. In: Kroboth PD, Smith RB, Juhl RP, eds. Pharmacokinetics and pharmacodynamics, vol 2. Current problems, potential solutions. Cincinnati: Harvey Whitney, 1988: 167-84.

19. Statistical Consultants, Inc. PCNONLIN and NONLIN84: software for the statistical analysis of nonlinear models. Am Stat 1986;40:52.
20. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 1985;62:234-41.
21. Bullingham RES, McQuay HJ, Moore RA. Extradural and intrathecal narcotics. In: Atkinson RS, Hewer CL, eds. Recent advances in anaesthesia and analgesia. New York: Churchill Livingstone, 1982:141-56.
22. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 1987;240:159-66.
23. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther 1976;197:517-32.
24. Jaffe JH, Martin WR. Opioid analgesics. In: Goodman LS, Gilman AG, eds. Goodman and Gilman's the pharmacological basis of therapeutics. 7th ed. New York: Macmillian, 1985:491-531.
25. Takemori AE, Ikeda M, Portoghese PS. The μ, κ and δ properties of various opioid agonists. Eur J Pharmacol 1986;123:357-61.
26. Inturrisi CE. Clinical pharmacology of opioid analgesics. Anesthesiol Clin North Am 1989;7:33-49.
27. Ling GSF, Tappe NS, Inturrisi CE. Methadone-induced physical dependence in the rat. Life Sci 1984;34:683-90.
28. Kanner RM, Foley KM. Patterns of narcotic drug use in a cancer pain clinic. Ann NY Acad Sci 1981;362: 161-72.
29. Houde RW, Wallenstein SL, Beaver WT. Clinical measurement of pain. In: deStevens G, ed. Analgetics. New York: Academic Press, 1965:75-127.
30. Gibaldi M, Perrier D. Prediction of drug concentrations on multiple dosing using the principle of superposition. In: Swarbrick J, ed. Pharmacokinetics, 2nd ed. New York: Marcel Dekker, 1981:451-7.