Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain

Concentrations of methadone in plasma, estimates of pain relief, and pupillary size were determined after a single intravenous dose (10 to 30 mg) of methadone hydrochloride to eight patients with chronic pain, five of whom had cancer. The pharmacokinetic parameter estimates reveal rapid and extensive distribution (V_{area}) and a slow apparent elimination half-life ($t_{1/2}$) (mean V_{area} = 3.59 L/kg and harmonic mean $t_{1/2}$ = 23 hours). The harmonic mean blood clearance is 106 ml/min, the harmonic mean renal clearance is 3.9 ml/min, the mean hepatic extraction ratio is 0.089, and plasma protein binding is 86% to 89%. These results suggest that only the free (unbound) fraction of methadone present in blood is extracted by the liver and that methadone can be classified as a low (hepatic)-extraction drug. The data were fit to a pharmacokinetic-pharmacodynamic model to obtain estimates of the steady-state plasma methadone concentration required to produce 50% of the maximum pain relief. This value varied from 0.04 to 1.13 μg/ml (mean = 0.29 μg/ml). These results indicate substantial interindividual variation in the relationship between changes in plasma methadone concentration and analgesia in patients with chronic pain receiving opioids. A pharmacokinetic-pharmacodynamic model may be useful for the individualization of analgesic dosage and therefore the optimization of pain management in patients with chronic pain. (CLIN PHARMACOL THER 1987;41:392-401.)

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Methadone is a synthetic opioid analgesic nearly equipotent with morphine when both are evaluated after intramuscular administration to patients with cancer.[1] Its favorable oral-to-parenteral potency ratio has led to its use by the oral route for chronic pain caused by cancer.[1,2] Attempts to develop guidelines for the use of methadone in chronic pain are limited in part by an inadequate knowledge of pharmacokinetic-pharmacodynamic (PK-PD) relationships. Analgesic studies employing single oral doses of 15 or 30 mg have concluded that methadone's average duration of analgesia is 4 to 6 hours,[1] whereas Gourlay et al.[3] report that an intravenous dose of 20 mg provides postoperative pain relief with a median duration of 27 hours. In normal subjects the miotic effect, measures of respiratory depression, and antidiuretic effect persist for at least 24 hours after an oral dose of 15 mg.[4,5] Methadone is biotransformed via *N*-demethylation reactions to apparently inactive metabolites.[6] Pharmacokinetic studies in normal individuals,[4] postoperative patients,[3,7] and methadone-maintenance patients[6,8] indicate that methadone has an elimination half-life ($t_{1/2}$) that varies from 13 to 58 hours. Thus the potential for toxic accumulation exists when methadone is given for pain at intervals of 4 to 6 hours.[9] These issues are of particular importance in the management of patients with chronic pain for whom pharmacokinetic data are limited and the decision on whether to use methadone often arises.

The purpose of this report is to describe the simultaneously determined pharmacokinetics and pharmacodynamics of methadone after intravenous administration to patients with chronic pain, some of whom had cancer. These data are analyzed by use of a

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Table I. Clinical characteristics of study patients

Pt. No.	*Sex*	*Age (yr)*	*Weight (kg)*	*Diagnosis*	*Opioid dosage (mg)*			*Prior opioid experience**
1	F	62	39.7	Adenocarcinoma, ovarian	Morphine	12 IV	q.3.h.	192
2-A	M	39	64.3	Multiple myeloma	Morphine	60 IM	q.4.h.	720
2-B†	M	40	54.4	—	Morphine	40 IM	q.3½.h.	549
3	F	56	55.7	Metastatic adenocarcinoma, breast	Morphine	15 IM	q.i.d.	120
4-A	M	48	75.0	Osteoporosis secondary to steroids	Levorphanol	8 PO	t.i.d.	120
4-B†	M	48	75.0	—	Levorphanol	8 PO	t.i.d.	120
5	F	67	44.7	Facial pain secondary to cranial chordoma	Meperidine	75 IM	q.i.d.	80
6-A	M	31	96.4	Chronic postsurgical pain	Meperidine	100 PO	q.4.h.	40
6-B†	M	31	96.4	—	Meperidine	100 PO	q.4.h.	40
7	F	46	37.6	Metastatic adenocarcinoma, breast	Hydromorphone	8 PO	q.i.d.	85
8	F	49	115.0	Sacral chordoma	Oxycodone	10 PO	q.3½.h.	46
Mean ± SD		50 ± 12	66.1 ± 27.9					

IV, intravenously; IM, intramuscularly; PO, orally.
*Expressed as morphine milligram equivalents received for the 48 hours before the study.
†Patient participated in a second study.

PK-PD model in an attempt to establish a quantitative relationship between changes in plasma methadone concentration and measures of analgesia.

METHODS

Patient selection. The clinical characteristics of the study patients are given in Table I. Five women and three men ranging in age from 31 to 67 years (mean 50 years) with chronic pain who were evaluated by the Pain Service of the Memorial Sloan–Kettering Cancer Center gave informed consent to participate in this study. 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 analgesics other than methadone and, based on their current dosage, had 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. Methadone HCl was administered intravenously in a single dose of 10 to 30 mg under single-blind conditions. Three subjects (Nos. 2, 4, and 6) received a second dose 1 week to several months after the first dose. The drug was administered if the patient requested medication for pain and had not received an analgesic for at least 3 hours and the pain was reported as moderate to severe. Nurse observers assessed subjective and objective measures of effect from each patient before and at selected intervals after drug administration, and venous blood samples (8 to 10 ml) were collected into a heparin syringe at −5, 2, 5, 10, 15, 30, 60, 120, 180, 240, 480, 1440, and 2880 minutes into the study. Urine was collected for 24 hours after administration of the drug. Plasma was separated from blood cells and plasma and urine samples were frozen at −20° C until they were analyzed. At each observation time the patient was requested to report the intensity of pain by use of a visual analogue scale (VAS) as described by Kaiko et al.[10] The pain intensity score in centimeters for each postdrug observation was subtracted from the predrug pain intensity score to yield the reported pain intensity difference (VAS) score. Each observation time also included the measurement of blood pressure by use of sphygmomanometer, pulse rate, respiratory rate, and photographic determination of pupil size.[11] Pharmacodynamic observations were continued until the patient requested remedication with the current analgesic. For most patients this occurred between 240 and 300 minutes after drug administration.

Analytic methods. Plasma methadone concentrations were determined by the RIA method of Ling et al.[12] The lower limit of sensitivity is 0.003 μg/ml and the interassay coefficient of variation is 9.5%. Neither the metabolites of methadone nor commonly used analgesics including those opioids that the study patients had been receiving (Table I) interfere with the methadone RIA.

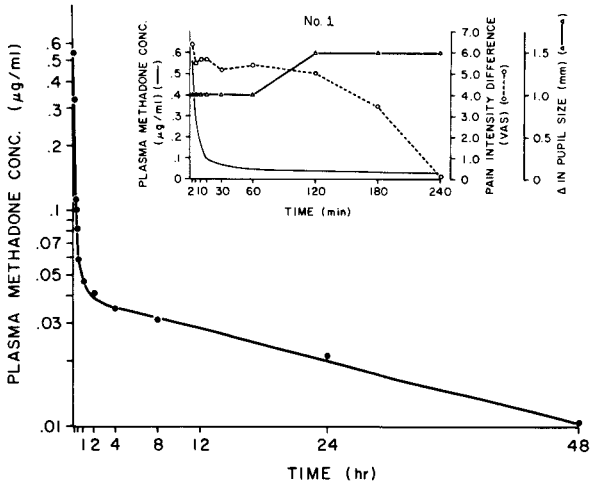

Fig. 1. Plasma concentration-time profiles of methadone after a single intravenous dose of 10 mg methadone HCl administered to patient No. 1. The points represent the observed concentrations and the solid line the theoretic line obtained by fitting the data with a triexponential equation. The insert shows measures of pharmacodynamic effect (pain intensity difference [VAS] and changes in pupil size) and the simultaneously determined plasma methadone profile for patient 1 for the 240 minutes after drug administration.

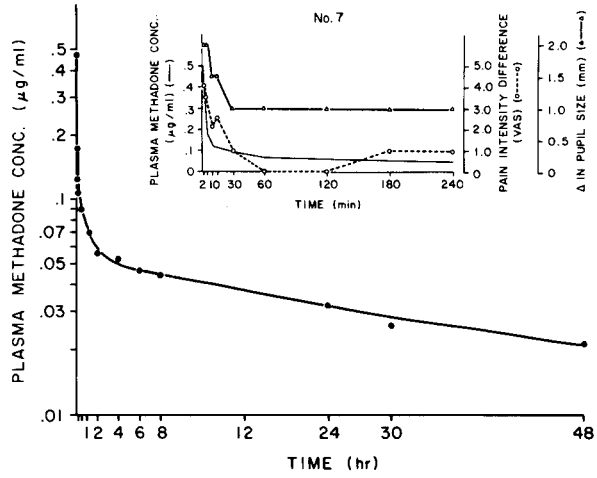

Fig. 2. Plasma concentration-time profiles of methadone after a single intravenous dose of 10 mg methadone HCl administered to patient No. 7. The points and solid line are as shown in Fig. 1. The insert shows measures of pharmacodynamic effect and the simultaneously determined plasma methadone profile for patient 7 (see also Fig. 1).

Plasma protein binding was measured in samples from patients 1, 2, 4, 6, 7, and 8 by equilibrium dialysis according to the method described by Szeto et al.[13] The outside buffer (Sorensen's phosphate, pH 7.4) contained 40,000 dpm/ml of tritiated d,l methadone [(±)-4,4-bis(phenyl-2-^{3}H)-6-dimethyl-amino-3-heptanone] at a specific activity of 16.7 Ci/mmol and a final methadone concentration of 0.020 or 0.200 μg/ml. The binding estimate was based on duplicate determinations.

The blood/plasma methadone ratio was calculated for each patient from the red cell to plasma partition coefficient by the formula, B/P = [H(R/P) + 1-H] (1), where H is each patient's hematocrit and R/P is the red cell:plasma partition coefficient of methadone. The R/P was determined in normal volunteer blood according to the method of McDevitt et al.[14] A 20 μl aliquot containing tritiated d,l methadone (11,000 dpm) and unlabeled methadone to a final blood methadone concentration of 0.1, 0.2, or 0.4 μg/ml was added to 2 ml heparin anticoagulated blood and the samples were incubated for 30 minutes at 37° C. The radioactivity in blood and plasma was determined by liquid scintillation counting and the R/P calculated by the formula,

$$R/P = \frac{b/p - (1 - H)}{H} \quad (2)$$

where b/p is the measured blood-to-plasma methadone ratio.

Pharmacokinetic analysis. Plasma methadone concentrations after intravenous administration were analyzed with the iterative weighted nonlinear least-squares regression program, NONLIN.[15] The data from each patient were fit with a triexponential equation.

The apparent volume of the central compartment (V_C), the volume of distribution of methadone in the body (V_{area}), and the half-lives ($t_{1/2}$ π, α, and β) were derived according to standard equations.[16] The AUC was calculated by trapezoidal summation and extrapolation to infinity.[17] The total plasma systemic clearance (CL) of methadone was calculated from:

$$CL = \frac{D}{AUC} \quad (3)$$

where D is the dose.

The clearance of methadone from blood (CL_B) was calculated from:

$$CL_B = \frac{Clp}{(B/P)} \quad (4)$$

where B/P is the blood/plasma ratio of methadone.

If we assume that the nonrenal clearance (CL_{NR}) of

Table II. Pharmacokinetic parameters for methadone after intravenous administration

Pt. No.	*Dose (mg)**	$t_{1/2}\ \pi$ *(min)*	$t_{1/2}\alpha$ *(min)*	$t_{1/2}\beta$ *(hr)*	V_C *(L/kg)*	V_{area} *(L/kg)*	CL_B *(ml/min)*	CL_R *(ml/min)*	CL_H *(ml/min)*	*ER*
1	10	1.2	20.0	25.8	0.18	5.34	122	8.3	133.7	0.076
2-A	20	0.7	39.1	51.1	0.14	3.08	57	1.3	55.7	0.037
2-B†	30	2.6	27.3	25.4	0.39	2.40	77	0.5	76.5	0.051
3	10	0.9	13.7	33.3	0.02	2.61	62	7.8	54.2	0.036
4-A	20	1.7	27.1	25.9	0.26	4.50	201	5.3	195.7	0.130
4-B†	30	4.7	145.0	28.9	1.34	4.95	200	2.3	197.7	0.133
5	10	1.8	45.6	13.0	0.24	4.09	216	6.1	209.9	0.140
6-A	15	1.9	36.2	14.4	0.17	1.71	184	16.3	167.7	0.112
6-B†	20	1.2	51.4	18.4	0.31	2.26	190	21.1	168.8	0.113
7	10	1.1	32.3	31.8	0.17	4.19	71	2.3	68.7	0.046
8	20	1.0	23.2	23.0	0.06	3.17	224	5.4	218.6	0.146
Mean ± SD		1.2‡	25.8‡	23.0‡	0.16 ± 0.08	3.59 ± 1.16‡	106	3.9‡	102.0‡	0.089 ± 0.047

*As HCl salt.
†Patient data not included in calculation of parameters.
‡Harmonic mean.

methadone occurs only in the liver, the hepatic clearance of methadone (CL_H) can be estimated from: $CL_H = CL_B - CL_R$ (5), where CL_R is the renal clearance of methadone estimated from:

$$CL_R = \frac{Xu(o \rightarrow 24)}{AUC(o \rightarrow 24)} \quad (6)$$

where $Xu(o \rightarrow 24)$ is the amount of methadone excreted unchanged in the urine in the first 24 hours after drug administration.

The hepatic extraction ratio (ER) is estimated from:

$$ER = \frac{CL_H}{Q} \quad (7)$$

where Q is hepatic blood flow that was assumed to be 1500 ml/min.[16,18]

PK-PD analysis. A compartmental model approach was used to simultaneously characterize the pharmacokinetics and pharmacodynamics of methadone. The PK-PD model, proposed by Sheiner et al.,[19] relates the pharmacologic-effect compartment to the central compartment by a first-order rate constant (k_{1e}). The resulting hypothetical amount in the effect compartment is related to the observed pharmacologic effect by use of the Hill equation (see Appendix, equation 8). Since the analgesic effect of opioids is mediated by specific drug receptor interactions, the simplest model that adequately describes the drug effect over the whole range of concentrations is the E_{max} model.[20,21] This model predicts the maximum effect a drug can achieve and predicts no effect when no drug is present. The equations describing the plasma drug concentration in the central compartment and the amounts in the hypothetical effect compartment for a three-compartment open model with intravenous injection input have been derived by Colburn[22] and are given in the Appendix (see equations 9 and 10). For the PK-PD analysis each patient's pain intensity difference (VAS) scores were divided by that patient's maximal possible pain intensity difference (VAS) score to yield the fraction of maximum effect value. Thus each patient could obtain a fraction of maximum effect value that ranged from 0 to 1.0.

RESULTS

Pharmacokinetics. Figs. 1 and 2 show examples of the observed plasma concentration-time profiles after intravenous methadone and the theoretic curves generated from computer-estimated parameters. A triexponential equation provided the best fit for the data. Both model-dependent and model-independent methods were used to obtain the parameter estimates given in Table II. The harmonic mean $t_{1/2}$s of the dispositional (distribution) and elimination phases are a $t_{1/2\ \pi}$ of 1.2 minutes, a $t_{1/2\ \alpha}$ of 25.8 minutes, and a $t_{1/2\ \beta}$ of 23 hours.

The R/P was 0.32 ± 0.01 (SD), a value independent of in vitro blood methadone concentrations of 0.1, 0.2 and 0.4 μg/ml. The mean B/P methadone ratio was 0.75 ± 0.03 (SD). The harmonic mean CL of methadone was 81 ml/min. From equation 4 the CL_B was estimated for each patient (Table II). The harmonic mean CL_B was 106 ml/min. During the 24 hours after methadone administration, 3.7% ± 3.0% (SD) of the dose appeared in the urine as unchanged methadone and the harmonic mean CL_R was 3.9 ml/min. The har-

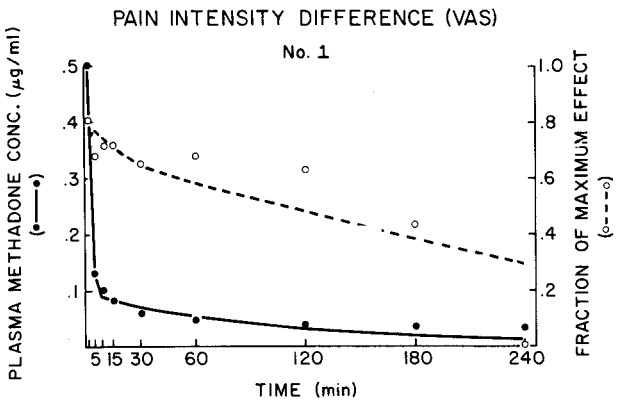

Fig. 3. Simultaneous plasma methadone concentration-time data (●) and fractional analgesic effect measured as pain intensity difference (VAS) (○) after intravenous administration of 10 mg methadone HCl to patient No. 1. The lines represent the theoretic lines obtained by the curve-fitting procedure of the PK-PD model.

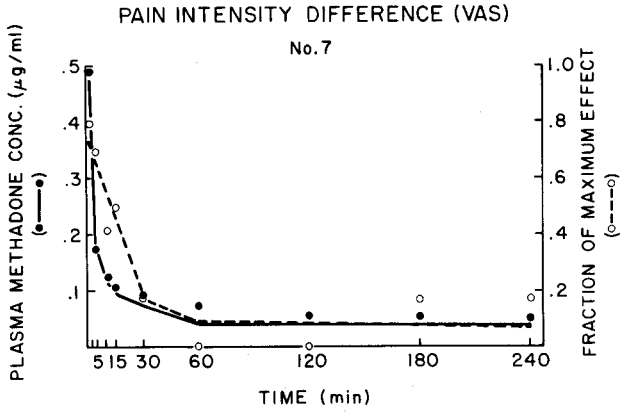

Fig. 4. Simultaneous plasma methadone concentration-time data (●) and fractional analgesic effect measured as pain intensity difference (VAS) (○) after intravenous administration of 10 mg methadone HCl to patient No. 7. The lines represent the theoretic lines obtained by the curve-fitting procedure of the PK-PD model.

monic mean CL_H was 102 ml/min (Table II). ER was found to have a mean value of 0.089 ± 0.047 (SD) (Table II).

The in vitro plasma protein binding studies revealed that methadone is 89.4% ± 2.9% (SD) bound (range 85% to 94%) when the equilibrium (total) plasma methadone concentration is 0.073 μg/ml and 85.8% ± 2.0% (SD) bound (range 82% to 88%) when total plasma methadone concentration inside the dialysis bag is 0.661 μg/ml. Thus the percent bound averaged approximately 88%, resulting in a free fraction of methadone in plasma of 12%.

Pharmacodynamics. When considering the pharmacodynamic effects that occurred in our patients, it must be borne in mind that each of the patients had prior opioid experience (Table I) that could be reflected in some degree of cross-tolerance to methadone. Two of the patients (Nos. 3 and 4) did not obtain any pain relief nor did they show any decrease in pupil size, and therefore their pharmacodynamic data could not be analyzed by the PK-PD model. For the remaining six patients, analgesia and miosis reached a peak effect by 2 to 5 minutes after drug administration. At 240 minutes the miotic effect persisted but analgesia had diminished to the point where each patient was given his or her current analgesic, precluding further measurement of methadone's pharmacodynamic effects. Figs. 1 and 2 *(inserts)* show the time-action profiles for analgesia (pain intensity difference, VAS) and miosis (change in pupil size) for patients 1 and 7, both of whom had received a 10 mg intravenous dose of methadone. The observations from patient 1 (Fig. 1, *insert*) show a rapid onset of analgesia and miosis. The analgesic effect persisted for at least 180 minutes and miosis remained at peak intensity until the last pharmacodynamic observation at 240 minutes after methadone administration. Patient 7 (Fig. 2, *insert*) also showed prompt analgesia and miosis. However, this patient's analgesia declined rapidly and had disappeared by 60 minutes after drug administration. Her miotic effect also declined during the first 30 minutes but in contrast to analgesia persisted until 240 minutes. Figs. 3 and 4 show that the data from patients 1 and 7 are well fit by the PK-PD model. This simultaneous analysis results in a nonlinear least-squares regression fit of plasma methadone concentration *(solid line)* and pain intensity difference *(broken line)* shown in Figs. 3 and 4 and estimates of pharmacodynamic parameters. The pharmacodynamic parameter estimates for the six patients who responded with analgesia are given in Table III. The $t_{1/2\ keo}$, which estimates the temporal lag between a change in plasma methadone concentration and a change in analgesia, ranged from 1.3 to 23.1 minutes with a harmonic mean of 3.6 minutes. The estimated steady-state concentration of methadone necessary to produce an analgesic effect that is 50% of maximum ($C_{ss\ (50)}$) varied from 0.04 to 1.13 μg/ml with a mean of 0.29 ± .38 (SD) μg/ml.

Mean predose blood pressure (132/86 mm Hg) and respiratory rate (16/min) remained constant for the 240-minute assessment period after methadone administration. Mean pulse rate declined slightly from a mean of

Table III. Pharmacodynamic parameters estimated by simultaneously curve fitting concentration-time data and analgesic effect data after intravenous administration of methadone to patients with chronic pain

Pt. No.	$t_{1/2\ keo}$ *(min)*	$C_{SS(50)}$ *(μg/ml)*	γ	r
1	6.3	0.04	0.74	0.960
2B	1.3	1.13	2.00	0.992
5	2.7	0.12	1.17	0.914
6A	23.1	0.22	1.99	0.975
6B	6.9	0.18	3.93	0.919
7	2.9	0.22	1.42	0.978
8	7.7	0.09	2.95	0.988
Mean ± SD	3.6*	0.29 ± 0.38	2.03 ± 1.10	0.961 ± 0.032

*Harmonic mean.

94/min to 80/min, reaching statistical significance ($P = <0.02$, paired t test) at 120 minutes. Four of the six patients had at least one side effect, including dizziness (one patient), nausea (one patient), sleepiness (one patient), sweating (two patients), feelings of tiredness (one patient), and heaviness (one patient).

DISCUSSION

After intravenous administration the plasma methadone concentrations in patients with chronic pain declined in a manner best fit by a triexponential equation. The pharmacokinetic parameters given in Table II describe methadone as a drug with rapid and extensive distribution phases followed by a slow elimination phase. The mean apparent V_c of 0.16 L/kg was equal to approximately 15% of body weight whereas the apparent V_{area} of 3.59 L/kg was equal to approximately 3.5 times body weight. The interindividual variation in elimination $t_{1/2}$ and CL_B was fourfold and fivefold, respectively. In contrast, we found these parameters to vary on the average by <30% in the three patients who participated in a second study. Our findings of a large interindividual variation in methadone $t_{1/2}$ and CL are consistent with previous observations made after oral administration in methadone-maintenance patients at apparent steady state[6] or after a single intravenous dose in patients after surgery.[3,7]

In attempting to understand the sources of interindividual variation, we have analyzed our data in terms of clearance concepts.[23] As can be seen in Table II, <4% of the CL_B can be accounted for as CL_R. So when urine pH remains above 6, as was the case for our patients with chronic pain, renal elimination of unchanged methadone is not a major route of elimination.[6]

The oxidative biotransformation of methadone is the primary route of drug elimination under most circumstances.[6] Since this occurs predominantly in the liver, it is reasonable to assume that the CL_B is a reflection of CL_H. CL_{NR} can be expressed quantitatively by subtracting the CL_R from the CL_B to yield the assumed CL_H (Table II). The efficiency of the CL_H can be estimated by calculating the hepatic extraction ratio, a value obtained by dividing the observed CL_H by the estimate of maximum CL_H of 1500 ml/min in the human.[16,18] As shown in Table II, this calculation indicates that <10% of the available methadone is cleared from the blood as it passes through the liver. Thus we can classify methadone as a low (hepatic)-extraction drug.[23] The CL_H of a low-extraction drug is a function of its binding in the blood and the intrinsic ability of the liver to eliminate the drug. Our estimate of the percent of methadone extracted from blood by the liver is approximately equal to the value of 12% for the free fraction of methadone in blood obtained from the protein-binding studies. These data suggest that the liver is able to extract only the free (unbound) methadone present in the blood perfusing the liver. Therefore it follows that a change in the binding of methadone in blood could alter hepatic extraction and the clearance of methadone. The free fraction of methadone in plasma varies directly with plasma α-glycoprotein levels.[24] Thus the plasma protein binding of methadone may be a source of interindividual variation in methadone clearance but its clinical significance, if any, remains to be determined.

The ER (Table II) predicts that if methadone is completely absorbed from the gastrointestinal tract the oral bioavailability of methadone should average 90%. This estimate is in general agreement with the mean value of 79% for methadone bioavailability found by Nilsson et al.[8] in methadone-maintenance patients.

The pioneering analgesic studies of Houde et al.[25,26]

and Beecher[27] established that a variety of psychologic factors (e.g., expectation, suggestion, and mood) can modify analgesic effectiveness by altering the reaction to pain. In addition to this source of variation, the early studies by Houde et al.[25] comparing oral with parenteral potency of opioids, such as morphine and codeine, provided the first evidence, albeit indirect, that pharmacokinetic factors such as oral bioavailability also can influence analgesic effectiveness. The demonstration of significant variation in methadone pharmacokinetics[3,4,6,8,28] together with the knowledge of interpatient variation in pain perception has led to the concept of individualization of methadone dosage for the management of chronic pain.[2] Pharmacokinetic considerations should play an important role in this concept. It has been suggested that the usual initial oral or intramuscular doses of methadone result in blood levels at the end of the distribution phase that are at or below the minimum effective blood concentration (MEC) necessary for analgesia.[3,7,29] Thus after these initial doses the duration of analgesia depends predominantly on the length of the distribution phases. Our combined PK-PD data after intravenous administration (Figs. 1 and 2) strongly support this suggestion. The onset of both analgesia and miosis occurs during the rapid initial distribution phase (Figs. 1 and 2). For some patients (e.g., No. 7; Fig. 2) the analgesic effect occurs almost entirely during the apparent distribution phase. In contrast, the miotic effect of methadone persists beyond the initial distribution phase. In this study the readministration of the patient's regular analgesia medication, when moderate to severe pain had returned, prevented continued observation of methadone-induced miosis. An earlier study in normal subjects[4] revealed that the 24-hour time course of methadone in plasma parallels the time action of the miotic effect. Although MECs for miosis could not be calculated in the present study, it would appear that much lower blood methadone concentrations are required to maintain the miotic effect than for continued analgesia. It is not known whether these differences in the pharmacodynamics of methadone result from preferential drug disposition or greater opioid receptor affinity or both at those subcortical brain sites that mediate miosis.[4] The administration of an initial loading dose sufficiently large to provide methadone blood levels above the analgesic MEC during the distribution and a substantial part of the elimination phase could permit continued analgesia as the blood level slowly declines during the long terminal elimination phase. This approach has been employed successfully in postoperative pain management by Gourlay et al.[3,7] However, as the authors point out, this approach has the potential to produce prolonged respiratory depression and therefore careful evaluation and dose titration must be used.[3] The relatively long elimination $t_{1/2}$ of methadone (Table II) dictates that from 2 to 9 days may be required to approach steady-state blood levels. Sawe et al.[28] have emphasized that advantage can be taken of the accumulation of methadone that occurs when frequent drug administration is necessary to control pain during the initial individualization of the dose. Under these circumstances, they argue that a significant increase in the duration of analgesia will occur during the initial 4 to 5 days of therapy.[28,29] Using an initial fixed oral dose of methadone with the interval between doses controlled by the patient, they found that the dosage interval increased during the first few days of treatment and the daily dose decreased from 30 to 80 mg on day 1 to 10 to 40 mg at the end of the first week.[28] These results suggest that the "usual" oral dose of methadone may in fact represent a loading dose requiring subsequent adjustment in many patients.

The next step in defining the contribution of pharmacokinetic factors to the analgesic effect of methadone is a more precise definition of the relationship between a change in measurable drug concentration in plasma or blood and a change in analgesia. This approach requires a linking of the observed pharmacokinetics and pharmacodynamics so that the concentration-time profile predicted by a pharmacokinetic model can be related to the drug concentration (not measurable) at the effect site. To accomplish this objective we have analyzed our analgesic data using a combined PK-PD model.[19,20] This type of modeling approach has been used to describe the PK-PD relationships of a number of drugs[21] including a comparison by Scott et al.[30] of the EEG effects of the opioids, fentanyl, and alfentanil in surgical patients. The PK-PD model features a hypothetical effect compartment and a concentration-effect relationship described by the Hill equation (see Appendix).[19,20] The PK-PD model estimates the lag time between a change in plasma drug concentration and effect (expressed as $t_{1/2\ keo}$). This is of value because the site of action of methadone is not in the plasma but rather at central nervous system opioid receptors. The time-dependent lag of effect behind a change in plasma drug concentration (hysteresis) has been reported for many drugs and is commonly seen after intravenous injection or infusion.[19,20] Furthermore, the PK-PD model allows measurements made under non-steady-state conditions such as an intravenous bolus to be related to the steady-

state concentration-effect relationship in which equilibrium has been achieved between plasma drug concentration and the site of effect. The PK-PD model estimates the $C_{ss\ (50)}$, which reflects the intrinsic sensitivity of the patient to the drug effect and provides γ, the slope function, so that a complete concentration-effect curve can be generated from experimentally determined data that may be much more limited.[31] The combined PK-PD data from each of the six patients who reported pain relief was analyzed by the PK-PD model and the results are given in Table III. Within the limitations detailed below, some illustration can be offered of the power of this analysis in obtaining quantitative data and increasing our understanding of PK-PD relationships. The harmonic mean value for the temporal lag expressed as $t_{1/2\ keo}$ was 3.6 minutes. This value is less than the $t_{1/2\ keo}$ estimates of 15 to 20 minutes for morphine analgesia[31] or the 6.4-minute value for fentanyl's EEG effects but longer than the lag time of 1.1 minute for alfentanil's EEG effects.[30] The relative order of these results reflects the more rapid penetration into the central nervous system of lipid soluble opioids such as methadone, alfentanil, and fentanyl compared with morphine, as well as differences in opioid receptor–binding characteristics. The shorter lag time for methadone compared with morphine suggests that better response control can be achieved with a methadone infusion because changes in analgesia more closely parallel changes in methadone plasma concentrations. The intrinsic sensitivity, as estimated by $C_{ss\ (50)}$, varied nearly thirtyfold from 0.04 μg/ml to 1.13 μg/ml (Table III). It is of interest that patient 2B, who had the highest prior opioid experience (Table I), also had the highest value for half maximum analgesic effect ($C_{ss\ (50)}$; Table III). However, no overall correlation was found between prior opioid experience and $C_{ss\ (50)}$ with this small number of patients. The different opioids the patients were receiving before the study (Table I) could be reflected in different degrees of cross-tolerance to methadone, further limiting this type of correlation. The study was not designed to measure the influence of tolerance. However, patient 6, who participated in the study on two occasions separated by 2½ months and remained on a stable dosage of opioid (Table I) during this period, showed no change in the estimate of $C_{ss\ (50)}$. This result indicates that his sensitivity to methadone was unaltered by chronic stable administration of meperidine during the interval between studies. Not surprisingly our mean estimate for analgesic $C_{ss\ (50)}$ of 0.29 μg/ml for patients with chronic pain is much higher than the estimate of 0.06 μg/ml for the minimum effective analgesic concentration of methadone required by relatively nontolerant patients after surgery.[7] Only one patient had a γ value <1.00 with the mean value equal to 2.02 (Table III). A γ value of approximately 2 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 tenfold change in plasma methadone concentration. Steeper concentration-effect relationships have been reported for the analgesic effects of meperidine[32] and for the EEG effects of fentanyl and alfentanil.[30]

In this report we demonstrate that data obtained under conditions commonly used in analgesic studies can be analyzed with a PK-PD model. The intravenous bolus mode of drug administration employed in this study can limit the precision of the pharmacodynamic parameter estimates obtained. The rapidly changing plasma methadone concentrations characteristic of the distribution phase seen after an intravenous bolus can be expected to produce relatively large errors in attempting to estimate the relationship between plasma drug concentration and analgesia as expressed by the $t_{1/2\ keo}$ and $C_{ss\ (50)}$ parameters.[20,30] Furthermore, we do not yet know the extent to which the individual pharmacodynamic parameter estimates we obtained can be used to predict therapeutic success with methadone in these patients with chronic pain.

However, we believe this approach has the potential to provide quantitative information on individual PK-PD relationships. This information can be used to determine whether observed differences in analgesic response have primarily a pharmacokinetic or a pharmacodynamic basis. Although not assessed in this study, the PK-PD model can be used to compare pain patients' relative sensitivity to analgesic effects with other pharmacodynamic effects including adverse effects. This approach will increase our understanding of PK-PD relationships and can result in a significant improvement in the use of opioid analgesics for the management of patients with chronic pain.

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APPENDIX

The Hill equation

$$E = \frac{KEO\ Ae/(KIE\ V_p)^{\gamma}}{KEO\ Ae/(KIE\ V_p)^{\gamma} + C_{ss\ (50)}{}^{\gamma}} \qquad (8)$$

where E is the effect expressed as fraction of maximum effect; KEO is the elimination rate constant from the hypothetical effect compartment; Ae is the hypothetical effect amount; KIE is the transfer rate constant from peripheral to the hypothetical

effect compartment; V_p is the volume of the driving (plasma) compartment; γ is a power factor for the Hill equation that determines the sigmoidicity of the concentration-effect curve; and $C_{SS\,(50)}$ is the steady state of drug in the driving pharmacokinetic compartment when the observed effect is 50% of maximum.

The concentration of methadone in the central compartment at any time is given by:

$$C_p = \frac{X_o(k_{21} - \pi)(k_{31} - \pi)}{V_p(\alpha - \pi)(\beta - \pi)} e^{-\pi t} + \frac{X_o(k_{21} - \alpha)(k_{31} - \alpha)}{V_p(\pi - \alpha)(\beta - \alpha)} e^{-\alpha t} + \frac{X_o(k_{21} - \beta)(k_{31} - \beta)}{V_p(\pi - \beta)(\alpha - \beta)} e^{-\beta t} \quad (9)$$

where X_o is the dose; π is the fastest hybrid rate constant; α is the intermediate hybrid rate constant; β is the slowest hybrid rate constant; K_{21} is the transfer rate constant from shallow peripheral to central compartment; K_{31} is the transfer rate constant from deep peripheral to central compartment; and t is the time after drug administration.

The amount of methadone in the hypothetical effect compartment is given by:

$$A_e = \frac{k_{IE} X_o (k_{21} - \pi)(k_{31} - \pi)}{(\alpha - \pi)(\beta - \pi)(k_{EO} - \pi)} e^{-\pi t} + \frac{k_{IE} X_o (k_{21} - \alpha)(k_{31} - \alpha)}{(\pi - \alpha)(\beta - \alpha)(k_{EO} - \alpha)} e^{-\alpha t} + \frac{k_{IE} X_o (k_{21} - \beta)(k_{31} - \beta)}{(\pi - \beta)(\alpha - \beta)(k_{EO}\beta)} e^{-\beta t} + \frac{k_{IE} X_o (k_{21} - k_{EO})(k_{31} - k_{EO})}{(\pi - k_{EO})(\alpha - k_{EO})(\beta - k_{EO})} e^{-k_{EO} t} \quad (10)$$